German Guideline Program in Oncology (GGPO)

Guideline Report on the Evidence-based Guideline on Prevention of Skin Cancer

Version 1.1 – April 2014

AWMF registration number: 032/052OL

Guideline-Report

DKG KREBSGESELLSCHAFT

Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

AWMF

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1. Information about the guideline report

1.1. Authors of the guideline report

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1.2. Editors

German Guideline Program in Oncology (GGPO) of the Association of Medical Scientific Societies (AWMF), the German Cancer Society (DKG) and German Cancer Aid (DKH).

1.3. Leading professional society

Association of Dermatological Prevention (ADP)

ARBEITSGEMEINSCHAFT
DERMATOLOGISCHE
PRÄVENTION

on behalf of the German Dermatological Society (DDG) and the Dermatological Oncology Working Group (ADO)

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1.4. Funding of the guideline

This guideline was funded by the German Cancer Aid as part of the German Guideline Program in Oncology.

1.5. Contact

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1.6. Citation

The German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Evidence-based guideline on prevention of skin cancer, guideline report 1.1, 2014, AWMF registration number: 032/052GGPO, http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html (accessed on DD.MM.YYYY)

1.7. Former changes of version 1

April 2014 Version 1.1.: modifications of the chapters 'Editors' and the 'Leading professional society', removing level of evidence '1--' (not included in the original citation and not relevant for this guideline), specification of the SAB's role in the development process.

1.8. Documents relating to the guideline

The evidence-based guideline on prevention of skin cancer (AWMF No 032/052 OL) is a guideline sponsored by the GGPO. It was compiled between January 2010 and December 2013 by the Association of Dermatological Prevention (ADP) with the involvement of 33 professional societies and patient representatives.

Both the long and short versions of the guideline can be accessed via the following websites and are available there for downloading. (Please note that all these websites are in German. Parts of the GGPO and German Cancer Aid websites have an English translation):

- http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html
- http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- http://www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html
- http://www.krebshilfe.de/
- http://www.arztbibliothek.de
- http://unserehaut.de/
- http://hautkrebs-screening.de.

In addition to the long and short versions, there will be the following documents supplementing this guideline:

- guideline report (the present document)
- evidence tables (extracts from and appraisals of the studies concerned, *only available in German*)
- checklists from the evidence appraisal
- information pack for briefing the working groups
- patient guideline (lay version)

The lay version is distributed primarily via medical practices and other healthcare institutions such as the DKG or DKH. It will also be available online on the above-mentioned websites.
Part of the method report has also been published in the international journal JAMA Dermatology [1].

2. Scope and objective

2.1. Target audience

The recommendations of the evidence-based guideline on prevention of skin cancer are directed at all doctors[1] and members of professional groups involved in the prevention and early detection of skin cancer. These include community-based doctors with a preventive role (dermatologists, general practitioners, medical practitioners, non-specialist physicians, internal specialists in primary care, gynaecologists, urologists, surgeons, paediatricians, otolaryngologists, oral and maxillofacial surgeons, histopathologists, dentists) as well as nursing staff and health assistants. Further audiences include medical scientific professional societies and professional associations, patient representatives and skin cancer self-help groups as well as quality assurance bodies and other institutions, such as the Federal Office for Radiation Prevention (BfS), the Central Institute for Outpatient Care Provision in Germany (ZI), the Joint Federal Committee (G-BA) and the Society of Epidemiological Cancer Registries in Germany (GEKID).

Lastly, the guideline is directed at the general population of Germany. A separate evidence-based lay guide has been produced to allow a direct approach to the population.

2.2. Aim

The aim of developing the evidence-based guideline on prevention of skin cancer is to adapt the primary and secondary prevention of skin cancer to the current state of international scientific knowledge. In so doing, the guideline is intended to contribute both to an improvement in the state of health and to a higher quality of life of the population. This aim is to be achieved primarily by reducing the incidence, morbidity and mortality of skin cancer.

It should be noted that this guideline is intended to furnish conclusions that provide answers to key questions in the areas of primary prevention, secondary prevention and diagnosis and that make due allowance for communication and quality assurance aspects (the key questions can be found in Appendix 1).

2.3. Interface with the evidence-based guideline on diagnosis, therapy and follow-up of melanoma (AWMF No 032/024)

The original plan was for a “skin cancer” guideline that was intended to cover the areas from prevention to palliative care. However, for pragmatic reasons such as scope and feasibility, it was instead decided in the preparatory and harmonisation phase to produce two guidelines linked via an interface group.

The interface group consisted of Prof. Dr. Breitbart (evidence-based guideline on prevention of skin cancer, co-ordinator) and Prof. Dr. Garbe and Prof. Dr. Schadendorf (evidence-based guideline on diagnosis, therapy and follow-up of melanoma, co-

[1] In the interest of greater legibility, the use of the masculine and feminine forms at the same time will be avoided. All references to persons will apply equally to members of both sexes.

ordinators). The respective representatives of the other interface group or their deputies were always present in the harmonisation processes of the two guidelines.

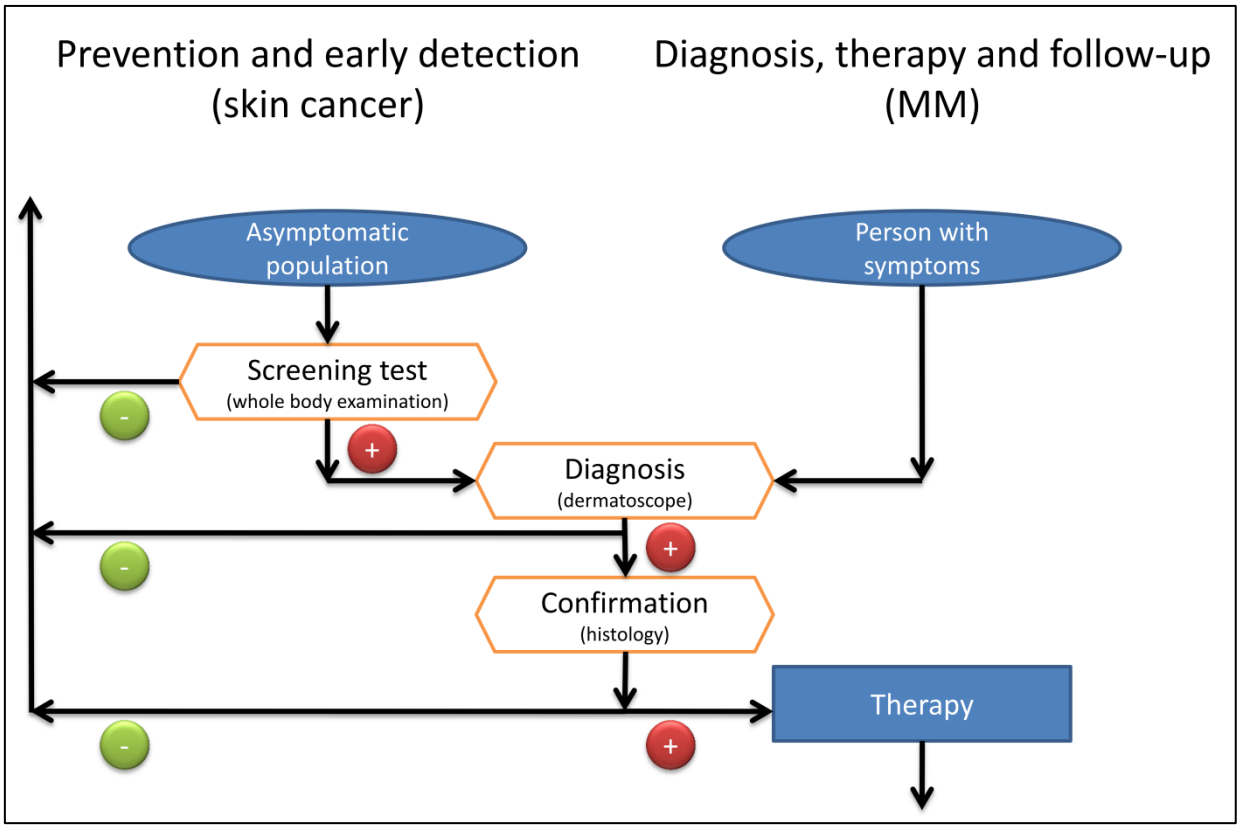

Figure 1: Overview of the interface with thee guideline on malignant melanoma (032/024OL)

2.4. Period of validity and update process

The estimated period of validity of the guideline on the prevention of skin cancer is 5 years.

To be able to convey the latest state of knowledge in the field of skin cancer prevention, updates of the guideline will be necessary. A revision will be undertaken five years after completion of the follow-up research, i.e. June 2017.

Where urgent changes are required, these will be published separately. Comments and advice on the update process are expressly requested and can be addressed to the guideline office:

c/o Prof. Dr. med. E.W. Breitbart
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2.5. Abbrevations used

Abbreviation	Explanation
ADH	Dermatological Histology Working Group
ADO	Dermatological Oncology Working Group
ADP	Association of Dermatological Prevention
AGKI	German Working Group on MaxillofacialSurgery
AHMO	Otorhinolaryngology, Oral and Maxillofacial Surgical Oncology Working Group
AKOPOM	Interdisciplinary Working Group on Oral Pathology and Oral Medizine
AWMF	Association of Medical Scientific Societies
ÄZQ	German Agency for Quality In Medicine
BAG Selbsthilfe	German Working Party for the Assistance of Persons with Disabilities and Chronic Diseases and their Relatives
BDP	Federal Association of German Pathologists
BCC	Basal cell carcinoma
BDU	Professional Association of German Urologists
BfS	Federal Office for Radiation Protection
BVA	Professional Association of German Ophthalmologists
BvF	Professional Association of Gynaecologists
BVKJ	Professional Association of Paediatric and Adolescent Physicians
CMN	Congenital melanocytic naevi
DAPO	German Association of Psychosocial Oncology
DDG	German Dermatological Society
DEGAM	German Society of General Practice and Family Medicine
DELBI	German Instrument for Methodological Guideline Appraisal
DGAUM	German Society for Occupational and Environmental Medicine
DGDC	German Society for Dermatosurgery
DGEpi	German Society for Epidemiology
DGGG	German Society of Obstetrics and Gynaecology
DGKJ	German Society of Paediatric and Adolescent Medicine
DGMKG	German Society for Oral and Maxillofacial Surgery
DGZMK	German Society for Dental and Oral Medicine
DGP	German Society of Pathology
DGSMP	German Society for Social Medicine and Prevention

Abbreviation	Explanation
DGU	German Society of Urology
DKG	German Cancer Society
DKH	German Cancer Aid
DOG	German Ophthalmological Society
DOM	Dental, oral and maxillofacial
DPB	German Psoriasis Association
ENT	Ear, nose and throat
EURO*SKIN*	European Society for Skin Cancer Prevention
G-BA	Federal Joint Committee
GEKID	Society of Epidemiological Cancer Registries in Germany
GGPO	German Guideline Program in Onlology
G-I-N	Guidelines International Network
GKV-Spitzenverband	National Association of Statutory Health Insurance Funds
IhF	German Institute for CME and CPD in General Practice
IQWiG	Institute for Quality and Efficiency in Health Care
ITFSCP	International Task Force Skin Cancer Prevention
KBV	National Association of Statutory Health Insurance Physicians
MDK	Medical Service Departments of the Health Insurance Funds
NGC	National Guideline Clearinghouse
NICE	National Institute for Clinical Excellence
NVL	National Supply Guideline
OMF	Oral and maxillofacial
PSO	Psycho-Oncology Working Group of the German Cancer Society
SAB	Scientific Advisory Board
SCC	Squamous cell carcinoma
SIGN	Scottish Intercollegiate Guidelines Network
VDBW	German Association of Occupational Physicians
WG	Working group
ZI	Central Institute for Outpatient Care Provision in Germany

3. Composition of the guideline group

Various professional societies, patient representative groups and national and international experts were inolved in compiling the S3-Guideline Prevention of Skin Cancer. As outlined in Figure 2, they can be divided into the following groups:

- Guideline steering committee
- Guideline co-ordinator
- Professional societies and patient representative groups who sent appointed representatives
- ADP scientific working group
- International scientists on the Scientific Advisory Board (SAB)
- Experts without a mandate and without voting rights
- Non-voting advisers

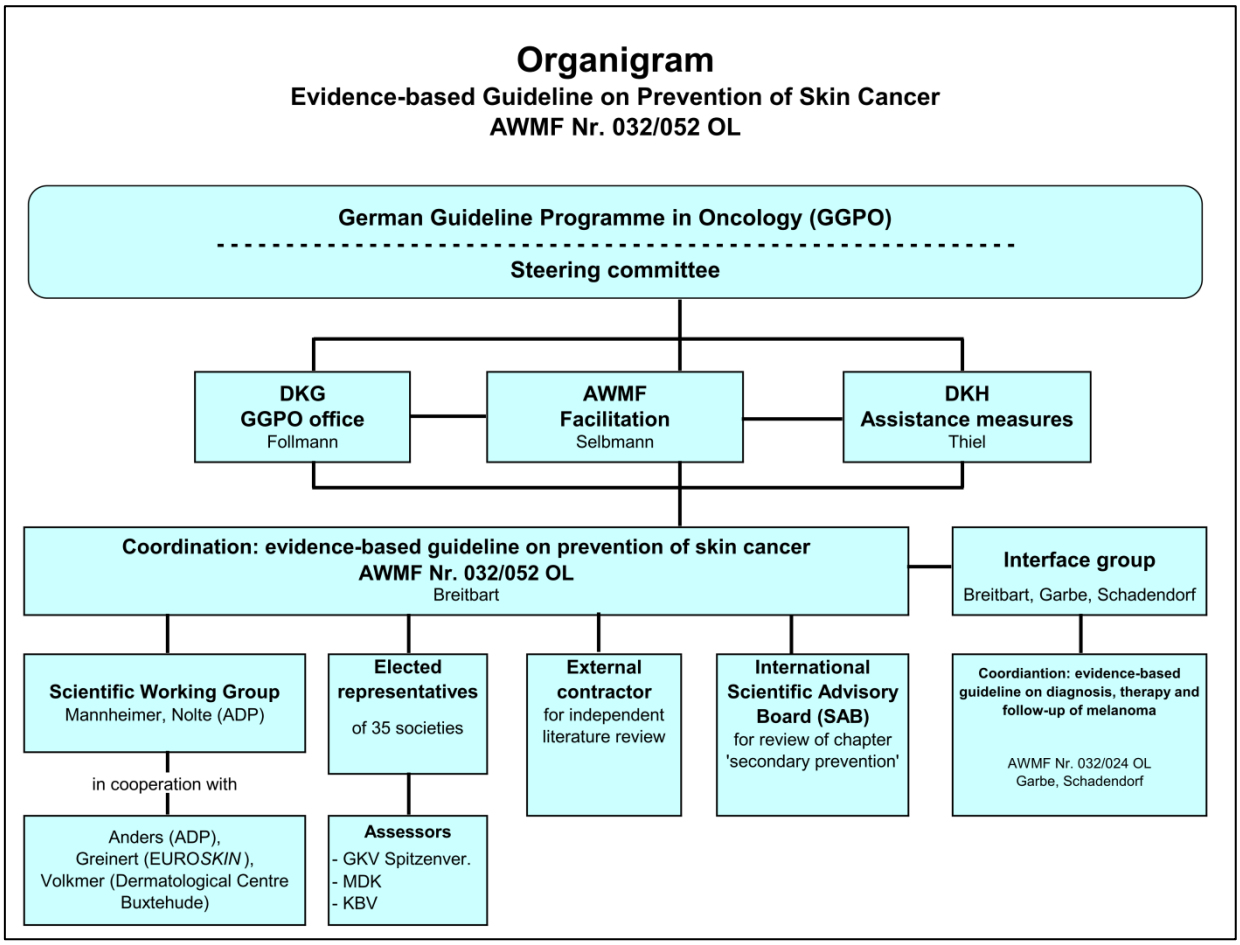

Figure 2: Organigram of the persons and institutions involved

Members of the guideline steering committee: Prof. Dr. Hans-Konrad Selbmann, Assiciation of Medical Scientific Societies (AWMF); Annika Thiel, German Cancer Aid (DKH); Dr. Markus Follmann, MPH, coordinator of the German Guideline Program in Oncology (GGPO) accomplished by the German Cancer Society (DKG). Not entitled to vote assessors: Petra Uschold, National Association of Statutory Health Insurance Funds (GKV-

Spitzenverband); Dr. Paul Reinberger, National Association of Statutory Health Insurance Physicians (KBV); Dr. Thomas Weihkopf, Medical Service Departments of the Health Insurance Funds (MDK).

The co-ordinator with primary responsibility for the evidence-based guideline on prevention of skin cancer was Prof. Dr. Eckhard Breitbart, Head of the Dermatology Department of the Elbe Hospital Buxtehude (ret.), deputy chairman of the ADP.

3.1. Professional societies

In accordance with the requirements of the GGPO, the guideline project was announced on the AWMF's home page immediately after the contract was awarded (section "Angemeldete Leitlinien" *["Notified guidelines"]*). This process serves the purpose of allowing all professional societies and other parties with an interest in the guideline project to declare their interest in participating. Following the official notification, all associations, professional societies, institutions and patient representative groups involved in skin cancer were invited in writing by the ADP on 8 February 2010 to participate in compiling the guideline. In addition, an approach was made to institutions that are not primarily involved with skin cancer but that can provide an important contribution to the compilation of the guideline. The aim was to ensure a multidisciplinary and multiprofessional composition of the working group consistent with the content and scope of the guideline. Representatives of self-help organisations were actively included in the compilation process from the outset with the aim of highlighting more effectively the problems of the disease and its care from the sufferers' perspective.
The following professional societies were invited:

1. Association of Dermatological Prevention (ADP)
2. Dermatological Histology Working Group (ADH)
3. Dermatological Oncology Working Group (ADO)
4. Professional Association of German Dermatologists (BvDD)
5. German Dermatological Society (DDG)
6. German Society for Dermatosurgery (DGDC)
7. German Institute for CME and CPD in General Practice (IhF)
8. German Society of General Practitice and Family Medicine (DEGAM)
9. German Cancer Society (DKG)
10. European Society for Skin Cancer Prevention (EURO*SKIN*)
11. German Working Party for the Assistance of Persons with Disabilities and Chronic Diseases and their Relatives (BAG Selbsthilfe)
12. German Psoriasis Association (DPB)
13. Skin cancer self-help group(s)
14. Society of Epidemiological Cancer Registries in Germany (GEKID)
15. German Society for Epidemiology (DGEpi)
16. German Society of Obstetrics and Gynaecology (DGGG)
17. German Society of Paediatric and Adolescent Medicine (DGKJ)
18. German Society for Educational Science (DGfE)
19. German Society for Journalism and Communication Science (DGPuK)
20. German Society of Dentistry and Oral Medicine (DGZMK)
21. German Society for Oral and Maxillofacial Surgery (DGMKG)
22. Otorhinolaryngology, Oral and Maxillofacial Surgical Oncology Working Group (AHMO)
23. German Society of Oto-Rhino-Laryngology, Head and Neck Surgery
24. German Society for Occupational and Environmental Medicine (DGAUM)
25. Society of Hygiene, Environmental and Public Health Sciences (GHUP)

26. Society for Medical Education (GMA)
27. Society for Quality Management in Health Care (GQMG)
28. German Agency for Quality in Medicine (ÄZQ)
29. Institute for Quality and Patient Safety (BQS)
30. Institute for Quality and Efficiency in Health Care (IQWIG)
31. German Society for Social Medicine and Prevention (DGSMP)
32. German Society of Pathology (DGP)
33. Federal Assiciation of German Pathologists (BDP)
34. Oncology Nursing Commission (KOK)
35. German Network for Evidence-Based Medicine (DNEbM)
36. German Society of Medical Psychology (DGMP)
37. German Society of Sports Medicine and Prevention (DGSP) (formerly German Sports Medical Association)
38. German Medical Society for Behavioural Therapy (DÄVT)
39. German Society for Behavioural Medicine and Behaviour Modification (DGVM)
40. German Association of Occupational Physicians (VDBW)
41. Professional Association of Paediatric and Adolescent Physicians (BVJK)
42. National Association of Statutory Health Insurance Physicians (KBV) (guest)
43. National Association of Statutory Health Insurance Funds
44. Federal Council of Parents
45. Robert-Koch Institute (RKI)
46. German Ophthalmological Society (DOG)
47. Professional Association of German Ophthalmologists (BVA)
48. Professional Association of German Urologists (BDU)
49. German Society of Urology (DGU)
50. Professional Association of Gynaecologists (BVF)
51. Federal Office for Radiation Protection (BfS)
52. German Association of Psychosocial Oncology (DAPO)
53. Rehabilitation in Dermatology Working Group (Ared)
54. Psycho-Oncology Working Group of the German Cancer Society (PSO)

Thirty-four institutions took up the invitation to participate in the evidence-based guideline on prevention of skin cancer. In the course of the project, the mandate of the Centre for Media and Health Communication was withdrawn, so that 33 institutions were actively involved in the whole process of compiling the guideline. Nine of these institutions appointed an additional representative, although the representative of the German Psoriasis Association later withdrew. The full list of institutions involved in compiling the guideline can be found in Table 1.

Table 1: Overview of the associations, professional societies, organisations and patient representative groups involved and their appointed representatives

Institution	Representative
1. Dermatological Histology Working Group (ADH)	Prof. Dr. Christian Sander
2. Dermatological Oncology Working Group (ADO)	Prof. Dr. Axel Hauschild (retired), Prof. Dr. Carola Berking
3. Psycho-Oncology Working Group of the German Cancer Society (PSO)	Prof. Dr. Susanne Singer
4. Otorhinolaryngology, Oral and Maxillofacial Surgical Oncology Working Group (AHMO)	Prof. Dr. Jochen A. Werner (retired), PD Dr. Andreas Gerstner
5. Professional Association of German Ophthalmologists (BVA)	Prof. Dr. Holger Mietz
6. Professional Association of German Urologists (BDU)	Dr. Bernt Göckel-Beining
7. Professional Association of Gynaecologists (BVF)	Dr. Wolfgang Cremer
8. Professional Association of Paediatric and Adolescent Physicians (BVKJ)	Dr. Herbert Grundhewer
9. German Working Party for the Assistance of Persons with Disabilities and Chronic Diseases and their Relatives (BAG Selbsthilfe)	Christiane Regensburger
10. Federal Office for Radiation Protection (BfS)	Dr. Monika Asmuß
11. Federal Association of German Pathologists (BDP)	Prof. Dr. Erhard Bierhoff*
12. German Association of Psychosocial Oncology (DAPO)	Annkatrin Rogge
13. German Dermatological Society (DDG)	PD Dr. Thomas Eigentler
14. German Dermatological Society (DDG) – Primary Prevention / Vitamin D	Prof. Dr. Jörg Reichrath
15. German College of General Practitioners and Family Physicians (DEGAM)	Prof. Dr. Jean-François Chenot, Dr. Günther Egidi
16. German Society for Occupational and Environmental Medicine (DGAUM)	Prof. Dr. Hans Drexler
17. German Society for Dermatosurgery (DGDC)	Dr. Christoph Löser
18. German Society for Epidemiology (DGEpi)	Prof. Dr. Andreas Stang
19. German Society of Obstetrics and Gynaecology (DGGG)	Dr. Grit Mehlhorn
20. German Society of Oto-Rhino-Laryngology, Head and Neck Surgery	Prof. Dr. Friedrich Bootz (retired), PD Dr. Andreas Gerstner

Institution	Representative
21. German Society of Paediatric and Adolescent (DGKJ)	Prof. Dr. Peter Höger
22. German Society for Oral and Maxillofacial Surgery (DGMKG)	Prof. Dr. Dr. Bernhard Frerich, Dr. Dr. Heidrun Schaaf (deputy)
23. German Society of Pathology (DGP)	PD Dr. Christian Rose*
24. German Society for Journalism and Communication Science (DGPuK)	Dr. Eva Baumann
25. German Society for Social Medicine and Prevention (DGSMP)	Prof. Dr. Alexander Katalinic, Dr. Annika Waldmann (deputy)
26. German Society of Urology (DGU)	Prof. Dr. Jürgen Gschwend
27. German Ophthalmological Society (DOG)	Prof. Dr. Rudolf F. Guthoff
28. German Institute for CME and CPD in General Practice (IhF)	Dr. Diethard Sturm, Dr. Manfred Diensberg (deputy)
29. German Psoriasis Association	Hans-Detlev Kunz, Christiane Rose (retired)
30. European Society for Skin Cancer Prevention (EURO*SKIN*)	Dr. Rüdiger Greinert
31. Society of Epidemiological Cancer Registries in Germany (GEKID)	Dr. Annika Waldmann
32. Buxtehude Skin Cancer Self-Help Group	Annegret Meyer, Martina Kiehl
33. German Association of Occupational Physicians (VDBW)	Dr. Uwe Gerecke
34. Association to Promote Dialogue in the Health System	Dr. Carsten Schwarz
35. Centre for Media and Health Communication	Dr. Bettina Fromm (retired)
* joint representative of the professional association and the professional society	

The representatives of the associations, professional societies and organisations in the guideline group were confirmed in writing by the relevant chairpersons. Possible conflicts of interest were ascertained before the kick-off meeting, which was held on 18 March 2010 in Hamburg, by means of the "Declaration of conflicts of interest in guideline projects form". Following review by the guideline co-ordinator, none of the reported conflicts of interested was classed as sufficiently critical to have an impact on the remits.

As the ADP, and with it in particular the guideline co-ordinator Prof. Dr Breitbart, has been active since the 1980s in the area of both primary and secondary prevention of skin cancer and in particular has designed, implemented and analysed the SCREEN project (SCREEN: Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) [2], which was the basis for the introduction of national skin cancer screening in Germany, a potential conflict of interests was envisaged by the GGPO. In order to address this point the promotion of the guideline project was subjected to a neutral appraisal of the guideline by international experts.

Thus, it was intended to ensure that the evidence on secondary prevention was assessed independently. In order to meet this precondition already in the creation process, international experts in the field of skin cancer prevention have been included in the development of the guideline's chapter on the early detection of skin cancer. These

experts are members of the Scientific Advisory Board (SAB) for the Prevention of Skin Cancer (see guideline report) that was founded in 2009 [3]. Furthermore neutrality of the assessment regarding scientific evidence was ensured through the commission of external institutions (see section 5.2 in this report).

3.2. Other institutions

For the substantive work on the guideline, eight subject-specific working groups were formed at the kick-off meeting. The respective leader of the working group concerned and their deputy acted as primary contacts for the ADP. Further experts were invited to provide support to the working groups, although – unlike the representatives with voting rights – they had only an advisory role and were not entitled to vote. The experts are listed in Table 2.

Table 2: Experts without a mandate and without voting rights

Experts	Institution
Dipl.-Ges.-Ök. Karolina Beifus	University of Wuppertal
Prof. Dr. Swen Malte John	University of Osnabrück
Prof. Dr. Juliane Köberlein-Neu	University of Wuppertal
Dr. Peter Mohr	Elbe Hospital Buxtehude
Dr. Harald Siekmann	German Statutory Accident Insurance
Dr. Beate Volkmer	Dermatology Centre Buxtehude

Table 3: Members of the Scientific Advisory Board (SAB)

Experts	Institution
Joanne Aitken	Cancer Council Queensland, Australia
Mathieu Boniol	IARC, France
Jean-Francois Doré	IARC, France
Mark Elwood	BC Cancer Agency, Canada
Suzanne W. Fletcher	Harvard Medical School, USA
Rick Gallagher	BC Cancer Agency, Canada
Sara Gandini	Instituto Europeo di Oncologia *[European Institute of Oncology]*, Italy
Alan Geller	Harvard, USA
Allan C. Halpern	Memorial Sloan Kettering Cancer Center, USA
Robyn Lucas	ANU College of Medicine and Health Sciences, Australia
Ashfaq A. Marghoob	Memorial Sloan Kettering Cancer Center, USA
Joachim Schüz	IARC, France
Craig Sinclair	Cancer Council Victoria, Australia
Margaret A. Tucker	National Cancer Institute, USA
Marty Weinstock	Brown University, USA

Following invitation of the experts listed in Table 2 and recruitment of the SAB (Table 3), the eight working groups were composed of the members listed in Table 4.

Table 4: Working groups (WG) of the evidence-based guideline on prevention of skin cancer

Member	Organisation
WG 1. Status quo – Key questions No 1 to No 4	
Ms Waldmann, WG leader (AR)	GEKID
Mr Katalinic (AR)	DGSMP
Ms Köberlein-Neu (E)	University of Wuppertal
Ms Beifus (E)	University of Wuppertal
Mr Greinert (AR)	EURO*SKIN*
Ms Volkmer (E)	Dermatology Centre Buxtehude
Mr Breitbart (C)	ADP
WG 2. Primary prevention – Key questions No 5 and No 6	
Mr Diensberg, WG leader (DR)	IhF
Ms Asmuß, deputy (AR)	BfS
Mr Drexler (AR)	DGAUM
Mr Grundhewer (AR)	BVKJ
Mr Reichrath (AR)	DDG
Mr Greinert (AR)	EURO*SKIN*
Ms Volkmer (E)	Dermatology Centre Buxtehude
Ms Singer (AR)	PSO
Mr Siekmann (E)	German Statutory Accident Insurance
Mr John (E)	University of Osnabrück
WG 3. Secondary prevention – Key question 7	
Scientific Advisory Board	see Table 3
Mr Göckel-Beining, WG leader (AR)	Professional Association of German Urologists
Mr Cremer, Vertreter (AR)	Professional Association of Gynaecologists
Mr Chenot (AR)	DEGAM
Mr Greinert (AR)	EUROSKIN
Ms Volkmer (E)	Dermatology Centre Buxtehude
Mr Stang (AR)	DGEpi
WG 4. Presumptive diagnosis / screening test – Key question 8	
Ms Berking, WG leaderin (DR)	ADO
Mr Eigentler, Vertreter (AR)	DDG
Ms Mehlhorn (AR)	DGGG
Mr Breitbart (C)	ADP
Mr Mohr (E)	Elbe Hospital Buxtehude
Mr Sturm (AR)	IhF
WG 5. Confirmatory diagnostic procedures – Key question 9	

Member	Organisation
Mr Rose, WG leader (AR)	DGP
Mr Sander, WG leader (AR)	ADH
Mr Breitbart (C)	ADP
Mr Eigentler (AR)	DDG
Mr Gerstner (DR)	AHMO
Mr Löser (AR)	DGDC
WG 6. Doctor-patient communication – Key question 10	
Mr Schwarz, WG leader (AR)	Association to Promote Dialogue in the Health System
Mr Egidi, deputy (AR)	DEGAM
Ms Rogge (AR)	DAPO
Mr Kunz (AR)	DPB
Mr Diensberg (DR)	IhF
Mr Sturm (AR)	IhF
Ms Meyer (AR)	Buxtehude Skin Cancer Self-Help Group
Ms Kiehl (DR)	Buxtehude Skin Cancer Self-Help Group
Mr Anders (E)	ADP
WG 7. Information of the population – Key question 11	
Mr Breitbart, WG leader (C)	ADP
Mr Kunz (AR)	DPB
Mr Schwarz (AR)	Association to Promote Dialogue in the Health System
Mr Egidi (AR)	DEGAM
Ms Baumann (AR)	DGPuK
Ms Meyer (AR)	Buxtehude Skin Cancer Self-Help Group
Ms Kiehl (AR)	Buxtehude Skin Cancer Self-Help Group
Ms Singer (AR)	PSO
Mr Anders (E)	ADP
WG 8. Implementation / quality assurance – Key question 12	
Mr Katalinic, WG leader (AR)	DGSMP
Mr Diensberg, deputy (DR)	IhF
Mr Sturm, (AR)	IhF
Mr Drexler (AR)	DEGAUM
Mr Breitbart (C)	ADP
Mr John (E)	University of Osnabrück
Mr Siekmann (E)	German Statutory Accident Insurance
Mr Anders (E)	ADP
Ms Löpker (E)	ADP
* AR =Appointed representatives, DR=Deputy representative, E=Experts, C=Co-ordinator	

3.3. Patient representatives

Ms Annegret Meyer and Ms Martina Kiehl from the Buxtehude Skin Cancer Self-Help Group and Mr Hans-Detlev Kunz from the German Psoriasis Association were invited as patient representatives. Ms Regensburger represented the German Working Party for the Assistance of Persons with Disabilities and Chronic Diseases and their Relatives (BAG). These representatives were included as appointed representatives with voting rights on the working groups compiling the guideline.

3.4. The ADP working group

The ADP scientific working group was composed of the members listed in Table 5.

Table 5: ADP scientific working group (alphabetical)

Member	Activity	Responsibility in the project
Markus Anders	ADP research associate	Scientific research (since Jan 2013)
Prof. Dr. Eckhard W. Breitbart	Head of Dermatology Depertment (ret.), Elbe Hospital Buxtehude	Guideline co-ordinator (appointed by ADP)
Marcus Capellaro	ADP research associate	Scientific research (Mar 2010 – Feb 2011)
Dr. Kohelia Choudhury	ADP research associate	Scientific research (since May 2013)
Friederike Erdmann	ADP research associate	Scientific research (Nov 2010 – Oct 2011)
Felix Greiner	ADP research associate	Scientific research (until June 2011; from Jan 2013
Dr. Rüdiger Greinert	ADP research associate	Scientific research (since Mar 2010)
Anna-Clara Mannheimer	ADP research associate	Proeject management (Jan 2012 – Dec 2012)
Dr. Cathleen Muche-Borowski	ADP research associate	Scientific research (Mar 2010 – Mar 2011)
Dr. Sandra Nolte	ADP research associate	Project management (Mar 2010 – Dec 2010 and Jun 2012 – Dec 2012
Sonia Petrarca	ADP research associate	Scientific research (Jan 2011 – Dec 2012)
Dr. Beate Volkmer	ADP research associate	Scientific research (since Mar 2010)

4. Questions and allocation

This evidence-based guideline prevention of skin cancer is intended to answer key questions in the area of primary and secondary prevention of skin cancer. These key questions were developed by the ADP scientific working group (Table 5) at the start of the project und agreed during the kick-off meeting in Hamburg by all appointed representatives (Table 1).

The following content matter of the key questions was defined and allocated to the eight WGs (Table 4) as follows:

1. Aetiology (WG1)
2. Incidence and prevalence (WG1)
3. Disease burden (WG1)
4. Risks (WG1)
5. Individual modes of behaviour (WG2)
6. Primary prevention measures for the population (WG2)
7. Early detection of skin cancer (WG3)
8. Presumptive diagnostic procedures / screening test (WG4)
9. Confirmatory diagnostic procedures (WG5)
10. Doctor-patient communication (WG6)
11. Information of the population / public (WG7)
12. Implementation of screenings and quality assurance (WG8)

As well as agreeing the key questions presented in Annex 1, it was decided at the kick-off meeting what level of evidence was to be used in answering the key questions. The following defintions were established:

- *Consensus-based statements:* all the topics to be considered by WG 1 were answered by statements. As no recommendations for action were to be issued here, it was decided that neither a systematic search nor a literature review in accordance with National Institute for Clinical Excellence (NICE) requirements was necessary to answer the key questions.
- *Evidence-basing:* all remaining key questions (with the exception of questions 9.3 and 9.4) were answered evidence-based by a systematic literature search. The need for a systematic search arose from the fact that existing national and international guidelines did not sufficiently answer any of the relevant topics (for further detail see section 5.3.1) [1].
- *Consensus:* The key questions on the issues of histopathological diagnostic procedures and quality assurance were to be answered by way of consensus, as legally binding provisions governing the quality assurance of histopathology in skin cancer screening already exist in Germany in the form of the “quality assurance agreement on histopathological examinations” of 12 August 2009.

The wording of key questions 1 to 9 was agreed during the kick-off meeting itself in a nominal group process. The remaining three key questions (10 to 12) were consented in a subsequent Delphi process by email. This involved two rounds. In the first round, slightly amended key questions taking into account the proposals from the kick-off meeting were sent by email to the appointed representatives with the request to comment on the text of the questions (agreement or alternative proposal where

applicable). The proposed changes submitted were summarised synoptically following an internal dicussion and the modified questions were edited accordingly. In the second round involving a synopsis of the reformulated questions, the moderator (Prof. Dr. Selbmann) was included. The aim of the Delphi process was to obtain agreement on the content of the key questions; the fine tuning of the questions was undertaken by the ADP scientific working group.

The discussion of the terms “population” versus “public” and “patient” versus “person” may be presented as an example. The choice of one of these terms should not have any effect on the literature search or the recommendations. The feedback from the second round was more editorial in nature, so that the questions were regarded as consented following revision and discussion with the moderator. All the contents can be obtained on request from the records kept by the ADP.

5. Methodology

5.1. Development of guidelines

"Guidelines are systematically developed statements reflecting the current state of knowledge and meant to support doctors and patients in making decisions concerning appropriate care for specific health problems" [4]. Guidelines are based on current scientific knowledge and well-established procedures in clinical practice and thus ensure greater safety in medicine. They should therefore make a decisive contribution to improving health care in the country concerned. Guidelines are of a purely recommendatory nature for doctors, i.e. they are not legally binding and therefore do not have the effect of establishing or excluding liability (http://www.awmf.org/leitlinien.html).

Under the AWMF rules, guidelines are classified into three classes, with class 3 guidelines potentially possessing the highest legitimation of the method and for implementation (Table 6). The following aspects characterise evidence- and consensus-based S3-guidelines: the committee is representative, evidence basing is systematic and consensus finding is structured. As lower-level guidelines lack the highest scientific methodological legitimation for implementation, the GGPO only supports S3-guidelines. The presented evidence-based guideline on prevention of skin cancer is classified as S3.

Table 6: AWMF guideline development classes

Class	Characteristics of development	Scientific legitimation of the method	Legitimation for implementation
S3	Representative committee Systematic evidence basing, structured consensus finding	high	high
S2e	Selected committee Systematic evidence basing, no structured consensus finding	high	moderate
S2k	Representative committee No systematic evidence basing, structured consensus finding	low	high
S1	Selected committee No systematic evidence basing, no structured consensus finding	low	slight

5.2. The guideline production process

The evidence-based guideline on prevention of skin cancer was developed in accordance with the AWMF rules and the criteria of the German Instrument for Methodological Guideline Appraisal (DELBI) [4, 5]. This involves a formal consensus procedure for elaborating the key questions (see chapter 4) and agreeing the final recommendations for action (see section 5.4). The key questions were agreed during the previously described kick-off meeting; the evidence- and consensus-based statements and recommendations for action were agreed at two consensus conferences described in section 5.4.3. In the case of the presented guideline, the various stages in the guideline production process illustrated in Figure 3 took a total of three years.

A large proportion of the working time was taken up by literature search for existing guidelines and primary literature as well as the subsequent evidence appraisal. This was undertaken by an external team consisting of methodologists from the universities of Witten-Herdecke and Duisburg-Essen.

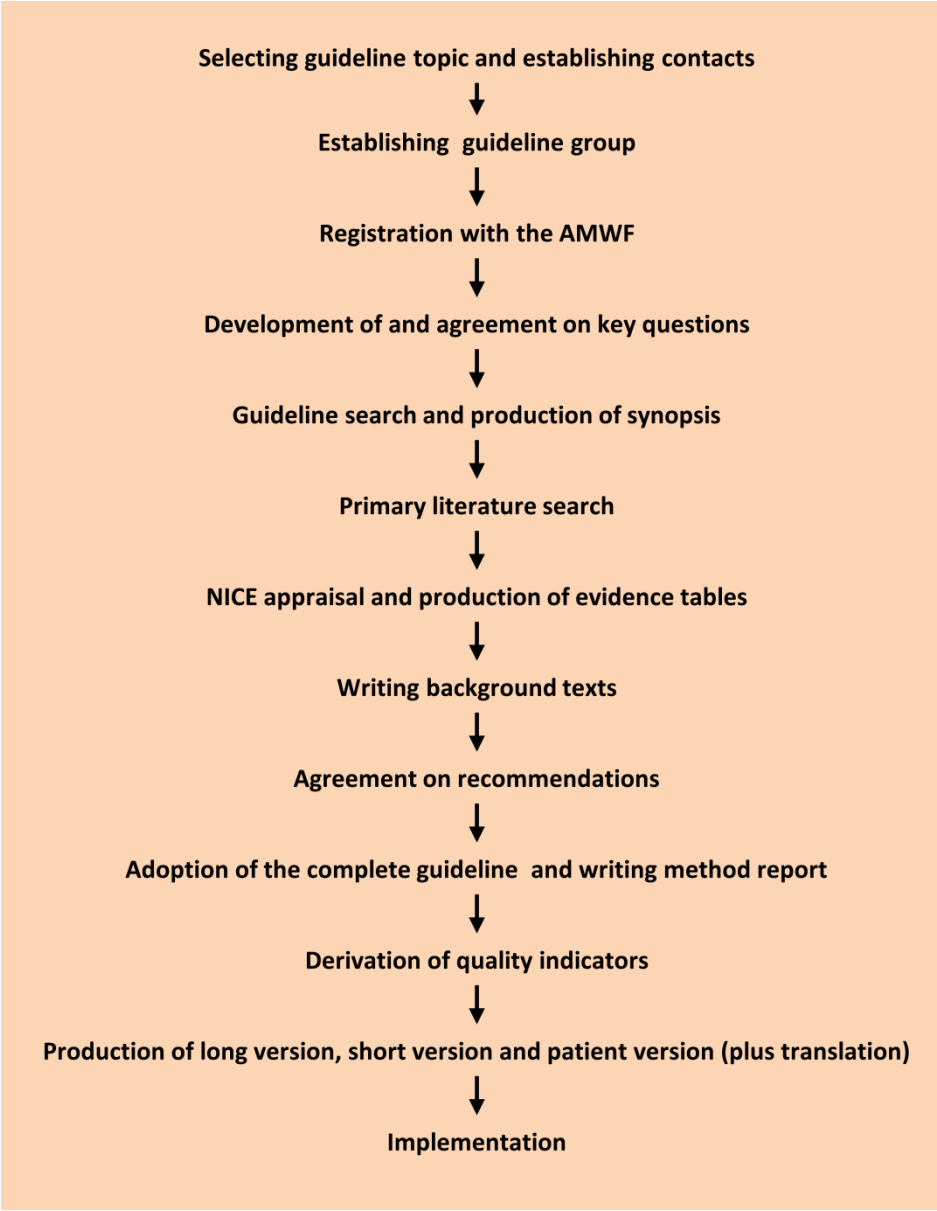

Figure 3: Stages in guideline development

5.3. Evidence basing

5.3.1. Adaptation of guidelines

5.3.1.1. Guideline search

As existing national and international guidelines represent an important source for the production of guidelines, a systematic guideline search was performed from 01.02.2010 to 31.03.2010 to gain an overview of existing recommendations on the primary and secondary prevention of skin cancer. The following databases and guideline portals were searched systematically for existing guidelines:

- PubMed (literature database)
- Guideline International Network (G-I-N, guideline database)
- National Guideline Clearinghouse (NGC, guideline database) and
- Home pages of institutions that develop guidelines:
    - Scottish Intercollegiate Guideline Network (SIGN)
    - National Institute for Clinical Excellence (NICE)
    - Cochrane Collaboration

Depending on the database, the following search terms were included in the guideline search: “skin”, “skin cancer”, “melanoma”, “basal cell carcinoma”, “squamous cell carcinoma”, “guideline”, “prevention”, “early detection”, “health promotion”, “skin neoplasms”.

In addition, a systematic search for available guidelines at the international level was conducted in multidisciplinary databases based on a template from the GGPO office; furthermore, subject experts were contacted directly. At the same time, a written approach was made to members of the SAB described in Table 3.

5.3.1.2. Selection of guidelines

The search for existing guidelines described in the previous section yielded 404 hits. These were selected using the following criteria:

Inclusion criteria

- Date of publication between 2000 and 2010
- At least one of the three diseases, MM, BCC or SCC

Exclusion criteria

- Studies of individuals with symptoms
- Diagnostic procedures in individuals with symptoms
- Treatment (including medicines) of skin cancer
- Animal studies
- Original articles/Primary literature
- No reference to the key questions
- Guideline is not based on evidence-based findings
- No statements/recommendations on primary and secondary prevention (early detection/screening defined as early detection examination up to the stage of confirmatory diagnostic procedures)

Of the 404 hits, twelve guidelines were classified as relevant. The possible adaptable

guidelines are presented in Table 7.

Table 7: Possible adaptable guidelines

Country	Year	Title of guideline
Australia / New Zealand	2008	Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand [6]
Australia / New Zealand	2008	Clinical Guide – BCC, SCC (and related lesions) – a guide to clinical management in Australia [7]
Canada	2007	Screening for Skin Cancer: A Clinical Practice Guideline [8]
UK	2003	SIGN 72 – Cutaneous melanoma – a national guideline [9]
UK	2007	The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines [10]
UK	2010	Revised U.K. guidelines for the management of cutaneous melanoma [11]
USA	2009	Health Care Guideline: Preventive Services for Adults [12]
USA	2009	Health Care Guideline: Preventive Services for Children and Adolescents [13]
USA	2003	Counseling to prevent skin cancer: USPSTF [14]
USA	2009	Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement [15]
USA	2010	NCCN Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancer [16]
USA	2010	NCCN Clinical Practice Guidelines in Oncology: Melanoma [17]

5.3.1.3. Guideline appraisal

The quality appraisal of the twelve guidelines included was undertaken using the German Instrument for Methodological Guideline Appraisal (DELBI), version 2005/2006 + Domain 8 (2008). DELBI contains 34 criteria relating to the methodological quality and feasibility of a guideline. These criteria can be assigned to eight domains, with each domain covering a separate dimension of the quality of a guideline.

- Domain 1 “Scope and purpose” (criteria 1-3) relates to the presence of data about the aims of a guideline, the medical questions / problems considered and the patient target group.
- Domain 2 “Stakeholder involvement” (criteria 4-7) relates to the extent to which the guideline embodies the viewpoint of its intended users and affected patients.
- Domain 3 “Methodological rigour of guideline development” (criteria 8-14) relates to the procedure by which the evidence is gathered and selected, and to the methods for formulating, assessing and updating the recommendations.
- Domain 4 “Clarity of presentation” (criteria 15-18) is concerned with the comprehensibility and format of the guideline.
- Domain 5 “Applicability” (criteria 19-21) concerns the probable impacts of the use of a guideline in terms of organisation, behaviour and costs.
- Domain 6 “Editorial independence” (criteria 22-23) deals with the independence of the recommendations and with the disclosure of possible conflicts of interest of the guideline development group.

- Domain 7 “Applicability to the German health care system” (criteria 24-29) describes additional quality criteria for a guideline that is intended to be used in the German health care system.
- Domain 8 “Methodological rigour of the guideline development using existing guidelines” (criteria 30-34) relates to the procedure by which existing guidelines are gathered, appraised, selected and taken into account in formulating recommendations.

Following the example of other evidence-based guidelines (class S3) produced under the GGPO (e.g. evidence-based guideline on diagnosis and treatment of hepatocellular carcinoma of the German Society for Digestive and Metabolic Diseases and the German Cancer Society [18]), the methodological quality of the guideline constituted the primary criterion of selection for the inclusion of the guideline in the guideline synopsis. This was defined as a domain value for Domain 3 of at least 0.5.
The systematic search, the selection of guidelines to be included and excluded and the appraisal of included guidelines by means of DELBI was undertaken by two independent methodologists. In the event of disagreements, a consensus was reached following discussion. Divergent results that emerged during the appraisal were also discussed until an agreement was reached. The results of the guideline appraisal are illustrated in Figure 4 (see also Appendix 2).

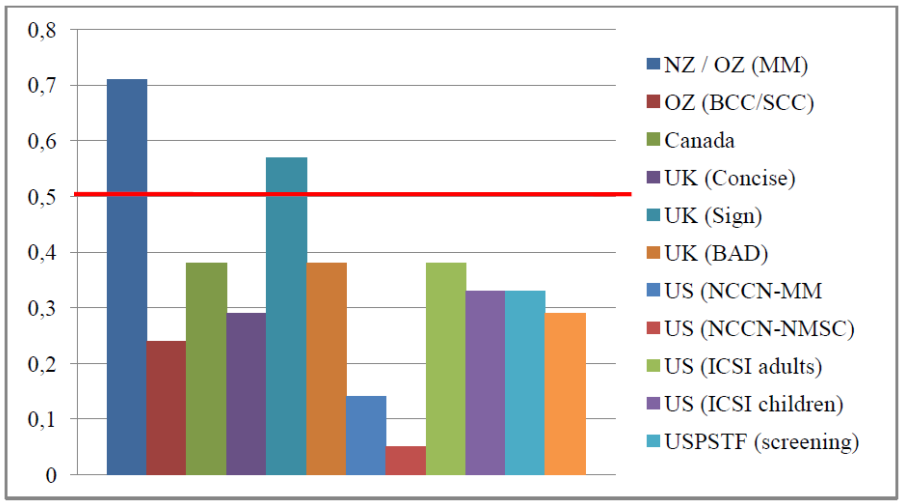

Figure 4: Results of the guideline appraisal, Domain 3 [1] *(Reproduced with permission of JAMA Dermatology)*

Selection on basis of DELBI resulted in ten of the twelve guidelines failing to fulfil the “Methodology” quality criterion sufficiently. Thus, two guidelines were identified by the independent assessors as meeting the methodological demands for guidelines and were therefore included. These were:

1. Australian Cancer Network/New Zealand Guidelines Group (2008). Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Wellington: The Cancer Council Australia, Australia Cancer Network, Sydney and New Zealand Guidelines Group [6]
2. Scottish Intercollegiate Guideline Network (2003). SIGN 72: Cutaneous Melanoma. A national clinical guideline. Edinburg: Scottish Intercollegiate Guideline Network [9]

5.3.1.4. Guideline synopsis / extracts

The respective statements and recommendations were reviewed in the synopsis presented in Appendix 3. This involved the following steps:

- Comparing statements and recommendations of the two guidelines (for content and wording),
- checking relevance of the statements and recommendations to the key questions of the evidence-based guideline on prevention of skin cancer and assigning them to the respective key questions,
- comparing the level of evidence and grades of recommendation and
- standardising the rating schemes used in the guidelines for level of evidence and grades of recommendation.

The outcome of the guideline synopsis showed that neither of the guidelines provided statements that sufficiently answered the key questions defined in the evidence-based guideline on prevention of skin cancer. This was due firstly, to the fact that some relevant recommendations were answered by "Good Practice Points" (GPP), i.e. by good clinical practice (GCP). This type of recommendation is not based on evidence-based scientific knowledge but reflects the opinions of the guideline development group. For a development class 3 guideline, GPPs are not a suitable basis for answering the key questions.
In addition, very strong grades of recommendation were only rarely issued. Once again, it was decided that weak recommendations were insufficient as a basis for answering the key questions of an S3 classified guideline.
It should also be stressed that the guidelines compared in the synopsis focus exclusively on malignant melanoma and give no recommendations for BCC or SCC.
Lastly, it remains to be said that some recommendations must be viewed against the background of the relevant national health care system and cannot be transposed unconditionally to the German health care system.
For this reason, neither of the two guidelines was regarded as potentially adaptable, i.e. the guidelines were at most used to confirm the newly defined recommendations. Accordingly, systematic searches were essential for the development of the evidence-based guideline on prevention of skin cancer.

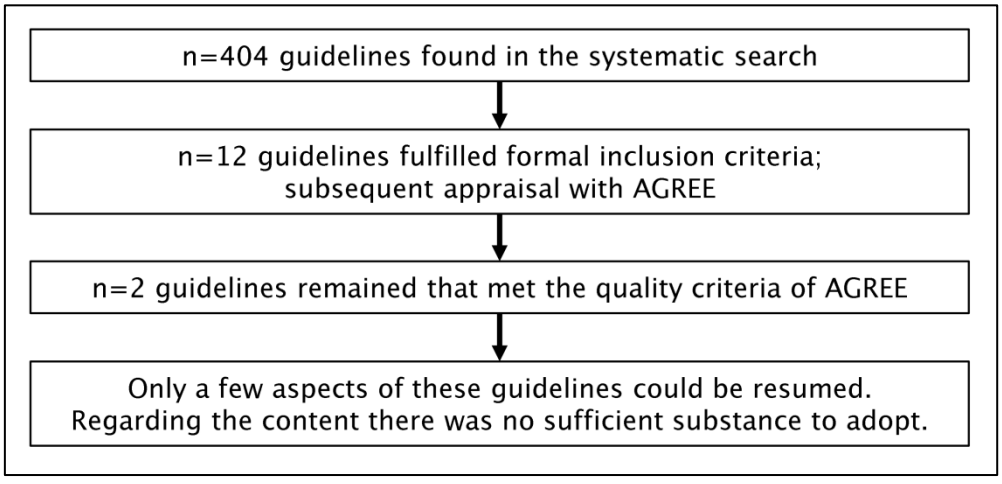

Figure 5: Guideline search flow chart [1] *(Reproduced with permission of JAMA Dermatology)*

5.3.1.5. Other guidelines used

Evidence-based guideline on diagnosis, treatment and follow-up of malignant melanoma [19].

5.3.2. Systematic searches

5.3.2.1. Search strategies

The systematic primary literature search took place from May to June 2010. This was supplemented by a methodologically identical follow-up search conducted from April to June 2012.

Since none of the key questions in guideline development of the evidence-based guideline on prevention of skin cancer could be sufficiently answered on the basis of a guideline adaptation (see section 5.3.1) and as the key questions encompassed a very broad area (from primary and secondary prevention to diagnostic procedures, communicational aspects, advanced education, etc.), the literature search was very extensive in respect of the chosen search terms. The searches covered the PubMed, EMBASE, Cochrane Collaboration and Current Contents Medicine databases, using the search terms and strategies described below for the respective databases:

5.3.2.1.1. PubMed

("Skin Neoplasms"[Mesh] OR "Melanoma"[Mesh] OR "Hutchinson's Melanotic Freckle"[Mesh] OR "Carcinoma, Basal Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh] OR "Dysplastic Nevus Syndrome"[Mesh] OR "Keratosis, Actinic"[Mesh] OR "Keratosis, Seborrheic"[Mesh] OR "Bowen's Disease"[Mesh] OR "Nevus"[Mesh] OR "Nevus, Pigmented"[Mesh] OR "Nevus, Epithelioid and Spindle Cell"[Mesh] OR "Lentigo"[Mesh] OR "Paget Disease Extramammary"[Mesh] OR skin tumour OR skin tumor OR bcc OR scc OR nmsc OR non melanocytic OR non-melanocytic OR naevus OR nevi OR naevi)

AND

("Primary Prevention"[Mesh] OR "prevention and control"[Subheading] OR "Secondary Prevention"[Mesh] OR "Health Promotion"[Mesh] OR "Education, Public Health Professional"[Mesh] OR "Early Detection of Cancer"[Mesh] OR "Early scalp tumor/ or skin turgor/ or skin ulcer/ or nevus/ or congenital nevus/ or nevus cell/ or hyperpigmentation/ or lentiginosis/

AND

primary prevention/ or "prevention and control"/ or secondary prevention/ or health promotion/ or health education/ or public health/ or community health nursing/ or adult education/ or cancer diagnosis/ or early diagnosis/ or cancer screening/ or mass screening/ or screening/ or self examination/ or self-examination/ or health behavior/ or physician patient relation/ or intervention study/ or health care quality/ or health care concepts/ or professional standard/ or "quality of nursing care"/ or "quality of life"/ or quality adjusted life year/ or "quality of life index"/ or behavior change/ or patient education/ or health knowledge/ or risk factor/ or risk assessment/ or risk reduction/ or diagnosis/ or "diagnosis, measurement and analysis"/ or biopsy/ or histology/ or continuing education/ or translation initiation/ or vitamin D/ or vitamin D deficiency/ or ultraviolet radiation/ or sunbathing/ or sunburn/ or sunscreening agents/ or psychological aspect/ or psychooncol*/ or behavioral research/ or behavioural research/ or medical decision making/ or shared decision/

Diagnosis"[Mesh] OR "Diagnosis"[Mesh] OR "Mass Screening"[Mesh] OR "Self-Examination"[Mesh] OR "Health Behavior"[Mesh] OR "Physician-Patient Relations"[Mesh] OR "Intervention Studies"[Mesh] OR "Quality of Life"[Mesh] OR "Health Knowledge, Attitudes, Practice"[Mesh] OR "Risk Factors"[Mesh] OR "Risk Assessment"[Mesh] OR "Risk

Reduction Behavior"[Mesh] OR "Biopsy"[Mesh] OR "Histology"[Mesh] OR "Education, Medical, Continuing"[Mesh] OR "Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Ultraviolet Rays"[Mesh] OR "Sunbathing"[Mesh] OR "Suntan"[Mesh] OR "Sunscreening Agents"[Mesh] OR "Sunburn"[Mesh] OR dermatohist* OR dermatopath* OR self examination OR psychosocial OR psycho-social OR psycho social OR psycho oncol* OR psychooncol* OR psycho-oncol* OR behavioural research OR risk reduction behaviour OR informed decision OR shared decision)

Limitation: Humans; English; German; Publication Date: 1995/01/01-2010/06/01 or 2010/04/01-current (30 April 2012)

5.3.2.1.2. EMBASE

skin cancer/ or skin tumor/ or skin carcinogenesis/ or skin carcinoma/ or skin metastasis/ or amelanotic melanoma/ or malignant lentigo/ or lentigo/ or melanoma/ or juvenile melanoma/ or melanoameloblastoma/ or paget skin disease/ or basal cell carcinoma/ or squamous cell carcinoma/ or bowen disease/ or eyelid cancer/ or eyelid tumor/ or dysplastic nevus/ or pigmented nevus/ or actinic keratosis/ or seborrheic keratosis/ or bowen disease/ or melanocytic nevus/ or nonmelanoma skin cancer/ or non-melanocytic/ or neoplasms subdivided by anatomical site/ or epithelium tumor/ or

Limitation: Humans; Publication Date from 1995 to CURRENT (7 June 2010) or 2010 to CURRENT (30 April 2012)

The search terms were adapted in accordance with the filed EMBASE thesaurus, as they were not identical to the PubMed keywords.

5.3.2.1.3. Cochrane Collaboration:

(Skin Neoplasms OR Melanoma OR Hutchinson's Melanotic Freckle OR Basal Cell Carcinoma OR Squamous Cell Carcinoma OR Dysplastic Nevus Syndrome OR Actinic Keratosis OR Seborrheic Keratosis OR Bowen's Disease OR Nevus OR Pigmented Nevus OR Epithelioid and Spindle Cell Nevus OR Lentigo OR Paget Disease Extramammary OR skin tumour OR skin tumor OR bcc OR scc OR nmsc OR non melanocytic OR non-melanocytic OR naevus OR nevi OR naevi)

AND

(Primary Prevention OR prevention OR Secondary Prevention OR Health Promotion OR Public Health OR Public Health Nursing OR Public Health Practice OR Education OR Early Detection of Cancer OR Early Diagnosis OR Mass Screening OR Self-Examination OR Health Behavior OR Physician-Patient Relations OR Intervention Studies OR Health Care Quality Indicators OR Quality of Life OR Behavioral Research OR Patient Education as Topic OR Health Education OR Health Knowledge OR Risk Factors OR Risk Assessment OR Risk Reduction Behavior OR Diagnosis OR diagnosis OR Biopsy OR Histology OR Continuing Medical Education OR CME OR Translational Research OR Vitamin D OR Vitamin D Deficiency OR Ultraviolet Rays OR Sunbathing OR Suntan OR Sunscreening Agents OR Sunburn OR dermatohist* OR dermatopath* OR self examination OR psychosocial OR psycho-social OR psycho social OR psycho oncol* OR psychooncol* OR psycho-oncol* OR behavioural research OR risk reduction behaviour OR informed decision OR shared decision)

Limitation: Publication Date 1995 to 2010 or 2010 to 2012

5.3.2.1.4. Current Contents Medicine

Hautkrebs OR Hautkrebsart OR Hautkrebsdiagnostik OR Hautkrebsepidemie OR Hautkrebserkrankung OR Hautkrebsfrüherkennung OR Hautkrebses OR Melanom OR Basalzellkarzinom OR Stachelzellenkarzinom OR mm OR bcc OR scc OR Keratose OR Naevus OR Lentigo OR Hauttumor

Limitation: English; German; Human; 1995 – 2010 or 2010 - 2012

In this search, the database indexing system was used and "AND" and "NOT" operators were omitted as these served no purpose here.

5.3.2.2. Selection of evidence

As shown in Figure 6, the systematic literature search overall yielded 103,570 hits. Of these, 77,816 hits were obtained in the first search (May/June 2010) and 25,754 hits in the follow-up search (April 2012).

Because of the large number of hits, a pragmatic method of dealing with the hits obtained had to be found. The hits were first of all checked for duplicates, which immediately ruled out 5,981 hits in the first search. In the follow-up search the number of duplicates ruled out was 4,309.

There was then a general exclusion of 13,458 texts from the first search in 2010 and 7,233 texts from the follow-up search in 2012 on the basis of the following criteria:

- Mice OR Mouse NOT human*
- P16 OR P27 OR P53 NOT skin (keyword) NOT melanom (keyword)
- Laryngeal NOT skin (keyword) NOT melanom (keyword)
- Pharyngeal NOT skin (keyword) NOT melanom (keyword)
- Pulmona NOT skin (keyword) NOT melanom (keyword)
- Metasta NOT skin (keyword) NOT melanom (keyword)
- Breast cancer NOT skin (keyword) NOT melanom (keyword)
- Lung cancer NOT skin (keyword) NOT melanom (keyword)
- Pancrea NOT skin (keyword) NOT melanom (keyword)
- Gastr NOT skin (keyword) NOT melanom (keyword)
- Prostat NOT skin (keyword) NOT melanom (keyword)
- Bone NOT skin (keyword) NOT melanom (keyword)
- Hepato OR hepati NOT skin (keyword) NOT melanom (keyword)
- Esophag OR Oesophag NOT skin (keyword) NOT melanom (keyword)
- Cervi NOT vulva NOT skin (keyword) NOT melanom (keyword)

This left 58,377 texts from the primary literature search and 14,212 texts from the follow-up search. These were screened systematically, first by title and then by abstract. Both steps were undertaken by four teams from the ADP, each consisting of two people. In the event of dissent, a discussion was held until an agreement could be found. In the event of doubt, a conservative decision was taken, i.e. the title was left in the literature database for more detailed examination in the next step, i.e. the abstract or full text screening. Since the type of study was not always clearly identifiable in these steps, particularly in the title screening, selection by study type was predominantly performed in the full text screening.

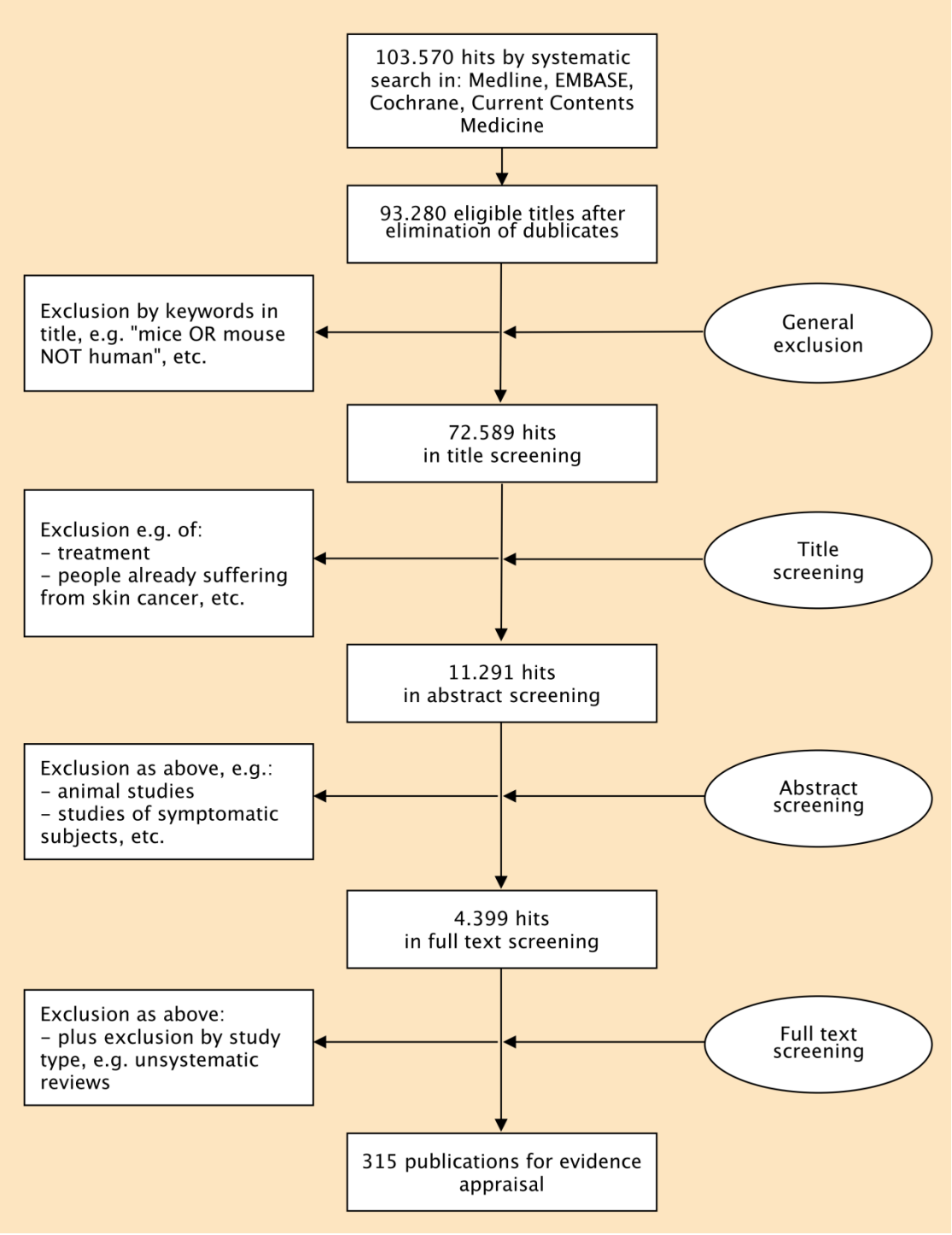

Figure 6: Flow chart primary literature search (including follow-up search)

Possible titles were included or excluded on the basis of the following criteria in the title and abstract screening steps:

Inclusion:

- Languages English/German
- Diseases (MM, BCC, SCC)
- Reference to interventions for certain risk groups

- Reference to inferable recommendations in relation to key questions (e.g. primary/secondary prevention, screening including clinical diagnosis with/without dermatoscope and confirmatory diagnostic procedures)
- Inclusion of the following keywords from the area of "Localisation & type of cancer": head & neck, eyelid, oral, vulvar, anal, penis cancer, Raman spectroscopy, Spitz, oral carcinogenesis, vulvar disorders, anal carcinogenesis, neoplastic, blue naevus

Exclusion:
- Animal studies
- Treatment (including medicines)
- People already suffering from skin cancer (keyword e.g. "recurrence", "metastasis" and, where applicable, "patient")
- Definition of risk groups/features
- Exclusion of the following keywords from the area of "Localisation & type of cancer": uveal, ocular, blue naevus, choroidal
- Exclusion of the following keywords from the area "Type of intervention": PET/CT, fine needle biopsy
- Type of article: case reports, editorial, congress papers, letters, commentaries, news

Following completion of the title and abstract screening, there remained 4,399 hits (n=3,564 first search, n=835 follow-up search), which were examined by full text screening. Selection was based on the following additional criteria:

Inclusion:
- Systematic reviews/meta-analyses
- Analytical types of studies
    - RCT
    - Clinical trials
    - Cohorts (secondary data analyses can also be cohort studies)
    - Case-controlled studies
    - Controlled study
- Diagnostic studies
- Ecological studies
- Relevant endpoint: relevant endpoint to the agreed key questions

Exclusion:
- No study
- Unsystematic reviews
- Descriptive studies
- Case reports
- Case series
- Expert opinion
- Thematic relevance: no guidance on answering the agreed key questions can be inferred from the article

A total of 315 texts remained from the systematic literature search for the evidence appraisal, which was performed by an external team of methodologists (see section 5.2). The resultant evidence table is available online as an additional document to the guideline (see section 1.8).

During the full text screening, an attempt was made to distribute the publications that were to be appraised to the different working groups at the outset on the basis of subject matter. However, since this allocation was done somewhat crudely, the final

allocation of publications was defined during the WG meetings held from June to September 2012 at the ADP in Hamburg. Table 8 shows the number of publications that the respective WGs received for processing. WG 1 was required to produce only consensus-based statements, so that the texts from this working group were not appraised methodologically and are accordingly not listed in the table.

Table 8: Distribution of the literature by working groups/key questions

WG	Total (n)
WG 2	149
WG 3	47
WG 4	61
WG 5	20
WG 6	1
WG 7	32
WG 8	24
Total	**289**

The 293 critically appraised texts from the first literature search were supplemented by a further 22 critically appraised texts following the second search. Of these 315 texts, some publications based on the same study were combined in one assessment. For this reason, this ultimately left 289 evidence-based publications that were distributed to the working groups.

5.3.2.3. Appraisal of the evidence

Because of the large amount of literature material, the appraisal of the full texts was assigned to external methodologists. The task was contracted to the private University of Witten/Herdecke under the leadership of Dr. Michaela Eikermann and to the University of Duisburg/Essen under the leadership of Dr. Barbara Buchberger. The evidence appraisal involved both the appraisal of the literature and the production of an extensive evidence table.

In order to classify the risk of bias of the studies identified, a modified system (see Table 9) has been used in this guideline based on that of the Scottish Intercollegiate Guidelines Network (SIGN, see http://www.sign.ac.uk/pdf/sign50.pdf). In the system presented here, cross-sectional studies on diagnostic questions have been included in level 2, as these have not previously been explicitly listed there.

Table 9: Modified evidence classification table

Evidence class	Description (modifications in italics)
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of systematic errors (bias)
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of systematic errors (bias)

Evidence class	Description (modifications in italics)
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of systematic errors (bias)
2++	High-quality systematic reviews of case-control or cohort studies (*including pre-post comparisons*) or High-quality case-control or cohort studies (*including pre-post comparisons*) with a very low risk of systemic distortions (confounding, bias or chance) and a high probability that the relationship is causal or *High-quality studies with a cross-sectional design to investigate diagnostic quality with a very low risk of systematic bias.*
2+	Well conducted case-control or cohort studies (*including pre-post comparisons*) with a low risk of systemic distortions (confounding, bias or chance) and a moderate probability that the relationship is causal or *Studies with a cross-sectional design to investigate diagnostic quality with a moderate risk of systematic bias.*
2-	Case-control or cohort studies (*including pre-post comparisons*) with a high risk of systematic distortions (confounding, bias, chance) and a significant risk that the relationship is not causal or *Studies with a cross-sectional design to investigate diagnostic quality with a high risk of systematic bias.*
3	Non-analytic studies, e.g. case reports, case series, *studies with a cross-sectional design without investigations for diagnostic quality.*
4	Expert opinion.

The literature appraisals were performed using the NICE appraisal forms (see Appendix 4). The checklists used for each type of study are listed in Table 10. In order to expedite the work of the WGs, it proved practicable to distribute the critically appraised literature and an accompanying evidence table to the WGs on a gradual basis, i.e. the files were provided gradually between March and July 2012; the previously mentioned WG meetings were held in parallel.

Table 10: Allocation of study types to the checklists

Type of study	Checklists
Systematic review	Methodology checklist: systematic reviews and meta-analyses (NICE)
Randomised controlled trial	randomised controlled trials (NICE)
Controlled clinical trial	cohort studies (NICE)
Controlled pre-post study	cohort studies (NICE)
Two-armed cohort study (prospective)	cohort studies (NICE)
One-armed cohort study (prospective)	cohort studies (NICE)
Retrospective cohort study	cohort studies (NICE)
Case-control studies	case-control studies (NICE)
Cross-sectional study (with measurement of diagnostic test accuracy)	QUADAS tool for studies of diagnostic test accuracy
Cross-sectional study (without measurement of diagnostic test accuracy)	No appraisal form available
Pre-post study (without control)	No appraisal form available

5.4. Formulation of the recommendation and formal consensus finding

The literature appraised on the basis of the NICE checklists formed the basis for recommendations for action and statements to be produced by the WGs. Even before receipt of the critically appraised literature, the working groups received an extensive briefing in the form of an information pack that was sent to each member as a CD-ROM. This included an overview of the methodology, a detailed explanation of the evidence grading and instructions for producing the background texts and deriving recommendations in the form of methodology sheets and a guide.

As soon as all the critically appraised publications on a given key question were available – including the summary evidence table –, these were sent to the WG so that the WG members could start their work. This involved analysing the texts, formulating a background text and deriving a statement or a recommendation for action with a grade of recommendation. All background texts and recommendations for action/statements had to be agreed within the WG. This was done at regular teleconferences moderated both by the WG leader or guideline co-ordinator and the project management.

The WGs had a period of three months to produce the recommendations for action/statements. If certain subquestions of the key question(s) could not be answered with the aid of the critically appraised literature, it was possible to resort to the use of other literature.

The answers to the key questions were collated by the ADP scientific team and prepared accordingly for the consensus conferences.

5.4.1. Recommendation grading

Table 11: Recommendation grading scheme based on an existing level of evidence

Grade of recommendation	Description	Wording
A	Strong recommendation	must
B	Recommendation	should
0	Neither recommended nor not recommended	can

The GGPO methodology provides for guideline's authors to assign grades of recommendation in the course of a formal consensus procedure. Accordingly, an AWMF-moderated formal consensus procedure consisting of existing structured consensus conferences was undertaken. In terms of the strength of the recommendation, three grades of recommendation are distinguished in this guideline (see Table 11), which are also reflected in the formulation of the recommendations. Recommendations decided on the basis of expert consensus and not on the basis of a systematic search or a guideline adaptation are indicated as such with the grade "**EC**". The strength of the recommendation derives implicitly from the wording (must/should/can, see also Table 12).

Table 12: Recommendation grading scheme for Expert consensus (EC)

Type of recommendation	Description	Wording
EC	Strong recommendation	must
EC	Recommendation	should
EC	Neither recommended nor not recommended	can

5.4.2. Grading

In terms of their grade of recommendation, the evidence-based recommendations are based in the first place on the evidence strength of the critically appraised publications.

In addition, as well as the underlying evidence, the following aspects were considered in assessing the grade of recommendation in the course of the structured consensus procedure:

- Consistency of the study results
- Clinical relevance of the endpoints and effect strengths
- Benefit-harm ratio
- Ethical and legal obligations

- Patient preferences
- Applicability to the patient target group and the German health care system
- Implementability in everyday medical practice, particularly in different care sectors.

In short, the grades of recommendation express the degree of certainty that the anticipated benefit of the intervention will outweigh the possible harm (net benefit) and the anticipated positive effects will reach a relevant level for the patients. In the event of negative recommendations (i.e. must not), safety is accordingly expressed in terms of a lack of benefit or possible harm.

5.4.3. Formal consensus procedure

Accordingly, AWMF- and DKG-moderated structured consensus conferences were held to agree the recommendations and statements, including the grades of recommendation.

1st consensus conference (kick-off meeting), 18 March 2010

At the previously described kick-off meeting, the key questions to be answered were agreed with all participating professional societies and patient representative groups. The meeting held in Hamburg was moderated by Prof. Dr. Hans-Konrad Selbmann, AWMF, and Dr. Markus Follmann, DKG. Further details on the kick-off meeting can be found in chapter 4.

2nd consensus conference at two meetings, 18-19 October 2012 and 28 November 2012

Following completion of the work in the WGs, i.e. production of the background texts and the finalised proposals for evidence- and consensus-based statements and recommendations for action, a first draft of the guideline was sent by email to all appointed representatives on 2 October 2012. This was done in good time and at least 14 days before the consensus conference scheduled for 18 and 19 October 2012. The appointed representatives with voting rights from the 33 professional societies and all members of the working groups were invited to the consensus conference held in Berlin. Each participating organisation, represented by the delegated representatives, had a single vote. An exception was the German Dermatology Society, which had two votes by virtue of the establishment of a mandate for primary prevention / vitamin D.

The first meeting of the 2nd consensus conference in Berlin was moderated by Prof. Dr. Hans-Konrad Selbmann and Dr. Markus Follmann. However, since not all key questions could be completed on 18 and 19 October 2012 because of the extensive nature of the statements and recommendations for action to be agreed, a second meeting had to be scheduled and was held on 28 November 2012 in Frankfurt. This meeting was moderated by Dr. Markus Follmann. Voting on the statements and recommendations for action was done anonymously using the TED system. In accordance with AWMF rules, the consensus strength of the recommendations for action was defined as follows:

Table 13: Overview of the definitions of consensus strength

Consensus strength	Definition
Strong consensus	≥ 95% of participants
Consensus	≥ 75% of participants
Majority agreement	≥ 50% of participants
No consensus	< 50% of participants

5.4.4. Methodology of cost analysis

The question in hand regarding the disease burden engendered by MM, BCC and SCC requires the topic to be considered from various angles. The players in the health care system and the affected patient are subject to various stress factors in the event of disease that can be both economic and physical or psychological in nature and assume a different form for each party concerned by virtue of their different spheres of duty and activity. The perspective determines how costs and effects are defined and assessed. The possible individual perspectives that pertain in Germany are mentioned below and their components described.

In the event of disease, the *patient* is affected individually by the type of disease, the severity, the disease course, invasive treatment methods, physical impairments such as pain, psychological burdens such as anxiety and depression, and possible associated reductions in the quality of life. Added to this are potential financial expenses not covered by insurance benefits. These are known as “out-of-pocket” benefits. Patients incur a further financial burden from downtime or even losses of productivity as a result of sick days, rehabilitation measures or becoming unfit for work.

The *third-party payers* (often the social security institutions) provide another perspective. Financial expenditure by the health insurance and long-term care insurance providers, both statutory and private, is considered in particular. Less pertinent from a health economic perspective, but equally relevant for estimating the consequences of illness are expenses incurred by pension insurance providers, employers’ liability insurance associations in accident insurance, the Federal Employment Agency and social welfare agencies.

With particular respect to the third-party payer perspective of the health insurance system, two viewpoints need to be distinguished conceptually from one another for Germany. Under German law (section 35b (1) SGB V) the perspective of the *SHI scheme insurants* is usually adopted [20-22]. This involves the disease-related benefits covered by the SHI (reimbursable direct medical and non-medical costs) as well as costs to be paid by the insurant himself (non-reimbursable services) e.g. top-up payments or out-of-pocket expenses for medicines, medical services and medical aids and appliances, outpatient medical contacts and disease-related net income losses. This must be distinguished from the *perspective of the statutory health insurance*, as this comprises only the reimbursable direct costs and transfer payments. In the present analysis, both perspectives are touched upon in content terms. The perspective of the SHI and patients, however, is also supplemented by the position of everyone affected by the disease, i.e. privately insured patients will also be considered.

In addition, in a health economic approach, an assessment is also possible from the *employer's* viewpoint. Continued payment of remuneration or benefits as well as rehabilitation measures and frictional costs engendered by work absences can also cause an economic burden.

The *service provider's perspective* reveals costs incurred by the service provider from direct medical treatment. Resource consumption is assessed in this case primarily from the viewpoint of the service provider, but more from the business management than the technical accounting angle.

In addition, from a health economic viewpoint, the perspective of the *relative* must not be overlooked, since burdens also arise in this case. Thus, the amount of time that must be invested in the care of sick relatives or also the amount of time for travel to medical interventions can result in possible absences from work and hence also a financial burden for the relative concerned. Impacts on quality of life are also possible.

Finally, when considering the disease burden from the *perspective of society*, this involves the most far-reaching approach to the discussion of costs. All direct and indirect resource consumption is assessed from this perspective, as well as intangible effects that arise following a disease, regardless of the player to which they may be ascribed.

Table 14: Perspectives and their cost types

Perspective / Cost components	Patient	Society	Social insurance provider	SHI	SHI insurant	Employer	Relative	Service provider
Direct medical costs, reimbursable		x		x	x			x
Direct medical costs, non-reimbursable	x	x			x			
Direct non-medical costs	x	x	x		x	x	x	
Indirect costs	x	x	x			x	x	
Intangible effects	x						x	

Source: [22]

5.4.4.1. Time horizon of cost appraisal

Fundamentally, the determination of the time horizon of a health economic evaluation depends on the subject of study and relevant perspective. In principle, the chosen time horizon should be sufficiently long to be able to encompass all cost components.

In a pure disease cost analysis, two approaches are adopted: the prevalence-based approach specifies a predefined time horizon and measures direct and indirect costs of a disease within this period. As a rule, a period of a year is considered. The incidence-based approach formulates all direct and indirect costs from the first onset of a disease until recovery or the end of life.

For the present analysis, an incidence-based approach was selected, although only one year from the time of diagnosis serves as the observation period. It is assumed that treatment engenders the most intensive cost factors during this period.

In addition, care measures in the follow-up period are assessed for each tumour entity, i.e. MM, BCC and SCC.

5.4.4.2. Discounting

In medical interventions, cost factors and other components relevant to the consideration accrue at different points in time. To obtain monetary and general comparability between costs (interventions), the costs should relate to the same time point. To this end, discounting is applied to the values in health economic analyses.

The choice of discount rate is based on general international guidelines, which are guided by current long-term capital market costs [23]. Accordingly, the discount rate was set at 3%.

In order to measure the robustness of all results in relation to variations in cost factors, sensitivity analyses were also performed with rates of 0%, 5%, 7% and 10% [24].

5.4.4.3. Cost analysis

The fundamental step in health economic evaluations is the identification and measurement of resource consumption that occurs following a case of disease or treatment and the associated costs.

In order to be able to serve as a decision-making aid and as basis for economic models, cost determinations must be sufficiently detailed and adapted to the particular context of the question. The division of cost types into direct and indirect costs is in line with internationally recognised principles.

Direct and indirect costs can be quantified in monetary terms. However, there are also intangible costs or effects of a disease that either cannot be quantified in monetary terms or only with great difficulty (e.g. in a willingness-to-pay approach).

5.4.4.3.1. Direct costs

a) Direct medical costs

Direct medical costs reflect the consumption of resources directly related to the disease and its treatment. These include:

a) Consultations with the family doctor or specialist,
b) diagnostic measures,
c) therapeutic measures (drugs, instrumental treatments, surgery, wound care products, medical services and medical aids and appliances, etc.),

d) hospital stays including all treatment measures,
e) rehabilitation measures including all treatment measures.

The uniform value scale (UVS), which is used for statutory insurance, and the Medical Fee Schedule (MFS) in the case of privately insured patients essentially do not provide a yardstick for the actual consumption of resources. However, they determine the actual volume of expenditure of the third-party payers concerned for the measure that is being evaluated [25]. From the service provider's viewpoint, business performance indicators must be used.

For this presentation, the cost situation of direct medical costs has been illustrated by means of two studies whose methodological description is given later.

b) Direct non-medical costs

Non-medical consumption includes resources that accrue outside the intervention effected or are engendered in other sectors of the economy.

These include for example:

- Travel costs (resulting from medical services and the disease itself),
- disease-related purchases that are not medical aids and appliances,
- alteration work,
- Costs for domestic help [26].

In the case of disease, other direct costs are sometimes incurred that cannot be allocated directly to direct medical or non-medical costs because of their specific nature. Nevertheless they cause direct costs as measures for treating the disease.

This category includes:

- Own preventive activities (sport or self-help group),
- time demands on patients without absence from work (e.g. time on treatment, slower pace of everyday life),
- occupational rehabilitation[2] after prolonged disease duration,
- time demands on relatives without absence from work.

No data could be obtained on the proportion of non-medical costs in the present analysis. No relevant hits were obtained from a literature search in the PubMed database and in Ovid databases.

5.4.4.3.2. Indirect costs

Indirect costs arise from the disease but are not medically related. These are the estimated costs that have arisen as a result of the absence from or even loss of work (loss of productivity) due to the disease and intervention. As well as losses due to absence, impaired performance at work must also be identified.

[2] By occupational rehabilitation is meant, for example, assistance from the German Federal Employment Agency or German Pension Insurance in retaining or acquiring a job.

In terms of downtime and productivity losses, the time demands on relatives that arise from the care of a patient (referred to as informal care) must also be taken into account as well as the patient's time [27].

In general, the indirect costs are calculated by the human capital approach (HCA). This method calculates lost productivity due to disease and premature death. Accordingly, the indirect costs arise from the economic loss of productivity by disease-related absence of a person or their premature death.

In best case, productivity losses are quantified in health economic evaluations by the individual period-related income of enrolled study participants. If these basic data are not available, a crude estimate can be made on the basis of statistical data on income levels from the (German) Federal Office of Statistics using the following formula [28]:

$$\text{Mean productivity loss} = \text{Days of incapacity for work} \times \frac{\text{Compensation per employee in Germnay / year}}{\text{(Employee x 365 Tage)}}$$

Figure 7: Productivity loss formula

A critical component of the HCA lies in the fact that this instrument assumes the full employment of persons who are fit for work. To a certain extent, this discriminates against children, housewives, students and pensioners, as no individual patient contributions are calculated and only the proportion of the productivity loss from the disease-related absence is counted. In the absence of methodologically more developed and practically applicable alternatives, however, the HCA is used in health economic practice [24].

In the current labour market process, jobs can be filled again in a short space of time. The frictional cost approach identifies the loss of productivity only as the period until the job is filled again. The calculation here approximates more closely to the actual production loss.

The frictional costs, a factor which from the employer's perspective is also relevant for the general economy, are not presented in this consideration.

Depending on the perspective of the evaluation to be performed, transfer payments such as pension payments or sickness pay can also be included in the indirect costs. While these expenses constitute a not inconsiderable sum of money from the viewpoint of the social service provider, they do not serve as reimbursement for resource consumption. In this case, only the losses of productivity from the patient's and society's viewpoint are included.

5.4.4.3.3. Intangible effects (costs)

As well as economic burdens, patients and also relatives are burdened by disease factors that apply individually, impair the quality of life and can only be evaluated subjectively by the patient. They may be of a physical nature, such as immobility, restrictions on everyday activities (work, leisure time activities) and pain, or of a psychological nature, such as anxiety, depression, feeling of loneliness, misunderstanding, etc., and are subject to individual perception and description [29]. Such impacts on the quality of life

also affect relatives when caring for a patient.

Allowance is also made for these restrictions in health economics, but they cannot be assessed directly by cost parameters.

There is a series of different instruments for recording the quality of life and changes in this. These instruments generally consist of questionnaires and are designed disease-specifically to include associated impairments of the disease and describe their course. A generic observation of the quality of life can be performed alternatively or additionally.

In order to be able to make a general statement about the situation of patients with skin tumours in relation to their quality of life and to be able to assess the data in general, a systematic literature search was organised. A literature search on each of the three tumour entities MM, BCC and SCC was undertaken in the PubMed database and in Ovid databases. The keywords used corresponded to the relevant tumour entity, i.e. “malignant melanoma” or “basal cell carcinoma” or “squamous cell carcinoma” associated with “quality of life”.

To filter out articles that merely describe the quality of life or its impairments in skin tumour patients, the following inclusion and exclusion criteria were defined:

Inclusion criteria:

- quality of life,
- disease burden,
- psychological aspects (mental burden from stress, anxiety, depression),
- patients and relatives,
- English or German language,
- malignant melanoma,
- basal cell carcinoma,
- squamous cell carcinoma,
- all stages of tumour entities in accordance with AJCC.

The exclusion criteria involved the following aspects:

- quality of life in relation to the treatment method,
- quality of life in relation to other skin tumours,
- quality of life in relation to other tumours.

German and international data were included in assessing the quality of life.

5.4.4.4. Quantitative determination of the types of cost

To analyse the costs, a quantitative matrix of the resource consumption incurred is first established. In addition, unit costs representing the costs of a unit consumed must be defined.

According to the Institute of Quality and Efficiency in Health Care (IQWiG), four basic steps should be taken to estimate disease costs [21, 22]:

1. Identification of resource consumption:

   In the present case, based on a typical disease course, the disease-specific symptoms, treatment methods and care pathways were assessed following the definition of a time window.

2. Measuring resource consumption:

   Statistical data on skin tumours from cancer registries, data from insurance providers on medical care and data from the German Federal Office of Statistics were used to evaluate the quantity of medical services, drugs, etc., consumed.

3. (Monetary) valuation of resource units:

   Specific consumption units, broken down by entity and stage of the individual types of tumour, are recorded and included here.

4. Calculating total costs:

   The calculation of the total costs relates to the respective cost type of direct (medical and non-medical) and indirect costs as well as the perspective concerned (e.g. third-party payer = accounting-related reimbursement units, service provider = business cost units). Intangible effects are not identified in monetary terms and in the present case are reported in narrative form.

Two procedures are primarily available for determining the quantity and subsequently assessing the cost:

The *top-down approach* is based on statistical data such as mortality and morbidity statistics, hospital statistics, etc. Here, global figures are divided by the number of patients affected by the disease to be evaluated and thus referred to the individual patient.

The *bottom-up approach* describes the average individual patient and determines the disease costs in the individual case. In this case, the direct costs can either be listed as they are actually incurred (in actual disease courses, for example in the cancer registry) or calculated on the basis of valid treatment guidelines using representative compensation figures (point values, flat-rate payments, etc.) [30].

Both approaches were used in the disease cost calculations presented in the guideline.

6. Quality indicators

As part of the German Guideline Program in Oncology, quality indicators are derived from the guideline recommendations according to a standardised process. The description of the methodology can be found on the home page of the GGPO (http://leitlinienprogramm-onkologie.de/Programm.3.0.htm) *(in German)*.

The following steps were adopted:

1. Identification of existing indicators

Search for existing international quality indicators using the following search strategy:

Database	Search strategy	Date	Hits
Pubmed	((("Skin Neoplasms"[Mesh] OR "Melanoma"[Mesh] OR "Hutchinson's Melanotic Freckle"[Mesh] OR "Carcinoma, Basal Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh] OR "Dysplastic Nevus Syndrome"[Mesh] OR "Keratosis, Actinic"[Mesh] OR "Keratosis, Seborrheic"[Mesh] OR "Bowen's Disease"[Mesh] OR "Nevus"[Mesh] OR "Nevus, Pigmented"[Mesh] OR "Nevus, Epithelioid and Spindle Cell"[Mesh] OR "Lentigo"[Mesh] OR "Paget Disease Extramammary"[Mesh] OR skin tumour OR skin tumor OR bcc OR scc OR nmsc OR non melanocytic OR non-melanocytic OR naevus OR nevi OR naevi) AND ("Primary Prevention"[Mesh] OR "prevention and control"[Subheading] OR "Secondary Prevention"[Mesh] OR "Health Promotion"[Mesh] OR "Education, Public Health Professional"[Mesh] OR "Early Detection of Cancer"[Mesh] OR "Early Diagnosis"[Mesh] OR "Diagnosis"[Mesh] OR "Mass Screening"[Mesh] OR "Self- Examination"[Mesh] OR "Health Behavior"[Mesh] OR "Physician-Patient Relations"[Mesh] OR "Intervention Studies"[Mesh] OR "Quality of Life"[Mesh] OR "Health Knowledge, Attitudes, Practice"[Mesh] OR "Risk Factors"[Mesh] OR "Risk Assessment"[Mesh] OR "Risk Reduction Behavior"[Mesh] OR "Biopsy"[Mesh] OR "Histology"[Mesh] OR "Education, Medical, Continuing"[Mesh] OR "Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Ultraviolet Rays"[Mesh] OR "Sunbathing"[Mesh] OR "Suntan"[Mesh] OR "Sunscreening Agents"[Mesh] OR "Sunburn"[Mesh] OR dermatohist* OR dermatopath* OR self examination OR psychosocial OR psycho-social OR psycho social OR psycho oncol* OR psychooncol* OR psycho-oncol* OR behavioural research OR risk reduction behaviour OR informed decision OR shared decision))) AND quality indicator	08.05.2013	65
Cochrane Library	Skin AND cancer AND prevention AND quality indicators	09.04.2013	9
AHRQ	Skin cancer prevention AND quality indicators	09.04.2013	0

KCE Belgium Health Care Knowledge Centre: 0

Healthcare Improvement Scotland: 0

No relevant sources could be identified from the hits.

2. Preparation of face-to-face meeting (production of a primary list of potential QI):

Prior to the face-to-face meeting (see section below 3), the evidence- and EC-based recommendations were collated in a list (48 recommendations). The list was sent out to the members of the WGs prior to the face-to-face meeting.

3. Face-to-face meeting (discussion and primary review)

The meeting of the QI WG, which consisted of members of the guideline group, representatives of the clinical cancer registries, the certification system and the GGPO, was held on 03.06.2013. At the meeting, the process of producing QIs and the GGPO appraisal instrument were explained to the participants. The list of guideline recommendations generated in section 2 above was discussed and a decision taken as to whether a potential QI could be generated from a particular recommendation. The present guideline is the first to deal exclusively with the topic of prevention. The other essential remit of a prevention guideline was discussed extensively in the QI working group. In particular, the definition of denominators and hence the definition of the cohorts to be observed (normal population) represented a core problem for the work of the QI WG.

Following a review of all recommendations, two possible QIs were finally identified.

4. Assessment

These potential QIs were assessed by the interdisciplinary committee of the guideline group with the appraisal instrument of the GGPO using a standardised checklist (based on [31]). In principle, indicators with at least 75% approval on criteria 1-4 were regarded as accepted (i.e. 1st-3rd criterion: “Rather agree” and “Agree” and 4th criterion: "No, no risk of inappropriate care”).

5. Final teleconference:

Following the written assessment, a moderated telephone conference was held (03.07.2013) in which the results of the assessed (see Appendix 6) were discussed. Both QIs identified were rejected (for reasons also see Appendix 6)

On the basis of this guideline, therefore, no quality indicators could be developed. A need for further research in this area was formulated in the guideline.

The lack of implementability of the guideline recommendations into clearly and unequivocally defined quality indicators, as well as the availability of relevant data about possible indicators, represented a core problem. In the area of primary prevention, behavioural indicators are the most important component of the evaluation with the aim of detecting changes in behaviour through appropriate interventions. However, in the context specifically of primary prevention, such behavioural indicators would frequently have to be recorded in the form of retrospective self-reporting; as a result, the data would be subject to subjective bias to a greater extent than in the case of measurements at or around the time of the behaviour or routine medical data and are therefore to be regarded as relatively limited in their objectivity and validity. This also applies to some extent to secondary preventive measures, where epidemiological data, health care

research data and behavioural indicators all play a part. Furthermore, when individual recommendations relate for example to modes of behaviour of large subpopulations or to the general population, it is difficult, if not impossible, to capture all the data on the basis simply of routine data collection.

Table 15: Members of the QI WG

Experts	Institution
Dr. Eva Baumann	German Society for Journalism and Communication Science
Prof. Dr. Jean-François Chenot	German Society of General Practice and Family Medicine
PD Dr. Monika Klinkhammer-Schalke	Tumour Centre Regensburg
Dr. Manfred Diensberg	German Association for General Practitioners
Dr. Markus Follmann, MPH	German Cancer Society
Detlef Kunz	German Psoriasis Association
Dr. Monika Nothacker, MPH	Association of Medical Scientific Societies
Annkatrin Rogge	German Association of Psychosocial Oncology
Dr. Simone Wesselmann	German Cancer Society
Prof. Dr. Breitbart	Association of Dermatological Prevention
Markus Anders, MPH	Association of Dermatological Prevention
Dr. Kohelia Choudhury	Association of Dermatological Prevention
Dr. Rüdiger Greinert	Association of Dermatological Prevention
Dr. Annika Waldmann	Institute for Cancer Epidemiology
Dr. Beate Volkmer	Association of Dermatological Prevention

7. Public consultation phase and adoption

The evidence-based guideline on prevention of skin cancer was open to public comment from 30.10.2013 to 22.11.2013. During this period, a total of 15 comments were received from four people or organisations. Of these comments, four related to background texts to the guideline, one to formal aspects and ten were general comments. The comments can be viewed at the ADP on request.

The project team first of all produced proposals (see Table 16, Table 17, Table 18) for dealing with the individual comments. The proposals were then sent to the whole guideline group with the request for approval or alternative proposals. During this process, no objection was raised to the proposed method of dealing with the comments.

7.1. Comments on background texts

Table 16: Comments on background texts

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
A proposal is submitted to amend the section on congenital naevi (see Appendix 7)	Long version: section 3.4.1 b)	The proposal is implemented following discussion with the authors, as this helps complete the subject matter.
A lack of understanding is expressed as to why only dermatologists could take biopsies in the German skin cancer screening. Other professions such as OMF surgeons could also take these. In this context, criticism was expressed of the connection with the publication by Pacifico *et al.* 2007, which was not presented clearly enough. A proposal was made to amend the relevant background text.	Long version: section 5.1.3.2 (2nd paragraph)	In the paragraph concerned, the word “dermatologist” is replaced by “specialists”; the word “specialists” is replaced by “plastic surgeon”. This is to a large extent in line with the proposal in the comment. The changes help make the content of the relevant publication clearer.
It is suggested that the section on the specialty-specific investigation of lesions of the skin and adjacent mucosae in the facial, genital and anal region should be supplemented to address all relevant specialist disciplines.	Long version: section 5.2.4.1 (background text on recommendation 5.25)	An additional paragraph has been inserted: “In the event of suspected melanocytic or non-melanocytic (squamous epithelial) precursor lesions or tumours of the oral mucosa, a further oral and maxillofacial consultation and diagnostic tests are required. Here again a tissue sample must be taken in the event of suspicious findings. The same applies to lesions in the facial region that cannot be sufficiently investigated by diagnostic

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
		procedures involving the use of dermatoscopy." The addition serves to complete the subject matter concerned.
Request to supplement the background text to take account of specific anatomical features during tissue sampling.	Long version: section 5.3.1 (4th paragraph)	The paragraph concerned is extended after the word "must" to include the passage "by calling upon the expertise of the relevant specialties (e.g. ENT, oral and maxillofacial surgery, ophthalmology, gynaecology)". This is in line with the proposal in the comment. The addition serves to complete the subject matter concerned.

7.2. Comments on formal aspects

Table 17: Comments on editorial changes

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
Reference to the effect that it was Mr Hauschild and not Ms Berking, as stated in the guideline documents, who retired as the appointed representative of the ADO.	Long version: Table 1 Short version: Table 1 Guideline report: Table 2	An appropriate editorial change will be made to correct the facts.

7.3. General comments

Table 18: General comments

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
Question why the DGZMK with its subgroups (AGKI and AKOPOM) was not involved in producing the guideline.	-	No changes were made to the guideline documents as this is a comment that relates to formal aspects of the guideline that can no longer be changed.
Question why a non-German organisation (EURO*SKIN*) is involved.	-	No changes were made to the guideline documents as this is a comment that relates to formal aspects of the guideline that can

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
		no longer be changed. NOTE: EURO*SKIN*, like the Scientific Advisory Board, was involved in the production of the guideline to allow the guideline to be harmonised with international experts.
Understanding is expressed for the separate opinions of DEGAM and at the same time support expressed for an experimental trial of skin cancer screening on condition that sufficient financial resources are available. Reference is also made to Australia, where extensive screening is not offered despite a high disease burden.	Long version: box 4.21, 5.5, 5.9 and 5.57	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
Demand that ENT and OMF specialists and dentists should also be included in skin cancer screening because of the high incidence of skin cancers in the area of the head.	-	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
Comment to the effect that teledermatology is overrated because of the high density of physicians in Germany.	Long version: section 5.2.4.3	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
The recommendation that screening physicians should learn 28 different aspects is described as counter-productive, as this would only benefit the course leaders concerned and the effect of training is not yet documented. It is requested that advanced education should be integrated into medical studies and specialty training.	Long version: section 5.5	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
In the section on histopathological examination, a general reference is made to redundancies, incomprehensible abbreviations and linguistic deficiencies.	Long version: section 5.3.3	No change was made to the guideline documents. The relevant section was checked. No deficiencies can be found. NOTE. The section is based on the *Skin Cancer Screening Histopathology*

Tenor of the comment	Relevant section in the guideline	Change to guideline and, where applicable, rationale
		Quality Assurance Agreement.
It is stated that the cost analyses presented in the guideline show the effectiveness of outpatient operations. However, these would be promoted less than pharmacological measures.	Long version: section 3.3	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
The recommendation on the contents of curricula for health professionals in the area of primary and secondary prevention is described as organisationally too overwhelming.	Long version: Recommendation 5.53	No change was made to the guideline documents as this is a general comment that does not provide for any specific changes to the guideline documents.
It is remarked that there is no section on therapeutic exposure in childhood in the guideline since there are probably no data/publications in this respect.	-	No change, as the revision is too time-consuming at the current time. However, the subject will be prioritised for the next update.

8. Editorial independence

German Cancer Aid (DKH) provided funding through the German Guideline Program in Oncology (GGPO). These funds were used for staff costs, office material, literature procurement and the consensus conferences (room hire, equipment, cleaning, moderator's fees, travel costs of participants). The travel costs were reimbursed in accordance with the German Business Travel Act. Production of the guideline was editorially independent of the funding organisation. During the guideline process, all members submitted a written declaration of any existing conflicts of interest.

An overview of the potential conflicts of interest of all those involved in the guideline can be found in Appendix 5.

The declarations of conflicts of interest were examined and assessed by the co-ordinator. Following review by the guideline co-ordinator, none of the declared conflicts of interest were classed as being so critical that they impacted on the remits.

As the ADP, and with it in particular the guideline co-ordinator Prof. Dr Breitbart, has been active since the 1980s in the area of both primary and secondary prevention of skin cancer and in particular has designed, implemented and analysed the SCREEN project (SCREEN: Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) [2], which was the basis for the introduction of national skin cancer screening in Germany, a potential conflict of interests was envisaged by the GGPO. In order to address this point the promotion of the guideline project was subjected to a neutral appraisal of the guideline by international experts.

Thus, it was intended to ensure that the evidence on secondary prevention was assessed independently. In order to meet this precondition already in the creation process, international experts in the field of skin cancer prevention have been included in the development of the guideline's chapter on the early detection of skin cancer. These experts are members of the Scientific Advisory Board (SAB) for the Prevention of Skin Cancer (see guideline report) that was founded in 2009 [3]. Furthermore neutrality of the assessment regarding scientific evidence was ensured through the commission of external institutions (see section 5.2 in this report).

We should like to take this opportunity to thank the experts involved for their entirely voluntary co-operation in the project.

9. Dissemination and implementation

The evidence-based guideline prevention of skin cancer comprises the following documents:

- *Long version:* recommendations and algorithms with detailed background information justifying the individual recommendations
- *Evidence tables:* issue of a separate document with all evidence-appraised texts based on a comprehensive literature search (only available in German)
- *Short version:* summary of the care recommendations, indicating the classes of evidence and degrees of recommendation
- *Guideline report:* detailed presentation of the methodology of the development process
- *Patient guideline (lay version):* summary of the recommendations of the guideline for the general population and for skin cancer patients (in preparation)

The guideline is disseminated in various ways:

Proposals:

- Publication in specialist journals
- Printed version of the patient guideline
- Available as a Pdf document (see section 1.8).
- As this guideline is addressed particularly to the general population (primary prevention), the Association of Dermatological Prevention's and German Cancer Aid's public relations measures (internet presentations, brochures, press conferences, congresses, lectures, seminars, specialist journals, book chapters) should ensure that it reaches that audience.
- Implementation in hospitals and practice: training courses and appropriate local development of aids: e.g. paperback formats and incorporation in electronic support media (incorporation in hospital and practice information systems as part of quality management)
- Integration of the information in public relations, e.g. integration in advanced and continuing education

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11. Appendices

11.1. Appendix 1: Key questions in the different subject areas

Key questions of the evidence-based guideline prevention of skin cancer	Level of response
Subject area: Status quo	
Aetiology (WG 1)	
1. What are the causes of malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)?	Statement
2. What is the clinical course of MM, BCC and SCC?	Statement
Incidence and prevalence (WG 1)	
How are the incidence and prevalence of MM, BCC and SCC changing in Germany and internationally?	Statement
Disease burden (WG 1)	
How great is the individual, social and economic burden of skin cancer (differentiated by tumour stages of the individual cancer entities)?	Statement
Risks (WG 1)	
1. What constitutional risk factors (phenotypical or genotypical) can be defined for MM, BCC and SCC?	Statement
2. What acquired risk factors can be defined for MM, BCC and SCC?	Statement
3. What risk factors for UV exposure can be defined for MM, BCC and SCC?	Statement
4. Are there any further risk factors for skin cancer?	Statement
5. With what absolute and relative risks are these aspects associated?	Statement
Subject area: Primary prevention (WG 2)	
Individual modes of behaviour (WG 2)	
1. What modes of behaviour reduce the risk of developing MM, BCC or SCC?	Evidence-based
2. What modes of behaviour are to be recommended for certain groups of people (e.g. persons at risk, children / adolescents and adults, certain occupational groups)?	Evidence-based
3. What potential side effects must be anticipated for which recommendations (e.g. vitamin D deficiency)?	Evidence-based
Primary prevention measures for the population (WG 2)	
1. What behavioural prevention measures are suitable for conveying knowledge and permanently changing the population's behaviour? (behavioural prevention = change of behaviour, e.g. skin cancer weeks, multimedia campaigns)	Evidence-based

Key questions of the evidence-based guideline prevention of skin cancer	Level of response
2. What environmental prevention measures are suitable for changing the population's behaviour? (environmental prevention = changes to the environment, e.g. sunbed law, no taxation of sunscreen, shading of play areas)	Evidence-based
3. Are there unwanted effects of primary prevention measures in the population (e.g. vitamin D deficiency)?	Evidence-based
Subject area: Secondary prevention	
Early detection of skin cancer (WG 3) – Assessment by Scientific Advisory Board	
1. Are there effective population-related and individual measures for the early detection of skin cancer? The effectiveness is defined by the following points: 1. To what extent is skin cancer identified earlier by the measures (stage shift)? 2. To what extent do the measures influence morbidity (disease stage at the time of diagnosis) and/or mortality?	Evidence-based
2. How should screening be performed (e.g. 2-stage)?	Evidence-based
3. What recommendations can be given for screening persons at risk?	Evidence-based
4. For which target groups should what kind of screening be offered?	Evidence-based
5. What examination intervals are recommended, differentiated by persons at risk and not at risk?	Evidence-based
6. What negative consequences may be associated with what kind of screening? (How often do these negative consequences occur [relative/absolute]?)	Evidence-based
Presumptive diagnosis / screening test (WG 4)	
1. What diagnostic measures exist?	Evidence-based
2. What diagnostic measure (or what combination of measures) is suitable for screening (e.g. whole-body examination with /without dermatoscope, ultrasound, confocal laser microscope)?	Evidence-based
Confirmatory diagnostic procedures (WG 5) (Interface with evidence-based guideline on diagnosis, therapy and follow-up of MM)	
1. What confirmatory diagnostic methods exist?	Evidence-based
2. Which of these methods are suitable for a confirmatory diagnosis, alone or in combination, for the unequivocal identification of cancer?	Evidence-based
3. How is a histopathological diagnosis to be performed?	Consensus
4. What aspects must be considered in quality assurance?	Consensus
Doctor-patient communication (WG 6) (Interface with evidence-based guideline on diagnosis, therapy and follow-up of MM)	
How should a doctor-patient interview be structured and what information should be conveyed in what form:	

Key questions of the evidence-based guideline prevention of skin cancer	Level of response
1. before the screening? (consider including assistant health care professions)	Evidence-based
2. after the screening if a. there is no suspicion of skin cancer? b. there is a suspicion of skin cancer, i.e. before referral to the dermatologist (if the examination had been performed by a non-dermatologist) or before the biopsy (if the examination has been performed by a dermatologist)?	Evidence-based
3. for reporting findings (after diagnosis)?	Evidence-based
Information of the population / public (WG 7)	
1. What information is necessary for the citizen to be able to take an informed decision for or against participation in an early detection examination?	Evidence-based
2. What strategies and measures are suitable for addressing the various target groups and allowing an informed decision for or against participation in skin cancer screening?	Evidence-based
3. How is this information to be conveyed?	Evidence-based
4. How can the communication process and information outcome / success of communication be evaluated adequately?	Evidence-based
Subject area: Implementation / quality assurance (WG 8)	
Training, advanced education and continuing education	
1.1 What specialist preconditions are required or need to be created for physicians and assistants in order for them to be able to carry out screening?	Evidence-based
1.2 How are these to be created?	Evidence-based
1.3 What content must be included in a curriculum for physicians and assistants?	Evidence-based
Data documentation and flow	
2.1 What data should be collected in skin cancer screening?	Evidence-based
2.2 Which of these data should be forwarded elsewhere?	Evidence-based
2.3 What are suitable methods of data recording and transmission?	Evidence-based
2.4 What needs to be considered from the perspective of data protection?	Evidence-based
3. Patient flow: what time intervals must be considered for which presumptive diagnoses referring patients? *(This key question also concerns WGs 3 and 4.)*	Evidence-based
4. Quality assurance: what quality assurance measures are suitable for screening (e.g. standardisation of the examination)?	Evidence-based

11.2. Appendix 2: Appraisal procedure using DELBI

Guide-line	NZ / OZ (MM)[1]	OZ (BCC/ SCC)[2]	Canada[3]	UK (Concise)[4]	UK (Sign)[5]	UK (BAD)[6]	US (NCCN-MM)[7]	US (NCCN-NMSC)[8]	US (ICSI adults)[9]	US (ICSI children)[10]	USPSTF (screen-ing)[11]	USPSTF (Counse-ling)[12]	Mean domain values
Domain 1: Scope and purpose													
Criterion 1	2	2	1	2	2	2	1	1	3	3	3	1	
Criterion 2	4	4	4	3	4	2	1	2	3	3	4	4	
Criterion 3	2	2	2	2	2	1	1	1	4	3	4	2	
Total 1	8	8	7	7	8	5	3	4	10	9	11	7	
STDV*	**0.56**	**0.56**	**0.44**	**0.44**	**0.56**	**0.22**	**0**	**0.11**	**0.78**	**0.67**	**0.89**	**0.44**	**0.47**
Domain 2: Stakeholder involvement													
Criterion 4	3	3	3	2	4	3	2	2	3	2	2	3	
Criterion 5	2	3	1	2	1	1	1	1	1	1	1	1	
Criterion 6	2	2	2	2	4	1	1	1	3	2	2	2	
Criterion 7	1	1	1	1	1	1	1	1	1	1	1	1	
Total 2	8	9	7	7	10	6	5	5	8	6	6	7	
STDV*	**0.33**	**0.42**	**0.25**	**0.25**	**0.5**	**0.17**	**0.08**	**0.08**	**0.33**	**0.17**	**0.17**	**0.25**	**0.25**
Domain 3: Methodological rigour of guideline development													
Criterion 8	4	1	4	2	2	3	1	1	2	2	3	4	

Guide-line	NZ / OZ (MM)[1]	OZ (BCC/ SCC)[2]	Canada[3]	UK (Concise)[4]	UK (Sign)[5]	UK (BAD)[6]	US (NCCN-MM)[7]	US (NCCN-NMSC)[8]	US (ICSI adults)[9]	US (ICSI children)[10]	USPSTF (screen-ing)[11]	USPSTF (Counse-ling)[12]	Mean domain values
Criterion 9	2	1	4	2	2	1	1	1	1	1	4	2	
Criterion 10	3	2	1	1	2	1	1	1	1	1	1	1	
Criterion 11	3	2	1	1	2	2	2	1	2	1	2	2	
Criterion 12	4	3	2	3	4	4	2	2	4	4	2	2	
Criterion 13	3	2	2	1	3	2	1	1	1	1	1	1	
Criterion 14	3	1	1	3	4	2	2	1	4	4	1	1	
Total 3	22	12	15	13	19	15	10	8	15	14	14	13	
STDV*	**0.71**	**0.24**	**0.38**	**0.29**	**0.57**	**0.38**	**0.14**	**0.05**	**0.38**	**0.33**	**0.33**	**0.29**	**0.34**
Domain 4: Clarity and presentation													
Criterion 15	4	4	3	3	3	4	4	4	4	4	4	4	
Criterion 16	3	3	3	3	3	3	3	3	3	1	1	1	
Criterion 17	4	4	4	4	4	4	4	4	3	4	4	3	
Criterion 18	3	1	3	1	3	3	2	3	2	3	4	2	
Total 4	14	12	13	11	13	14	13	14	12	12	13	10	
STDV*	**0.83**	**0.67**	**0.75**	**0.58**	**0.75**	**0.83**	**0.75**	**0.83**	**0.67**	**0.67**	**0.75**	**0.5**	**0.72**
Domain 5: Applicability													

Guide-line	NZ / OZ (MM)[1]	OZ (BCC/ SCC)[2]	Canada[3]	UK (Concise)[4]	UK (Sign)[5]	UK (BAD)[6]	US (NCCN-MM)[7]	US (NCCN-NMSC)[8]	US (ICSI adults)[9]	US (ICSI children)[10]	USPSTF (screen-ing)[11]	USPSTF (Counse-ling)[12]	Mean domain values
Criterion 19	1	2	1	1	1	1	1	1	2	2	1	1	
Criterion 20	1	1	1	1	2	1	1	1	2	2	1	1	
Criterion 21	1	1	1	1	1	1	1	1	2	2	1	1	
Total 5	3	4	3	3	4	3	3	3	6	6	3	3	
STDV*	**0**	**0.11**	**0**	**0**	**0.11**	**0**	**0**	**0**	**0.33**	**0.33**	**0**	**0**	**0.07**
Domain 6: Editorial independence													
Criterion 22	2	2	3	2	1	1	1	1	1	1	2	2	
Criterion 23	3	3	4	2	2	2	1	1	4	4	2	1	
Total 6	5	5	7	4	3	3	2	2	5	5	4	3	
STDV*	**0.5**	**0.5**	**0.83**	**0.33**	**0.17**	**0.17**	**0**	**0**	**0.5**	**0.5**	**0.33**	**0.17**	**0.33**
Domain 7: Applicability to the German health care system													
Criterion 24	1	1	3	1	1	2	1	1	1	1	1	1	
Criterion 25	3	3	2	2	4	2	2	2	2	1	1	1	
Criterion 26	1	2	1	1	1	1	4	4	2	2	2	1	
Criterion 27	4	3	3	3	3	3	3	3	3	3	3	3	
Criterion 28	4	1	1	1	1	1	1	1	4	4	1	1	

Guide-line	NZ / OZ (MM)[1]	OZ (BCC/ SCC)[2]	Canada[3]	UK (Concise)[4]	UK (Sign)[5]	UK (BAD)[6]	US (NCCN-MM)[7]	US (NCCN-NMSC)[8]	US (ICSI adults)[9]	US (ICSI children)[10]	USPSTF (screen-ing)[11]	USPSTF (Counse-ling)[12]	Mean domain values
Criterion 29	3	1	4	2	4	2	1	1	2	2	3	3	
Total 7	16	11	14	10	14	11	12	12	14	13	11	10	
STDV*	**0.56**	**0.28**	**0.44**	**0.22**	**0.44**	**0.28**	**0.33**	**0.33**	**0.44**	**0.39**	**0.28**	**0.22**	**0.35**
Domain 8: Methodological rigour of the guideline development using existing guidelines													
Criterion 30	1	1	4	1	1	1	1	1	1	1	1	1	
Criterion 31	1	1	4	1	1	1	1	1	1	1	1	1	
Criterion 32	1	1	1	1	1	1	1	1	1	1	1	1	
Criterion 33	1	1	1	1	1	1	1	1	1	1	1	1	
Criterion 34	1	1	1	1	1	1	1	1	1	1	1	1	
Total 8	5	5	11	5	5	5	5	5	5	5	5	5	
STDV*	**0**	**0**	**0.4**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.03**

* **Standardised domain value**

Note: All guidelines were appraised by 2 assessors (CMB / FG). In the event of divergences of opinion, a mean was not formed but instead a consensus was reached following discussion.

1 [6], 2 [7], 3 [8], 4 [9], 5 [10], 6 [11], 7 [12], 8 [13], 9 [14] 10 [15], 11 [16], 12 [17]

11.3. Appendix 3: Guidelines synopsis

Table 19: Synopsis of the included guidelines that satisfied the methodological quality criteria of DELBI *(reproduced with permission from JAMA Dermatology)*

	Australian Cancer Network/ New Zealand Guidelines Group [6]	**Scottish Intercollegiate Guideline Network** [9]
Country	Australia and New Zealand	Scotland
Title	Clinical practice guidelines for the management of melanoma in Australia and New Zealand	72 – Cutaneous Melanoma. A national clinical guideline
Year	2008	2003
Aim	Raising standards and producing greater uniformity of care by specifying evidence-based protocols for melanoma prevention, diagnosis, treatment, and follow-up.	This guideline provides advice at all stages of the patient's pathway of care, from primary prevention to early recognition, treatment and follow up.
Target population	All practitioners and health workers (and patients)	Primary care provider, dermatologists, surgeons, pathologists, oncologist, public health physicians, nurses, health promotion professionals and epidemiologists
Source of funding	Cancer Institute NSW, New Zealand Guidelines Group, NSW Melanoma Network	NHS Quality Improvement Scotland
Patient version	no	yes

	Australian Cancer Network/ New Zealand Guidelines Group [6]	Scottish Intercollegiate Guideline Network [9]
AGREE score Domain 3	0.71	0.57
Rating scheme for level of evidence	Levels of Evidence Levels ranging from I, II, III-1, III-2, III-3 to IV Within each level, the authors of this guideline further differentiated each level according to the type of research question, i.e. intervention, diagnosis, prognosis, etiology, screening	Levels of Evidence Levels ranging from 1++, 1+, 1-, 2++, 2+, 2-, 3 to 4, for example: 1++: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias 2++: High quality systematic reviews of case control or cohort studies, high quality case control, cohort studies with very low risk of bias, etc. 3: Non-analytic studies, e.g. case reports, case series 4: Expert opinion
Rating scheme for recommen-dations	Grades of recommendation (shortened): A: Body of evidence can be trusted to guide practice B: Body of evidence can be trusted in most situations C: Body of evidence provides some support for recommendation(s) but care should be taken in its application D: Body of evidence is weak; recommendation applied with caution	Grades of recommendation (shortened): A: e.g., at least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population B: e.g., a body of evidence including studies rated as 2++ C: e.g., a body of evidence including studies rated as 2+ D: e.g., evidence level 3 or 4
Primary prevention	<u>Prevention of melanoma</u> ▪ Sunburn be avoided and UV protection (physical methods complemented by sunscreens) adopted **(grade of recommendation: (B)) -> relevant for research question (RQ) 5.1** ▪ Sunscreens be used to complement but not to replace physical methods of UV protection **(C) -> RQ 5.1** ▪ Risks associated with exposure to tanning booths and sunbeds be explained **(C) -> RQ 6.1**	<u>Public education to promote primary prevention</u> ▪ Brochures and leaflets should be used to deliver preventive information on melanoma to the general public **(D) -> RQ 6.1** <u>Public education to promote early detection</u> ▪ Healthcare professionals and members of the public should be aware of the risk factors for melanoma **(B) -> RQ 5.2 & 6.1** ▪ Individuals identified as being at higher risk should be: - advised about appropriate methods of sun protection **(C) RQ**

	Australian Cancer Network/ New Zealand Guidelines Group [6]	Scottish Intercollegiate Guideline Network [9]
	▪ As brief sun exposures are needed to maintain vitamin D levels, total lack of sun exposure is not advised w/out vitamin D supplementation **(C) -> RQ 5.3**	**5.2** - educated about the diagnostic features of melanoma **(C) -> RQ 7.1** - encouraged to perform skin self-examination**(C) -> RQ 7.1**
Secondary prevention	<u>Population-based whole-body skin screening for melanoma</u> ▪ In the absence of substantive evidence as to its effectiveness in reducing mortality from melanoma, population-based skin screening cannot be recommended **(C) -> RQ 7.1** <u>Management of high-risk Individuals</u> ▪ Individuals at high risk of melanoma and their partner or carer be educated to recognize and document lesions suspicious of melanoma, and to be regularly checked by a clinician with six-monthly full body examination supported by photography and dermoscopy as required **(C) -> RQ 7.1, 7.3, 7.5 & 8.2**	<u>Mass Screening</u> ▪ Recommendation based on Good Practice Points only
Tentative diagnosis	<u>Clinical diagnosis</u> ▪ Training and utilization of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions **(A) -> RQ 8.1, 8.2, 12.1.1 & 12.1.3** ▪ Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma **(B) -> RQ 8.1 & 8.2** ▪ Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma **(C) -> RQ 7.3, 8.1 & 8.2**	<u>Clinical diagnosis</u> ▪ Clinicians should be familiar with the 7 point or ABCD checklist for assessing lesions **(D) -> RQ 8.1, 8.2 & 12.1** ▪ Clinicians using hand held dermoscopy should be appropriately trained **(D) -> RQ 12.1.1 & 12.1.3** <u>Delay in diagnosis</u> ▪ Health professionals should be encouraged to examine patients' skin during other examinations **(D) -> RQ 7.1**
Confirmation of diagnosis	<u>Biopsy</u> ▪ The optimal biopsy approach is complete excision with a 2mm margin and upper subcutis **(C) -> RQ 9.1 & 9.2** ▪ Partial biopsies may not be fully representative of the lesion and need to be interpreted in light of the clinical findings **(C) -> RQ 9.1**	<u>Biopsy</u> ▪ A suspect melanoma should be excised with a 2mm margin and a cuff of fat **(D) -> RQ 9.1 & 9.2** ▪ If complete excision cannot be performed as a primary procedure a full thickness incisional or punch biopsy of the most suspicious area

	Australian Cancer Network/ New Zealand Guidelines Group [6]	Scottish Intercollegiate Guideline Network [9]
	▪ Incisional, punch or shave biopsies may be appropriate in carefully selected clinical circumstances, for example, for large facial or acral lesions, or where the suspicion of melanoma is low **(C) -> RQ 9.1** Histopathological reporting of cutaneous melanoma ▪ The essential components of a histological report: Breslow thickness, Margins of excision (microscopic), Mitotic rate/mm², Level of invasion (Clark), Ulceration **(A) -> RQ 9.3 & 9.4** ▪ The following components of a histological report are of prognostic or other value: Vascular invasion, local metastases, microsatellites and in-transit metastases, tumor-infiltrating lymphocytes, regression, desmoplasia, neurotropism, associated benign melanocytic lesion, solar elastosis, predominant cell type, histological growth pattern, growth phase and immunohistochemistry **(C) -> RQ 9.3** ▪ Histological criteria, review of the primary melanoma and clinicopathological correlation be used for distinguishing between persistent primary melanoma and local metastasis **(C) -> RQ 9.3** ▪ The synoptic report be used in conjunction with, but not as a replacement for, the descriptive report **(C) -> RQ 9.3 & 9.4** ▪ Pathology reports should include information from sentinel lymph biopsies, derived from multiple histological sections of sentinel nodes (including sections stained with H&E and immunohistochemically for melanoma-associated antigens including S-100) **(C) -> RQ 9.3 & 9.4** ▪ Non-sentinel lymph nodes should be carefully examined and reported **(D) -> RQ 9.3 & 9.4**	is advised **(C) -> RQ 9.1** ▪ A superficial shave biopsy is inappropriate for suspicious pigmented lesions **(C) -> RQ 9.1** Pathological Diagnosis ▪ The macroscopic description of a suspected melanoma should: - state the biopsy type excision, incision, or punch - describe and measure (in mm) the biopsy - state the size of lesion in mm; describe the lesion in detail - state the clearance of the lesion (in mm) from the nearest lateral margin and the deep margin **(D) RQ 9.3 & 9.4** ▪ Selection of tissue blocks: - the entire lesion should be submitted for histopathological examination - the lesion should be sectioned transversely at 3 mm intervals and the blocks loaded into labeled cassettes - cruciate blocks should not be selected (they limit the assessment of low power architectural features such as symmetry) **(D) RQ 9.3 & 9.4** Prognostic Indicators ▪ Histogenetic type should be included in pathology report **(B) RQ 9.3 & 9.4** ▪ The growth phase characteristics should be stated in the pathology report of all melanomas except nodular melanomas which, by the time of diagnosis, show only vertical growth phase characteristics **(B) RQ 9.3 & 9.4** ▪ An accurate (to within 0.1 mm) measurement of the Breslow thickness should be included in the pathology report for any melanoma that has an invasive component **(B) RQ 9.3 & 9.4** ▪ The Clark level of invasion should be provided when the lesion has a Breslow thickness < 1mm **(B) RQ 9.3 & 9.4** ▪ The presence or absence of histological evidence of epidermal ulceration should be noted in the pathology report **(B) RQ 9.3 & 9.4** ▪ If late regression is apparent it should be included in the pathology

	Australian Cancer Network/ New Zealand Guidelines Group [6]	Scottish Intercollegiate Guideline Network [9]
		report **(C) RQ 9.3 & 9.4** ▪ Identification of lymphatic space invasion and/or microscopic satellites should be included in the pathology report **(B) RQ 9.3 & 9.4** ▪ If the likelihood of survival is calculated using the Cochran model, the breadth of any epidermal ulcer be measured by micrometer and stated in the pathology report **(B) RQ 9.3 & 9.4**
Doctor-patient communication	Doctor-patient communication	Doctor-patient communication
	▪ Communication skills training be provided to health professionals treating people with melanoma to assist them in effectively providing information, patient-centered care, shared decision-making where desired, empathy and support **(C) -> RQ 10.3, 12.1.1, RQ 12.1.3**	▪ Patients should receive target information throughout their journey of care (C) **RQ 10.3**
Implementation of the screening and quality assurance (Training)		Implementation of the screening and quality assurance (Training)
		▪ Targeted education can enhance health professionals' ability to diagnose melanoma **(GPP) RQ 12.1.1 & 12.1.2**
Legend **(A) to (D)** respectively	Grade of recommendation as provided by the Australian Cancer Network/ New Zealand Guidelines Group and the Scottish Intercollegiate Guideline Network,	
RQ	Research question to be answered in the S3-guideline "Prevention of skin cancer"	

11.4. Appendix 4: NICE checklists

Appendix C: Methodology checklist: systematic reviews and meta-analyses

Study identification *Include author (year of publication) title*	
Guideline topic: Prävention von Hautkrebs	**Review question no:** AG
Checklist completed by: (Initialen)	☐ Essen ☐ Köln
SCREENING QUESTIONS	
In a well-conducted, relevant systematic review:	***Circle one option for each question***
The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	Yes ☐ No ☐ Unclear ☐
The review collects the type of studies you consider relevant to the guideline review question	Yes ☐ No ☐ Unclear ☐
The literature search is sufficiently rigorous to identify all the relevant studies	Yes ☐ No ☐ Unclear ☐
Study quality is assessed and reported	Yes ☐ No ☐ Unclear ☐
An adequate description of the methodology used is included, and the methods used are appropriate to the question	Yes ☐ No ☐ Unclear ☐

If the review does not meet some or all of these criteria, it may still be useful as a source of references, but should not be relied upon on its own to address a review question.

If you have insufficient information on the design or quality of individual studies, you should use the checklists for studies on interventions (see appendices D, E and F) to appraise each study. Each study should appear as a separate entry in the evidence table (see appendix K); the review should not appear in the evidence table.

If you plan to use the review as a whole, you will need to complete a row in an evidence table for the systematic review and input the results into an evidence profile as appropriate.

Appendix D: Methodology checklist: randomised controlled trials

Study identification *Include author (year of publication) title*		
Guideline topic: Prävention von Hautkrebs	**Review question no:** AG	
Checklist completed by: (Initialen)	☐ Essen ☐ Köln	
		Circle one option for each question
A. Selection bias (systematic differences between the comparison groups)		
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes ☐ No ☐ Unclear ☐ N/A ☐
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes ☐ No ☐ Unclear ☐ N/A ☐
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐	Unclear/unknown risk ☐	High risk of bias ☐
Likely direction of effect:		
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes ☐ No ☐ Unclear ☐ N/A ☐
B2	Participants receiving care were kept blind to treatment allocation	Yes ☐ No ☐ Unclear ☐ N/A ☐
B3	Individuals administering care were kept blind to treatment allocation	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐	Unclear/unknown risk ☐	High risk of bias ☐
Likely direction of effect:		

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C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes ☐ No ☐ Unclear ☐ N/A ☐
C2	a. How many participants did not complete treatment in each group?	
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes ☐ No ☐ Unclear ☐ N/A ☐
C3	a. For how many participants in each group were no outcome data available?	
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐ Unclear/unknown risk ☐ High risk of bias ☐		
Likely direction of effect:		
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)		
D1	The study had an appropriate length of follow-up	Yes ☐ No ☐ Unclear ☐ N/A ☐
D2	The study used a precise definition of outcome	Yes ☐ No ☐ Unclear ☐ N/A ☐
D3	A valid and reliable method was used to determine the outcome	Yes ☐ No ☐ Unclear ☐ N/A ☐
D4	Investigators were kept blind to participants exposure to the intervention	Yes ☐ No ☐ Unclear ☐ N/A ☐
D5	Investigators were kept blind to other important confounding and prognostic factors	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐ Unclear/unknown risk ☐ High risk of bias ☐		
Likely direction of effect:		

Appendix E: Methodology checklist: cohort studies

Study identification *Include author (year of publication) title*					
Guideline topic: Prävention von Hautkrebs		**Review question no:** AG			
Checklist completed by: (Initialen) ☐ Essen ☐ Köln					
		Circle one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome(s) under study)	Yes ☐	No ☐	Unclear ☐	N/A ☐
A2	Were any attempts made within the design or analysis to balance the comparison groups for potential confounders?	Yes ☐	No ☐	Unclear ☐	N/A ☐
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes ☐	No ☐	Unclear ☐	N/A ☐
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias ☐		Unclear/unknown risk ☐		High risk of bias ☐	
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes ☐	No ☐	Unclear ☐	N/A ☐
B2	Participants receiving care were kept blind to treatment allocation	Yes ☐	No ☐	Unclear ☐	N/A ☐
B3	Individuals administering care were kept blind to treatment allocation	Yes ☐	No ☐	Unclear ☐	N/A ☐
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias ☐		Unclear/unknown risk ☐		High risk of bias ☐	
Likely direction of effect:					

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C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes ☐ No ☐ Unclear ☐ N/A ☐
C2	a. How many participants did not complete treatment in each group?	
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes ☐ No ☐ Unclear ☐ N/A ☐
C3	a. For how many participants in each group were no outcome data available?	
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐ Unclear/unknown risk ☐ High risk of bias ☐		
Likely direction of effect:		
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)		
D1	The study had an appropriate length of follow-up	Yes ☐ No ☐ Unclear ☐ N/A ☐
D2	The study used a precise definition of outcome	Yes ☐ No ☐ Unclear ☐ N/A ☐
D3	A valid and reliable method was used to determine the outcome	Yes ☐ No ☐ Unclear ☐ N/A ☐
D4	Investigators were kept blind to participants exposure to the intervention	Yes ☐ No ☐ Unclear ☐ N/A ☐
D5	Investigators were kept blind to other important confounding/prognostic factors	Yes ☐ No ☐ Unclear ☐ N/A ☐
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?		
Low risk of bias ☐ Unclear/unknown risk ☐ High risk of bias ☐		
Likely direction of effect:		

Appendix F: Methodology checklist: case control studies

Study identification *Include author (year of publication) title*		
Guideline topic: Prävention von Hautkrebs		**Review question no:** AG
Checklist completed by: (Initialen)		☐ Essen ☐ Köln
Section 1: Internal validity		
		Circle one option for each question
1.1	The study addresses an appropriate and clearly focused question.	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
Selection of participants		
1.2	The cases and controls are taken from comparable populations	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
1.3	The same exclusion criteria are used for both cases and controls	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
1.4	What was the participation rate for each group (cases and controls)?	Cases: Controls:
1.5	Participants and non-participants are compared to establish their similarities or differences	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
1.6	Cases are clearly defined and differentiated from controls	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
1.7	It is clearly established that controls are not cases	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐
Assessment		
1.8	Measures were taken to prevent knowledge of primary exposure influencing case ascertainment	Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable ☐

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1.9	Exposure status is measured in a standard, valid and reliable way	Well covered ☐ Adequately addressed ☐ Poorly addressed ☐	Not addressed ☐ Not reported ☐ Not applicable ☐
Confounding factors			
1.10	The main potential confounders are identified and taken into account in the design and analysis	Well covered ☐ Adequately addressed ☐ Poorly addressed ☐	Not addressed ☐ Not reported ☐ Not applicable ☐
Statistical analysis			
1.11	Have confidence intervals been provided?		

Appendix G: Methodology checklist: the QUADAS tool for studies of diagnostic test accuracy[1]

Study identification *Including author (year of publication) title*				
Guideline topic: Prävention von Hautkrebs				**Review question no:** A3
Checklist completed by: (Initialen) ☐ Essen ☐ Köln				
	Circle one option for each question			
Was the spectrum of participants representative of the patients who will receive the test in practice?	Yes	No	Unclear	N/A
Were selection criteria clearly described?	Yes	No	Unclear	N/A
Was the reference standard likely to classify the target condition correctly?	Yes ✓	No	Unclear	N/A
Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	No	Unclear	N/A
Did the whole sample or a random selection of the sample receive verification using the reference standard?	Yes	No	Unclear	N/A
Did participants receive the same reference standard regardless of the index test result?	Yes	No	Unclear	N/A
Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard)	Yes	No	Unclear	N/A
Was the execution of the index test described in sufficient detail to permit its replication?	Yes	No	Unclear	N/A
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	No	Unclear	N/A
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	No	Unclear	N/A
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	No	Unclear	N/A
Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?	Yes	No	Unclear	N/A
Were uninterpretable, indeterminate or intermediate test results reported?	Yes	No	Unclear	N/A
Were withdrawals from the study explained?	Yes	No	Unclear	N/A

11.5. Appendix 5: Results of conflicts of interest declarations

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Anders, Markus	-	-	-	-	-	-	-	-	ADP
Dr. Asmuß, Monika	-	-	-	-	-	-	Federal Office for Radiation Protection	-	Federal Office for Radiation Protection
Dr. Baumann, Eva	04/2010-02/2011: self-employed consultant for strategic health communication	Remuneration/fees for lectures in connection with anniversaries, prize awards, hospital workshops	Yes, but scientific and independent third party research, e.g. for the Federal Highway Research Institute, University Hospital of Schleswig-Holstein	-	Shareholder of thalamo GmbH (strategic health communication) (but liquidation on 31.10.2010)	-	-	-	Winter semester 2012/2013: Ludwig-Maximilian University of Munich Summer semester 2012: University of Erfurt 03/2011-03/2012: Hannover University of Music, Drama and Media 04/2010-12/2010: thalamo GmbH
Dipl. Ges. ök. Becker, Monika	-	-	Janssen-Cilag GmbH Dr. Ausbüttel & Co.	-	-	-	-	-	University of Witten/Herdecke Institute for Research in Operative Medicine (IFOM)

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Dipl. Ges. ök. Beifus, Karolina	-	-	-	-	-	-	-	-	Bergisch Regional Competence Centre for Health Management and Public Health University of Wuppertal
Prof. Dr. Berking, Carola	Biofrontera, Roche Pharma, Bristol-Myers Squibb, Almirall-Hermal, Leo-Pharma	MSD, Biofrontera, Roche Pharma, Glaxo-Smith Kline, Bristol-Myers Squibb, Almirall-Hermal, Galderma, Leo Pharma, Novartis, La Roche Posay	Exosome Diagnostics: scientific co-operation in the analysis of blood from tumour patients for tumour-specific mutations	-	-	-	ADO DDG	Clinical scientific studies on non-invasive diagnostic procedures for skin tumours by confocal laser scanning microscopy, optical coherence tomography, ultrasound, dermatoscopy	Department of Dermatology of the Ludwig-Maximilian University of Munich
Prof. Dr. Bierhoff, Erhard	-	-	-	-	-	-	DGP BVP	-	self-employed
Breitbart, Eckhard. W.	-	-	-	-	-	-	-	-	Retired; until 12/2012 Elbekliniken Stade/ Buxtehude GmbH

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Prof. Dr. Chenot, Jean-Francois	Böhringer Ingelheim	-	Central Institute for Outpatient Care Provision in Germany	-	-	-	Drug Commission of the German Medical Association DEGAM DNebM	EBM	Since 2011: University Medical Centre Greifswald 2001-2011: University Medical Centre Göttingen
Dr. Cremer, Wolfgang	-	-	-	-	-	-	Hamburg regional chairman of the Professional Association of Gynaecologists	-	self-employed
Dr. Diensberg, Manfred	- -	German Association of General Practitioners: IhF (German Institute for CME and CPD in General Practice)	-	-	-	-	German Association of General Practitioners	-	Self-employed community-based general practitioner, research assistant at the Ruhr University Bochum
Prof. Dr. Drexler, Hans	-	-	-	-	-	-	President of DGAUM	-	Institute of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Dr. Egidi, Günther	G-BA expert in diabetes	Lecture fees from the AOK Bremen health insurance company	-	-	-	-	DEGAM (German Society of General Practice and Family Medicine)	EBM	self-employed
Dr. Egler, Peter	-	-	-	-	-	-	-	-	Consilius GmbH
Dr. Eigentler, Thomas	Consultancy work for BMS, Philogen	Lecture fees for BMS, La Roche Posay, Leo Pharma, Almirall-Hermal	-	-	-	-	DKG ADO	-	University Skin Clinic Tübingen
Dr. Eikermann, Michaela	-	EBM training courses (Grünenthal, AG Endoprothetik)	Janssen-Cilag GmbH, Dr. Ausbüttel & Co.	-	-	-	-	-	Since 07/2012: IFOM (Institute for Research in operative Medicine) Previously since 10/2005 IQWiG
Dr. Follmann, Markus	-	-	-	-	-	-	Co-ordinator German Guideline Programme in Oncology of the DKG, DKH, AWMF, certified guideline consultant	-	DKG

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Prof. Dr. Dr. Frerich, Bernhard	Sanofi Pasteur	Med. Update GmbH Merck Serono Oncology	Ihde Dental GmbH	Bioreactor procedures for tissue engineering	Novatissue GmbH, (biotechnology)	-	DGMKG	-	since April 2009: University Hospital Rostock AöR *(public law institution)* Until March 2009: University Hospital Leipzig AöR
Prof. Dr. Gerstner, Andreas	-	-	-	-	-	German Society for Otolaryngology DKG	-	-	Department of Otorhinolaryngology of the University Hospital of Bonn
Dr. Göckel-Beining, Bernt	-	-	-	-	-	DHU BDU	-	-	self-employed
Dr. Greinert, Rüdiger	-	-	-	-	-	-	-	-	Elbekliniken Stade/Buxtehude GmbH
Dr. Grundhewer, Herbert	-	-	-	-	-	Profes-sional Associa-tion of Paediatric and Adolescent Physicians	-	-	self-employed

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Dr. rer. pol. Heymann, Romy	-	-	Sponsor from the pharmaceutical industry	-	-	-	-	-	Chair for medical management, University of Duisburg-Essen
Dipl.-Psych. Hornemann, Beate	-	-	-	-	-	PSO of the DKG	-	-	University Cancer Centre UCC of the University Hospital Dresden
Dipl-Ges. ök Jaschinski, Thomas	-	Yes, EBM training courses	Janssen-Cilag GmbH, Dr. Ausbüttel & Co. GmbH	-	-	-	-	-	University of Witten/Herdecke
Prof. Dr. John, Swen-Malte	-	Astellas company, Smartpractice company, Spirig company	-	-	-	-	Study Group for Occupational and Environmental Dermatology	-	Department of Dermatology, Environmental Medicine and Health Theory of the University of Osnabrück
Prof. Dr. Katalinic, Alexander	-	Various scientific lectures for which travel costs or lecture fees were paid (LEO Pharma, Novartis)	-	-	-	-	DGSMP DGEpi GMDS	-	Institute for Epidemiology of the University Hospital of Lübeck
Kiehl, Martina	-	-	-	-	-	-	-	-	Diocese of Hildesheim

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Prof- Dr. Köberlein-Neu, Juliane	-	Mundipharma GmbH	Third party funds from, among others, Barmenia Versicherungen *(insurance company)*, Barmer GEK, Helios Clinic Wuppertal, Radprax GmbH	-	-	-	-	-	Bergisch Regional Competence Centre for Health Management and Public Health University of Wuppertal
Kunz, Hans-Detlev	-	-	Research grants with relevance to psoriasis from employer	-	-	-	The employer is a member of the DDG and BvDD	-	German Psoriasis Associations
Dr. Löser, Christoph	-	Surgical courses on the pig skin model for community-based dermatologists and seminars for health care professionals, Janssen-Cilag, Ethicon	-	-	-	-	DDG, ÖGDC, DGDC	-	Dermatology Clinic Ludwigshafen, Skin Tumour Centre, Ludwigshafen Hospital since 2005
Mannheimer, Anna-Clara	-	-	-	-	-	-	-	-	01/2012- 12/2012: ADP Since 01/2013: Elbekliniken Stade/ Buxtehude GmbH

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Dr. Mehlhorn, Grit	-	-	-	-	-	-	Appointed representative of DGGG	-	Department of Gynaecology of the University Hospital of Erlangen
Meyer, Annegret	-	-	-	-	-	-	-	-	State of Lower Saxony
Dr. Mohr, Peter	Merck, MSD, Roche, BMS, GSK	BMS, MSD, Merck	MSD	- -	-	-	ADO ADP ASCO BvDD DDG	-	Elbekliniken Stade/ Buxtehude GmbH
Dipl.-Ges.ök Mosch, Christoph	-	-	Janssen-Cilag GmbH Dr. Ausbüttel & Co. GmbH	-	-	-	-	-	IFOM (Institute for Research in Operative Medicine) University of Witten/Herdecke
Dr. Nolte, Sandra	-	-	-	-	-	-	-	-	Until 12/2010 and 2012: ADP Since 08/2012: Medical Department, Division of Psychosomatic Medicine Charité Berlin

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Petrarca, Sonia	-	-	-	-	-	-	-	-	Until 12/2012 Association of Dermatological Prevention (ADP)
Regensburger, Cristiane	-	-	-	-	-	-	-	-	Bag Selbsthilfe
Dipl.-Psych. Rogge, Annkatrin	-	-	-	-	-	-	Member of the board of DAPO (German Association of Psychosocial Oncology)	-	Helios Clinics Schloß Schönhagen

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PD Dr. Rose, Christian	-	Lecture fees from Roche Pharma and Basilea	-	-	-	-	Federal Association of German Pathologists, Committee for Dermatological Histology (ADH) of the German Dermatological Society (DDG) Appointed representative of the Guideline Diagnosis, Therapy and Follow-Up of Malignant Melanoma	-	self-employed, previously University Hospital of Schleswig-Holstein, Lübeck Campus (UK -SH)

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Prof. Dr. Sander, Christian	-	-	-	-	-	-	DDG BvDD ADH Appointed representative of the evidence-based guideline on diagnosis, therapy and follow-up of malignant melanoma	-	Dermatology of the Asklepios Clinic St. Georg, Hamburg
Dipl.-Soz. Schmidt-Pokrzywniak, Andrea	-	-	-	-	-	-	DGEpi – German Society for Epidemiology	-	Medical Faculty Halle
Prof. Dr. Schneider, Dominik	-	-	-	-	-	-	Board of the GPOH Society for Paediatric Oncology and Haematology; Member of DGKJ	-	Dortmund-Mitte Hospital Centre Department of Paediatric and Adolescent Medicine

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Dr. Schopperth, Thomas	-	-	-	-	-	-	DAPO Chairman German Association of Psychosocial Oncology	-	Rhineland-Palatinate Cancer Society
Dr. Schwarz, Carsten	Advisory board for Novartis, Forest, Vertex	Lectures for Novartis, Chiesi Pharmaceuticals, Leufen, Forest	Novartis	-	-	-	-	-	Charité University Medical Centre Berlin
Selbmann, Hans-Konrad	-	-	-	-	-	-	AWMF	Methodologist	retired
Dr. Siekmann, Harald	-	-	-	-	-	-	-	-	Institute for Occupational Safety and Health of the German Statutory Accident Insurance Active service until November 2011
Prof. Dr. Singer, Susanne	-	-	Research projects, e.g. for Sanofi	-	-	-	PSO DGEpi GMDS	-	Institute for Medical Biometry, Epidemiology and Informatics of the Johannes-Gutenberg University Mainz

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Prof. Dr. Stang, Andreas	Sanofi-Pasteur MSD	Bristol-Myers Squibb	-	-	-	-	DGEpi – German Society for Epidemiology	-	Martin Luther University Halle- Wittenberg Institute of Clinical Epidemiology
Dr. Sturm, Diethard	Roche Diagnostics, Grünenthal GmbH, Biologische Heilmittel Heel GmbH	Lecture fees for Biologische Heilmittel Heel GmbH, German Institute for CME and CPD in General Practice	-	-	-	-	Appointed representative of the German Association of General Practitioners IhF Member of DEGAM	-	retired, until 2010 self-employed
Dr. Volkmer, Beate	-	-	-	-	-	-	-	-	Elbekliniken Stade/ Buxtehude GmbH
Dr. Waldmann, Annika	-	Lecture/training fees Böhringer	Research project Takeda Pharma AG	-	-	-	Member DGEpi, GEKID	-	Institute of Clinical Epidemiology/Institute of Cancer Epidemiology University Hospital Schleswig-Holstein, Lübeck Campus

	Activities as consultant or external expert or paid collaboration[1]	Fees for speaking or training activities or paid authorships or co-authorships[2]	Financial contributions (third party funds)[3]	Proprietary interest (e.g. patent, copyright, sales licence)[4]	Share-holding in a business, shares, investment funds[5]	Personal relations[6]	Membership of professional societies/ associations, other guideline groups[7]	Scientific or personal interests[8]	Current employer, relevant former employers in last 3 years
Dr. Wörle, Birgit	Pharm Allergan (Latisse Advisory Board)	Lecture fees for Merz Pharmaceuticals	-	-	-	-	Deputy appointed representative of DGDC Member of DDG, GÄCD	-	Department of Cosmetic Dermatology and Plastic Surgery Rosenpark Clinic Darmstadt

1 = Activities as a consultant or external expert or paid collaboration on a scientific board of a company in the health care sector (e.g. drug industry, medical devices industry), of a commercially-based contract research institute or an insurance company
2 = Fees for lecturing or training activities or paid authorships or co-authorships on behalf of a company in the health care sector, a commercially-based contract research institute or an insurance company
3 = Financial contributions (third party funds) for research projects or direct funding of employees of the institution by a company in the health care sector, a commercially-based contract research institute or an insurance company
4 = Proprietary interest in drugs/medical devices (e.g. patent, copyright, sales licence)
5 = Shareholding in a business, shares, investment funds with involvement of companies in the health care sector
6 = Personal relations with an authorised representative of a company in the health care sector
7 = Member of professional societies/associations of relevance to the development of the guideline,appointed representative in connection with guideline development
8 = Political, academic (e.g. membership of certain “schools”), scientific or personal interests that could engender potential conflicts

11.6. Appendix 6: Assessments of potential quality indicators

<table>
<tr><th>QI No

1</th><th>Possible quality indicator</th><th>Guideline recommendation</th><th>Information in the evidence-based guideline prevention of skin cancer relating to: a) Quality objective, b) Evidence basis</th></tr>
<tr><td>Numerator:</td><td>Number of patients with malignant melanoma and in toto excision</td><td rowspan="4">5.3.2.a

On clinical suspicion of a malignant melanoma, this lesion must first of all be completely excised with a small safety margin.

Remark:

- Excision in toto is captured through the Skin Cancer Screening Histopathology Quality Assurance Agreement

- A link between the data captured to date by skin cancer screening (MM from suspected MM) and the data from Clinical Cancer Registries and centres corresponding to QI 1 and 2 of the evidence based guideline on diagnosis, therapy and follow-up of MM (curative excision) is not possible as these are different basic entities.</td><td rowspan="4">a)

b) EC</td></tr>
<tr><td>Denominator:</td><td>All patients with suspected malignant melanoma</td></tr>
<tr><td rowspan="2">Stakeholder:</td><td>Health care providers who can influence the degree of expression of the QI:</td></tr>
<tr><td>Health care providers who undertake the documentation:</td></tr>
</table>

	1 Disagree	2 Rather disagree	3 Rather agree	4 Agree
1st criterion: Importance of the quality characteristic captured with the QI for the health care system (significance) The following statement is assessed: "The indicator captures essential aspects of quality of life, morbidity or mortality."	3	1	1	4
2nd criterion: Clarity of definitions The following statement is assessed: "The indicator is clearly and unambiguously defined."		1	5	3

3rd criterion: Indicator expression can be influenced by providers The following statement is assessed: “The quality indicator refers to an aspect of care that can be influenced by the stakeholders mentioned.”		5	1	3
	Yes		**No**	
4th criterion: Consideration of potential risks / side effects. The following question has to be answered (partial aspect): “Are there risks for inappropriate care as a result of the indicator which cannot be compensated for?”	3		6	
	Comment			
Risk adjustment The following statement is considered as part of the preliminary assessment: “All known relevant factors that have an influence on the outcome of the quality indicator can be considered.” Are there people to whom the QI does not apply, e.g. age, stage, comorbidity, etc.?	no QI is rejected unclear dependent on training, continuing education and experience of the first examiner (two-stage diagnostic procedure)			
Barriers to implementation The following statement is assessed: “There are no known barriers to implementation, or they can be taken account of through adequate measures.” Are there any barriers to implementation that need to be noted?	yes QI is rejected cannot be assessed experience of first examiner: direct feedback to him should be implemented			
Data availability The following statement is considered: "The data will be routinely documented by the health care provider, or an acceptable level of effort is needed to collect additional data.”	No QI is rejected does not appear to be the case yes correct			

QI No 2	Possible quality indicator	Guideline recommendation	Information of the evidence-based guideline prevention of skin cancer in respect of: *a) Quality aim, b) Evidence basis*
Numerator:	Number of reports of findings detailing: Size of preparation Examination of surgical margins Growth pattern Degree of tumour differentiation Cytomorphological characteristics Micrometric measurement of depth of penetration Micrometric measurement of lateral and (where applicable) deep safety margin Details on ulceration For malignant melanoma: regression and where applicable mitotic rate Micrometastases Diagnosis Indication of subtype/ differentiation pattern Invasiveness Indication of ICD code UICC classification with indication of pTNM and grading For malignant melanoma: additionally Clark level and Breslow index Tissue excision in toto	**5.3.3** Each histopathological report on diagnosis of a malignancy must contain a description of the microscopic findings and the formulation of a diagnosis. The type of tumour must be stated in accordance with the WHO classification and the histological staging in accordance with the currently valid TNM classification. Remark: The numerator data are the contents of the Skin Cancer Screening Quality Assurance Agreement and hence the **mandatory** precondition for the possibility of billing the histopathological findings Recommendation 5.43. refers (particularly in the background text) to the data from the quality assurance agreement	a) b) **EC**
Denominator:	All reports of findings for malignant tumours		

	associated with skin cancer screening					
Stakeholder:	**Health care providers who can influence the degree of expression of the QI:**					
	Health care providers who undertake the documentation:					
			1 Disagree	2 Rather disagree	3 Rather agree	4 Agree
1st criterion: Importance of the quality characteristic captured with the QI for the health care system (significance) The following statement is assessed: "The indicator captures essential aspects of quality of life, morbidity or mortality."			4	1	1	3
2nd criterion: Clarity of definitions The following statement is assessed: "The indicator is clearly and unambiguously defined."				3	3	3
3rd criterion: Indicator expression can be influenced by providers The following statement is assessed: "The quality indicator refers to an aspect of care that can be influenced by the stakeholders mentioned."					5	4
			Yes		**No**	
4th criterion: Consideration of potential risks / side effects. The following question has to be answered (partial aspect): "Are there risks for inappropriate care as a result of the indicator which cannot be compensated for?"			4		5	
			Comment			
Risk adjustment The following statement is considered as part of the preliminary assessment: "All known relevant factors that have an influence on the outcome of the quality indicator can be considered." Are there people to whom the QI does not apply, e.g. age, stage, comorbidity, etc.?			unclear no dependent on training, continuing education and experience of the first examiner (two-stage diagnostic procedure)			

Barriers to implementation The following statement is assessed: “There are no known barriers to implementation, or they can be taken account of through adequate measures.” Are there any barriers to implementation that need to be noted?	cannot be assessed no experience of the first examiner: direct feedback to him should be implemented
Data availability The following statement is considered: "The data will be routinely documented by the health care provider, or an acceptable level of effort is needed to collect additional data.”	does not always appear to be the case yes correct

Comments:

As what is described is defined exactly by the guideline and the Skin Cancer Screening Quality Assurance Agreement, there is no requirement for a quality indicator. In particular, all the criteria examined are redundant since statutory and other requirements apply in respect of adaptation, implementation and verification. For this reason, a quality indicator of this kind serves no purpose.

Quality indicator is rejected.

11.7. Appendix 7: Consultation phase: proposed amendment to section 3.4.1.b)

b.) Congenital naevi

Congenital (i.e. present at birth) melanocytic naevi indisputably present a risk of malignant degeneration, which is particularly significant in the case of very large congenital naevi. “Giant naevi” (> 40 cm in diameter) in particular are at increased risk of developing into MM (Price and Schaffer, 2010, Kinsler et al., 2009, Krengel et al., 2006). However, such naevi are extremely rare (Castilla et al., 1981).

According to the current international classification based on good clinical practice (Krengel et al., 2013), congenital melanocytic naevi (CMN) with a diameter of more than 20 cm to 40 cm are defined as “large congenital naevi” and naevi over 40 cm as “giant naevi”. This classification is based on the expected maximum diameter of the naevus in adulthood.

The risk of degeneration of congenital naevi is correlated with size. The development of melanomas on CMN of up to 20 cm in diameter has been described (Illig et al., 1985), but epidemiologically the risk of degeneration is not demonstrably increased in comparison with “acquired”, non-congenital naevi. In particular, up until puberty the development of a melanoma on these CMN appears to occur only very rarely. “Small” (up to 1.5 cm diameter) and “intermediate” CMN (1.5 to 20 cm) should therefore be examined (like all naevi) in the skin cancer screening programme and any changes recorded.

By contrast, “giant CMN”, which frequently exhibit a number of what are known as satellite naevi as well as central nervous system pigment cell proliferation in some cases, are a pathogenetically distinct entity due to NRAS mutations of the embryonal neural crest (Kinsler et al., 2013). These CMN are associated with a markedly higher risk for the development of a cutaneous or even central nervous system melanoma from early childhood onwards (Kinsler et al., 2009). Cutaneous melanomas that arise from these naevi are typically deep, dermal or subcutaneous nodules that can be detected by palpation. On a molecular pathological level, these melanomas must be differentiated from what are known as benign proliferative nodules (Bastian et al., 2002).

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