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Diagnosing malignant melanoma in primary care: a systematic review of clinical prediction rules

Authors:

Emma Harrington[1], Nieneke Wesseling[2], Barbara Clyne*[1], Harkiran Sandhu[1], Laura Armstrong[1], Holly Bennett[1], Tom Fahey[1]

Author affiliations:

[1] HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 Stephen's Green, Dublin 2, Ireland

www.hrbcentreprimarycare.ie

[2] Medical School, Radboud University, Nijmegen, Netherlands

***Corresponding author:** Barbara Clyne PhD, HRB Centre for Primaty Care Research, Department og General Practice, Royal College of Surgeons in Ireland, Lower Mercer Street, Dublin 2, Ireland barbaraclyne@rcsi.ie

Abstract

Objectives: Malignant melanoma has high morbidity and mortality rates. Early diagnosis improves prognosis. Clinical prediction rules (CPRs) can be used to stratify patients with symptoms of suspected malignant melanoma to improve early diagnosis.

We conducted a systematic review of CPRs for melanoma diagnosis in primary care.

Design: Systematic review

Data Sources: A comprehensive search of PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS was conducted in May 2015, using combinations of keywords and MeSH terms.

Study selection and data extraction: Studies deriving and validating, validating, or assessing the impact of a CPR for predicting melanoma diagnosis in ambulatory care were included. Data extraction and methodological quality assessment were guided by the CHARMS checklist.

Results: From 16,334 studies reviewed, 51 were included, validating the performance of 24 unique CPRs. Three impact analysis studies were identified. Five studies were set in primary care. The most commonly evaluated CPRs were the ABCD dermoscopy rule (at a cut point of >4.75; 8 studies; pooled sensitivity 0.85, 95% CI 0.73-0.93, specificity 0.72, 95% CI 0.65-0.78) and the 7 point dermoscopy checklist (at a cut point of ≥1 recommending ruling in melanoma; 11 studies; pooled sensitivity 0.77, 95% CI 0.61-0.88, specificity 0.80, 95% CI 0.59-0.92). The methodological quality of studies varied.

Conclusion: At their recommended cut-points, the ABCD dermoscopy rule is more useful for ruling out melanoma than the 7 point dermoscopy checklist. A focus on impact analysis will help translate melanoma risk prediction rules into useful tools for clinical practice.

PROSPERO registration

The protocol for this systematic review is registered at the PROSPERO database, registration number CRD42015020898

Strengths and limitations of this study

- The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. Quality assessment criteria were used to assess risk of bias and the majority of studies were at low risk in relation to the randomisation procedure and monitoring of loss to follow-up.
- A large proportion of studies did not provide sufficient information and data to perform substantial meta-analysis
- Current research shows that dermoscopic CPRs may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients but future impact analysis research is necessary to establish their impact on patient outcomes.

Introduction

Despite being among the most preventable types of cancer (through avoiding skin exposure to UV radiation), melanoma incidence has been increasing globally over the past number of decades. [1] Simultaneously, there has been a significant rise in overall 5-year survival in melanoma patients, largely attributable to earlier detection and diagnosis of thinner tumours.[2]

While early detection followed by curative surgery greatly improves prognosis, the differential diagnosis of pigmented lesions is a challenge. Particularly in primary care where the evaluation of suspected skin lesions is imposing an increasing burden due to rising incidences of skin cancer.[3] It has been suggested that primary care practitioners' skills of diagnosing skin lesions could be improved.[4] A number of Clinical Prediction Rules (CPRs) and computer-assisted diagnostic tools have been developed to assist in distinguishing malignant melanoma from benign pigmented skin lesions. However, the UK National Institute for Clinical Excellence (NICE) guidelines advise against routine use of computer-assisted diagnostic tools in the initial evaluation of a pigmented skin lesion. When used by dermatologists for the diagnosis of melanoma, certain CPRs have demonstrated high sensitivity and specificity.[2] Although each CPR has its own unique elements, there is significant overlap in terms of their content (Appendix 1), and while their use is promoted, it is unclear which rules are most suitable for use in primary care.

CPRs may be for use in clinical (i.e. naked eye) examination, or in conjunction with dermoscopy. Dermoscopy, dermatoscopy, or epiluminescent microscopy refers to the examination of pigmented skin lesions using surface microscopy. [5,6] The use of dermoscopy, primarily by dermatologists, has been found to increase diagnostic accuracy compared with naked eye inspection, as it allows the visualization of features that are not visible to the naked eye.[5-7] However, the effectiveness of dermoscopy depends clinical experience and training. Dermatologists with formal training in dermoscopy have higher melanoma detection rates compared with untrained dermatologists and primary care physicians.[7-9]

As the initial presentation of melanoma occurs most frequently in primary care or ambulatory settings, it is essential to identify tools to aid primary care practitioners to differentiate patients with clinically significant lesions, requiring referral, from those who can be treated and monitored in primary care. The aim of this study was to perform a systematic review of CPRs for the diagnosis of malignant melanoma, to evaluate their diagnostic accuracy in primary care and specialist outpatient settings, among patients with a pigmented skin lesion. Secondary aims were to review studies that have examined the implementation of CPRs in clinical practice through impact analysis studies.

Methods

The protocol for this systematic review was published on PROSPERO (CRD42015020898) and was conducted according to PRISMA guidelines.[10]

Search strategy and data sources

A systematic literature search was conducted (May 2015) including the following databases: PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS, using combinations of the following keywords and MeSH terms: melanoma/diagnosis, melanoma, prediction, score, model, decision, sensitivity, specificity, validate, derived. Hand searches of references of retrieved full-text articles and key author searches supplemented the search. No date or language limits were imposed.

Study selection

All articles were initially screened for inclusion according to title and abstract by two reviewers (NW, EH). Full text articles of studies considered eligible for inclusion were independently read by both reviewers, with any disagreements resolved by a third reviewer (BC).

Validation studies

Validation studies were eligible for inclusion if they met the following criteria;

1) *Population:* Adults (age ≥18 years) with a pigmented skin lesion in ambulatory care settings in general practice/ family medicine, dermatology, plastic surgery, and other relevant specialties.
2) *Risk:* Derivation and/or validation of a CPR for melanoma diagnosis to aid decision-making about referral or investigation of a pigmented skin lesion. CPRs were defined as "a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and investigations make toward the diagnosis, prognosis, or likely response to treatment in a patient".

3) *Comparison:* Usual clinical judgment for decision making about referral or investigation OR another CPR for melanoma diagnosis.
4) *Primary Outcome:* Performance of a CPR for predicting diagnosis of malignant melanoma (in terms of sensitivity, specificity, negative predictive values and positive predictive values).

Observational study designs (e.g. cohort, cross-sectional, case-control) were included. Studies were excluded where they had undergone derivation only, reported individual predictors only, or utilised computer assisted diagnostic tools, following the NICE guideline recommendation against the routine use of computer assisted diagnostic tools.[11]

Impact analysis

The following study designs were included impact analysis: (cluster) randomized controlled trials (RCTs), controlled before-after studies, or interrupted time series studies. We excluded uncontrolled study designs. We included studies where a melanoma CPR was used to predict melanoma compared to usual care in the clinical setting. The outcomes of interest included physician behaviour, process of care, patient outcomes and/or cost-effectiveness. A requirement for inclusion was that the CPR comprised the entire intervention. Studies where the CPR was implemented as part of a broader guideline, protocol or decision aid were excluded. Studies that used a CPR to determine eligibility for trial inclusion but were not part of the intervention were also excluded.

Data extraction

Data were extracted by four reviewers (LA, HB, HS, EH) using a data form based on the CHARMS checklist.[12] Data extracted included study design and setting, patient demographics and inclusion criteria, CPR name, CPR type (clinical or dermoscopic), predictive accuracy of the CPR (sensitivity/specificity) and, for impact analysis, the impact on the primary outcome.

Critical appraisal of studies

Two reviewers (EH, NW) critically appraised included studies using the CHARMS checklist, developed to provide guidance on data extraction and critical appraisal of prediction modelling studies. [12] The checklist contains 11 domains of critical appraisal. The methodological quality of each study was independently evaluated by two reviewers and by a third reviewer if consensus was not reached. The methodological quality of each impact analysis study was also independently assessed, using an appropriate quality assessment checklist. RCTs were assessed using the Cochrane risk of bias tool and controlled before-after studies were evaluated using Cochrane criteria for these study designs. [13]

Statistical analysis

Statistical analysis was conducted using Stata version 12 (StataCorp., College Station, Texas, USA). For each CPR, a standard cut point was identified (Table 1). From each included study we extracted (where available) the numbers of true positives, false positives, true negatives, false negatives, sensitivity and specificity and their corresponding 95% confidence intervals (95% CIs). Where sensitivity/specificity for more than one observer was reported, the mean value was included in the analysis. Studies were grouped for analysis by CPR type (i.e. clinical or dermoscopic).

Individual and summary estimates of sensitivity and specificity were plotted on a receiver-operating characteristic (ROC) graph. Sensitivity (true positive) was graphed on the y-axis and 1-specificity (false negative) on the x-axis. The 95% confidence region and the 95% prediction region were also plotted around the pooled estimates in order to depict the precision with which the pooled estimates were determined (confidence ellipse around the mean value) and to illustrate the amount of between-study variation (prediction ellipse).

Results

Study Selection

The search strategy yielded a total of 25,816 articles. Of these 9,481 were duplicates and 16,166 were deemed irrelevant based on title/abstract. The remaining 171 were reviewed in full with 51 meeting the inclusion criteria (Appendix 2). From these, 24 unique melanoma CPRs were identified (Table 1). Twelve papers reported both derivation and validation studies, 36 were validation studies only and three were impact analyses.

Summary of studies

Table 2 summarises the characteristics of the included studies. The majority (11, 22%) were conducted in Italy [5,6,14-23] and ranged from an analysis of 40 lesions to 1,580 lesions. From 13 studies providing information, mean age of included patients ranged from 36.7 to 53 [14,17,20,24-33]. From the 14 studies that reported gender, the proportion of males ranged from 22-60% [14,20,22,24-34]. Thirty-one of the 50 studies were published in or after 2000 [5,14,17,18,20-26,31-33,35-51]. Five studies were set in primary care [25,33,38,51,52], with the remainder undertaken in specialist outpatient settings.

Summary of CPRs identified

Of the 24 rules identified, four were clinical (i.e. naked eye), 17 were dermoscopic and the remaining three utilised novel diagnostic technologies. The most commonly applied clinical CPR was the ABCDE rule (5 studies) [2,6,17,53,54], while for dermoscopy the most common were the ABCD rule of dermoscopy (23 studies) [5,14,15,18,20,21,28,31,32,36-38,41,42,46,54-59] and the 7 point checklist for dermoscopy (17 studies)[5,14,15,18,24,26,31,32,35-39,41,45,46,48].

Each of the elements included in the 24 rules identified are presented in Table 3.a and 3.b. All four clinical rules included the elements of diameter and colour variegation (Table 3Table 3.a and Appendix 1). The most frequently included elements in the 17 dermoscopic rules

were multiple colours (13 rules), asymmetry (12 rules), and streaks (10 rules) (**Error! Reference source not found.**Table 3.b and Appendix 1).

Methodological quality of validation studies

Based on the CHARMS checklist, the quality of included studies varied.[12] None of the studies reported on missing data. Full results of the quality assessment are shown in Appendix 3.

Predictive accuracy of melanoma CPRs

The results for the most commonly applied CPRs, the ABCD rule and the 7 point checklist are presented here. The sensitivity and specificity of all rules identified (including the ABCDE clinical rule, the 7 features for melanoma rule and Menzies dermoscopy for melanoma rule) are summarised in Table 4.

Clinical (naked-eye) CPRs for melanoma diagnosis

Four studies validating the ABCDE clinical rule [2,6,17,53] and one validating the ABCD clinical rule [54] were included. There was insufficient data to conduct any meta-analysis. Rao et al reported a sensitivity of 0.84 and specificity of 0.78, for an unspecified cut-point.[54]

Six studies validating the original and revised 7 point checklist were included. The data was not of sufficient quality for meta-analysis. Of the four studies validating the original 7 point checklist (cut-point ≥ 3), three reported sensitivity (range 0.44-0.86, mean 0.70) and specificity (range 0.62-0.94, mean 0.74)[29,30,33]. Only one of the four studies validating the revised 7 point checklist (cut-point ≥ 1) reported sensitivity (0.92) and specificity (0.33) (Table 4).[33]

Dermoscopic CPRs for melanoma diagnosis

ABCD rule of dermoscopy

The ABCD rule of dermoscopy (also described as the ABCD rule of Stolz), was validated in 23 studies, 15 of which applied a cut point of >4.75 (indicating a suspicious lesion) and 6 studies a cut-point of 5.45 (highly suggestive for melanoma). At a cut point of >4.75, 8 studies provided sufficient information for meta-analysis, [31,32,36,41,54,60] resulting in a pooled sensitivity of 0.85 (95% CI 0.73-0.93) and specificity of 0.72 (95% CI 0.65-0.78) (Figure 1.a and Appendix 4). This indicates that at this cut point, the dermoscopy CPR is more useful for ruling out rather than ruling in melanoma, with a higher pooled sensitivity than specificity. I^2 were high (>70%), indicating a high degree of heterogeneity. Of the seven studies excluded from meta-analysis, sensitivity ranged from 0.71-0.91 (mean 0.79) and specificity ranged from 0.43-0.92 (mean 0.72). None of the six studies that applied a cut-point of 5.45 were suitable for meta-analysis. From 4 studies that presented the information, sensitivity ranged from 0.73-0.98 (mean 0.85) and specificity ranged from 0.46-0.91 (mean 0.79) (Table 4).

7 point checklist for dermoscopy

The 7 point checklist for dermoscopy was validated in 18 studies, 17 of which applied a cut point of 3. 11 studies provided sufficient information for meta-analysis, revealing a pooled sensitivity of 0.77 (95% CI 0.61-0.88) and pooled specificity of 0.80 (95% CI 0.59-0.92) (See figure 1.b and appendix 5). [14-16,24,26,31,32,36,39,41,60] There was a high degree of heterogeneity in the results (I^2 >90%). Removing two outliers [16,39] made minimal difference to the pooled result. Only one study validated the revised 7 point checklist for dermoscopy and reported sensitivity 0.78 and specificity 0.65 for a cut point of 3 (Table 4).[16]

Impact analysis

We identified three unique studies that examined the impact of a melanoma CPR on processes of care (melanoma diagnosis and referrals), however, no patient outcomes were examined (Table 2). [51,52] The methodological quality of these studies is presented in Appendix 6.

Using a controlled before and after design, Westerhoff et al investigated the impact of an educational intervention about the Menzies 1996 rule on melanoma diagnosis by Family Physicians (FP). The control group did not receive the training. Post-intervention, there was

a significant improvement in melanoma diagnosis (75.9% vs 62.7%, P < .001). No significant improvement was seen in the control group (54.8% vs 53.7%, P = .59). [51]

Walter et al. conducted a RCT to compare the use of a new imaging device, the MoleMate system (SIAscopy with a primary care scoring algorithm), to current best practice (clinical history, naked eye examination, seven point checklist). The authors found no difference between these two approaches in terms of appropriate referrals (the proportion of referred lesions that secondary care experts biopsied or monitored) to urgent skin cancer clinics (intervention 56.8% v control 64.5% *P* = 0.11) or the proportion of benign lesions appropriately managed in primary care (intervention 99.6% v control 99.2%, P=0.46). [52]

Argenziano et al's RCT [61], involved primary care physicians first attending a 1-day training course describing the ABCD rule (cut point unspecified) and the 3-point checklist. They were then randomly assigned to assess patients with skin lesions, either by clinical (i.e. naked eye) examination, or by dermoscopy using the 3-point checklist. The referral assessments were checked for accuracy by dermatologists. The dermoscopy arm demonstrated a 25% improvement in the sensitivity of primary care referrals of pigmented lesions compared with the naked-eye examination (79.2% vs 54.1%, *P* = 0.002), without a reduction in specificity (71.8% vs 71.3%, *P* =0.915) [61].

Discussion

Summary of findings

This systematic review identified 48 studies validating a total of 24 CPRs for melanoma. Overall, the majority of validation studies utilised dermoscopic CPRs, with very few studies validating clinical CPRs. Meta-analysis of the dermoscopic CPRs demonstrated relatively high pooled estimates of sensitivity (0.77-0.86). The clinical implication is that applying dermoscopy CPRs will enable low risk patients to be observed and kept under review in a primary care setting, without immediate referral for excision to secondary care. Meta-analysis was not possible for clinical CPRs but individual studies report variable sensitivity, ranging from 0.44-0.86. Three impact analysis studies were identified, with two reporting an improvement in melanoma diagnosis with the use of a CPR.

Context of previous research

The sensitivities and specificities we report indicate that currently available CPRs are reasonably good at ruling out melanoma. The pooled sensitivity of the ABCD rule for dermoscopy (cutpoint of >4.75) was 0.85 (95% CI 0.73-0.93), higher than that of the seven point checklist (0.77, 95% CI 0.61-0.88). While this evidence would support the use of such rules in prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients, there are a number of important caveats that may prevent their adoption in primary care.

Melanoma is a high stakes condition, one which doctors tend to be cautious in diagnosing, often preferring to excise a benign lesion rather than to miss a potentially fatal cancer.[62] In such cases, a CPR with near perfect sensitivity would be desirable, however, it has been argued that a lower sensitivity should not prevent CPR use unless usual decisions, made without the rule, are demonstrably better. [63] Our results are comparable with previous systematic reviews focused on melanoma diagnosis across healthcare settings in highlighting that dermoscopic CPRs are demonstrably better in terms of diagnostic accuracy in comparison with inspection by the naked eye. [7,64] However, even a rule with almost 100% sensitivity such as the Canadian CT Head Rule may not be adopted for fear of missing a high-stakes diagnosis. [65]

Before considering whether to use a CPR in clinical practice, it is essential that its performance be established through external validation (i.e. in settings outside where it was derived). We identified a number of external validation studies in this review, however, in keeping with much CPR research, the reporting of these studies was often poor.[66,67] In particular, the common issues of limited acknowledgement and handling of missing data and key performance measures of prediction models i.e. calibration, being omitted was encountered.[66] The lack of available data in some papers meant not all studies could be combined in the meta-analysis, meaning the sensitivities and specificities reported here are not based on totality of existing evidence. Furthermore, we were unable to assess diagnostic accuracy at different cut-point thresholds for respective CPRs. Improved reporting of CPRs at cut-point thresholds will enable pooling of diagnostic accuracy data, and will provide more robust measures of diagnostic accuracy. After validation, impact analysis studies are undertaken to determine the impact of the implementation of a CPR on processes and outcomes of care. Despite increasing interest in developing and validating CPRs relevant to primary care, relatively few have undergone impact analysis. [68] Despite the large number of CPRs identified in this review, we identified only three impact analysis studies, with only two studies reporting an improvement in correct melanoma diagnosis in primary care as a result. Arguably, the dearth of well-conducted and clearly reported external validation and impact analysis studies undermines trust in the use of such rules in practice. [66]

Current NICE guidelines for melanoma detection and management recommend dermoscopy of any suspicious lesion, advising against using computer assisted diagnostic tools.[11] Based on the findings of this review, the ABCD rule for dermoscopy had a higher sensitivity than the seven point checklist at their respective cut-points, indicating its potential for use in primary care. Dermoscopy, however, requires training and equipment, and is less commonly performed in primary care. Evidence suggests that dermatologists have better diagnostic accuracy than primary care physicians. [9] Three studies retrieved in our search assessed dermoscopy CPR performance when applied by non-experts, with two studies reporting that the CPRs performed well overall when used by non-experts, mainly primary care physicians. [38,55,61] Both Westerhoff et al [51]and Argenziano et al [69] demonstrated that training primary

care physicians to use dermoscopy with CPRs showed significant improvement in the diagnosis of melanoma compared with naked eye inspection Alongside the use of CPRs, training in dermoscopy would seem to be a strategy that will enhance diagnostic accuracy of melanoma in the future. Of the 24 rules identified in this review, four were clinical (i.e. naked eye) and 17 were dermoscopic. Due to the limited number of studies and available data, no meta-analysis of clinical CPRs could be conducted. The range of reported sensitivities from individual studies indicates that there is insufficient evidence to recommend their use in practice.

Strengths and limitations of our study

The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. However, the findings of this systematic review need to be interpreted in the context of the limitations of the original studies. The lack of available data in some papers meant not all studies could be combined in the meta-analysis. A number of studies that validated CPRs and algorithms using novel diagnostic technologies which incorporated computerised image analysis and artificial intelligence were excluded from the review as routine use of these is not currently recommended in UK NICE clinical guidelines.

Implications for practice and future research

Early detection followed by curative surgery greatly improves the prognosis of malignant melanoma. As the incidence of melanoma skin cancer increases, primary care physicians are increasingly required to screen for melanoma.[3] Therefore, efforts to increase the early detection of melanoma must focus on supporting primary care physicians in performing skin cancer screenings.[9] This systematic review identified 24 separate clinical (naked eye) and dermoscopic CPRs, with some overlap in the included the elements. Our analysis highlights that dermoscopic CPRs have reasonable sensitivity, with the ABCD rule for dermoscopy

having better sensitivity than the seven point checklist for dermoscopy. Further development of new rules is unlikely to benefit the field of research. An increased emphasis on better reporting of validation studies, particularly at different cut-point thresholds, would allow for the conduct of more robust diagnostic accuracy meta-analysis to inform decision making. Further methodologically robust randomised controlled trials are necessary also to examine the impact of implementing CPRs in clinical practice, in terms of patient outcomes, physician behaviour, processes of care, and cost-effectiveness. Lastly, whilst guidelines promote the use of dermoscopy in the assessment of pigmented skin lesions, there needs to be greater emphasis on training in primary care on this examination technique.

Conclusion

This systematic review and meta-analysis shows that dermoscopic CPRs have reasonably high pooled estimates of sensitivity and may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients. The ABCD rule of dermoscopy has higher pooled sensitivity than the 7 point checklist for dermoscopy, when consideration about ruling out melanoma is being made. A focus on impact analysis may help translate melanoma CPRs into useful and effective triage tools for use in primary care.

Footnotes

Contributors: EH, NW, and BC drafted the manuscript. EH, NW, and BC contributed to development of the selection criteria, the risk of bias assessment strategy, and the data extraction criteria. EH and PM developed the search strategy. HB, LA, and HS contributed the data extraction and quality assessments. BC and TF read, provided feedback and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Data Sharing

No additional data available

References

1. Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *Journal of the European Academy of Dermatology and Venereology : JEADV.* Sep 2014;28(9):1170-1178.
2. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology.* 1998;197(1):11-17.
3. Koelink CJL, Kollen BJ, Groenhof F, van der Meer K, van der Heide WK. Skin lesions suspected of malignancy: an increasing burden on general practice. *BMC Fam Pract.* 2014;15:29.
4. Pockney P, Primrose J, George S, et al. Recognition of skin malignancy by general practitioners: observational study using data from a population-based randomised controlled trial. *Br J Cancer.* Jan 13 2009;100(1):24-27.
5. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. *Journal of the American Academy of Dermatology.* 2003;48(5):679-693.
6. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. *Eur J Dermatol.* Sep 1999;9(6):470-476.
7. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* Mar 2002;3(3):159-165.
8. Piccolo D, Ferrari A, Peris K, Diadone R, Ruggeri B, Chimenti S. Dermoscopic diagnosis by a trained clinician vs. a clinician with minimal dermoscopy training vs. computer-aided diagnosis of 341 pigmented skin lesions: a comparative study. *Br J Dermatol.* Sep 2002;147(3):481-486.
9. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and Managing Cutaneous Pigmented Lesions: Primary Care Physicians Versus Dermatologists. *Journal of General Internal Medicine.* 2006;21(7):678-682.
10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews.* 2015;4(1):1-9.
11. Macbeth F, Newton-Bishop J, O'Connell S, Hawkins JE. Melanoma: summary of NICE guidance. *BMJ.* 2015-07-29 09:46:21 2015;351.
12. Moons KGM dGJ, Bouwmeester W, Vergouwe, Y., Mallett, S., Altman, D. G., Reitsma J.B., Collins, G. S. Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist. *PLoS Medicine.* 2014;11(10):e1001744.
13. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: updated March 2011.* 2011.
14. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. *Journal of the American Academy of Dermatology.* 2007;56(5):759-767.
15. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions:

Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Archives of Dermatology.* 1998;134(12):1563-1570.

16. Argenziano G, Catricalà C, Ardigo M, et al. Seven-point checklist of dermoscopy revisited. *British Journal of Dermatology.* 2011;164(4):785-790.
17. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. *Eur J Dermatol.* Jun 2000;10(4):282-287.
18. Carli P, Quercioli E, Sestini S, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. *British Journal of Dermatology.* 2003;148(5):981-984.
19. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. *European Journal of Dermatology.* 1999;9(4):303-308.
20. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. *European Journal of Dermatology.* 2014;24(4):477-481.
21. Pizzichetta MA, Talamini R, Piccolo D, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. *Tumori.* 2002;88(3):234-238.
22. Soyer HP, Argenziano G, Zalaudek I, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. *Dermatology.* 2004;208(1):27-31.
23. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. *Melanoma Research.* 2003;13(6):631-632.
24. Buhl T, Hansen-Hagge C, Korpas B, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. *Journal of the American Academy of Dermatology.* 2012;66(1):27-36.
25. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. *BMC Dermatology.* 2010;10:9-9.
26. Haenssle HA, Korpas B, Hansen-Hagge C, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. *Journal of the American Academy of Dermatology.* 2010;62(5):785-793.
27. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. *Clinical and Experimental Dermatology.* 1992;17(5):313-315.
28. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. *Journal of the American Academy of Dermatology.* 1999;40(4):558-562.
29. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. *Clinical and Experimental Dermatology.* 1990;15(3):167-171.
30. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's

ABCDs of pigmented lesions. *Journal of Dermatologic Surgery and Oncology.* 1992;18(1):22-26.

31. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. *Archives of Dermatology.* 2005;141(2):155-160.
32. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. *Journal of Dermatology.* 2014;41(7):598-603.
33. Walter FM, Prevost AT, Vasconcelos J, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. *British Journal of General Practice.* 2013;63(610):345-353.
34. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. *British Journal of Dermatology.* 1999;140(5):902-908.
35. Argenziano G, Longo C, Cameron A, et al. Blue-black rule: A simple dermoscopic clue to recognize pigmented nodular melanoma. *British Journal of Dermatology.* 2011;165(6):1251-1255.
36. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. *Journal of the American Academy of Dermatology.* 2003;48(5):672-678.
37. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. *British Journal of Dermatology.* 2004;151(5):1029-1038.
38. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. *Archives of Dermatology.* 2005;141(8):1008-1014.
39. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. *International Journal of Dermatology.* 2010;49(1):33-38.
40. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. *Australasian Journal of Dermatology.* 2012;53:7-8.
41. Henning JS, Stein JA, Yeung J, et al. CASH algorithm for dermoscopy revisited. *Arch Dermatol.* Apr 2008;144(4):554-555.
42. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. *Acta Derm Venereol.* Mar-Apr 2000;80(2):122-126.
43. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. *British Journal of Dermatology.* 2012;167(5):1037-1041.
44. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. *British Journal of Dermatology.* 2002;146(3):481-484.

45. Menzies SW, Kreusch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Archives of Dermatology.* 2008;144(9):1120-1127.
46. Menzies SW, Moloney FJ, Byth K, et al. Dermoscopic evaluation of nodular melanoma. *JAMA Dermatology.* 2013;149(6):699-709.
47. Argenziano G, Soyer HP, Chimenti S, Ruocco V. Impact of dermoscopy on the clinical management of pigmented skin lesions. *Clin Dermatol.* May-Jun 2002;20(3):200-202.
48. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference.* 2011;2011:3180-3183.
49. Zalaudek I, Argenziano G, Soyer HP, et al. Three-point checklist of dermoscopy: An open internet study. *British Journal of Dermatology.* 2006;154(3):431-437.
50. Walter FM, Prevost AT, Vasconcelos J, et al. The diagnostic accuracy of the 7-point checklist to assess pigmented skin lesions in primary care. *Asia-Pacific Journal of Clinical Oncology.* 2012;8:311.
51. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. *British Journal of Dermatology.* 2000;143(5):1016-1020.
52. Walter FM, Morris HC, Humphrys E, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. *BMJ (Online).* 2012;345(7866).
53. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. *British Journal of Dermatology.* 1994;130(1):48-50.
54. Rao BK, Marghoob AA, Stolz W, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. *Skin Research and Technology.* 1997;3(1):8-14.
55. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. *Journal of the American Academy of Dermatology.* 1999;40(2 I):171-176.
56. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. *Hautarzt.* 1998;49(6):473-476.
57. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. *Acta Dermato-Venereologica.* 1999;79(6):469-472.
58. Nachbar F, Stolz W, Merkle T, et al. The ABCD rule of dermatoscopy. *Journal of the American Academy of Dermatology.* 1994;30(4):551-559.
59. Stolz W, Riemann A, Cognetta AB, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. *European Journal of Dermatology.* 1994;4(7):521-527.
60. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. *British Journal of Dermatology.* 2004;150(5):1040.
61. Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy Improves Accuracy of Primary Care Physicians to Triage Lesions Suggestive of Skin Cancer. *Journal of Clinical Oncology.* April 20, 2006 2006;24(12):1877-1882.

62. Carli P, Nardini P, Crocetti E, De Giorgi V, Giannotti B. Frequency and characteristics of melanomas missed at a pigmented lesion clinic: a registry-based study. *Melanoma research.* Oct 2004;14(5):403-407.
63. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med.* Feb 7 2006;144(3):201-209.
64. Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. *Br J Dermatol.* Sep 2009;161(3):591-604.
65. Stiell IG, Clement CM, Grimshaw JM, et al. A prospective cluster-randomized trial to implement the Canadian CT Head Rule in emergency departments. *CMAJ : Canadian Medical Association Journal.* 2010;182(14):1527-1532.
66. Collins GS, de Groot JA, Dutton S, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology.* 2014;14(1):1-11.
67. Riley RD, Ensor J, Snell KIE, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ.* 2016-06-22 12:16:05 2016;353.
68. Wallace E, Uijen MJM, Clyne B, et al. Impact analysis studies of clinical prediction rules relevant to primary care: a systematic review. *BMJ Open.* 2016;6(3).
69. Blum A, Clemens J, Argenziano G. Modified dermoscopic algorithm for the differentiation between melanocytic and nonmelanocytic skin tumors. *Journal of Cutaneous Medicine and Surgery.* 2006;10(2):73-78.
70. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. *Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society.* 1992;Suppl 2:295-298.
71. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Archives of Dermatology.* 1996;132(10):1178-1182.
72. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. *British Journal of Dermatology.* 1994;130(3):349-355.

Table 1 CPRs identified for inclusion with cut points for identification of melanoma

Rule name	Cut point used	Number of validation studies
Clinical rules		
ABCDE clinical rule	≥ 1 or ≥ 2	4
ABCD clinical rule	≥ 1	4
Revised 7 point checklist (clinical)	≥ 3	4
7 point checklist (clinical)	≥ 3	4
Dermoscopic rules		
ABCD rule of dermoscopy*	≥ 4.75	15
	≥ 5.45	6
	≥4.2	1
	Not reported	1
7-point checklist for dermoscopy	≥ 3	17
Menzies 1996 dermoscopy for melanoma	≥ 1, no negative features	8
3-point checklist for dermoscopy	≥ 1	6
7 features for melanoma (7FFM)	≥ 2	5
CASH dermoscopy algorithm	≥ 8	3
ABCDE rule (dermoscopy)	Not reported	2
The 3 colour dermoscopy test	≥ 3	2
Revised 7-point checklist for dermoscopy	≥ 1	1
Kreusch 1992 dermoscopy	Not reported	1
Nilles 1994 dermoscopy	Not reported	1
Menzies 2008 dermoscopy for melanoma	≥ 1	1
DynaMel algorithm	≥ 3	1
Menzies 2008 dermoscopy for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	1
Simplified ABC-point list for dermoscopy	≥ 4	1
AC rule for dermoscopy	Not reported	1
Emery 2010 SIAscopy	≥ 6	1
Guitera RCM 2012	Not reported	1
Digital dermoscopy algorithms	Multiple algorithms, different cutoffs.	1

* Score = (A score x 1.3) + (B score x 0.1) + (C score x 0.5) + (D score x 0.5)

Table 2 Characteristics of validation and impact analysis studies included

Validation Studies						
Author Year Country	**Setting**	**CPR utilised**	**Lesions**	**Patient: n, sex, mean age**	**CPR applied by: n, experience**	**Reported sensitivity/specificity**
Annessi 2007[14] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	198 96 melanomas, 102 nonmelanoma	N = 195 54% male Mean age: 43	2 ELM-experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 84.4 Sp: 74.5 7-point checklist for dermoscopy (cut point ≥3) Se: 78.1 Sp: 64.7
Argenziano 1998[15] Italy	Deparment of Dermatology	7-point checklist for dermoscopy ABCD rule of dermoscopy	342 117 melanoma, 225 nonmelanoma	NR	5 3 experienced 2 less-experienced	7-point checklist for dermoscopy (cut point ≥3) *Expert user:* Se: 95.0 Sp: 75.0 *Non-expert user (mean):* Se: 89.0 Sp: 61.5 ABCD rule of dermoscopy (cut point ≥4.75) *Expert user:* Se: 85.0 Sp: 66.0 *Non-expert user (mean):* Se: 91.5

						Sp: 31.0
Argenziano 2003[5] 9 countries	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	108	NR	40 experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 82.6 Sp: 70.0 7-point checklist for dermoscopy Se: 85.7 Sp: 71.1 Menzies 1996 dermoscopy for melanoma Se: 85.7 Sp: 71.1
Argenziano 2011[16] Italy	Deparment of Dermatology	7-point checklist for dermoscopy Revised 7-point checklist for dermoscopy	300 100 excised melanoma, 100 excised nonmelanoma, 100 nonexcised nonmelanoma	NR	8 experienced	7-point checklist for dermoscopy (cut point ≥3) Se: 77.9 Sp: 85.6 Revised 7-point checklist for dermoscopy (cut point ≥1) Se: 87.8 Sp: 74.5
Benelli 1999[6] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	401 60 melanomas, 341 nonmelanoma	NR	2 research team	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 80.0 Sp: 89.1 ABCDE Clinical rule (cut point

						≥2) Se: 85.0 Sp: 44.5
Benelli 2000[17] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	600 76 melanomas, 524 nonmelanoma	Mean age: 53	3	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 68.8 Sp: 86.0 ABCDE Clinical rule (cut point of ≥2) Se: 47.3 Sp: 56.0
Binder 1999[55] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	250	NR	17 12 experienced 5 trainee	ABCD rule of dermoscopy (cut point ≥4.75) Se: 81.0 Sp: 77.0 ABCD rule of dermoscopy (cut point ≥5.45) Se: 73.0 Sp: 90.0
Blum 2003[60] Germany	Deparment of Dermatology	The 3 colour dermoscopy test	249	NR	NR	The 3 colour dermoscopy test Se: 76.9 Sp: 90.1
Blum 2004[36] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma Simplified ABC-point list for	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy

		dermoscopy 7FFM (7 features for melanoma) dermoscopy				Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8 7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6 Simplified ABC-point list for dermoscopy Se: 90.5 Sp: 87.0
Blum 2004[37] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma 7FFM (7 features for melanoma) dermoscopy	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8

						7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6
Buhl 2012[24] Germany	Deparment of Dermatology	DynaMel Algorithm 7-point checklist for dermoscopy	675	N= 688 57% male Mean age: 42	Dermatology residents	DynaMel Algorithm Se: 77.1 Sp: 98.1 7-point checklist for dermoscopy (cut point ≥3) Se: 47.5 Sp: 99.0
Carli 2002[18] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	200 44 melanomas, 156 nonmelanoma	NR	5 dermatology residents	ABCD rule of dermoscopy (cut point ≥5.45) Se: 88.1 Sp: 45.7 7-point checklist for dermoscopy (cut point ≥3) Se: 91.9 Sp: 35.2
Dal Pozzo 1999[19] Italy	Department of dermatology	7FFM (7 features for melanoma) dermoscopy	713 168 melanomas, 545 nonmelanoma	NR	3	7FFM (7 features for melanoma) dermoscopy Se: 94.6 Sp: 85.5
Dolianitis 2005[38] Australia	Primary care and Dermatology department	7-point checklist for dermoscopy ABCD rule of dermoscopy Menzies 1996 dermoscopy for	40 20 melanomas, 20 nonmelanoma	NR	61 35 Primary care physicians, 10	7-point checklist for dermoscopy Se: 81.4 Sp: 73.0

		melanoma			dermatologists, 16 trainee dermatologists	ABCD rule of dermoscopy (cut point ≥5.45) Se: 77.5 Sp: 80.4 Menzies 1996 dermoscopy for melanoma Se: 84.6 Sp: 77.7
Emery 2010[25] UK	Family practice	Emery 2010 SIAscopy in primary care for melanoma	1211	N=858 52% male Mean age: 50	1 SIAscopy expert	Emery 2010 SIAscopy in primary care for melanoma Se: 50.0 Sp: 84.0
Feldman 1998[56] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	500 30 melanomas, 470 nonmelanoma	NR	NR	ABCD rule of dermoscopy (cut point ≥4.2) Se: 88.0 Sp: 64.0
Gereli 2010[39] Turkey	Deparment of Dermatology	7-point checklist for dermoscopy 3-point checklist for dermoscopy	96 48 melanoma, 48 nonmelanoma	NR	3 2 experienced 1 inexperienced	7-point checklist for dermoscopy (cut point ≥3) Se: 87.5 Sp: 16.2 3-point checklist for dermoscopy (cut point ≥2) Se: 89.6 Sp: 31.2
Guitera 2012[40] Multiple	Skin cancer clinic	Guitera 2012 confocal microscopy for melanoma	710 216 melanomas, 494 nonmelanoma	N = 663	NR	Guitera 2012 confocal microscopy for melanoma Se: 87.6

						Sp: 70.8
Haenssle 2010[26] Germany	Deparment of Dermatology	7 point checklist for dermoscopy	1219 127 melanomas, 1092 nonmelanoma	N= 688 57% male Mean age: 42	Inexperienced	7 point checklist for dermoscopy (cut point ≥3) Se: 62.0 Sp: 97.0
Healsmith 1993[53] UK	Pigmented lesion clinic	Revised 7-point checklist (clinical) ABCDE clinical rule	165 65 melanoma, 100 nonmelanoma	NR	NR	Revised 7-point checklist (clinical) Se: 100 Sp: nr ABCDE clinical rule Se: 92.3 Sp: nr
Henning 2008[41] USA	Deparment of Dermatology	CASH dermoscopy algorithm ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	150 50 melanoma, 100 nonmelanoma	NR	2 Inexperienced	CASH dermoscopy algorithm Se: 87.0 Sp: 67.0 ABCD rule of dermoscopy Se: 86.0 Sp: 74.0 7-point checklist for dermoscopy Se: 76.0 Sp: 57.0 Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 38

Higgins 1992[27] UK	Deparment of Dermatology	7 point checklist (clinical) 7 point checklist (clinical) revised	100 0 melanoma, 100 nonmelanoma	N=100 30% male Mean age: 36.7	NR	7 point checklist (clinical) revised Se: NR Sp: 70.0
Kittler 1999[28] Austria	Deparment of Dermatology	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	356 73 melanomas, 283 nonmelanoma	N= 352 43% male Mean age: 52	NR	NR
Keefe 1989[29] Scotland	Hospital dermatology clinic	7-point checklist (clinical)	222	N=195 22% male Mean age: 43	Dermatologists 195 patients	7-point checklist (clinical) (cut point ≥3) *Dermatologists:* Se: 85.7 Sp: 66.5 *Patients:* Se: 71.4 Sp: 66.2
Kreusch 1992[70] Germany	Deparment of Dermatology	Kreusch 1992 dermoscopy for melanoma	317 96 melanomas, 221 nonmelanoma	NR	2 1 experienced 1 inexperienced	Kreusch 1992 dermoscopy for melanoma *Experienced:* Se: 98.9 Sp: 94.1 *Inexperienced:* Se: 97.0 Sp: 94.2
Lorentzen 1999[57] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	232	NR	8 4 experienced 4 inexperienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 59.0 Sp: 92.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 41.0 Sp: 98.0
Lorentzen 2000[42] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	258 64 melanoma, 194 nonmelanoma	NR	3 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 70.7 Sp: 88.0
Luttrell 2012[43] Austria	Deparment of Dermatology	AC rule for dermoscopy	200 25 melanoma, 178 nonmelanoma	NR	17 Lay persons	AC rule for dermoscopy Se: 91.2 Sp: 94.0
Mackie 2002[44] Scotland	Pigmented lesion clinic	The 3 colour dermoscopy test	126 69 melanoma 57 nonmelanoma	NR	3 Experienced	The 3 colour dermoscopy test Se: 97.0 Sp: 55.0
McGovern 1992[30] USA	Dermatology clinic	7 point checklist (clinical) BCD clinical rule	237 16 malignant, 221 nonmelanoma	N=179 50% male Mean age: 44	NR	7 point checklist (clinical) Se: 0.44 Sp: 0.94
Menzies 1996[71] Australia	Melanoma unit	Menzies 1996 dermoscopy for melanoma	385 107 melanomas,	NR	NR	Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 71.0
Menzies 2008[45]		7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma Menzies 2008 dermoscopy for melanoma Menzies 2008 dermoscopy for skin cancer	497 105 melanomas, 392 nonmelanoma	NR	12 Experienced	7-point checklist for dermoscopy Se: 41.0 Sp: 83.0 3-Point checklist of dermoscopy Se: 50.0 Sp: 71.0 Menzies 1996 dermoscopy for melanoma

						Se: 54.0 Sp: 76.0 Menzies 2008 dermoscopy for melanoma Se: 70.0 Sp: 56.0 Menzies 2008 dermoscopy for skin cancer Se: 95.0 Sp: 80.0
Menzies 2013[46]		ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma CASH dermoscopy algorithm Menzies 2013 dermoscopy for nodular melanoma	465 217 melanomas, 248 nonmelanoma	NR	12	ABCD rule of dermoscopy Se: 81.5 Sp: NR 7-point checklist for dermoscopy Se: 94.4 Sp: NR 3-Point checklist of dermoscopy Se: 83.9 Sp: NR Menzies 1996 dermoscopy for melanoma Se: 98.4 Sp: NR CASH dermoscopy algorithm

						Se: 41.0 Sp: 83.0 Menzies 2013 dermoscopy for nodular melanoma Se: 93.0 Sp: 70.0
Nachbar 1994[58] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	194 69 melanomas	NR	NR	ABCD rule of dermoscopy (cut point ≥5.45) Se: 92.8 Sp: 91.2
Nilles 1994[72] Germany	Deparment of Dermatology	Nilles 1994 dermoscopy for melanoma	260 72 melanomas, 188 nonmelanoma	NR	NR	Nilles 1994 dermoscopy for melanoma Se: 90.0 Sp: 85.0
Osborne 1999[34] UK	Deparment of Dermatology	Revised 7-Point Checklist (clinical)	778 778 melanomas, 0 nonmelanoma	N=733 35% male	NR	Revised 7-Point Checklist (clinical) False negative rate: 18.5
Piccolo 2014[20] Italy	Deparment of Dermatology	ABCD rule of dermoscopy	165 33 melanomas, 129 nonmelanoma	N =165 59% male Mean age: 43.5	4 3 dermatologists 1 FP	ABCD rule of dermoscopy Se: 91.0 Sp: 52.0
Pizzichetta 2002[21] Italy	Department of Oncology	ABCD rule of dermoscopy	129	N = 123	2 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 43.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 90.0 Sp: 53.5
Rao 1997[54]	Deparment of Dermatology	ABCD rule of dermoscopy ABCD clinical rule	73	N =63	4 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 57.0 ABCD clinical rule Se: 84.0 Sp: 78.0
Skvara 2005[31] Austria	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	325 63 melanomas, 262 nonmelanoma	N =297 44% male Mean age: 39	2 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 31.7 Sp: 87.3 7-point checklist for dermoscopy Se: 11.1 Sp: 95.2
Soyer 2004[22] Italy	Deparment of Dermatology	3-point checklist of dermoscopy	231 68 melanomas, 163 nonmelanomas	N = 225 49% male	6 Inexperienced	3-point checklist of dermoscopy Se: 96.3 Sp: 32.8
Stolz 1994[59] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	157	NR	NR	ABCD rule of dermoscopy(cut point ≥5.45) Se: 97.9 Sp: 90.3
Strumia 2003[23] Italy	Deparment of	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	49	NR	2	

	Dermatology					
Thomas 1998[2] France	Deparment of Dermatology	ABCDE clinical rule	1140	NR	NR	ABCDE clinical rule (cut point ≥2) Se: 89.3 Sp: 65.3
Unlu 2014[32] Turkey	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-point checklist of dermoscopy CASH dermoscopy algorithm	115 24 melanomas, 91 nonmelanoma	N= 115 49% male Mean age: 39	3 experienced dermatoscopists	ABCD rule of dermoscopy Se: 91.6 Sp: 60.4 7-point checklist for dermoscopy Se: 79.1 Sp: 62.6 3-point checklist of dermoscopy Se: 87.5 Sp: 65.9 CASH dermoscopy algorithm Se: 91.6 Sp: 64.8
Wadhawan 2011[48] USA	Images from library of skin cancer	7-point checklist for dermoscopy	347	NR	NR	7-point checklist for dermoscopy Se: 87.3 Sp: 71.3
Walter 2013[33] UK	Family practice	7 point checklist (clinical) Revised 7-point checklist (clinical)	1436 36 melanomas, 1400 nonmelanoma	N= 1182 35.9% male Mean age: 44.7	NR	7 point checklist (clinical) Se: 80.6 Sp: 61.7

						Revised 7-point checklist (clinical) Se: 91.7 Sp: 33.1
Zalaudek 2006[49] 29 Countries	Pigmented lesion clinic	3-point checklist for dermoscopy	150 44 malignant, 106 nonmelanoma	NR	150 varying levels of experience	3-point checklist for dermoscopy Se: 94.0 Sp: 71.9
Impact Analysis Sudies						
Author Year Country	**Study design**	**Participant selection**	**Lesions**	**Intervention**	**Control**	**Outcomes**
Westerhof f 2000[51] Australia Primary care	Controlled before & after	74 FPs	n=100 (50 melanoma, 50 non-melanoma) selected randomly from the Sydney Melanoma Unit image database	Educaional intervention. FPs given educational material on Menzies 1996 rule, followed by a 1-h presentation on surface microscopy	Usual care	**Correct diagnosis of melanoma, percent (SD):** Intervention 75.9 (12) Control 54.8 (22) **Correct diagnosis of non-melanoma, percent (SD):** Intervention 57.8 (14) Control 55.8(15)
Walter 2012[52] England Primary care	RCT	15 FP practices	1580 from 1297 patients	Patients assessed using the MoleMate system (SIAscopy with primary care	Best practice (clinical history, naked eye examination, seven point	**Primary, appropriateness of referral (defined as the proportion of referred lesions that secondary care experts decided to biopsy or monitor):** no statistically significant

				scoring algorithm)	checklist clinical)	difference between intervention or control; 56.8% v 64.5%; difference −8.1% (95% CI −18.0% to 1.8%). **Secondary:** • Appropriate management of benign lesions in primary care: no statistically significant difference between intervention or control (99.6% v 99.2%, P=0.46). • Agreement with an expert decision to biopsy or monitor: no statistically significant difference between intervention and control (98.5% v control 95.7%, P=0.26). • Patient satisfaction: more intervention patients ranked their consultation very good/excellent for thoroughness than control (83.1% v 71.2%, P<0.001). Patient anxiety: no statistically significant difference between intervention and control in anxiety scores (32.56 v 34.72,

						P=0.013)
Argenziano 2006 [61] Spain, Italy Primary Care	RCT	73 FPs	2548 lesions from 2522 patients presenting to primary care with a pigmented skin lesion. 1203 lesions in dermoscopy group (6 melanoma) 1345 lesions in control group (6 melanoma)	Use of dermoscopy in addition to "naked eye" lesion screening. Both groups received a 4 hour educational intervention incorporating clinical examination and use of the 3 point checklist (dermoscopy algorithm)	Naked eye screening alone.	**Primary outcome:** Referral accuracy of PCPs (defined as the ability of the PCP to correctly determine a lesion may be malignant or benign, when the gold standard is diagnosis by a second expert clinician) reported as sensitivity, specificity, PPV, NPV. • Significant difference in sensitivity (dermoscopy 79.2%, naked-eye 54.1%, P=0.002) and negative predictive value (dermoscopy 9801%, naked-eye 95.8%, P=0.004) **Secondary outcome:** Number of malignant tumours missed by PCPs using naked eye examination (n=23) and using dermoscopy (n=6) (P=0.002)

NR: Not reported
Se: Sensitivity
Sp: Specificity

Table 3.a Comparison of elements in clinical prediction rules for malignant melanoma (clinical rules)

Elements	Clinical CPR name			
	ABCD	**ABCDE**	**7 point checklist**	**Revised 7 point checklist**
Asymmetry	X	X		X
Border irregularity	X	X	X	
Colour variegation	X	X	X	X
Diameter (>6mm)	X	X	X (>7mm)	X (>7mm)
Evolving (e.g. size, shape, colour)		X	X (size)	X
Altered sensation			X	X
Inflammation			X	X
Crusting, bleeding			X	X
Cut point	*≥ 1*	*≥ 1 or ≥2*	*≥ 3*	*≥ 3*

Table 3.b Comparison of elements in clinical prediction rules for malignant melanoma (dermoscopic rules)

Elements	Clinical CPR name															
	ABCD Rule	7 point checklist	Revised 7 point checklist	Menzies 1996	3-point checklist	7 features for melanoma (7FFM)	CASH algorithm	ABCDE Rule	The 3 colour test	Kreusch 1992	Nilles 1994	Menzies 2008 dermoscopy for melanoma	Menzies 2008 dermoscopy for skin cancer	DynaMel algorithm	Simplified ABC	AC rule
Asymmetry	X			X	X	X	X	X		X	X	X		X	X	X
Multiple colours (light/dark brown, black, red, white, blue)	X	X	X	X			X	X	X	X	X	X		X	X	X
Architectural disorder (structures & colours)						X	X			X	X		X	X	X	
Atypical network	X	X	X	X	X	X	X	X						X		
Blue-white veil		X	X	X		X	X					X		X		
Blue white structures					X			X					X			
Streaks/ radial streaming/pseudo-pods	X	X	X	X		X	X	X		X	X			X		
Dots, globules	X	X	X	X			X	X				X	X	X		
Regression structures or regression erythema		X	X			X	X			X	X		X	X		
Scarring				X			X									
Blotches (structure less region >10%)	X						X	X								
Atypical vascular pattern		X	X				X			X		X	X	X		
Recognisable as benign													X			
Abrupt cut-off of border pigment pattern	X					X		X							X	
Blue-grey dots												X				
Change								X				X		X	X	
Cut point	≥ 4.75, ≥5.45	*≥ 3*	*≥ 1*	≥ 1, no negative features	*≥ 1*	*≥ 2*	*≥ 2*	*Not reported*	*≥ 3*	*Not reported*	*Not reported*	*≥ 1*	≥ 0 (high sensitivity); ≥ 1 (high specificity)	≥ 3	≥ 4	*Not reported*

Table 4 Sensitivity and specificity of all clinical and dermoscopy CPRs

Rule name	Cut point	Sensitivity *	Specificity*
Clinical rules			
ABCDE	≥ 1	*2 studies* 0.47-0.92 (mean 0.70)	*1 study* 0.56
	≥ 2	0.85	0.44
7 point checklist	≥ 3	*3 studies* 0.44-0.86 (mean 0.70)	*3 studies* 0.62-0.94 (mean 0.74)
Revised 7 point checklist	≥ 3	0.92	0.33
ABCD rule	≥ 1	0.84	0.78
Dermoscopic rules			
ABCD rule	≥ 4.75	*Meta-analysis* *(8 studies)* 0.85 (95% CI 0.73-0.93)	*Meta-analysis* *(8 studies)* 0.72 (95% CI 0.65-0.78)
	≥ 5.45	*4 studies* 0.73-0.98 (mean 0.85)	*4 studies* 0.46-0.91 (mean 0.79)
	≥4.2	0.88	0.64
7-point checklist	≥ 3	*Meta-analysis* *(11 studies)* 0.77 (95% CI 0.61-0.88)	*Meta-analysis* *(11 studies)* 0.80 (95% CI 0.59-0.92)
Menzies 1996 for melanoma	≥ 1	*6 studies* 0.85-0.95 (mean 0.91)	*6 studies* 0.38-0.78 (mean 0.69)
3-point checklist	≥ 1	*5 studies* 0.50-0.96 (mean 0.84)	*4 studies* 0.31-0.72 (mean 0.55)
7 features for melanoma (7FFM)	≥ 2	*5 studies* 0.69-0.95 (mean 0.86)	*5 studies* 0.74-0.86 (mean 0.82)
CASH algorithm	≥ 8	*3 studies* 0.41-0.92 (mean 0.73)	*3 studies* 0.65-0.97 (mean 0.82)
The 3 colour test	≥ 3	*2 studies* 0.77-0.97 (mean 0.87)	*2 studies* 0.55-0.90 (mean 0.73)
Revised 7-point checklist	≥ 1	0.88	0.28
Kreusch 1992	Not reported	0.99	0.94
Nilles 1994	Not reported	0.90	0.85
Menzies 2008 for melanoma	≥ 1	0.70	0.56
DynaMel algorithm	≥ 3	0.77	0.98
Menzies 2008 for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	0.95	0.80
Simplified ABC-point list	≥ 4	0.90	0.87
AC rule	Not reported	0.91	0.94
Emery 2010 SIAscopy	≥ 6	0.50	0.84
Guitera RCM 2012	Not reported	0.88	0.71
ABCDE rule	Not reported	Not reported	Not reported

* Where sensitivity and specificity are presented for more than one study, the range and mean are presented. Where meta-analysis was possible, values from meta-analysis are presented with 95% confidence intervals (CI).

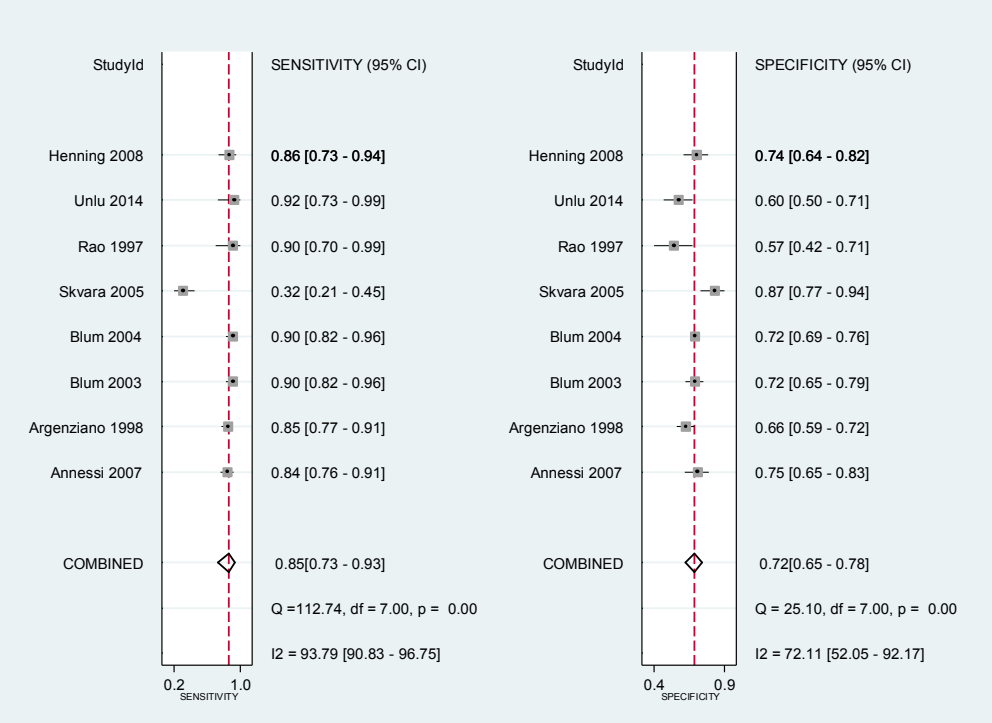


Figure 1.a Diagnostic accuracy ABCD rule with dermoscopy - pooled sensitivity and specificity (8 studies)

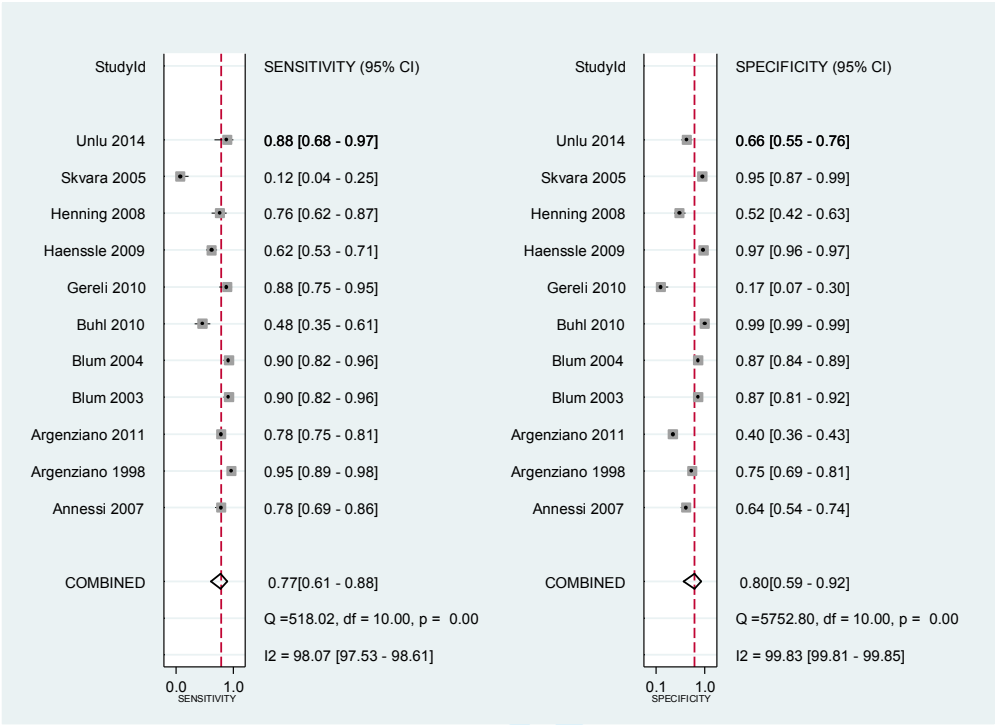


Figure 1.b Diagnostic accuracy of 7 point checklist with dermoscopy - pooled sensitivity and specificity (11 studies)

Appendix 1: Elements in Clinical Prediction Rules for cutaneous malignant melanoma

CPR name	*Clinical* **ABCD (1)**	*Clinical* **ABCDE (2)**	*Clinical* **Glasgow 7-point checklist (3)**	*Clinical* **Revised 7-point checklist (4)**	*Dermoscopy* **AC Rule for dermoscopy (5)**	*Dermoscopy* **3-point checklist (6)**
Elements	Asymmetry one half not identical to the other half	Asymmetry one half not identical to the other half	Change in size of lesion	***Major features:*** *(2 points each)* Change in size	Asymmetry score between 0 (no asymmetry) and 10 (marked asymmetry)	Asymmetry of colour and structure in one or two perpendicular axes
	Border irregularity uneven or ragged border	Border irregularity uneven or ragged border	Irregular pigmentation	Irregular pigmentation	Colour variation score between 0 (no colour variation) and 10 (marked colour variation)	Atypical pigment network with irregular holes and thick lines
	Colour variegation presence of at least 2 different colours within the lesion	Colour variegation presence of at least 2 different colours within the lesion	Irregular border	Irregular border		Blue white structures
	Diameter	Diameter	Inflammation	***Minor features:***		

	Maximum diameter > 6mm	Maximum diameter >6mm		Inflammation		
		Evolution Patient description of lesion change including elevation, enlargement or colour change	Itch or altered sensation	Itch or altered sensation		
			Larger than other lesions (diameter > 7mm)	Larger than other lesions (diameter > 7mm)		
			Oozing/crusting of lesion	Oozing/crusting of lesion		
Cut point/ specialist referral	Presence of any one element	Presence of any one element	Presence of 3 or more elements	Any one major feature OR 3 points or greater	Participant assessment of whether lesion suspicious or not (no score specified)	Presence of 2 or more elements

CPR name	*Dermoscopy* **C.A.S.H. algorithm (7)**	*Dermoscopy* **Menzies method (8)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma (9)**	*Dermoscopy* **Menzies 2008 dermoscopy for skin cancer (9)**	*Dermoscopy* **7 Features for Melanoma (7FFM) (10)**
Elements	Colour: light brown, dark brown, black, red, white, blue *(each colour=1 point)*	***Benign:*** Symmetry of pattern	**Negative features** (if present, nonmelanoma): >3 milialike cysts	**Negative features (score -1 each)** Multiple (>3) milialike cysts	***Stage 1:*** *determine whether lesion is melanocytic (pigment network or globules); if so, proceed.*
	Architectural disorder *(none=0, moderate=1, marked=2 points)*	One colour; black, grey, blue, dark brown, tan, red	**Positive features** (if any 1 present in a lesion lacking significant pigment, then melanoma): Irregularly sized or distributed brown dots/globules	Symmetrical pigmentation pattern	***Stage 2:*** ***Major features*** (2 points each): Pseudopods
	Symmetry of lesion and within lesion *(biaxial=0, monaxial symmetry=1, biaxial asymmetry=2 points)*	***Positive features:*** Blue-white veil	Multiple blue-grey dots	Comma vessels in regular distribution	Radial streaming
	Homogeneity/heterogeneity	Peripheral black	Irregularlay	Multiple brown dots	Regression-erythema

	network/ dots, globules/ streaks, pseudopods/ blue-white veil/ regression structures (grey areas with or without peppering)/ scarring/ blotches (structureless region of any colour occupying >10% of area)/ polymorphous blood vessels *each structure=1 point*	dots/globules	shaped depigmentation		
		Multiple brown dots	Blue-white veil	**Positive features (score +1 each)** Depigmentation	Grey-blue veil
		Pseudopods	>1 shade of pink	Small diameter arborizing vessels	**Minor features** (1 point each): Unhomogeneity
		Radial streaming	Predominant central vessels	Leaflike areas	Irregular pigment network
		Scarlike depigmentation	Dotted and linar irregular vessels	Ulceration	Sharp margin
		Multiple colours (5 or 6); black, grey, blue, dark brown, tan, red		Irregular size or distributed blu-grey globules	
		Multiple blue/grey dots		Grey colour	
		Broad pigment network		Large-diameter vessels	
Cut	8 points or more	Absent benign	Presence of ≥ 1	Total score ≥ 1	Score of 2 or more

point/ specialist referral		features and 1 or more positive features	positive feature		

CPR name	*Dermoscopy* **ABCD Rule of Dermoscopy/Stolz (11)**	*Dermoscopy* **7 point checklist for dermoscopy (12)**	*Dermoscopy* **Revised 7 point checklist for dermoscopy (13)**	*Dermoscopy* **Simplified ABC-point list of dermoscopy (14)**
Elements	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	***Major criteria:*** *(2 points each)* Atypical pigment network: black, brown, grey thickened and irregular line segments	*Criteria (1 point each):* Atypical pigment network: black, brown, grey thickened and irregular line segments	Asymmetry of outer shape *(1 point)*
	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Asymmetry of differential structures inside the lesion in at least 1 axis *(1 point)*
	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Border: abrupt cutoff of network at the border in at least ¼ of the circumference
	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(1 point each)*	***Minor criteria:*** *(1 point each)* Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Colour: Three or more colours *(1 point)*
		Irregular pigmentation: black,	Irregular pigmentation:	Differential structures:

		brown, grey featureless areas with irregular shape/ distribution.	black, brown, grey featureless areas with irregular shape/ distribution.	Three or more differential structures *(1 point)*
		Irregular dots/ globules: black, brown, grey round to oval, variously sized structures irregularly distributed	Irregular dots/ globules: black, brown, grey round to oval, variously sized structures irregularly distributed	Evolution: Evolution/change noticed by the patient during the last 3 months *(1 point)* No information (0) No change (-1)
(15)		Regression structures: white scarlike areas, blue pepper-like areas	Regression structures: white scarlike areas, blue pepper-like areas	
Cut point/ specialist referral	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Score of 3 or more A **revised 7 point checklist for dermoscopy** allocates 1 point for each of the above criteria and recommends excision or referral if score is 1 or greater.	Score of 1 or more	Score of 4 or more

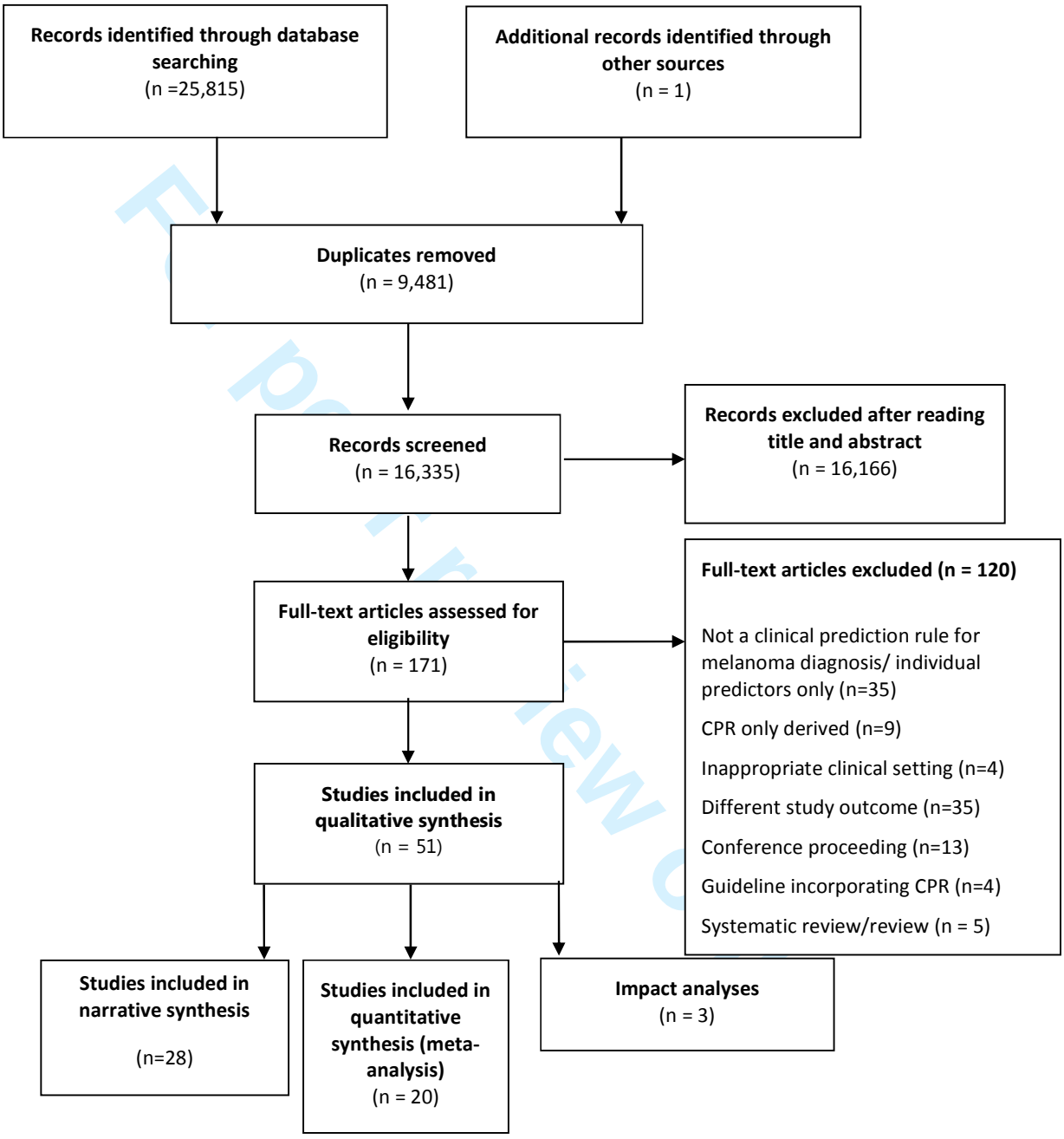
CPR name	*Dermoscopy* **Three-colour dermoscopy test (15)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma lacking significant pigment (9)**	*Dermoscopy* **ABCDE rule for dermoscopy (16)**	*Dermoscopy* **Kreusch 1992 for dermoscopy (17)**	*Dermoscopy* **Nilles 1994 for dermoscopy (18)**
Elements	Presence of 3 or more colours seen in the lesion on dermoscopy	**Negative features** (if present, not a melanoma: >3 milialike cysts	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	Diameter >5mm (1 point)	Clues for malignancy: Asymmetrical pigment distribution
		Positive features Irregularly sized or distributed brown dots or globules	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Border irregularity (1 point)	More than 3 colours
		Multiple blue/grey dots	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Loss of surface microstructure (1 point)	Asymmetrical depigmentation
		Irregularly shaped depigmentation	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(Each component=1 point)*	Scaling/erosion/ulcer (1 point)	Black pigment
		Blue-white veil	Enlargement *(Add 1.2 points if present Subtract 0.8 points if absent)*	Capillaries (1 point)	Sharp pigment border
		>1 shade of pink		Multicomponent	Atypical radial

				architecture (3 points)	streaming
		Predominant central vessels		Greyish colour (3 points)	
		Dotted and linear irregular vessels		Melanophages (6 points)	
				Pseudopods (10 points)	
				Regression (10 points)	
Cut point/ specialist referral	Presence of single element.	Presence of 1 or more positive features	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) + (E) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Not specified	Not specified

CPR name	*Dermoscopy* **DynaMel algorithm (19)**	*SIAoscopy* **Emery 2010 SIAoscopy (20)**	*Reflectance confocal microscopy* **Guitera 2012 RCM (21)**
Elements	**Dynamic major criteria:** Asymmetric-multifocal enlargement (2 points)	*If no specified features of seborrhoeic keratosis or haemangioma presen, a score is allocated for specific features seen on SIAoscopy:* Dermal melanin within the lesion (3 points)	*Reflectance confocal microscopy features:* Cerebriform nests
	Architectural change (2 points)	Presence of any blood vessels (2 points)	Atypical cobblestone with small nucleated cells
	Dynamic minor criteria: Focal increase in pigmentation (1	Blood displacement with erythematous blush (1 point)	Marked cytologic atypia

	point)		
	Focal decrease in pigmentation (1 point)	Maximum diameter greater than 6mm (1 point)	Pageoid cells
	Overall decrease in pigmentation not accompanied by lighter pigmentation of adjacent skin (1 point)	For every completed 15 years of age (1 point)	Epidermal disarray
	7 point checklist for dermoscopy score		Large interpapillary space
			Dense nest
	Add dynamic score to 7 point checklist for dermoscopy score		Constant
Cut point/ specialist referral	≥ 3 points	≥ 6 points	Algorithm or scoring system not specified

Appendix 2: Flow of studies in the review



Appendix 3: CHARMS checklist for included validation studies

	Annessi 2007(22)	Argenziano 1998(12)	Argenziano 2003(23)	Argenziano 2011(13)	Benelli 1999(10)	Benelli 2000(24)
Objective	Validation of ABCD rule of dermoscopy, and the 7-point checklist for dermoscopy	Derivation and validation of 7-point checklist for dermoscopy. Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/stolz, Menzies 1996 dermoscopy for melanoma, and 7-point checklist for dermoscopy	Validation of 7-point checklist and revised 7-point checklist for dermoscopy	Validation of 7 FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.	Validation of 7FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.
Source of data	Cross sectional	Cross-sectional			Cross-sectional, prospective	Cross-sectional retrospective study
Participants	• Consecutive recruitment of atypical melanocytic lesions • December 2004 and June 2006 • 1 department of dermatology	• Atypical melanocytic skin lesions, excised and reviewed for histological diagnosis • Inclusion period: NR • Number of departments of dermatology NR	• Dermoscopy images of lesions preselected from 5 departments of dermatology worldwide • then reviewed by 6 histopathologists, who selected histopathologically unequivocal lesions to include in study.	• Digital database of lesions • Screened between 2006 and 2008 • 1 department of dermatology	All the pigmented lesions observed and excised at the dermatologic surgery department September 1997 – September 1998. 1 dermatology surgery department	Retrospective recruitment; all melanomas <6mm and melanocytic naevi <6mm excised during the study period January 1993 – December 1998. 1 Dermatology surgery department, dermatological sciences institute, university.
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate predictors	NA	11 candidate predictors	NA	NA	NA	NA
Sample Size	198 lesions • 96 melanomas • 102 benign	342 • Derivation 196 (57 melanoma, 139 non-melanoma) • Validation 146 (60 melanoma, 86 non-melanoma) • EPV = 5.18 (57/11)	108 • Number of menaloma not specified	300 Lesions • 100 melanoma randomly selected from 349 excised melanomas • 100 melanocytic naevi from 1512 excised naevi • 100 from a larger database of monitored naevi	401 lesions • 60 melanomas	600 lesions • 76 melanomas
Missing data	Not reported	Not reported	Not reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	• predictor selection: identified in the literature • multivariate regression • shrinkage: NR	NA	NA	NA	NA
Model Performance	• Discrimination and calibration: NR. • Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Discrimination: AUC ROC curve • Calibration: NR	• Discrimination and Calibration: NR • Interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of	• Discrimination and calibration: NR. • Sensitivity, specificity reported	Calibration and discrimination: NR Sensitivity , specificity, positive predictive value, negative predictive value, accuracy, efficiency reported.	Calibration and Discrimination: NR Sensitivity and specificity reported.

			consensus diagnosis reported			
Model evaluation	NA	• internal validation: random split-sample	NA	NA	NA	NA
Results	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Final model with odds ratios and score • Comparison of sensitivity, specificity	• Comparison of interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of consensus diagnosis	Comparison of sensitivity, specificity	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, efficiency.	Comparison of sensitivity and specificity.

	Binder 1999(25)	Blum 2003(14)	Blum 2004(26)	Blum 2004(27)	Buhl 2010(19)
Objective	Validation of ABCD rule for dermoscopy/Stolz	Validation of ABCD Rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 7-Point Checklist for dermoscopy, and 7FFM (7 features for melanoma) dermoscopy Derivation and validation of Simplified ABC-point list for dermoscopy.	Validation of the 3 colour dermoscopy test	Derivation and validation of Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions), and Digital dermoscopy analysis (partially imaged lesions) ABCD rule. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, 7FFM (7 features for melanoma) dermoscopy, and ABCD rule of dermoscopy/Stolz.	Derivation and narrow validation of DynaMel Algorithm. Validation of 7-point checklist for dermoscopy.
Source of Data	Cross-sectional, retrospective	Cross-sectional, prospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional, prospective
Participants	• Randomly selected images from a pigmented skin lesion database • 17 dermatologists • Ambulatory care	• Consecutive patients with suspicious melanocytic lesion • 1 department of dermatology	• Benign and malignant melanocytic and non-melanocytic lesions • 1 department of dermatology	• consecutive patients with melanocytic lesions • 1 department of dermatology Pigmented lesion clinic.	• Non-Consecutive patients with excised lesions with 7-point checklist score ≥ 3. • Number of departments of

				• November 1998 – March 2000	dermatology NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	6 candidate predictors	NA	Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions): 6 candidate predictors Digital dermoscopy analysis (partially imaged lesions) ABCD rule: 3 candidate predictors	12 candidate predictors
Sample Size	250 • 41 malignant melanomas • 209 benign melanomas	269 • 84 malignant melanomas • 185 benign melanomas • EPV = 14 (84/6)	249 lesions • 73 non-melanocytic tumours • 176 melanocytic lesions: 65 melanomas, 111 benign	837 lesions • 84 malignant melanomas • 753 benign (melanocytic + other) • EPV = 1.31 (84/64)	675 lesions • 61 melanomas • EPV = 5.083 (61/12)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported

Model Development	NA	• Based on established dermoscopy algorithms and univariate analysis • All predictors included in multivariate modelling • shrinkage: NR	NA	• All 3 derivations developed independently of the established dermoscopic rules. • Logistic regression analysis • shrinkage: NR	• 7-point checklist chosen as it is a valid and reliable method to distinguish benign and malignant melanocytic lesions. • 5 Dynamic predictors included for modelling based on the analysis of data from a prospective observational trial using long-term follow-up by sequential digital dermatoscopy • Used Akaike criterion, logistical regression framework, Brier score, and ROC AUC to select predictors during multivariable modelling. • Shrinkage: NR
Model Performance	• Discrimination and calibration: NR • ROC AUC sensitivity,	• Discrimination and calibration: NR. • Sensitivity, specificity,	• Calibration and discrimination: NR • Sensitivity and	• Discrimination: ROC AUC • Calibration: NR	• Calibration and Discrimination: NR • Sensitivity and

	and specificity reported. • Reported performance at cut points 4.75 and 5.45	and diagnostic accuracy reported. • Cut point 4.	specificity reported	• Sensitivity, specificity, and diagnostic accuracy reported	specificity reported. Cut point >/=3
Model Evaluation	NA	Internal validation: Development dataset was randomly divided into two collectives for cross validation	NA	• internal validation: complete collection of lesions randomly divided into training and test sets	internal validation: developed and tested on same dataset
Results	• Comparison of ROC AUC sensitivity and specificity for different cut points.	• Final model with score and cut point of 4 • Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity and specificity.	• Final digital image analysis model • Comparison of sensitivity, specificity, and diagnostic accuracy.	• Final model with score. • Comparison of sensitivity and specificity.

	Carli 2002(28)	Dal Pozzo 1999(29)	Dolianitis 2005(30)	Emery 2010(20)	Feldmann 1998(31)
Objective	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy	Derivation and narrow validation of 7FFM (7 features for melanoma) dermoscopy	Validation of 7-point checklist for dermoscopy, ABCD Rule of dermoscopy/Stolz, and Menzies 1996 dermoscopy for melanoma	Derivation and validation of Emery 2010 SIAscopy in primary care for melanoma	Validation of ABCD rule of dermoscopy/Stolz.
Source of Data	Cross-sectional	Cross-sectional		Cross-sectional	Cross-sectional prospective study.
Participants	• Clinically equivocal melanocytic lesions, <14 mm in diameter. • 1 department of dermatology Pigmented lesion clinic.	Pigmented skin lesions observed by the authors between 1992-1997 1 Department of Dermatology	• Random selection from a collection of images • 61 medical practitioners from either primary care or dermatology	• Patients presenting with a pigmented lesion and additional lesions identified as potentially suspicious during clinical examination • 6 General Practices in UK and 3 GP Primary Care Skin Cancer Clinics in Australia	Lesions that were being excised on clinical grounds or because of patient request 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	7 Candidate Predictors	NA	9 candidate predictors	NA

Sample Size	200 lesions • 44 melanomas	Training set: 218 lesions • 45 melanomas Test set: 713 lesions • 168 melanomas EPV training set: 2.81 (45/16) test set: 24 (168/7)	40 • 20 melanomas • 20 non-melanomas	1211 • derivation 422 (3 melanomas, 419 non-melanomas) • UK validation 208 (2 melanomas, 206 non-melanomas) • Australian validation 581 (7 melanomas, 574 non-melanomas) • EPV = 0.33 (3/9)	500 lesions • 30 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Of 16 features evaluated in the test set, 7 were selected because of specificity >80% and sensitivity > 5% and p < 0.05, in the derivation study. Shrinkage: NR	NA	• 5 predictors taken from Moncrieff scoring system; additional features considered • Sensitivity, specificity, positive predictive value, negative predictive value, ROC curves and associated AUC used for criteria for selection of predictors during multivariable modelling • shrinkage: NR	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity	Calibration and Discrimination: NR Sensitivity, specificity,	• Discrimination and calibration: NR. • Sensitivity, Specificity,	• Discrimination: AUC ROC curve • Calibration: NR	Calibration and Discrimination: NR Mean score of naevi,

	and diagnostic accuracy reported. Cut off point of 2 (lesions 3 or greater = melanoma) for 7-point checklist and 5.45 for ABCD rule.	PPV, NPV, and efficiency reported.	Diagnostic accuracy, and Likelihood ratios reported.	• Sensitivity, specificity, positive predictive value, and negative predictive value reported. Cut point 6 (6 or more: suspicious)	dysplastic naevi and melanomas reported
Model Evaluation	NA	Narrow internal validation: separate training and test sets.	NA	External validation using 1st a test set which was part of the dataset of 630 lesions from which 422 lesions were used for model derivation and 2nd using a separate dataset	NA
Results	• Comparison of sensitivity, specificity and diagnostic accuracy	Comparison of sensitivity, specificity, PPV, NPV, and efficiency.	• Comparison of Sensitivity, Specificity, Diagnostic accuracy, and Likelihood ratios	• Final model with score • Comparison of sensitivity, specificity, positive predictive value, and negative predictive value.	Comparison of mean score of naevi, dysplastic naevi and melanomas.

	Gereli 2010(32)	**Guitera 2012(21)**	**Haenssle 2010(33)**	**Healsmith 1993(34)**	**Henning 2008(35)**
Objective	Validation of 7-point checklist for dermoscopy and 3-point checklist for dermoscopy.	Derivation and narrow validation of Guitera 2012 confocal microscopy for melanoma.	Validation of 7 point checklist for dermoscopy	Validation of Revised 7-point checklist (clinical) and ABCDE clinical rule	Validation of CASH dermoscopy algorithm, ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy

					for melanoma, and 7 point checklist for dermoscopy .
Source of data	Cross sectional	Cross-sectional.	Cohort Study	Cross-sectional	Cross-sectional retrospective study
Participants	• NR • 96 dermoscopic images of skin lesions • Number of departments of dermatology NR	Consecutive lesions excised to exclude malignancy at a skin cancer clinic (included other skin cancer types) 2 specialised skin cancer clinics	Recruitment method NR Dermatology outpatient clinic. Number of centres NR	• Consecutively diagnosed melanomas. • Randomly selected, clinically diagnosed benign pigmented lesions	Clinical and dermoscopic images of melanocytic neoplasms (50 melanomas, 50 dysplastic naevi, 50 common naevi) from a database of 1535 images on an American Academy of Dermatology database 1 Department of Dermatology, university
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	35 candidate predictors (reflex confocal microscopy	NA	NA	NA

		features)			
Sample Size	96 lesions • 48 melanoma • 48 non-melanoma	710 lesions • 216 melanomas • EPV = 6.17 (216/35	688 participants with increased risk of melanoma; 1219 lesions • 127 melanomas	165 lesions • 65 Melanomas • 100 clinically diagnosed benign pigmented lesion	150 lesions • 50 melanomas
Missing data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	35 RCM (reflex confocal microscopy) features that showed significant association with melanoma diagnosis on univariate modelling. Multivariate discriminant analysis based on the training set using the 35 RCM features identified in univariate modelling, identified 7 independently significant features for the diagnosis of malignant melanomas. Shrinkage: A coefficient is	NA	NA	NA

		estimated for each included variable in relation to likeliness to predict a BCC, then an MM.			
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity, positive predictive value and negative predictive value reported	Discrimination: Multivariate discriminant analysis to determine variables for model. ROC analysis to investigate sensitivity and specificity of discriminant analysis equations for BCC and MM algorithms Calibration: NR Sensitivity and specificity reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	• Calibration and discrimination: NR • Sensitivity reported	Calibration and Discrimination: NR Sensitivity, specificity, relative sensitivity and specificity compared with CASH rule reported.
Model evaluation	NA	Validation (NR internal or external)	NA	NA	NA

Results	Comparison of sensitivity, specificity, positive predictive value and negative predictive value	Comparison of sensitivity, specificity, and AUC.	Comparison of sensitivity and specificity.	• Comparison of sensitivity.	Comparison of sensitivity, specificity, relative sensitivity and specificity.

	Higgins 1992(36)	Kittler 1999(16)	Keefe 1989(37)	Kreusch 1992(17)	Lorentzen 1999(38)
Objective	Validation of 7 point checklist (clinical) and revised 7 point checklist (clinical).	Validation of ABCD rule of dermoscopy/Stolz. Derivation of ABCDE rule (dermoscopy).	Validation of 7-point checklist (clinical)	Validation of Kreusch 1992 dermoscopy for melanoma	Validation of ABCD rule of dermoscopy/Stolz
Source of Data	Cross-sectional prospective study.	Cross-sectional prospective study	Cross-sectional	Cross-sectional	Cross-sectional
Participants	Consecutive clinically benign lesions excised in a pigmented lesion clinic 1 Department of Dermatology, pigmented lesion clinic	Consecutively excised pigmented lesions in a dermatology clinic 1 Department of Dermatology	Consecutive patients referred for assessment or treatment of pigmented lesions 4 departments of dermatology	Over 1.5 years, pigmented lesions suspected to be malignant melanoma were examined clinically and by ELM. Lesions to be excised were photographed. 1 Dermatology Clinic	Patients referred to dermatology clinic for evaluation of a pigmented skin lesion 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	5 Candidate Predictors	NA	NA	NA
Sample Size	100 lesions • 0 melanomas	356 lesions • 73 melanomas • EPV = 14.6 (73/5)	216 lesions • 8 melanoma (of 68 lesions excised)	317 lesions • 96 malignant melanoma • 221 benign melanocytic	232 patients • number of melanomas NR

				lesions and non-melanocytic lesions	
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Predictors 1-4: as per ABCD dermoscopy rule. 1 new variable (E: status of morphologic change) added to create new model Shrinkage: NR	NA	NA	NA
Model Performance	Calibration and Discrimination: NR Specificity reported.	Validation model: Calibration and discrimination: NR Derivation model: Discrimination: area under ROC; Calibration: NR Sensitivity and specificity reported for both models.	Calibration and Discrimination: NR Predictive value for melanoma and Predictive value for non-melanoma reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45 reported.
Model Evaluation	NA	Derivation only.	NA	NA	NA
Results	Specificity.	Comparison of sensitivity and specificity, AUC.	Comparison of predictive value for melanoma and predictive value for non-melanoma reported.	Comparison of sensitivity and specificity	Comparison of sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45.

	Lorentzen 2000(39)	Luttrell 2012(5)	MacKie 2002(15)	McGovern 1992(40)	Menzies 1996(8)
Objective	Validation of ABCD rule of dermoscopy/Stolz	Validation of AC dermoscopy rule	Derivation and validation of the 3 colour dermoscopy test	Validation of 7-point checklist (clinical) and ABCD rule.	Derivation and validation of Menzies 1996 dermoscopy for melanoma
Source of Data	Cross-sectional				Cross-sectional
Participants	Clinical photographs and dermatophotographs obtained from patients consecutively referred to the skin cancer outpatient clinic, and who had a subsequent excision biopsy 1 Department of Dermatology Skin cancer Outpatient clinic	• lesions drawn at random from 312 dermoscopic images of melanocytic lesions • 1 department of dermatology	• Sequential recruitment of patients referred to a specialist rapid-referral pigmented lesion clinic by their GP, for whom a dermatologist had considered that the lesion required excision biopsy • 1 specialist rapid-referral pigmented lesion clinic	• All pigmented lesions biopsied in a dermatology clinic suspicious for dysplasia or malignancy • 1st November 1989 to 31st October 1990; along with 2 melanomas added from earlier in 1989. • 1 dermatology clinic	Random sample of patients whose lesions were excised, selected from a larger database Number of departments of dermatology: NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	10 candidate predictors	NA	11 candidate predictors
Sample Size	258 patients • 64 melanoma	200 dermoscopic images of lesions • 25 melanoma	126 • 69 melanoma • 57 non-melanoma.	205 • 6 melanoma, 6 lentigo maligna	385 lesions • 107 melanomas • EPV = 1.486

		• 178 non-melanoma	• Derivation dataset 74 (37 melanoma, 37 non-melanoma) • Validation dataset 52 (32 melanoma, 20 non-melanoma) • EPV = 3.7 (37/10)		(107/72)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	• Method of selection of predictors for inclusion for multivariable modelling: NR • Sensitivity, specificity, p values, c-index, likelihood ratio tests, multivariable modelling with a forward stepwise philosophy, ROC curve, AUC • shrinkage: NR	NA	• Morphological features, seen with surface microscopy, not visible with the naked eye, that enhance the clinical diagnosis of nearly all pigmented lesions, including invasive melanoma • Classification and regression tree constructed on the training set producing a 7 node tree with cross validated sensitivity and specificity. Individual features were then selected for low sensitivity and high specificity to create a model suitable for clinician use. Images from the test set were then scored by

					means of the model as developed from the training set. Shrinkage: NR
Model Performance	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC reported.	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Discrimination: AUC, ROC curve, c-index • Calibration: NR • Sensitivity, specificity, p-value and c-index reported. No cut point chosen after derivation.	• Discrimination and Calibration: NR • Sensitivity, specificity and accuracy reported	Calibration and Discrimination: NR Sensitivity and Specificity of the training set, the test set, and the total combined sets reported.
Model Evaluation	NA	NA	Internal validation: test set for derivation and separate validation dataset	NA	Internal validation: A test set of 45 invasive melanomas and 119 non-melanomas was used to test the model performance.
Results	Comparison of sensitivity, specificity, and area under ROC.	Comparison of sensitivity and specificity.	• Final model with cut point of 3 colours or more on dermoscopy • Sensitivity, specificity, p-value, and c-index reported.	• Comparison of sensitivity, specificity and accuracy at different cut points.	• Final model: For diagnosis of invasive melanoma it must have neither of the two morphological negative features and 1 or more of the nine positive morphological features. • Comparison of sensitivity and specificity of the training set, the test set, and the total combined sets.

	Menzies 2008(9)	Menzies 2013(41)	Nachbar 1994(42)	Nilles 1994(18)	Osborne 1998(43)
Objective	Derivation of Menzies 2008 dermoscopy for melanoma and Menzies 2008 dermoscopy for skin cancer. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, and 3-point checklist for dermoscopy.	Derivation of Menzies 2013 dermoscopy for nodular melanoma. Validation of ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 3-point checklist, CASH dermoscopy algorithm, and 7-point checklist for dermoscopy.	Derivation of ABCD rule of dermoscopy/Stolz	Derivation and narrow validation of Nilles 1994 dermoscopy for melanoma.	Validation of Revised 7-Point Checklist (clinical)
Source of Data	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional retrospective study	Cross-sectional, retrospective
Participants	Dermoscopic images from multiple centres retrospectively May not have been from consecutive patients Predominantly hospital-based clinics from 5 continents (exact number NR)	Random selection of images of lesions from members of the International Dermoscopy Society Predominantly hospital-based clinics from 5 continents (exact number NR)	Consecutively excised pigmented skin lesions Number of departments of dermatology: NR	Retrospective recruitment; 260 histologically confirmed melanocytic skin tumours 1 Department of Dermatology	All patients with histologically proven cutaneous melanoma in study area between the years 1982 – 1996 1 department of dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate Predictors	Menzies 2008 dermoscopy for melanoma: 8 candidate predictors Menzies 2008 dermoscopy for skin cancer: 11 candidate predictors	17 candidate predictors	5 candidate predictors	8 Candidate Predictors	NA
Sample Size	497 lesions • 105 melanomas • EPV = 1.06 (105/99)	467 lesions • 217 melanomas (83 nodular melanomas, 134 invasive non-nodular melanomas) • EPV = 2.19 (217/99)	194 lesions • 69 melanomas • EPV = 13.8 (69/5)	260 lesions: • 72 malignant melanomas • 188 benign naevi • EPV = 9 (72/8)	778 lesions • 778 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	Both models: determined by consensus of members of the International Dermoscopy Society, either based on the existing literature or on clinicians' anecdotal experience Both models: 99 individual morphological features were scored by 12 clinicians in 55 preselected lesions to	Determined by consensus of the members of the International Dermoscopy Society 12 scorers blinded to the lesion diagnosis scored 99 individual features in each lesion. One feature was scored by one of the investigators after the clinician scoring was completed. Shrinkage: NR	• Development NR • Individual scores multiplied by different weight factors obtained by multivariate analysis • Shrinkage: NR	Selected based on previous studies examining predictive value of individual dermoscopic features. Stepwise logistic regression for data for each feature. Shrinkage: NR	NA

	assess interobserver concordance. 1 feature was scored by 1 of the investigators after the clinician scoring was completed. A random sample of 80% of the lesions was used as a training set and the remaining 20% used as a test set. The possible positive features were restricted to those with high specificity. Low sensitivity features were included for model development. Using all features as candidate variables, multiple logistic regression analysis with backward stepwise variable selection was also used to identify the independent predictors of malignant lesions from benign lesions in the training set. Shrinkage: NR				
Model Performance	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features and	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features	Calibration and Discrimination: NR Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative	Calibration and Discrimination: NR Validation dataset: sensitivity and specificity	Calibration and discrimination: NR Frequency of melanomas and rate of false negative diagnosis of melanoma at

	models reported.	and models reported.	predictive value reported. Cut-off point 5.45.	reported.	different sites.
Model Evaluation	Tested on independent, randomly selected lesions	Uncertain	Internal validation: using development dataset	Narrow external validation: new dataset of 209 lesions in 1991	NA
Results	Comparison of sensitivity and specificity in training vs independent test set.	Comparison of sensitivity for diagnosing nodular melanoma and non-nodular melanoma, and amelanocytic/hypomelanotic malignant lesions.	• Final model composed of 4 morphological features of malignant melanoma with different weight factors • Comparison of sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.	Comparison of frequency of melanomas and rate of false negative diagnosis of melanoma at different sites.

	Piccolo 2014(44)	Pizzichetta 2002(45)	Rao 1997(46)	Skvara 2005(47)	Soyer 2004(6)
Objective	Validation of ABCD rule of dermoscopy/Stolz and DDA (digital dermoscopic analysis) - computer-assisted diagnosis	Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/Stolz and ABCD clinical rule	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy.	Validation of 3-point checklist of dermoscopy
Source of Data	Cross-sectional	Cross-sectional, retrospective	Cross-sectional prospective	Cross-sectional, retrospective	Cross-sectional, retrospective
Participants	Dermoscopically atypical PSLs retrospectively selected from the archives of the department of dermatology 1 Department of Dermatology	Lesions selected from all lesions observed in consecutive patients seen between April 1996 - September 1998 1 Oncology Referral Centre	Consecutive patients, with lesions suspected of either benign melanocytic naevi or early malignant melanoma 1 private dermatology practice	Consecutive lesions demonstrating change over time during follow up 2 specialised dermatology centres	Consecutively excised lesions in specialized pigmented lesion clinic 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	NA	NA	NA
Sample Size	165 lesions • 33 malignant melanomas • 132 benign	129 lesions • 5 malignant melanomas • 124 benign	72 lesions • 21 melanomas	325 lesions • 63 melanomas	231 lesions • 68 melanomas • 163 non-melanomas (9 pigmented basal cell carcinomas,

					154 benign PSLs)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	NA	NA	NA
Model Performance	Calibration and discrimination: NR Kappa statistic (overall intra-observer agreement), sensitivity, specificity, positive predictive value and negative predictive value reported.	Calibration and discrimination: NR Kappa statistic (inter-observer agreement), sensitivity, and specificity reported.	Calibration and Discrimination: NR Cut-point 5.45 Sensitivity, specificity, and diagnostic accuracy reported.	Discrimination and Calibration: NR Cut-point not reported AUC, sensitivity, and specificity reported.	Calibration and discrimination: NR Sensitivity, specificity, and odds ratio reported.
Model Evaluation	NA	NA	NA	NA	NA
Results	Comparison of Kappa statistic, sensitivity, specificity, positive predictive value and negative predictive value.	Comparison of Kappa statistic, sensitivity, and specificity.	Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity, specificity and area under ROC.	Comparison of sensitivity, specificity, and odds ratio.

	Stolz 1994(11)	Strumia 2003(48)	Thomas 1998(49)	Unlu 2014(50)	Wadhawan 2011(51)
Objective	Derivation and narrow validation of ABCD rule of dermoscopy/Stolz.	Validation of ABCD rule of dermoscopy/Stolz and ABCDE rule (dermoscopy)	Validation of ABCD clinical rule and ABCDE clinical rule	Validation of ABCD rule of dermoscopy/Stolz, 7-point checklist for dermoscopy, 3-point checklist of dermoscopy, and CASH dermoscopy algorithm.	Validation of 7-point checklist for dermoscopy
Source of Data	Cross-sectional retrospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional	Feasibility Study implementing the 7-point checklist for dermoscopy features on a smart hand-held device.
Participants	Consecutively excised melanocytic naevi and malignant melanoma that met inclusion criteria 1 Department of Dermatology, University Hospital	Small melanocytic skin lesions, consecutively excised 1 Department of Dermatology	Prospective, consecutively diagnosed melanomas, and a prospective control group of benign lesions 1 Department of Dermatology	Random selection of digital dermoscopic images of melanocytic lesions collected at pigmented lesion clinic between Jan 2008-Jan 2010. 1 department of dermatology	Unknown number of skin cancer images annotated by expert dermatologists Commercial library of skin cancer images
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Use of the 7 point checklist for dermoscopy on smart hand-held devices.
Candidate Predictors	31 Candidate Predictors	NA	NA	NA	NA

Sample Size	157 lesions • 48 melanomas • EPV = 1.55 (48/31)	49 lesions • Number of melanomas and non-melanomas not reported.	1140 lesions • 460 melanomas • 680 non-melanomas	115 lesions • 24 malignant melanomas • 91 benign	347 lesions • 110 malignant melanoma (based on 7 point checklist) No histological diagnosis • 237 benign
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	28 features listed in the Consensus Conference of Surface Microscopy, Hamburg, 1989, and three new features (asymmetry in no, one, or two axes; colour; differential structure). "8 features with p values <=0.0001 in the training set were used for multivariate analysis to obtain a formula which led to a calculated score termed the final dermatoscopy score (FDS)" Shrinkage: "Multivariate analysis of the 8 features with lowest p values in the training set was performed, and The following formula for the best differentiation of	NA	NA	NA	NA

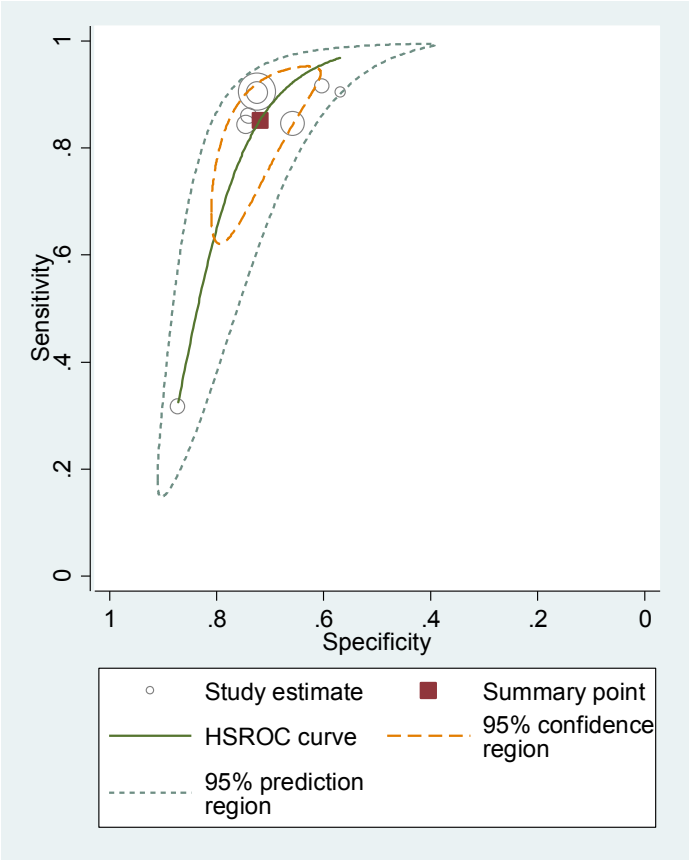
	melanocytic skin lesions was created: Asymmetry score x 1.3 + Border score x 0.1 + Colour score x 0.5 + Differential structure score x 0.5 = Final Dermatoscopy Score"				
Model Performance	Calibration and Discrimination: NR Cut-point: 5.45 Sensitivity and specificity reported.	Calibration and discrimination: NR Cut-point 5.45 Positive and negative predictive values reported.	Calibration and discrimination: NR Sensitivity and specificity of individual criteria, and Chi square statistic reported.	Calibration and discrimination: NR Sensitivity, specificity, diagnostic accuracy, false positive, ratio, false negative ratio, positive predictive value, and negative predictive value reported.	Calibration and discrimination: NR Sensitivity, specificity, and classification accuracy reported.
Model Evaluation	Internal validation: dataset split into derivation and test sets	NA	NA	NA	NA
Results	Comparison of sensitivity and specificity.	Comparison of positive and negative predictive values.	Comparison of sensitivity and specificity of individual criteria, and Chi square statistic.	Comparison of sensitivity, specificity, diagnostic accuracy, false positive, ratio, false negative ratio, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.

	Walter 2013(52)	Zalaudek 2006(53)
Objective	Validation of 7-point checklist (clinical) and revised 7-point checklist (clinical)	Validation of 3-point checklist for dermoscopy.
Source of data		
Participants	• Consecutive recruitment of patients presenting to general practice with a pigmented lesion which could not be immediately diagnosed as benign, for a RCT of a SIAscopic diagnostic aid for primary care • 15 General Practices	• Random selection from a collection of 2621 excised lesions • 1 department of dermatology specialised pigmented lesion clinic
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	NA
Sample Size	1436 • 36 melanomas	150 • 26 melanoma • 106 benign

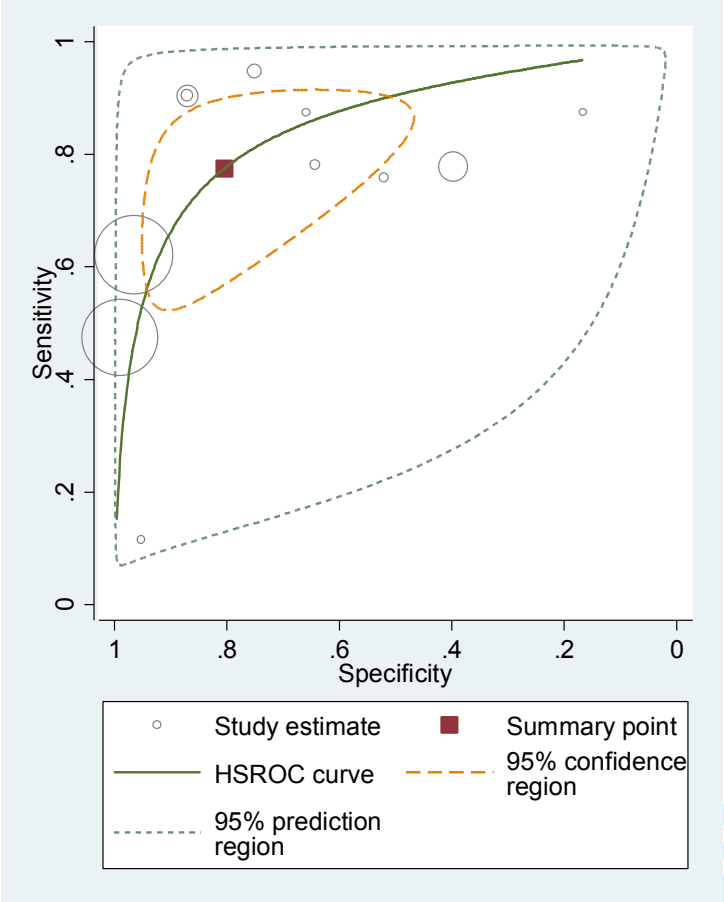
Missing data	No missing data reported	No missing data reported
Model development	NA	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Calibration and discrimination: NR • Reproducibility, sensitivity, and specificity reported
Model evaluation	NA	NA
Results	Comparison of sensitivity and specificity at different cut points.	Comparison of reproducibility, sensitivity, and specificity.

NR= not reported; NA= not applicable

Appendix 4: ROC curve illustrating performance of ABCD rule of dermoscopy



Appendix 5: ROC curve illustrating performance of 7 point checklist for dermoscopy



Appendix 6: Methodological quality assessment of the impact analysis studies

a: Studies with a RCT study design

Authors	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Walter (2012)(54)	Low	Low	Low	High	Low	Low	Low	Low
Argenziano 2006	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear

b: Study with a controlled before-after study design

Authors	Selection bias			Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Allocation generation	Allocation concealment	Baseline measures	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Westerhoff (2000)(55)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High	High

References (Appendices)

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA: a cancer journal for clinicians. 1985;35(3):130-51.
2. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, et al. Early diagnosis of cutaneous melanoma: Revisiting the ABCD criteria. Journal of the American Medical Association. 2004;292(22):2771-6.
3. MacKie RM. An illustrated guide to the recognition of early malignant melanoma. University of Glasgow. 1986.
4. MacKie RM. Malignant melanoma: a guide to early diagnosis University of Glasgow. 1989:28-43.
5. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. British Journal of Dermatology. 2012;167(5):1037-41.
6. Soyer HP, Argenziano G, Zalaudek I, Corona R, Sera F, Talamini R, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. Dermatology. 2004;208(1):27-31.
7. Henning JS, Dusza SW, Wang SQ, Marghoob AA, Rabinovitz HS, Polsky D, et al. The CASH (color, architecture, symmetry, and homogeneity) algorithm for dermoscopy. Journal of the American Academy of Dermatology. 2007;56(1):45-52.
8. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Archives of Dermatology. 1996;132(10):1178-82.
9. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Archives of Dermatology. 2008;144(9):1120-7.
10. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999;9(6):470-6.
11. Stolz W, Riemann A, Cognetta AB, Pillet L, Abmayer W, Holzel D, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. European Journal of Dermatology. 1994;4(7):521-7.
12. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Archives of Dermatology. 1998;134(12):1563-70.
13. Argenziano G, Catricalà C, Ardigo M, Buccini P, De Simone P, Eibenschutz L, et al. Seven-point checklist of dermoscopy revisited. British Journal of Dermatology. 2011;164(4):785-90.
14. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. Journal of the American Academy of Dermatology. 2003;48(5):672-8.
15. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. British Journal of Dermatology. 2002;146(3):481-4.

16. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. Journal of the American Academy of Dermatology. 1999;40(4):558-62.
17. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society. 1992;Suppl 2:295-8.
18. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. British Journal of Dermatology. 1994;130(3):349-55.
19. Buhl T, Hansen-Hagge C, Korpas B, Kaune KM, Haas E, Rosenberger A, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. Journal of the American Academy of Dermatology. 2012;66(1):27-36.
20. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. BMC Dermatology. 2010;10:9-.
21. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. Australasian Journal of Dermatology. 2012;53:7-8.
22. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. Journal of the American Academy of Dermatology. 2007;56(5):759-67.
23. Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. Journal of the American Academy of Dermatology. 2003;48(5):679-93.
24. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. Eur J Dermatol. 2000;10(4):282-7.
25. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. Journal of the American Academy of Dermatology. 1999;40(2 I):171-6.
26. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. British Journal of Dermatology. 2004;150(5):1040.
27. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. British Journal of Dermatology. 2004;151(5):1029-38.
28. Carli P, Quercioli E, Sestini S, Stante M, Ricci L, Brunasso G, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. British Journal of Dermatology. 2003;148(5):981-4.
29. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. European Journal of Dermatology. 1999;9(4):303-8.
30. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. Archives of Dermatology. 2005;141(8):1008-14.

31. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. Hautarzt. 1998;49(6):473-6.
32. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. International Journal of Dermatology. 2010;49(1):33-8.
33. Haenssle HA, Korpas B, Hansen-Hagge C, Buhl T, Kaune KM, Rosenberger A, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. Journal of the American Academy of Dermatology. 2010;62(5):785-93.
34. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. British Journal of Dermatology. 1994;130(1):48-50.
35. Henning JS, Stein JA, Yeung J, Dusza SW, Marghoob AA, Rabinovitz HS, et al. CASH algorithm for dermoscopy revisited. Arch Dermatol. 2008;144(4):554-5.
36. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. Clinical and Experimental Dermatology. 1992;17(5):313-5.
37. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. Clinical and Experimental Dermatology. 1990;15(3):167-71.
38. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. Acta Dermato-Venereologica. 1999;79(6):469-72.
39. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. Acta Derm Venereol. 2000;80(2):122-6.
40. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. Journal of Dermatologic Surgery and Oncology. 1992;18(1):22-6.
41. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I, et al. Dermoscopic evaluation of nodular melanoma. JAMA Dermatology. 2013;149(6):699-709.
42. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. Journal of the American Academy of Dermatology. 1994;30(4):551-9.
43. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. British Journal of Dermatology. 1999;140(5):902-8.
44. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. European Journal of Dermatology. 2014;24(4):477-81.
45. Pizzichetta MA, Talamini R, Piccolo D, Trevisan G, Veronesi A, Carbone A, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. Tumori. 2002;88(3):234-8.
46. Rao BK, Marghoob AA, Stolz W, Kopf AW, Slade J, Wasti Q, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. Skin Research and Technology. 1997;3(1):8-14.
47. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. Archives of Dermatology. 2005;141(2):155-60.

48. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. Melanoma Research. 2003;13(6):631-2.
49. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. Dermatology. 1998;197(1):11-7.
50. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. Journal of Dermatology. 2014;41(7):598-603.
51. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2011;2011:3180-3.
52. Walter FM, Prevost AT, Vasconcelos J, Hall PN, Burrows NP, Morris HC, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. British Journal of General Practice. 2013;63(610):345-53.
53. Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Three-point checklist of dermoscopy: An open internet study. British Journal of Dermatology. 2006;154(3):431-7.
54. Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. BMJ (Online). 2012;345(7866).
55. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. British Journal of Dermatology. 2000;143(5):1016-20.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6/7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6/7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6/7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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Diagnosing malignant melanoma in ambulatory care: a systematic review of clinical prediction rules

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Diagnosing malignant melanoma in ambulatory care: a systematic review of clinical prediction rules

Authors:

Emma Harrington[1], Barbara Clyne*[1], Nieneke Wesseling[2], Harkiran Sandhu[1], Laura Armstrong[1], Holly Bennett[1], Tom Fahey[1]

Author affiliations:

[1]HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 Stephen's Green, Dublin 2, Ireland

www.hrbcentreprimarycare.ie

[2] Medical School, Radboud University, Nijmegen, Netherlands

***Corresponding author:** Barbara Clyne PhD, HRB Centre for Primaty Care Research, Department og General Practice, Royal College of Surgeons in Ireland, Lower Mercer Street, Dublin 2, Ireland barbaraclyne@rcsi.ie

Abstract

Objectives: Malignant melanoma has high morbidity and mortality rates. Early diagnosis improves prognosis. Clinical prediction rules (CPRs) can be used to stratify patients with symptoms of suspected malignant melanoma to improve early diagnosis.

We conducted a systematic review of CPRs for melanoma diagnosis in ambulatory care.

Design: Systematic review

Data Sources: A comprehensive search of PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS was conducted in May 2015, using combinations of keywords and MeSH terms.

Study selection and data extraction: Studies deriving and validating, validating, or assessing the impact of a CPR for predicting melanoma diagnosis in ambulatory care were included. Data extraction and methodological quality assessment were guided by the CHARMS checklist.

Results: From 16,334 studies reviewed, 51 were included, validating the performance of 24 unique CPRs. Three impact analysis studies were identified. Five studies were set in primary care. The most commonly evaluated CPRs were the ABCD dermoscopy rule (at a cut point of >4.75; 8 studies; pooled sensitivity 0.85, 95% CI 0.73-0.93, specificity 0.72, 95% CI 0.65-0.78) and the 7 point dermoscopy checklist (at a cut point of ≥1 recommending ruling in melanoma; 11 studies; pooled sensitivity 0.77, 95% CI 0.61-0.88, specificity 0.80, 95% CI 0.59-0.92). The methodological quality of studies varied.

Conclusion: At their recommended cut-points, the ABCD dermoscopy rule is more useful for ruling out melanoma than the 7 point dermoscopy checklist. A focus on impact analysis will help translate melanoma risk prediction rules into useful tools for clinical practice.

PROSPERO registration

The protocol for this systematic review is registered at the PROSPERO database, registration number CRD42015020898

Strengths and limitations of this study

- The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. Quality assessment criteria were used to assess risk of bias and the majority of studies were at low risk in relation to the randomisation procedure and monitoring of loss to follow-up.
- A large proportion of studies did not provide sufficient information and data to perform stratified meta-analysis according to different levels of risk
- Current research shows that dermoscopic CPRs may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients but future impact analysis research is necessary to establish their impact on patient outcomes.

Introduction

The incidence of malignant melanoma in most developed countries has been steadily rising (faster than other cancer types) in recent decades. [1,2] Increases in the age-standardized incidence of at least 4–6% per annum have been reported internationally in many fair skinned populations including Australia, the USA and most of Europe. [3-5] Simultaneously, there has been a significant rise in overall 5-year survival in melanoma patients, largely attributable to earlier detection and diagnosis of thinner tumours.[6] While the majority of patients may survive melanoma, the disease has a significant impact on patient quality of life[7] and health care expenditure, with the average annual total treatment costs for melanoma in the USA increasing to $3.3 billion in 2011. [8] Melanoma is potentially preventable since a significant risk factor, exposure to ultraviolet (UV) radiation, is modifiable.[9] However, other risk factors (e.g. number naevi, eye and hair colour, freckles, familial history and genetic predisposition) also play an important role in the risk of developing melanoma. [10,11]

While early detection followed by curative surgery greatly improves prognosis, the differential diagnosis of pigmented lesions is a challenge. Particularly in primary care where the evaluation of suspected skin lesions is imposing an increasing burden due to rising incidences of skin cancer.[12] It has been suggested that primary care practitioners' skills of diagnosing skin lesions could be improved.[13] A number of Clinical Prediction Rules (CPRs) and computer-assisted diagnostic tools have been developed to assist in distinguishing malignant melanoma from benign pigmented skin lesions. The UK National Institute for Clinical Excellence (NICE) guidelines advise against routine use of computer-assisted diagnostic tools in the initial evaluation of a pigmented skin lesion (NG14) and promote use of the weighted 7-point checklist in primary care to guide referral (NG12). When used by dermatologists for the diagnosis of melanoma, certain CPRs have demonstrated high sensitivity and specificity.[6] Although each CPR has its own unique elements, there is significant overlap in terms of their content (Appendix 1), and while their use is promoted, it is unclear which rules are most suitable for use in primary care.

CPRs may be for use in clinical (i.e. naked eye) examination, or in conjunction with dermoscopy. Dermoscopy, dermatoscopy, or epiluminescent microscopy refers to the examination of pigmented skin lesions using surface microscopy. [14,15] The use of dermoscopy, primarily by dermatologists, has been found to increase diagnostic accuracy compared with naked eye inspection, as it allows the visualization of features that are not visible to the naked eye.[14-16] However, the effectiveness of dermoscopy depends on clinical experience and training. Dermatologists with formal training in dermoscopy have higher melanoma detection rates compared with untrained dermatologists and primary care physicians.[16-18]

As the initial presentation of melanoma occurs most frequently in primary care or ambulatory settings, it is essential to identify tools to aid primary care practitioners to differentiate patients with clinically significant lesions, requiring referral, from those who can be treated and monitored in primary care. The aim of this study was to perform a systematic review of CPRs for the diagnosis of malignant melanoma, to evaluate their diagnostic accuracy in primary care and specialist outpatient settings, among patients with a pigmented skin lesion. Secondary aims were to review studies that have examined the implementation of CPRs in clinical practice through impact analysis studies.

Methods

The protocol for this systematic review was published on PROSPERO (CRD42015020898) and was conducted according to PRISMA guidelines.[19]

Search strategy and data sources

A systematic literature search was conducted (May 2015) including the following databases: PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS, using combinations of the following keywords and MeSH terms: melanoma/diagnosis, melanoma, prediction, score, model, decision, sensitivity, specificity, validate, derived. Hand searches of references of retrieved full-text articles and key author searches supplemented the search. No date or language limits were imposed.

Study selection

All articles were initially screened for inclusion according to title and abstract by two reviewers (NW, EH). Full text articles of studies considered eligible for inclusion were independently read by both reviewers, with any disagreements resolved by a third reviewer (BC).

Validation studies

Validation studies were eligible for inclusion if they met the following criteria;

1) *Population:* Adults (age ≥18 years) with a pigmented skin lesion in ambulatory care settings in general practice/ family medicine, dermatology, plastic surgery, and other relevant specialties.
2) *Risk:* Derivation and/or validation of a CPR for melanoma diagnosis to aid decision-making about referral or investigation of a pigmented skin lesion. CPRs were defined as "a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and investigations make toward the diagnosis, prognosis, or likely response to treatment in a patient".

3) *Comparison:* Usual clinical judgment for decision making about referral or investigation OR another CPR for melanoma diagnosis.
4) *Primary Outcome:* Performance of a CPR for predicting diagnosis of malignant melanoma (in terms of sensitivity, specificity, negative predictive values and positive predictive values).

Observational study designs (e.g. cohort, cross-sectional, case-control) were included. Studies were excluded where they had undergone derivation only, reported individual predictors only, or utilised computer assisted diagnostic tools, following the NICE guideline recommendation against the routine use of computer assisted diagnostic tools.[20]

Impact analysis

The following study designs were included for impact analysis: (cluster) randomized controlled trials (RCTs), controlled before-after studies, or interrupted time series studies. We excluded uncontrolled study designs. We included studies where a melanoma CPR was used to predict melanoma compared to usual care in the clinical setting. The outcomes of interest included physician behaviour, process of care, patient outcomes and/or cost-effectiveness. A requirement for inclusion was that the CPR comprised the entire intervention. Studies where the CPR was implemented as part of a broader guideline, protocol or decision aid were excluded. Studies that used a CPR to determine eligibility for trial inclusion but were not part of the intervention were also excluded.

Data extraction

Data were extracted by four reviewers (LA, HB, HS, EH) using a data form based on the CHARMS checklist.[21] Data extracted included study design and setting, patient demographics and inclusion criteria, CPR name, CPR type (clinical or dermoscopic), predictive accuracy of the CPR (sensitivity/specificity) and, for impact analysis, the impact on the primary outcome.

Critical appraisal of studies

Two reviewers (EH, NW) critically appraised included studies using the CHARMS checklist, developed to provide guidance on data extraction and critical appraisal of prediction modelling studies. [21] The checklist contains 11 domains of critical appraisal. The methodological quality of each study was independently evaluated by two reviewers and by a third reviewer if consensus was not reached. The methodological quality of each impact analysis study was also independently assessed, using an appropriate quality assessment checklist. RCTs were assessed using the Cochrane risk of bias tool and controlled before-after studies were evaluated using Cochrane criteria for these study designs. [22]

Statistical analysis

Statistical analysis was conducted using Stata version 12 (StataCorp., College Station, Texas, USA), in particular the metandi and midas commands. For each CPR, a standard cut point was identified (Table 1). From each included study we extracted (where available) the numbers of true positives, false positives, true negatives, false negatives, sensitivity and specificity and their corresponding 95% confidence intervals (95% CIs). Where sensitivity/specificity for more than one observer was reported, the mean value was included in the analysis. Studies were grouped for analysis by CPR type (i.e. clinical or dermoscopic). Summary estimates of sensitivity and specificity and their corresponding 95% CIs were calculated using the bivariate random effects model (midas). The bivariate model has the benefits of being easily interpretable, is technically straightforward to undertake and takes into account both the sample and heterogeneity beyond chance between studies.[23]

Individual and summary estimates of sensitivity and specificity were plotted on a hierarchical summary receiver-operating characteristic (HSROC) graph. This approach incorporates both sensitivity and specificity, while taking into account the correlation between the two.[24] Sensitivity (true positive) was graphed on the y-axis and 1-specificity (false negative) on the x-axis. The 95% confidence region and the 95% prediction region were also plotted around the pooled estimates in order to depict the precision with which

the pooled estimates were determined (confidence ellipse around the mean value) and to illustrate the amount of between-study variation (prediction ellipse).

Results

Study Selection

The search strategy yielded a total of 25,816 articles. Of these 9,481 were duplicates and 16,166 were deemed irrelevant based on title/abstract. The remaining 171 were reviewed in full with 51 meeting the inclusion criteria (Appendix 2). From these, 24 unique melanoma CPRs were identified (Table 1). Twelve papers reported both derivation and validation studies, 36 were validation studies only and three were impact analyses.

Summary of studies

Table 2 summarises the characteristics of the included studies. The majority (11, 22%) were conducted in Italy [14,15,25-34] and ranged from an analysis of 40 lesions to 1,580 lesions. From 13 studies providing information, mean age of included patients ranged from 36.7 to 53 [25,28,31,35-44]. From the 14 studies that reported gender, the proportion of males ranged from 22-60% [25,31,33,35-45]. Thirty-one of the 50 studies were published in or after 2000 [14,25,28,29,31-37,42-44,46-62]. Five studies were set in primary care [36,44,49,62,63], with the remainder undertaken in specialist outpatient settings.

Summary of CPRs identified

Of the 24 rules identified, four were clinical (i.e. naked eye), 17 were dermoscopic and the remaining three utilised novel diagnostic technologies. The most commonly applied clinical CPR was the ABCDE rule (5 studies) [6,15,28,64,65], while for dermoscopy the most common were the ABCD rule of dermoscopy (23 studies) [14,25,26,29,31,32,39,42,43,47-49,52,53,57,65-70] and the 7 point checklist for dermoscopy (17 studies)[14,25,26,29,35,37,42,43,46-50,52,56,57,59].

Each of the elements included in the 24 rules identified are presented in Table 3.a and 3.b. All four clinical rules included the elements of diameter and colour variegation (Table 3.a and Appendix 1). The most frequently included elements in the 17 dermoscopic rules were multiple colours (13 rules), asymmetry (12 rules), and streaks (10 rules) (**Error! Reference source not found.**Table 3.b and Appendix 1).

Methodological quality of validation studies

Based on the CHARMS checklist, the quality of included studies varied.[21] All studies had weaknesses in study design and quality assessment was often hindered by poor reporting of methods. The studies had reasonable sample sizes and all provided adequate definitions of the outcome of interest. However, a number of important weaknesses were identified. None of the studies reported on missing data and key performance measures of model performance (e.g. calibration) were often missing. Derivation studies typically reported information on model development, in terms of selection of candidate predictors, selection of predictors during modelling, and model evaluation. However, often the methods applied introduced a strong risk of bias, for example, a number of studies described splitting the original sample into a development and validation sample which is considered statistically inefficient and results in overfitting of the model. [21] Full results of the quality assessment are shown in Appendix 3.

Predictive accuracy of melanoma CPRs

The results for the most commonly applied CPRs, the ABCD rule and the 7 point checklist are presented here. The sensitivity and specificity of all rules identified (including the ABCDE clinical rule, the 7 features for melanoma rule and Menzies dermoscopy for melanoma rule) are summarised in Table 4.

Clinical (naked-eye) CPRs for melanoma diagnosis

Four studies validating the ABCDE clinical rule [6,15,28,64] and one validating the ABCD clinical rule [65] were included. There was insufficient data to conduct any meta-analysis. Rao et al reported a sensitivity of 0.84 and specificity of 0.78, for an unspecified cut-point.[65]

Six studies validating the original and revised 7 point checklist were included. There was insufficient data to conduct a meta-analysis. Of the four studies validating the original 7 point checklist (cut-point ≥ 3), three reported sensitivity (range 0.44-0.86, mean 0.70) and specificity (range 0.62-0.94, mean 0.74)[40,41,44]. Only one of the four studies validating the revised 7 point checklist (cut-point ≥ 1) reported sensitivity (0.92) and specificity (0.33) (Table 4).[44]

Dermoscopic CPRs for melanoma diagnosis

ABCD rule of dermoscopy

The ABCD rule of dermoscopy (also described as the ABCD rule of Stolz), was validated in 23 studies, 15 of which applied a cut point of >4.75 (indicating a suspicious lesion) and 6 studies a cut-point of 5.45 (highly suggestive for melanoma). At a cut point of >4.75, 8 studies provided sufficient information for meta-analysis, [42,43,47,52,65,71] resulting in a pooled sensitivity of 0.85 (95% CI 0.73-0.93) and specificity of 0.72 (95% CI 0.65-0.78) (Figures 1.a and 1.b). This indicates that at this cut point, the dermoscopy CPR is more useful for ruling out rather than ruling in melanoma, with a higher pooled sensitivity than specificity. I^2 were high (>70%), indicating a high degree of heterogeneity. Of the seven studies excluded from meta-analysis, sensitivity ranged from 0.71-0.91 (mean 0.79) and specificity ranged from 0.43-0.92 (mean 0.72). None of the six studies that applied a cut-point of 5.45 were suitable for meta-analysis. From 4 studies that presented the information, sensitivity ranged from 0.73-0.98 (mean 0.85) and specificity ranged from 0.46-0.91 (mean 0.79) (Table 4).

7 point checklist for dermoscopy

The 7 point checklist for dermoscopy was validated in 18 studies, 17 of which applied a cut point of 3. 11 studies provided sufficient information for meta-analysis, revealing a pooled sensitivity of 0.77 (95% CI 0.61-0.88) and pooled specificity of 0.80 (95% CI 0.59-0.92) (See figures 2.a and2.b). [25-27,35,37,42,43,47,50,52,71] There was a high degree of heterogeneity in the results (I^2 >90%). Removing two outliers [27,50] made minimal difference to the pooled result. Only one study validated the revised 7 point checklist for dermoscopy and reported sensitivity 0.78 and specificity 0.65 for a cut point of 3 (Table 4).[27]

Impact analysis

We identified three unique studies that examined the impact of a melanoma CPR on processes of care (melanoma diagnosis and referrals), however, no patient outcomes were examined (Table 2). [62,63] The methodological quality of these studies is presented in Appendix 4.

Using a controlled before and after design, Westerhoff et al investigated the impact of an educational intervention about the Menzies 1996 rule on melanoma diagnosis by Family Physicians (FP). The control group did not receive the training. Post-intervention, there was a significant improvement in melanoma diagnosis (75.9% vs 62.7%, P < .001). No significant improvement was seen in the control group (54.8% vs 53.7%, P = .59). [62]

Walter et al. conducted a RCT to compare the use of a new imaging device, the MoleMate system (SIAscopy with a primary care scoring algorithm), to current best practice (clinical history, naked eye examination, seven point checklist). The authors found no difference between these two approaches in terms of appropriate referrals (the proportion of referred lesions that secondary care experts biopsied or monitored) to urgent skin cancer clinics (intervention 56.8% v control 64.5% *P* = 0.11) or the proportion of benign lesions appropriately managed in primary care (intervention 99.6% v control 99.2%, P=0.46). [63]

Argenziano et al's RCT [72], involved primary care physicians first attending a 1-day training course describing the ABCD rule (cut point unspecified) and the 3-point checklist. They were then randomly assigned to assess patients with skin lesions, either by clinical (i.e. naked eye) examination, or by dermoscopy using the 3-point checklist. The referral assessments were checked for accuracy by dermatologists. The dermoscopy arm demonstrated a 25% improvement in the sensitivity of primary care referrals of pigmented lesions compared with the naked-eye examination (79.2% vs 54.1%, *P* = 0.002), without a reduction in specificity (71.8% vs 71.3%, *P* =0.915) [72].

Discussion

Summary of findings

This systematic review identified 48 studies validating a total of 24 CPRs for melanoma. Overall, the majority of validation studies utilised dermoscopic CPRs, with very few studies validating clinical CPRs. Meta-analysis of the dermoscopic CPRs demonstrated relatively high pooled estimates of sensitivity (0.77-0.86). The clinical implication is that applying dermoscopy CPRs will enable low risk patients to be observed and kept under review in a primary care setting, without immediate referral for excision to secondary care. Meta-analysis was not possible for clinical CPRs but individual studies report variable sensitivity, ranging from 0.44-0.86. Three impact analysis studies were identified, with two reporting an improvement in melanoma diagnosis with the use of a CPR.

Context of previous research

The sensitivities and specificities we report indicate that currently available CPRs are reasonably good at ruling out melanoma. The pooled sensitivity of the ABCD rule for dermoscopy (cutpoint of >4.75) was 0.85 (95% CI 0.73-0.93), higher than that of the seven point checklist for dermoscopy (0.77, 95% CI 0.61-0.88). While this evidence would support the use of such rules in prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients, there are a number of important caveats that may prevent their adoption in primary care.

Melanoma is a high stakes condition, one which doctors tend to be cautious in diagnosing, often preferring to excise a benign lesion rather than to miss a potentially fatal cancer.[73] In such cases, a CPR with near perfect sensitivity would be desirable, however, it has been argued that a lower sensitivity should not prevent CPR use unless usual decisions, made without the rule, are demonstrably better. [74] Our results are comparable with previous systematic reviews focused on melanoma diagnosis across healthcare settings in highlighting that dermoscopic CPRs are demonstrably better in terms of diagnostic accuracy in comparison with inspection by the naked eye. [16,75] However, even a rule with almost 100% sensitivity may not be adopted. For instance, implementation of the Canadian CT Head Rule, despite 100% sensitivity in validation studies, did not result in a reduction in

imaging rates, with clinicians' reporting unease with certain components of the rule and fear of missing a high-stakes diagnosis as reasons for not adopting the CPR.[76]

Before considering whether to use a CPR in clinical practice, it is essential that its performance be established through external validation (i.e. in settings outside where it was derived). We identified a number of external validation studies in this review, however, in keeping with much CPR research, the reporting of these studies was often poor.[77,78] In particular, the common issues of limited acknowledgement and handling of missing data and key performance measures of prediction models i.e. calibration, being omitted was encountered.[77] The lack of available data in some papers meant not all studies could be combined in the meta-analysis, meaning the sensitivities and specificities reported here are not based on the totality of existing evidence. Furthermore, we were unable to assess diagnostic accuracy at different cut-point thresholds for respective CPRs. Improved reporting of CPRs at cut-point thresholds will enable pooling of diagnostic accuracy data, and will provide more robust measures of diagnostic accuracy. After validation, impact analysis studies are undertaken to determine the impact of the implementation of a CPR on processes and outcomes of care. Despite increasing interest in developing and validating CPRs relevant to primary care, relatively few have undergone impact analysis. [79] Despite the large number of CPRs identified in this review, we identified only three impact analysis studies, with only two studies reporting an improvement in correct melanoma diagnosis in primary care as a result. Arguably, the dearth of well-conducted and clearly reported external validation and impact analysis studies undermines trust in the use of such rules in practice. [77]

Current NICE guidelines for melanoma detection and management recommend dermoscopy of any suspicious lesion, advising against using computer assisted diagnostic tools (NG14) while promoting use of the weighted 7-point checklist in primary care to guide referral (NG12).[20] Based on the findings of this review, the ABCD rule for dermoscopy had a higher sensitivity than the seven point for dermoscopy checklist at their respective cut-points, indicating its potential for use in primary care. Dermoscopy, however, requires training and equipment, and is less commonly performed in primary care. Evidence suggests that

dermatologists have better diagnostic accuracy than primary care physicians. [18] Three studies retrieved in our search assessed dermoscopy CPR performance when applied by non-experts, with two studies reporting that the CPRs performed well overall when used by non-experts, mainly primary care physicians. [49,66,72] Both Westerhoff et al [62] and Argenziano et al [80] demonstrated that training primary care physicians to use dermoscopy with CPRs showed significant improvement in the diagnosis of melanoma compared with naked eye inspection. Alongside the use of CPRs, training in dermoscopy would seem to be a strategy that will enhance diagnostic accuracy of melanoma in the future particularly in light of emerging evidence of differences in dermoscopic features of melanoma such as head and neck melanoma.[81] It has also been highlighted that significant efforts are needed to standardize and improve dermoscopic terminology to more broadly promote the use of dermoscopy in the primary care setting. [82] Of the 24 rules identified in this review, four were clinical (i.e. naked eye) and 17 were dermoscopic. Due to the limited number of studies and available data, no meta-analysis of clinical CPRs could be conducted. The range of reported sensitivities from individual studies indicates that there is insufficient evidence to recommend their use in practice.

Strengths and limitations of our study

The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. However, the findings of this systematic review need to be interpreted in the context of the limitations of the original studies. The lack of available data in some papers meant not all studies could be combined in the meta-analysis. A number of studies that validated CPRs and algorithms using novel diagnostic technologies which incorporated computerised image analysis and artificial intelligence were excluded from the review as routine use of these is not currently recommended in UK NICE clinical guidelines. Significant heterogeneity existed between the studies with respect to differences in the study populations and application of the CPR. Lastly, individual patient data that enables pooling of risk scores at the different cut-points would enable researchers

to explore the clinical utility of applying risk scores at different cut-points with the purpose of assessing the role of melanoma CPRs at the different diagnostic thresolds of "ruling out" (utilising highest pooled sensivity) or "ruling in" (utilising highest pooled specificity) of respective melanoma CPRs.

Implications for practice and future research

Early detection followed by curative surgery greatly improves the prognosis of malignant melanoma. As the incidence of melanoma skin cancer increases, primary care physicians are increasingly required to screen for melanoma.[12] Therefore, efforts to increase the early detection of melanoma must focus on supporting primary care physicians in performing skin cancer screenings with recent evidence highlighting the benefits of developing targeted screening strategies in high risk patients in primary care.[18,83] This systematic review identified 24 separate clinical (naked eye) and dermoscopic CPRs, with some overlap in the included the elements. Our analysis highlights that dermoscopic CPRs have reasonable sensitivity, with the ABCD rule for dermoscopy having better sensitivity than the seven point checklist for dermoscopy. Further development of new rules is unlikely to benefit the field of research. An increased emphasis on better reporting of validation studies, particularly at different cut-point thresholds, would allow for the conduct of more robust diagnostic accuracy meta-analysis to inform decision making. Further methodologically robust randomised controlled trials are necessary also to examine the impact of implementing CPRs in clinical practice, in terms of patient outcomes, physician behaviour, processes of care, and cost-effectiveness. Lastly, whilst guidelines promote the use of dermoscopy in the assessment of pigmented skin lesions, there needs to be greater emphasis on training in primary care on this examination technique.

Conclusion

This systematic review and meta-analysis shows that dermoscopic CPRs have reasonably high pooled estimates of sensitivity and may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients. The ABCD rule of dermoscopy has higher pooled sensitivity

than the 7 point checklist for dermoscopy, when consideration about ruling out melanoma is being made. A focus on impact analysis may help translate melanoma CPRs into useful and effective triage tools for use in primary care.

Footnotes

Contributors: EH, NW, and BC drafted the manuscript. EH, NW, and BC contributed to development of the selection criteria, the risk of bias assessment strategy, and the data extraction criteria. EH and PM developed the search strategy. HB, LA, and HS contributed the data extraction and quality assessments. BC and TF read, provided feedback and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Legends

Figure 1.b

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

Figure 2.b

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies

References

1. Erdmann F, Lortet-Tieulent J, Schüz J, et al. International trends in the incidence of malignant melanoma 1953–2008—are recent generations at higher or lower risk? *International Journal of Cancer.* 2013;132(2):385-400.
2. Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *Journal of the European Academy of Dermatology and Venereology : JEADV.* Sep 2014;28(9):1170-1178.
3. Coory M, Baade P, Aitken J, Smithers M, McLeod GRC, Ring I. Trends for in situ and Invasive Melanoma in Queensland, Australia, 1982–2002. *Cancer Causes & Control.* 2006;17(1):21-27.
4. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. *Journal of the American Academy of Dermatology.* Nov 2011;65(5 Suppl 1):S17-25.e11-13.
5. de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. *Int J Cancer.* Oct 20 2003;107(1):119-126.
6. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology.* 1998;197(1):11-17.
7. Cornish D, Holterhues C, van de Poll-Franse LV, Coebergh JW, Nijsten T. A systematic review of health-related quality of life in cutaneous melanoma. *Annals of Oncology.* 2009;20(Suppl 6):vi51-vi58.
8. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002–2006 and 2007–2011. *American journal of preventive medicine.* 11/10 2015;48(2):183-187.
9. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer.* 2005 41(1):45-60.
10. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer.* 2005;41(1):28-44.
11. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer.* 2005;41(14):2040-2059.
12. Koelink CJL, Kollen BJ, Groenhof F, van der Meer K, van der Heide WK. Skin lesions suspected of malignancy: an increasing burden on general practice. *BMC Fam Pract.* 2014;15:29.
13. Pockney P, Primrose J, George S, et al. Recognition of skin malignancy by general practitioners: observational study using data from a population-based randomised controlled trial. *Br J Cancer.* Jan 13 2009;100(1):24-27.
14. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. *Journal of the American Academy of Dermatology.* 2003;48(5):679-693.
15. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. *Eur J Dermatol.* Sep 1999;9(6):470-476.
16. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* Mar 2002;3(3):159-165.

17. Piccolo D, Ferrari A, Peris K, Diadone R, Ruggeri B, Chimenti S. Dermoscopic diagnosis by a trained clinician vs. a clinician with minimal dermoscopy training vs. computer-aided diagnosis of 341 pigmented skin lesions: a comparative study. *Br J Dermatol.* Sep 2002;147(3):481-486.
18. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and Managing Cutaneous Pigmented Lesions: Primary Care Physicians Versus Dermatologists. *Journal of General Internal Medicine.* 2006;21(7):678-682.
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews.* 2015;4(1):1-9.
20. Macbeth F, Newton-Bishop J, O'Connell S, Hawkins JE. Melanoma: summary of NICE guidance. *BMJ.* 2015-07-29 09:46:21 2015;351.
21. Moons KGM dGJ, Bouwmeester W, Vergouwe, Y., Mallett, S., Altman, D. G., Reitsma J.B., Collins, G. S. Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist. *PLoS Medicine.* 2014;11(10):e1001744.
22. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: updated March 2011.* 2011.
23. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* Oct 2005;58(10):982-990.
24. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Y T. Analysing and Presenting Results. In: Deeks JJ BP, Gatsonis C, , ed. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0*. Available from: http://methods.cochrane.org/sdt/handbook-dta-reviews/: The Cochrane Collaboration; 2010.
25. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. *Journal of the American Academy of Dermatology.* 2007;56(5):759-767.
26. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Archives of Dermatology.* 1998;134(12):1563-1570.
27. Argenziano G, Catricalà C, Ardigo M, et al. Seven-point checklist of dermoscopy revisited. *British Journal of Dermatology.* 2011;164(4):785-790.
28. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. *Eur J Dermatol.* Jun 2000;10(4):282-287.
29. Carli P, Quercioli E, Sestini S, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. *British Journal of Dermatology.* 2003;148(5):981-984.
30. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. *European Journal of Dermatology.* 1999;9(4):303-308.

31. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. *European Journal of Dermatology.* 2014;24(4):477-481.
32. Pizzichetta MA, Talamini R, Piccolo D, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. *Tumori.* 2002;88(3):234-238.
33. Soyer HP, Argenziano G, Zalaudek I, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. *Dermatology.* 2004;208(1):27-31.
34. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. *Melanoma Research.* 2003;13(6):631-632.
35. Buhl T, Hansen-Hagge C, Korpas B, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. *Journal of the American Academy of Dermatology.* 2012;66(1):27-36.
36. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. *BMC Dermatology.* 2010;10:9-9.
37. Haenssle HA, Korpas B, Hansen-Hagge C, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. *Journal of the American Academy of Dermatology.* 2010;62(5):785-793.
38. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. *Clinical and Experimental Dermatology.* 1992;17(5):313-315.
39. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. *Journal of the American Academy of Dermatology.* 1999;40(4):558-562.
40. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. *Clinical and Experimental Dermatology.* 1990;15(3):167-171.
41. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. *Journal of Dermatologic Surgery and Oncology.* 1992;18(1):22-26.
42. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. *Archives of Dermatology.* 2005;141(2):155-160.
43. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. *Journal of Dermatology.* 2014;41(7):598-603.
44. Walter FM, Prevost AT, Vasconcelos J, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. *British Journal of General Practice.* 2013;63(610):345-353.

45. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. *British Journal of Dermatology.* 1999;140(5):902-908.
46. Argenziano G, Longo C, Cameron A, et al. Blue-black rule: A simple dermoscopic clue to recognize pigmented nodular melanoma. *British Journal of Dermatology.* 2011;165(6):1251-1255.
47. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. *Journal of the American Academy of Dermatology.* 2003;48(5):672-678.
48. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. *British Journal of Dermatology.* 2004;151(5):1029-1038.
49. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. *Archives of Dermatology.* 2005;141(8):1008-1014.
50. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. *International Journal of Dermatology.* 2010;49(1):33-38.
51. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. *Australasian Journal of Dermatology.* 2012;53:7-8.
52. Henning JS, Stein JA, Yeung J, et al. CASH algorithm for dermoscopy revisited. *Arch Dermatol.* Apr 2008;144(4):554-555.
53. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. *Acta Derm Venereol.* Mar-Apr 2000;80(2):122-126.
54. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. *British Journal of Dermatology.* 2012;167(5):1037-1041.
55. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. *British Journal of Dermatology.* 2002;146(3):481-484.
56. Menzies SW, Kreusch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Archives of Dermatology.* 2008;144(9):1120-1127.
57. Menzies SW, Moloney FJ, Byth K, et al. Dermoscopic evaluation of nodular melanoma. *JAMA Dermatology.* 2013;149(6):699-709.
58. Argenziano G, Soyer HP, Chimenti S, Ruocco V. Impact of dermoscopy on the clinical management of pigmented skin lesions. *Clin Dermatol.* May-Jun 2002;20(3):200-202.
59. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference.* 2011;2011:3180-3183.

60. Zalaudek I, Argenziano G, Soyer HP, et al. Three-point checklist of dermoscopy: An open internet study. *British Journal of Dermatology.* 2006;154(3):431-437.
61. Walter FM, Prevost AT, Vasconcelos J, et al. The diagnostic accuracy of the 7-point checklist to assess pigmented skin lesions in primary care. *Asia-Pacific Journal of Clinical Oncology.* 2012;8:311.
62. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. *British Journal of Dermatology.* 2000;143(5):1016-1020.
63. Walter FM, Morris HC, Humphrys E, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. *BMJ (Online).* 2012;345(7866).
64. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. *British Journal of Dermatology.* 1994;130(1):48-50.
65. Rao BK, Marghoob AA, Stolz W, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. *Skin Research and Technology.* 1997;3(1):8-14.
66. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. *Journal of the American Academy of Dermatology.* 1999;40(2 I):171-176.
67. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. *Hautarzt.* 1998;49(6):473-476.
68. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. *Acta Dermato-Venereologica.* 1999;79(6):469-472.
69. Nachbar F, Stolz W, Merkle T, et al. The ABCD rule of dermatoscopy. *Journal of the American Academy of Dermatology.* 1994;30(4):551-559.
70. Stolz W, Riemann A, Cognetta AB, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. *European Journal of Dermatology.* 1994;4(7):521-527.
71. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. *British Journal of Dermatology.* 2004;150(5):1040.
72. Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy Improves Accuracy of Primary Care Physicians to Triage Lesions Suggestive of Skin Cancer. *Journal of Clinical Oncology.* April 20, 2006 2006;24(12):1877-1882.
73. Carli P, Nardini P, Crocetti E, De Giorgi V, Giannotti B. Frequency and characteristics of melanomas missed at a pigmented lesion clinic: a registry-based study. *Melanoma research.* Oct 2004;14(5):403-407.
74. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med.* Feb 7 2006;144(3):201-209.
75. Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. *Br J Dermatol.* Sep 2009;161(3):591-604.
76. Stiell IG, Clement CM, Grimshaw JM, et al. A prospective cluster-randomized trial to implement the Canadian CT Head Rule in emergency departments. *CMAJ : Canadian Medical Association Journal.* 2010;182(14):1527-1532.

77. Collins GS, de Groot JA, Dutton S, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology.* 2014;14(1):1-11.
78. Riley RD, Ensor J, Snell KIE, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ.* 2016-06-22 12:16:05 2016;353.
79. Wallace E, Uijen MJM, Clyne B, et al. Impact analysis studies of clinical prediction rules relevant to primary care: a systematic review. *BMJ Open.* 2016;6(3).
80. Blum A, Clemens J, Argenziano G. Modified dermoscopic algorithm for the differentiation between melanocytic and nonmelanocytic skin tumors. *Journal of Cutaneous Medicine and Surgery.* 2006;10(2):73-78.
81. Cengiz FP, Cengiz AB, Emiroglu N, Comert E, Wellenhof RH. Dermoscopic and clinical features of head and neck melanoma. *Anais Brasileiros de Dermatologia.* 2015;90(4):488-493.
82. Carrera C, Marchetti MA, Dusza SW, et al. Validity and reliability of dermoscopic criteria used to differentiate nevi from melanoma: A web-based international dermoscopy society study. *JAMA Dermatology.* 2016;152(7):798-806.
83. Rat C, Grimault C, Quereux G, et al. Proposal for an annual skin examination by a general practitioner for patients at high risk for melanoma: a French cohort study. *BMJ Open.* July 1, 2015 2015;5(7).
84. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. *Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society.* 1992;Suppl 2:295-298.
85. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Archives of Dermatology.* 1996;132(10):1178-1182.
86. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. *British Journal of Dermatology.* 1994;130(3):349-355.

Table 1 CPRs identified for inclusion with cut points for identification of melanoma

Rule name	Cut point used	Number of validation studies
Clinical rules		
ABCDE clinical rule	≥ 1 or ≥ 2	4
ABCD clinical rule	≥ 1	4
Revised 7 point checklist (clinical)	≥ 3	4
7 point checklist (clinical)	≥ 3	4
Dermoscopic rules		
ABCD rule of dermoscopy*	≥ 4.75	15
	≥ 5.45	6
	≥4.2	1
	Not reported	1
7-point checklist for dermoscopy	≥ 3	17
Menzies 1996 dermoscopy for melanoma	≥ 1, no negative features	8
3-point checklist for dermoscopy	≥ 1	6
7 features for melanoma (7FFM)	≥ 2	5
CASH dermoscopy algorithm	≥ 8	3
ABCDE rule (dermoscopy)	Not reported	2
The 3 colour dermoscopy test	≥ 3	2
Revised 7-point checklist for dermoscopy	≥ 1	1
Kreusch 1992 dermoscopy	Not reported	1
Nilles 1994 dermoscopy	Not reported	1
Menzies 2008 dermoscopy for melanoma	≥ 1	1
DynaMel algorithm	≥ 3	1
Menzies 2008 dermoscopy for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	1
Simplified ABC-point list for dermoscopy	≥ 4	1
AC rule for dermoscopy	Not reported	1
Emery 2010 SIAscopy	≥ 6	1
Guitera RCM 2012	Not reported	1
Digital dermoscopy algorithms	Multiple algorithms, different cutoffs.	1

* Score = (A score x 1.3) + (B score x 0.1) + (C score x 0.5) + (D score x 0.5)

Table 2 Characteristics of validation and impact analysis studies included

Validation Studies						
Author Year Country	**Setting**	**CPR utilised**	**Lesions**	**Patient: n, sex, mean age**	**CPR applied by: n, experience**	**Reported sensitivity/specificity**
Annessi 2007[25] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	198 96 melanomas, 102 nonmelanoma	N = 195 54% male Mean age: 43	2 ELM-experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 84.4 Sp: 74.5 7-point checklist for dermoscopy (cut point ≥3) Se: 78.1 Sp: 64.7
Argenziano 1998[26] Italy	Deparment of Dermatology	7-point checklist for dermoscopy ABCD rule of dermoscopy	342 117 melanoma, 225 nonmelanoma	NR	5 3 experienced 2 less-experienced	7-point checklist for dermoscopy (cut point ≥3) *Expert user:* Se: 95.0 Sp: 75.0 *Non-expert user (mean):* Se: 89.0 Sp: 61.5 ABCD rule of dermoscopy (cut point ≥4.75) *Expert user:* Se: 85.0 Sp: 66.0 *Non-expert user (mean):* Se: 91.5

						Sp: 31.0
Argenziano 2003[14] 9 countries	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	108	NR	40 experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 82.6 Sp: 70.0 7-point checklist for dermoscopy Se: 85.7 Sp: 71.1 Menzies 1996 dermoscopy for melanoma Se: 85.7 Sp: 71.1
Argenziano 2011[27] Italy	Deparment of Dermatology	7-point checklist for dermoscopy Revised 7-point checklist for dermoscopy	300 100 excised melanoma, 100 excised nonmelanoma, 100 nonexcised nonmelanoma	NR	8 experienced	7-point checklist for dermoscopy (cut point ≥3) Se: 77.9 Sp: 85.6 Revised 7-point checklist for dermoscopy (cut point ≥1) Se: 87.8 Sp: 74.5
Benelli 1999[15] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	401 60 melanomas, 341 nonmelanoma	NR	2 research team	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 80.0 Sp: 89.1 ABCDE Clinical rule (cut point

						≥2) Se: 85.0 Sp: 44.5
Benelli 2000[28] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	600 76 melanomas, 524 nonmelanoma	Mean age: 53	3	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 68.8 Sp: 86.0 ABCDE Clinical rule (cut point of ≥2) Se: 47.3 Sp: 56.0
Binder 1999[66] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	250	NR	17 12 experienced 5 trainee	ABCD rule of dermoscopy (cut point ≥4.75) Se: 81.0 Sp: 77.0 ABCD rule of dermoscopy (cut point ≥5.45) Se: 73.0 Sp: 90.0
Blum 2003[71] Germany	Deparment of Dermatology	The 3 colour dermoscopy test	249	NR	NR	The 3 colour dermoscopy test Se: 76.9 Sp: 90.1
Blum 2004[47] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma Simplified ABC-point list for	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy

		dermoscopy 7FFM (7 features for melanoma) dermoscopy				Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8 7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6 Simplified ABC-point list for dermoscopy Se: 90.5 Sp: 87.0
Blum 2004[48] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma 7FFM (7 features for melanoma) dermoscopy	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8

						7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6
Buhl 2012[35] Germany	Deparment of Dermatology	DynaMel Algorithm 7-point checklist for dermoscopy	675	N= 688 57% male Mean age: 42	Dermatology residents	DynaMel Algorithm Se: 77.1 Sp: 98.1 7-point checklist for dermoscopy (cut point ≥3) Se: 47.5 Sp: 99.0
Carli 2002[29] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	200 44 melanomas, 156 nonmelanoma	NR	5 dermatology residents	ABCD rule of dermoscopy (cut point ≥5.45) Se: 88.1 Sp: 45.7 7-point checklist for dermoscopy (cut point ≥3) Se: 91.9 Sp: 35.2
Dal Pozzo 1999[30] Italy	Department of dermatology	7FFM (7 features for melanoma) dermoscopy	713 168 melanomas, 545 nonmelanoma	NR	3	7FFM (7 features for melanoma) dermoscopy Se: 94.6 Sp: 85.5
Dolianitis 2005[49] Australia	Primary care and Dermatology department	7-point checklist for dermoscopy ABCD rule of dermoscopy Menzies 1996 dermoscopy for	40 20 melanomas, 20 nonmelanoma	NR	61 35 Primary care physicians, 10	7-point checklist for dermoscopy Se: 81.4 Sp: 73.0

		melanoma			dermatologists, 16 trainee dermatologists	ABCD rule of dermoscopy (cut point ≥5.45) Se: 77.5 Sp: 80.4 Menzies 1996 dermoscopy for melanoma Se: 84.6 Sp: 77.7
Emery 2010[36] UK	Family practice	Emery 2010 SIAscopy in primary care for melanoma	1211	N=858 52% male Mean age: 50	1 SIAscopy expert	Emery 2010 SIAscopy in primary care for melanoma Se: 50.0 Sp: 84.0
Feldman 1998[67] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	500 30 melanomas, 470 nonmelanoma	NR	NR	ABCD rule of dermoscopy (cut point ≥4.2) Se: 88.0 Sp: 64.0
Gereli 2010[50] Turkey	Deparment of Dermatology	7-point checklist for dermoscopy 3-point checklist for dermoscopy	96 48 melanoma, 48 nonmelanoma	NR	3 2 experienced 1 inexperienced	7-point checklist for dermoscopy (cut point ≥3) Se: 87.5 Sp: 16.2 3-point checklist for dermoscopy (cut point ≥2) Se: 89.6 Sp: 31.2
Guitera 2012[51] Multiple	Skin cancer clinic	Guitera 2012 confocal microscopy for melanoma	710 216 melanomas, 494 nonmelanoma	N = 663	NR	Guitera 2012 confocal microscopy for melanoma Se: 87.6

						Sp: 70.8
Haenssle 2010[37] Germany	Deparment of Dermatology	7 point checklist for dermoscopy	1219 127 melanomas, 1092 nonmelanoma	N= 688 57% male Mean age: 42	Inexperienced	7 point checklist for dermoscopy (cut point ≥3) Se: 62.0 Sp: 97.0
Healsmith 1993[64] UK	Pigmented lesion clinic	Revised 7-point checklist (clinical) ABCDE clinical rule	165 65 melanoma, 100 nonmelanoma	NR	NR	Revised 7-point checklist (clinical) Se: 100 Sp: nr ABCDE clinical rule Se: 92.3 Sp: nr
Henning 2008[52] USA	Deparment of Dermatology	CASH dermoscopy algorithm ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	150 50 melanoma, 100 nonmelanoma	NR	2 Inexperienced	CASH dermoscopy algorithm Se: 87.0 Sp: 67.0 ABCD rule of dermoscopy Se: 86.0 Sp: 74.0 7-point checklist for dermoscopy Se: 76.0 Sp: 57.0 Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 38

Higgins 1992[38] UK	Deparment of Dermatology	7 point checklist (clinical) 7 point checklist (clinical) revised	100 0 melanoma, 100 nonmelanoma	N=100 30% male Mean age: 36.7	NR	7 point checklist (clinical) revised Se: NR Sp: 70.0
Kittler 1999[39] Austria	Deparment of Dermatology	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	356 73 melanomas, 283 nonmelanoma	N= 352 43% male Mean age: 52	NR	NR
Keefe 1989[40] Scotland	Hospital dermatology clinic	7-point checklist (clinical)	222	N=195 22% male Mean age: 43	Dermatologists 195 patients	7-point checklist (clinical) (cut point ≥3) *Dermatologists:* Se: 85.7 Sp: 66.5 *Patients:* Se: 71.4 Sp: 66.2
Kreusch 1992[84] Germany	Deparment of Dermatology	Kreusch 1992 dermoscopy for melanoma	317 96 melanomas, 221 nonmelanoma	NR	2 1 experienced 1 inexperienced	Kreusch 1992 dermoscopy for melanoma *Experienced:* Se: 98.9 Sp: 94.1 *Inexperienced:* Se: 97.0 Sp: 94.2
Lorentzen 1999[68] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	232	NR	8 4 experienced 4 inexperienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 59.0 Sp: 92.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 41.0 Sp: 98.0
Lorentzen 2000[53] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	258 64 melanoma, 194 nonmelanoma	NR	3 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 70.7 Sp: 88.0
Luttrell 2012[54] Austria	Deparment of Dermatology	AC rule for dermoscopy	200 25 melanoma, 178 nonmelanoma	NR	17 Lay persons	AC rule for dermoscopy Se: 91.2 Sp: 94.0
Mackie 2002[55] Scotland	Pigmented lesion clinic	The 3 colour dermoscopy test	126 69 melanoma 57 nonmelanoma	NR	3 Experienced	The 3 colour dermoscopy test Se: 97.0 Sp: 55.0
McGovern 1992[41] USA	Dermatology clinic	7 point checklist (clinical) BCD clinical rule	237 16 malignant, 221 nonmelanoma	N=179 50% male Mean age: 44	NR	7 point checklist (clinical) Se: 0.44 Sp: 0.94
Menzies 1996[85] Australia	Melanoma unit	Menzies 1996 dermoscopy for melanoma	385 107 melanomas,	NR	NR	Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 71.0
Menzies 2008[56]		7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma Menzies 2008 dermoscopy for melanoma Menzies 2008 dermoscopy for skin cancer	497 105 melanomas, 392 nonmelanoma	NR	12 Experienced	7-point checklist for dermoscopy Se: 41.0 Sp: 83.0 3-Point checklist of dermoscopy Se: 50.0 Sp: 71.0 Menzies 1996 dermoscopy for melanoma

						Se: 54.0 Sp: 76.0 Menzies 2008 dermoscopy for melanoma Se: 70.0 Sp: 56.0 Menzies 2008 dermoscopy for skin cancer Se: 95.0 Sp: 80.0
Menzies 2013[57]		ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma CASH dermoscopy algorithm Menzies 2013 dermoscopy for nodular melanoma	465 217 melanomas, 248 nonmelanoma	NR	12	ABCD rule of dermoscopy Se: 81.5 Sp: NR 7-point checklist for dermoscopy Se: 94.4 Sp: NR 3-Point checklist of dermoscopy Se: 83.9 Sp: NR Menzies 1996 dermoscopy for melanoma Se: 98.4 Sp: NR CASH dermoscopy algorithm

						Se: 41.0 Sp: 83.0 Menzies 2013 dermoscopy for nodular melanoma Se: 93.0 Sp: 70.0
Nachbar 1994[69] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	194 69 melanomas	NR	NR	ABCD rule of dermoscopy (cut point ≥5.45) Se: 92.8 Sp: 91.2
Nilles 1994[86] Germany	Deparment of Dermatology	Nilles 1994 dermoscopy for melanoma	260 72 melanomas, 188 nonmelanoma	NR	NR	Nilles 1994 dermoscopy for melanoma Se: 90.0 Sp: 85.0
Osborne 1999[45] UK	Deparment of Dermatology	Revised 7-Point Checklist (clinical)	778 778 melanomas, 0 nonmelanoma	N=733 35% male	NR	Revised 7-Point Checklist (clinical) False negative rate: 18.5
Piccolo 2014[31] Italy	Deparment of Dermatology	ABCD rule of dermoscopy	165 33 melanomas, 129 nonmelanoma	N =165 59% male Mean age: 43.5	4 3 dermatologists 1 FP	ABCD rule of dermoscopy Se: 91.0 Sp: 52.0
Pizzichetta 2002[32] Italy	Department of Oncology	ABCD rule of dermoscopy	129	N = 123	2 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 43.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 90.0 Sp: 53.5
Rao 1997[65]	Deparment of Dermatology	ABCD rule of dermoscopy ABCD clinical rule	73	N =63	4 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 57.0 ABCD clinical rule Se: 84.0 Sp: 78.0
Skvara 2005[42] Austria	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	325 63 melanomas, 262 nonmelanoma	N =297 44% male Mean age: 39	2 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 31.7 Sp: 87.3 7-point checklist for dermoscopy Se: 11.1 Sp: 95.2
Soyer 2004[33] Italy	Deparment of Dermatology	3-point checklist of dermoscopy	231 68 melanomas, 163 nonmelanomas	N = 225 49% male	6 Inexperienced	3-point checklist of dermoscopy Se: 96.3 Sp: 32.8
Stolz 1994[70] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	157	NR	NR	ABCD rule of dermoscopy(cut point ≥5.45) Se: 97.9 Sp: 90.3
Strumia 2003[34] Italy	Deparment of	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	49	NR	2	

	Dermatology					
Thomas 1998[6] France	Deparment of Dermatology	ABCDE clinical rule	1140	NR	NR	ABCDE clinical rule (cut point ≥2) Se: 89.3 Sp: 65.3
Unlu 2014[43] Turkey	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-point checklist of dermoscopy CASH dermoscopy algorithm	115 24 melanomas, 91 nonmelanoma	N= 115 49% male Mean age: 39	3 experienced dermatoscopists	ABCD rule of dermoscopy Se: 91.6 Sp: 60.4 7-point checklist for dermoscopy Se: 79.1 Sp: 62.6 3-point checklist of dermoscopy Se: 87.5 Sp: 65.9 CASH dermoscopy algorithm Se: 91.6 Sp: 64.8
Wadhawan 2011[59] USA	Images from library of skin cancer	7-point checklist for dermoscopy	347	NR	NR	7-point checklist for dermoscopy Se: 87.3 Sp: 71.3
Walter 2013[44] UK	Family practice	7 point checklist (clinical) Revised 7-point checklist (clinical)	1436 36 melanomas, 1400 nonmelanoma	N= 1182 35.9% male Mean age: 44.7	NR	7 point checklist (clinical) Se: 80.6 Sp: 61.7

						Revised 7-point checklist (clinical) Se: 91.7 Sp: 33.1
Zalaudek 2006[60] 29 Countries	Pigmented lesion clinic	3-point checklist for dermoscopy	150 44 malignant, 106 nonmelanoma	NR	150 varying levels of experience	3-point checklist for dermoscopy Se: 94.0 Sp: 71.9
Impact Analysis Sudies						
Author Year Country	**Study design**	**Participant selection**	**Lesions**	**Intervention**	**Control**	**Outcomes**
Westerhof f 2000[62] Australia Primary care	Controlled before & after	74 FPs	n=100 (50 melanoma, 50 non-melanoma) selected randomly from the Sydney Melanoma Unit image database	Educaional intervention. FPs given educational material on Menzies 1996 rule, followed by a 1-h presentation on surface microscopy	Usual care	**Correct diagnosis of melanoma, percent (SD):** Intervention 75.9 (12) Control 54.8 (22) **Correct diagnosis of non-melanoma, percent (SD):** Intervention 57.8 (14) Control 55.8(15)
Walter 2012[63] England Primary care	RCT	15 FP practices	1580 from 1297 patients	Patients assessed using the MoleMate system (SIAscopy with primary care	Best practice (clinical history, naked eye examination, seven point	**Primary, appropriateness of referral (defined as the proportion of referred lesions that secondary care experts decided to biopsy or monitor):** no statistically significant

				scoring algorithm)	checklist clinical)	difference between intervention or control; 56.8% v 64.5%; difference −8.1% (95% CI −18.0% to 1.8%). **Secondary:** • Appropriate management of benign lesions in primary care: no statistically significant difference between intervention or control (99.6% v 99.2%, P=0.46). • Agreement with an expert decision to biopsy or monitor: no statistically significant difference between intervention and control (98.5% v control 95.7%, P=0.26). • Patient satisfaction: more intervention patients ranked their consultation very good/excellent for thoroughness than control (83.1% v 71.2%, P<0.001). Patient anxiety: no statistically significant difference between intervention and control in anxiety scores (32.56 v 34.72,

						P=0.013)
Argenziano 2006 [72] Spain, Italy Primary Care	RCT	73 FPs	2548 lesions from 2522 patients presenting to primary care with a pigmented skin lesion. 1203 lesions in dermoscopy group (6 melanoma) 1345 lesions in control group (6 melanoma)	Use of dermoscopy in addition to "naked eye" lesion screening. Both groups received a 4 hour educational intervention incorporating clinical examination and use of the 3 point checklist (dermoscopy algorithm)	Naked eye screening alone.	**Primary outcome:** Referral accuracy of PCPs (defined as the ability of the PCP to correctly determine a lesion may be malignant or benign, when the gold standard is diagnosis by a second expert clinician) reported as sensitivity, specificity, PPV, NPV. • Significant difference in sensitivity (dermoscopy 79.2%, naked-eye 54.1%, P=0.002) and negative predictive value (dermoscopy 9801%, naked-eye 95.8%, P=0.004) **Secondary outcome:** Number of malignant tumours missed by PCPs using naked eye examination (n=23) and using dermoscopy (n=6) (P=0.002)

NR: Not reported
Se: Sensitivity
Sp: Specificity

Table 3.a Comparison of elements in clinical prediction rules for malignant melanoma (clinical rules)

Elements	Clinical CPR name			
	ABCD	**ABCDE**	**7 point checklist**	**Revised 7 point checklist**
Asymmetry	X	X		X
Border irregularity	X	X	X	
Colour variegation	X	X	X	X
Diameter (>6mm)	X	X	X (>7mm)	X (>7mm)
Evolving (e.g. size, shape, colour)		X	X (size)	X
Altered sensation			X	X
Inflammation			X	X
Crusting, bleeding			X	X
Cut point	*≥ 1*	*≥ 1 or ≥2*	*≥ 3*	*≥ 3*

Table 3.b Comparison of elements in clinical prediction rules for malignant melanoma (dermoscopic rules)

Element	CPR Name															
	ABCD	7-point checklist	Revised 7-point checklist	Menzies 1996	3-point checklist	7FFM	CASH	ABCDE	3 colour test	Kreusch 1992	Nilles 1994	Menzies 2008 - melanoma	Menzies 2008- skin cancer	DynaMel	Simplified ABC	AC rule
Asymmetry	X			X	X	X	X	X		X	X	X		X	X	X
Multiple colours (light/dark brown, black, red white, blue)	X	X	X	X			X	X	X	X	X	X		X	X	X
Architectural disorder (structures & colours)		X				X	X			X	X		X	X	X	
Atypical network	X	X	X	X	X	X	X	X					X			
Blue-white veil			X	X	X	X	X					X				
Blue white structures								X					X			
Streaks/radial streaming/ psuedo-pods	X	X	X	X		X	X	X		X	X			X		
Dots, globules	X	X	X	X			X	X				X	X	X		
Regression structures		X	X			X	X			X	X		X	X		

or erythema																
Scarring				X			X									
Blotches (structureless region >10%	X						X	X								
Atypical vascular pattern		X	X				X			X		X	X	X		
Recognisable as benign													X			
Abrupt cut-off border pigment	X					X		X							X	
Blue-grey dots												X				
Change								X				X		X	X	
Cut point	≥4.75 ≥5.45	≥3	≥1	≥1, no - features	≥1	≥2	≥2	Not reported	≥3	Not reported	Not reported	≥1	≥0 (High sensitivity) ≥1 (High specificity)	≥3	≥4	Not reported

Table 4 Sensitivity and specificity of all clinical and dermoscopy CPRs

Rule name	Cut point	Sensitivity *	Specificity*
Clinical rules			
ABCDE	≥ 1	*2 studies* 0.47-0.92 (mean 0.70)	*1 study* 0.56
	≥ 2	0.85	0.44
7 point checklist	≥ 3	*3 studies* 0.44-0.86 (mean 0.70)	*3 studies* 0.62-0.94 (mean 0.74)
Revised 7 point checklist	≥ 3	0.92	0.33
ABCD rule	≥ 1	0.84	0.78
Dermoscopic rules			
ABCD rule	≥ 4.75	*Meta-analysis* *(8 studies)* 0.85 (95% CI 0.73-0.93)	*Meta-analysis* *(8 studies)* 0.72 (95% CI 0.65-0.78)
	≥ 5.45	*4 studies* 0.73-0.98 (mean 0.85)	*4 studies* 0.46-0.91 (mean 0.79)
	≥4.2	0.88	0.64
7-point checklist	≥ 3	*Meta-analysis* *(11 studies)* 0.77 (95% CI 0.61-0.88)	*Meta-analysis* *(11 studies)* 0.80 (95% CI 0.59-0.92)
Menzies 1996 for melanoma	≥ 1	*6 studies* 0.85-0.95 (mean 0.91)	*6 studies* 0.38-0.78 (mean 0.69)
3-point checklist	≥ 1	*5 studies* 0.50-0.96 (mean 0.84)	*4 studies* 0.31-0.72 (mean 0.55)
7 features for melanoma (7FFM)	≥ 2	*5 studies* 0.69-0.95 (mean 0.86)	*5 studies* 0.74-0.86 (mean 0.82)
CASH algorithm	≥ 8	*3 studies* 0.41-0.92 (mean 0.73)	*3 studies* 0.65-0.97 (mean 0.82)
The 3 colour test	≥ 3	*2 studies* 0.77-0.97 (mean 0.87)	*2 studies* 0.55-0.90 (mean 0.73)
Revised 7-point checklist	≥ 1	0.88	0.28
Kreusch 1992	Not reported	0.99	0.94
Nilles 1994	Not reported	0.90	0.85
Menzies 2008 for melanoma	≥ 1	0.70	0.56
DynaMel algorithm	≥ 3	0.77	0.98
Menzies 2008 for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	0.95	0.80
Simplified ABC-point list	≥ 4	0.90	0.87
AC rule	Not reported	0.91	0.94
Emery 2010 SIAscopy	≥ 6	0.50	0.84
Guitera RCM 2012	Not reported	0.88	0.71
ABCDE rule	Not reported	Not reported	Not reported

* Where sensitivity and specificity are presented for more than one study, the range and mean are presented. Where meta-analysis was possible, values from meta-analysis are presented with 95% confidence intervals (CI).

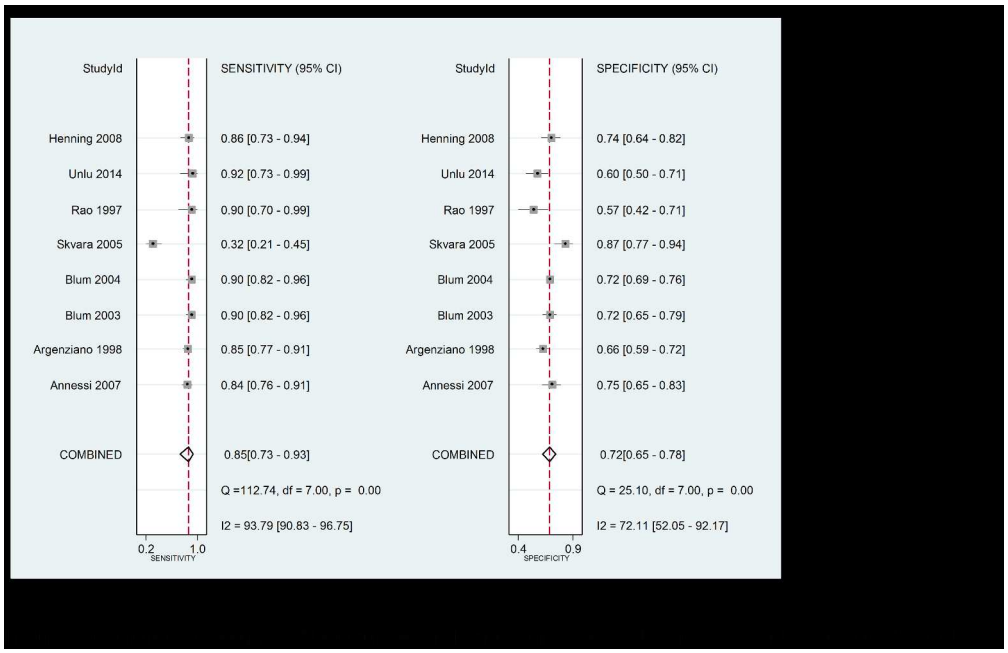


Figure 1.a Diagnostic accuracy ABCD rule with dermoscopy - pooled sensitivity and specificity (8 studies)

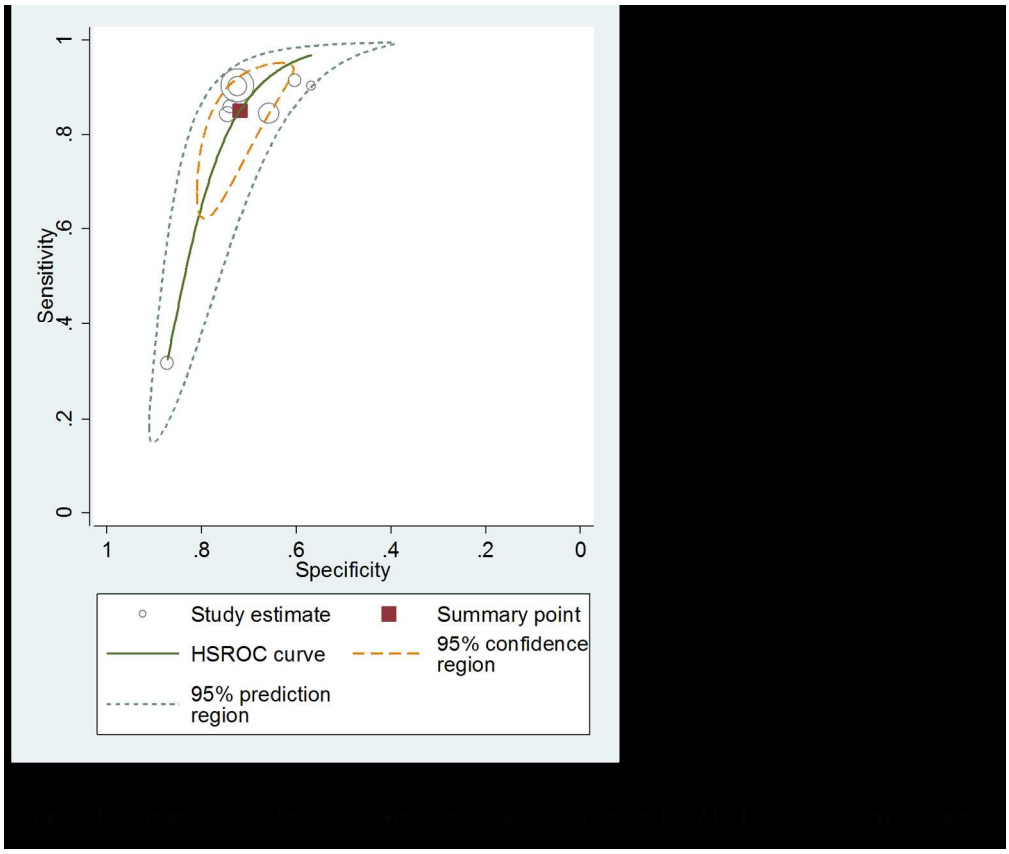


Figure 1.b Summary receiver operating characteristic curves for ABCD rule of dermoscopy

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

159x134mm (300 x 300 DPI)

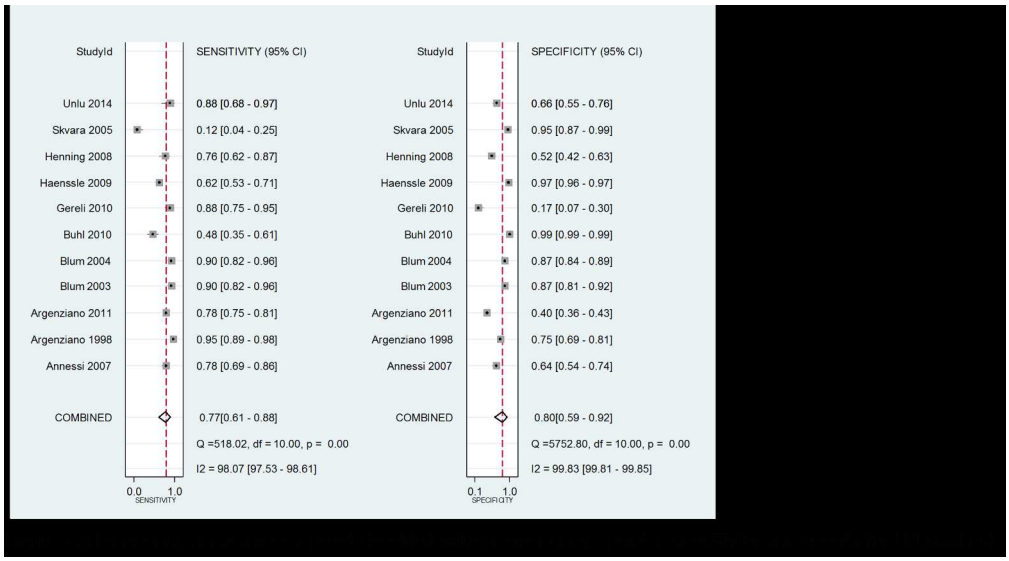


Figure 2.a Diagnostic accuracy of 7 point checklist with dermoscopy - pooled sensitivity and specificity (11 studies)

198x109mm (300 x 300 DPI)

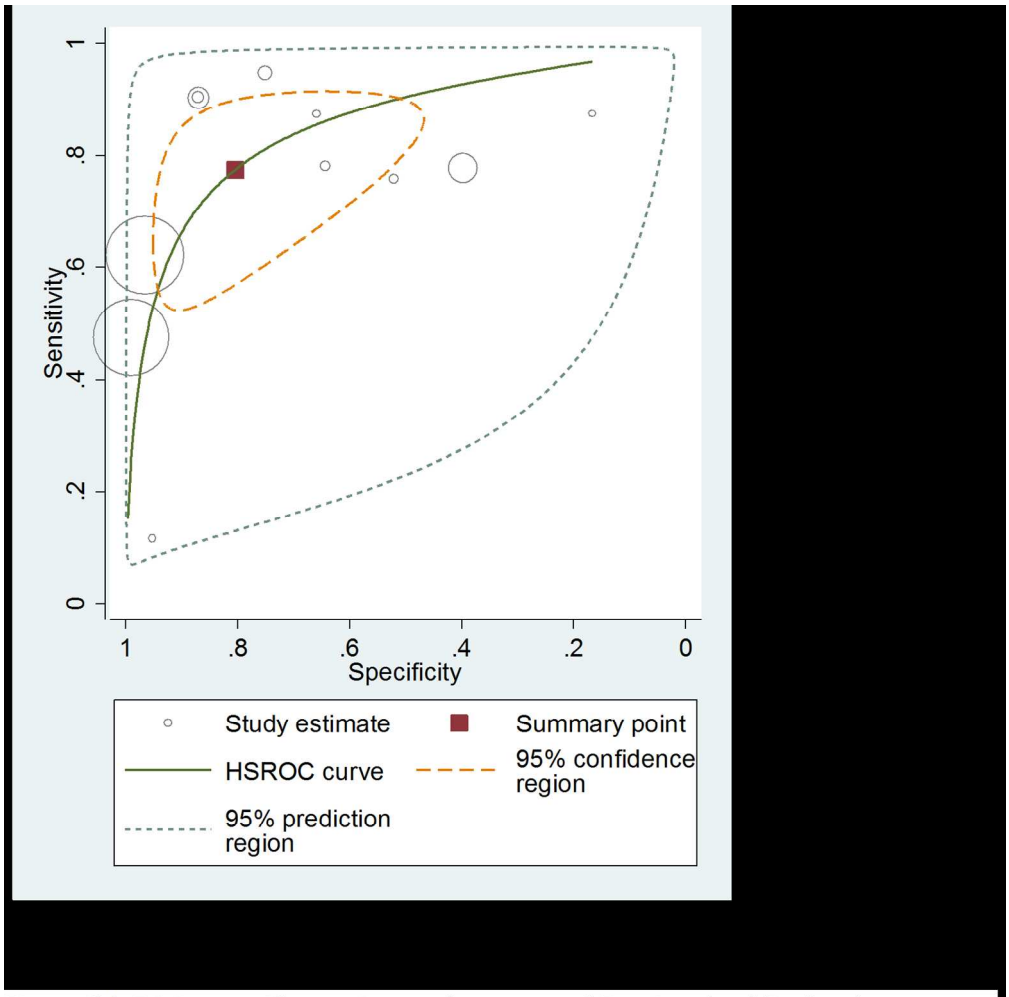


Figure 2.b ROC curve illustrating performance of 7 point checklist for dermoscopy

Figure 2.b Summary receiver operating characteristic curves for ABCD rule of dermoscopy

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

141x144mm (300 x 300 DPI)

Appendix 1: Elements in Clinical Prediction Rules for cutaneous malignant melanoma

CPR name	*Clinical* **ABCD (1)**	*Clinical* **ABCDE (2)**	*Clinical* **Glasgow 7-point checklist (3)**	*Clinical* **Revised 7-point checklist (4)**	*Dermoscopy* **AC Rule for dermoscopy (5)**	*Dermoscopy* **3-point checklist (6)**
Elements	Asymmetry one half not identical to the other half	Asymmetry one half not identical to the other half	Change in size of lesion	***Major features:*** *(2 points each)* Change in size	Asymmetry score between 0 (no asymmetry) and 10 (marked asymmetry)	Asymmetry of colour and structure in one or two perpendicular axes
	Border irregularity uneven or ragged border	Border irregularity uneven or ragged border	Irregular pigmentation	Irregular pigmentation	Colour variation score between 0 (no colour variation) and 10 (marked colour variation)	Atypical pigment network with irregular holes and thick lines
	Colour variegation presence of at least 2 different colours within the lesion	Colour variegation presence of at least 2 different colours within the lesion	Irregular border	Irregular border		Blue white structures
	Diameter	Diameter	Inflammation	***Minor features:***		

	Maximum diameter > 6mm	Maximum diameter >6mm		Inflammation		
		Evolution Patient description of lesion change including elevation, enlargement or colour change	Itch or altered sensation	Itch or altered sensation		
			Larger than other lesions (diameter > 7mm)	Larger than other lesions (diameter > 7mm)		
			Oozing/crusting of lesion	Oozing/crusting of lesion		
Cut point/ specialist referral	Presence of any one element	Presence of any one element	Presence of 3 or more elements	Any one major feature OR 3 points or greater	Participant assessment of whether lesion suspicious or not (no score specified)	Presence of 2 or more elements

CPR name	*Dermoscopy* **C.A.S.H. algorithm (7)**	*Dermoscopy* **Menzies method (8)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma (9)**	*Dermoscopy* **Menzies 2008 dermoscopy for skin cancer (9)**	*Dermoscopy* **7 Features for Melanoma (7FFM) (10)**
Elements	Colour: light brown, dark brown, black, red, white, blue *(each colour=1 point)*	***Benign:*** Symmetry of pattern	**Negative features** (if present, nonmelanoma): >3 milialike cysts	**Negative features (score -1 each)** Multiple (>3) milialike cysts	***Stage 1:*** *determine whether lesion is melanocytic (pigment network or globules); if so, proceed.*
	Architectural disorder *(none=0, moderate=1, marked=2 points)*	One colour; black, grey, blue, dark brown, tan, red	**Positive features** (if any 1 present in a lesion lacking significant pigment, then melanoma): Irregularly sized or distributed brown dots/globules	Symmetrical pigmentation pattern	***Stage 2:*** ***Major features*** (2 points each): Pseudopods
	Symmetry of lesion and within lesion *(biaxial=0, monaxial symmetry=1, biaxial asymmetry=2 points)*	***Positive features:*** Blue-white veil	Multiple blue-grey dots	Comma vessels in regular distribution	Radial streaming
	Homogeneity/heterogeneity	Peripheral black	Irregularlay	Multiple brown dots	Regression-erythema

	network/ dots, globules/ streaks, pseudopods/ blue-white veil/ regression structures (grey areas with or without peppering)/ scarring/ blotches (structureless region of any colour occupying >10% of area)/ polymorphous blood vessels *each structure=1 point*	dots/globules	shaped depigmentation		
		Multiple brown dots	Blue-white veil	**Positive features (score +1 each)** Depigmentation	Grey-blue veil
		Pseudopods	>1 shade of pink	Small diameter arborizing vessels	**Minor features** (1 point each): Unhomogeneity
		Radial streaming	Predominant central vessels	Leaflike areas	Irregular pigment network
		Scarlike depigmentation	Dotted and linar irregular vessels	Ulceration	Sharp margin
		Multiple colours (5 or 6); black, grey, blue, dark brown, tan, red		Irregular size or distributed blu-grey globules	
		Multiple blue/grey dots		Grey colour	
		Broad pigment network		Large-diameter vessels	
Cut	8 points or more	Absent benign	Presence of ≥ 1	Total score ≥ 1	Score of 2 or more

point/ specialist referral		features and 1 or more positive features	positive feature		

CPR name	*Dermoscopy* **ABCD Rule of Dermoscopy/Stolz (11)**	*Dermoscopy* **7 point checklist for dermoscopy (12)**	*Dermoscopy* **Revised 7 point checklist for dermoscopy (13)**	*Dermoscopy* **Simplified ABC-point list of dermoscopy (14)**
Elements	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	***Major criteria:*** *(2 points each)* Atypical pigment network: black, brown, grey thickened and irregular line segments	*Criteria (1 point each):* Atypical pigment network: black, brown, grey thickened and irregular line segments	Asymmetry of outer shape *(1 point)*
	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Asymmetry of differential structures inside the lesion in at least 1 axis *(1 point)*
	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Border: abrupt cutoff of network at the border in at least ¼ of the circumference
	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(1 point each)*	***Minor criteria:*** *(1 point each)* Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Colour: Three or more colours *(1 point)*
		Irregular pigmentation: black,	Irregular pigmentation:	Differential structures:

		brown, grey featureless areas with irregular shape/ distribution.	black, brown, grey featureless areas with irregular shape/ distribution.	Three or more differential structures *(1 point)*
		Irregular dots/ globules: black, brown, grey round to oval, variously sized structures irregularly distributed	Irregular dots/ globules: black, brown, grey round to oval, variously sized structures irregularly distributed	Evolution: Evolution/change noticed by the patient during the last 3 months *(1 point)* No information (0) No change (-1)
(15)		Regression structures: white scarlike areas, blue pepper-like areas	Regression structures: white scarlike areas, blue pepper-like areas	
Cut point/ specialist referral	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Score of 3 or more A **revised 7 point checklist for dermoscopy** allocates 1 point for each of the above criteria and recommends excision or referral if score is 1 or greater.	Score of 1 or more	Score of 4 or more

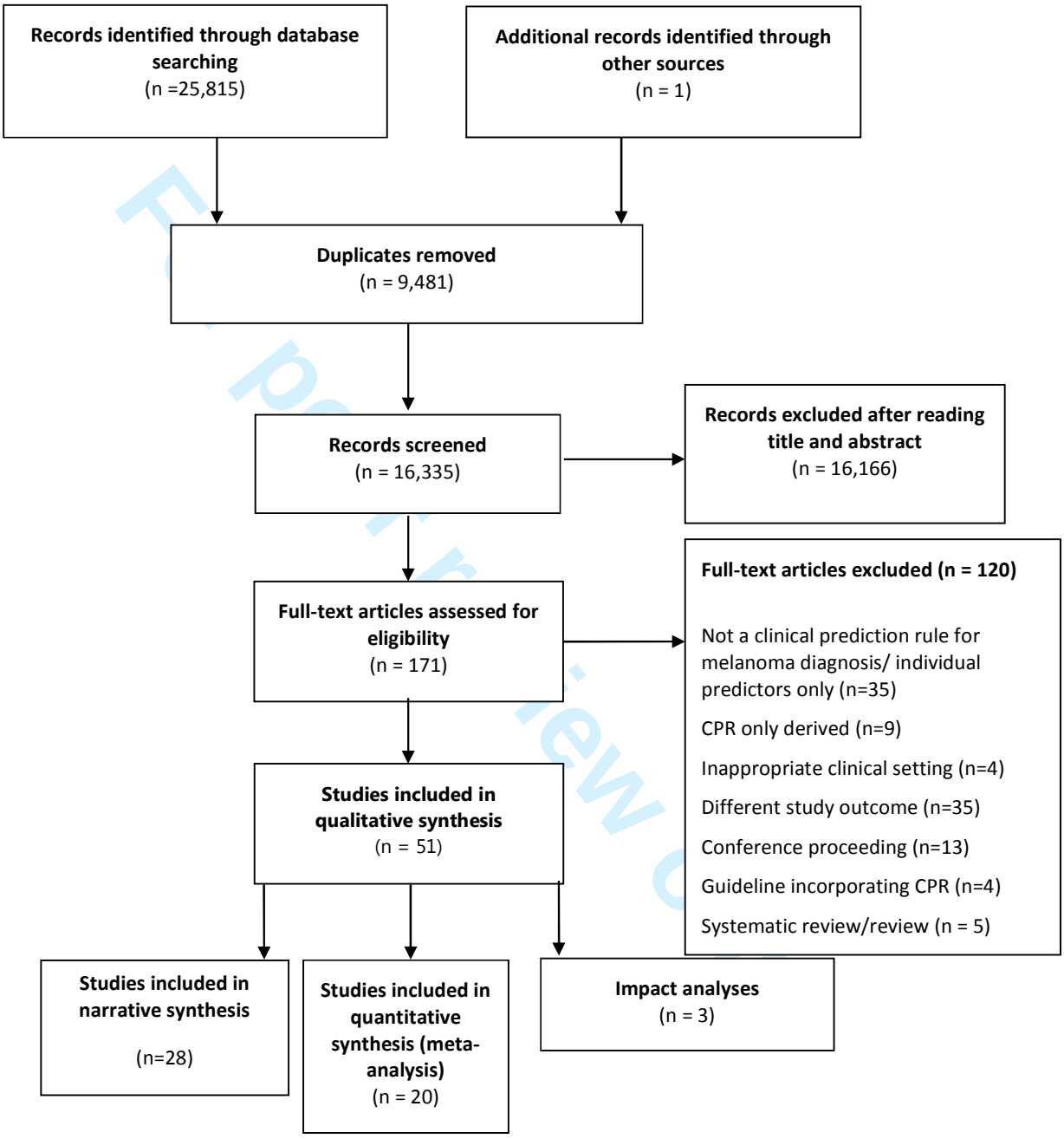
CPR name	*Dermoscopy* **Three-colour dermoscopy test (15)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma lacking significant pigment (9)**	*Dermoscopy* **ABCDE rule for dermoscopy (16)**	*Dermoscopy* **Kreusch 1992 for dermoscopy (17)**	*Dermoscopy* **Nilles 1994 for dermoscopy (18)**
Elements	Presence of 3 or more colours seen in the lesion on dermoscopy	**Negative features** (if present, not a melanoma: >3 milialike cysts	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	Diameter >5mm (1 point)	Clues for malignancy: Asymmetrical pigment distribution
		Positive features Irregularly sized or distributed brown dots or globules	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Border irregularity (1 point)	More than 3 colours
		Multiple blue/grey dots	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Loss of surface microstructure (1 point)	Asymmetrical depigmentation
		Irregularly shaped depigmentation	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(Each component=1 point)*	Scaling/erosion/ulcer (1 point)	Black pigment
		Blue-white veil	Enlargement *(Add 1.2 points if present Subtract 0.8 points if absent)*	Capillaries (1 point)	Sharp pigment border
		>1 shade of pink		Multicomponent	Atypical radial

				architecture (3 points)	streaming
		Predominant central vessels		Greyish colour (3 points)	
		Dotted and linear irregular vessels		Melanophages (6 points)	
				Pseudopods (10 points)	
				Regression (10 points)	
Cut point/ specialist referral	Presence of single element.	Presence of 1 or more positive features	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) + (E) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Not specified	Not specified

CPR name	*Dermoscopy* **DynaMel algorithm (19)**	*SIAoscopy* **Emery 2010 SIAoscopy (20)**	*Reflectance confocal microscopy* **Guitera 2012 RCM (21)**
Elements	**Dynamic major criteria:** Asymmetric-multifocal enlargement (2 points)	*If no specified features of seborrhoeic keratosis or haemangioma presen, a score is allocated for specific features seen on SIAoscopy:* Dermal melanin within the lesion (3 points)	*Reflectance confocal microscopy features:* Cerebriform nests
	Architectural change (2 points)	Presence of any blood vessels (2 points)	Atypical cobblestone with small nucleated cells
	Dynamic minor criteria: Focal increase in pigmentation (1	Blood displacement with erythematous blush (1 point)	Marked cytologic atypia

	point)		
	Focal decrease in pigmentation (1 point)	Maximum diameter greater than 6mm (1 point)	Pageoid cells
	Overall decrease in pigmentation not accompanied by lighter pigmentation of adjacent skin (1 point)	For every completed 15 years of age (1 point)	Epidermal disarray
	7 point checklist for dermoscopy score		Large interpapillary space
			Dense nest
	Add dynamic score to 7 point checklist for dermoscopy score		Constant
Cut point/ specialist referral	≥ 3 points	≥ 6 points	Algorithm or scoring system not specified

Appendix 2: Flow of studies in the review



Appendix 3: CHARMS checklist for included validation studies

	Annessi 2007(22)	Argenziano 1998(12)	Argenziano 2003(23)	Argenziano 2011(13)	Benelli 1999(10)	Benelli 2000(24)
Objective	Validation of ABCD rule of dermoscopy, and the 7-point checklist for dermoscopy	Derivation and validation of 7-point checklist for dermoscopy. Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/stolz, Menzies 1996 dermoscopy for melanoma, and 7-point checklist for dermoscopy	Validation of 7-point checklist and revised 7-point checklist for dermoscopy	Validation of 7 FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.	Validation of 7FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.
Source of data	Cross sectional	Cross-sectional			Cross-sectional, prospective	Cross-sectional retrospective study
Participants	• Consecutive recruitment of atypical melanocytic lesions • December 2004 and June 2006 • 1 department of dermatology	• Atypical melanocytic skin lesions, excised and reviewed for histological diagnosis • Inclusion period: NR • Number of departments of dermatology NR	• Dermoscopy images of lesions preselected from 5 departments of dermatology worldwide • then reviewed by 6 histopathologists, who selected histopathologically unequivocal lesions to include in study.	• Digital database of lesions • Screened between 2006 and 2008 • 1 department of dermatology	All the pigmented lesions observed and excised at the dermatologic surgery department September 1997 – September 1998. 1 dermatology surgery department	Retrospective recruitment; all melanomas <6mm and melanocytic naevi <6mm excised during the study period January 1993 – December 1998. 1 Dermatology surgery department, dermatological sciences institute, university.
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate predictors	NA	11 candidate predictors	NA	NA	NA	NA
Sample Size	198 lesions • 96 melanomas • 102 benign	342 • Derivation 196 (57 melanoma, 139 non-melanoma) • Validation 146 (60 melanoma, 86 non-melanoma) • EPV = 5.18 (57/11)	108 • Number of menaloma not specified	300 Lesions • 100 melanoma randomly selected from 349 excised melanomas • 100 melanocytic naevi from 1512 excised naevi • 100 from a larger database of monitored naevi	401 lesions • 60 melanomas	600 lesions • 76 melanomas
Missing data	Not reported	Not reported	Not reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	• predictor selection: identified in the literature • multivariate regression • shrinkage: NR	NA	NA	NA	NA
Model Performance	• Discrimination and calibration: NR. • Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Discrimination: AUC ROC curve • Calibration: NR	• Discrimination and Calibration: NR • Interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of	• Discrimination and calibration: NR. • Sensitivity, specificity reported	Calibration and discrimination: NR Sensitivity , specificity, positive predictive value, negative predictive value, accuracy, efficiency reported.	Calibration and Discrimination: NR Sensitivity and specificity reported.

			consensus diagnosis reported			
Model evaluation	NA	• internal validation: random split-sample	NA	NA	NA	NA
Results	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Final model with odds ratios and score • Comparison of sensitivity, specificity	• Comparison of interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of consensus diagnosis	Comparison of sensitivity, specificity	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, efficiency.	Comparison of sensitivity and specificity.

	Binder 1999(25)	Blum 2003(14)	Blum 2004(26)	Blum 2004(27)	Buhl 2010(19)
Objective	Validation of ABCD rule for dermoscopy/Stolz	Validation of ABCD Rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 7-Point Checklist for dermoscopy, and 7FFM (7 features for melanoma) dermoscopy Derivation and validation of Simplified ABC-point list for dermoscopy.	Validation of the 3 colour dermoscopy test	Derivation and validation of Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions), and Digital dermoscopy analysis (partially imaged lesions) ABCD rule. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, 7FFM (7 features for melanoma) dermoscopy, and ABCD rule of dermoscopy/Stolz.	Derivation and narrow validation of DynaMel Algorithm. Validation of 7-point checklist for dermoscopy.
Source of Data	Cross-sectional, retrospective	Cross-sectional, prospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional, prospective
Participants	• Randomly selected images from a pigmented skin lesion database • 17 dermatologists • Ambulatory care	• Consecutive patients with suspicious melanocytic lesion • 1 department of dermatology	• Benign and malignant melanocytic and non-melanocytic lesions • 1 department of dermatology	• consecutive patients with melanocytic lesions • 1 department of dermatology Pigmented lesion clinic.	• Non-Consecutive patients with excised lesions with 7-point checklist score ≥ 3. • Number of departments of

				• November 1998 – March 2000	dermatology NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	6 candidate predictors	NA	Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions): 6 candidate predictors Digital dermoscopy analysis (partially imaged lesions) ABCD rule: 3 candidate predictors	12 candidate predictors
Sample Size	250 • 41 malignant melanomas • 209 benign melanomas	269 • 84 malignant melanomas • 185 benign melanomas • EPV = 14 (84/6)	249 lesions • 73 non-melanocytic tumours • 176 melanocytic lesions: 65 melanomas, 111 benign	837 lesions • 84 malignant melanomas • 753 benign (melanocytic + other) • EPV = 1.31 (84/64)	675 lesions • 61 melanomas • EPV = 5.083 (61/12)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported

Model Development	NA	• Based on established dermoscopy algorithms and univariate analysis • All predictors included in multivariate modelling • shrinkage: NR	NA	• All 3 derivations developed independently of the established dermoscopic rules. • Logistic regression analysis • shrinkage: NR	• 7-point checklist chosen as it is a valid and reliable method to distinguish benign and malignant melanocytic lesions. • 5 Dynamic predictors included for modelling based on the analysis of data from a prospective observational trial using long-term follow-up by sequential digital dermatoscopy • Used Akaike criterion, logistical regression framework, Brier score, and ROC AUC to select predictors during multivariable modelling. • Shrinkage: NR
Model Performance	• Discrimination and calibration: NR • ROC AUC sensitivity,	• Discrimination and calibration: NR. • Sensitivity, specificity,	• Calibration and discrimination: NR • Sensitivity and	• Discrimination: ROC AUC • Calibration: NR	• Calibration and Discrimination: NR • Sensitivity and

	and specificity reported. • Reported performance at cut points 4.75 and 5.45	and diagnostic accuracy reported. • Cut point 4.	specificity reported	• Sensitivity, specificity, and diagnostic accuracy reported	specificity reported. Cut point >/=3
Model Evaluation	NA	Internal validation: Development dataset was randomly divided into two collectives for cross validation	NA	• internal validation: complete collection of lesions randomly divided into training and test sets	internal validation: developed and tested on same dataset
Results	• Comparison of ROC AUC sensitivity and specificity for different cut points.	• Final model with score and cut point of 4 • Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity and specificity.	• Final digital image analysis model • Comparison of sensitivity, specificity, and diagnostic accuracy.	• Final model with score. • Comparison of sensitivity and specificity.

	Carli 2002(28)	Dal Pozzo 1999(29)	Dolianitis 2005(30)	Emery 2010(20)	Feldmann 1998(31)
Objective	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy	Derivation and narrow validation of 7FFM (7 features for melanoma) dermoscopy	Validation of 7-point checklist for dermoscopy, ABCD Rule of dermoscopy/Stolz, and Menzies 1996 dermoscopy for melanoma	Derivation and validation of Emery 2010 SIAscopy in primary care for melanoma	Validation of ABCD rule of dermoscopy/Stolz.
Source of Data	Cross-sectional	Cross-sectional		Cross-sectional	Cross-sectional prospective study.
Participants	• Clinically equivocal melanocytic lesions, <14 mm in diameter. • 1 department of dermatology Pigmented lesion clinic.	Pigmented skin lesions observed by the authors between 1992-1997 1 Department of Dermatology	• Random selection from a collection of images • 61 medical practitioners from either primary care or dermatology	• Patients presenting with a pigmented lesion and additional lesions identified as potentially suspicious during clinical examination • 6 General Practices in UK and 3 GP Primary Care Skin Cancer Clinics in Australia	Lesions that were being excised on clinical grounds or because of patient request 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	7 Candidate Predictors	NA	9 candidate predictors	NA

Sample Size	200 lesions • 44 melanomas	Training set: 218 lesions • 45 melanomas Test set: 713 lesions • 168 melanomas EPV training set: 2.81 (45/16) test set: 24 (168/7)	40 • 20 melanomas • 20 non-melanomas	1211 • derivation 422 (3 melanomas, 419 non-melanomas) • UK validation 208 (2 melanomas, 206 non-melanomas) • Australian validation 581 (7 melanomas, 574 non-melanomas) • EPV = 0.33 (3/9)	500 lesions • 30 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Of 16 features evaluated in the test set, 7 were selected because of specificity >80% and sensitivity > 5% and p < 0.05, in the derivation study. Shrinkage: NR	NA	• 5 predictors taken from Moncrieff scoring system; additional features considered • Sensitivity, specificity, positive predictive value, negative predictive value, ROC curves and associated AUC used for criteria for selection of predictors during multivariable modelling • shrinkage: NR	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity	Calibration and Discrimination: NR Sensitivity, specificity,	• Discrimination and calibration: NR. • Sensitivity, Specificity,	• Discrimination: AUC ROC curve • Calibration: NR	Calibration and Discrimination: NR Mean score of naevi,

	and diagnostic accuracy reported. Cut off point of 2 (lesions 3 or greater = melanoma) for 7-point checklist and 5.45 for ABCD rule.	PPV, NPV, and efficiency reported.	Diagnostic accuracy, and Likelihood ratios reported.	• Sensitivity, specificity, positive predictive value, and negative predictive value reported. Cut point 6 (6 or more: suspicious)	dysplastic naevi and melanomas reported
Model Evaluation	NA	Narrow internal validation: separate training and test sets.	NA	External validation using 1st a test set which was part of the dataset of 630 lesions from which 422 lesions were used for model derivation and 2nd using a separate dataset	NA
Results	• Comparison of sensitivity, specificity and diagnostic accuracy	Comparison of sensitivity, specificity, PPV, NPV, and efficiency.	• Comparison of Sensitivity, Specificity, Diagnostic accuracy, and Likelihood ratios	• Final model with score • Comparison of sensitivity, specificity, positive predictive value, and negative predictive value.	Comparison of mean score of naevi, dysplastic naevi and melanomas.

	Gereli 2010(32)	**Guitera 2012(21)**	**Haenssle 2010(33)**	**Healsmith 1993(34)**	**Henning 2008(35)**
Objective	Validation of 7-point checklist for dermoscopy and 3-point checklist for dermoscopy.	Derivation and narrow validation of Guitera 2012 confocal microscopy for melanoma.	Validation of 7 point checklist for dermoscopy	Validation of Revised 7-point checklist (clinical) and ABCDE clinical rule	Validation of CASH dermoscopy algorithm, ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy

					for melanoma, and 7 point checklist for dermoscopy .
Source of data	Cross sectional	Cross-sectional.	Cohort Study	Cross-sectional	Cross-sectional retrospective study
Participants	• NR • 96 dermoscopic images of skin lesions • Number of departments of dermatology NR	Consecutive lesions excised to exclude malignancy at a skin cancer clinic (included other skin cancer types) 2 specialised skin cancer clinics	Recruitment method NR Dermatology outpatient clinic. Number of centres NR	• Consecutively diagnosed melanomas. • Randomly selected, clinically diagnosed benign pigmented lesions	Clinical and dermoscopic images of melanocytic neoplasms (50 melanomas, 50 dysplastic naevi, 50 common naevi) from a database of 1535 images on an American Academy of Dermatology database 1 Department of Dermatology, university
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	35 candidate predictors (reflex confocal microscopy	NA	NA	NA

		features)			
Sample Size	96 lesions • 48 melanoma • 48 non-melanoma	710 lesions • 216 melanomas • EPV = 6.17 (216/35	688 participants with increased risk of melanoma; 1219 lesions • 127 melanomas	165 lesions • 65 Melanomas • 100 clinically diagnosed benign pigmented lesion	150 lesions • 50 melanomas
Missing data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	35 RCM (reflex confocal microscopy) features that showed significant association with melanoma diagnosis on univariate modelling. Multivariate discriminant analysis based on the training set using the 35 RCM features identified in univariate modelling, identified 7 independently significant features for the diagnosis of malignant melanomas. Shrinkage: A coefficient is	NA	NA	NA

		estimated for each included variable in relation to likeliness to predict a BCC, then an MM.			
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity, positive predictive value and negative predictive value reported	Discrimination: Multivariate discriminant analysis to determine variables for model. ROC analysis to investigate sensitivity and specificity of discriminant analysis equations for BCC and MM algorithms Calibration: NR Sensitivity and specificity reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	• Calibration and discrimination: NR • Sensitivity reported	Calibration and Discrimination: NR Sensitivity, specificity, relative sensitivity and specificity compared with CASH rule reported.
Model evaluation	NA	Validation (NR internal or external)	NA	NA	NA

Results	Comparison of sensitivity, specificity, positive predictive value and negative predictive value	Comparison of sensitivity, specificity, and AUC.	Comparison of sensitivity and specificity.	• Comparison of sensitivity.	Comparison of sensitivity, specificity, relative sensitivity and specificity.

	Higgins 1992(36)	Kittler 1999(16)	Keefe 1989(37)	Kreusch 1992(17)	Lorentzen 1999(38)
Objective	Validation of 7 point checklist (clinical) and revised 7 point checklist (clinical).	Validation of ABCD rule of dermoscopy/Stolz. Derivation of ABCDE rule (dermoscopy).	Validation of 7-point checklist (clinical)	Validation of Kreusch 1992 dermoscopy for melanoma	Validation of ABCD rule of dermoscopy/Stolz
Source of Data	Cross-sectional prospective study.	Cross-sectional prospective study	Cross-sectional	Cross-sectional	Cross-sectional
Participants	Consecutive clinically benign lesions excised in a pigmented lesion clinic 1 Department of Dermatology, pigmented lesion clinic	Consecutively excised pigmented lesions in a dermatology clinic 1 Department of Dermatology	Consecutive patients referred for assessment or treatment of pigmented lesions 4 departments of dermatology	Over 1.5 years, pigmented lesions suspected to be malignant melanoma were examined clinically and by ELM. Lesions to be excised were photographed. 1 Dermatology Clinic	Patients referred to dermatology clinic for evaluation of a pigmented skin lesion 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	5 Candidate Predictors	NA	NA	NA
Sample Size	100 lesions • 0 melanomas	356 lesions • 73 melanomas • EPV = 14.6 (73/5)	216 lesions • 8 melanoma (of 68 lesions excised)	317 lesions • 96 malignant melanoma • 221 benign melanocytic	232 patients • number of melanomas NR

				lesions and non-melanocytic lesions	
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Predictors 1-4: as per ABCD dermoscopy rule. 1 new variable (E: status of morphologic change) added to create new model Shrinkage: NR	NA	NA	NA
Model Performance	Calibration and Discrimination: NR Specificity reported.	Validation model: Calibration and discrimination: NR Derivation model: Discrimination: area under ROC; Calibration: NR Sensitivity and specificity reported for both models.	Calibration and Discrimination: NR Predictive value for melanoma and Predictive value for non-melanoma reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45 reported.
Model Evaluation	NA	Derivation only.	NA	NA	NA
Results	Specificity.	Comparison of sensitivity and specificity, AUC.	Comparison of predictive value for melanoma and predictive value for non-melanoma reported.	Comparison of sensitivity and specificity	Comparison of sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45.

	Lorentzen 2000(39)	Luttrell 2012(5)	MacKie 2002(15)	McGovern 1992(40)	Menzies 1996(8)
Objective	Validation of ABCD rule of dermoscopy/Stolz	Validation of AC dermoscopy rule	Derivation and validation of the 3 colour dermoscopy test	Validation of 7-point checklist (clinical) and ABCD rule.	Derivation and validation of Menzies 1996 dermoscopy for melanoma
Source of Data	Cross-sectional				Cross-sectional
Participants	Clinical photographs and dermatophotographs obtained from patients consecutively referred to the skin cancer outpatient clinic, and who had a subsequent excision biopsy 1 Department of Dermatology Skin cancer Outpatient clinic	• lesions drawn at random from 312 dermoscopic images of melanocytic lesions • 1 department of dermatology	• Sequential recruitment of patients referred to a specialist rapid-referral pigmented lesion clinic by their GP, for whom a dermatologist had considered that the lesion required excision biopsy • 1 specialist rapid-referral pigmented lesion clinic	• All pigmented lesions biopsied in a dermatology clinic suspicious for dysplasia or malignancy • 1st November 1989 to 31st October 1990; along with 2 melanomas added from earlier in 1989. • 1 dermatology clinic	Random sample of patients whose lesions were excised, selected from a larger database Number of departments of dermatology: NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	10 candidate predictors	NA	11 candidate predictors
Sample Size	258 patients • 64 melanoma	200 dermoscopic images of lesions • 25 melanoma	126 • 69 melanoma • 57 non-melanoma.	205 • 6 melanoma, 6 lentigo maligna	385 lesions • 107 melanomas • EPV = 1.486

		• 178 non-melanoma	• Derivation dataset 74 (37 melanoma, 37 non-melanoma) • Validation dataset 52 (32 melanoma, 20 non-melanoma) • EPV = 3.7 (37/10)		(107/72)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	• Method of selection of predictors for inclusion for multivariable modelling: NR • Sensitivity, specificity, p values, c-index, likelihood ratio tests, multivariable modelling with a forward stepwise philosophy, ROC curve, AUC • shrinkage: NR	NA	• Morphological features, seen with surface microscopy, not visible with the naked eye, that enhance the clinical diagnosis of nearly all pigmented lesions, including invasive melanoma • Classification and regression tree constructed on the training set producing a 7 node tree with cross validated sensitivity and specificity. Individual features were then selected for low sensitivity and high specificity to create a model suitable for clinician use. Images from the test set were then scored by

					means of the model as developed from the training set. Shrinkage: NR
Model Performance	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC reported.	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Discrimination: AUC, ROC curve, c-index • Calibration: NR • Sensitivity, specificity, p-value and c-index reported. No cut point chosen after derivation.	• Discrimination and Calibration: NR • Sensitivity, specificity and accuracy reported	Calibration and Discrimination: NR Sensitivity and Specificity of the training set, the test set, and the total combined sets reported.
Model Evaluation	NA	NA	Internal validation: test set for derivation and separate validation dataset	NA	Internal validation: A test set of 45 invasive melanomas and 119 non-melanomas was used to test the model performance.
Results	Comparison of sensitivity, specificity, and area under ROC.	Comparison of sensitivity and specificity.	• Final model with cut point of 3 colours or more on dermoscopy • Sensitivity, specificity, p-value, and c-index reported.	• Comparison of sensitivity, specificity and accuracy at different cut points.	• Final model: For diagnosis of invasive melanoma it must have neither of the two morphological negative features and 1 or more of the nine positive morphological features. • Comparison of sensitivity and specificity of the training set, the test set, and the total combined sets.

	Menzies 2008(9)	Menzies 2013(41)	Nachbar 1994(42)	Nilles 1994(18)	Osborne 1998(43)
Objective	Derivation of Menzies 2008 dermoscopy for melanoma and Menzies 2008 dermoscopy for skin cancer. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, and 3-point checklist for dermoscopy.	Derivation of Menzies 2013 dermoscopy for nodular melanoma. Validation of ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 3-point checklist, CASH dermoscopy algorithm, and 7-point checklist for dermoscopy.	Derivation of ABCD rule of dermoscopy/Stolz	Derivation and narrow validation of Nilles 1994 dermoscopy for melanoma.	Validation of Revised 7-Point Checklist (clinical)
Source of Data	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional retrospective study	Cross-sectional, retrospective
Participants	Dermoscopic images from multiple centres retrospectively May not have been from consecutive patients Predominantly hospital-based clinics from 5 continents (exact number NR)	Random selection of images of lesions from members of the International Dermoscopy Society Predominantly hospital-based clinics from 5 continents (exact number NR)	Consecutively excised pigmented skin lesions Number of departments of dermatology: NR	Retrospective recruitment; 260 histologically confirmed melanocytic skin tumours 1 Department of Dermatology	All patients with histologically proven cutaneous melanoma in study area between the years 1982 – 1996 1 department of dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate Predictors	Menzies 2008 dermoscopy for melanoma: 8 candidate predictors Menzies 2008 dermoscopy for skin cancer: 11 candidate predictors	17 candidate predictors	5 candidate predictors	8 Candidate Predictors	NA
Sample Size	497 lesions • 105 melanomas • EPV = 1.06 (105/99)	467 lesions • 217 melanomas (83 nodular melanomas, 134 invasive non-nodular melanomas) • EPV = 2.19 (217/99)	194 lesions • 69 melanomas • EPV = 13.8 (69/5)	260 lesions: • 72 malignant melanomas • 188 benign naevi • EPV = 9 (72/8)	778 lesions • 778 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	Both models: determined by consensus of members of the International Dermoscopy Society, either based on the existing literature or on clinicians' anecdotal experience Both models: 99 individual morphological features were scored by 12 clinicians in 55 preselected lesions to	Determined by consensus of the members of the International Dermoscopy Society 12 scorers blinded to the lesion diagnosis scored 99 individual features in each lesion. One feature was scored by one of the investigators after the clinician scoring was completed. Shrinkage: NR	• Development NR • Individual scores multiplied by different weight factors obtained by multivariate analysis • Shrinkage: NR	Selected based on previous studies examining predictive value of individual dermoscopic features. Stepwise logistic regression for data for each feature. Shrinkage: NR	NA

	assess interobserver concordance. 1 feature was scored by 1 of the investigators after the clinician scoring was completed. A random sample of 80% of the lesions was used as a training set and the remaining 20% used as a test set. The possible positive features were restricted to those with high specificity. Low sensitivity features were included for model development. Using all features as candidate variables, multiple logistic regression analysis with backward stepwise variable selection was also used to identify the independent predictors of malignant lesions from benign lesions in the training set. Shrinkage: NR				
Model Performance	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features and	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features	Calibration and Discrimination: NR Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative	Calibration and Discrimination: NR Validation dataset: sensitivity and specificity	Calibration and discrimination: NR Frequency of melanomas and rate of false negative diagnosis of melanoma at

	models reported.	and models reported.	predictive value reported. Cut-off point 5.45.	reported.	different sites.
Model Evaluation	Tested on independent, randomly selected lesions	Uncertain	Internal validation: using development dataset	Narrow external validation: new dataset of 209 lesions in 1991	NA
Results	Comparison of sensitivity and specificity in training vs independent test set.	Comparison of sensitivity for diagnosing nodular melanoma and non-nodular melanoma, and amelanocytic/hypomelanotic malignant lesions.	• Final model composed of 4 morphological features of malignant melanoma with different weight factors • Comparison of sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.	Comparison of frequency of melanomas and rate of false negative diagnosis of melanoma at different sites.

	Piccolo 2014(44)	Pizzichetta 2002(45)	Rao 1997(46)	Skvara 2005(47)	Soyer 2004(6)
Objective	Validation of ABCD rule of dermoscopy/Stolz and DDA (digital dermoscopic analysis) - computer-assisted diagnosis	Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/Stolz and ABCD clinical rule	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy.	Validation of 3-point checklist of dermoscopy
Source of Data	Cross-sectional	Cross-sectional, retrospective	Cross-sectional prospective	Cross-sectional, retrospective	Cross-sectional, retrospective
Participants	Dermoscopically atypical PSLs retrospectively selected from the archives of the department of dermatology 1 Department of Dermatology	Lesions selected from all lesions observed in consecutive patients seen between April 1996 - September 1998 1 Oncology Referral Centre	Consecutive patients, with lesions suspected of either benign melanocytic naevi or early malignant melanoma 1 private dermatology practice	Consecutive lesions demonstrating change over time during follow up 2 specialised dermatology centres	Consecutively excised lesions in specialized pigmented lesion clinic 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	NA	NA	NA
Sample Size	165 lesions • 33 malignant melanomas • 132 benign	129 lesions • 5 malignant melanomas • 124 benign	72 lesions • 21 melanomas	325 lesions • 63 melanomas	231 lesions • 68 melanomas • 163 non-melanomas (9 pigmented basal cell carcinomas,

					154 benign PSLs)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	NA	NA	NA
Model Performance	Calibration and discrimination: NR Kappa statistic (overall intra-observer agreement), sensitivity, specificity, positive predictive value and negative predictive value reported.	Calibration and discrimination: NR Kappa statistic (inter-observer agreement), sensitivity, and specificity reported.	Calibration and Discrimination: NR Cut-point 5.45 Sensitivity, specificity, and diagnostic accuracy reported.	Discrimination and Calibration: NR Cut-point not reported AUC, sensitivity, and specificity reported.	Calibration and discrimination: NR Sensitivity, specificity, and odds ratio reported.
Model Evaluation	NA	NA	NA	NA	NA
Results	Comparison of Kappa statistic, sensitivity, specificity, positive predictive value and negative predictive value.	Comparison of Kappa statistic, sensitivity, and specificity.	Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity, specificity and area under ROC.	Comparison of sensitivity, specificity, and odds ratio.

	Stolz 1994(11)	Strumia 2003(48)	Thomas 1998(49)	Unlu 2014(50)	Wadhawan 2011(51)
Objective	Derivation and narrow validation of ABCD rule of dermoscopy/Stolz.	Validation of ABCD rule of dermoscopy/Stolz and ABCDE rule (dermoscopy)	Validation of ABCD clinical rule and ABCDE clinical rule	Validation of ABCD rule of dermoscopy/Stolz, 7-point checklist for dermoscopy, 3-point checklist of dermoscopy, and CASH dermoscopy algorithm.	Validation of 7-point checklist for dermoscopy
Source of Data	Cross-sectional retrospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional	Feasibility Study implementing the 7-point checklist for dermoscopy features on a smart hand-held device.
Participants	Consecutively excised melanocytic naevi and malignant melanoma that met inclusion criteria 1 Department of Dermatology, University Hospital	Small melanocytic skin lesions, consecutively excised 1 Department of Dermatology	Prospective, consecutively diagnosed melanomas, and a prospective control group of benign lesions 1 Department of Dermatology	Random selection of digital dermoscopic images of melanocytic lesions collected at pigmented lesion clinic between Jan 2008-Jan 2010. 1 department of dermatology	Unknown number of skin cancer images annotated by expert dermatologists Commercial library of skin cancer images
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Use of the 7 point checklist for dermoscopy on smart hand-held devices.
Candidate Predictors	31 Candidate Predictors	NA	NA	NA	NA

Sample Size	157 lesions • 48 melanomas • EPV = 1.55 (48/31)	49 lesions • Number of melanomas and non-melanomas not reported.	1140 lesions • 460 melanomas • 680 non-melanomas	115 lesions • 24 malignant melanomas • 91 benign	347 lesions • 110 malignant melanoma (based on 7 point checklist) No histological diagnosis • 237 benign
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	28 features listed in the Consensus Conference of Surface Microscopy, Hamburg, 1989, and three new features (asymmetry in no, one, or two axes; colour; differential structure). "8 features with p values <=0.0001 in the training set were used for multivariate analysis to obtain a formula which led to a calculated score termed the final dermatoscopy score (FDS)" Shrinkage: "Multivariate analysis of the 8 features with lowest p values in the training set was performed, and The following formula for the best differentiation of	NA	NA	NA	NA

	melanocytic skin lesions was created: Asymmetry score x 1.3 + Border score x 0.1 + Colour score x 0.5 + Differential structure score x 0.5 = Final Dermatoscopy Score"				
Model Performance	Calibration and Discrimination: NR Cut-point: 5.45 Sensitivity and specificity reported.	Calibration and discrimination: NR Cut-point 5.45 Positive and negative predictive values reported.	Calibration and discrimination: NR Sensitivity and specificity of individual criteria, and Chi square statistic reported.	Calibration and discrimination: NR Sensitivity, specificity, diagnostic accuracy, false positive, ratio, false negative ratio, positive predictive value, and negative predictive value reported.	Calibration and discrimination: NR Sensitivity, specificity, and classification accuracy reported.
Model Evaluation	Internal validation: dataset split into derivation and test sets	NA	NA	NA	NA
Results	Comparison of sensitivity and specificity.	Comparison of positive and negative predictive values.	Comparison of sensitivity and specificity of individual criteria, and Chi square statistic.	Comparison of sensitivity, specificity, diagnostic accuracy, false positive, ratio, false negative ratio, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.

	Walter 2013(52)	Zalaudek 2006(53)
Objective	Validation of 7-point checklist (clinical) and revised 7-point checklist (clinical)	Validation of 3-point checklist for dermoscopy.
Source of data		
Participants	• Consecutive recruitment of patients presenting to general practice with a pigmented lesion which could not be immediately diagnosed as benign, for a RCT of a SIAscopic diagnostic aid for primary care • 15 General Practices	• Random selection from a collection of 2621 excised lesions • 1 department of dermatology specialised pigmented lesion clinic
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	NA
Sample Size	1436 • 36 melanomas	150 • 26 melanoma • 106 benign

Missing data	No missing data reported	No missing data reported
Model development	NA	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Calibration and discrimination: NR • Reproducibility, sensitivity, and specificity reported
Model evaluation	NA	NA
Results	Comparison of sensitivity and specificity at different cut points.	Comparison of reproducibility, sensitivity, and specificity.

NR= not reported; NA= not applicable

Appendix 4: Methodological quality assessment of the impact analysis studies

a: Studies with a RCT study design

Authors	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Walter (2012)(54)	Low	Low	Low	High	Low	Low	Low	Low
Argenziano 2006	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear

b: Study with a controlled before-after study design

Authors	Selection bias			Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Allocation generation	Allocation concealment	Baseline measures	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Westerhoff (2000)(55)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High	High

References (Appendices)

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA: a cancer journal for clinicians. 1985;35(3):130-51.
2. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, et al. Early diagnosis of cutaneous melanoma: Revisiting the ABCD criteria. Journal of the American Medical Association. 2004;292(22):2771-6.
3. MacKie RM. An illustrated guide to the recognition of early malignant melanoma. University of Glasgow. 1986.
4. MacKie RM. Malignant melanoma: a guide to early diagnosis University of Glasgow. 1989:28-43.
5. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. British Journal of Dermatology. 2012;167(5):1037-41.
6. Soyer HP, Argenziano G, Zalaudek I, Corona R, Sera F, Talamini R, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. Dermatology. 2004;208(1):27-31.
7. Henning JS, Dusza SW, Wang SQ, Marghoob AA, Rabinovitz HS, Polsky D, et al. The CASH (color, architecture, symmetry, and homogeneity) algorithm for dermoscopy. Journal of the American Academy of Dermatology. 2007;56(1):45-52.
8. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Archives of Dermatology. 1996;132(10):1178-82.
9. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Archives of Dermatology. 2008;144(9):1120-7.
10. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999;9(6):470-6.
11. Stolz W, Riemann A, Cognetta AB, Pillet L, Abmayer W, Holzel D, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. European Journal of Dermatology. 1994;4(7):521-7.
12. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Archives of Dermatology. 1998;134(12):1563-70.
13. Argenziano G, Catricalà C, Ardigo M, Buccini P, De Simone P, Eibenschutz L, et al. Seven-point checklist of dermoscopy revisited. British Journal of Dermatology. 2011;164(4):785-90.
14. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. Journal of the American Academy of Dermatology. 2003;48(5):672-8.
15. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. British Journal of Dermatology. 2002;146(3):481-4.

16. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. Journal of the American Academy of Dermatology. 1999;40(4):558-62.
17. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society. 1992;Suppl 2:295-8.
18. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. British Journal of Dermatology. 1994;130(3):349-55.
19. Buhl T, Hansen-Hagge C, Korpas B, Kaune KM, Haas E, Rosenberger A, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. Journal of the American Academy of Dermatology. 2012;66(1):27-36.
20. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. BMC Dermatology. 2010;10:9-.
21. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. Australasian Journal of Dermatology. 2012;53:7-8.
22. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. Journal of the American Academy of Dermatology. 2007;56(5):759-67.
23. Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. Journal of the American Academy of Dermatology. 2003;48(5):679-93.
24. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. Eur J Dermatol. 2000;10(4):282-7.
25. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. Journal of the American Academy of Dermatology. 1999;40(2 I):171-6.
26. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. British Journal of Dermatology. 2004;150(5):1040.
27. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. British Journal of Dermatology. 2004;151(5):1029-38.
28. Carli P, Quercioli E, Sestini S, Stante M, Ricci L, Brunasso G, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. British Journal of Dermatology. 2003;148(5):981-4.
29. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. European Journal of Dermatology. 1999;9(4):303-8.
30. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. Archives of Dermatology. 2005;141(8):1008-14.

31. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. Hautarzt. 1998;49(6):473-6.
32. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. International Journal of Dermatology. 2010;49(1):33-8.
33. Haenssle HA, Korpas B, Hansen-Hagge C, Buhl T, Kaune KM, Rosenberger A, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. Journal of the American Academy of Dermatology. 2010;62(5):785-93.
34. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. British Journal of Dermatology. 1994;130(1):48-50.
35. Henning JS, Stein JA, Yeung J, Dusza SW, Marghoob AA, Rabinovitz HS, et al. CASH algorithm for dermoscopy revisited. Arch Dermatol. 2008;144(4):554-5.
36. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. Clinical and Experimental Dermatology. 1992;17(5):313-5.
37. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. Clinical and Experimental Dermatology. 1990;15(3):167-71.
38. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. Acta Dermato-Venereologica. 1999;79(6):469-72.
39. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. Acta Derm Venereol. 2000;80(2):122-6.
40. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. Journal of Dermatologic Surgery and Oncology. 1992;18(1):22-6.
41. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I, et al. Dermoscopic evaluation of nodular melanoma. JAMA Dermatology. 2013;149(6):699-709.
42. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. Journal of the American Academy of Dermatology. 1994;30(4):551-9.
43. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. British Journal of Dermatology. 1999;140(5):902-8.
44. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. European Journal of Dermatology. 2014;24(4):477-81.
45. Pizzichetta MA, Talamini R, Piccolo D, Trevisan G, Veronesi A, Carbone A, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. Tumori. 2002;88(3):234-8.
46. Rao BK, Marghoob AA, Stolz W, Kopf AW, Slade J, Wasti Q, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. Skin Research and Technology. 1997;3(1):8-14.
47. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. Archives of Dermatology. 2005;141(2):155-60.

48. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. Melanoma Research. 2003;13(6):631-2.
49. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. Dermatology. 1998;197(1):11-7.
50. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. Journal of Dermatology. 2014;41(7):598-603.
51. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2011;2011:3180-3.
52. Walter FM, Prevost AT, Vasconcelos J, Hall PN, Burrows NP, Morris HC, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. British Journal of General Practice. 2013;63(610):345-53.
53. Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Three-point checklist of dermoscopy: An open internet study. British Journal of Dermatology. 2006;154(3):431-7.
54. Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. BMJ (Online). 2012;345(7866).
55. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. British Journal of Dermatology. 2000;143(5):1016-20.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6/7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6/7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6/7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Diagnosing malignant melanoma in ambulatory care: a systematic review of clinical prediction rules

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Diagnosing malignant melanoma in ambulatory care: a systematic review of clinical prediction rules

Authors:

Emma Harrington[1], Barbara Clyne*[1], Nieneke Wesseling[2], Harkiran Sandhu[1], Laura Armstrong[1], Holly Bennett[1], Tom Fahey[1]

Author affiliations:

[1]HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 Stephen's Green, Dublin 2, Ireland

www.hrbcentreprimarycare.ie

[2] Medical School, Radboud University, Nijmegen, Netherlands

***Corresponding author:** Barbara Clyne PhD, HRB Centre for Primaty Care Research, Department of General Practice, Royal College of Surgeons in Ireland, Lower Mercer Street, Dublin 2, Ireland barbaraclyne@rcsi.ie

Abstract

Objectives: Malignant melanoma has high morbidity and mortality rates. Early diagnosis improves prognosis. Clinical prediction rules (CPRs) can be used to stratify patients with symptoms of suspected malignant melanoma to improve early diagnosis.

We conducted a systematic review of CPRs for melanoma diagnosis in ambulatory care.

Design: Systematic review

Data Sources: A comprehensive search of PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS was conducted in May 2015, using combinations of keywords and MeSH terms.

Study selection and data extraction: Studies deriving and validating, validating, or assessing the impact of a CPR for predicting melanoma diagnosis in ambulatory care were included. Data extraction and methodological quality assessment were guided by the CHARMS checklist.

Results: From 16,334 studies reviewed, 51 were included, validating the performance of 24 unique CPRs. Three impact analysis studies were identified. Five studies were set in primary care. The most commonly evaluated CPRs were the ABCD dermoscopy rule (at a cut point of >4.75; 8 studies; pooled sensitivity 0.85, 95% CI 0.73-0.93, specificity 0.72, 95% CI 0.65-0.78) and the 7 point dermoscopy checklist (at a cut point of ≥1 recommending ruling in melanoma; 11 studies; pooled sensitivity 0.77, 95% CI 0.61-0.88, specificity 0.80, 95% CI 0.59-0.92). The methodological quality of studies varied.

Conclusion: At their recommended cut-points, the ABCD dermoscopy rule is more useful for ruling out melanoma than the 7 point dermoscopy checklist. A focus on impact analysis will help translate melanoma risk prediction rules into useful tools for clinical practice.

PROSPERO registration

The protocol for this systematic review is registered at the PROSPERO database, registration number CRD42015020898

Strengths and limitations of this study

- The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. Quality assessment criteria were used to assess risk of bias and the majority of studies were at low risk in relation to the randomisation procedure and monitoring of loss to follow-up.
- A large proportion of studies did not provide sufficient information and data to perform stratified meta-analysis according to different levels of risk
- Current research shows that dermoscopic CPRs may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients but future impact analysis research is necessary to establish their impact on patient outcomes.

Introduction

The incidence of malignant melanoma in most developed countries has been steadily rising (faster than other cancer types) in recent decades. [1,2] Increases in the age-standardized incidence of at least 4–6% per annum have been reported internationally in many fair skinned populations including Australia, the USA and most of Europe. [3-5] Simultaneously, there has been a significant rise in overall 5-year survival in melanoma patients, largely attributable to earlier detection and diagnosis of thinner tumours.[6] While the majority of patients may survive melanoma, the disease has a significant impact on patient quality of life[7] and health care expenditure, with the average annual total treatment costs for melanoma in the USA increasing to $3.3 billion in 2011. [8] Melanoma is potentially preventable since a significant risk factor, exposure to ultraviolet (UV) radiation, is modifiable.[9] However, other risk factors (e.g. number naevi, eye and hair colour, freckles, familial history and genetic predisposition) also play an important role in the risk of developing melanoma. [10,11]

Early detection followed by curative surgery greatly improves melanoma prognosis. However, early detection may be affected by the challenging natures of differential diagnosis of pigmented lesions. Particularly in primary care where the evaluation of suspected skin lesions is imposing an increasing burden due to rising incidences of skin cancer.[12] It has been suggested that primary care practitioners' skills of diagnosing skin lesions could be improved.[13] A number of Clinical Prediction Rules (CPRs) and computer-assisted diagnostic tools have been developed to assist in distinguishing malignant melanoma from benign pigmented skin lesions. The UK National Institute for Clinical Excellence (NICE) guidelines advise against routine use of computer-assisted diagnostic tools in the initial evaluation of a pigmented skin lesion (NG14) and promote use of the weighted 7-point checklist in primary care to guide referral (NG12). When used by dermatologists for the diagnosis of melanoma, certain CPRs have demonstrated high sensitivity and specificity.[6] Although each CPR has its own unique elements, there is significant overlap in terms of their content (Appendix 1), and while their use is promoted, it is unclear which rules are most suitable for use in primary care.

CPRs may be for use in clinical (i.e. naked eye) examination, or in conjunction with dermoscopy. Dermoscopy, dermatoscopy, or epiluminescent microscopy refers to the examination of pigmented skin lesions using surface microscopy. [14,15] The use of dermoscopy, primarily by dermatologists, has been found to increase diagnostic accuracy compared with naked eye inspection, as it allows the visualization of features that are not visible to the naked eye.[14-16] However, the effectiveness of dermoscopy depends on clinical experience and training. Dermatologists with formal training in dermoscopy have higher melanoma detection rates compared with untrained dermatologists and primary care physicians.[16-18]

As primary care or ambulatory care physicians are frequently and increasingly confronted with the care of skin lesions suspected of malignancy[12], it is essential to identify tools to aid primary care practitioners to differentiate patients with clinically significant lesions, requiring referral, from those who can be treated and monitored in primary care. The aim of this study was to perform a systematic review of CPRs for the diagnosis of malignant melanoma, to evaluate their diagnostic accuracy in primary care and specialist outpatient settings, among patients with a pigmented skin lesion. Secondary aims were to review studies that have examined the implementation of CPRs in clinical practice through impact analysis studies.

Methods

The protocol for this systematic review was published on PROSPERO (CRD42015020898) and was conducted according to PRISMA guidelines.[19]

Search strategy and data sources

A systematic literature search was conducted (May 2015) including the following databases: PubMed, EMBASE, PROSPERO, CINAHL, the Cochrane Library, CINAHL, and SCOPUS, using combinations of the following keywords and MeSH terms: melanoma/diagnosis, melanoma, prediction, score, model, decision, sensitivity, specificity, validate, derived. Hand searches of references of retrieved full-text articles and key author searches supplemented the search. No date or language limits were imposed.

Study selection

All articles were initially screened for inclusion according to title and abstract by two reviewers (NW, EH). Full text articles of studies considered eligible for inclusion were independently read by both reviewers, with any disagreements resolved by a third reviewer (BC).

Validation studies

Validation studies were eligible for inclusion if they met the following criteria;

1) *Population:* Adults (age ≥18 years) with a pigmented skin lesion in ambulatory care settings in general practice/ family medicine, dermatology, plastic surgery, and other relevant specialties.
2) *Risk:* Derivation and/or validation of a CPR for melanoma diagnosis to aid decision-making about referral or investigation of a pigmented skin lesion. CPRs were defined as "a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and investigations make toward the diagnosis, prognosis, or likely response to treatment in a patient".

3) *Comparison:* Usual clinical judgment for decision making about referral or investigation OR another CPR for melanoma diagnosis.
4) *Primary Outcome:* Performance of a CPR for predicting diagnosis of malignant melanoma (in terms of sensitivity, specificity, negative predictive values and positive predictive values).

Observational study designs (e.g. cohort, cross-sectional, case-control) were included. Studies were excluded where they had undergone derivation only, reported individual predictors only, or utilised computer assisted diagnostic tools, following the NICE guideline recommendation against the routine use of computer assisted diagnostic tools.[20]

Impact analysis

The following study designs were included for impact analysis: (cluster) randomized controlled trials (RCTs), controlled before-after studies, or interrupted time series studies. We excluded uncontrolled study designs. We included studies where a melanoma CPR was used to predict melanoma compared to usual care in the clinical setting. The outcomes of interest included physician behaviour, process of care, patient outcomes and/or cost-effectiveness. A requirement for inclusion was that the CPR comprised the entire intervention. Studies where the CPR was implemented as part of a broader guideline, protocol or decision aid were excluded. Studies that used a CPR to determine eligibility for trial inclusion but were not part of the intervention were also excluded.

Data extraction

Data were extracted by four reviewers (LA, HB, HS, EH) using a data form based on the CHARMS checklist.[21] Data extracted included study design and setting, patient demographics and inclusion criteria, CPR name, CPR type (clinical or dermoscopic), predictive accuracy of the CPR (sensitivity/specificity) and, for impact analysis, the impact on the primary outcome.

Critical appraisal of studies

Two reviewers (EH, NW) critically appraised included studies using the CHARMS checklist, developed to provide guidance on data extraction and critical appraisal of prediction modelling studies. [21] The checklist contains 11 domains of critical appraisal. The methodological quality of each study was independently evaluated by two reviewers and by a third reviewer if consensus was not reached. The methodological quality of each impact analysis study was also independently assessed, using an appropriate quality assessment checklist. RCTs were assessed using the Cochrane risk of bias tool and controlled before-after studies were evaluated using Cochrane criteria for these study designs. [22]

Statistical analysis

Statistical analysis was conducted using Stata version 12 (StataCorp., College Station, Texas, USA), in particular the metandi and midas commands. For each CPR, a standard cut point was identified (Table 1). From each included study we extracted (where available) the numbers of true positives, false positives, true negatives, false negatives, sensitivity and specificity and their corresponding 95% confidence intervals (95% CIs). Where sensitivity/specificity for more than one observer was reported, the mean value was included in the analysis. Studies were grouped for analysis by CPR type (i.e. clinical or dermoscopic). Summary estimates of sensitivity and specificity and their corresponding 95% CIs were calculated using the bivariate random effects model (midas). The bivariate model has the benefits of being easily interpretable, is technically straightforward to undertake and takes into account both the sample and heterogeneity beyond chance between studies.[23]

Individual and summary estimates of sensitivity and specificity were plotted on a hierarchical summary receiver-operating characteristic (HSROC) graph. This approach incorporates both sensitivity and specificity, while taking into account the correlation between the two.[24] Sensitivity (true positive) was graphed on the y-axis and 1-specificity (false negative) on the x-axis. The 95% confidence region and the 95% prediction region were also plotted around the pooled estimates in order to depict the precision with which

the pooled estimates were determined (confidence ellipse around the mean value) and to illustrate the amount of between-study variation (prediction ellipse).

Results

Study Selection

The search strategy yielded a total of 25,816 articles. Of these 9,481 were duplicates and 16,166 were deemed irrelevant based on title/abstract. The remaining 171 were reviewed in full with 51 meeting the inclusion criteria (Appendix 2). From these, 24 unique melanoma CPRs were identified (Table 1). Twelve papers reported both derivation and validation studies, 36 were validation studies only and three were impact analyses.

Summary of studies

Table 2 summarises the characteristics of the included studies. The majority (11, 22%) were conducted in Italy [14,15,25-34] and ranged from an analysis of 40 lesions to 1,580 lesions. From 13 studies providing information, mean age of included patients ranged from 36.7 to 53 [25,28,31,35-44]. From the 14 studies that reported gender, the proportion of males ranged from 22-60% [25,31,33,35-45]. Thirty-one of the 50 studies were published in or after 2000 [14,25,28,29,31-37,42-44,46-62]. Five studies were set in primary care [36,44,49,62,63], with the remainder undertaken in specialist outpatient settings.

Summary of CPRs identified

Of the 24 rules identified, four were clinical (i.e. naked eye), 17 were dermoscopic and the remaining three utilised novel diagnostic technologies. The most commonly applied clinical CPR was the ABCDE rule (5 studies) [6,15,28,64,65], while for dermoscopy the most common were the ABCD rule of dermoscopy (23 studies) [14,25,26,29,31,32,39,42,43,47-49,52,53,57,65-70] and the 7 point checklist for dermoscopy (17 studies)[14,25,26,29,35,37,42,43,46-50,52,56,57,59].

Each of the elements included in the 24 rules identified are presented in Table 3.a and 3.b. All four clinical rules included the elements of diameter and colour variegation (Table 3.a and Appendix 1). The most frequently included elements in the 17 dermoscopic rules were multiple colours (13 rules), asymmetry (12 rules), and streaks (10 rules) (**Error! Reference source not found.**Table 3.b and Appendix 1).

Methodological quality of validation studies

Based on the CHARMS checklist, the quality of included studies varied.[21] All studies had weaknesses in study design and quality assessment was often hindered by poor reporting of methods. The studies had reasonable sample sizes and all provided adequate definitions of the outcome of interest. However, a number of important weaknesses were identified. None of the studies reported on missing data and key performance measures of model performance (e.g. calibration) were often missing. Derivation studies typically reported information on model development, in terms of selection of candidate predictors, selection of predictors during modelling, and model evaluation. However, often the methods applied introduced a strong risk of bias, for example, a number of studies described splitting the original sample into a development and validation sample which is considered statistically inefficient and results in overfitting of the model. [21] Full results of the quality assessment are shown in Appendix 3.

Predictive accuracy of melanoma CPRs

The results for the most commonly applied CPRs, the ABCD rule and the 7 point checklist are presented here. The sensitivity and specificity of all rules identified (including the ABCDE clinical rule, the 7 features for melanoma rule and Menzies dermoscopy for melanoma rule) are summarised in Table 4.

Clinical (naked-eye) CPRs for melanoma diagnosis

Four studies validating the ABCDE clinical rule [6,15,28,64] and one validating the ABCD clinical rule [65] were included. There was insufficient data to conduct any meta-analysis. Rao et al reported a sensitivity of 0.84 and specificity of 0.78, for an unspecified cut-point.[65]

Six studies validating the original and revised 7 point checklist were included. There was insufficient data to conduct a meta-analysis. Of the four studies validating the original 7 point checklist (cut-point ≥ 3), three reported sensitivity (range 0.44-0.86, mean 0.70) and specificity (range 0.62-0.94, mean 0.74)[40,41,44]. Only one of the four studies validating the revised 7 point checklist (cut-point ≥ 1) reported sensitivity (0.92) and specificity (0.33) (Table 4).[44]

Dermoscopic CPRs for melanoma diagnosis

ABCD rule of dermoscopy

The ABCD rule of dermoscopy (also described as the ABCD rule of Stolz), was validated in 23 studies, 15 of which applied a cut point of >4.75 (indicating a suspicious lesion) and 6 studies a cut-point of 5.45 (highly suggestive for melanoma). At a cut point of >4.75, 8 studies provided sufficient information for meta-analysis, [42,43,47,52,65,71] resulting in a pooled sensitivity of 0.85 (95% CI 0.73-0.93) and specificity of 0.72 (95% CI 0.65-0.78) (Figures 1.a and 1.b). This indicates that at this cut point, the dermoscopy CPR is more useful for ruling out rather than ruling in melanoma, with a higher pooled sensitivity than specificity. I^2 were high (>70%), indicating a high degree of heterogeneity. Of the seven studies excluded from meta-analysis, sensitivity ranged from 0.71-0.91 (mean 0.79) and specificity ranged from 0.43-0.92 (mean 0.72). None of the six studies that applied a cut-point of 5.45 were suitable for meta-analysis. From 4 studies that presented the information, sensitivity ranged from 0.73-0.98 (mean 0.85) and specificity ranged from 0.46-0.91 (mean 0.79) (Table 4).

7 point checklist for dermoscopy

The 7 point checklist for dermoscopy was validated in 18 studies, 17 of which applied a cut point of 3. 11 studies provided sufficient information for meta-analysis, revealing a pooled sensitivity of 0.77 (95% CI 0.61-0.88) and pooled specificity of 0.80 (95% CI 0.59-0.92) (See figures 2.a and2.b). [25-27,35,37,42,43,47,50,52,71] There was a high degree of heterogeneity in the results (I^2 >90%). Removing two outliers [27,50] made minimal difference to the pooled result. Only one study validated the revised 7 point checklist for dermoscopy and reported sensitivity 0.78 and specificity 0.65 for a cut point of 3 (Table 4).[27]

Impact analysis

We identified three unique studies that examined the impact of a melanoma CPR on processes of care (melanoma diagnosis and referrals), however, no patient outcomes were examined (Table 2). [62,63] The methodological quality of these studies is presented in Appendix 4.

Using a controlled before and after design, Westerhoff et al investigated the impact of an educational intervention about the Menzies 1996 rule on melanoma diagnosis by Family Physicians (FP). The control group did not receive the training. Post-intervention, there was a significant improvement in melanoma diagnosis (75.9% vs 62.7%, P < .001). No significant improvement was seen in the control group (54.8% vs 53.7%, P = .59). [62]

Walter et al. conducted a RCT to compare the use of a new imaging device, the MoleMate system (SIAscopy with a primary care scoring algorithm), to current best practice (clinical history, naked eye examination, seven point checklist). The authors found no difference between these two approaches in terms of appropriate referrals (the proportion of referred lesions that secondary care experts biopsied or monitored) to urgent skin cancer clinics (intervention 56.8% v control 64.5% *P* = 0.11) or the proportion of benign lesions appropriately managed in primary care (intervention 99.6% v control 99.2%, P=0.46). [63]

Argenziano et al's RCT [72], involved primary care physicians first attending a 1-day training course describing the ABCD rule (cut point unspecified) and the 3-point checklist. They were then randomly assigned to assess patients with skin lesions, either by clinical (i.e. naked eye) examination, or by dermoscopy using the 3-point checklist. The referral assessments were checked for accuracy by dermatologists. The dermoscopy arm demonstrated a 25% improvement in the sensitivity of primary care referrals of pigmented lesions compared with the naked-eye examination (79.2% vs 54.1%, *P* = 0.002), without a reduction in specificity (71.8% vs 71.3%, *P* =0.915) [72].

Discussion

Summary of findings

This systematic review identified 48 studies validating a total of 24 CPRs for melanoma. Overall, the majority of validation studies utilised dermoscopic CPRs, with very few studies validating clinical CPRs. Meta-analysis of the dermoscopic CPRs demonstrated relatively high pooled estimates of sensitivity (0.77-0.86). The clinical implication is that applying dermoscopy CPRs will enable low risk patients to be observed and kept under review in a primary care setting, without immediate referral for excision to secondary care. Meta-analysis was not possible for clinical CPRs but individual studies report variable sensitivity, ranging from 0.44-0.86. Three impact analysis studies were identified, with two reporting an improvement in melanoma diagnosis with the use of a CPR.

Context of previous research

The sensitivities and specificities we report indicate that currently available CPRs are reasonably good at ruling out melanoma. The pooled sensitivity of the ABCD rule for dermoscopy (cutpoint of >4.75) was 0.85 (95% CI 0.73-0.93), higher than that of the seven point checklist for dermoscopy (0.77, 95% CI 0.61-0.88). While this evidence would support the use of such rules in prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients, there are a number of important caveats that may prevent their adoption in primary care.

Melanoma is a high stakes condition, one which doctors tend to be cautious in diagnosing, often preferring to excise a benign lesion rather than to miss a potentially fatal cancer.[73] In such cases, a CPR with near perfect sensitivity would be desirable, however, it has been argued that a lower sensitivity should not prevent CPR use unless usual decisions, made without the rule, are demonstrably better. [74] Our results are comparable with previous systematic reviews focused on melanoma diagnosis across healthcare settings in highlighting that dermoscopic CPRs are demonstrably better in terms of diagnostic accuracy in comparison with inspection by the naked eye. [16,75] However, even a rule with almost 100% sensitivity may not be adopted. For instance, implementation of the Canadian CT Head Rule, despite 100% sensitivity in validation studies, did not result in a reduction in

imaging rates, with clinicians' reporting unease with certain components of the rule and fear of missing a high-stakes diagnosis as reasons for not adopting the CPR.[76]

Before considering whether to use a CPR in clinical practice, it is essential that its performance be established through external validation (i.e. in settings outside where it was derived). We identified a number of external validation studies in this review, however, in keeping with much CPR research, the reporting of these studies was often poor.[77,78] In particular, the common issues of limited acknowledgement and handling of missing data and key performance measures of prediction models i.e. calibration, being omitted was encountered.[77] The lack of available data in some papers meant not all studies could be combined in the meta-analysis, meaning the sensitivities and specificities reported here are not based on the totality of existing evidence. Furthermore, we were unable to assess diagnostic accuracy at different cut-point thresholds for respective CPRs. Improved reporting of CPRs at cut-point thresholds will enable pooling of diagnostic accuracy data, and will provide more robust measures of diagnostic accuracy. After validation, impact analysis studies are undertaken to determine the impact of the implementation of a CPR on processes and outcomes of care. Despite increasing interest in developing and validating CPRs relevant to primary care, relatively few have undergone impact analysis. [79] Despite the large number of CPRs identified in this review, we identified only three impact analysis studies, with only two studies reporting an improvement in correct melanoma diagnosis in primary care as a result. Arguably, the dearth of well-conducted and clearly reported external validation and impact analysis studies undermines trust in the use of such rules in practice. [77]

Current NICE guidelines for melanoma detection and management recommend dermoscopy of any suspicious lesion, advising against using computer assisted diagnostic tools (NG14) while promoting use of the weighted 7-point checklist in primary care to guide referral (NG12).[20] Based on the findings of this review, the ABCD rule for dermoscopy had a higher sensitivity than the seven point for dermoscopy checklist at their respective cut-points, indicating its potential for use in primary care. Dermoscopy, however, requires training and equipment, and is less commonly performed in primary care. Evidence suggests that

dermatologists have better diagnostic accuracy than primary care physicians. [18] Three studies retrieved in our search assessed dermoscopy CPR performance when applied by non-experts, with two studies reporting that the CPRs performed well overall when used by non-experts, mainly primary care physicians. [49,66,72] Both Westerhoff et al [62] and Argenziano et al [80] demonstrated that training primary care physicians to use dermoscopy with CPRs showed significant improvement in the diagnosis of melanoma compared with naked eye inspection. Alongside the use of CPRs, training in dermoscopy would seem to be a strategy that will enhance diagnostic accuracy of melanoma in the future particularly in light of emerging evidence of differences in dermoscopic features of melanoma such as head and neck melanoma.[81] It has also been highlighted that significant efforts are needed to standardize and improve dermoscopic terminology to more broadly promote the use of dermoscopy in the primary care setting. [82] Of the 24 rules identified in this review, four were clinical (i.e. naked eye) and 17 were dermoscopic. Due to the limited number of studies and available data, no meta-analysis of clinical CPRs could be conducted. The range of reported sensitivities from individual studies indicates that there is insufficient evidence to recommend their use in practice.

Strengths and limitations of our study

The main strengths of this review are the use of broad inclusion criteria, the systematic search of multiple databases not limited by language, use of the CHARMS checklist to assess methodological quality, pooling data from a broad range of studies to enhance generalisability and the use of a broad definition of primary care to account for the variation in primary care services and access internationally. However, the findings of this systematic review need to be interpreted in the context of the limitations of the original studies. The lack of available data in some papers meant not all studies could be combined in the meta-analysis. A number of studies that validated CPRs and algorithms using novel diagnostic technologies which incorporated computerised image analysis and artificial intelligence were excluded from the review as routine use of these is not currently recommended in UK NICE clinical guidelines. Significant heterogeneity existed between the studies with respect to differences in the study populations and application of the CPR. Lastly, individual patient data that enables pooling of risk scores at the different cut-points would enable researchers

to explore the clinical utility of applying risk scores at different cut-points with the purpose of assessing the role of melanoma CPRs at the different diagnostic thresolds of "ruling out" (utilising highest pooled sensivity) or "ruling in" (utilising highest pooled specificity) of respective melanoma CPRs.

Implications for practice and future research

Early detection followed by curative surgery greatly improves the prognosis of malignant melanoma. As the incidence of melanoma skin cancer increases, primary care physicians are increasingly required to screen for melanoma.[12] Therefore, efforts to increase the early detection of melanoma must focus on supporting primary care physicians in performing skin cancer screenings with recent evidence highlighting the benefits of developing targeted screening strategies in high risk patients in primary care.[18,83] This systematic review identified 24 separate clinical (naked eye) and dermoscopic CPRs, with some overlap in the included the elements. Our analysis highlights that dermoscopic CPRs have reasonable sensitivity, with the ABCD rule for dermoscopy having better sensitivity than the seven point checklist for dermoscopy. Further development of new rules is unlikely to benefit the field of research. An increased emphasis on better reporting of validation studies, particularly at different cut-point thresholds, would allow for the conduct of more robust diagnostic accuracy meta-analysis to inform decision making. Further methodologically robust randomised controlled trials are necessary also to examine the impact of implementing CPRs in clinical practice, in terms of patient outcomes, physician behaviour, processes of care, and cost-effectiveness. Lastly, whilst guidelines promote the use of dermoscopy in the assessment of pigmented skin lesions, there needs to be greater emphasis on training in primary care on this examination technique.

Conclusion

This systematic review and meta-analysis shows that dermoscopic CPRs have reasonably high pooled estimates of sensitivity and may be a useful tool for primary care physicians prioritising appropriate referrals for higher risk patients and adopting a watchful waiting strategy in lower risk patients. The ABCD rule of dermoscopy has higher pooled sensitivity

than the 7 point checklist for dermoscopy, when consideration about ruling out melanoma is being made. A focus on impact analysis may help translate melanoma CPRs into useful and effective triage tools for use in primary care.

Footnotes

Contributors: EH, NW, and BC drafted the manuscript. EH, NW, and BC contributed to development of the selection criteria, the risk of bias assessment strategy, and the data extraction criteria. EH and PM developed the search strategy. HB, LA, and HS contributed the data extraction and quality assessments. BC and TF read, provided feedback and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Legends

Figure 1.b

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

Figure 2.b

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies

References

1. Erdmann F, Lortet-Tieulent J, Schüz J, et al. International trends in the incidence of malignant melanoma 1953–2008—are recent generations at higher or lower risk? *International Journal of Cancer.* 2013;132(2):385-400.
2. Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *Journal of the European Academy of Dermatology and Venereology : JEADV.* Sep 2014;28(9):1170-1178.
3. Coory M, Baade P, Aitken J, Smithers M, McLeod GRC, Ring I. Trends for in situ and Invasive Melanoma in Queensland, Australia, 1982–2002. *Cancer Causes & Control.* 2006;17(1):21-27.
4. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. *Journal of the American Academy of Dermatology.* Nov 2011;65(5 Suppl 1):S17-25.e11-13.
5. de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. *Int J Cancer.* Oct 20 2003;107(1):119-126.
6. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology.* 1998;197(1):11-17.
7. Cornish D, Holterhues C, van de Poll-Franse LV, Coebergh JW, Nijsten T. A systematic review of health-related quality of life in cutaneous melanoma. *Annals of Oncology.* 2009;20(Suppl 6):vi51-vi58.
8. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002–2006 and 2007–2011. *American journal of preventive medicine.* 11/10 2015;48(2):183-187.
9. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer.* 2005 41(1):45-60.
10. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer.* 2005;41(1):28-44.
11. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer.* 2005;41(14):2040-2059.
12. Koelink CJL, Kollen BJ, Groenhof F, van der Meer K, van der Heide WK. Skin lesions suspected of malignancy: an increasing burden on general practice. *BMC Fam Pract.* 2014;15:29.
13. Pockney P, Primrose J, George S, et al. Recognition of skin malignancy by general practitioners: observational study using data from a population-based randomised controlled trial. *Br J Cancer.* Jan 13 2009;100(1):24-27.
14. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. *Journal of the American Academy of Dermatology.* 2003;48(5):679-693.
15. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. *Eur J Dermatol.* Sep 1999;9(6):470-476.
16. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* Mar 2002;3(3):159-165.

17. Piccolo D, Ferrari A, Peris K, Diadone R, Ruggeri B, Chimenti S. Dermoscopic diagnosis by a trained clinician vs. a clinician with minimal dermoscopy training vs. computer-aided diagnosis of 341 pigmented skin lesions: a comparative study. *Br J Dermatol.* Sep 2002;147(3):481-486.
18. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and Managing Cutaneous Pigmented Lesions: Primary Care Physicians Versus Dermatologists. *Journal of General Internal Medicine.* 2006;21(7):678-682.
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews.* 2015;4(1):1-9.
20. Macbeth F, Newton-Bishop J, O'Connell S, Hawkins JE. Melanoma: summary of NICE guidance. *BMJ.* 2015-07-29 09:46:21 2015;351.
21. Moons KGM dGJ, Bouwmeester W, Vergouwe, Y., Mallett, S., Altman, D. G., Reitsma J.B., Collins, G. S. Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist. *PLoS Medicine.* 2014;11(10):e1001744.
22. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: updated March 2011.* 2011.
23. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* Oct 2005;58(10):982-990.
24. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Y T. Analysing and Presenting Results. In: Deeks JJ BP, Gatsonis C, , ed. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0*. Available from: http://methods.cochrane.org/sdt/handbook-dta-reviews/: The Cochrane Collaboration; 2010.
25. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. *Journal of the American Academy of Dermatology.* 2007;56(5):759-767.
26. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Archives of Dermatology.* 1998;134(12):1563-1570.
27. Argenziano G, Catricalà C, Ardigo M, et al. Seven-point checklist of dermoscopy revisited. *British Journal of Dermatology.* 2011;164(4):785-790.
28. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. *Eur J Dermatol.* Jun 2000;10(4):282-287.
29. Carli P, Quercioli E, Sestini S, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. *British Journal of Dermatology.* 2003;148(5):981-984.
30. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. *European Journal of Dermatology.* 1999;9(4):303-308.

31. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. *European Journal of Dermatology.* 2014;24(4):477-481.
32. Pizzichetta MA, Talamini R, Piccolo D, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. *Tumori.* 2002;88(3):234-238.
33. Soyer HP, Argenziano G, Zalaudek I, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. *Dermatology.* 2004;208(1):27-31.
34. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. *Melanoma Research.* 2003;13(6):631-632.
35. Buhl T, Hansen-Hagge C, Korpas B, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. *Journal of the American Academy of Dermatology.* 2012;66(1):27-36.
36. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. *BMC Dermatology.* 2010;10:9-9.
37. Haenssle HA, Korpas B, Hansen-Hagge C, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. *Journal of the American Academy of Dermatology.* 2010;62(5):785-793.
38. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. *Clinical and Experimental Dermatology.* 1992;17(5):313-315.
39. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. *Journal of the American Academy of Dermatology.* 1999;40(4):558-562.
40. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. *Clinical and Experimental Dermatology.* 1990;15(3):167-171.
41. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. *Journal of Dermatologic Surgery and Oncology.* 1992;18(1):22-26.
42. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. *Archives of Dermatology.* 2005;141(2):155-160.
43. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. *Journal of Dermatology.* 2014;41(7):598-603.
44. Walter FM, Prevost AT, Vasconcelos J, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. *British Journal of General Practice.* 2013;63(610):345-353.

45. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. *British Journal of Dermatology.* 1999;140(5):902-908.
46. Argenziano G, Longo C, Cameron A, et al. Blue-black rule: A simple dermoscopic clue to recognize pigmented nodular melanoma. *British Journal of Dermatology.* 2011;165(6):1251-1255.
47. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. *Journal of the American Academy of Dermatology.* 2003;48(5):672-678.
48. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. *British Journal of Dermatology.* 2004;151(5):1029-1038.
49. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. *Archives of Dermatology.* 2005;141(8):1008-1014.
50. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. *International Journal of Dermatology.* 2010;49(1):33-38.
51. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. *Australasian Journal of Dermatology.* 2012;53:7-8.
52. Henning JS, Stein JA, Yeung J, et al. CASH algorithm for dermoscopy revisited. *Arch Dermatol.* Apr 2008;144(4):554-555.
53. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. *Acta Derm Venereol.* Mar-Apr 2000;80(2):122-126.
54. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. *British Journal of Dermatology.* 2012;167(5):1037-1041.
55. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. *British Journal of Dermatology.* 2002;146(3):481-484.
56. Menzies SW, Kreusch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Archives of Dermatology.* 2008;144(9):1120-1127.
57. Menzies SW, Moloney FJ, Byth K, et al. Dermoscopic evaluation of nodular melanoma. *JAMA Dermatology.* 2013;149(6):699-709.
58. Argenziano G, Soyer HP, Chimenti S, Ruocco V. Impact of dermoscopy on the clinical management of pigmented skin lesions. *Clin Dermatol.* May-Jun 2002;20(3):200-202.
59. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference.* 2011;2011:3180-3183.

60. Zalaudek I, Argenziano G, Soyer HP, et al. Three-point checklist of dermoscopy: An open internet study. *British Journal of Dermatology.* 2006;154(3):431-437.
61. Walter FM, Prevost AT, Vasconcelos J, et al. The diagnostic accuracy of the 7-point checklist to assess pigmented skin lesions in primary care. *Asia-Pacific Journal of Clinical Oncology.* 2012;8:311.
62. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. *British Journal of Dermatology.* 2000;143(5):1016-1020.
63. Walter FM, Morris HC, Humphrys E, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. *BMJ (Online).* 2012;345(7866).
64. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. *British Journal of Dermatology.* 1994;130(1):48-50.
65. Rao BK, Marghoob AA, Stolz W, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. *Skin Research and Technology.* 1997;3(1):8-14.
66. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. *Journal of the American Academy of Dermatology.* 1999;40(2 I):171-176.
67. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. *Hautarzt.* 1998;49(6):473-476.
68. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. *Acta Dermato-Venereologica.* 1999;79(6):469-472.
69. Nachbar F, Stolz W, Merkle T, et al. The ABCD rule of dermatoscopy. *Journal of the American Academy of Dermatology.* 1994;30(4):551-559.
70. Stolz W, Riemann A, Cognetta AB, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. *European Journal of Dermatology.* 1994;4(7):521-527.
71. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. *British Journal of Dermatology.* 2004;150(5):1040.
72. Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy Improves Accuracy of Primary Care Physicians to Triage Lesions Suggestive of Skin Cancer. *Journal of Clinical Oncology.* April 20, 2006 2006;24(12):1877-1882.
73. Carli P, Nardini P, Crocetti E, De Giorgi V, Giannotti B. Frequency and characteristics of melanomas missed at a pigmented lesion clinic: a registry-based study. *Melanoma research.* Oct 2004;14(5):403-407.
74. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med.* Feb 7 2006;144(3):201-209.
75. Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. *Br J Dermatol.* Sep 2009;161(3):591-604.
76. Stiell IG, Clement CM, Grimshaw JM, et al. A prospective cluster-randomized trial to implement the Canadian CT Head Rule in emergency departments. *CMAJ : Canadian Medical Association Journal.* 2010;182(14):1527-1532.

77. Collins GS, de Groot JA, Dutton S, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology.* 2014;14(1):1-11.
78. Riley RD, Ensor J, Snell KIE, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ.* 2016-06-22 12:16:05 2016;353.
79. Wallace E, Uijen MJM, Clyne B, et al. Impact analysis studies of clinical prediction rules relevant to primary care: a systematic review. *BMJ Open.* 2016;6(3).
80. Blum A, Clemens J, Argenziano G. Modified dermoscopic algorithm for the differentiation between melanocytic and nonmelanocytic skin tumors. *Journal of Cutaneous Medicine and Surgery.* 2006;10(2):73-78.
81. Cengiz FP, Cengiz AB, Emiroglu N, Comert E, Wellenhof RH. Dermoscopic and clinical features of head and neck melanoma. *Anais Brasileiros de Dermatologia.* 2015;90(4):488-493.
82. Carrera C, Marchetti MA, Dusza SW, et al. Validity and reliability of dermoscopic criteria used to differentiate nevi from melanoma: A web-based international dermoscopy society study. *JAMA Dermatology.* 2016;152(7):798-806.
83. Rat C, Grimault C, Quereux G, et al. Proposal for an annual skin examination by a general practitioner for patients at high risk for melanoma: a French cohort study. *BMJ Open.* July 1, 2015 2015;5(7).
84. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. *Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society.* 1992;Suppl 2:295-298.
85. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Archives of Dermatology.* 1996;132(10):1178-1182.
86. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. *British Journal of Dermatology.* 1994;130(3):349-355.

Table 1 CPRs identified for inclusion with cut points for identification of melanoma

Rule name	Cut point used	Number of validation studies
Clinical rules		
ABCDE clinical rule	≥ 1 or ≥ 2	4
ABCD clinical rule	≥ 1	4
Revised 7 point checklist (clinical)	≥ 3	4
7 point checklist (clinical)	≥ 3	4
Dermoscopic rules		
ABCD rule of dermoscopy*	≥ 4.75	15
	≥ 5.45	6
	≥4.2	1
	Not reported	1
7-point checklist for dermoscopy	≥ 3	17
Menzies 1996 dermoscopy for melanoma	≥ 1, no negative features	8
3-point checklist for dermoscopy	≥ 1	6
7 features for melanoma (7FFM)	≥ 2	5
CASH dermoscopy algorithm	≥ 8	3
ABCDE rule (dermoscopy)	Not reported	2
The 3 colour dermoscopy test	≥ 3	2
Revised 7-point checklist for dermoscopy	≥ 1	1
Kreusch 1992 dermoscopy	Not reported	1
Nilles 1994 dermoscopy	Not reported	1
Menzies 2008 dermoscopy for melanoma	≥ 1	1
DynaMel algorithm	≥ 3	1
Menzies 2008 dermoscopy for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	1
Simplified ABC-point list for dermoscopy	≥ 4	1
AC rule for dermoscopy	Not reported	1
Emery 2010 SIAscopy	≥ 6	1
Guitera RCM 2012	Not reported	1
Digital dermoscopy algorithms	Multiple algorithms, different cutoffs.	1

* Score = (A score x 1.3) + (B score x 0.1) + (C score x 0.5) + (D score x 0.5)

Table 2 Characteristics of validation and impact analysis studies included

Validation Studies						
Author Year Country	**Setting**	**CPR utilised**	**Lesions**	**Patient: n, sex, mean age**	**CPR applied by: n, experience**	**Reported sensitivity/specificity**
Annessi 2007[25] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	198 96 melanomas, 102 nonmelanoma	N = 195 54% male Mean age: 43	2 ELM-experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 84.4 Sp: 74.5 7-point checklist for dermoscopy (cut point ≥3) Se: 78.1 Sp: 64.7
Argenziano 1998[26] Italy	Deparment of Dermatology	7-point checklist for dermoscopy ABCD rule of dermoscopy	342 117 melanoma, 225 nonmelanoma	NR	5 3 experienced 2 less-experienced	7-point checklist for dermoscopy (cut point ≥3) *Expert user:* Se: 95.0 Sp: 75.0 *Non-expert user (mean):* Se: 89.0 Sp: 61.5 ABCD rule of dermoscopy (cut point ≥4.75) *Expert user:* Se: 85.0 Sp: 66.0 *Non-expert user (mean):* Se: 91.5

						Sp: 31.0
Argenziano 2003[14] 9 countries	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	108	NR	40 experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 82.6 Sp: 70.0 7-point checklist for dermoscopy Se: 85.7 Sp: 71.1 Menzies 1996 dermoscopy for melanoma Se: 85.7 Sp: 71.1
Argenziano 2011[27] Italy	Deparment of Dermatology	7-point checklist for dermoscopy Revised 7-point checklist for dermoscopy	300 100 excised melanoma, 100 excised nonmelanoma, 100 nonexcised nonmelanoma	NR	8 experienced	7-point checklist for dermoscopy (cut point ≥3) Se: 77.9 Sp: 85.6 Revised 7-point checklist for dermoscopy (cut point ≥1) Se: 87.8 Sp: 74.5
Benelli 1999[15] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	401 60 melanomas, 341 nonmelanoma	NR	2 research team	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 80.0 Sp: 89.1 ABCDE Clinical rule (cut point

						≥2) Se: 85.0 Sp: 44.5
Benelli 2000[28] Italy	Deparment of Dermatology	7FFM (7 features for melanoma) dermoscopy ABCDE Clinical rule	600 76 melanomas, 524 nonmelanoma	Mean age: 53	3	7FFM (7 features for melanoma) dermoscopy (cut point of ≥2) Se: 68.8 Sp: 86.0 ABCDE Clinical rule (cut point of ≥2) Se: 47.3 Sp: 56.0
Binder 1999[66] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	250	NR	17 12 experienced 5 trainee	ABCD rule of dermoscopy (cut point ≥4.75) Se: 81.0 Sp: 77.0 ABCD rule of dermoscopy (cut point ≥5.45) Se: 73.0 Sp: 90.0
Blum 2003[71] Germany	Deparment of Dermatology	The 3 colour dermoscopy test	249	NR	NR	The 3 colour dermoscopy test Se: 76.9 Sp: 90.1
Blum 2004[47] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma Simplified ABC-point list for	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy

		dermoscopy 7FFM (7 features for melanoma) dermoscopy				Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8 7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6 Simplified ABC-point list for dermoscopy Se: 90.5 Sp: 87.0
Blum 2004[48] Germany	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma 7FFM (7 features for melanoma) dermoscopy	269 84 melanomas, 185 nonmelanoma	NR	NR	ABCD rule of dermoscopy Se: 90.5 Sp: 72.4 7-point checklist for dermoscopy Se: 90.5 Sp: 87.0 Menzies 1996 dermoscopy for melanoma Se: 95.2 Sp: 77.8

						7FFM (7 features for melanoma) dermoscopy Se: 94.0 Sp: 74.6
Buhl 2012[35] Germany	Deparment of Dermatology	DynaMel Algorithm 7-point checklist for dermoscopy	675	N= 688 57% male Mean age: 42	Dermatology residents	DynaMel Algorithm Se: 77.1 Sp: 98.1 7-point checklist for dermoscopy (cut point ≥3) Se: 47.5 Sp: 99.0
Carli 2002[29] Italy	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	200 44 melanomas, 156 nonmelanoma	NR	5 dermatology residents	ABCD rule of dermoscopy (cut point ≥5.45) Se: 88.1 Sp: 45.7 7-point checklist for dermoscopy (cut point ≥3) Se: 91.9 Sp: 35.2
Dal Pozzo 1999[30] Italy	Department of dermatology	7FFM (7 features for melanoma) dermoscopy	713 168 melanomas, 545 nonmelanoma	NR	3	7FFM (7 features for melanoma) dermoscopy Se: 94.6 Sp: 85.5
Dolianitis 2005[49] Australia	Primary care and Dermatology department	7-point checklist for dermoscopy ABCD rule of dermoscopy Menzies 1996 dermoscopy for	40 20 melanomas, 20 nonmelanoma	NR	61 35 Primary care physicians, 10	7-point checklist for dermoscopy Se: 81.4 Sp: 73.0

		melanoma			dermatologists, 16 trainee dermatologists	ABCD rule of dermoscopy (cut point ≥5.45) Se: 77.5 Sp: 80.4 Menzies 1996 dermoscopy for melanoma Se: 84.6 Sp: 77.7
Emery 2010[36] UK	Family practice	Emery 2010 SIAscopy in primary care for melanoma	1211	N=858 52% male Mean age: 50	1 SIAscopy expert	Emery 2010 SIAscopy in primary care for melanoma Se: 50.0 Sp: 84.0
Feldman 1998[67] Austria	Deparment of Dermatology	ABCD rule of dermoscopy	500 30 melanomas, 470 nonmelanoma	NR	NR	ABCD rule of dermoscopy (cut point ≥4.2) Se: 88.0 Sp: 64.0
Gereli 2010[50] Turkey	Deparment of Dermatology	7-point checklist for dermoscopy 3-point checklist for dermoscopy	96 48 melanoma, 48 nonmelanoma	NR	3 2 experienced 1 inexperienced	7-point checklist for dermoscopy (cut point ≥3) Se: 87.5 Sp: 16.2 3-point checklist for dermoscopy (cut point ≥2) Se: 89.6 Sp: 31.2
Guitera 2012[51] Multiple	Skin cancer clinic	Guitera 2012 confocal microscopy for melanoma	710 216 melanomas, 494 nonmelanoma	N = 663	NR	Guitera 2012 confocal microscopy for melanoma Se: 87.6

						Sp: 70.8
Haenssle 2010[37] Germany	Deparment of Dermatology	7 point checklist for dermoscopy	1219 127 melanomas, 1092 nonmelanoma	N= 688 57% male Mean age: 42	Inexperienced	7 point checklist for dermoscopy (cut point ≥3) Se: 62.0 Sp: 97.0
Healsmith 1993[64] UK	Pigmented lesion clinic	Revised 7-point checklist (clinical) ABCDE clinical rule	165 65 melanoma, 100 nonmelanoma	NR	NR	Revised 7-point checklist (clinical) Se: 100 Sp: nr ABCDE clinical rule Se: 92.3 Sp: nr
Henning 2008[52] USA	Deparment of Dermatology	CASH dermoscopy algorithm ABCD rule of dermoscopy 7-point checklist for dermoscopy Menzies 1996 dermoscopy for melanoma	150 50 melanoma, 100 nonmelanoma	NR	2 Inexperienced	CASH dermoscopy algorithm Se: 87.0 Sp: 67.0 ABCD rule of dermoscopy Se: 86.0 Sp: 74.0 7-point checklist for dermoscopy Se: 76.0 Sp: 57.0 Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 38

Higgins 1992[38] UK	Deparment of Dermatology	7 point checklist (clinical) 7 point checklist (clinical) revised	100 0 melanoma, 100 nonmelanoma	N=100 30% male Mean age: 36.7	NR	7 point checklist (clinical) revised Se: NR Sp: 70.0
Kittler 1999[39] Austria	Deparment of Dermatology	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	356 73 melanomas, 283 nonmelanoma	N= 352 43% male Mean age: 52	NR	NR
Keefe 1989[40] Scotland	Hospital dermatology clinic	7-point checklist (clinical)	222	N=195 22% male Mean age: 43	Dermatologists 195 patients	7-point checklist (clinical) (cut point ≥3) *Dermatologists:* Se: 85.7 Sp: 66.5 *Patients:* Se: 71.4 Sp: 66.2
Kreusch 1992[84] Germany	Deparment of Dermatology	Kreusch 1992 dermoscopy for melanoma	317 96 melanomas, 221 nonmelanoma	NR	2 1 experienced 1 inexperienced	Kreusch 1992 dermoscopy for melanoma *Experienced:* Se: 98.9 Sp: 94.1 *Inexperienced:* Se: 97.0 Sp: 94.2
Lorentzen 1999[68] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	232	NR	8 4 experienced 4 inexperienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 59.0 Sp: 92.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 41.0 Sp: 98.0
Lorentzen 2000[53] Denmark	Deparment of Dermatology	ABCD rule of dermoscopy	258 64 melanoma, 194 nonmelanoma	NR	3 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 70.7 Sp: 88.0
Luttrell 2012[54] Austria	Deparment of Dermatology	AC rule for dermoscopy	200 25 melanoma, 178 nonmelanoma	NR	17 Lay persons	AC rule for dermoscopy Se: 91.2 Sp: 94.0
Mackie 2002[55] Scotland	Pigmented lesion clinic	The 3 colour dermoscopy test	126 69 melanoma 57 nonmelanoma	NR	3 Experienced	The 3 colour dermoscopy test Se: 97.0 Sp: 55.0
McGovern 1992[41] USA	Dermatology clinic	7 point checklist (clinical) BCD clinical rule	237 16 malignant, 221 nonmelanoma	N=179 50% male Mean age: 44	NR	7 point checklist (clinical) Se: 0.44 Sp: 0.94
Menzies 1996[85] Australia	Melanoma unit	Menzies 1996 dermoscopy for melanoma	385 107 melanomas,	NR	NR	Menzies 1996 dermoscopy for melanoma Se: 92.0 Sp: 71.0
Menzies 2008[56]		7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma Menzies 2008 dermoscopy for melanoma Menzies 2008 dermoscopy for skin cancer	497 105 melanomas, 392 nonmelanoma	NR	12 Experienced	7-point checklist for dermoscopy Se: 41.0 Sp: 83.0 3-Point checklist of dermoscopy Se: 50.0 Sp: 71.0 Menzies 1996 dermoscopy for melanoma

						Se: 54.0 Sp: 76.0 Menzies 2008 dermoscopy for melanoma Se: 70.0 Sp: 56.0 Menzies 2008 dermoscopy for skin cancer Se: 95.0 Sp: 80.0
Menzies 2013[57]		ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-Point checklist of dermoscopy Menzies 1996 dermoscopy for melanoma CASH dermoscopy algorithm Menzies 2013 dermoscopy for nodular melanoma	465 217 melanomas, 248 nonmelanoma	NR	12	ABCD rule of dermoscopy Se: 81.5 Sp: NR 7-point checklist for dermoscopy Se: 94.4 Sp: NR 3-Point checklist of dermoscopy Se: 83.9 Sp: NR Menzies 1996 dermoscopy for melanoma Se: 98.4 Sp: NR CASH dermoscopy algorithm

						Se: 41.0 Sp: 83.0 Menzies 2013 dermoscopy for nodular melanoma Se: 93.0 Sp: 70.0
Nachbar 1994[69] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	194 69 melanomas	NR	NR	ABCD rule of dermoscopy (cut point ≥5.45) Se: 92.8 Sp: 91.2
Nilles 1994[86] Germany	Deparment of Dermatology	Nilles 1994 dermoscopy for melanoma	260 72 melanomas, 188 nonmelanoma	NR	NR	Nilles 1994 dermoscopy for melanoma Se: 90.0 Sp: 85.0
Osborne 1999[45] UK	Deparment of Dermatology	Revised 7-Point Checklist (clinical)	778 778 melanomas, 0 nonmelanoma	N=733 35% male	NR	Revised 7-Point Checklist (clinical) False negative rate: 18.5
Piccolo 2014[31] Italy	Deparment of Dermatology	ABCD rule of dermoscopy	165 33 melanomas, 129 nonmelanoma	N =165 59% male Mean age: 43.5	4 3 dermatologists 1 FP	ABCD rule of dermoscopy Se: 91.0 Sp: 52.0
Pizzichetta 2002[32] Italy	Department of Oncology	ABCD rule of dermoscopy	129	N = 123	2 Experienced	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 43.0 ABCD rule of dermoscopy (cut point ≥5.45)

						Se: 90.0 Sp: 53.5
Rao 1997[65]	Deparment of Dermatology	ABCD rule of dermoscopy ABCD clinical rule	73	N =63	4 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 90.0 Sp: 57.0 ABCD clinical rule Se: 84.0 Sp: 78.0
Skvara 2005[42] Austria	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy	325 63 melanomas, 262 nonmelanoma	N =297 44% male Mean age: 39	2 experienced dermatologists	ABCD rule of dermoscopy (cut point ≥4.75) Se: 31.7 Sp: 87.3 7-point checklist for dermoscopy Se: 11.1 Sp: 95.2
Soyer 2004[33] Italy	Deparment of Dermatology	3-point checklist of dermoscopy	231 68 melanomas, 163 nonmelanomas	N = 225 49% male	6 Inexperienced	3-point checklist of dermoscopy Se: 96.3 Sp: 32.8
Stolz 1994[70] Germany	Deparment of Dermatology	ABCD rule of dermoscopy	157	NR	NR	ABCD rule of dermoscopy(cut point ≥5.45) Se: 97.9 Sp: 90.3
Strumia 2003[34] Italy	Deparment of	ABCD rule of dermoscopy ABCDE rule (dermoscopy)	49	NR	2	

	Dermatology					
Thomas 1998[6] France	Deparment of Dermatology	ABCDE clinical rule	1140	NR	NR	ABCDE clinical rule (cut point ≥2) Se: 89.3 Sp: 65.3
Unlu 2014[43] Turkey	Deparment of Dermatology	ABCD rule of dermoscopy 7-point checklist for dermoscopy 3-point checklist of dermoscopy CASH dermoscopy algorithm	115 24 melanomas, 91 nonmelanoma	N= 115 49% male Mean age: 39	3 experienced dermatoscopists	ABCD rule of dermoscopy Se: 91.6 Sp: 60.4 7-point checklist for dermoscopy Se: 79.1 Sp: 62.6 3-point checklist of dermoscopy Se: 87.5 Sp: 65.9 CASH dermoscopy algorithm Se: 91.6 Sp: 64.8
Wadhawan 2011[59] USA	Images from library of skin cancer	7-point checklist for dermoscopy	347	NR	NR	7-point checklist for dermoscopy Se: 87.3 Sp: 71.3
Walter 2013[44] UK	Family practice	7 point checklist (clinical) Revised 7-point checklist (clinical)	1436 36 melanomas, 1400 nonmelanoma	N= 1182 35.9% male Mean age: 44.7	NR	7 point checklist (clinical) Se: 80.6 Sp: 61.7

						Revised 7-point checklist (clinical) Se: 91.7 Sp: 33.1
Zalaudek 2006[60] 29 Countries	Pigmented lesion clinic	3-point checklist for dermoscopy	150 44 malignant, 106 nonmelanoma	NR	150 varying levels of experience	3-point checklist for dermoscopy Se: 94.0 Sp: 71.9
Impact Analysis Sudies						
Author Year Country	**Study design**	**Participant selection**	**Lesions**	**Intervention**	**Control**	**Outcomes**
Westerhof f 2000[62] Australia Primary care	Controlled before & after	74 FPs	n=100 (50 melanoma, 50 non-melanoma) selected randomly from the Sydney Melanoma Unit image database	Educaional intervention. FPs given educational material on Menzies 1996 rule, followed by a 1-h presentation on surface microscopy	Usual care	**Correct diagnosis of melanoma, percent (SD):** Intervention 75.9 (12) Control 54.8 (22) **Correct diagnosis of non-melanoma, percent (SD):** Intervention 57.8 (14) Control 55.8(15)
Walter 2012[63] England Primary care	RCT	15 FP practices	1580 from 1297 patients	Patients assessed using the MoleMate system (SIAscopy with primary care	Best practice (clinical history, naked eye examination, seven point	**Primary, appropriateness of referral (defined as the proportion of referred lesions that secondary care experts decided to biopsy or monitor):** no statistically significant

				scoring algorithm)	checklist clinical)	difference between intervention or control; 56.8% v 64.5%; difference −8.1% (95% CI −18.0% to 1.8%). **Secondary:** • Appropriate management of benign lesions in primary care: no statistically significant difference between intervention or control (99.6% v 99.2%, P=0.46). • Agreement with an expert decision to biopsy or monitor: no statistically significant difference between intervention and control (98.5% v control 95.7%, P=0.26). • Patient satisfaction: more intervention patients ranked their consultation very good/excellent for thoroughness than control (83.1% v 71.2%, P<0.001). Patient anxiety: no statistically significant difference between intervention and control in anxiety scores (32.56 v 34.72,

						P=0.013)
Argenziano 2006 [72] Spain, Italy Primary Care	RCT	73 FPs	2548 lesions from 2522 patients presenting to primary care with a pigmented skin lesion. 1203 lesions in dermoscopy group (6 melanoma) 1345 lesions in control group (6 melanoma)	Use of dermoscopy in addition to "naked eye" lesion screening. Both groups received a 4 hour educational intervention incorporating clinical examination and use of the 3 point checklist (dermoscopy algorithm)	Naked eye screening alone.	**Primary outcome:** Referral accuracy of PCPs (defined as the ability of the PCP to correctly determine a lesion may be malignant or benign, when the gold standard is diagnosis by a second expert clinician) reported as sensitivity, specificity, PPV, NPV. • Significant difference in sensitivity (dermoscopy 79.2%, naked-eye 54.1%, P=0.002) and negative predictive value (dermoscopy 9801%, naked-eye 95.8%, P=0.004) **Secondary outcome:** Number of malignant tumours missed by PCPs using naked eye examination (n=23) and using dermoscopy (n=6) (P=0.002)

NR: Not reported
Se: Sensitivity
Sp: Specificity

Table 3.a Comparison of elements in clinical prediction rules for malignant melanoma (clinical rules)

Elements	Clinical CPR name			
	ABCD	**ABCDE**	**7 point checklist**	**Revised 7 point checklist**
Asymmetry	X	X		X
Border irregularity	X	X	X	
Colour variegation	X	X	X	X
Diameter (>6mm)	X	X	X (>7mm)	X (>7mm)
Evolving (e.g. size, shape, colour)		X	X (size)	X
Altered sensation			X	X
Inflammation			X	X
Crusting, bleeding			X	X
Cut point	*≥ 1*	*≥ 1 or ≥2*	*≥ 3*	*≥ 3*

Table 3.b Comparison of elements in clinical prediction rules for malignant melanoma (dermoscopic rules)

Element	CPR Name															
	ABCD	7-point checklist	Revised 7-point checklist	Menzies 1996	3-point checklist	7FFM	CASH	ABCDE	3 colour test	Kreusch 1992	Nilles 1994	Menzies 2008 - melanoma	Menzies 2008- skin cancer	DynaMel	Simplified ABC	AC rule
Asymmetry	X			X	X	X	X	X		X	X	X		X	X	X
Multiple colours (light/dark brown, black, red white, blue)	X	X	X	X			X	X	X	X	X	X		X	X	X
Architectural disorder (structures & colours)		X				X	X			X	X		X	X	X	
Atypical network	X	X	X	X	X	X	X	X					X			
Blue-white veil			X	X	X	X	X					X				
Blue white structures								X					X			
Streaks/radial streaming/ psuedo-pods	X	X	X	X		X	X	X		X	X			X		
Dots, globules	X	X	X	X			X	X				X	X	X		
Regression structures		X	X			X	X			X	X		X	X		

or erythema																
Scarring				X			X									
Blotches (structureless region >10%	X						X	X								
Atypical vascular pattern		X	X				X			X		X	X	X		
Recognisable as benign													X			
Abrupt cut-off border pigment	X					X		X							X	
Blue-grey dots												X				
Change								X				X		X	X	
Cut point	≥4.75 ≥5.45	≥3	≥1	≥1, no - features	≥1	≥2	≥2	Not reported	≥3	Not reported	Not reported	≥1	≥0 (High sensitivity) ≥1 (High specificity)	≥3	≥4	Not reported

Table 4 Sensitivity and specificity of all clinical and dermoscopy CPRs

Rule name	Cut point	Sensitivity *	Specificity*
Clinical rules			
ABCDE	≥ 1	*2 studies* 0.47-0.92 (mean 0.70)	*1 study* 0.56
	≥ 2	0.85	0.44
7 point checklist	≥ 3	*3 studies* 0.44-0.86 (mean 0.70)	*3 studies* 0.62-0.94 (mean 0.74)
Revised 7 point checklist	≥ 3	0.92	0.33
ABCD rule	≥ 1	0.84	0.78
Dermoscopic rules			
ABCD rule	≥ 4.75	*Meta-analysis* *(8 studies)* 0.85 (95% CI 0.73-0.93)	*Meta-analysis* *(8 studies)* 0.72 (95% CI 0.65-0.78)
	≥ 5.45	*4 studies* 0.73-0.98 (mean 0.85)	*4 studies* 0.46-0.91 (mean 0.79)
	≥4.2	0.88	0.64
7-point checklist	≥ 3	*Meta-analysis* *(11 studies)* 0.77 (95% CI 0.61-0.88)	*Meta-analysis* *(11 studies)* 0.80 (95% CI 0.59-0.92)
Menzies 1996 for melanoma	≥ 1	*6 studies* 0.85-0.95 (mean 0.91)	*6 studies* 0.38-0.78 (mean 0.69)
3-point checklist	≥ 1	*5 studies* 0.50-0.96 (mean 0.84)	*4 studies* 0.31-0.72 (mean 0.55)
7 features for melanoma (7FFM)	≥ 2	*5 studies* 0.69-0.95 (mean 0.86)	*5 studies* 0.74-0.86 (mean 0.82)
CASH algorithm	≥ 8	*3 studies* 0.41-0.92 (mean 0.73)	*3 studies* 0.65-0.97 (mean 0.82)
The 3 colour test	≥ 3	*2 studies* 0.77-0.97 (mean 0.87)	*2 studies* 0.55-0.90 (mean 0.73)
Revised 7-point checklist	≥ 1	0.88	0.28
Kreusch 1992	Not reported	0.99	0.94
Nilles 1994	Not reported	0.90	0.85
Menzies 2008 for melanoma	≥ 1	0.70	0.56
DynaMel algorithm	≥ 3	0.77	0.98
Menzies 2008 for skin cancer	≥ 0 (high sensitivity); ≥ 1 (high specificity)	0.95	0.80
Simplified ABC-point list	≥ 4	0.90	0.87
AC rule	Not reported	0.91	0.94
Emery 2010 SIAscopy	≥ 6	0.50	0.84
Guitera RCM 2012	Not reported	0.88	0.71
ABCDE rule	Not reported	Not reported	Not reported

* Where sensitivity and specificity are presented for more than one study, the range and mean are presented. Where meta-analysis was possible, values from meta-analysis are presented with 95% confidence intervals (CI).

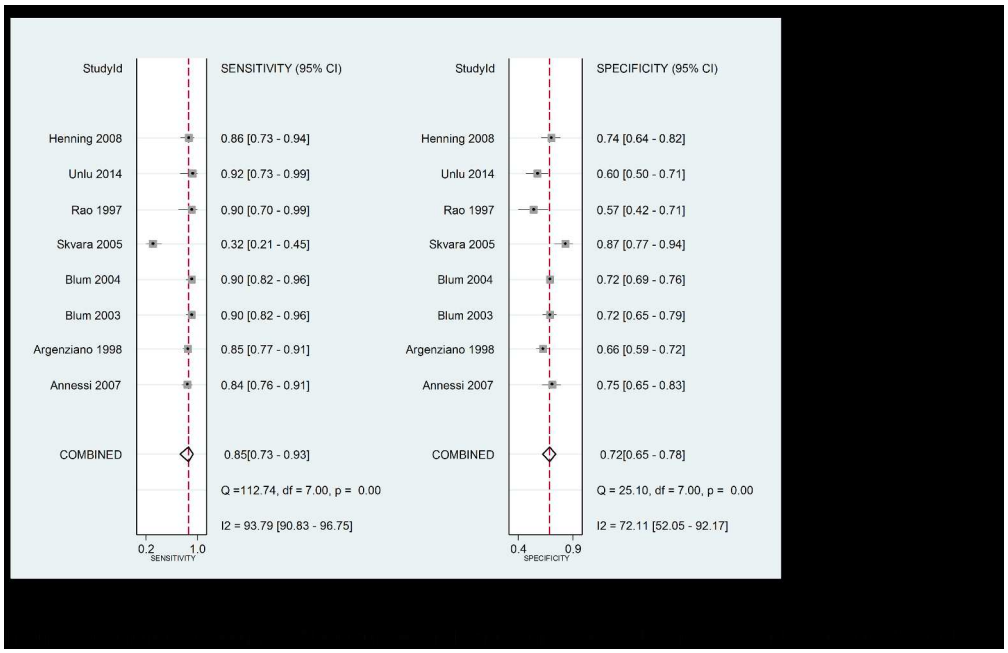


Figure 1.a Diagnostic accuracy ABCD rule with dermoscopy - pooled sensitivity and specificity (8 studies)

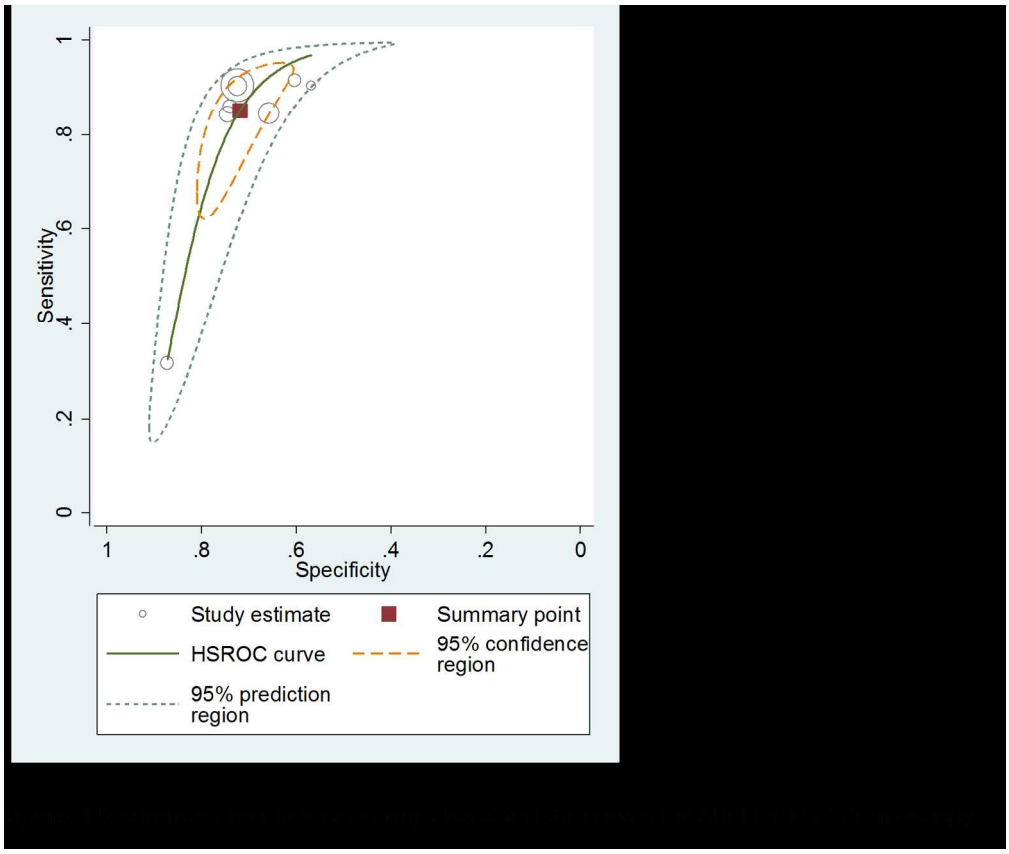


Figure 1.b Summary receiver operating characteristic curves for ABCD rule of dermoscopy

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

159x134mm (300 x 300 DPI)

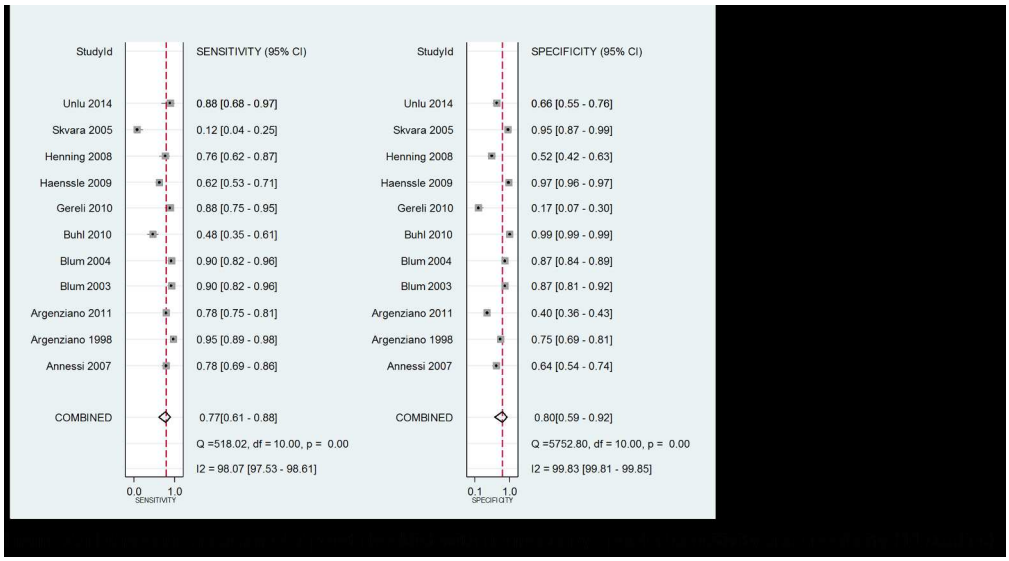


Figure 2.a Diagnostic accuracy of 7 point checklist with dermoscopy - pooled sensitivity and specificity (11 studies)

198x109mm (300 x 300 DPI)

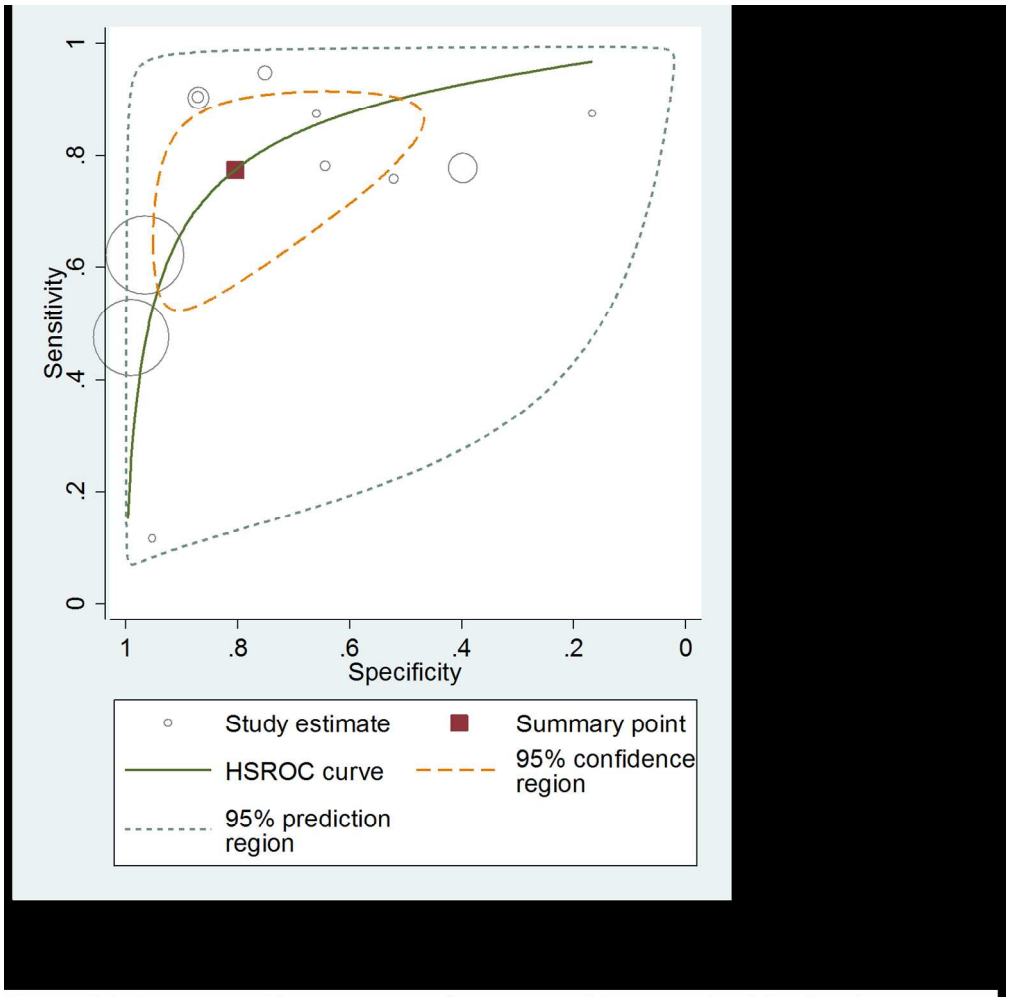


Figure 2.b ROC curve illustrating performance of 7 point checklist for dermoscopy

Figure 2.b Summary receiver operating characteristic curves for ABCD rule of dermoscopy

The circles represent individual studies and the size reflects the sample size. The red square represents the summary estimates of sensitivity and specificity and the dotted ellipses around this represent the 95% CI around the estimate. The 95% prediction region (amount of variation between studies) was wide, suggesting heterogeneity between studies.

141x144mm (300 x 300 DPI)

Appendix 1: Elements in Clinical Prediction Rules for cutaneous malignant melanoma

CPR name	*Clinical* **ABCD (1)**	*Clinical* **ABCDE (2)**	*Clinical* **Glasgow 7-point checklist (3)**	*Clinical* **Revised 7-point checklist (4)**	*Dermoscopy* **2C Rule for dermoscopy (5)**	*Dermoscopy* **3-point checklist (6)**
Elements	Asymmetry one half not identical to the other half	Asymmetry one half not identical to the other half	Change in size of lesion	***Major features:*** *(2 points each)* Change in size	Asymmetry score between 0 (no asymmetry) and 10 (marked asymmetry)	Asymmetry of colour and structure in one or two perpendicular axes
	Border irregularity uneven or ragged border	Border irregularity uneven or ragged border	Irregular pigmentation	Irregular pigmentation	Colour variation score between 0 (no colour variation) and 10 (marked colour variation)	Atypical pigment network with irregular holes and thick lines
	Colour variegation presence of at least 2 different colours within the lesion	Colour variegation presence of at least 2 different colours within the lesion	Irregular border	Irregular border		Blue white structures
	Diameter	Diameter	Inflammation	***Minor features:***		

	Maximum diameter > 6mm	Maximum diameter >6mm		Inflammation		
		Evolution Patient description of lesion change including elevation, enlargement or colour change	Itch or altered sensation	Itch or altered sensation		
			Larger than other lesions (diameter > 7mm)	Larger than other lesions (diameter > 7mm)		
			Oozing/crusting of lesion	Oozing/crusting of lesion		
Cut point/ specialist referral	Presence of any one element	Presence of any one element	Presence of 3 or more elements	Any one major feature OR 3 points or greater	Participant assessment of whether lesion suspicious or not (no score specified)	Presence of 2 or more elements

CPR name	*Dermoscopy* **C.A.S.H. algorithm (7)**	*Dermoscopy* **Menzies method (8)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma (9)**	*Dermoscopy* **Menzies 2008 dermoscopy for skin cancer (9)**	*Dermoscopy* **7 Features for Melanoma (7FFM) (10)**
Elements	Colour: light brown, dark brown, black, red, white, blue *(each colour=1 point)*	***Benign:*** Symmetry of pattern	**Negative features** (if present, nonmelanoma): >3 milialike cysts	**Negative features (score -1 each)** Multiple (>3) milialike cysts	***Stage 1:*** *determine whether lesion is melanocytic (pigment network or globules); if so, proceed.*
	Architectural disorder *(none=0, moderate=1, marked=2 points)*	One colour; black, grey, blue, dark brown, tan, red	**Positive features** (if any 1 present in a lesion lacking significant pigment, then melanoma): Irregularly sized or distributed brown dots/globules	Symmetrical pigmentation pattern	***Stage 2:*** ***Major features*** (2 points each): Pseudopods
	Symmetry of lesion and within lesion *(biaxial=0, monaxial symmetry=1, biaxial asymmetry=2 points)*	***Positive features:*** Blue-white veil	Multiple blue-grey dots	Comma vessels in regular distribution	Radial streaming
	Homogeneity/heterogeneity	Peripheral black	Irregularlay	Multiple brown dots	Regression-erythema

	network/ dots, globules/ streaks, pseudopods/ blue-white veil/ regression structures (grey areas with or without peppering)/ scarring/ blotches (structureless region of any colour occupying >10% of area)/ polymorphous blood vessels *each structure=1 point*	dots/globules	shaped depigmentation		
		Multiple brown dots	Blue-white veil	**Positive features (score +1 each)** Depigmentation	Grey-blue veil
		Pseudopods	>1 shade of pink	Small diameter arborizing vessels	**Minor features** (1 point each): Unhomogeneity
		Radial streaming	Predominant central vessels	Leaflike areas	Irregular pigment network
		Scarlike depigmentation	Dotted and linar irregular vessels	Ulceration	Sharp margin
		Multiple colours (5 or 6); black, grey, blue, dark brown, tan, red		Irregular size or distributed blu-grey globules	
		Multiple blue/grey dots		Grey colour	
		Broad pigment network		Large-diameter vessels	
Cut	8 points or more	Absent benign	Presence of ≥ 1	Total score ≥ 1	Score of 2 or more

point/ specialist referral		features and 1 or more positive features	positive feature		

CPR name	*Dermoscopy* **ABCD Rule of Dermoscopy/Stolz (11)**	*Dermoscopy* **7 point checklist for dermoscopy (12)**	*Dermoscopy* **Revised 7 point checklist for dermoscopy (13)**	*Dermoscopy* **Simplified ABC-point list of dermoscopy (14)**
Elements	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	***Major criteria:*** *(2 points each)* Atypical pigment network: black, brown, grey thickened and irregular line segments	*Criteria (1 point each):* Atypical pigment network: black, brown, grey thickened and irregular line segments	Asymmetry of outer shape *(1 point)*
	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Blue-white veil: irregular, confluent, grey-blue to whitish-blue diffuse pigmentation, dots/globules, streaks	Asymmetry of differential structures inside the lesion in at least 1 axis *(1 point)*
	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Atypical vascular pattern: linear-irregular and/or dotted red vessels not in regression areas	Border: abrupt cutoff of network at the border in at least ¼ of the circumference
	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(1 point each)*	***Minor criteria:*** *(1 point each)* Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Irregular streaks: pseudopods or irregular radial streaming at lesion periphery	Colour: Three or more colours *(1 point)*
		Irregular pigmentation: black,	Irregular pigmentation:	Differential structures:

		brown, grey featureless areas with irregular shape/ distribution.	black, brown, grey featureless areas with irregular shape/ distribution.	Three or more differential structures *(1 point)*
		<u>Irregular dots/ globules:</u> black, brown, grey round to oval, variously sized structures irregularly distributed	<u>Irregular dots/ globules:</u> black, brown, grey round to oval, variously sized structures irregularly distributed	<u>Evolution:</u> Evolution/change noticed by the patient during the last 3 months *(1 point)* No information (0) No change (-1)
(15)		<u>Regression structures:</u> white scarlike areas, blue pepper-like areas	<u>Regression structures:</u> white scarlike areas, blue pepper-like areas	
Cut point/ specialist referral	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Score of 3 or more A **revised 7 point checklist for dermoscopy** allocates 1 point for each of the above criteria and recommends excision or referral if score is 1 or greater.	Score of 1 or more	Score of 4 or more

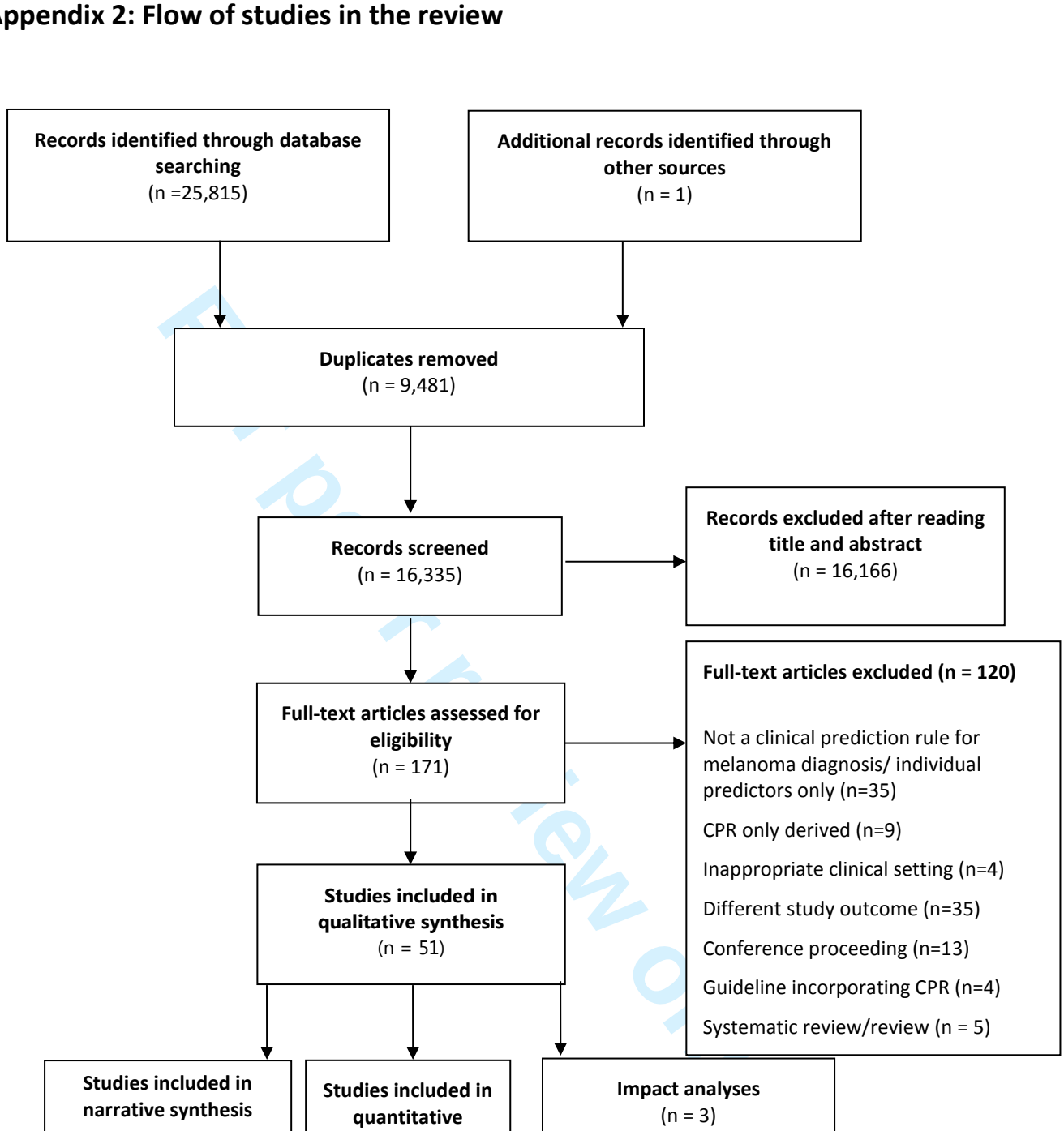
CPR name	*Dermoscopy* **Three-colour dermoscopy test (15)**	*Dermoscopy* **Menzies 2008 dermoscopy for melanoma lacking significant pigment (9)**	*Dermoscopy* **ABCDE rule for dermoscopy (16)**	*Dermoscopy* **Kreusch 1992 for dermoscopy (17)**	*Dermoscopy* **Nilles 1994 for dermoscopy (18)**
Elements	Presence of 3 or more colours seen in the lesion on dermoscopy	**Negative features** (if present, not a melanoma: >3 milialike cysts	Asymmetry of colour, contour, structure *(Symmetrical=0, asymmetric one axis=1, asymmetric in both axes=2 points)*	Diameter >5mm (1 point)	Clues for malignancy: Asymmetrical pigment distribution
		Positive features Irregularly sized or distributed brown dots or globules	Borders 8 segments: abrupt cut-off at the margins of pigment pattern *(Yes=1 point for each affected segment)*	Bordure irregularity (1 point)	More than 3 colours
		Multiple blue/grey dots	Colours: red, white, light and dark brown, blue-grey, black. *(Each colour=1 point)*	Loss of surface microstructure (1 point)	Asymmetrical depigmentation
		Irregularly shaped depigmentation	Different structural components pigment network, branched streaks, structure less or homogeneous areas >10%, dots, globules. *(Each component=1 point)*	Scaling/erosion/ulcer (1 point)	Black pigment
		Blue-white veil	Enlargement *(Add 1.2 points if present Subtract 0.8 points if absent)*	Capillaries (1 point)	Sharp pigment border
		>1 shade of pink		Multicomponent	Atypical radial

				architecture (3 points)	streaming
		Predominant central vessels		Greyish colour (3 points)	
		Dotted and linear irregular vessels		Melanophages (6 points)	
				Pseudopods (10 points)	
				Regression (10 points)	
Cut point/ specialist referral	Presence of single element.	Presence of 1 or more positive features	(A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5) + (E) = total dermoscopy score (TDS) < 4.75 = benign 4.8-5.45 = suspicious for melanoma > 5.45 = highly suspicious for melanoma	Not specified	Not specified

CPR name	*Dermoscopy* **DynaMel algorithm (19)**	*SIAoscopy* **Emery 2010 SIAoscopy (20)**	*Reflectance confocal microscopy* **Guitera 2012 RCM (21)**
Elements	**Dynamic major criteria:** Asymmetric-multifocal enlargement (2 points)	*If no specified features of seborrhoeic keratosis or haemangioma presen,a score is allocated for specific features seen on SIAoscopy:* Dermal melanin within the lesion (5 points)	*Reflectance confocal microscopy features:* Cerebriform nests
	Architectural change (2 points)	Presence of any blood vessels (2 points)	Atypical cobblestone with small nucleated cells
	Dynamic minor criteria: Focal increase in pigmentation (1	Blood displacement with erythematous blush (1 point)	Marked cytologic atypia

	point)		
	Focal decrease in pigmentation (1 point)	Maximum diameter greater than 6mm (1 point)	Pageoid cells
	Overall decrease in pigmentation not accompanied by lighter pigmentation of adjacent skin (1 point)	For every completed 15 years of age (1 point)	Epidermal disarray
	7 point checklist for dermoscopy score		Large interpapillary space
			Dense nest
	Add dynamic score to 7 point checklist for dermoscopy score		Constant
Cut point/ specialist referral	≥ 3 points	≥ 6 points	Algorithm or scoring system not specified

Appendix 2: Flow of studies in the review



Appendix 3: CHARMS checklist for included validation studies

	Annessi 2007(22)	Argenziano 1998(12)	Argenziano 2003(23)	Argenziano 2011(13)	Benelli 1999(10)	Benelli 2000(24)
Objective	Validation of ABCD rule of dermoscopy, and the 7-point checklist for dermoscopy	Derivation and validation of 7-point checklist for dermoscopy. Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/stolz, Menzies 1996 dermoscopy for melanoma, and 7-point checklist for dermoscopy	Validation of 7-point checklist and revised 7-point checklist for dermoscopy	Validation of 7 FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.	Validation of 7FFM (7 features for melanoma) dermoscopy and ABCDE clinical rule.
Source of data	Cross sectional	Cross-sectional			Cross-sectional, prospective	Cross-sectional retrospective study
Participants	• Consecutive recruitment of atypical melanocytic lesions • December 2004 and June 2006 • 1 department of dermatology	• Atypical melanocytic skin lesions, excised and reviewed for histological diagnosis • Inclusion period: NR • Number of departments of dermatology NR	• Dermoscopy images of lesions preselected from 5 departments of dermatology worldwide • then reviewed by 6 histopathologists, who selected histopathologically unequivocal lesions to include in study.	• Digital database of lesions • Screened between 2006 and 2008 • 1 department of dermatology	All the pigmented lesions observed and excised at the dermatologic surgery department September 1997 – September 1998. 1 dermatology surgery department	Retrospective recruitment; all melanomas <6mm and melanocytic naevi <6mm excised during the study period January 1993 – December 1998. 1 Dermatology surgery department, dermatological sciences institute, university.
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate predictors	NA	11 candidate predictors	NA	NA	NA	NA
Sample Size	198 lesions • 96 melanomas • 102 benign	342 • Derivation 196 (57 melanoma, 139 non-melanoma) • Validation 146 (60 melanoma, 86 non-melanoma) • EPV = 5.18 (57/11)	108 • Number of menaloma not specified	300 Lesions • 100 melanoma randomly selected from 349 excised melanomas • 100 melanocytic naevi from 1512 excised naevi • 100 from a larger database of monitored naevi	401 lesions • 60 melanomas	600 lesions • 76 melanomas
Missing data	Not reported	Not reported	Not reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	• predictor selection: identified in the literature • multivariate regression • shrinkage: NR	NA	NA	NA	NA
Model Performance	• Discrimination and calibration: NR. • Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Discrimination: AUC ROC curve • Calibration: NR	• Discrimination and Calibration: NR • Interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of	• Discrimination and calibration: NR. • Sensitivity, specificity reported	Calibration and discrimination: NR Sensitivity , specificity, positive predictive value, negative predictive value, accuracy, efficiency reported.	Calibration and Discrimination: NR Sensitivity and specificity reported.

			consensus diagnosis reported			
Model evaluation	NA	• internal validation: random split-sample	NA	NA	NA	NA
Results	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, false positive, false negative reported	• Final model with odds ratios and score • Comparison of sensitivity, specificity	• Comparison of interobserver agreement, intraobserver agreement, sensitivity, specificity, positive likelihood ratio, sensitivity of consensus diagnosis, and specificity of consensus diagnosis	Comparison of sensitivity, specificity	Comparison of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, efficiency.	Comparison of sensitivity and specificity.

	Binder 1999(25)	Blum 2003(14)	Blum 2004(26)	Blum 2004(27)	Buhl 2010(19)
Objective	Validation of ABCD rule for dermoscopy/Stolz	Validation of ABCD Rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 7-Point Checklist for dermoscopy, and 7FFM (7 features for melanoma) dermoscopy Derivation and validation of Simplified ABC-point list for dermoscopy.	Validation of the 3 colour dermoscopy test	Derivation and validation of Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions), and Digital dermoscopy analysis (partially imaged lesions) ABCD rule. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, 7FFM (7 features for melanoma) dermoscopy, and ABCD rule of dermoscopy/Stolz.	Derivation and narrow validation of DynaMel Algorithm. Validation of 7-point checklist for dermoscopy.
Source of Data	Cross-sectional, retrospective	Cross-sectional, prospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional, prospective
Participants	• Randomly selected images from a pigmented skin lesion database • 17 dermatologists • Ambulatory care	• Consecutive patients with suspicious melanocytic lesion • 1 department of dermatology	• Benign and malignant melanocytic and non-melanocytic lesions • 1 department of dermatology	• Consecutive patients with melanocytic lesions • 1 department of dermatology Pigmented lesion clinic.	• Non-Consecutive patients with excised lesions with 7-point checklist score ≥ 3. • Number of departments of

				• November 1998 – March 2000	dermatology NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	6 candidate predictors	NA	Digital dermoscopy analysis (all lesions), Digital dermoscopy analysis (completely imaged lesions): 6 candidate predictors Digital dermoscopy analysis (partially imaged lesions) ABCD rule: 3 candidate predictors	12 candidate predictors
Sample Size	250 • 41 malignant melanomas • 209 benign melanomas	269 • 84 malignant melanomas • 185 benign melanomas • EPV = 14 (84/6)	249 lesions • 73 non-melanocytic tumours • 176 melanocytic lesions: 65 melanomas, 111 benign	837 lesions • 84 malignant melanomas • 753 benign (melanocytic + other) • EPV = 1.31 (84/64)	675 lesions • 61 melanomas • EPV = 5.083 (61/12)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported

Model Development	NA	• Based on established dermoscopy algorithms and univariate analysis • All predictors included in multivariate modelling • shrinkage: NR	NA	• All 3 derivations developed independently of the established dermoscopic rules. • Logistic regression analysis • shrinkage: NR	• 7-point checklist chosen as it is a valid and reliable method to distinguish benign and malignant melanocytic lesions. • 5 Dynamic predictors included for modelling based on the analysis of data from a prospective observational trial using long-term follow-up by sequential digital dermatoscopy • Used Akaike criterion, logistical regression framework, Brier score, and ROC AUC to select predictors during multivariable modelling. • Shrinkage: NR
Model Performance	• Discrimination and calibration: NR • ROC AUC sensitivity,	• Discrimination and calibration: NR. • Sensitivity, specificity,	• Calibration and discrimination: NR • Sensitivity and	• Discrimination: ROC AUC • Calibration: NR	• Calibration and Discrimination: NR • Sensitivity and

	and specificity reported. • Reported performance at cut points 4.75 and 5.45	and diagnostic accuracy reported. • Cut point 4.	specificity reported	• Sensitivity, specificity, and diagnostic accuracy reported	specificity reported. Cut point >/=3
Model Evaluation	NA	Internal validation: Development dataset was randomly divided into two collectives for cross validation	NA	• internal validation: combined collection of lesions randomly divided into training and test sets	internal validation: developed and tested on same dataset
Results	• Comparison of ROC AUC sensitivity and specificity for different cut points.	• Final model with score and cut point of 4 • Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity and specificity.	• Final digital image analysis model • Comparison of sensitivity, specificity, and diagnostic accuracy	• Final model with score. • Comparison of sensitivity and specificity.

	Carli 2002(28)	Dal Pozzo 1999(29)	Dolianitis 2005(30)	Emery 2003(29)	Feldmann 1998(31)
Objective	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy	Derivation and narrow validation of 7FFM (7 features for melanoma) dermoscopy	Validation of 7-point checklist for dermoscopy, ABCD Rule of dermoscopy/Stolz, and Menzies 1996 dermoscopy for melanoma	Derivation and validation of Emery 2003 IAscopy in primary care for melanoma	Validation of ABCD rule of dermoscopy/Stolz.
Source of Data	Cross-sectional	Cross-sectional		Cross-sectional	Cross-sectional prospective study.
Participants	• Clinically equivocal melanocytic lesions, <14 mm in diameter. • 1 department of dermatology Pigmented lesion clinic.	Pigmented skin lesions observed by the authors between 1992-1997 1 Department of Dermatology	• Random selection from a collection of images • 61 medical practitioners from either primary care or dermatology	• Patients presenting with a pigmented lesion and additional lesion identified as potentially suspicious during clinical examination • 6 General Practices in UK and 3 GP Primary Care Skin Cancer Clinics in Australia	Lesions that were being excised on clinical grounds or because of patient request 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	7 Candidate Predictors	NA	9 candidate predictors	NA

Sample Size	200 lesions • 44 melanomas	Training set: 218 lesions • 45 melanomas Test set: 713 lesions • 168 melanomas EPV training set: 2.81 (45/16) test set: 24 (168/7)	40 • 20 melanomas • 20 non-melanomas	1211 • derivation 422 (3 melanomas, 419 non-melanomas) • UK validation 208 (2 melanomas, 206 non-melanomas) • Australian validation 581 (7 melanomas, 574 non-melanomas) • EPV = 3 (3/9)	500 lesions • 30 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Of 16 features evaluated in the test set, 7 were selected because of specificity >80% and sensitivity > 5% and p < 0.05, in the derivation study. Shrinkage: NR	NA	• 5 predictors taken from Monrieff scoring system; additional features considered • Sensitivity, specificity, positive predictive value, negative predictive value, ROC curves and associated AUC used for criteria for selection of predictors during multivariate modelling • shrinkage: NR	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity	Calibration and Discrimination: NR Sensitivity, specificity,	• Discrimination and calibration: NR. • Sensitivity, Specificity,	• Discrimination: AUC ROC curve • Calibration: NR	Calibration and Discrimination: NR Mean score of naevi,

	and diagnostic accuracy reported. Cut off point of 2 (lesions 3 or greater = melanoma) for 7-point checklist and 5.45 for ABCD rule.	PPV, NPV, and efficiency reported.	Diagnostic accuracy, and Likelihood ratios reported.	• Sensitivity, specificity, positive predictive value, and negative predictive value reported. Cut point 3 or more: suspicious	dysplastic naevi and melanomas reported
Model Evaluation	NA	Narrow internal validation: separate training and test sets.	NA	External validation using 1st a test set which was part of the dataset of 630 lesions from which 422 lesions were used for model derivation and 2nd using a separate dataset	NA
Results	• Comparison of sensitivity, specificity and diagnostic accuracy	Comparison of sensitivity, specificity, PPV, NPV, and efficiency.	• Comparison of Sensitivity, Specificity, Diagnostic accuracy, and Likelihood ratios	• Final model with score • Comparison of sensitivity, specificity, positive predictive value, and negative predictive value	Comparison of mean score of naevi, dysplastic naevi and melanomas.

	Gereli 2010(32)	**Guitera 2012(21)**	**Haenssle 2010(33)**	**Healsmith 1993(36)**	**Henning 2008(35)**
Objective	Validation of 7-point checklist for dermoscopy and 3-point checklist for dermoscopy.	Derivation and narrow validation of Guitera 2012 confocal microscopy for melanoma.	Validation of 7 point checklist for dermoscopy	Validation of Revised 7 point checklist (clinical) and ABCDE clinical rule	Validation of CASH dermoscopy algorithm, ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy

					for melanoma, and 7 point checklist for dermoscopy .
Source of data	Cross sectional	Cross-sectional.	Cohort Study	Cross-sectional	Cross-sectional retrospective study
Participants	• NR • 96 dermoscopic images of skin lesions • Number of departments of dermatology NR	Consecutive lesions excised to exclude malignancy at a skin cancer clinic (included other skin cancer types) 2 specialised skin cancer clinics	Recruitment method NR Dermatology outpatient clinic. Number of centres NR	• Consecutive diagnoses of melanoma, • Randomly selected, clinically diagnosed benign pigmented lesions	Clinical and dermoscopic images of melanocytic neoplasms (50 melanomas, 50 dysplastic naevi, 50 common naevi) from a database of 1535 images on an American Academy of Dermatology database 1 Department of Dermatology, university
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	35 candidate predictors (reflex confocal microscopy	NA	NA	NA

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		features)			
Sample Size	96 lesions • 48 melanoma • 48 non-melanoma	710 lesions • 216 melanomas • EPV = 6.17 (216/35	688 participants with increased risk of melanoma; 1219 lesions • 127 melanomas	165 lesions • 65 Melanoma • 100 clinically benign diagnosed as benign pigmented lesion	150 lesions • 50 melanomas
Missing data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model development	NA	35 RCM (reflex confocal microscopy) features that showed significant association with melanoma diagnosis on univariate modelling. Multivariate discriminant analysis based on the training set using the 35 RCM features identified in univariate modelling, identified 7 independently significant features for the diagnosis of malignant melanomas. Shrinkage: A coefficient is	NA	NA	NA

		estimated for each included variable in relation to likeliness to predict a BCC, then an MM.			
Model Performance	• Calibration and discrimination: NR • Sensitivity, specificity, positive predictive value and negative predictive value reported	Discrimination: Multivariate discriminant analysis to determine variables for model. ROC analysis to investigate sensitivity and specificity of discriminant analysis equations for BCC and MM algorithms Calibration: NR Sensitivity and specificity reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	• Calibration and discrimination: NR • Sensitivity reported	Calibration and Discrimination: NR Sensitivity, specificity, relative sensitivity and specificity compared with CASH rule reported.
Model evaluation	NA	Validation (NR internal or external)	NA	NA	NA

Results	Comparison of sensitivity, specificity, positive predictive value and negative predictive value	Comparison of sensitivity, specificity, and AUC.	Comparison of sensitivity and specificity.	• Comparison of sensitivity	Comparison of sensitivity, specificity, relative sensitivity and specificity.

	Higgins 1992(36)	Kittler 1999(16)	Keefe 1989(37)	Kreusch 1992(17)	Lorentzen 1999(38)
Objective	Validation of 7 point checklist (clinical) and revised 7 point checklist (clinical).	Validation of ABCD rule of dermoscopy/Stolz. Derivation of ABCDE rule (dermoscopy).	Validation of 7-point checklist (clinical)	Validation of Kreusch 1992 dermatoscopy for melanoma	Validation of ABCD rule of dermoscopy/Stolz
Source of Data	Cross-sectional prospective study.	Cross-sectional prospective study	Cross-sectional	Cross-sectional	Cross-sectional
Participants	Consecutive clinically benign lesions excised in a pigmented lesion clinic 1 Department of Dermatology, pigmented lesion clinic	Consecutively excised pigmented lesions in a dermatology clinic 1 Department of Dermatology	Consecutive patients referred for assessment or treatment of pigmented lesions 4 departments of dermatology	Over 1.5 years, pigmented lesions suspected to be malignant melanoma were examined clinically and by ELM. Lesions to be excised were photographed. 1 Dermatology Clinic	Patients referred to dermatology clinic for evaluation of a pigmented skin lesion 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	5 Candidate Predictors	NA	NA	NA
Sample Size	100 lesions • 0 melanomas	356 lesions • 73 melanomas • EPV = 14.6 (73/5)	216 lesions • 8 melanoma (of 68 lesions excised)	317 lesions • 96 malignant melanoma • 221 benign melanocytic	232 patients • number of melanomas NR

				lesions and non-melanocytic lesions	
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	Predictors 1-4: as per ABCD dermoscopy rule. 1 new variable (E: status of morphologic change) added to create new model Shrinkage: NR	NA	NA	NA
Model Performance	Calibration and Discrimination: NR Specificity reported.	Validation model: Calibration and discrimination: NR Derivation model: Discrimination: area under ROC; Calibration: NR Sensitivity and specificity reported for both models.	Calibration and Discrimination: NR Predictive value for melanoma and Predictive value for non-melanoma reported.	Calibration and discrimination: NR Sensitivity and specificity reported.	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45 reported.
Model Evaluation	NA	Derivation only.	NA	NA	NA
Results	Specificity.	Comparison of sensitivity and specificity, AUC.	Comparison of predictive value for melanoma and predictive value for non-melanoma reported.	Comparison of sensitivity and specificity.	Comparison of sensitivity, specificity, and area under ROC for cut-off points of 4.75 and 5.45.

	Lorentzen 2000(39)	Luttrell 2012(5)	MacKie 2002(15)	McGovern 1992(40)	Menzies 1996(8)
Objective	Validation of ABCD rule of dermoscopy/Stolz	Validation of AC dermoscopy rule	Derivation and validation of the 3 colour dermoscopy test	Validation of 7-point checklist (clinical) and ABCD rule	Derivation and validation of Menzies 1996 dermoscopy for melanoma
Source of Data	Cross-sectional				Cross-sectional
Participants	Clinical photographs and dermatophotographs obtained from patients consecutively referred to the skin cancer outpatient clinic, and who had a subsequent excision biopsy 1 Department of Dermatology Skin cancer Outpatient clinic	• lesions drawn at random from 312 dermoscopic images of melanocytic lesions • 1 department of dermatology	• Sequential recruitment of patients referred to a specialist rapid-referral pigmented lesion clinic by their GP, for whom a dermatologist had considered that the lesion required excision biopsy • 1 specialist rapid-referral pigmented lesion clinic	• All pigmented lesions biopsied in a dermatology clinic suspicious for dysplasia or malignancy • 1st November 1989 to 31st October 1990; along with 2 melanoma added from earlier in 1989. • 1 dermatology clinic	Random sample of patients whose lesions were excised, selected from a larger database Number of departments of dermatology: NR
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	10 candidate predictors	NA	11 candidate predictors
Sample Size	258 patients • 64 melanoma	200 dermoscopic images of lesions • 25 melanoma	126 • 69 melanoma • 57 non-melanoma.	205 • 6 melanoma, 6 lentigo maligna	385 lesions • 107 melanomas • EPV = 1.486

		• 178 non-melanoma	• Derivation dataset 74 (37 melanoma, 37 non-melanoma) • Validation dataset 52 (32 melanoma, 20 non-melanoma) • EPV = 3.7 (37/10)		(107/72)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	• Method of selection of predictors for inclusion for multivariable modelling: NR • Sensitivity, specificity, p values, c-index, likelihood ratio tests, multivariable modelling with a forward stepwise philosophy, ROC curve, AUC • shrinkage: NR	NA	• Morphological features, seen with surface microscopy, not visible with the naked eye, that enhance the clinical diagnosis of nearly all pigmented lesions, including invasive melanoma • Classification and regression tree constructed on the training set producing a 7 node tree with cross validated sensitivity and specificity. Individual features were then selected for low sensitivity and high specificity to create a model suitable for clinician use. Images from the test set were then scored by

					means of the model as developed from the training set. Shrinkage: NR
Model Performance	Calibration and Discrimination: NR Sensitivity, specificity, and area under ROC reported.	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Discrimination: AUC, ROC curve, c-index • Calibration: NR • Sensitivity, specificity, p-value and c-index reported. No cut point chosen after derivation.	• Discrimination and Calibration: NR • Sensitivity, specificity and accuracy reported.	Calibration and Discrimination: NR Sensitivity and Specificity of the training set, the test set, and the total combined sets reported.
Model Evaluation	NA	NA	Internal validation: test set for derivation and separate validation dataset	NA	Internal validation: A test set of 45 invasive melanomas and 119 non-melanomas was used to test the model performance.
Results	Comparison of sensitivity, specificity, and area under ROC.	Comparison of sensitivity and specificity.	• Final model with cut point of 3 colours or more on dermoscopy • Sensitivity, specificity, p-value, and c-index reported.	• Comparison of sensitivity, specificity and accuracy at different cut points.	• Final model: For diagnosis of invasive melanoma it must have neither of the two morphological negative features and 1 or more of the nine positive morphological features. • Comparison of sensitivity and specificity of the training set, the test set, and the total combined sets.

	Menzies 2008(9)	Menzies 2013(41)	Nachbar 1994(42)	Nilles 1994(18)	Osborne 1998(43)
Objective	Derivation of Menzies 2008 dermoscopy for melanoma and Menzies 2008 dermoscopy for skin cancer. Validation of Menzies 1996 dermoscopy for melanoma, 7-point checklist for dermoscopy, and 3-point checklist for dermoscopy.	Derivation of Menzies 2013 dermoscopy for nodular melanoma. Validation of ABCD rule of dermoscopy/Stolz, Menzies 1996 dermoscopy for melanoma, 3-point checklist, CASH dermoscopy algorithm, and 7-point checklist for dermoscopy.	Derivation of ABCD rule of dermoscopy/Stolz	Derivation and narrow validation of Nilles 1994 dermoscopy for melanoma.	Validation of Revised 7-Point Checklist (clinical)
Source of Data	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional retrospective study	Cross-sectional, retrospective
Participants	Dermoscopic images from multiple centres retrospectively May not have been from consecutive patients Predominantly hospital-based clinics from 5 continents (exact number NR)	Random selection of images of lesions from members of the International Dermoscopy Society Predominantly hospital-based clinics from 5 continents (exact number NR)	Consecutively excised pigmented skin lesions Number of departments of dermatology: NR	Retrospective recruitment; 260 histologically confirmed melanocytic skin tumours 1 Department of Dermatology	All patients with histologically proven cutaneous melanoma in study area between the years 1982 – 1996 1 department of dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis

Candidate Predictors	Menzies 2008 dermoscopy for melanoma: 8 candidate predictors Menzies 2008 dermoscopy for skin cancer: 11 candidate predictors	17 candidate predictors	5 candidate predictors	8 Candidate Predictors	NA
Sample Size	497 lesions • 105 melanomas • EPV = 1.06 (105/99)	467 lesions • 217 melanomas (83 nodular melanomas, 134 invasive non-nodular melanomas) • EPV = 2.19 (217/99)	194 lesions • 69 melanomas • EPV = 13.8 (69/5)	2[illegible] lesions: • 72 malignant melanomas 188 benign naevi • EPV = 9 (72/8)	778 lesions • 778 melanomas
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	Both models: determined by consensus of members of the International Dermoscopy Society, either based on the existing literature or on clinicians' anecdotal experience Both models: 99 individual morphological features were scored by 12 clinicians in 55 preselected lesions to	Determined by consensus of the members of the International Dermoscopy Society 12 scorers blinded to the lesion diagnosis scored 99 individual features in each lesion. One feature was scored by one of the investigators after the clinician scoring was completed. Shrinkage: NR	• Development NR • Individual scores multiplied by different weight factors obtained by multivariate analysis • Shrinkage: NR	Selected based on previous studies examining predictive value of individual dermoscopic features. Stepwise logistic regression for data for each feature. Shrinkage: NR	NA

	assess interobserver concordance. 1 feature was scored by 1 of the investigators after the clinician scoring was completed. A random sample of 80% of the lesions was used as a training set and the remaining 20% used as a test set. The possible positive features were restricted to those with high specificity. Low sensitivity features were included for model development. Using all features as candidate variables, multiple logistic regression analysis with backward stepwise variable selection was also used to identify the independent predictors of malignant lesions from benign lesions in the training set. Shrinkage: NR				
Model Performance	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features and	Calibration and discrimination: NR Sensitivity, specificity, and odds ratios for individual features	Calibration and Discrimination: NR Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative	Calibration and Discrimination: NR Validation dataset: sensitivity and specificity	Calibration and discrimination: NR Frequency of melanomas and rate of false negative diagnosis of melanoma at

	models reported.	and models reported.	predictive value reported. Cut-off point 5.45.	reported.	different sites.
Model Evaluation	Tested on independent, randomly selected lesions	Uncertain	Internal validation: using development dataset	Narrow external validation: new dataset of 200 lesions in 1991	NA
Results	Comparison of sensitivity and specificity in training vs independent test set.	Comparison of sensitivity for diagnosing nodular melanoma and non-nodular melanoma, and amelanocytic/hypomelanotic malignant lesions.	• Final model composed of 4 morphological features of malignant melanoma with different weight factors • Comparison of sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.	Comparison of frequency of melanomas and rate of false negative diagnosis of melanoma at different sites.

	Piccolo 2014(44)	Pizzichetta 2002(45)	Rao 1997(46)	Skvara 2005(47)	Soyer 2004(6)
Objective	Validation of ABCD rule of dermoscopy/Stolz and DDA (digital dermoscopic analysis) - computer-assisted diagnosis	Validation of ABCD rule of dermoscopy/Stolz	Validation of ABCD rule of dermoscopy/Stolz and ABCD clinical rule	Validation of ABCD Rule of dermoscopy/Stolz and 7-point checklist for dermoscopy	Validation of 3-point checklist of dermoscopy
Source of Data	Cross-sectional	Cross-sectional, retrospective	Cross-sectional prospective	Cross-sectional, retrospective	Cross-sectional, retrospective
Participants	Dermoscopically atypical PSLs retrospectively selected from the archives of the department of dermatology 1 Department of Dermatology	Lesions selected from all lesions observed in consecutive patients seen between April 1996 - September 1998 1 Oncology Referral Centre	Consecutive patients, with lesions suspected of either benign melanocytic naevi or early malignant melanoma 1 private dermatology practice	Consecutive lesions demonstrating change over time during follow up 2 specialised dermatology centres	Consecutively excised lesions in specialized pigmented lesion clinic 1 Department of Dermatology
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate Predictors	NA	NA	NA	NA	NA
Sample Size	165 lesions • 33 malignant melanomas • 132 benign	129 lesions • 5 malignant melanomas • 124 benign	72 lesions • 21 melanomas	325 lesions • 63 melanomas	231 lesions • 68 melanomas • 163 non-melanomas (9 pigmented basal cell carcinomas,

					154 benign PSLs)
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	NA	NA	NA	NA	NA
Model Performance	Calibration and discrimination: NR Kappa statistic (overall intra-observer agreement), sensitivity, specificity, positive predictive value and negative predictive value reported.	Calibration and discrimination: NR Kappa statistic (inter-observer agreement), sensitivity, and specificity reported.	Calibration and Discrimination: NR Cut-point 5.45 Sensitivity, specificity, and diagnostic accuracy reported.	Discrimination and Calibration: NR Cut-point not reported AUC, sensitivity, and specificity reported.	Calibration and discrimination: NR Sensitivity, specificity, and odds ratio reported.
Model Evaluation	NA	NA	NA	NA	NA
Results	Comparison of Kappa statistic, sensitivity, specificity, positive predictive value and negative predictive value.	Comparison of Kappa statistic, sensitivity, and specificity.	Comparison of sensitivity, specificity, and diagnostic accuracy.	Comparison of sensitivity, specificity and area under ROC.	Comparison of sensitivity, specificity, and odds ratio.

	Stolz 1994(11)	Strumia 2003(48)	Thomas 1998(49)	Unlu 2014(50)	Wadhawan 2011(51)
Objective	Derivation and narrow validation of ABCD rule of dermoscopy/Stolz.	Validation of ABCD rule of dermoscopy/Stolz and ABCDE rule (dermoscopy)	Validation of ABCD clinical rule and ABCDE clinical rule	Validation of ABCD rule of dermoscopy/Stolz, 7-point checklist for dermoscopy, 3-point checklist of dermoscopy, and CASH dermoscopy algorithm	Validation of 7-point checklist for dermoscopy
Source of Data	Cross-sectional retrospective	Cross-sectional	Cross-sectional, prospective	Cross-sectional	Feasibility Study implementing the 7-point checklist for dermoscopy features on a smart hand-held device.
Participants	Consecutively excised melanocytic naevi and malignant melanoma that met inclusion criteria 1 Department of Dermatology, University Hospital	Small melanocytic skin lesions, consecutively excised 1 Department of Dermatology	Prospective, consecutively diagnosed melanomas, and a prospective control group of benign lesions 1 Department of Dermatology	Random selection of digital dermoscopic images of melanocytic lesions collected at pigmented lesion clinic between Jan 2008-Jan 2010. 1 department of dermatology	Unknown number of skin cancer images annotated by expert dermatologists Commercial library of skin cancer images
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Use of the 7 point checklist for dermoscopy on smart hand-held devices.
Candidate Predictors	31 Candidate Predictors	NA	NA	NA	NA

Sample Size	157 lesions • 48 melanomas • EPV = 1.55 (48/31)	49 lesions • Number of melanomas and non-melanomas not reported.	1140 lesions • 460 melanomas • 680 non-melanomas	115 lesions • 24 malignant melanomas • 91 benign	347 lesions • 110 malignant melanoma (based on 7 point checklist) No histological diagnosis • 237 benign
Missing Data	No missing data reported	No missing data reported	No missing data reported	No missing data reported	No missing data reported
Model Development	28 features listed in the Consensus Conference of Surface Microscopy, Hamburg, 1989, and three new features (asymmetry in no, one, or two axes; colour; differential structure). "8 features with p values <=0.0001 in the training set were used for multivariate analysis to obtain a formula which led to a calculated score termed the final dermatoscopy score (FDS)" Shrinkage: "Multivariate analysis of the 8 features with lowest p values in the training set was performed, and The following formula for the best differentiation of	NA	NA	NA	NA

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	melanocytic skin lesions was created: Asymmetry score x 1.3 + Border score x 0.1 + Colour score x 0.5 + Differential structure score x 0.5 = Final Dermatoscopy Score"				
Model Performance	Calibration and Discrimination: NR Cut-point: 5.45 Sensitivity and specificity reported.	Calibration and discrimination: NR Cut-point 5.45 Positive and negative predictive values reported.	Calibration and discrimination: NR Sensitivity and specificity of individual criteria, and Chi square statistic reported.	Calibration and discrimination: NR Sensitivity, specificity, diagnostic accuracy, false positive ratio, false negative ratio, positive predictive value, and negative predictive value reported.	Calibration and discrimination: NR Sensitivity, specificity, and classification accuracy reported.
Model Evaluation	Internal validation: dataset split into derivation and test sets	NA	NA	NA	NA
Results	Comparison of sensitivity and specificity.	Comparison of positive and negative predictive values.	Comparison of sensitivity and specificity of individual criteria, and Chi square statistic.	Comparison of sensitivity, specificity, diagnostic accuracy, false positive, ratio, false negative ratio, positive predictive value, and negative predictive value.	Comparison of sensitivity and specificity.

	Walter 2013(52)	Zalaudek 2006(53)
Objective	Validation of 7-point checklist (clinical) and revised 7-point checklist (clinical)	Validation of 3-point checklist for dermoscopy.
Source of data		
Participants	• Consecutive recruitment of patients presenting to general practice with a pigmented lesion which could not be immediately diagnosed as benign, for a RCT of a SIAscopic diagnostic aid for primary care • 15 General Practices	• Random selection from a collection of 2621 excised lesions • 1 department of dermatology specialised pigmented lesion clinic
Outcomes to be predicted	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis	Accuracy in diagnosing melanoma, measured by comparison with histological diagnosis
Candidate predictors	NA	NA
Sample Size	1436 • 36 melanomas	150 • 26 melanoma • 106 benign

Missing data	No missing data reported	No missing data reported
Model development	NA	NA
Model Performance	• Calibration and discrimination: NR • Sensitivity and specificity reported.	• Calibration and discrimination: NR • Reproducibility, sensitivity, and specificity reported
Model evaluation	NA	NA
Results	Comparison of sensitivity and specificity at different cut points.	Comparison of reproducibility, sensitivity, and specificity.

NR= not reported; NA= not applicable

Appendix 4: Methodological quality assessment of the impact analysis studies

a: Studies with a RCT study design

Authors	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Walter (2012)(54)	Low	Low	Low	High	Low	Low	Low	Low
Argenziano 2006	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear

b: Study with a controlled before-after study design

Authors	Selection bias			Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Risk of bias
	Allocation generation	Allocation concealment	Baseline measures	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Westerhoff (2000)(55)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High	High

References (Appendices)

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA: a cancer journal for clinicians. 1985;35(3):130-51.
2. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, et al. Early diagnosis of cutaneous melanoma: Revisiting the ABCD criteria. Journal of the American Medical Association. 2004;292(22):2771-6.
3. MacKie RM. An illustrated guide to the recognition of early malignant melanoma. University of Glasgow. 1986.
4. MacKie RM. Malignant melanoma: a guide to early diagnosis University of Glasgow. 1989:28-43.
5. Luttrell MJ, McClenahan P, Hofmann-Wellenhof R, Fink-Puches R, Soyer HP. Laypersons' sensitivity for melanoma identification is higher with dermoscopy images than clinical photographs. British Journal of Dermatology. 2012;167(5):1037-41.
6. Soyer HP, Argenziano G, Zalaudek I, Corona R, Sera F, Talamini R, et al. Three-point checklist of dermoscopy: A new screening method for early detection of melanoma. Dermatology. 2004;208(1):27-31.
7. Henning JS, Dusza SW, Wang SQ, Marghoob AA, Rabinovitz HS, Polsky D, et al. The CASH (color, architecture, symmetry, and homogeneity) algorithm for dermoscopy. Journal of the American Academy of Dermatology. 2007;56(1):45-52.
8. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Archives of Dermatology. 1996;132(10):1178-82.
9. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Archives of Dermatology. 2008;144(9):1120-7.
10. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999;9(6):470-6.
11. Stolz W, Riemann A, Cognetta AB, Pillet L, Abmayer W, Holzel D, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. European Journal of Dermatology. 1994;4(7):521-7.
12. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Archives of Dermatology. 1998;134(12):1563-70.
13. Argenziano G, Catricalà C, Ardigo M, Buccini P, De Simone P, Eibenschutz L, et al. Seven-point checklist of dermoscopy revisited. British Journal of Dermatology. 2011;164(4):785-90.
14. Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. Journal of the American Academy of Dermatology. 2003;48(5):672-8.
15. MacKie RM, Fleming C, McMahon AD, Jarrett P. The use of the dermatoscope to identify early melanoma using the three-colour test. British Journal of Dermatology. 2002;146(3):481-4.

16. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: A useful extension of the ABCD rule for dermatoscopy. Journal of the American Academy of Dermatology. 1999;40(4):558-62.
17. Kreusch J, Rassner G, Trahn C, Pietsch-Breitfeld B, Henke D, Selbmann HK. Epiluminescent microscopy: a score of morphological features to identify malignant melanoma. Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society. 1992;Suppl 2:295-8.
18. Nilles M, Boedeker RH, Schill WB. Surface microscopy of naevi and melanomas - Clues to melanoma. British Journal of Dermatology. 1994;130(3):349-55.
19. Buhl T, Hansen-Hagge C, Korpas B, Kaune KM, Haas E, Rosenberger A, et al. Integrating static and dynamic features of melanoma: The DynaMel algorithm. Journal of the American Academy of Dermatology. 2012;66(1):27-36.
20. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. BMC Dermatology. 2010;10:9-.
21. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a 2-step method: Analysis of 710 consecutive clinically equivocal cases. Australasian Journal of Dermatology. 2012;53:7-8.
22. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. Journal of the American Academy of Dermatology. 2007;56(5):759-67.
23. Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the internet. Journal of the American Academy of Dermatology. 2003;48(5):679-93.
24. Benellii C, Roscetti E, Dal Pozzo V. The dermoscopic (7FFM) versus the clinical (ABCDE) diagnosis of small diameter melanoma. Eur J Dermatol. 2000;10(4):282-7.
25. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. Journal of the American Academy of Dermatology. 1999;40(2 I):171-6.
26. Blum A, Clemens J, Argenziano G. Three-colour test in dermoscopy: A re-evaluation [8]. British Journal of Dermatology. 2004;150(5):1040.
27. Blum A, Luedtke H, Ellwanger U, Schwabe R, Rassner G, Garbe C. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. British Journal of Dermatology. 2004;151(5):1029-38.
28. Carli P, Quercioli E, Sestini S, Stante M, Ricci L, Brunasso G, et al. Pattern analysis, not simplified algorithms, is the most reliable method for teaching dermoscopy for melanoma diagnosis to residents in dermatology. British Journal of Dermatology. 2003;148(5):981-4.
29. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. European Journal of Dermatology. 1999;9(4):303-8.
30. Dolianitis C, Kelly J, Wolfe R, Simpson P. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. Archives of Dermatology. 2005;141(8):1008-14.

31. Feldmann R, Fellenz C, Gschnait F. The ABCD rule in dermatoscopy: Analysis of 500 melanocytic lesions. Hautarzt. 1998;49(6):473-6.
32. Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: Seven-point and three-point checklists. International Journal of Dermatology. 2010;49(1):33-8.
33. Haenssle HA, Korpas B, Hansen-Hagge C, Buhl T, Kaune KM, Rosenberger A, et al. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. Journal of the American Academy of Dermatology. 2010;62(5):785-93.
34. Healsmith MF, Bourke JF, Osborne JE, Graham-Brown RAC. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. British Journal of Dermatology. 1994;130(1):48-50.
35. Henning JS, Stein JA, Yeung J, Dusza SW, Marghoob AA, Rabinovitz HS, et al. CASH algorithm for dermoscopy revisited. Arch Dermatol. 2008;144(4):554-5.
36. Higgins EM, Hall P, Todd P, Murthi R, Du Vivier AWP. The application of the seven-point check-list in the assessment of benign pigmented lesions. Clinical and Experimental Dermatology. 1992;17(5):313-5.
37. Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. Clinical and Experimental Dermatology. 1990;15(3):167-71.
38. Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. Acta Dermato-Venereologica. 1999;79(6):469-72.
39. Lorentzen H, Weismann K, Kenet RO, Secher L, Larsen FG. Comparison of dermatoscopic ABCD rule and risk stratification in the diagnosis of malignant melanoma. Acta Derm Venereol. 2000;80(2):122-6.
40. McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions: A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. Journal of Dermatologic Surgery and Oncology. 1992;18(1):22-6.
41. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I, et al. Dermoscopic evaluation of nodular melanoma. JAMA Dermatology. 2013;149(6):699-709.
42. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. Journal of the American Academy of Dermatology. 1994;30(4):551-9.
43. Osborne JE, Bourke JF, Graham-Brown RAC, Hutchinson PE. False negative clinical diagnoses of malignant melanoma. British Journal of Dermatology. 1999;140(5):902-8.
44. Piccolo D, Crisman G, Schoinas S, Altamura D, Peris K. Computer-automated abcd versus dermatologists with different degrees of experience in dermoscopy. European Journal of Dermatology. 2014;24(4):477-81.
45. Pizzichetta MA, Talamini R, Piccolo D, Trevisan G, Veronesi A, Carbone A, et al. Interobserver agreement of the dermoscopic diagnosis of 129 small melanocytic skin lesions. Tumori. 2002;88(3):234-8.
46. Rao BK, Marghoob AA, Stolz W, Kopf AW, Slade J, Wasti Q, et al. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in vivo techniques? Part I. Clinical and dermoscopic characteristics. Skin Research and Technology. 1997;3(1):8-14.
47. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. Archives of Dermatology. 2005;141(2):155-60.

48. Strumia R, Montanari A. Low positive predictive value of ABCD-E rule for dermatoscopy of small melanocytic naevi [1]. Melanoma Research. 2003;13(6):631-2.
49. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. Dermatology. 1998;197(1):11-7.
50. Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. Journal of Dermatology. 2014;41(7):598-603.
51. Wadhawan T, Situ N, Rui H, Lancaster K, Yuan X, Zouridakis G. Implementation of the 7-point checklist for melanoma detection on smart handheld devices. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2011;2011:3180-3.
52. Walter FM, Prevost AT, Vasconcelos J, Hall PN, Burrows NP, Morris HC, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. British Journal of General Practice. 2013;63(610):345-53.
53. Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Three-point checklist of dermoscopy: An open internet study. British Journal of Dermatology. 2006;154(3):431-7.
54. Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: Randomised controlled trial. BMJ (Online). 2012;345(7866).
55. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. British Journal of Dermatology. 2000;143(5):1016-20.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6/7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6/7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6/7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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