Reflectance confocal microscopy for the diagnosis of cutaneous melanoma in adults

Dinnes, Jacqueline; Deeks, Jonathan; Saleh, Daniel; Chuchu, Naomi; Bayliss, Susan; Patel, Lopa ; Davenport, Clare; Takwoingi, Yemisi; Godfrey, Kathie; Matin, Rubeta N.; Patalay, Rakesh ; Williams, Hywel C.; Cochrane Skin Cancer Diagnostic Test Accuracy Group

DOI:
10.1002/14651858.CD013190

Reflectance confocal microscopy for the diagnosis of cutaneous melanoma in adults

Review information

Review type: Diagnostic test accuracy

Review number: #164b

Authors

Jacqueline Dinnes[1], Jonathan J Deeks[1], Daniel Saleh[2,3], Naomi Chuchu[1], Susan E Bayliss[1], Lopa Patel[4], Clare Davenport[1], Yemisi Takwoingi[1], Kathie Godfrey[5], Rubeta N Matin[6], Rakesh Patalay[7], Hywel C Williams[8], Cochrane Skin Cancer Diagnostic Test Accuracy Group[1]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]Newcastle Hospitals, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle, UK
[3]School of Clinical Medicine, The University of Queensland, PA-Southside Clinical Unit, Brisbane, Australia
[4]Plastic Surgery, Royal Stoke Hospital, Staffordshire, UK
[5]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK
[6]Department of Dermatology, Churchill Hospital, Oxford, UK
[7]Department of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[8]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK

Citation example: Dinnes J, Deeks JJ, Saleh D, Chuchu N, Bayliss SE, Patel L, Davenport C, Takwoingi Y, Godfrey K, Matin RN, Patalay R, Williams HC, Cochrane Skin Cancer Diagnostic Test Accuracy Group. Reflectance confocal microscopy for the diagnosis of cutaneous melanoma in adults. Cochrane Database of Systematic Reviews , Issue . Art. No.: . DOI: .

Contact person

Jacqueline Dinnes

Institute of Applied Health Research
University of Birmingham
Birmingham
B15 2TT
UK

E-mail: j.dinnes@bham.ac.uk

Dates

Assessed as Up-to-date:	23 May 2017
Date of Search:	28 August 2016
Next Stage Expected:	23 May 2017
Protocol First Published:	Not specified
Review First Published:	Not specified
Last Citation Issue:	Not specified

What's new

Date	Event	Description

History

Date	Event	Description

Abstract

Background

Melanoma has one of the fastest rising incidence rates of any cancer. It accounts for a small percentage of skin cancer cases but is responsible for the majority of skin cancer deaths. Early detection and treatment is key to improving survival; however, anxiety around missing early cases needs to be balanced against appropriate levels of referral and excision of benign lesions. Used in conjunction with clinical or dermoscopic suspicion of malignancy, or both, reflectance confocal microscopy (RCM) may reduce unnecessary excisions without missing melanoma cases.

Objectives

To determine the diagnostic accuracy of reflectance confocal microscopy for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with a) any lesion suspicious for melanoma and b) lesions that are difficult to diagnose, and to compare its accuracy with that of dermoscopy.

Search methods

We undertook a comprehensive search of the following databases from inception up to 28 August 2016: Cochrane Central Register of Controlled Trials; MEDLINE; Embase; CINAHL; CPCI; Zetoc; Science Citation Index; US National Institutes of Health Ongoing Trials Register; NIHR Clinical Research Network Portfolio Database; and the World Health Organization International Clinical Trials Registry Platform. We studied reference lists and published systematic review articles.

Selection criteria

Studies of any design that evaluated RCM alone, or RCM in comparison to dermoscopy, in adults with lesions suspicious for melanoma or atypical intraepidermal melanocytic variants, compared with a reference standard of either histological confirmation or clinical follow-up.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). We contacted authors of included studies where information related to the target condition or diagnostic threshold were missing. We estimated summary sensitivities and specificities per algorithm and threshold using the bivariate hierarchical model. To compare RCM with dermoscopy, we grouped studies by population (defined by difficulty of lesion diagnosis) and combined data using hierarchical summary ROC methods. Analysis of studies allowing direct comparison between tests was undertaken. To facilitate interpretation of results, we computed values of specificity at the point on the SROC curve with 90% sensitivity as this value lies within the estimates for the majority of analyses. We investigated the impact of using a purposely developed RCM algorithm and in-person test interpretation.

Main results

Eighteen publications reporting on a total of 19 study cohorts with 2838 lesions (including 658 with melanoma) were included, providing 67 datasets for RCM and 7 for dermoscopy. Studies were generally at high or unclear risk of bias across almost all domains and of high or unclear concern regarding applicability of the evidence. Selective participant recruitment, lack of blinding of the reference test to the RCM result, and differential verification were particularly problematic. Studies may not be representative of populations eligible for RCM, and test interpretation was often undertaken remotely from the patient and blinded to clinical information.

Meta-analysis found RCM to be more accurate than dermoscopy in studies of participants with any lesion suspicious for melanoma and in those with lesions that are more difficult to diagnose (equivocal lesion populations). Assuming a fixed sensitivity of 90% for both tests, specificities were 82% for RCM and 42% for dermoscopy for any lesion suspicious for melanoma (9 RCM datasets; 1452 lesions and 370 melanomas). For a hypothetical population of 1000 lesions at the median observed melanoma prevalence of 30%, this equates to a reduction in unnecessary excisions with RCM of 280 compared to dermoscopy, with 30 melanomas missed by both tests. For studies in equivocal lesions, specificities of 86% and 49% would be observed for RCM and for dermoscopy (7 RCM datasets; 1177 lesions and 180 melanomas). At the median observed melanoma prevalence of 20%, this reduces unnecessary excisions by 296 with RCM compared with dermoscopy, with 20 melanomas missed by both tests. Across all populations, algorithms and thresholds assessed, the sensitivity and specificity of the Pellacani RCM score at a threshold of ≥3 were estimated at 92% (95% confidence interval (CI) 87 to 95) and 72% (95% CI 62 to 81), respectively.

Authors' conclusions

RCM may have a potential role in clinical practice, particularly for the assessment of lesions that are difficult to diagnose using visual inspection and dermoscopy alone, where the evidence suggests that RCM may be both more sensitive and specific in comparison to dermoscopy. Given the paucity of data to allow comparison with dermoscopy, the results presented require further confirmation in prospective studies comparing RCM with dermoscopy in a real world setting in a representative population.

Plain language summary

What is the diagnostic accuracy of the imaging test reflectance confocal microscopy (RCM) for the detection of melanoma in adults?

What is the aim of the review?

The aim of this Cochrane Review was to find out how accurate reflectance confocal microscopy (RCM) is on its own and used in addition to dermoscopy compared to dermoscopy alone for diagnosing melanoma. Researchers in Cochrane included 18 publications to answer this question.

Why is improving the diagnosis of melanoma important?

Melanoma is one of the most dangerous forms of skin cancer. Not recognising a melanoma when it is present (a false negative test result) delays surgery to remove it, risking cancer spreading to other organs in the body and possibly death. Diagnosing a skin lesion as a melanoma when it is not present (a false positive result) may result in unnecessary surgery, further investigations and patient anxiety.

What was studied in the review?

Microscopic techniques are used by skin cancer specialists to allow a more detailed, magnified examination of suspicious skin lesions than can be achieved using the naked eye alone. Currently, dermoscopy (a handheld device using natural light) can be used as part of the clinical examination of suspicious skin lesions. RCM is a new microscopic technique (a handheld

device or static unit using infrared light) that can visualise deeper layers of the skin compared to dermoscopy. Both techniques are painless procedures, but RCM is more expensive, time consuming, and requires additional training. Dermoscopy can be used by general practitioners whereas RCM is likely to only be used by secondary care specialists in people who have been referred with a lesion suspicious for skin cancer. Researchers sought to find out whether RCM should be used instead of, or in addition to dermoscopy, to diagnose melanoma in any suspicious skin lesion or only in particularly difficult to diagnose skin lesions.

What are the main results of the review?

The review included 18 publications reporting data for 19 groups of participants with lesions suspected of melanoma. The main results are based on 16 of the 19 datasets.

The review included 9 datasets with 1452 lesions in participants with any suspicious skin lesion, 3/9 comparing RCM to dermoscopy. The results suggest that in a cohort of 1000 lesions, of which 300 (30%) actually are melanoma:

- An estimated 396 will have an RCM result indicating melanoma is present, and of these, 126 (32%) will not be melanoma (false positive results).
- In the same group of 1000 lesions, dermoscopy would produce 406 false positive results, meaning RCM would avoid unnecessary surgery in 280 lesions compared to dermoscopy.
- Of the 604 lesions with an RCM result indicating that melanoma is not present (and 324 lesions with a dermoscopy result indicating that melanoma is not present), 30 will actually be melanoma (false negative results). This equates to a false negative rate of 5% for RCM and 9% for dermoscopy.

The review also included 7 datasets with 1177 lesions in participants with particularly difficult to diagnose skin lesions, three comparing RCM to dermoscopy. The results suggest that if RCM was to be used by skin specialists in a group of 1000 lesions, of which 200 (20%) actually are melanoma:

- An estimated 292 will have an RCM result indicating melanoma is present, and of these, 112 (38%) will not be melanoma (false positive results).
- In the same group of 1000 lesions, dermoscopy would produce 408 false positive results, meaning RCM would avoid unnecessary surgery in 296 lesions compared to dermoscopy.
- Of the 708 lesions with an RCM result indicating that melanoma is not present (and 412 lesions with a dermoscopy result indicating that melanoma is not present), 20 will actually have melanoma (false negative results). This equates to a false negative rate of 3% for RCM and 5% for dermoscopy.

How reliable are the results of the studies of this review?

In all included studies, the diagnosis of melanoma was made by lesion biopsy (RCM/dermoscopy positive) (a biopsy involves taking a sample of body cells and examining them under a microscope), and the absence of melanoma was confirmed by biopsy or by follow up over time to make sure the skin lesion remained negative for melanoma (RCM/dermoscopy negative)*. This is likely to have been a reliable method for deciding whether patients really had melanoma. Only a small number of studies compared the accuracy of dermoscopy and RCM. Most were conducted by specialist research teams with high levels of experience with RCM. RCM may therefore appear more accurate than it actually is. Participants in the 9 studies of any suspicious lesion may have had very obvious disease compared to that seen in practice leading to a lower number of false positive results than would actually occur. It is not possible to recommend a definition of a positive RCM test that will reliably produce the results presented here due to differences between studies.

Who do the results of this review apply to?

Eleven studies were undertaken in Europe (61%), with the remainder undertaken in Oceania, North America or more than one continent. Mean age ranged from 39 to 54.7 years. The percentage of individuals with melanoma ranged between 1.9% and 41.5% (a median of 19% for difficult to diagnose skin lesions and 32% for any suspicious lesion). The majority of studies only included people with certain types of skin lesion. In many studies it was not clear what tests participants had received before RCM.

What are the implications of this review?

RCM appears to be an accurate test for identifying melanoma, and it may reduce the number of individuals receiving unnecessary surgery by up to three quarters compared to dermoscopy. There is considerable variation and uncertainty in results and in study conduct, reducing the reliability of findings. Use of RCM may be of most benefit in those with particularly difficult to diagnose lesions rather than those with any lesion suspicious for melanoma. Further research comparing RCM and dermoscopy in well described groups of people with difficult to diagnose skin lesions is needed.

How up-to-date is this review?

The review authors searched for and used studies published up to August 2016.

*In these studies biopsy or clinical follow up were the reference standards.

Background

Target condition being diagnosed

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. Melanoma can occur in any organ that contains melanocytes, including mucosal surfaces, the back of the eye, and lining around the spinal cord and brain, but most commonly arises in the skin. The incidence of melanoma

rose to over 200,000 newly diagnosed cases worldwide in 2012 (Erdmann 2013; Ferlay 2015), with an estimated 55,000 deaths (Ferlay 2015). In the UK, melanoma has one of the fastest rising incidence rates of any cancer, and has had the biggest projected increase in incidence between 2007 and 2030 (Mistry 2011). In the decade leading up to 2013, age standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2,459 deaths in 2014 (Cancer Research UK 2017b). Rates are higher in women than in men; however, the rate of incidence in men is increasing faster than in women (Arnold 2014).

Definitions: Cutaneous melanoma refers to any skin lesion with malignant melanocytes present in the dermis, and includes superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma variants (Figure 1). Melanoma in situ refers to malignant melanocytes that are contained within the epidermis and have not yet invaded the dermis (i.e. intraepidermal), but are at risk of progression to melanoma if left untreated. Lentigo maligna, a subtype of melanoma-in-situ in chronically sun-damaged skin, denotes another form of proliferation of abnormal melanocytes. Lentigo maligna can progress to invasive melanoma if its growth breaches the dermo-epidermal junction during a vertical growth phase (when it becomes known as 'lentigo maligna melanoma'), however its malignant transformation is both lower and slower than for melanoma in situ (Kasprzak 2015). Melanoma in situ and lentigo maligna are both atypical intraepidermal melanocytic variants (also referred to as 'borderline evolving melanoma') (www.seer.cancer.gov/tools/mphrules/2007/melanoma/terms_defs.pdf). Melanoma is one of the most dangerous forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and blood stream. It accounts for only a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths (Boring 1994; Cancer Research UK 2017a).

In this diagnostic test accuracy review we define (a) cutaneous invasive melanoma and atypical intraepidermal melanocytic variants as the primary target condition. We will also examine accuracy for target conditions of (b) cutaneous invasive melanoma alone, and (c) any skin cancer or skin lesion with a high risk of progression to melanoma.

Prognosis: US data from 2007 to 2013 indicate five-year survival of 98.5% for localised melanoma, dropping to 62.9% for those with regional spread (nodal disease) and 19.9% for disseminated disease (SEER 2017). Before the advent of targeted and immuno-therapies, melanoma disseminated to distant sites and visceral organs was associated with median survival of six to nine months, a one-year survival rate of 25%, and three-year survival of 15% (Balch 2009; Korn 2008). Between 1975 and 2010, five-year relative survival for melanoma in the US increased from 80% to 94%, with survival for localised, regional, and distant disease estimated at 99%, 70%, and 18%, respectively in 2010 (Cho 2014). Overall, mortality rates however showed little change, at 2.1 per 100,000 deaths in 1975 and 2.7 per 100,000 in 2010 (Cho 2014). Increasing incidence in localised disease over the same period (from 5.7 to 21 per 100,000) suggests that much of the observed improvement in survival may be due to earlier detection and heightened vigilance (Cho 2014), however targeted therapies for stage IV melanoma (e.g. BRAF inhibitors) have improved survival expectation and immunotherapies are evolving such that long term survival is being documented (see below).

Treatment of melanoma

For primary melanoma, the mainstay of definitive treatment is wide local excision of the lesion, to remove both the tumour and any malignant cells that might have spread into the surrounding skin (Garbe 2016; Marsden 2010; NICE 2015a; SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness (Garbe 2016) and stage of disease at presentation (NICE 2015a).

Following histological confirmation of diagnosis, the lesion is staged according to the American Joint Committee on Cancer (AJCC) Staging System to guide treatment (Balch 2009). Stage 0 refers to melanoma in situ; stages I to II indicate localised melanoma; stage III occurs where there is regional metastasis; and stage IV indicates distant metastasis (Balch 2009). The main prognostic indicators can be divided into histological and clinical factors. Histologically, Breslow thickness is the single most important predictor of survival, as it is a quantitative measure of tumour invasion which correlates with the propensity for metastatic spread (Balch 2001). Microscopic ulceration, mitotic rate, microscopic satellites, regression, lymphovascular invasion, and nodular (rapidly growing) or amelanotic (lacking in melanin pigment) subtypes (Moreau 2013; Shaikh 2012) are also associated with worse prognosis. Independent of tumour thickness, prognosis is worse in: older people, males, those with recurrent lesions, and in those with distant lymph node involvement (micro or macroscopic) and/or metastatic disease at the time of primary presentation. There is debate regarding the prognostic effect from primary lesion site, with some evidence suggesting a worse prognosis for truncal lesions or those on the scalp or neck (Zemelman 2014).

In terms of local or regional interventions beyond wide local excision for primary lesions, completion lymphadenectomy (removal of all regional lymph nodes) is undertaken for those with clinically palpable lymph nodes and may be considered if micrometastatic disease is identified on sentinel lymph node biopsy (NICE 2015a) although no survival benefit has been shown to date for those undergoing sentinel node staging (Kyrgidis 2015; Morton 2014). Elective lymph node dissection (Eggermont 2007), adjuvant radiotherapy or adjuvant systemic treatments are not recommended for routine use in stage I, II or III disease in the UK (NICE 2015a), and in many parts of Europe (Garbe 2016), other than interferon-alpha (licensed by FDA and EMEA) (Garbe 2016), which has been shown to be effective for the treatment of high-risk groups in terms of both disease-free and overall survival in a Cochrane review found evidence for its effectiveness for disease-free survival but not for overall survival (Mocellin 2013).

For stage IV melanoma, two distinct therapeutic approaches suggesting survival benefits in metastatic melanoma are available: targeting mutated signal transduction in the RAS-RAF signalling pathway, e.g. BRAF-inhibitors (Chapman

2012; Villanueva 2010) and MEK inhibitors (Dummer 2014; Larkin 2014), and immunomodulation (Chapman 2011; Hamid 2013; Hodi 2010). Molecular targeted therapies recommended in the UK for unresectable or metastatic BRAF V600 mutation-positive melanoma (around 45% of patients (Garbe 2016)) include BRAF-inhibitors dabrafenib (NICE 2014a), vemurafenib (NICE 2012b) or trametinib (MEK inhibitor) in combination with dabrafenib (NICE 2016b). European guidelines recommend combinations of BRAF- and MEK-inhibitors as standard treatment where indicated (Garbe 2016). Immunotherapy-based approaches including ipilimumab (CTLA-4 inhibitor) and PD-1 inhibitors (nivolumab and pembrolizumab) have been approved in the US and Europe (Hodi 2010) and by NICE in the UK both as single agents (NICE 2012a; NICE 2014b; NICE 2015b; NICE 2015c) and in combination (NICE 2016a; NICE 2016b). These have shown high response rates, and demonstrate the potential for a durable clinical response for the first time in the treatment of melanoma (Chapman 2011; Hamid 2013; Hodi 2010; Hodi 2016; Larkin 2015; Maio 2015; Sznol 2013).

An update of a Cochrane review comparing the efficacy of available systemic therapies for stage IIIc and stage IV melanoma is currently underway (Pasquali 2014), as are a number of further NICE appraisals of new therapeutic agents including binimetinib, talimogene laherparepvec (TVEC) and temozolomide (NICE 2017).

Index test(s)

Reflectance confocal microscopy (RCM), also known as confocal laser scanning microscopy or confocal microscopy, was first developed for skin imaging in the early 1990s (Rajadhyaksha 1995) and is emerging as a potential alternative or adjunct to dermoscopy for the diagnosis of skin cancer. It is a non-invasive technology, which can be used to visualise horizontally sectioned images of the skin at a cellular lateral resolution of ~1micron, in vivo to the depth of the upper dermis. The contrast for the monochrome images produced is achieved by the variation of the optical properties within the skin when illuminated by a near-infrared light (830nm) (see Figure 2). The greatest contrast is achieved from melanin, so that RCM is advocated as being particularly useful for assessing pigmented lesions.

The Caliber I.D. VivaScope® imaging systems are the only commercially available RCM devices (distributed by MAVIG in Europe). The Vivascope 1500 (and the previously available 1000 version) is a console based unit with an integrated dermoscope, whereas the Vivascope 3000 is a handheld device designed for superior ergonomics, allowing imaging of lesions inaccessible for the 1500 version (Figure 3). Imaging can be undertaken by clinicians or technicians following appropriate training (Edwards 2016). The length of time required for diagnosis has been estimated at 15 minutes for Vivascope 1500 (10 minutes of a technician's time for imaging and 5 minutes of a dermatologists for image interpretation) and 10 minutes for Vivascope 3000 (Edwards 2016). The company has estimated the average cost per use of the 1500 system, including dermoscopy, as £120 based on 2014 NHS reference costs and an indicative price for Vivascope 1500 of £95,224 (Edwards 2016).

Various algorithms have been proposed for the interpretation of RCM images, relying on either numeric thresholds or qualitative indicators of test positivity according to the presence or absence of particular lesion characteristics. The lesion characteristics that are accepted as being associated with melanomas are: absence of the normal epidermis architecture, lack of delineation of the papillae (non-edged papillae), irregular nests of atypical melanocytes, and the presence of large and highly refractile cells with prominent nuclei in higher epidermal layers (Edwards 2016; Pellacani 2007).

Clinical Pathway

The diagnosis of melanoma occurs in primary, secondary, and tertiary care settings by both generalist and specialist healthcare providers. People with concerns about a new or changing lesion will either present to their general practitioner or directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, general surgeon or other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist (Figure 4). Current UK guidelines recommend that all suspicious pigmented lesions presenting in primary care should be assessed by taking a clinical history and visual inspection using the seven-point checklist (MacKie 1990); lesions suspected to be melanoma should be referred for appropriate specialist assessment within two weeks (Chao 2013; Marsden 2010; NICE 2015d).

The specialist clinician will use history-taking, visual inspection of the lesion (in comparison with other lesions on the skin), and usually dermoscopy to inform a clinical decision. If melanoma is suspected, then urgent excision is recommended. Other lesions such as suspected dysplastic naevi or pre-malignant lesions such as lentigo maligna may also be referred for a diagnostic biopsy, further surveillance or reassurance and discharge. This is the point at which RCM is generally thought to have a role in patient management, most likely as an *additional* test to better identify patients with lesions that can be monitored or reassured instead of being sent for urgent excision (Edwards 2016). RCM could also be considered as a primary diagnostic test, i.e. as a potential replacement for dermoscopy.

Prior test(s)

Fundamental to the diagnosis of skin cancer is clinical examination and history-taking, however a range of technologies have emerged to aid diagnosis to ideally reduce the number of excision biopsies. Dermoscopy in particular has become the most widely used tool for clinicians to try and obtain an accurate assessment of melanoma following visual inspection (Argenziano 1998; Argenziano 2012; Haenssle 2010; Kittler 2002).

Visual inspection of the skin is undertaken iteratively, using both implicit pattern recognition (non-analytical reasoning) and more explicit ‘rules’ based on conscious analytical reasoning (Norman 2009), the balance of which will vary according to experience and familiarity with the diagnostic question. Various attempts have been made to formalise the "mental rules" involved in analytical pattern recognition for melanoma, ranging from a setting out of

lesion characteristics that should be considered (Friedman 1985; Sober 1979) to formal scoring systems with explicit numerical thresholds. The seven-point checklist, for example, assesses change in lesion size, shape, colour, inflammation, crusting or bleeding, sensory change, or diameter ≥ 7 mm (MacKie 1985; MacKie 1990). Other available tools include the ABCD(E) approach (Friedman 1985; Thomas 1998) and ugly duckling (Grob 1998).

Dermoscopy is a non-invasive, in vivo technique that uses a hand-held microscope and incident light (with or without oil immersion) to reveal subsurface images of the skin at increased magnification of x 10 to x 100 (Kittler 2011). Although widely used, the accuracy of dermoscopy largely depends on the experience and training of the examiner (Binder 1997; Kittler 2002; Kittler 2011). Pattern analysis (Pehamberger 1987; Steiner 1987) is thought to be the most specific and reliable technique to aid dermoscopy interpretation when used by specialists (Maley 2014); however, dermoscopic histological correlations have been established and diagnostic algorithms have been developed based on colour, aspect, pigmentation pattern, and skin vessels, including the ABCD rule for dermoscopy (Nachbar 1994; Stolz 1994), the Menzies approach (Menzies 1996), the seven-point dermoscopy checklist (Annessi 2007; Argenziano 1998; Argenziano 2001), and the three-point checklist (Gereli 2010).

The accuracy, and comparative accuracy, of visual inspection and dermoscopy and their associated scoring systems is summarised in a further review in this series (Dinnes 2018).

Role of index test(s)

Used in conjunction with clinical and/or dermoscopic suspicion of malignancy in pigmented lesions, RCM is primarily advocated as a tool to reduce the number of unnecessary excisions (Ferrari 2015), especially in lesions that may be difficult to diagnose by clinical examination and dermoscopy alone (Guitera 2009). RCM features have been shown to be strongly correlated with dermoscopic patterns (Pellacani 2014). Moreover, small diameter melanomas (less than 5 mm diameter) may demonstrate specific dermoscopic and confocal features, such as marked cytological atypia and irregular nesting, which help to differentiate them from naevi (Pupelli 2013). One of the postulated advantages of RCM is its ability to differentiate seborrheic keratosis or non-melanocytic lesions from a population of pigmented lesions.

Although the primary aim in diagnosing potentially life-threatening conditions such as melanoma is to minimise false negative diagnoses (to avoid delay to diagnosis and even death), a test that can reduce false positive clinical diagnoses without missing true cases of disease has patient and resource benefits. False-positive clinical diagnoses not only cause unnecessary morbidity from the biopsy, but also increase patient anxiety. Pigmented lesions are common so the resource implication for even a slight increase in the threshold to excise lesions in populations where melanoma rates are increasing, will avoid a considerable healthcare burden to both patient and healthcare provider, as long as such lesions turn out to be harmless.

RCM is also being explored for its ability to differentiate lentigo maligna from actinic or seborrhoeic keratosis (de Carvalho 2015; Menge 2016). RCM could also develop a future role in guiding definitive therapeutic margins (Edwards 2016) and to evaluate response to topical chemotherapy for lentigo maligna, however these uses are not under consideration in this review.

Alternative test(s)

A number of other tests are being reviewed as part of our series of Cochrane DTA reviews on the diagnosis of melanoma, including visual inspection and dermoscopy, teledermatology, mobile phone applications, computer-aided diagnosis (CAD) techniques, optical coherence tomography (OCT) and high frequency ultrasound (New Reference).

OCT is an emerging optical imaging technology based on interferometry using a near infra-red light source. It exploits differences in the refractive index in the skin to create vertically sectioned images in vivo, in real time. Vascular flow information can be extracted from the images, allowing neovascularisation to be visualised, which has potential for earlier diagnosis of melanoma (Kokolakis 2012; Themstrup 2015). High frequency ultrasound has shown good correlation with histology for measurement of melanoma thickness, but may also differentiate pigmented lesions, particularly for colour Doppler (Scotto di Santolo 2015). CAD or artificial intelligence-based techniques process and manipulate lesion images using predefined algorithms to identify the features that discriminate malignant from benign lesions (Esteva 2017; Rajpara 2009). These techniques have been incorporated into commercially available handheld devices for ease of use in a clinic setting, including SIAscopy™ (Moncrieff 2002; Walter 2012), MelaFind® (Hauschild 2014; Monheit 2011; Wells 2012), and the Nevisense™ Electrical Impedance Spectroscopy system (Malvehy 2014). CAD has however most commonly been applied to digital dermoscopy images (Esteva 2017; Rajpara 2009).

Evidence permitting, the accuracy of available tests will be compared in an overview review, exploiting within-study comparisons of tests and allowing the analysis and comparison of commonly used diagnostic strategies where tests may be used singly or in combination.

Other tests identified as potential candidates for review but for which no eligible studies were found include volatile organic compounds (including canine odour detection) (Abaffy 2010; Church 2001; D'Amico 2008; Gallagher 2008; Kwak 2013; Williams 1989), and gene expression analysis (Ferris 2012; Wachsman 2011).

We also considered and excluded a number of tests from review including exfoliative cytology, which involves microscopic examination of a scraping taken from a skin lesion stained with Giemsa (Ruocco 2011); tests used in the context of monitoring people, such as total body photography of those with large numbers of typical or atypical naevi; and finally histopathological confirmation following lesion excision. The latter is the established reference standard for melanoma diagnosis and will be one of the standards against which the index tests are evaluated in these reviews.

Rationale

Our series of reviews of diagnostic tests used to assist clinical diagnosis of melanoma aims to identify the most accurate approaches to diagnosis and provide clinical and policy decision-makers with the highest possible standard of evidence on which to base decisions. With increasing rates of melanoma incidence and the push towards the use of dermoscopy and other high resolution image analysis in primary care, the anxiety around missing early cases needs to be balanced in order to avoid referring too many people with benign lesions for a specialist opinion. It is questionable whether all skin cancers picked up by sophisticated techniques, even in specialist settings, help to reduce morbidity and mortality or whether newer technologies run the risk of increasing false-positive diagnoses. It is also possible that use of some technologies, e.g. widespread use of dermoscopy in primary care with no training, could actually result in harm by missing melanomas if they are used as replacement technologies for traditional history-taking and clinical examination of the entire skin. Many branches of medicine have noted the danger of such 'gizmo idolatry' amongst doctors (Leff 2008).

To date, the use of RCM has been limited by expense (in terms of both equipment and staff time) and the need for specialised training. Recent studies have demonstrated high sensitivity and specificity amongst experienced RCM users, however, in at least one study, the accuracy of the group on average was higher than that of any one individual observer (Farnetani 2015). A standardised system that is reproducible across users is therefore desirable. Ultimately it is thought that although RCM may augment diagnostic sensitivity when used in conjunction with clinical inspection and dermoscopy, its main contribution is an increase in specificity. However the exact contribution of RCM as an adjunct to dermoscopy is not entirely clear (Edwards 2016; Stevenson 2013), and the number of RCM cases required to offset an unnecessary excision biopsy has not been assessed in a UK setting.

Although a set of billing codes for the USA have been agreed since January 2016 (Rajadhyaksha 2017), RCM is not recommended for routine use in the UK (Edwards 2016), Australia (Guitera 2017), or New Zealand (Sobarun 2015). Available systematic reviews are limited by currency (Stevenson 2013) and methods (Xiong 2016 for example failing to consider the nature of the target population, varying definitions of the target condition, and using an out of date meta-analytic approach), or focus on selected studies considered to be more applicable to a UK setting (Edwards 2016). Furthermore, in a rapidly advancing field, there is a need for an up-to-date analysis of the accuracy of RCM in comparison to dermoscopy at different points in the clinical pathway.

This is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers as part of the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. As several reviews for each topic area followed the same methodology, generic protocols were prepared in order to avoid duplication of effort, one for diagnosis of melanoma (Dinnes 2015b) and one for diagnosis of keratinocyte skin cancers (Dinnes 2015a). The Background and Methods sections of this review therefore use some text that was originally published in the protocol concerning the evaluation of tests for the diagnosis of melanoma (Dinnes 2015b) and text that overlaps some of our other reviews (Dinnes 2018). Table 1 provides a glossary of terms used.

Objectives

To determine the diagnostic accuracy of reflectance confocal microscopy for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults, and to compare its accuracy with that of dermoscopy.

Accuracy was estimated separately according to the point in the clinical pathway at which RCM is evaluated:

- where it might be used as an alternative to dermoscopy in participants with any lesion suspicious for melanoma
- where it might be used in addition to dermoscopy in participants with equivocal lesions in whom a clear management decision could not be made following visual inspection and dermoscopy

Secondary objectives

To determine the diagnostic accuracy of reflectance confocal microscopy in comparison to dermoscopy for the detection of

- cutaneous invasive melanoma alone
- any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma.

Accuracy was estimated separately according to the point in the clinical pathway at which RCM is evaluated:

- where it might be used in addition to current practice (which may or may not include dermoscopy) in participants with any lesion suspicious for melanoma
- where it might be used as an addition to dermoscopy in participants with equivocal lesions in whom a clear management decision could not be made following visual inspection and dermoscopy

For identifying cutaneous invasive melanoma and atypical intraepidermal melanocytic variants (the primary target condition):

- To compare the accuracy of RCM to dermoscopy where both tests have been evaluated in the same studies (direct test comparisons)
- To determine the diagnostic accuracy of individual algorithms for RCM
- To determine the effect of observer experience.

Investigation of sources of heterogeneity

We aimed to consider a range of potential sources of heterogeneity for investigation across the series of reviews, as outlined in our generic protocol (Dinnes 2015b).

i. Population characteristics

- general versus higher risk populations
- patient population: primary /secondary / specialist unit
- lesion type: any pigmented; melanocytic
- inclusion of multiple lesions per participant
- ethnicity

ii. Index test characteristics

- in-person versus remote image-based RCM interpretations
- the nature of and definition of criteria for test positivity
- observer experience with the index test

iii. Reference standard characteristics

- reference standard used
- whether histology-reporting meets pathology-reporting guidelines
- use of excisional versus diagnostic biopsy
- whether two independent dermatopathologists reviewed histological diagnosis

iv. Study quality

- consecutive or random sample of participants recruited
- index test interpreted blinded to the reference standard result
- index test interpreted blinded to the result of any other index test
- presence of partial or differential verification bias (whereby only a sample of those subject to the index test are verified by the reference test or by the same reference test with selection dependent on the index test result)
- use of an adequate reference standard
- overall risk of bias

Methods

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that allow comparison of the result of the index test with that of a reference standard, including the following:

- studies where all participants receive a single index test and a reference standard;
- studies where all participants receive more than one index test(s) and reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests and all receive a reference standard (between-person comparative studies (BPC));
- studies that recruit series' of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (see Rutjes 2005);
- both prospective and retrospective studies; and
- studies where previously acquired clinical or dermoscopic images were retrieved and prospectively interpreted for study purposes.

We excluded studies from which we could not extract 2x2 contingency data or if they included less than five melanoma cases.

Participants

We included studies in adults with pigmented skin lesions or lesions suspicious for melanoma.

We excluded studies that recruited only participants with malignant diagnoses and studies that compared test results in participants with malignancy compared with test results based on 'normal' skin as controls, due to the bias inherent in such comparisons (Rutjes 2006).

We excluded studies with more than 50% of participants aged 16 and under.

Index tests

Studies evaluating reflectance confocal microscopy alone, or reflectance confocal microscopy in comparison to dermoscopy were included.

All established algorithms or checklists to assist diagnosis were included. Studies developing new algorithms or methods of diagnosis (i.e. derivation studies) were included if they used a separate independent 'test set' of participants or images to evaluate the new approach. Studies that did not report data for a separate test set of patients or images were included only if the lesion characteristics investigated had previously been suggested as associated with melanoma and the study reported accuracy based on the presence or absence of particular combinations of characteristics. Studies using a statistical model to produce a data driven equation, or algorithm based on multiple diagnostic features, with no separate test set were excluded. Studies using cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983) were excluded.

No exclusions were made according to test observer.

Target conditions

The primary target condition was defined as the detection of:

- any form of invasive cutaneous melanoma, or
- atypical intraepidermal melanocytic variants (i.e. including melanoma in situ, or lentigo maligna, which has a risk of progression to invasive melanoma).

Two additional definitions of the target condition were considered in secondary analyses, the detection of:

- any form of invasive cutaneous melanoma alone, and
- any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma. This latter definition includes other forms of skin cancer, such as basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), as well as melanoma in situ, lentigo maligna, and lesions with severe melanocytic dysplasia.

The diagnosis of the keratinocyte skin cancers, basal cell carcinoma, and squamous cell carcinoma as primary target conditions are the subject of a separate series of reviews (New Reference).

Reference standards

The ideal reference standard was histopathological diagnosis of the excised lesion or biopsy sample in all eligible lesions. A qualified pathologist or dermatopathologist should perform histopathology. Ideally, reporting should be standardised detailing a minimum dataset to include the histopathological features of melanoma to determine the American Joint Committee on Cancer (AJCC) Staging System (e.g. Slater 2014). We did not apply the reporting standard as a necessary inclusion criterion, but extracted any pertinent information.

Partial verification (applying the reference test only to a subset of those undergoing the index test) was of concern given that lesion excision or biopsy are unlikely to be carried out for all benign-appearing lesions within a representative population sample. Therefore, we accepted clinical follow-up of benign-appearing lesions as an eligible reference standard, whilst recognising the risk of differential verification bias (as misclassification rates of histopathology and follow-up will differ) in our quality assessment of studies.

Additional eligible reference standards included cancer registry follow-up and 'expert opinion' with no histology or clinical follow-up. Cancer registry follow-up is considered less desirable than active clinical follow-up, as follow-up is not carried out within the control of the study investigators. Furthermore, if participant-based analyses as opposed to lesion-based analyses are presented, it may be difficult to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test.

All of the above were considered eligible reference standards with the following caveats:

- all study participants with a final diagnosis of the target disorder must have a histological diagnosis, either subsequent to the application of the index test or after a period of clinical follow-up, and
- at least 50% of all participants with benign lesions must have either a histological diagnosis or clinical follow-up to confirm benignity.

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 1 for a summary of reviews included in the programme grant). This allowed for the screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease-related terms with terms related to the test names, using both text words and subject headings was formulated (Appendix 2). The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As the majority of records were related to the searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search, to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for the staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter, was subsequently applied to all bibliographic databases as listed below. The final search result was cross-checked against the list of studies included in five systematic reviews; our search identified all but one of the studies, and this study is not indexed on MEDLINE. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.

We searched the following bibliographic databases to August 2016 for relevant published studies:

- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library;
- Centre for Reviews and Dissemination (CRD) Database of Abstracts of Reviews of Effects (DARE);
- CRD HTA (Health Technology Assessment) database;
- MEDLINE via OVID (from 1946);
- MEDLINE In-Process & Other Non-Indexed Citations via OVID;
- EMBASE via OVID (from 1980); and

- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960 to the present).

We searched the following databases for relevant unpublished studies:

- CPCI (Conference Proceedings Citation Index) via Web of Science™ (from 1990);
- Zetoc (from 1993); and
- SCI Science Citation Index Expanded™ via Web of Science™ (from 1900, using the "Proceedings and Meetings Abstracts" Limit function).

We searched the following trials registers:

- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- NIHR Clinical Research Network Portfolio Database (www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/);
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress). No date limits were applied. Update searches will be time and resource dependent.

Searching other resources

We have included information about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' tables. We have screened relevant systematic reviews identified by the searches for their included primary studies, and included any missed by our searches. We have checked the reference lists of all included papers, and subject experts within the author team have reviewed the final list of included studies. No citation searching has been conducted.

Data collection and analysis

Selection of studies

Titles and abstracts were screened by at least one author (JDi or NC), with any queries discussed and resolved by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. Primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC were included at initial screening. Inclusion criteria (Appendix 3) were applied independently by both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JDi or NC) to all full text articles, disagreements were resolved by consensus or by a third party (JDe, CD, HW, and RM). Authors of eligible studies were contacted when insufficient data were presented to allow for the construction of 2x2 contingency tables.

Data extraction and management

One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently extracted data concerning details of the study design, participants, index test(s) or test combinations and criteria for index test positivity, reference standards, and data required to populate a 2x2 diagnostic contingency table for each index test using a piloted data extraction form. Data were extracted at all available index test thresholds. Disagreements were resolved by consensus or by a third party (JDe, CD, HW, and RM).

Authors of included studies were contacted where information related to the target condition (in particular to allow the differentiation of invasive cancers from ‘in situ’ variants) or diagnostic threshold were missing. Authors of conference abstracts published from 2013 to 2015 were contacted to ask whether full data were available. If no full paper was identified, we marked conference abstracts as 'pending' and will revisit them in a future review update.

Dealing with multiple publications and companion papers

Where multiple reports of a primary study were identified, we maximised yield of information by collating all available data. Where there were inconsistencies in reporting or overlapping study populations, we contacted study authors for clarification in the first instance. If this contact with authors was unsuccessful, we used the most complete and up-to-date data source where possible.

Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the QUADAS-2 checklist (Whiting 2011), tailored to the review topic (see Appendix 4). The modified QUADAS-2 tool was piloted on a small number of included full text articles. One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently assessed quality for the remaining studies; any disagreement was resolved by consensus or by a third party where necessary (JDe, CD, HW, and RM).

Statistical analysis and data synthesis

For the primary outcome of detection of invasive melanoma or atypical intraepidermal melanocytic variants, we conducted separate analyses according to the point in the clinical pathway that RCM was applied. Three groups of studies were formed:

i. RCM used as a replacement for dermoscopy in participants with lesions suspicious for melanoma, i.e. no attempt to exclude those diagnosed as definite melanomas or as obviously benign on dermoscopy was described (denoted as studies in 'any lesion suspicious for melanoma' or 'any potential melanoma').

ii. RCM used as an addition to dermoscopy in participants with equivocal lesions in whom a clear management decision could not be made following visual inspection and dermoscopy (denoted as studies in ‘equivocal’ lesions).

iii. ‘Other’ studies which did not fit into either of these categories.

Our unit of analysis was the lesion rather than the person. This is because (i) in skin cancer initial treatment is directed to the lesion rather than systemically (thus it is important to be able to correctly identify cancerous lesions for each person), and (ii) it is the most common way in which the primary studies reported data. Although there is a theoretical possibility of correlations of test errors when the same people contribute data for multiple lesions, most studies include very few people with multiple lesions and any potential impact on findings is likely to be very small, particularly in comparison with other concerns regarding risk of bias and applicability. For each analysis, only one dataset was included per study to avoid multiple counting of lesions.

For each analysis undertaken, only one dataset was included per study to avoid over-counting of lesions. Where multiple algorithms were assessed in an individual study, datasets were selected on the following preferential basis:

i. ‘no algorithm’ reported; data presented for clinician’s overall diagnosis or management decision

ii. pattern analysis or pattern recognition

iii. Pellacani’s RCM score

iv. Segura algorithm

v. Presence of statistically significant lesion characteristics

Where multiple thresholds per algorithm were reported, we included the standard or most commonly used threshold. If data for multiple observers was reported, data for the most experienced observer was used, and data for a single observer’s diagnosis was used in preference to a consensus or average across observers. If we were unable to choose a dataset based on the above ‘rules’, a random selection of one dataset per study was made.

For each index test, algorithm or checklist under consideration, estimates of sensitivity and specificity were plotted on coupled forest plots and in receiver operating characteristic (ROC) space. For tests where commonly used thresholds were reported we estimated summary operating points (summary sensitivities and specificities) with 95% confidence and prediction regions using the bivariate hierarchical model (Chu 2006; Reitsma 2005). Where inadequate data were available for the model to converge the model was simplified, first by assuming no correlation between estimates of sensitivity and specificity and secondly by setting estimates of near zero variance terms to zero (Takwoingi 2015). Where all studies reported 100% sensitivity (or 100% specificity) the number with disease (or no disease) was summed across studies and used to compute a binomial exact 95% confidence interval. Heterogeneity in estimates of sensitivity and specificity was assessed by inspection of the magnitude and statistical significance of the estimates of variance terms in the bivariate model.

We made comparisons between tests and in investigating heterogeneity by comparing summary ROC curves using the hierarchical summary receiver-operator curves (HSROC) model (Rutter 2001). This allowed incorporation of data at different thresholds and from different algorithms or checklists. We used an HSROC model that assumed a constant SROC shape between tests and subgroups, but allowed for differences in threshold and accuracy by addition of covariates. The significance of the differences between tests or subgroups was assessed by the likelihood ratio test assessing differences in both accuracy and threshold, and by a Wald test on the parameter estimate testing for differences in accuracy alone. Simpler models were fitted when convergence was not achieved due to small numbers of studies, first assuming symmetric SROC curves (setting the shape term to zero), and then setting random effects variance estimates to zero.

Data on the accuracy of dermoscopy, to allow comparisons of tests, was included only if reported in the studies of RCM due to the known substantial unexplained heterogeneity in all studies of the accuracy of dermoscopy (Dinnes 2018). Comparisons were made between dermoscopy results with RCM data from all RCM studies, and then only using RCM data from studies that also reported dermoscopy data for the same patients to enable a robust direct comparison (Takwoingi 2013).

Estimates of accuracy from HSROC models are presented as diagnostic odds ratios (estimated where the SROC curve crosses the sensitivity=specificity line) with 95% confidence intervals. Differences between tests and subgroups from HSROC analyses are presented as relative diagnostic odds ratios with 95% confidence intervals. To facilitate interpretation in terms of rates of false positive and false negative diagnoses, values of specificity at the point on the SROC curve with 90% sensitivity have been computed. This value was chosen as it lies within the estimates for the majority of analyses. Results should only be considered as illustrative examples of possible specificities and differences in specificities that could be expected.

For computation of likely numbers of true positive, false positive, false negative and true negative findings in the 'Summary of findings' tables, these indicative values were applied to lower quartile, median and upper quartiles of the prevalence observed in the study groups.

Bivariate models were fitted using the meqrlogit command in STATA 13 and HSROC models fitted using the NLMIXED procedure in the SAS statistical software package (SAS 2012, version 9.3; SAS Institute, Cary, NC, USA) and the metadas macro (Takwoingi 2010).

Investigations of heterogeneity

We examined heterogeneity between studies by visually inspecting the forest plots of sensitivity and specificity and summary ROC plots. Where a sufficient number of studies were identified, meta-regression was performed by adding the potential source of heterogeneity as a covariate to a hierarchical model.

Sensitivity analyses

No sensitivity analyses were done.

Assessment of reporting bias

Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), no tests to detect publication bias were performed.

Results

Results of the search

A total of 34,347 unique references were identified and screened for inclusion. Of these, 1051 full text papers were reviewed for eligibility for any one of the suite of reviews of tests to assist in the diagnosis of melanoma or keratinocyte skin cancer. Of the 1051 full text papers assessed, 848 were excluded from all reviews in our series (Figure 5 documents a PRISMA flow diagram of search and eligibility results). A total of 85 studies were tagged as potentially eligible for the two RCM reviews; ultimately, 22 publications were included, 18 in this review and 10 in the review of RCM for the detection of keratinocyte skin cancers (6 were included in both). Reasons for exclusion included publications not being primary test accuracy studies (n = 13), lack of test accuracy data (12 studies), because they were derivation studies developing new algorithms or approaches to diagnosis without the use of separate training and test sets of data (n = 8), included ineligible populations, e.g. including only malignant lesions (n = 6), did not assess eligible target conditions or did not adequately define the target condition (n = 10), inadequate sample size (n = 15), assessed the accuracy of individual RCM characteristics (n = 5) or used ineligible reference standards (i.e. less than 50% of benign group with final diagnosis established by histology or follow-up; n = 3). A list of the 67 studies excluded from this review with reasons for exclusion is provided in Characteristics of excluded studies, with a list of all studies excluded from the full series of reviews available as a supplementary file.

The corresponding authors of five studies were contacted and asked to supply further information for this review. Responses were received from two authors who provided additional data in relation to Pupelli 2013 and Alarcon 2014. Professor Pellacani further provided information on lesion overlap between several included studies that were co-authored by him.

This review reports on a total of 19 cohorts of participants with lesions suspected of melanoma, published in 18 study publications, and providing 67 datasets for RCM and 7 for dermoscopy. A total of 2838 lesions were included, 658 with a diagnosis of melanoma. The total number of study participants cannot be estimated due to lack of reporting in study publications. Two publications were split into two cohorts for the purposes of this review, one by Pellacani and colleagues (Pellacani 2014a (cons) and Pellacani 2014b (doc)) and one by Guitera and colleagues (Guitera 2009a (Modena); Guitera 2009b (Sydney)). One of the 18 study publications (Pellacani 2007) was based on a combined analysis of the two cohorts of lesions reported in the Guitera 2009 study and was included only to allow analysis of additional algorithm thresholds and was not included in the main analyses. A description of the various algorithms and thresholds used for diagnosis across the studies is provided in Appendix 5.

Methodological quality of included studies

The overall methodological quality of all included study cohorts is summarised in Figure 6 and Figure 7. The denominator for this section is 20 cohorts because of the inclusion of two reports for the same group of lesions (Pellacani 2007; Guitera 2009). Studies were generally at high or unclear risk of bias across all domains and of high or unclear concern regarding applicability of the evidence.

Just under 50% (n = 8) were at high risk of bias for participant selection due to inappropriate participant exclusions Exclusions were variously made according to imaging failure, image quality or particular lesion types such as lentigo maligna. Those at unclear risk of bias (n = 4) did not clearly describe participant recruitment as random or consecutive. All cohorts were at high (n = 17) or unclear (n = 3) concern regarding included participants and setting, due to restricted study populations (with 16 studies including only participants with melanocytic lesions, or even more narrowly defined populations such as nodular lesions) and inclusion of multiple lesions per patient (with seven including over 5% more lesions than participants and four not reporting the number of patients). Sixteen of the 20 cohorts included lesions selected for excision based on the clinical or dermoscopic diagnosis or selected retrospectively from histopathology databases; this was not considered of high concern regarding applicability for RCM studies as the primary role for RCM is to reduce unnecessary excisions.

Three quarters of cohorts were at low risk of bias in the index test domain; all studies reported blinding of RCM interpretation to the reference standard diagnosis and 16 reported pre-specification of the diagnostic threshold. Over half of studies were at high concerns around the applicability of the index test, due to blinded interpretation of RCM images (fully blinded in six and providing only information on patient age and lesion site in four), lack of detail regarding the diagnostic threshold used (n = 2), or interpretation by a non-expert observer (n = 1). It is of note that 15 of the 20 cohorts were produced by, or in collaboration with, the same expert research team, led by Prof Pellacani which may further reduce the generalisability of results.

Almost all cohorts reported use of an acceptable reference standard (n = 16), but only two clearly reported blinding of the reference standard to the RCM result. None of the cohorts reported blinding of histology to the referral diagnosis (based on clinical examination or dermoscopy), but this was not incorporated into the overall risk of bias for this domain. For the applicability of the reference standard, two reported using expert diagnosis for some lesions and 13 were unclear regarding histopathology interpretation by an experienced histopathologist or by a dermatopathologist.

Six cohorts did not use the same reference standard for all participants (differential verification), 11 were unclear on the interval between the application of the index test and excision for histology, and seven did not include all participants in the analysis primarily due to technical difficulties in imaging.

For the 6 cohorts comparing RCM with dermoscopy, three reported blinding between tests and three reported no blinding, but this did not contribute to the overall assessment of risk of bias. One study did not clearly report the interval between tests. The clinical applicability of the application of the tests was of high concern due to reporting of average results for both tests (n = 1) and of unclear concern due to the image-based nature of test interpretation (n = 5).

Findings

Primary target condition: invasive melanoma and atypical intraepidermal melanocytic variants

In this section we present the results for studies of RCM versus dermoscopy for the primary target condition of invasive melanoma and atypical intraepidermal melanocytic variants, i.e. invasive malignant melanoma and melanoma in situ or lentigo maligna, according to the study population: studies in all those with 'any lesion suspicious for melanoma' versus those in participants with equivocal lesions. A number of different algorithms to assist RCM diagnosis were used across the included studies; these are described in detail in Appendix 5.

Studies using RCM in any lesion suspicious for melanoma

The following section documents studies where RCM was used in all participants with lesions scheduled for excision. These populations include both clinically or dermoscopically obvious melanomas, along with some lesions that are likely to be benign, and a proportion of more difficult to diagnose (equivocal) lesions so that RCM was being evaluated as an addition to current practice (which may or may not have included dermoscopy).

Eight publications provided data for 9 evaluations of RCM alone (Curchin 2011; Guitera 2009a (Modena); Guitera 2009b (Sydney); Guitera 2012; Koller 2011; Langley 2007; Pellacani 2014b (doc); Rao 2013; Segura 2009) 3 of which also included dermoscopy (Guitera 2009b (Sydney); Guitera 2009a (Modena); Langley 2007) (Table 2 and Figure 8). All studies were case series (seven prospective in design and two unclear). Studies were undertaken in Europe (n = 4; 44%), Oceania (n = 2; 22%), North America (n = 2; 22%), or in more than one continent (n = 1; 11%). Four studies (44%) were undertaken in a secondary care setting, 3 (33) in specialist skin cancer units and two (22%) in mixed secondary care and specialist units. Six cohorts reported inclusion of lesions scheduled for excision on the basis of clinical (Guitera 2012; Langley 2007) or dermoscopic (Guitera 2009a (Modena); Guitera 2009b (Sydney); Guitera 2012; Pellacani 2014b (doc)) suspicion of melanoma or due to lesions changes on follow-up (Guitera 2009a (Modena); Guitera 2009b (Sydney); Langley 2007; Segura 2009). Two further cohorts included lesions scheduled for excision but did not describe any prior testing of participants (Curchin 2011; Rao 2013) and one (Koller 2011) provided no information as to lesion selection. Two studies reported including any type of lesion (22%), three restricted to pigmented lesions only (33%), and four restricted to melanocytic (44%) lesions only. Three studies (33%) excluded acral or awkwardly sited lesions and five (56%) reported excluding on RCM image quality.

The median sample size was 137 patients (range 42 to 195; reported in 6 studies) and 131 lesions (range 50 to 323). The median lesion to patient ratio was 1.07 (range 1 to 1.19) in 7 studies (and not stated in Koller 2011 or Rao 2013). Mean age was given in five studies and ranged from 41 to 53 years and mean percentage of male participants ranged from 39.9 to 54.3%. The mean prevalence of disease was 27.6% (range 2.8% to 41.5%). On average melanoma in situ lesions made up 25% of the disease positive group, ranging from 7.7% to 51.4%. The spectrum in the disease negative groups also varied between studies with three studies including only benign melanocytic naevi (Koller 2011; Langley 2007; Segura 2009), three also including Spitz naevi (ranging from 3% (Guitera 2009b (Sydney)) to over 10% (Guitera 2009a (Modena); Guitera 2012)), and the three remaining studies including BCC, SCC, and seborrhoeic and/or actinic keratosis (Curchin 2011; Pellacani 2014b (doc); Rao 2013) amongst others (Pellacani 2014b (doc); Rao 2013).

More than half of studies used the Vivascope 1500 imaging system (n = 5), two used Vivascope 1000, and the remaining two initially used the 1000 and moved on to the 1500 model during the course of the study. Six studies reported the use of dermoscopic images to help guide acquisition of RCM images. In all studies, diagnosis was reported for a single observer rather than for a consensus of observers or average value. Observers were dermatologists in four studies (44%), with three studies reporting observers to be expert or with high levels of experience in practice and six (67%) with high levels of experience with RCM. These characteristics were not reported in the remaining studies. In three studies diagnosis was undertaken in-person with real time interpretation of RCM images; in the remaining six, test interpretation was undertaken remotely based on RCM images alone (n = 2), alongside the dermoscopic image of the same lesion (n = 1), or with information provided only on lesion site, patient age or gender (n = 3).

In 8 studies the reference standard diagnosis was made by histology alone (i.e. all lesions either excised or biopsied) and in the remaining study expert diagnosis opinion based on “unequivocal clinical and conventional dermoscopic criteria” was used to establish the final diagnosis for 46% (n = 31) of the disease negative group (Koller 2011).

Reflectance confocal microscopy

The 9 evaluations of RCM reported using Pellacani’s RCM score for four datasets (50%). One of these (Curchin 2011) also applied the Guitera score (Guitera 2010) for lesions suspected of lentigo maligna of the face. One study developed and applied the Segura algorithm (Segura 2009). The remaining studies reported test accuracy for selected RCM characteristics (Langley 2007) or for observer diagnosis of melanoma (Koller 2011; Rao 2013).

Estimates of sensitivities ranged from 63% to 100% and specificities from 57% to 95% (Figure 8). The low sensitivity of 63%

in Koller 2011 appeared as an outlier, all other studies having values at or above 86%. Similarly, specificities were above 82% in all studies except Pellacani 2014b (doc) (57%), Guitera 2009a (Modena) (58%), and Guitera 2012 (62%). Guitera 2009a (Modena) and Guitera 2012 both had higher than expected percentages of Spitz nevi (19% and 11% respectively) whereas Koller 2011 was one of two studies to use the Vivascope 1000 throughout. The lower specificity in Pellacani 2014b (doc) is more difficult to explain, but may be related to the fact that all included lesions were considered to require excision based on dermoscopy alone, which may have affected the case-mix of lesions in a way that we are not able to identify. Correctly identified basal cell carcinoma lesions were considered true negatives for the purposes of these calculations for Guitera 2012 and Rao 2013.

Results were pooled across algorithms and thresholds as a summary ROC curve (Figure 9). Estimates of accuracy obtained from the curve suggest that the specificity of RCM would be 82% at a fixed threshold of 90% sensitivity (Table 3).

Comparison of RCM versus dermoscopy

The three evaluations of dermoscopy that were included in these RCM studies reported using pattern analysis to assist dermoscopy interpretation; two were conducted in-person (Guitera 2009a (Modena); Langley 2007) and one was based on dermoscopic images with information on lesion site and patient age only (Guitera 2009b (Sydney)). Sensitivities for dermoscopy ranged from 86% to 91%; specificities ranged from 28% to 84% (Figure 8). The accuracy of dermoscopy was compared with the accuracy of RCM estimated from (a) all 9 RCM studies (Figure 9) and estimated from direct comparisons in (b) with the subset of 3 studies that evaluated both RCM and dermoscopy (Figure 10). In both comparisons the accuracy of RCM exceeded that of dermoscopy (Table 3). In (a) the diagnostic odds ratio (DOR) for RCM was 4.82 (95% CI 2.16 to 10.8; P = 0.0001) times that of the dermoscopy, in (b) it was 4.96 (95% CI 1.1 to 21.5; P = 0.03) times that of the dermoscopy. These effects correspond to predicted differences in specificity of (a) 40% (82% versus 42%) and (b) 52% (93% versus 41%) at a fixed sensitivity of 90% (Table 3).

Equivocal lesion studies

We defined equivocal lesion studies as those in which RCM was used in participants with equivocal lesions in whom a clear management decision could not be made following visual inspection and/or dermoscopy, i.e. RCM was being evaluated as a potential addition to dermoscopy.

Seven publications provided data for 7 evaluations of RCM alone (Alarcon 2014; Farnetani 2015; Ferrari 2015; Lovatto 2015; Pellacani 2012; Pellacani 2014a (cons); Stanganelli 2015) and 3 of dermoscopy (Alarcon 2014; Ferrari 2015; Stanganelli 2015) (Table 3 and Figure 11). All studies were case series; three (43%) were prospective in design and four (57%) retrospective, three of which prospectively reinterpreted previously acquired RCM images. Studies were all undertaken in Europe (100%). Three studies (43%) were undertaken in a secondary care setting and four (57%) in specialist skin cancer units. All studies reported some degree of prior testing of participants, with two (29%) selecting lesions that were equivocal on either clinical examination or dermoscopy (Farnetani 2015; Pellacani 2012), three (43%) with all lesions equivocal on dermoscopy (Alarcon 2014; Ferrari 2015; Pellacani 2014a (cons)), and two (29%) selecting lesions showing changes on digital follow-up (Lovatto 2015; Stanganelli 2015). One study reported including any type of lesion (14%), one restricted to pigmented lesions only (14%) and five restricted to melanocytic (71%) lesions only. Three (43%) studies reported excluding lesions on RCM image quality.

The median sample size was 70 patients (range 62 to 264; reported in 5 studies) and 100 lesions (range 60 to 308), giving a median lesion to patient ratio of 1.05 (range 1 to 1.22). Mean age was reported in 5 studies and ranged from 39 to 54.7 years and mean percentage of male participants was from 44.0 to 54.0%. The mean prevalence of the primary target condition of 18.2% (range 1.9% to 34.8%) was lower compared to the studies in any lesion suspicious for melanoma as would be expected in a group of more difficult to diagnose lesions. On average melanoma in situ lesions made up 28.6% of the disease positive group, ranging from 8.3% to 61.5% (breakdown reported for four datasets). The spectrum in the disease negative groups also varied with four studies including only (Lovatto 2015) or primarily (Ferrari 2015; Pellacani 2012; Stanganelli 2015) benign naevi, although in one of these non-dysplastic naevi made up 41% of the disease negative group. Three included BCC and a range of other diagnoses including seborrheic or actinic keratosis (Alarcon 2014; Farnetani 2015) or Spitz naevi (Pellacani 2014a (cons)).

All studies in this group used the Vivascope 1500 imaging system (100%); none reported the use of dermoscopic images to help guide acquisition of RCM images. Diagnosis was reported for a single observer in 71% of studies (n = 5), for a consensus of three observers in one study and was not reported in the remaining study. Observers were qualified dermatologists in five studies (71%), and four studies reported observers to have high levels of experience in practice and five (71%) reported high levels of experience with (or training in) RCM. These observer characteristics were not reported in the remaining studies. In one study, diagnosis was undertaken in-person with real time interpretation of RCM images; in the remaining six, test interpretation was undertaken remotely based on RCM images alone (n = 3) or alongside the dermoscopic image of the same lesion (n = 3), with information provided only on lesion site, patient age or gender in one of these.

In six studies the reference standard diagnosis was made by histology alone (i.e. all lesions either excised or biopsied) and in the remaining study 227 of 308 lesions referred for RCM consultation underwent surveillance using sequential digital dermoscopy follow-up and cancer registry searches for those lost to follow-up; 28 lesions were excised during follow-up and found to be benign (Pellacani 2014a (cons)).

Reflectance confocal microscopy

The 7 evaluations of RCM reported using Pellacani's RCM score (Lovatto 2015) or use of the RCM score was

assumed due to study authorship (Pellacani 2014a (cons)), the Segura algorithm (Alarcon 2014) or the Pellacani two step algorithm for dysplastic naevi and melanoma (Pellacani 2012; Stanganelli 2015). The remaining studies reported test accuracy for the presence of statistically significant RCM characteristics (Ferrari 2015) or for observer diagnosis of melanoma (Farnetani 2015).

Estimates of sensitivities ranged from 80% to 100% and specificities from 67% to 95% (Figure 11). There were no obvious outliers or heterogeneity in sensitivities, and no consistent differences to potentially explain the observed heterogeneity in specificities. Correctly identified BCC lesions were considered true negatives for the purposes of these calculations for Farnetani 2015 and Pellacani 2014a (cons).

Results were pooled across algorithms and thresholds as a summary ROC curve (Figure 12). Estimates of accuracy obtained from the curve suggest that specificity would be 86% at a fixed threshold of 90% sensitivity (Table 3). These values for specificity are higher than those observed in studies in any lesion suspicious for melanoma, reflecting the marginally higher values and lower variability of sensitivities in the equivocal lesion studies.

Comparison of RCM versus dermoscopy

The three evaluations of dermoscopy that were included in these RCM studies reported using the seven point checklist for dermoscopy (Ferrari 2015) or a revised version thereof (Stanganelli 2015), or did not report the approach to dermoscopy interpretation (Alarcon 2014). All were image-based diagnoses; two studies provided the RCM image with (Alarcon 2014) or without (Ferrari 2015) additional patient or lesion information to assist diagnosis, and one providing a baseline dermoscopic image (Stanganelli 2015).

The accuracy of dermoscopy was compared with the accuracy of RCM estimated from (a) all 7 RCM studies (Figure 12) and estimated from direct comparisons in (b) with the subset of 3 studies that evaluated both RCM and dermoscopy (Figure 13). The meta-analytical model for the paired analysis (b) required assumptions of a symmetrical SROC curve and fixed effects for accuracy and threshold to obtain convergence.

It is notable that the accuracy of dermoscopy in these studies (DOR=3.0 (95% CI 1.3 to 6.8)) is much lower than in those in any lesion suspicious for melanoma (DOR = 14.4 (95% CI 2.7 to 77.6)), as would be expected given by definition these studies are those in where diagnoses involving dermoscopy are equivocal, i.e. they include lesions to be excised because a clear diagnosis could not be reached on clinical examination or dermoscopy. In both comparisons the accuracy of RCM exceeded that of dermoscopy (Table 3). In (a) the diagnostic odds ratio (DOR) for RCM was 20.1 (95% CI 6.6 to 61.3; P<0.001) times that for dermoscopy, in (b) it was 22.1 (95% CI 1.7 to 283.6; P = 0.03) times that of the dermoscopy. These effects correspond to predicted differences in specificity of (a) 37% (86% versus 49%) and (b) 50% (94% versus 44%) at a fixed sensitivity of 90% (Table 3).

Analyses by algorithms used to assist RCM – all studies

The 18 included studies provided 25 datasets evaluating the accuracy of different algorithms or approaches to diagnosis with RCM at a number of different thresholds for test positivity for the detection of invasive melanoma or atypical intraepidermal melanocytic variants. A description of the various algorithms and thresholds is provided in Appendix 5. One dataset from Pellacani and colleagues (Pellacani 2007) was excluded due to overlap in study population, algorithm and threshold with a study by Guitera and colleagues (Guitera 2009a (Modena); Guitera 2009b (Sydney)).

Figure 14 provides forest plots of all algorithms for the detection of invasive melanoma or atypical intraepidermal melanocytic variants, with meta-analytical estimates at each threshold presented in Table 4. We did not formally make any comparisons between the algorithms due to the small number of studies available evaluating each algorithm. Whilst the specificity of the computer–assisted approach to analysis of RCM images (Koller 2011) appears to be much lower than any other algorithm, the ranges of values for different algorithms are largely comparable.

Pellacani's RCM score

Pellacani's RCM score (Pellacani 2005; Pellacani 2007) was the most commonly evaluated formal algorithm for the detection of melanoma (8 studies; 10 datasets), with data reported at thresholds of ≥ 2, ≥ 3 and ≥ 4. One study (Pellacani 2014b (doc); Pellacani 2014a (cons)) did not report the threshold used and contact with authors was unsuccessful; as it cited one of the original Pellacani and colleagues papers (Pellacani 2007), the recommended threshold of ≥ 3 was assumed. The majority of datasets were image-based, with only two studies providing data for in-person evaluations (Curchin 2011; Pellacani 2014b (doc); Pellacani 2014a (cons)). The majority of datasets were from studies in any lesion suspicious for melanoma (Curchin 2011; Guitera 2012; Guitera 2009a (Modena); Guitera 2009b (Sydney); Guitera 2012; Pellacani 2007; Pellacani 2014b (doc)) with only two from studies of equivocal lesions (Lovatto 2015; Pellacani 2014a (cons)). One study provides two datasets at different thresholds (Pellacani 2007); hence, the total number of datasets is 10.

The pooled accuracy combining data from all 6 studies reporting (or assumed to be) at RCM score ≥ 3 was a sensitivity of 92% (95% CI 87% to 95%) and specificity of 72% (95% CI 62% to 81%). Lower thresholds had higher sensitivity but lower specificity, higher thresholds had lower sensitivity but higher specificity (Table 4).

Segura score

The Segura algorithm, developed in Segura 2009 was evaluated in three further studies (Alarcon 2014; Guitera 2012; Lovatto 2015) at the standard threshold of >-1. All datasets were image-based; test interpretation was blinded to any further information in two (Lovatto 2015; Segura 2009), two one provided the observer with patient age and lesion site (Alarcon 2014; Guitera 2012), one of which also provided the dermoscopic image (Alarcon 2014). Two studies

were conducted in equivocal lesions (Alarcon 2014; Lovatto 2015) and two in 'any lesion suspicious for melanoma' populations (Segura 2009; Guitera 2012). The pooled accuracy combining data from all four studies was a sensitivity of 92.6% (76.2% to 98.0%) and specificity of 87.5% (72.2% to 95.0%) (Table 4).

Other formally developed algorithms

Guitera 2012 reported a two-step algorithm to firstly differentiate BCC from other lesions and then melanoma from the remaining lesions. In this single study the melanoma component of the algorithm demonstrated a sensitivity of 78% (95% CI 69% to 86%) and specificity of 84% (95% CI 79% to 88%).

Pellacani 2012 also developed a two-step algorithm, this time to differentiate dysplastic from non-dysplastic lesions and then melanoma from dysplastic lesions. The same algorithm was evaluated in Stanganelli 2015. Combined accuracy was a sensitivity of 96% (95% CI 72% to 100%) and specificity of 71% (95% CI 61% to 79%) (Table 4).

Finally, Koller 2011 reports a computer–assisted approach to analysis of RCM images. This demonstrated a perfect sensitivity of 100% (95% CI 86% to 100%) but a very poor specificity of 24% (95% CI 14% to 35%) (Table 4).

'No algorithm' evaluations

Seven studies reported accuracy data for RCM without the use of a formally developed algorithm.

The three datasets reporting accuracy based on the presence of statistically significant characteristics (Ferrari 2015; Pupelli 2013) or selected lesion characteristics (Langley 2007), had sensitivities ranging from 89% to 97% and specificities from 70% to 90%.

The four datasets reporting accuracy for observer diagnosis of melanoma were all image-based (all except one (Koller 2011) also providing the dermoscopic image to test interpreters), two conducted in 'any lesion suspicious for melanoma' populations (Koller 2011; Rao 2013), one in equivocal lesions (Farnetani 2015) and one in 'other' populations (Figueroa Silva 2016). The pooled accuracy of the four studies gave an estimated sensitivity of 81% (95% CI 65% to 91%) and specificity of 88% (95% CI 78% to 94%).

Rao 2013 also provides a direct comparison of image-based test interpretation by an experienced observer to in-person real-time diagnosis by a less experience observer. Sensitivity was lower for the in-person evaluation (67%, 95% CI 30% to 93%) compared to image-based (89%, 95% CI 52% to 100%), although confidence intervals were wide and overlapping. Specificities were almost identical for the two approaches (96% versus 95%).

Overall, observed sensitivities appeared higher for studies reporting the use of a 'named' algorithm and were very similar (92%) between studies using the most widely used algorithms (Pellacani's RCM score and the Segura score). Summary specificity was higher for the Segura algorithm (87.5%) compared to the RCM score (72%), although it was used in fewer studies (4 versus 6), the number of lesions evaluated was higher (784 versus 420).

Investigations of heterogeneity

Results for formal investigations of heterogeneity are presented in Table 5, investigating the effects of use of any RCM scale versus no scale (Figure 15), in-person versus image-based (Figure 16), and whether RCM is used in all lesions or only equivocal lesions (Figure 17). Although RCM appeared to be more accurate when interpreted using a scale (relative diagnostic odds ratio (DOR) compared to studies not reporting use of a scale of 1.81, 95% CI 0.41 to 8.03), from in-person studies (relative DOR in comparison to image-based studies 4.77, 95% CI 0.56 to 40.8), and when used on equivocal lesions (relative DOR in comparison to 'any lesion suspicious for melanoma' populations 2.88, 95% CI 0.80 to 10.4), none of the differences reached levels of statistical significance (Table 5).

The impact of observer experience on RCM accuracy is shown in Figure 18 for equivocal lesions and Figure 19 for 'any lesion suspicious for melanoma' populations. Overall, only three studies classified any observer as having low experience (Curchin 2011; Farnetani 2015; Rao 2013), too few to allow any conclusive analyses.

We were unable to undertake investigations of heterogeneity for other characteristics listed in the protocol due to lack of variation in characteristics, or absence of information in the study reports.

Target condition: invasive melanoma alone

In this section we present the results for studies of RCM for the target condition of invasive melanoma only; no comparisons with dermoscopy were identified for this target condition. All studies were conducted in 'any lesion suspicious for melanoma' populations, i.e. no attempt was described to exclude those diagnosed as definite melanomas or as obviously benign on dermoscopy.

Three study cohorts provided data for 3 evaluations of RCM (Curchin 2011; Guitera 2012; Segura 2009) (Figure 20). All studies were case series (two prospective in design and one unclear). Studies were undertaken in Europe (n = 1), Oceania (n = 1), or in more than one continent (n = 1). All studies were undertaken in a secondary care setting (n = 2) or a mixed secondary care specialist unit setting (n = 1). Two studies reported including any type of lesion and one restricted to melanocytic lesions only. One study excluded keratotic lesions. The sample size ranged from 42 to 330 patients and 50 to 356 lesions. The mean lesion to patient ratio was 1.11 (range 1.07 to 1.19). Mean age was given in two studies and ranged from 49.5 to 53 years; the percentage of male participants ranged from 39.9 to 53.4%. The mean prevalence of disease was 20.4% (range 14.3% to 24.0%). The percentage of melanoma in situ lesions in the disease negative group ranged from 2.6% to 17.7%.

All studies used the Vivascope 1500 imaging system; two reporting the use of dermoscopic images to help the guide

acquisition of RCM images. All studies reported diagnosis for a single observer, though only one clearly reported that this was by an experienced dermatologist. One reported in-person real time interpretation of RCM images and two reported RCM interpretation remotely from the patient (one blinded to any other information an done supplied details of patient age and lesion site). The reference standard diagnosis was made by histology alone in all studies.

Segura 2009 developed and applied a new algorithm (denoted the Segura algorithm) to a set of melanocytic lesions at a threshold of >-1 (BCCs and benign non melanocytic lesions were excluded); sensitivity was 96% (95% CI 78% to 100%) and specificity 84% (95% CI 74% to 92%) (Figure 21).

One study (Curchin 2011) used Pellacani's RCM score at a threshold of ≥ 3 and also applied the Guitera score (Guitera 2010) for lesions suspected of lentigo maligna of the face; sensitivity was 100% (95% CI 74% to 100%) and specificity 92% (95% CI 79% to 98%). The remaining study (Guitera 2012) reported the melanoma component of a two-step algorithm to have a sensitivity of 78% (95% CI 65% to 89%) and specificity of 86% (95% CI 81% to 90%). Correctly identified melanoma in situ, BCC and SCC were considered true negative results for the purposes of these calculations.

Insufficient data were available to make any overall summary of test accuracy for this target condition.

Target condition: any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma

In this section we present the results for studies of RCM versus dermoscopy for the target condition of any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma, i.e. any invasive skin cancer, melanoma in situ or lentigo maligna and lesions with severe dysplasia, according to the study population: studies in any lesion suspicious for melanoma versus those in participants with equivocal lesions.

Studies in any lesion suspicious for melanoma

Four study cohorts provided data for four RCM evaluations (Curchin 2011; Guitera 2012; Pellacani 2014b (doc); Rao 2013) (Figure 20). All studies were case series (two prospective in design and two unclear). Studies were undertaken in Europe (n = 1), North America (n = 1), Oceania (n = 1), or in more than one continent (n = 1). All studies were undertaken in a secondary care setting (n = 2) or a mixed secondary care specialist unit setting (n = 2). Three studies included all lesion types and Pellacani 2014b (doc) included pigmented lesions only. The sample size ranged from 42 to 330 patients (reported in three studies) and 50 to 356 lesions. The lesion to patient ratio ranged from 1.07 to 1.19. Mean age was given in three studies and ranged from 41 to 53 years; the percentage of male participants was ranged from 44% to 54% (n = 3). The mean prevalence of disease was 33.8% (range 22.9% to 44.1%). The percentage of invasive melanoma or melanoma in situ lesions in the disease positive group was 12% (Rao 2013), 46% (Pellacani 2014b (doc); 59% (Curchin 2011) and 63% (Guitera 2012); invasive SCCs were included as disease positive for both Rao 2013 (5% of disease positive group) and Guitera 2012 (54% of disease positive group) but could not be differentiated from sebhorrheic keratoses in Curchin 2011 and were therefore included in the disease negative group (n = 6; or 21% of disease negative group). Pellacani 2014b (doc) did not report including any cSCCs.

All studies used the Vivascope 1500 imaging system and reported the use of dermoscopic images to help the guide acquisition of RCM images. All studies reported diagnosis for a single observer, though only one clearly reported that this was by an experienced dermatologist. Two reported in-person real time interpretation of RCM images (Curchin 2011; Pellacani 2014b (doc)) and two reported RCM interpretation remotely from the patient (Guitera 2012 supplied details of patient age and lesion site and Rao 2013 presented the dermoscopic image to aid interpretation). The reference standard diagnosis was made by histology alone in all studies.

Curchin 2011 and Pellacani 2014b (doc) used Pellacani's RCM score at a threshold of ≥ 3, Guitera 2012 reported data for their new two-step algorithm for detection of BCC or melanoma and Rao 2013 reported observer diagnosis. Estimates of sensitivities ranged from 85% to 100% and specificities from 52% to 89%.

Equivocal lesion studies

Three studies provided data for three evaluations of RCM alone (Farnetani 2015; Pellacani 2012; Pellacani 2014a (cons)) (Figure 20). All studies were case series (two prospective in design and one retrospective with prospective reinterpretation of images). All studies were undertaken in Europe, all in Italy. Two studies were undertaken in a secondary care setting (n = 2) and one in a specialist clinic. One study recruited any lesion type, one restricted to pigmented lesions and one to melanocytic lesions only. The sample size ranged from 62 to 252 patients (reported in two studies) and 60 to 308 lesions. The lesion to patient ratios where reported were 1.03 (Pellacani 2012) and 1.22 (Pellacani 2014a (cons)). Mean age was given in two studies and ranged from 41 to 47.7 years; the percentage of male participants ranged from 44% to 52% (2 studies). The mean prevalence of disease was 24.9% (range 8.1% to 35.0%). The mean percentage of invasive melanoma or melanoma in situ lesions in the disease positive group was 51.6% (range 24% to 73.6%).

All studies used the Vivascope 1500 imaging system and reported diagnosis for a single observer. Observers were described as dermatologists in two studies. One reported in-person real time interpretation of RCM images (Pellacani 2014a (cons)) and two reported RCM interpretation remotely from the patient (one blinded (Pellacani 2012) and one appeared to supply dermoscopic image to aid interpretation (Farnetani 2015), although this was not well reported). The reference standard diagnosis was made by histology alone in two studies and was supplemented by clinical and cancer registry follow-up in the other (Pellacani 2014a (cons)).

One study developed a two step algorithm to differentiate dysplastic from non-dysplastic lesions and then

melanomas from dysplastic lesions (Pellacani 2012), one reported the observers overall diagnosis (Farnetani 2015), and one did not report the algorithm used but was assumed to have used Pellacani's RCM score, based on study authorship (Pellacani 2014a (cons)). Estimates of sensitivities ranged from 86% to 100% and specificities from 80% to 91%.

Analyses by algorithms used to assist RCM – all studies

The 6 included studies provided 11 datasets evaluating the accuracy of different algorithms or approaches to diagnosis with RCM at different thresholds for test positivity for the detection of any skin cancer or skin lesion with a high risk of progression to melanoma. A description of the various algorithms and thresholds used for diagnosis across the studies is provided in Appendix 5. One dataset from Pellacani and colleagues (Pellacani 2007) was excluded due to overlap in study population, algorithm and threshold with a study by Guitera and colleagues (Guitera 2009a (Modena); Guitera 2009b (Sydney)).

Figure 22 provides forest plots of all algorithms and thresholds, with meta-analytical estimates at each threshold presented in Table 4. We did not formally make any comparisons between the algorithms due to the small number of studies available evaluating each algorithm.

Pellacani's RCM score

Pellacani's RCM score was evaluated in three datasets, one (Curchin 2011 in an 'any potential melanoma' population) reported results at a threshold of ≥ 3 and two (from a single study in equivocal lesions (Pellacani 2014b (doc); Pellacani 2014a (cons)) that did not report the threshold used but the recommended threshold of ≥ 3 was assumed, as discussed above. All three datasets were from in-person evaluations of RCM, one with interpretation by an RCM novice (Curchin 2011), and the other two by members of a 'confocal unit' assumed to be expert in RCM use.

RCM sensitivities were relatively high in all studies (≥ 86%), with lower specificities in the two studies of dermoscopically equivocal lesions (Pellacani 2014b (doc); Pellacani 2014a (cons)). The pooled accuracy combining data from all 3 datasets reporting (or assumed to be) at RCM score ≥ 3 was a sensitivity of 98% (95% CI 91% to 99%) and specificity of 75% (95% CI 54% to 89%) (Table 4).

Other formally developed algorithms

Three other algorithms were each evaluated in a single dataset each for detection of any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma. The Segura algorithm and Guitera two-step algorithm were both evaluated in Guitera 2012, and the Pellacani two-step algorithm in Pellacani 2012.

All studies used image-based evaluations of RCM, one study conducted in equivocal lesions was blinded to any further information (Pellacani 2012) and the other (in an any potential melanoma population) provided details of patient age and lesion site only (Guitera 2012).

Guitera 2012 reported a sensitivity of 92% and specificity of 68% for their two-step algorithm (with 9 SCCs considered as disease positive) compared to a sensitivity of 80% and specificity 70% for the Segura algorithm (the 9 SCCs could only be considered disease negative for this calculation due to lack of disaggregated data however, classing the 9 SCCs as disease negative for the Guitera two-step algorithm made very little difference to the estimate of sensitivity and specificity). Pellacani 2012 estimated sensitivity and specificity for their two-step algorithm as 89% and 80% respectively.

'No algorithm' evaluations

Two studies reported accuracy data for observer diagnosis with RCM without the use of a formally developed algorithm by different observers and at more than one threshold.

Farnetani 2015 reports data for in-person diagnosis of malignancy by nine different observers with varying levels of experience. Rao 2013 provides a comparison of image-based test interpretation by an experienced observer to in-person real-time diagnosis by a less experienced observer in an 'any lesion suspicious for melanoma' population for the diagnosis of any malignancy and for the decision to excise a lesion. There was a slight discrepancy in the number of lesions between in-person (n = 318) and image-based (n = 323) interpretations. For the diagnosis of any malignancy, the sensitivity was 78% (95% CI 67% to 87%) for in-person diagnosis and 85% (95% CI 75% to 92%) for image-based; specificities were 85% (95% CI 80% to 89%) and 86% (95% CI 81% to 90%), respectively. For the decision to excise a lesion, the sensitivity was 85% (95% CI 75% to 92%) for in-person diagnosis and 90% (95% CI 81% to 95%) for image-based; specificities were 61% (95% CI 55% to 68%) and 79% (95% CI 73% to 84%), respectively.

For the diagnosis of malignancy by an experienced observer, the pooled data across the two studies (using the image-based data from Rao 2013) gave an estimated sensitivity of 85% (95% CI 77% to 90%) and specificity of 87% (95% CI 83% to 90%).

Evaluations of RCM in other study populations

Three evaluations of RCM in other study populations were identified.

Pupelli 2013 selected confocal images of 24 melanomas of < 5 mm diameter and three histologically proven small-diameter naevi controls per melanoma (n = 72) that were excised within the same time frame. Images were interpreted alongside the dermoscopic image plus information on patient age and site. The presence of three statistically significant lesion characteristics led to an estimated sensitivity of 83% (95% CI 63% to 95%) and specificity of 90% (95% CI 81% to 96%) for the detection of invasive melanoma and atypical intraepidermal melanocytic variants.

Figueroa Silva 2016 included a series of 63 images of pigmented lesions with a clear-cut 'dermoscopy island', defined as "a

well-circumscribed area showing a uniform dermoscopic pattern, different from the rest of the lesion". A single observer assessed the RCM images (blinded to all other information apart from dermoscopy) for the presence or absence of a number of lesion characteristics and provided an overall diagnosis. The estimated sensitivity and specificity for the detection of invasive melanoma and atypical intraepidermal melanocytic variants was 89% (95% CI 71% to 98%) and 89% (95% CI 74% to 97%). For the detection of invasive melanoma only (n = 7) and considering the 19 melanoma in situ lesions as disease negative, the sensitivity is 88% and specificity 62%.

Longo 2013 examined the use of RCM for the diagnosis of nodular melanoma. A series of images of clinically nodular lesions (defined as cutaneous palpable or superficial seated lesions) were interpreted by a single dermatologist blinded to all other information. For the diagnosis of invasive nodular lesions, the sensitivity was 100% and specificity 91%.

Discussion

Summary of main results

RCM has been evaluated in a range of study populations and using a number of different algorithms. Sensitivity is generally high across studies and target conditions, but there is considerable heterogeneity in specificity. Studies were generally at high or unclear risk of bias across almost all domains and of high or unclear concern regarding applicability of the evidence, limiting the strength of conclusion that can be drawn. The Summary of findings table 1 presents key results for the primary target condition of cutaneous invasive melanoma or atypical intraepidermal melanocytic variants.

Across all algorithms and thresholds assessed, the Pellacani RCM score at a threshold of ≥ 3 has the largest number of datasets for any one threshold; sensitivity was estimated at 92% and specificity at 72%. RCM accuracy was similar between 'any lesion suspicious for melanoma' studies and equivocal lesion studies, with sensitivities consistently around or above 90% but with much greater variation in specificities. In comparison to dermoscopy, RCM was found to be more accurate in both participant groups, i.e. those with all lesions suspected of melanoma, and in equivocal lesion populations. Due to differences in the algorithms and thresholds used between studies, analysis required use of a summary ROC curve, and to aid interpretation we quote 'typical' summary results assuming a fixed sensitivity of 90% for both tests. The Summary of findings table 1 translates these estimates to a hypothetical cohort of 1000 lesions. For 'any lesion suspicious for melanoma' studies, specificities were 82% for RCM and 42% for dermoscopy at a sensitivity of 90% for both tests. At disease prevalences of 26, 30 and 36%, using RCM as an alternative to dermoscopy would reduce false positives (or number of excisions that would be performed) by 296, 280 and 256 per 1000 compared with dermoscopy alone. Both tests would miss 26, 30 and 36 melanomas at each respective prevalence of melanoma. For equivocal lesion studies, specificities were 86% for RCM and 49% for dermoscopy at a sensitivity of 90% for both tests. At disease prevalences of 10%, 20% and 23%, using RCM in addition to dermoscopy would reduce the number of excisions by 333, 296 and 285 per 1000. Both tests would miss 10, 20 and 23 melanomas at each respective prevalence of melanoma. Investigations of heterogeneity were limited due to paucity of data but suggested higher RCM accuracy in equivocal lesions and from in-person evaluations of RCM images.

Strengths and weaknesses of the review

The strengths of this review include an in-depth and comprehensive electronic literature search, systematic review methods including double extraction of papers by both clinicians and methodologists, and contact with authors to allow study inclusion or clarify data. A clear analysis structure according to patient pathway was adopted to allow test accuracy in different study populations to be estimated and a detailed and replicable analysis of methodologic quality was undertaken.

The main concerns for the review are a result of the poor reporting of primary studies, in particular forcing some assumptions to be made to allow studies to be split by pathway and in separating studies by the different definitions of the target condition. In terms of the separation of studies by pathway, although some assumptions were made, it emerged that the studies in each group could almost have been separated by disease prevalence, with higher rates in the 'any lesion suspicious for melanoma' group (ranging from 26% to 42% with one outlier at 3%), as would be expected in studies that included more obvious melanomas, and lower rates in the equivocal lesion group (ranging from 2% to 27%), again as would be expected with more clinically difficult lesions.

Clear identification of the target condition was not provided in three of the 16 cohorts included in our primary analyses for detection of invasive melanoma or atypical intraepidermal melanocytic variants. The inclusion of melanoma in situ lesions as disease positive was eventually discerned from the text of two papers (Alarcon 2014; Ferrari 2015) and was assumed for the third study (Farnetani 2015). Where studies included other invasive skin cancers in the study population, we attempted to class any that were correctly identified as true negative results as opposed to false positives, on the basis that removal of any skin cancer in the attempt to identify melanomas would not be a negative consequence of the test. This relied on studies providing a disaggregation of test results according to final lesion classification and was not always possible, particularly when invasive SCCs were not separated from 'in situ' lesions such as Bowen's disease.

Finally, observer expertise is key for any diagnostic process based on visual inspection, with both non-analytical pattern recognition (implicit identification) and analytical pattern recognition (using more explicit 'rules' based on conscious analytical reasoning) employed to varying extents between clinicians, according to factors such as experience and familiarity with the diagnostic question (Norman 2009). Notably, research in this field has been dominated by a single expert group and results obtained from a more typical range of specialists in different countries, health care systems and settings are needed. A lack of clear reporting of observer training and experience in RCM made analysis difficult.

Given these limitations, our results should be considered as exploratory rather than conclusive. Our results are however, generally in accord with those of other recently published systematic reviews (Xiong 2016; Edwards 2016), one of which was conducted as part of a technology assessment report for NICE (Edwards 2016), despite differences in

methodological approaches. Xiong 2016 did not consider varying definitions of the target condition in their primary analysis but pooled all studies regardless of detection of melanoma, BCC or SCC (our examination of RCM for the diagnosis of keratinocyte skin cancers is reported in a separate systematic review in our series (Dinnes 2015a)). In a secondary analysis, eight studies with melanoma as the 'focus' were pooled, producing estimates of sensitivity of 92.7% (95% CI 90.0 to 94.9) and specificity of 78.3% (95% CI 0.76 to 0.81) (Xiong 2016). No consideration was given to differences in patient populations, two studies were excluded from our review (Gerger 2005; Guitera 2010) and two of the included studies reported on the same set of lesions (Guitera 2009; Pellacani 2007).

The Edwards 2016 review did not conduct a meta-analysis, instead selecting studies considered to be more applicable to a UK setting. Using studies with 'optimistic' accuracy data (sensitivity 97% and specificity 94% in Alarcon 2014) and with 'less favourable' (sensitivity 100% and specificity 51% from Pellacani 2014) accuracy, deterministic incremental cost-effectiveness ratios (ICER) for RCM in comparison to 'usual practice' were estimated for patients with dermoscopically equivocal lesions (assuming that two thirds of lesions would be excised and the remainder monitored). Resulting QALYs ranged £8877 using 'optimistic' data to £19,095 (Edwards 2016). The report concluded that data are lacking to allow generalisability to a UK setting.

Applicability of findings to the review question

The data included in this review is generally applicable to the clinical setting. Most of the studies used the current version of the only commercially available RCM system, the Vivascope 1500. Narrow definitions of the eligible study populations and lack of clarity regarding the patient pathway and any prior testing may restrict applicability, and the use of remote image-based diagnosis largely by RCM experts further restrict the transferability of results to a clinical setting.

Authors' conclusions

Implications for practice

RCM may have a potential role in clinical practice, particularly for the assessment of melanocytic lesions identified as equivocal following visual inspection and dermoscopy, where the evidence suggests that RCM may be both more sensitive and specific in comparison to dermoscopy. Given the paucity of data to allow comparison with dermoscopy, we presented illustrative data assuming that both tests are similarly sensitive. On this basis, for all lesions suspicious for melanoma, with RCM essentially used as a replacement for dermoscopy, the number of inappropriate excisions could potentially be reduced by up to two thirds. Given the additional expense and training required for RCM, the evidence for improved accuracy is insufficient to support its widespread use in a general population of people with lesions suspicious for melanoma. For an equivocal lesion population, the evidence for equivalent sensitivity between RCM and dermoscopy is more tenuous (with RCM likely to be the more sensitive test given that this group of lesions has already been identified as equivocal on dermoscopy), but even assuming equivalent sensitivity, inappropriate excisions could be reduced by as much as three quarters. If superior sensitivity of RCM could be demonstrated for this group, considerable patient benefit could be gained in terms of fewer missed melanomas and reduced morbidity. Digital monitoring in those considered negative on RCM could further reduce harms from any missed cases; however, resource implications and patient impact from such a policy would have to be taken into account.

Implications for research

Further prospective evaluation of RCM in a standard healthcare setting with a clearly defined and representative population of participants with dermoscopically equivocal lesions and with RCM results interpreted in a usual practice setting by observers representative of those who would normally interpret images is appropriate in order to confirm the suggested increase in accuracy over dermoscopy. A multicentre approach would allow confirmation that results are replicable across centres and that the technology can be implemented across a health service. Prospective recruitment of consecutive series of participants, with test interpretation blinded to the reference standard diagnosis and with pre-specified and clearly defined diagnostic thresholds for determining test positivity are easily achieved. Systematic follow-up of non-excised lesions avoids over-reliance on a histological reference standard and allows results to be more generalisable to routine practice. A standardised approach to diagnosis, and clear identification of the level of training and experience required to achieve good results is also required. Any future research study needs to be clear about the diagnostic pathway followed by study participants prior to study enrolment, and should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

Acknowledgements

Members of the Cochrane Skin Cancer Diagnostic Test Accuracy Group include:

- the full project team (Susan Bayliss, Naomi Chuchu, Clare Davenport, Jonathan Deeks, Jac Dinnes, Kathie Godfrey, Rubeta Matin, Colette O'Sullivan, Yemisi Takwoingi, Hywel Williams)
- our 12 clinical reviewers (Rachel Abbott, Ben Aldridge, Oliver Bassett, Sue Anne Chan, Alana Durack, Monica Fawzy, Abha Gulati, Jacqui Moreau, Lopa Patel, Daniel Saleh, David Thompson, Kai Yuen Wong) and 2 methodologists (Lavinia Ferrante di Ruffano and Louise Johnston) who assisted with full text screening, data extraction and quality assessment across the entire suite of reviews of diagnosis and staging and skin cancer,
- and all members of our Advisory Group (Jonathan Bowling, Colin Fleming, Matthew Gardiner, Abhilash Jain, Susan O'Connell , Pat Lawton, John Lear, Mariska Leeflang, Richard Motley, Paul Nathan, Julia Newton-Bishop, Miranda Payne, Rachael Robinson, Simon Rodwell, Julia Schofield, Neil Shroff, Hamid Tehrani, Zoe Traill, Fiona Walter).

Cochrane Skin editorial base wishes to thank Michael Bigby, who was the Dermatology Editor for this review; the clinical

referees, Emma Craythorne and a referee who wishes to remain anonymous; and the consumer referee, Brian Stafford. We also wish to thank the Cochrane DTA editorial base and colleagues.

Contributions of authors

JD was the contact person with the editorial base.
JD co-ordinated contributions from the co-authors and wrote the final draft of the review.
JD, NC, DS and LP screened papers against eligibility criteria.
JD and NC obtained data on ongoing and unpublished studies.
JD, NC, DS and LP appraised the quality of papers.
JD, NC, DS and LP extracted data for the review and sought additional information about papers.
JD entered data into RevMan.
JD and JJD analysed and interpreted data.
JD, JJD, NC, YT and CD worked on the methods sections.
JD, DS, RP, RNM and HCW drafted the clinical sections of the background and responded to the clinical comments of the referees.
JD, JJD, CD and YT responded to the methodology and statistics comments of the referees.
KG was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
JD is the guarantor of the update.

Disclaimer

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group and Cochrane Programme Grant funding. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

Declarations of interest

Jac Dinnes: I am employed by the University of Birmingham under a NIHR Cochrane Programme Grant to produce the reviews.
Jonathan J Deeks: nothing to declare.
Daniel Saleh: nothing to declare.
Naomi Chuchu: nothing to declare.
Susan E Bayliss: nothing to declare.

Lopa Patel: nothing to declare.
Clare Davenport: My employer (The University of Birmingham) received funding for my participation in this review as part of an NIHR clinical fellowship awarded to Alex Heazell (the lead author and contact person).

Yemisi Takwoingi: nothing to declare.

Rubeta N Matin: nothing to declare.
Kathie Godfrey: I have received reimbursement of travel expenses incurred by attending meetings.
Rakesh Patalay: nothing to declare.
Hywel C Williams: I am director of the NIHR HTA Programme. HTA is part of the NIHR which also supports the NIHR systematic reviews programme from which this work is funded.

Differences between protocol and review

- Inclusion criteria amended to remove inclusion of participants "at high risk of developing melanoma, including those with a family history or previous history of melanoma skin cancer, atypical or dysplastic naevus syndrome, or genetic cancer syndromes" as these are not a target population for RCM use.
- Primary objectives and primary target condition have been changed from detection of invasive melanoma alone, to the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, as the latter is more clinically relevant to the practicing clinician.
- For the primary objective, study populations that could not be clearly identified as either 'any lesion suspicious for melanoma ' or 'equivocal lesions' were considered separately as 'other lesion' studies.
- Secondary objectives have been tailored to the individual test, with three objectives added: to compare the accuracy of RCM to dermoscopy where both tests have been evaluated in the same studies; to determine the diagnostic accuracy of individual algorithms for RCM; and to determine the effect of observer experience. Heterogeneity investigations were limited by the data available.
- Studies using cross-validation, such as 'leave-one-out' cross-validation were *excluded* rather than included as these methods are not sufficiently robust and are likely to produce unrealistic estimates of test accuracy. To improve clarity of methods, this text from the protocol "We will include studies developing new algorithms or methods of diagnosis (i.e. derivation studies) if they use a separate independent 'test set' of participants or images to evaluate the new approach. We will also include studies using other forms of cross validation, such as 'leave-one-out' cross-validation (Efron 1983). We will note for future reference (but not extract) any data on the accuracy of lesion characteristics individually, e.g. the presence or absence of a pigment network or detection of asymmetry" has been replaced with "All established algorithms or checklists to assist diagnosis were included. Studies developing new algorithms or

methods of diagnosis (i.e. derivation studies) were included if they used a separate independent 'test set' of participants or images to evaluate the new approach. Studies that did not report data for a separate test set of patients or images were included only if the lesion characteristics investigated had previously been suggested as associated with melanoma and the study reported accuracy based on the presence or absence of particular combinations of characteristics. Studies using a statistical model to produce a data driven equation, or algorithm based on multiple diagnostic features, with no separate test set were excluded. Studies using cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983) were excluded."

- We proposed to supplement the database searches by searching the annual meetings of appropriate organisations (e.g. British Association of Dermatologists Annual Meeting, American Academy of Dermatology Annual Meeting, European Academy of Dermatology and Venereology Meeting, Society for Melanoma Research Congress, World Congress of Dermatology, European Association of Dermato Oncology), however due to volume of evidence retrieved from database searches and time restrictions we were unable to do this.
- For quality assessment, the QUADAS-2 tool was further tailored according to the review topic. In terms of analysis, restriction to analysis of per patient data was not performed due to lack of data. Sensitivity analyses were not performed as planned due to lack of data.

Published notes

Characteristics of studies

Characteristics of included studies

Alarcon 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective. Recruitment: 1 June 2011 and 30 May 2012; Country: Spain
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Dermoscopically equivocal pigmented lesions, assumed to be melanocytic, seen at Melanoma Unit **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) Melanoma Unit of the Hospital Clinic of Barcelona. **Prior testing:** Dermatoscopic suspicion in all cases **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Non-melanocytic appearance and lesions referred for immediate excision or scheduled for digital follow-up based on dermoscopy. **Sample size (patients):** No. eligible: unclear, No. included: unclear **Sample size (lesions):** No. eligible: 343, No. included: 264 **Participant characteristics:** **Age:** Mean: unknown; Median: 54.7; Range: 8-89 (for 264 excised) **Gender:** Male: 136 (51.5% of 264 excised) **Fitzpatrick phototype:** Type I to II 42 (46%) of melanoma; Type III to IV 50 (54%) of melanoma **Lesion characteristics:** Pigmented: 100% **Lesion site:** Head/Neck: 73 (27.7%); Trunk: 135 (51.1%); Limbs: 49 (18.6%); Acral 7 (7%). **Thickness/depth:** ≤ 1 mm: 86 of 92 melanoma; 6 > 1 mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** No algorithm used **Method of diagnosis:** Dermoscopic images **Prior test data:** Clinical examination and/or case notes site and age; dermoscopy and RCM interpretation appear to have been conducted by same observer with no indication of blinding **Diagnostic threshold:** Not reported; no details **Diagnosis based on:** Single observer; 1 of 3 examiners **Observer qualifications:** Dermatologist. **Experience in practice:** Not described **Experience with index test:** High experience/'Expert' users; three dermatologists with expertise in RCM Any other detail All of the lesions were imaged with a digital camera (Canon PowerShot G10; Canon, Tokyo, Japan) and a high-resolution dermatoscope dermatoscope (DermLite Photo; 3Gen LLC, Dana Point, CA, U.S.A.). **Reflectance confocal microscopy (RCM)** Segura algorithm used. RCM-VivaScope Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only; dermoscopy and RCM intepretation appear to have been conducted by same observer with no indication of blinding **Diagnostic threshold:** > -1(The presence of two protective criteria in the basal layer with a score of -1 was considered (i) edged papillae and (ii) presence of typical cells in the basal layer; and the presence of two risk criteria with a score of 1 was also considered: (i) presence of round pagetoid cells in upper layers of the epidermis; and (ii) presence of the nucleated cells found within the dermal papillae. A threshold score >-1 was used to obtain a diagnosis of melanoma) **Diagnosis based on:** Single observer; 1 of 3 examiners **Observer qualifications:** Dermatologist **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users **Other detail:** In vivo confocal microscopy was performed with a commercially available reflectance confocal microscope (Vivascope 1500; Caliber Imaging and Diagnostics, Rochester, NY, U.S.A.), which uses a near-infrared laser at a wavelength of 830 nm with a maximum power of 35 mW

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology and clinical follow-up of one year **Details:** Histology of excision: 264; follow-up: 79 **Target condition (Final diagnoses):** Melanoma (in situ and invasive, or not reported): 92; BCC: 12; Benign naevus: 107; other (including sebhorrheic keratosis and actinic keratosis: 53); plus 79 followed up with no histological classification .
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	**Excluded participants:** Following the use of dermoscopy, 343 of the lesions classified as equivocal would eventually have been excised. After the addition of RCM, 77% of lesions (264/343) were judged as suggestive of malignancy according to the criteria followed in the study, and therefore were excised. The 79 lesions without criteria of malignancy upon RCM examination were scheduled for clinical or digital follow-up; these were not included in accuracy calculations by the authors but data provided to allow their inclusion. **Time interval between index test(s) and reference standard:** Histology undertaken on the same day as RCM. Unclear time gap from dermoscopy.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias	
Comparative	**Time interval between index test(s):** Not specified but appears consecutive
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	No
Was the interval between application of the index tests less than one month?	Unclear
Are there any concerns that the test comparison could have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	No
Are there concerns that the test comparison differs from the review question?	High

Notes

Notes	—

Curchin 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective; Period of data collection Jan 2010 to May 2010 Country Australia
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Consecutive patients from dermatology department's minor excision booking list. **Setting:** Secondary (general dermatology) **Prior testing:** Selected for excision (no further detail) **Setting for prior testing:** Unspecified **Exclusion criteria:** None reported **Sample size (patients):** No. included: 42 **Sample size (lesions):** No. included: 50 **Participant characteristics:** None reported **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM)** RCM-VivaScope Vivascope 1500 RCM score Used RCM score and LM score for suspected lentigo maligna of the face (Guitera 2010) **Method of diagnosis:** In person **Prior test data:** Dermoscopy "dermoscopic and RCM images were aligned over the top of each other so that correlation between the two could be made" **Diagnostic threshold:** RCM score: ≥ 3; LM score for suspected lentigo maligna of the face (Guitera 2010); threshold NR **Diagnosis based on:** Single observer; Number of examiners 1? **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Low experience / novice users; analysis was performed by a novice to RCM analysis after completing a RCM analysis course in Modena, Italy. **Other detail** Macroscopic images were obtained using a 14.7 megapixeldigital camera (Canon Power Shot G10, Canon, Tokyo,Japan). A dermoscopic image was taken using the dermoscopic camera attached to the Vivascope 1500 RCM System. RCM images were then captured using the Vivascope 1500 (Lucid Inc, Rochester, NY, USA).

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** No. patients/lesions: Disease positive: 21; Disease negative: 29 **Target condition (Final diagnoses)** Melanoma (invasive): 12; Melanoma (in situ): 1; BCC: 9; cSCC: 6 (includes SK and/or AK); 'Benign' diagnoses: 23
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Time interval to reference test: patients asked to come to the clinic (for imaging) 1h prior to their scheduled surgery.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Farnetani 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series series of cases consecutively and retrospectively selected by an expert dermoscopist for a web-based inter-observer reliability study **Data collection:** Retrospective image selection / Prospective interpretation Period of data collection: not reported Country: Italy (lesion image acquisition); Observers were located in the US (3), Europe (4), Australia (1) and Israel (1).
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Diagnostically equivocal lesions excised due to clinical or dermoscopic suspicion of melanoma, where a specific clinical and dermoscopic diagnosis could not be rendered with certainty. Lesions selected by an expert dermoscopist blinded to final diagnosis **Setting:** Secondary (general dermatology) All included RCM images were collected at the Department of Dermatology of the University of Modena and ReggioEmilia (Modena, Italy), **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** Poor quality index test image; No additional selection criteria were considered in case selection **Sample size (patients):** No. included: NR **Sample size (lesions):** No. included: 100 **Participant characteristics:** None reported **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Reflectance confocal microscopy (RCM):** No algorithm. Vivascope 1500 **Method of diagnosis:** Confocal images (remote) 3 RCM mosaic images presented per lesion **Prior test data:** Dermoscopy "Each case for evaluation had a high-resolution dermoscopic image obtained with a dermoscopic lens that was attached to a digital camera"; "No additional clinical information (eg, age and melanoma or lesion history) was provided to evaluators." **Diagnostic threshold:** Evaluators completed a 'pattern description' (presence/absence of a number of RCM features) and gave an overall diagnosis of malignant (melanoma or BCC) or benign; no specific threshold used. **Derivation aspect to study:** Discriminant analysis used to identified RCM features independently associated with malignancy, melanoma and BCC. Three of 6 discriminatory RCM features were more frequently observed in melanoma: the presence of pagetoid cells, the presence of atypical cells at the DEJ, and irregular epidermal architecture; 3 of 6 discriminatory RCM features were more frequently observed in BCCs: basaloid cord–like structures, presence of ulceration, and a specific DEJ pattern. Accuracy was not estimated for combinations of these particular features **Diagnosis based on:** Results presented for each of 9 observers and for majority diagnosis; i.e. consensual diagnosis by ≥5 of 9 evaluators. Also present average across 9 observers and across 6 more experienced and 3 less experienced observers. Number of examiners: 9. Fifteen individuals were invited to participate, 9 of whom agreed. Between June 15, 2010, and August 24, 2010, participants were asked to evaluate 10 cases per week for 10 consecutive weeks. **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** Low experience/novice users: 3 with < 3 years RCM experience High experience/'Expert' users: 6 with ≥ 3 years RCM experience

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Unclear
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** none reported No. patients/lesions: Disease positive: 35 Disease negative: 65 **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 20; BCC: 15 Sebhorrheic keratosis: 7; melanocytic nevi 55 ; actinic keratoses 3.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: Excised lesions only included Time interval to reference test: not reported Time interval between index test(s): N/A
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Unclear risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Ferrari 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection:** 2010 **Country**: Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanocytic lesions with equivocal clinical and/or dermoscopic features that underwent excision and had a complete set of dermoscopy and RCM images with histopathology report. Only dermoscopically featureless (retrospectively scoring 0-2 on 7-point checklist) or equivocal lesions (those scoring 3-4 on dermoscopy 7-point checklist) were included in RCM evaluation. **Setting:** Secondary (general dermatology) **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** non-melanocytic appearance; unequivocal appearance - 90 ‘positive-clear cut’ lesions (scoring 5 or more on 7-point checklist) were excluded from RCM evaluation; poor quality index test image "Only lesions with high quality dermoscopic images, a complete set of confocal images and histopathology report available were included in the study"; Other characteristic: incomplete histopathathology report. **Sample size (patients):** No. included: NR **Sample size (lesions):** No. eligible: 322 / No. included: 322* for dermoscopy; 232 for RCM (*232 for each test included in this review) **Participant characteristics:** None reported **Lesion characteristics:** Thickness/depth - Overall mean 1.05 +/16 mm, range 0–10 mm (70 melanomas); Those scoring 0-2 on 7-point checklist: mean 0.18 +/0.42 mm; range 0–0.94 mm) (6 melanomas)Those scoring 3-4 on 7-point checklist: mean 0.36 +/-0.42, range 0-1.4mm (17 melanomas)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** 7-point checklist **Method of diagnosis:** Dermoscopic images **Prior test data:** lesion site and age provided; dermoscopy and RCM interpretation appear to have been conducted by same observer with no indication of blinding **Diagnostic threshold:** All thresholds reported. Data extracted using standard threshold ≥ 3 **Diagnosis based on:** Single observer; Number of examiners 1 of 3 **Observer qualifications:** Dermatologist. All the images were interpreted independently by one of the three dermatologists with expertise in RCM **Experience in practice:** Not described **Experience with index test:** High experience /'Expert' users; three dermatologists with expertise in RCM Any other detail All of the lesions were imaged with a digital camera (Canon PowerShot G10; Canon, Tokyo, Japan) and a high-resolution dermatoscope dermatoscope (DermLite Photo; 3Gen LLC, Dana Point, CA, U.S.A.). # **Reflectance confocal microscopy (RCM).** No algorithm (presence of significant characteristics); criteria taken from Pellacani (Two step) - four features described as 'melanoma clues', referenced to Pellacani 2012. Final criteria tested on data and only those predictive used. RCM-VivaScope Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** Dermoscopy "Dermoscopic and confocal microscopic images were evaluated, in blind from histological diagnosis, by a dermatologist trained in dermoscopy and RCM." **Diagnostic threshold:** 2x2 data for chosen qualitative threshold For featureless lesions (score 0 to 2 on dermoscopy 7PCL), presence of at least one of: • ≥ 5 round pagetoid cells • architectural disorder. • For equivocal lesions (score 3 to 4 on dermoscopy 7PCL), presence of at least one of: • any number of round pagetoid cells • five or more atypical cells at the junction **Derivation aspect to study:** Previously published RCM parameters demonstrated useful for melanoma detection were selected. Evaluated confocal features were as follows: • presence of pagetoid cells, • cell shape (roundish or dendritic) and number (< 5 or > 5 cells per mm2), • overall DEJ architecture (ringed, meshwork, clods and non-specific pattern); • architectural disorder (irregular alternation of different RCM patterns, non-edged papillae extended over the 10% of lesion, and/or angled filaments/dendrites crossing the papillae), • presence of cytological atypia (> 5 cells per mm2) and • atypical nucleated cells arranged in nests Selection of characteristics indicative of skin cancer: Logistic regression Characteristics selected: as above **Diagnosis based on:** Consensus (3 observers) Number of examiners 3 **Observer qualifications:** Dermatologists **Experience in practice:** High/Expert **Experience with index test:** High/Expert **Other detail** Confocal imaging was performed with near-infrared reflectancemode confocal laser scanning microscope (Vivascope1500 ; MAVIG GmbH, Munich, D)

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** not further described No. patients/lesions: 232 out of originally selected 322; Disease positive: 23 Disease negative: 209 **Target condition (Final diagnoses):** Melanoma (in situ or invasive): 23 Benign nevus: 195; Spitz nevus 14;
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 90 ‘positive-clear cut’ lesions scoring 5 or more were excluded from RCM evaluation Time interval to reference test: Images taken 'before excision'
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias	
Comparative	Dermoscopy and RCM interpretation appear to have been conducted by same observer with no indication of blinding
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Unclear
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	No
Are there concerns that the test comparison differs from the review question?	High

Notes

Notes	—

Figueroa Silva 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection/Prospective interpretation **Period of data collection** January 2010 and February 2015 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** All pigmented lesions with a clear-cut dermoscopy island (DI) and available dermoscopic and RCM images were included **Setting:** Secondary (general dermatology) **Prior testing:** Dermatoscopic suspicion in all cases **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: not reported/ No. included: 61 **Sample size (lesions):** No. eligible: 1964 pigmented lesions / No. included: 63 **Participant characteristics:** mean age 44.1 (SD=14.8); % Male 43% **Lesion characteristics:** Lesion site - trunk: 37 lesions (60%)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM)** No algorithm (observer diagnosis) RCM-VivaScope Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** Dermoscopic image provided but blinded to histology and clinical information **Diagnostic threshold:** Melanoma or not based on pattern analysis. RCM mosaics were evaluated for the presence/absence of: cobblestone pattern, pagetoid cells, architecture type (ringed, meshwork or clod prevalent pattern at DEJ, regular/irregular) and atypical cells at the DEJ. All RCM criteria were evaluated on both the DI and the rest of the lesion **Diagnosis based on:** Single observer (n = 1). One investigator reviewed all RCM images and rendered a diagnosis; two other investigators separately reviewed the dermoscopic images according to four DI patterns. **Observer qualifications:** Not reported - probably dermatologist given setting **Experience in practice:** Not described **Experience with index test:** Not described **Other detail:** Dermoscopic images had previously been collected by using a digital camera (Canon Powershot; Canon, New York, NY, USA) equipped with a contact, nonpolarized dermatoscope (DermLite Photo 3Gen, San Juan Capistrano, CA, USA) using a 20-fold magnification. RCM images were acquired with a near-infrared, reflectance mode, confocal microscope (VivaScope1500 MAVIG GmbH, Munich, Germany). A minimum of three mosaics were obtained per lesion at three different skin level (superficial epidermal layers, dermo-epidermal junction (DEJ) and papillary dermis) as described elsewhere (Debarbieux 2013).

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis plus follow up **Details:** Histology (not further described): Disease positive: 27; Disease negative: 19 Clinical FU plus histology of suspicious lesions: Lesions were followed up on the basis of original RCM interpretation, i.e. at time of patient presentation. All lesions would have been excised on basis of dermoscopy alone; Length of FU: ≥ 1 year (mean 22 months); No. patients: 17 lesions (47% of all disease negative) **Target condition (Final diagnoses)** Melanoma (invasive): 8; Melanoma (in situ): 19 Benign naevus: 36
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: not reported Time interval to reference test: not reported Time interval between index test(s): N/A
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	Yes
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Guitera 2009a (Modena)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series (random sample of 50% of benign lesions included to increase the prevalence of melanoma) **Data collection:** Prospective **Period of data collection** Sept 2004 Aug 2007 **Country** Italy and Australia; NB data have been separated by country for the purposes of this review due to mixed use of imaged based and in-person dermoscopy interpretation according to country. Guitera 2009a (Modena) reports data for lesions recruited in Modena, Italy * The dataset also overlaps Pellacani 2007 which reports data for RCM only but at alternative RCM score thresholds.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanocytic lesions suspicious of melanoma based on dermatoscopic diagnostic criteria or lesion change; only 50% of observed benign lesions included **Setting:** Secondary (general dermatology). **Prior testing:** Clinical and/or dermatoscopic suspicion or changes on digital monitoring **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** lesions on soles/palms excluded; Lentigo maligna excluded; lesions used in previous assessments or RCM model development **Sample size (patients):** No. included: 195 **Sample size (lesions):** No. eligible: 195 **Participant characteristics:** Median age : 42 (7-88yrs); IQR 32, 59 yrs; Male: 54.3% **Lesion characteristics:** Pigmented: 92%; Non-pigmented: 8% (included amelanotic lesions or those with tan, light gray, or pale blue pigment only); Lesion thickness/depth: median 0.65mm (IQ 25, 75: 0.23, 1.01)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy:** Pattern analysis **Method of diagnosis:** In person; dermoscopy diagnosis made at time of first consultation, prior to RCM **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** Not reported **Diagnosis based on:** Single observer (n = 1). **Observer qualifications:** Dermatologist (described as Modena expert based in Dermatology Dept) **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users 'Expert'; no further details **Other detail:** hand-held dermoscope (Delta 10, Heine, Herrsching, Germany). **Reflectance confocal microscopy (RCM):** Pellacani RCM score RCM-VivaScope Vivascope 1000 and Vivascope 1500, Lucid Inc., Henrietta, NY **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only were provided. Confocal images from Modena were scored by PG (located inSydney) retrospectively and blinded to dermoscopy and pathological diagnosis, but not to information of site and age. **Diagnostic threshold:** Six diagnostic features scored: non-edged papillae and cytological atypia at the dermal-epidermal junction scored 2each; round pagetoid cells intraepidermally, widespread pagetoid infiltration in the epidermis, nucleated cells found within the dermal papillae, and cerebriform nests in the dermis scored 1 each. Total score >3 indicated MM. **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** NR; presumed dermatologist based on study setting and expert nature of observers **Experience in practice:** NR; based on study setting **Experience with index test:** NR, but both observers co-authored studies developing RCM **Other detail** Some differences between Vivascope 1000 and Vivascope 1500 exist. "The former is a more cumbersome instrument, as 4 mm images required laborious reprocessing. Furthermore,single capture images were slightly smaller in size, however,showing a similar quality with respect to the Vivascope 1500."

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** None provided. Disease positive: 79; Disease negative: 116 **Target condition (Final diagnoses)** Melanoma (invasive): 61; Melanoma (in situ): 18 Benign naevus: 94; Spitz nevus 22
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: none reported Time interval to reference test: imaged prior to biopsy Time interval between index test(s): imaged prior to biopsy
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias	
Comparative	Confocal images from Modena were scored in Sydney retrospectively and blinded to dermoscopy but not age and lesion site
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	Unclear
Are there concerns that the test comparison differs from the review question?	Unclear

Notes

Notes	—

Guitera 2009b (Sydney)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Sept 2004 Aug 2007 **Country** Italy and Australia NB data have been separated by country for the purposes of this review due to mixed use of imaged based and in-person dermoscopy interpretation according to country. Guitera 2009b (Sydney) reports data for lesions recruited in Sydney, Australia * The dataset also overlaps Pellacani 2007 which reports data for RCM only but at alternative RCM score thresholds.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanocytic lesions suspicious of melanoma based on dermatoscopic diagnostic criteria or lesion change **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) Australia Melanoma Diagnostic centre **Prior testing:** Clinical and/or dermatoscopic suspicion or changes on digital monitoring **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** lesions on soles/palms excluded; Lentigo maligna excluded; lesions used in previous assessments or RCM model development; 25 lesions out of 156 were rejected for poor quality dermoscopy image, **Sample size (patients):** No. included: 156 **Sample size (lesions):** No. eligible: 156; No included: 131 **Participant characteristics:** Median age : 52 (19-90yrs); IQR 40, 63 yrs; Male: 59% **Lesion characteristics:** Pigmented: 75%; Non-pigmented: 25% (included amelanotic lesions or those with tan, light gray, or pale blue pigment only); Lesion thickness/depth: median 0.40mm (IQ 25, 75: 0, 0.84)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** Pattern analysis **Method of diagnosis:** Dermoscopic images **Prior test data:** lesion site and age available **Diagnostic threshold:** Not reported **Diagnosis based on:** Single observer (n = 1); Dermoscopy diagnosis of Sydney lesions was made retrospectively on the images in a random order, blinded to RCM and pathological diagnosis but not to information of site and age, by a Modena expert (GP) using pattern analysis (Pehamberger 1993). **Observer qualifications:** Dermatologist; Not clearly reported, but described as Modena expert based in Dermatology Dept **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users 'Expert'; no further details **Other detail:** high-resolution digital oil immersion dermoscopy camera (Sentry, Polartechnics Ltd, Sydney, NSW, Australia). **Reflectance confocal microscopy (RCM):** Pellacani RCM score Vivascope 1000 and Vivascope 1500, Lucid Inc., Henrietta, NY **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only. Confocal images from Sydney were scored by GP (located in Modena), retrospectively and blinded to dermoscopy and pathological diagnosis, but not to information of site and age. **Diagnostic threshold:** Six diagnostic features scored: non-edged papillae and cytological atypia at the dermal-epidermal junction scored 2each; round pagetoid cells intraepidermally, widespread pagetoid infiltration in the epidermis, nucleated cells found within the dermal papillae, and cerebriform nests in the dermis scored 1 each. Total score >3 indicated MM. **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** NR - Dermatologist assumed based on study setting and expert nature of observers **Experience in practice:** NR; based on study setting **Experience with index test:** NR, but both observers co-authored studies developing RCM **Other detail** Some differences between Vivascope 1000 and Vivascope 1500 exist. "The former is a more cumbersome instrument, as4 4 mm images required laborious reprocessing. Furthermore,single capture images were slightly smaller in size, however,showing a similar quality with respect to the Vivascope 1500."

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** None provided. Disease positive: 44; Disease negative: 87 **Target condition (Final diagnoses):** Melanoma (invasive): 28; Melanoma (in situ): 16 Benign naevus: 84; Spitz nevus 3
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 25 lesions out of 156 were rejected for poor quality dermoscopy image, blinded to the diagnostician Time interval to reference test: NR Time interval between index test(s): NR
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias	
Comparative	Confocal images from Sydney were scored by GP (located in Modena), retrospectively and blinded to dermoscopy and pathological diagnosis, but not to information of site and age.
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	Unclear
Are there concerns that the test comparison differs from the review question?	Unclear

Notes

Notes	—

Guitera 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported **Period of data collection** NR **Country** Australia and Italy **Test set derived:** randomly split into training and test sets
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Consecutive Patients presenting or found with suspicious lesions, including all macules of the face and neck suspicious for lentigo maligna, and which would be subjected to biopsy or excision to rule out an epithelial tumor or an MM following conventional clinical and dermoscopy diagnosis and with lesion location amenable to RCM; described as predominantly melanocytic or suspicious for BCC **Setting:** Mixed, lesions recruited from Modena (general dermatology) and Sydney (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical and/or dermatoscopic suspicion **Exclusion criteria:** Location/site of lesion keratotic, sole, and palm lesions were excluded **Sample size (patients):** No. eligible: 663 **Sample size (lesions):** No. eligible: 710 / No included: 356 in test set, 253 melanocytic **Participant characteristics:** Median age (full sample): 53, IQR 39 to 66 (for full sample), Range: 6-90; Male: 354; 53.4% (of full sample) **Lesion characteristics:** Not reported
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM):** RCM score and Segura algorithm; also derived own independently significant features for MM and BCC. Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only "RCM features were described by two expert observers (GP and PG), blinded from any clinical information, dermoscopy, and clinical aspects, but not for the location and age of the patient" **Diagnostic threshold:** Pellacani RCM score (Pellacani 2007): >3 and >2; Segura (Segura 2009) "calculated with a threshold of zero"; own new two step model identified 7 independently significant features for MM (assume presence of any one indicated T+): - cerebriform nests,- atypical cobblestone pattern with small nucleated cells in the epidermis, - marked cytological atypia, and - pagetoid cells, and- disarranged epidermal layer with no honey comb - Large inter-papillae spaces filled with honeycomb- Dense nest. 8 independently significant features for BCC: - Polarized in the honeycomb - Linear telangiectasia-like horizontal vessels- Basaloid cord or nodule - Epidermal shadow - Convoluted glomerular-like vessels - Non-visible papillae - Cerebriform nests- Disarray of the epidermal layer **Derivation aspect to study:** Lesion characteristics assessed A series of 48 features, corresponding to previous observations (Pellacani 2007; Guitera 2009), and new descriptors were considered at three different depth levels. Descriptions and definitions provided. Selection of characteristics indicative of skin cancer by multivariate discriminant analysis performed on the training set **Diagnosis based on:** Single observer (n = 2) **Observer qualifications:** Dermatologist **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** not further described; full sample Disease positive: 335 / disease negative 375 **Target condition (Final diagnoses):** Test set only Melanoma (in situ and invasive, or not reported): 105; BCC: 52; cSCC: 9 Benign nevus 132; SPitz nevus 16; actinic keratosis 8; 31 benign macule of the face and 3 dermatofibroma
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	No exclusions Imaged prior to biopsy
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Koller 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective (retrospective image selection / prospective interpretation for training set) **Period of data collection:** July 2007 to June 2008 **Country** Austria Training set lesions were evaluated retrospectively (also reported in Gerger 2005)
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanocytic skin lesions recruited from department of dermatology; lesions were not selected according to presence or absence of particular RCM features **Setting:** Secondary (general dermatology) **Prior testing:** Unclear; some assessment conducted as only melanocytic lesions included **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** non-melanocytic appearance **Sample size (patients):** No. included: NR **Sample size (lesions):** No. included: 92 (test set only) **Participant characteristics:** None reported **Lesion characteristics:** Ulcerated : 1/24 melanomas; mean thickness/depth: 0.75mm (SD 1.06; range in situ to 3.7 mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM):** No algorithm overall diagnosis and development of new CAD model using training set of lesions Vivascope 1000 **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used observer was blinded with regard to the clinical or histopathological diagnosis **Diagnostic threshold:** Human observer: diagnosis based on 'expert experience'; RCM characteristics not reported CAD interpretation: 30.47% (set for sensitivity of 100%) **Derivation aspect to study:** Lesion characteristics assessed: In each RCM image, a set of 39 analysis parameters were measured. Selection of characteristics indicative of skin cancer classification: procedure was performed by the CART (Classification and Regression Trees) analysis software from Salford Systems (San Diego, CA, USA). Characteristics selected N/A **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Independent clinical dermatologist interpreted RCM images but image acquisition not described in detail. **Experience in practice:** Not described **Experience with index test:** High experience /'Expert' users

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Unclear
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis plus expert diagnosis **Details:** Histology (not further described): Disease positive: 24 / Disease negative: 37 Expert opinion based on unequivocal clinical and conventional dermoscopic criteria: Disease positive: 0 / Disease negative: 31 **Target condition (Final diagnoses)** Melanoma invasive: 18; Melanoma in situ: 6 Benign naevus: 68
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	No
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Suspicious lesions were excised after clinical, dermoscopic and confocal examination and subjected to standard histopathological assessment.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Langley 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** February 2002 to May 2005 **Country** Canada
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with suspicious pigmented lesions scheduled for biopsy due to clinical suspicion of malignancy determined by clinical appearance or a history of change in the lesion. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** non-pigmented; poor quality index test image; lesion site or previous diagnostic biopsy **Sample size (patients):** No. eligible: 127 / No. included: 125 **Sample size (lesions):** No. eligible: 127 / No. included: 125 **Participant characteristics:** Mean age: 44.2y (16 to 84) **Lesion characteristics:** median thickness 0.62 mm 0.20 mm to 7.92 mm)
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Dermoscopy** Pattern analysis **Method of diagnosis:** In person **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** Qualitative pattern analysis; no further details **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Not reported likely dermatologist **Experience in practice:** Not described **Experience with index test:** Not described **Any other detail:** dermoscopy was performed and a diagnosis rendered using the pattern analysis method. A clinical photograph was obtained with a Nikon D1X digital camera, and with a Nikon F401s camera with a 60-mm lens with dermatophot attachment **Reflectance confocal microscopy (RCM):** No algorithm - selected characteristics based on the criteria described in authors' initial series (Langley 2001) Vivascope 1000 **Method of diagnosis:** In person **Prior test data:** "Clinical, dermoscopic and confocal examinations were conducted sequentially by a single reviewer (R.L.)." **Diagnostic threshold:** Any one of: epidermal disarray with loss of the normal honeycomb pattern; a grainy image; pagetoid cells in the epidermis; complex branching dendrites or dendritic cells; atypical and pleomorphic refractile cells, and the presence of bright, highly refractile particles. **Diagnosis based on:** Single observer (n = 1). A single observer with experience in CSLM performed the imaging and examined all images in real-time (R.L.) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** High experience /'Expert' users

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Definitive diagnosis was made by a dermatopathologist. Disease positive: 37 / Disease negative: 88 **Target condition (Final diagnoses)** Melanoma (invasive): 22; Melanoma (in situ): 15 Benign naevus: 88
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: Two patients were excluded from the database due to technical difficulties with the imaging. Interval: When CSLM imaging was complete, the lesions were removed by excisional biopsy.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias	
Comparative	Clinical, dermoscopic and confocal examinations were conducted sequentially by a single reviewer
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	No
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	Yes
Are there concerns that the test comparison differs from the review question?	Low concern

Notes

Notes	—

Longo 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** NR **Country** Italy
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Clinically nodular lesions (defined as cutaneous palpable/superficial seated lesions and not subcutaneous ones) that underwent excision **Setting:** Department of Dermatology, University of Modena and Reggio Emilia and Dermatology and Skin Cancer Unit, Arcispedale S. Maria Nuova IRCCS, Reggio **Prior testing:** Selected for excision (no further detail) **Exclusion criteria:** None reported **Sample size (patients):** No. included: 140 **Sample size (lesions):** No. included: 140 **Participant characteristics:** Mean age: 50 years (SD 19.7); 45.7% male **Lesion characteristics:** 'most' lesions on the trunk; dermatofibroma mainly located on extremities; mean thickness 16mm (SD 1.82); 23 'pure' nodular melanomas
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM):** No algorithm (correct diagnosis of each histological category); also identifies independently significant features [cannot include data for MM as does not give breakdown of nodular melanoma and melanoma metastases; no response to author contacted] VivaScope Model NR; likely Vivascope 1500 given publication date **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used; blinded to dermoscopic image **Diagnostic threshold:** 'RCM pattern analysis' (referenced to Longo 2011; Pellacani 2007; amongst others). Multivariate analysis id 3 positive independent significant features for MM+Mets [- widespread pagetoid distribution (graded as focal, localized, widespread); - many atypical cells; - cerebriform nests] and 4 positive independent significant features for BCC [- tumour islands (dark silhouettes or tightly packed basaloid islands); - cauliflower architecture; - bright filaments within the tumour islands; and - presence of bright collagen.] **Derivation aspect to study:** Each of 36 criteria were also scored for presence or absence. MM - Epidermis: Honeycombed or cobblestone pattern; Disarray of epidermis; Pagetoid spread; Pagetoid cell shape; Pagetoid cell distribution Dermo epidermal junction: Nonspecific architecture; Cytological atypia (moderate, severe); Dermis: Sheet-like structures; Dermal nesting; Prominent vascularity (enlarged vessels covering more than 50% of the lesion surface); Inflammatory infiltrate covering more than 50% of the lesion surface BCC - Epidermis: Honeycombed or cobblestone pattern; Disarray of epidermis; Ulceration or erosions; Dermo epidermal junction: Cauliflower architecture; Nonspecific architectureDermis: Dark silhouettes; Tightly packed cells; Bright filaments within tumour islands; Prominent vascularity (enlarged vessels covering more than 50% of the lesion surface); Inflammatory infiltrate (covering more than 50% of the lesion surface. SCC - Epidermis: Honeycombed or cobblestone pattern; Disarray of epidermis; Ulceration or erosions; Scales; Keratin inclusion/plugsDermis: Prominent vascularity (enlarged vessels covering more than 50% of the lesion surface); Inflammatory infiltrate (covering more than 50% of the lesion surface) Selection of characteristics indicative of skin cancer : Univariate and then multivariate discriminant analysis was also performed to identify independently significant RCM criteria for NM+Mets vs. all other diagnoses, BCC vs. all other diagnoses, SCC vs. all other diagnoses. **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Dermatologist **Experience in practice:** 5 years' experience in RCM and therefore presumably in practice **Experience with index test:** 5 years' experience in RCM

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Unclear
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** (not further described); Disease positive: 23 nodular melanoma Disease negative: 117 **Target condition (Final diagnoses)** Melanoma (invasive): 23 nodular; BCC: 28; cSCC: 6; Other malignant: 9 melanoma metastases Benign naevus: 25 (14 compound, 8 intradermal, 3 blue naevi); 7 Spitz naevi; Sebhorrheic keratosis: 14; 5 vascular and 6 other benign lesions;
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 8 not evaluable and 3 'nonspecific' RCM results reported (appear to be excluded from derivation of independently significant characteristics) Not evaluable: lesions where all the three levels (epidermis, DEJ and upper dermis) were not explorable for any reason that hampered the collection of quality images or the exploration of DEJ/superficial dermis. 2 Nonspecific: lesions where a diagnosis could not be formulated, despite the possibility of exploring all three levels, because of the impossibility of recognizing diagnostic features with enough confidence."
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Unclear risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Lovatto 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** January 2006 to January 2009 **Country** Spain
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Consecutive high risk patients with atypical melanocytic lesions excised because of change following sequential digital dermoscopy follow-up. Required to have at least two of the following characteristics: >100 melanocytic naevi; high number of atypical melanocytic lesions under dermoscopy; personal or familial history of melanoma; or, predisposing genetic mutations for melanoma (i.e. CDKN2A mutation-carriers, xeroderma pigmentosum). **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Changes on digital monitoring FU with total body photography and digital dermoscopy **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Unequivocal appearance/diagnosis **Sample size (patients):** No. included: 51 **Sample size (lesions):** No. included: 64 **Participant characteristics:** Mean age: 42y (25-69), SD 11.7; Male: 47%; History of melanoma/skin cancer 25%; Family history of melanoma 24%; Genetic predisposition 4% (CDKN2A mutation); 20% with both personal and familial history of melanoma. Fitzpatrick phototype I to II 71%; Type III to IV 15; 29% **Lesion characteristics:** Mean total dermoscopy score at follow-up (ie. on excision): 5.44 for neavus group and 5.55 for melanoma group. Lesio thickness 5 ≤ 1 mm (3 with Breslow 0.5 mm, and one each at 0.6 and 0.7 mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM):** RCM score; Segura algorithm Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used; blinded to dermoscopy and histopathologic diagnosis **Diagnostic threshold:** Segura algorithm (Segura 2009) includes four diagnostic features: two protective criteria in the basal layer with a score of -1 these are i) edged papillae and (ii2) typical cells in the basal layer; and two risk criteria with a score of +1, these are (i) roundish pagetoid cells in upper layers of the epidermis and (ii) nucleated cells within the dermal papillae. Melanoma must be considered when the total score is ≥0. RCM score (Pellacani 2007): two major criteria scoring two points; these are (i) presence of cytologic atypia and (ii) non-edged papillae at basal layer and four minor criteria scoring 1 point; these are (i) presence of roundish cells in superficial layers spreading upward in a pagetoid fashion (ii) pagetoid cells widespread throughout the lesion, (iii) cerebriform clusters in the papillary dermis and (iv) nucleated cells within dermal papilla. Score ≥ 3 **Diagnosis based on:** Unclear; could be consensus or average (n = 3) **Observer qualifications:** Not reported - Likely dermatologists (based in Dept Dermatology) **Experience in practice:** Not described **Experience with index test:** Not described **Other detail**Any other detail (Vivascope 1500; Lucid Inc, Henrietta, NY, USA).

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** consensus of 3 skilled histopathologists with experience in the field of melanocytic skin lesions; reviewed at the dermatopathology conference. Disease positive: 13; Disease negative: 51 **Target condition (Final diagnoses)** Melanoma (invasive): 5; Melanoma (in situ): 8 Benign naevus: 51 melanocytic naevus with variable degree of atypia
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: NR Time interval to reference test: consecutive; Images taken 'before excision' Time interval between index test(s): N/A
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	Yes
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Pellacani 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** NR **Country** Italy and Australia **Test set derived** For multivariate analysis, the study sample was randomly divided into a training set and a test set, each comprising 50% of the lesions. Data included relate to full sample. * The dataset also overlaps Guitera 2009 which reports data for dermoscopy as well as RCM; have only included Pellacani 2007 data related to alternative RCM score thresholds; not included in primary analysis
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** All melanocytic lesions excised to exclude melanoma, based upon dermoscopy, sequential digital monitoring, or history of change in standard clinical practice, were included **Setting:** Secondary (general dermatology) Italy; Specialist unit (skin cancer/pigmented lesions clinic) Australia **Prior testing:** Clinical and/or dermatoscopic suspicion; Changes on digital monitoring **Exclusion criteria:** lesions of palms and soles were not included; non-melanocytic appearance; lesions excised for cosmetic reasons or solely due to a patient request; lentigo maligna excluded **Sample size (patients):** No. included: 332 **Sample size (lesions):** No. included: 351; 156 from Australia and 195 from Italy **Participant characteristics:** Median age: 47.7 (IQR 35.9, 60.4); Male: 52% **Lesion characteristics: Lesion site -** Head/Neck: 15; Trunk: 68; abdomen and chest: 135 on the back;Upper limbs/shoulder: 50; Lower limbs/hip: 83. ≤ 1 mm thickness: 66% (62/136); 1.01-2.00 mm: 25% (23); 2.01-4.00 mm: 9% (8); median thickness 0.49mm (IQR: 0, 0.89 mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Reflectance confocal microscopy (RCM):** RCM score Also identifies features independently correlated with malignancy by means of discriminant analysis on the training set, unable to include as only AUC presented. Vivascope 1000s and Vivascope 1500s **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only **Diagnostic threshold:** Data presented for all RCM scores from ≥ 1 to ≥ 8; data extracted for ≥ 2, ≥ 3 and ≥ 4 (included here only for ≥ 2, ≥ 3). **Diagnosis based on:** Single observer (n = 2); one from the University of Modena evaluated the Sydney cases, and one from Sydney evaluated the Modena cases **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** High experience /'Expert' users **Other detail** Vivascope 1000s and Vivascope 1500s, Lucid Inc., Henrietta, New York

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** not further described; Disease positive: 136; Disease negative: 215 **Target condition (Final diagnoses)** Melanoma (invasive): 94; Melanoma (in situ): 42 Benign naevus: 215
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	RCM images were acquired before biopsy
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Pellacani 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Jan 1-March 31 2008 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanocytic lesions with equivocal clinical and/or dermatoscopic features **Setting:** Secondary (general dermatology) not mentioned in text, just in author institution details **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Secondary (general dermatology) [it is inferred that the patient was evaluated in the same unit] **Exclusion criteria:** non-melanocytic appearance; Unequivocal appearance/diagnosis; Disagreement between evaluators on tumour histological classification **Sample size (patients):** No. included: 62 **Sample size (lesions):** No. eligible: 64 /No. included: 60 **Participant characteristics:** None reported **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM)** Pellacani (Two step) Own new algorithm based on evaluation of a list of previously published parameters and some new descriptors (cites Pellacani 2009 and Pellacani 2009a, and Scope 2007); Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used "blinded from any clinical, dermatoscopic, or histopathologic information" **Diagnostic threshold:** (≥ 3 chars present, two at step 1 and one at step 2). Step 1: to identify dysplastic nevus - Presence of cytologic atypia (≥ 1 present) including - round pagetoid cells - atypical cells at DEJ. Presence of architectural atypia (≥ 1 present)- irregular junctional nests - short interconnections between junctional nests - nonhomogenous cellularity within junctional nests. Step 2: to identify melanoma from dysplastic nevus (≥ 1 present) - widespread (≥ 50% of lesional area) round pagetoid cells, - widespread (≥ 50% of lesional area) atypical cells at the DEJ, and - nonedged papillae (≥ 10% of the lesional area) **Derivation aspect to study:** Lesions were evaluated for a list of previously published parameters and for some new descriptors specifically introduced for this study. Selection of characteristics indicative of skin cancer: For multivariate analysis, binary logistic regression was performed for the identification of the independently significant features in distinguishing among nondysplastic nevi, dysplastic nevi, and MM. Stepwise forward selection and goodness-of-fit statistics were used to select the features and determine whether the model adequately described the data.A P value less than .01 was considered significant for the correlation tests, whereas a P less than .05 was used for the other statistical tests. **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Dermatologist **Experience in practice:** High experience or ‘Expert’ **Experience with index test:** High experience /‘Expert’ users **Other detail.** Any other detail RCM uses a low-power 830-nmlaser beam that generates horizontal sections of the skin of 1.0-um lateral resolution up to approximately200 um in depth.15 A minimum of 3 mosaics, with a maximum area of 8 3 8 mm,were obtained per lesion, one in the superficial epidermis (stratum granulosum/spinosum), one at the dermoepidermal junction (DEJ), and one in papillary dermis.

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Disease positive 14; Disease negative 46 **Target condition (Final diagnoses)** Melanoma (invasive): 10; Melanoma in situ 4 Benign: Severe dysplasia: 5; 7 showed mild dysplasia, 15 moderate; 19 nondysplastic nevi
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	**Excluded participants**: 4 lesions were excluded as dermatopathologists could not agree on pathology (in two cases discordance was for MM versus dysplastic nevus diagnosis, and in the other two between dysplastic and nondysplastic nevus) Time interval to reference test: Before excision, all lesions were recorded by means of digital dermatoscopy and RCM
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Pellacani 2014a (cons)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** January 2010 to December 2010 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients requesting a mole check or with suspicion of melanoma who were referred to pigmented lesion clinic and who were then found to have atypical lesions on dermoscopy. Those in whom diagnosis could not be determined on dermoscopy were referred for an 'outcome decision' (consultation group). Patients were referred on the basis of both urgent access (melanoma suspected in a single lesion by GP or other dermatologist) and scheduled access (referred for dermoscopy and total body examination). **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Dermatoscopic suspicion in all cases. All patients underwent dermoscopy in the PLC; those with dermoscopically atypical lesions were referred for RCM, either to document a lesion already selected for excision (documentation group, reported in Pellacani 2014b (doc)) or for an 'outcome decision' (consultation group), i.e. diagnosis could not be determined on dermoscopy **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Clinically and/or dermatoscopically clear-cut epithelial tumours were not enrolled; Poor quality index test image - In nine cases RCM could not be performed (five RCM documentation and four RCM consultation) due to the presence of artefacts, hyperkeratosis, and/or ulcerations, impeding imaging. **Sample size (patients):** No. eligible: 1005 examined with dermoscopy; No. included: 252 referred for RCM consultation **Sample size (lesions):** No. eligible: NR; No. included: 308 for RCM documentation **Participant characteristics:** Median age 41.7 (IQR 31.9, 52.1); For all referred patients (n = 1005): 443 male (44%); Consultation group only: History of melanoma/skin cancer 23 (7%); Family history of melanoma 30 (10%). Fitzpatrick phototype I to II: 150 (49%); Type III to IV 116 (38%) **Lesion characteristics:** Lesion site (full sample) Head/Neck: 9%; Trunk: 59%; Upper limbs/shoulder: 12%; Lower limbs/hip: 20%
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM).** RCM score Vivascope 1500 **Method of diagnosis:** In person **Prior test data:** Patients were "referred to confocal unit"; confocal reader was blinded to the patient pathway and aware that lesions were dermoscopically atypical for 'RCM documentation' or for 'RCM consultation'. **Diagnostic threshold:** Not reported Pellacani 2005 cited **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described but 'confocal unit' described **Other detail** Any other detail Dermatoscopy examinations were conducted using the Dermlite HR (3Gen LLC, San Juan Capistrano, CA, U.S.A.). Lesions that were scheduled for digital monitoring were also acquired by means of FotoFinder (TeachScreen GmbH, Bad Birnbach, Germany) using 20-fold magnification.

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis plus FU and cancer registry follow-up Histology (not further described): 81 (consultation group) [overall dataset 292 excised (see Pellacani 2014a (cons)) Clinical FU: 227, 28 of which were subsequently excised (incl above) because of observed dermatoscopic changes (all benign). Most non excised lesions (89.4% 178/199) were followed up for 1 year; the others were lost at the 1-year follow-up. Cancer registry FU: Those lost to clinical follow-up were checked on the tumour registry; no melanomas were diagnosed in patients scheduled for follow-up after baseline examinations. **Target condition (Final diagnoses)** Melanoma (invasive): 13; Melanoma (in situ): 9; BCC: 19; 1 melanoma metastasis Clark naevus 71; Spitz nevus 5; solar lentigo, seborrhoeic keratosis or lichen planus-like keratosis 0; other benign 207 (8 with histological diagnosis (25 Clark naevi, two Spitz naevi and one benign nonmelanocytic lesion) and 199 benign on FU)
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 9 excluded due to RCM failure
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	Yes
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Pellacani 2014b (doc)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** January 2010 to December 2010 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients requesting a mole check or with suspicion of melanoma who were referred to pigmented lesion clinic and who were then found to have atypical lesions on dermoscopy. Those in whom excision was required on dermoscopy were referred for RCM documentation (documentation group). Patients were referred on the basis of both urgent access (melanoma suspected in a single lesion by GP or other dermatologist) and scheduled access (referred for dermoscopy and total body examination). **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Dermatoscopic suspicion in all cases. All patients underwent dermoscopy in the PLC; those with dermoscopically atypical lesions were referred for RCM, either to document a lesion already selected for excision (documentation group, as reported here) or for an 'outcome decision' (consultation group, reported in Pellacani 2014a (cons)), i.e. diagnosis could not be determined on dermoscopy. **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Clinically and/or dermatoscopically clear-cut epithelial tumours were not enrolled; Poor quality index test image - In nine cases RCM could not be performed (five RCM documentation and four RCM consultation) due to the presence of artefacts, hyperkeratosis, and/or ulcerations, impeding imaging. **Sample size (patients):** No. eligible: 1005 examined with dermoscopy; No. included: 171 referred for RCM documentation **Sample size (lesions):** No. eligible: NR; No. included: 183 for RCM documentation **Participant characteristics:** Median age 41.2 (IQR 35, 63); For all referred patients (n = 1005): 443 male (44%); History of melanoma/skin cancer 8 (5%); Family history of melanoma 13 (8%). Fitzpatrick phototype I to II: 99 (58%); Type III to IV 72 (42%) **Lesion characteristics:** Lesion site (full sample) Head/Neck: 9%; Trunk: 59%; Upper limbs/shoulder: 12%; Lower limbs/hip: 20%
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM).** RCM score Vivascope 1500 **Method of diagnosis:** In person **Prior test data:** Patients were "referred to confocal unit"; confocal reader was blinded to the patient pathway and aware that lesions were dermoscopically atypical for 'RCM documentation' or for 'RCM consultation'. **Diagnostic threshold:** Not reported; Pellacani 2005 cited **Diagnosis based on:** Single observer (n = 1) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described but 'confocal unit' described **Other detail** Any other detail Dermatoscopy examinations were conducted using the Dermlite HR (3Gen LLC, San Juan Capistrano, CA, U.S.A.). Lesions that were scheduled for digital monitoring were also acquired by means of FotoFinder (TeachScreen GmbH, Bad Birnbach, Germany) using 20-fold magnification.

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histology alone for documentation group; 227 from consultation group were referred for follow-up (see Pellacani 2014a (cons)) **Target condition (Final diagnoses)** Melanoma (invasive): 13; Melanoma (in situ): 9; BCC: 19; 1 melanoma metastasis Clark naevus 121; Spitz nevus 8; solar lentigo, seborrhoeic keratosis or lichen planus-like keratosis 7; other benign 5 (haemosiderotic dermatofibroma, xanthogranuloma, viral wart and two nonspecific inflammatory dermatoses)
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 9 excluded due to RCM failure
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	Yes
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Pupelli 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective **Period of data collection** 2007-2011 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanomas <5 mm consecutively excised; plus 3 histologically proven small-diameter naevi per included melanoma **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) [from Author institution] **Prior testing:** Selected for excision (no further detail) All had undergone dermoscopy and RCM in order to be included **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** lesion size > 5 mm excluded; disagreement between evaluators on tumour histological classification **Sample size (patients):** No. included: 96 **Sample size (lesions):** No. included: 96 **Participant characteristics:** Mean age: MM 48 (IQR 17, 77); Naevi 41 (IQR 6, 82); Male: MM 54% / naevi 58% **Lesion characteristics:** Lesion site: Trunk: 62% naevi; Lower limbs/hip: 46% melanomas. Mean thickness 0.37 mm (SD 0.44 mm); Melanoma diameter in situ MM: 10 < 1 mm, 3 ≥ 1 mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** 7-point checklist **Method of diagnosis:** Dermoscopic images **Prior test data:** body site and age provided; RCM images may also have been available at time of image interpretation **Diagnostic threshold:** ≥ 3 **Diagnosis based on:** likely single observer (n = NR) **Observer qualifications:** Not reported likely dermatologist **Experience in practice:** Not described **Experience with index test:** Not described **Any other detail** Dermoscopic images were acquired by means of a polarized dermatoscope (DermLite FOTO; 3Gen Inc., San Juan Capistrano, CA, U.S.A.)." **Reflectance confocal microscopy (RCM):** No algorithm independently significant features Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** Lesion site and/or patient age only. "Dermoscopic and confocal microscopic images were evaluated – in blind from histological diagnosis, but not from the body site or the age of the patient." **Diagnostic threshold:** appears to be ≥ 1 characteristic present. 3 characteristics were identified as independently significant (presence of at least five pagetoid cells per mm2, tangled lines within the epidermis, and atypical roundish cells at the dermoepidermal junction). Sensitivity and specificity to allow 2x2 estimation were obtained from authors **Derivation aspect to study:** Lesion characteristics assessed. RCM parameters as published previously (all described). Selection of characteristics indicative of skin cancer multivariate analysis (logistic regression) **Diagnosis based on:** likely single observer (n = NR) **Observer qualifications:** Not reported likely dermatologist **Experience in practice:** Not described **Experience with index test:** Not described **Other detail**Any other detail Confocal imaging was performed with a near-infrared reflectance-mode confocal laser scanning microscope (Vivascope1500 ; Lucid Inc., Rochester, NY, U.S.A.). The instrument and acquisition methods have been describedelsewhere.16,18

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Disease positive: 24 / Disease negative: 72 **Target condition (Final diagnoses)** Melanoma (invasive): 13; Melanoma (in situ): 11 Benign naevus: 65 (29 junctional, 19 compound, intra-dermal, eight blue, four lentigo simplex) ; Spitz nevus 7.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: not reported Time interval to reference test: not reported Time interval between index test(s): not reported
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Unclear risk

Comparative

A. Risk of Bias	
Comparative	"Dermoscopic and confocal microscopic images were evaluated – in blind from histological diagnosis, but not from the body site or the age of the patient."
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	No
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	Unclear
Are there concerns that the test comparison differs from the review question?	Unclear

Notes

Notes	—

Rao 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported; appear to be prospective but not explicitly stated **Period of data collection** Jun 2010-Sep 2011 **Country** US
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Lesions removed for cosmetic or medical reasons (no further detail; 'teleconsultation setting' **Setting:** Secondary (general dermatology); Private (Based on author institutions) **Prior testing:** Not reported; unclear whether selection for excision was based on clinical assessment alone or including dermoscopy **Setting for prior testing:** Unspecified **Exclusion criteria:** Six cases were excluded due to "insufficient information" **Sample size (patients):** NR **Sample size (lesions):** No. eligible: 340; No. included: 334. 318/334 reported for Reader 1; 323/334 reported for Reader 2 **Participant characteristics:** None reported **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Reflectance confocal microscopy (RCM).** No algorithm; Overall observer diagnosis Vivascope 1500 **Method of diagnosis:** In person US (Reader 1; less experienced) Confocal images (remote) Modena, Italy; Reader 2 (more experienced) (*data used for primary analysis and QUADAS scoring) **Prior test data:** Clinical examination and/or case notes and dermoscopy "diagnosis was based on the dermoscopic image and confocal microscopy evaluation before excision." **Diagnostic threshold:** Not reported Observers gave diagnosis and excise decision (no further details) **Diagnosis based on:** Single observer (n = 2) **Observer qualifications:** Not reported Presume dermaologists **Experience in practice:** Not described **Experience with index test:** Low experience / novice users Reader 1 (US) had 1 year of experience at the beginning of the study High experience /'Expert' users Reader 2 (Italy) had over 9 years of experience with RCM. **Other detail** Images were sent via Vivanet (CaliberID, Rochester, NY), a Health Insurance Portability and Accountability Act-compliant server.15

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were sufficient details of diagnostic thresholds provided?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** not further described; Disease positive: 78; Disease negative: 256 **Target condition (Final diagnoses)** Melanoma (invasive): 8; Melanoma (in situ); 1; BCC: 27; cSCC: 42 Benign nevi 176; sebhorrheic keratosis 22; actinic keratosis 24; 23 other
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: 6 described as excluded because of insufficient information; 318/334 reported for Reader 1323/334 reported for Reader 2
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Segura 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series. Authors separately describe recruitment of 'possibly malignant' and clinically/dermoscopically benign but seem to be from same overall population **Data collection:** Prospective **Period of data collection** November 2005 to June 2006 **Country** Spain
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** All patients attending dermatology dept or melanoma unit with a lesion suggestive of malignancy (study participation did not affect the clinical decision or the excision schedule) and patients with lesions known to be clinically and dermatoscopically benign; only melanocytic included in 2x2 **Setting:** Mixed (Dermatology Department and the Melanoma Unit of the Hospital Clinic, Barcelona, Spain) **Prior testing:** Clinical and/or dermatoscopic suspicion **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 143 **Sample size (lesions):** No. eligible: 154 / No. included: 100 (melanocytic only) **Participant characteristics:** Mean age: 49.45 years; Male: 39.9%; 13 had personal or family history of melanoma; 'most' described as having dysplastic mole syndrome and 'most' with dermatoscopic changes recorded during follow-up examinations **Lesion characteristics:** Lesion site Head/Neck: 34 (22%); Trunk: 82 (53%); Lower limbs/hip: 22 (14%) head2 (1.3%) neck
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Reflectance confocal microscopy (RCM).** Segura Own new algorithm Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used "stored confocal images were evaluated afterward, without regard to clinical or dermatoscopic data" **Diagnostic threshold:** Cutoff of >-1 = 'most probable melanoma' Within melanocytic lesions (ML) 2 protective features associated with benign lesions (score -1 each) - typical basal cells and - edged papillae 2 risk features associated with melanoma (score +1 each) - roundish pagetoid cells and - atypical dermal nucleated cells. Lesions were assigned a value from -2 to 2 according to the presence or absence of these factors **Derivation aspect to study:** Lesion characteristics assessed - Superficial layer: honeycombed pattern, cobblestone pattern, epidemral disarray, pagetoid cellsDermoepidermal junction: visible dermal papilla, typical basal cells, marked atypia basal cells, cells in sheet like structures, junctional clustersPapillary dermis: dermal nests, nucleated dermal cells, plump bright cells, bright hyper reflecting spots, enlarged dermal vessels Selection of characteristics indicative of skin cancer Multivariate analysis using logistic regression to develop an algorithm in which benign (protective) features given a value of -1 and malignant (risk) features a value of +1 **Diagnosis based on:** Single observer (n = NR) **Observer qualifications:** Not reported Two observers described for the interobserver reproducibility study (120 images) but this appears separate to RCM interpretations used for the accuracy study. **Experience in practice:** Not described **Experience with index test:** Not described **Other detail** Study participation (RCM) did not affect the clinical decision or the excision schedule. Study aimed to develop a 2-step process, firstly to differentiate melanocytic from nonmelanocytic lesions, then to differentiate malignant from benign within the melanocytic group. The first step has not been extracted but note that relatively poor accuracy was observed (sensitivity for detection of ML 59%. specificity 96.7%)

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis plus expert diagnosis **Details:** Both diagnostic and therapeutic excisions performed No. patients/lesions: 139 in total; including 92 melanocytic lesions Disease positive: Melanocytic: 36 melanomas; Nonmelanocytic: 27 BCC Disease negative: Melanocytic: 56; Non melanocytic: 20 Expert opinion: of the 154 included lesions, 15 clinically and dermatoscopically benign did not undergo excision: 8 were melanocytic benign nevi and 7 were non-melanocytic **Target condition (Final diagnoses)** T Melanoma (invasive): 23; Melanoma (in situ): 13; BCC 0 (27 BCC in non melanocytic lesion group; not included in 2x2) Benign naevus: 64 (32 dysplastic, 20 common, 7 congenital, 2 blue,2 Reed, and 1 Meyerson nevi) 27 benign NML not included in 2x2 (8 SK, 5 solar lentigines, 4 benign lichenoid keratoses, 4 vascular lesions, 3 actinic keratoses, 2 dermatofibromas, and 1 sebaceous hyperplasia)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	No
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: All non-melanocytic (n = 54)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias
Comparative

B. Concerns regarding applicability

Notes

Notes	—

Stanganelli 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective **Period of data collection** July 2010 to July 2012 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Lesions excised at the Skin Cancer Unit on the basis of clinical and/ or dermoscopic changes at follow-up suggesting a malignancy and with available dermoscopy, RCM and histological images and reports. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Lesions showing clinical or dermoscopic changes on follow-up **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Unequivocal appearance/diagnosis **Sample size (patients):** No. included: 70 **Sample size (lesions):** No. included: 70 **Participant characteristics:** Mean age: women: 39 years, men: 40 years; Male: 38 (54%). History of melanoma/skin cancer 26 (37%). Total naevus counts, 27 (39%) > 50 melanocytic naevi, 33 (47%) 10–50 naevi; and 10 (14%) <10 naevi. Fitzpatrick phototype Type I to II 19 (27%); Type III to IV 50 (73%) **Lesion characteristics:** Lesion site Head/Neck: 5; Trunk: 56; Upper limbs/shoulder: 1; Lower limbs/hip: 8. Median thickness 0.4mm (0.2-1 mm). Mean diameter at baseline 8 mm (range 2–22 mm) mean at FU 9 mm (range 3–24 mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy.** Revised 7-point checklist **Method of diagnosis:** Dermoscopic images. Appears to be image-based comparison of follow-up images with baseline images to determine criteria indicating significant change **Prior test data:** Baseline and follow-up dermoscopic images were compared to detect structural or chromatic changes or the development of new dermoscopic features indicative of melanoma **Diagnostic threshold:** A score of 'no change' was assigned if all variables remained constant, with a tolerance of major axis change of 2 mm (Beer 2011; Terushkin 2012); 'minor change' if there was only symmetrical change in structural or chromatic pattern; 'moderate change' if either structural or chromatic changes were asymmetrical, but there were no melanoma-specific criteria; and 'major change' if there were asymmetrical structural and chromatic changes, or the appearance of melanoma-specific criteria. **Diagnosis based on:** Unclear; NR for dermoscopy **Observer qualifications:** Not reported likely dermatologists (RCM images in same study were evaluated jointly by three expert dermatologists who had no knowledge of the clinical, dermoscopic or histopathology information) **Experience in practice:** Not described **Experience with index test:** Not described # **Reflectance confocal microscopy (RCM).** Pellacani (Two step algorithm). Methods cites RCM score (Pellacani 2005); also refers to weighting according to extent and distribution for differential diagnosis with dysplastic naevus (Pellacani 2012). From discussion: "We were able to distinguish benign and malignant lesions accurately using a previously proposed algorithm for differentiating dysplastic naevus and melanoma that considers the extent and distribution of RCM parameters (Pellacani 2012). Vivascope 1500 **Method of diagnosis:** Confocal images (remote) **Prior test data:** No further information used observers "had no knowledge of the clinical, dermoscopic or histopathology information, and reached a consensus or majority opinion" **Diagnostic threshold:** Not reported in detail. "Each lesion was classified considering the main melanoma features (Pellacani 2005) and weighted according to extent and distribution for differential diagnosis with dysplastic naevus (Pellacani 2012)." **Diagnosis based on:** Consensus three expert dermatologists (n = 3) **Observer qualifications:** Dermatologist **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users **Other detail**Any other detail RCM images were obtained with a Vivascope 1500 (Lucid Inc., MAVIG GmbH, Munich, Germany) using an 830-nm laser at a maximum power of 20 mW. Methods and acquisition settings have been described previously (Pellacani 2007). RCM images of 0.5 x 0.5 mm were acquired with a lateral resolution of 1 lm and an axial resolution of 3–5 lm and assembled into composite images that covered 4–8 mm2 mosaics (Pellacani 2009). Composite images were obtained at three different depths, corresponding to the stratum granulosum/spinosum, the dermo-epidermal junction and the papillary dermis.

Reflectance confocal microscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were sufficient details of diagnostic thresholds provided?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** not further described. Disease positive: 12; Disease negative: 58 **Target condition (Final diagnoses)** Melanoma (invasive): 11, Melanoma (in situ): 1 55 melanocytic naevi (79%) and three nonmelanocytic lesions (4%)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	RCM imaging performed before surgical excision
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Was the minimum clinical follow-up after application of index test(s) adequate?	
If more than one algorithm evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias	
Comparative	(RCM) observers "had no knowledge of the clinical, dermoscopic or histopathology information, and reached a consensus or majority opinion"
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	No
Are there concerns that the test comparison differs from the review question?	High

Notes

Notes	—

Footnotes

NR – not reported; PSL – pigmented skin lesion; PLC – pigmented lesion clinic; MM – malignant melanoma; MiS – melanoma *in situ* (or lentigo maligna); BCC – basal cell carcinoma; cSCC – cutaneous squamous cell carcinoma; LS – lentigo simplex; SK – seborrheic keratosis; SN – Spitz nevi; AK – actinic keratosis; BN – benign naevi; BD – Bowen's disease; DF – dermatofibroma; FU – follow-up; R –retrospective; P – prospective; CS – case series; CCS – case control study; WPC – within person comparison (of tests); BPC – between person comparison (of tests); NC – non comparative; RCM – reflectance confocal microscopy; CAD – computer-assisted diagnosis; Cons - consensus diagnosis; exp - experience; obs - observer; VI visual inspection.

Characteristics of excluded studies

Agero 2006

Reason for exclusion	EXCLUDE on sample size *only 5 lesions*

Ahlgrimm-Siess 2010

Reason for exclusion	EXCLUDE on study population ~EXCLUDE on sample size. Two cases of BCC.

Ahlgrimm-Siess 2011

Reason for exclusion	EXCLUDE on study population ~EXCLUDE on sample size. Two cases of SCC.

Alarcon 2014a

Reason for exclusion	EXCLUDE on sample size

Amjadi 2011

Reason for exclusion	EXCLUDE on study population - *Includes only BCC (82)/SCC (48) and 8 AK/SK lesions; primary aim appears to be to differentiate BCC and SCC despite describing inclusion of clinically difficult to diagnose non-pigmented lesions.*

Bassoli 2012

Reason for exclusion	EXCLUDE on target condition *The aim of this study was to identify criteria for specific diagnosis of LPLK using in vivo RCM.*

Benati 2015

Reason for exclusion	EXCLUDE if individual lesion characteristics

Braga 2009

Reason for exclusion	EXCLUDE on sample size *case reports*

Carrera 2015

Reason for exclusion	EXCLUDE not a primary study

Castro 2015

Reason for exclusion	EXCLUDE on target condition; eligible for keratinocyte review only

de Carvalho 2015

Reason for exclusion	EXCLUDE if individual lesion characteristics EXCLUDE on 2x2 data

de Carvalho 2016

Reason for exclusion	EXCLUDE on target condition EXCLUDE on sample size

Edwards 2016

Reason for exclusion	EXCLUDE not a primary study systematic review

Eichert 2010

Reason for exclusion	Review/comment paper

Gareau 2009

Reason for exclusion	EXCLUDE on study population *Only BCC cases*

Gerger 2005

Reason for exclusion	EXCLUDE on reference standard *only 1/3 of disease negative group had adequate ref test* EXCLUDE duplicate or related publication; d*ata reported as training set in Koller 2011 (#860)*

Gerger 2006

Reason for exclusion	EXCLUDE on reference standard *Only 30/120 benign were excised (30/90 benign nevi and 0/30 SK)*

Gerger 2008a

Reason for exclusion	EXCLUDE on reference standard *all MMs were excised plus 14/50 benign; remainder diagnosed on clinical/dermoscopic criteria*

Gerger 2008b

Reason for exclusion	EXCLUDE on reference standard; i*ncludes 70 melanocytic lesions - 20 MM (all histologically verified); 70 benign naevi (28% histologically verified, and the rest diagnosed with dermoscopy only).*

Giambrone 2015

Reason for exclusion	EXCLUDE on target condition EXCLUDE but contact authors *they do not give information on the target condition-only state malignant/benign cutaneous lesions??? Contacted 8-5-17*

Gill 2014

Reason for exclusion	EXCLUDE if derivation study; *looking for correlation with histological features* EXCLUDE on 2x2 data; *Looks at correlation between RCM features and histological features; not test accuracy* EXCLUDE duplicate or related publication; *Same lesions reportedly included in Pellacani 2012*

Gonzalez 2002

Reason for exclusion	EXCLUDE on study population. BCC only.

Gonzalez 2013

Reason for exclusion	EXCLUDE not a primary study

Guida 2015

Reason for exclusion	EXCLUDE not a primary study systematic review

Guitera 2010

Reason for exclusion	EXCLUDE on target condition; *only looking at LM and not LMM*

Guitera 2013

Reason for exclusion	EXCLUDE on study population; *LM and LMM only* EXCLUDE on target condition; *data only available for LM* EXCLUDE on 2x2 data

Haenssle 2006

Reason for exclusion	EXCLUDE on index test; *surveillance study estimating accuracy of different approaches to follow-up*

Hennessy 2010

Reason for exclusion	EXCLUDE on 2x2 data

Hoogedoorn 2014

Reason for exclusion	EXCLUDE conference abstract

Hoogedoorn 2015

Reason for exclusion	EXCLUDE on sample size

Humphrey 2006

Reason for exclusion	EXCLUDE on study population EXCLUDE as derivation study - assesses lesion vascularity

Incel 2015

Reason for exclusion	EXCLUDE on 2x2 data ~EXCLUDE but contact authors. se/sp given in Table 3 but not clear how the disease negative groups are comprised (i.e. BCC vs what? the 37 benign or some other definition?) and not clear what threshold was used.

Kadouch 2015

Reason for exclusion	systematic review

Kadouch 2015a

Reason for exclusion	EXCLUDE not a primary study *clinical trial protocol*

Kose 2014

Reason for exclusion	EXCLUDE not a test accuracy study EXCLUDE on 2x2 data

Langley 2001

Reason for exclusion	EXCLUDE on 2x2 EXCLUDE but contact authors; *contact authors for RCM 2x2 data can only get 2x2 for clinical diagnosis*

Langley 2006

Reason for exclusion	EXCLUDE on sample size

Losi 2014

Reason for exclusion	EXCLUDE if individual lesion characteristics EXCLUDE on 2x2 data

Maier 2013

Reason for exclusion	EXCLUDE on study population; *all study participants had final diagnosis of melanoma*

Malvehy 2012

Reason for exclusion	EXCLUDE not a primary study; review article

Menge 2016

Reason for exclusion	EXCLUDE on target population; *includes participants with primary possible recurrent and/or previously treated lesions and does not disaggregate results. Also includes multiple lesions per participant (63 'sites' from 17 participants; unclear how many of the 39 LM positive on histology had melanoma).*

Miller 2011

Reason for exclusion	EXCLUDE on target condition EXCLUDE on 2x2 data; *not an accuracy study*

Nobre 2011

Reason for exclusion	EXCLUDE on sample size; *case report*

Nori 2004

Reason for exclusion	EXCLUDE on target condition; eligible for keratinocyte review only

Pellacani 2005

Reason for exclusion	EXCLUDE if derivation study; *uses leave one out*

Pellacani 2007a

Reason for exclusion	EXCLUDE if individual lesion characteristics; *looking at blue hue not overall diagnosis* EXCLUDE if derivation study

Pellacani 2008

Reason for exclusion	EXCLUDE on 2x2 data; *no accuracy data provided in the study, looking at correlation of RCM features to dermoscopy and histology*

Pellacani 2009

Reason for exclusion	EXCLUDE on 2x2 data; *Study is testing concordance of terminology used in RCM...not accuracy.*

Peppelman 2013

Reason for exclusion	EXCLUDE on study population; *only present data for subtypes of BCC* EXCLUDE on 2x2 data; *does not give accuracy data*

Peppelman 2015

Reason for exclusion	EXCLUDE if derivation study EXCLUDE on 2x2 data; *no data for overall accuracy*

Peppelman 2016

Reason for exclusion	EXCLUDE not a primary study; *RCT protocol*

Puig 2012

Reason for exclusion	EXCLUDE on sample size; *case report*

Reggiani 2015

Reason for exclusion	EXCLUDE not a primary study; systematic review

Rishpon 2009

Reason for exclusion	EXCLUDE on sample size; *only 3 invasive SCC* EXCLUDE if derivation study *RCM characteristics for SCC*

Röwert-Huber 2007

Reason for exclusion	Review/comment paper

Salerni 2011

Reason for exclusion	EXCLUDE on sample size; *<5 cases*

Scope 2009

Reason for exclusion	EXCLUDE on sample size

Scope 2014

Reason for exclusion	EXCLUDE not a primary study; e*ditorial paper*

Soyer 2013

Reason for exclusion	EXCLUDE not a primary study; *comment on a primary study (Longo 2013)*

Steiner 1992

Reason for exclusion	EXCLUDE on sample size *only two melanomas*

Stephens 2013

Reason for exclusion	EXCLUDE on sample size

Stevenson 2013

Reason for exclusion	EXCLUDE not a primary study *systematic review of RCM*

Tannous 2009

Reason for exclusion	EXCLUDE on sample size; *only two malignant melanomas*

Willard 2011

Reason for exclusion	EXCLUDE on sample size; *case study*

Witkowski 2016

Reason for exclusion	EXCLUDE on target condition; eligible for keratinocyte review only

Xiong 2016

Reason for exclusion	EXCLUDE not a primary study *systematic review of RCM*

Yelamos 2016

Reason for exclusion	EXCLUDE not a primary study

Footnotes

Characteristics of studies awaiting classification

Borsari 2016

Patient Sampling	—
Patient characteristics and setting	—
Index tests	—
Target condition and reference standard(s)	—
Flow and timing	—
Comparative	—
Notes	Published October 2016; after search dates

Guitera 2016

Patient Sampling	—
Patient characteristics and setting	—
Index tests	—
Target condition and reference standard(s)	—
Flow and timing	—
Comparative	—
Notes	Published October 2016; after search dates

Jain 2017

Patient Sampling	—
Patient characteristics and setting	—
Index tests	—
Target condition and reference standard(s)	—
Flow and timing	—
Comparative	—
Notes	Published March 2017; conference abstract only

Ludzik 2016

Patient Sampling	—
Patient characteristics and setting	—
Index tests	—
Target condition and reference standard(s)	—
Flow and timing	—
Comparative	—
Notes	Published September 2016; after search dates

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of results tables

1 Summary of findings table

Question:	**What is the diagnostic accuracy of reflectance confocal microscopy for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?**
Population:	Adults with lesions suspicious for melanoma, including: • Any lesion excised due to suspicion of melanoma, and • Equivocal lesions where a clear management decision could not be made following visual inspection or dermoscopy
Index test:	Reflectance confocal microscopy (RCM)
Comparator test:	Dermoscopy
Target condition:	Cutaneous invasive melanoma and atypical intraepidermal melanocytic variants
Reference standard:	Histology with or without long term follow-up
Action:	If accurate, negative results of RCM will stop patients having unnecessary excision of skin lesions
Quantity of evidence	

Question:	What is the diagnostic accuracy of reflectance confocal microscopy for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?				
Number of cohorts	19[1]	Total lesions with test results	2838	Total with melanoma	658
Limitations					
Risk of bias:	High risk for patient selection from exclusion of some difficult to diagnose types of lesion (8/20). High risk for the index test from data driven RCM threshold (4/20). High risk from inadequate reference standard (4/20) and unclear risk as it was not clear that the reference standard was interpreted blind to the RCM results in 18/20 studies. High risk from differential verification (6/20), timing of tests was not mentioned in 11/20.				
Applicability of evidence to question:	High concern from narrowly defined populations (12/20) and multiple lesions per patient (7/20). High concern for RCM applicability from blinded interpretation of images (10/20). Studies are dominated by one particularly expert research group (15/20). Little information was given concerning the expertise of the histopathologist.				
Findings:	All analyses are undertaken on subgroups of the studies				

Test:

RCM – using 'RCM score' algorithm at threshold ≥3 or likely ≥3 regardless of population

Datasets	Lesions	Melanomas	Sensitivity (95% CI)	Specificity (95% CI)
6	1209	296	92% (87, 95)	72% (62, 81)

Consistency: Significant heterogeneity in specificity between studies. Includes both equivocal (4) and 'any suspicious lesion' (2) populations; both in-person (3) and image based 3).

Numbers observed in a cohort of 1000 lesions being tested[2]

	True positive (receive necessary excision)	False negative (do not receive required excision)	False positive (inappropriately receive excision)	True negative (appropriately do not receive excision)
At prevalence 13%	120	10	244	626
At prevalence 23%	212	18	216	554
At prevalence 39%	359	31	171	439

Test:

RCM versus dermoscopy[3] – any algorithm or threshold in 'any lesion suspicious for melanoma' populations [dermoscopy data denoted in brackets]

Datasets	Lesions	Melanomas	Sensitivity (fixed) RCM [Dermoscopy]	Specificity RCM [Dermoscopy]
9 [3]	1452 [451]	370 [160]	90% [90%]	82% [42%]

Numbers observed in a cohort of 1000 lesions being tested[2,3,4]

	True positive (receive necessary excision)	False negative (do not receive required excision)	False positive (inappropriately receive excision)	True negative (appropriately do not receive excision)
At prevalence 26%	234	26	133 [429] ↓296	607 [311] ↑296
At prevalence 30%	270	30	126 [406] ↓280	574 [294] ↑280
At prevalence 36%	324	36	115 [371] ↓256	525 [269] ↑256

Test:

RCM versus dermoscopy – any algorithm or threshold in equivocal lesion populations [dermoscopy data denoted in brackets]

Question:	What is the diagnostic accuracy of reflectance confocal microscopy for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?			
Datasets	**Lesions**	**Melanomas**	**Sensitivity (fixed)** **RCM [Dermoscopy]**	**Specificity** **RCM [Dermoscopy]**
7 [3]	1177 [645]	180 [127]	90% [90%]	86% [49%]
Numbers observed in a cohort of 1000 lesions being tested[2]				
	True positive	**False negative**	**False positive**	**True negative**
	(receive necessary excision)	(do not receive required excision)	(inappropriately receive excision)	(appropriately do not receive excision)
At prevalence 10%	90	10	126 [459] ↓333	774 [441] ↑333
At prevalence 20%	180	20	112 [408] ↓296	688 [392] ↑296
At prevalence 23%	207	23	108 [393] ↓285	662 [377] ↑285

Footnotes

RCM - reflectance confocal microscopy.

[1] The denominator for the Limitations section is 20 because methodologic quality was assessed separately for each of the 19 cohorts of lesions, and a further publication (Pellacani 2007) reporting data for two of these cohorts (Guitera 2009a (Modena); Guitera 2009b (Sydney)) was also included and separately quality assessed, taking the total to 20. Pellacani 2007 was included only to allow analysis of additional algorithm thresholds and was not included in the main analyses.

[2] The numbers observed in a hypothetical cohort of lesions have been estimated at the median and interquartile range in prevalence across the pooled datasets for each test.

[3] [ ] Dermoscopy data is denoted by square brackets throughout.

[4] The arrows ↓ ↑ indicate the change in number of false positive and true negative results as a result of RCM use.

Additional tables

1 Glossary of terms

Term	Definition
Amelanotic	Without melanin
Anti-CTLA-4 therapy system	Monoclonal antibody to CTLA-4 (cytotixc T-lymphocyte-associated protein 4) – a protein that is involved in regulating the immune system
BRAF-inhibitors	Therapeutic agents that inhibit the serine-threonine protein kinase BRAF-mutated metastatic melanoma
Driver mutations	Somatic gene mutations that are responsible for tumour progression
Elective lymph node dissection	Surgical removal of 1 or more lymph nodes in the absence of proven involvement with melanoma
Hybridised	The process of combining 2 biological molecules
Immune checkpoint targets	Signalling pathways that are inhibitory and switch off T cells in the immune system
Immunomodulation	Adjustment of the immune system in an individual
Irregular nesting	Unbalanced asymmetrical arrangement of groups of melanocytes in the skin
Lymphovascular invasion	Tumour cells that have spread to involve the blood vessels and lymphatic vessels within the skin
MEK inhibitors	Drugs that inhibit the mitogen-activated protein kinase enzymes that are often upregulated in melanoma
Microscopic satellites	Foci of melanoma observed histologically that are distinct from the original primary tumour
Mitotic rate	Microscopic evaluation of a number of cells actively dividing in a tumour
Mutated signal transduction	Activation of Ras proteins such that unintended and overactive signalling occurs and causes overgrowth of cells and higher rates of cell division
PD1	Programmed cell death protein 1: a protein involved in downregulating the immune system
PD1-L	Programmed cell death protein 1 receptor – expressed on T and B cells
Phenotypic risk	The various clinical/physical traits of an individual determined by genetic and environmental factors that predispose individuals to melanoma
Prophylactic isolated limb perfusion	A medical procedure that directly delivers a drug through the bloodstream in a limb to the site affected by melanoma
Pseudopods	Temporary projections from cells that help cellular movement
RAS-RAF signalling pathway	Family of proteins that serve as intermediary in transmitting extracellular signals from growth factor receptors that control cell growth, proliferation, and differentiation
RNA	Ribonucleic acid involved in coding, decoding, regulation, and expression of genes
Signal transduction	Occurs when extracellular signalling molecules activate a specific receptor, which then triggers cellular pathways
Spectroscopy	Study of the interaction between matter and electromagnetic radiation
Stratum corneum	Uppermost layer of the epidermis composed of dead keratinocytes (corneocytes)
Xeroderma pigmentosum	Autosomal recessive genetic disorder of DNA repair, resulting in an inability to repair damage caused by ultraviolet light leading to skin malignancies

Footnotes

2 Summary characteristics for studies reporting RCM accuracy for the primary outcome

Characteristic	Any suspicious lesion	Equivocal
Number of publications	8	7
RCM datasets	9	7
Dermoscopy datasets	3; 33.3%	3; 42.9%
Study design		
Prospective case series	7; 77.8%	3; 42.9%
Retrospective case series	-	4; 57.1%

Characteristic	Any suspicious lesion	Equivocal
- with prospective re-interpretation of images		3; 75.0%
Case series (unclear data collection)	2; 22.2%	-
Continent		
Europe	4; 44.4%	7; 100.0%
North America	2; 22.2%	-
Australasia	2; 22.2%	-
Multicentre	1; 11.1%	-
Setting		
Secondary	4; 44.4%	3; 42.9%
Specialist clinic	3; 33.3%	4; 57.1%
Mixed	2; 22.2%	-
Prior testing		
Clinical examination	1; 11.1%	-
Clinical examination or dermoscopy	2; 22.2%	2; 28.6%
Clinical examination and dermoscopy	4; 44.4%	3; 42.9%
Follow-up of atypical lesions	-	2; 28.6%
Selected for biopsy or excision	2; 22.2%	-
Lesion characteristics		
Any lesion (pigmented or nonpigmented)	2; 22.2%	1; 14.3%
Pigmented	3; 33.3%	1; 14.3%
Melanocytic only	4; 44.4%	5; 71.4%
Exclusion criteria		
Excludes by site (acral/awkwardly sited)	3; 33.3%	-
Excludes on image quality	5; 55.6%	3; 42.9%
Participant characteristics		
Number of participants (median (range))	137 (42 to 195); 6 studies	70 (62 to 264); 5 studies
Number of lesions (median (range))	131 (50 to 323)	100 (60 to 308)
Lesion to patient ratio (median (range))	1.07 (1 to 1.19); 7 studies	1.05 (1 to 1.22); 5 studies
Disease prevalence (mean (range))	27.6% (2.8% to 41.5%)	18.2% (1.9 to 34.8%)
Melanoma *in situ* as % of disease positive	25.0% (7.7% to 51.4%)	28.6% (8.3 to 61.5%)
Vivascope		
Vivascope 1000	2; 22.2%	-
Vivascope 1500	5; 55.6%	7; 100.0%
Vivascope 1000 followed by 1500	2; 22.2%	-
RCM algorithms		
No algorithm - observer diagnosis	2; 22.2%	1; 14.3%
No algorithm - selected lesion characteristics	1; 11.1%	
No algorithm - significant lesion characteristics		1; 14.3%

Characteristic	Any suspicious lesion	Equivocal
RCM score (including NR)	5; 55.6%	2; 28.6%
Segura algorithm	1; 11.1%	1; 14.3%
Pellcani two-step algorithm (including modified)	0; 0.0%	2; 28.6%
Diagnostic method		
In person (real-time interpretation)	3; 33.3%	1; 14.3%
Image-based (remote interpretation)	6; 66.7%	6; 85.7%
RCM guided by dermoscopic image		
Yes	6; 66.7%	-
NR	3; 33.3%	7; 100.0%
Other test data available to observer		
None	2; 22.2%	3; 42.9%
Lesion site, patient age or gender	3; 33.3%	-
Dermoscopy image alone	1; 11.1%	2; 28.6%
Dermoscopy image plus patient age, site, or gender	-	1; 14.3%
In person (including dermoscopy)	2; 22.2%	-
Unclear	1; 11.1%	1; 14.3%
Test interpretation		
Number of observers (median (range))	n = 1 (3 studies) n = 2 (4 studies)	n = 1 (4 studies) n = 3 (3 studies)
Single	9; 100.0%	5; 71.4%
Consensus of 3	-	1; 14.3%
Not reported	-	1; 14.3%
Observer qualifications		
Dermatologist	4; 44.4%	5; 71.4%
Not reported	5; 55.6%	2; 28.6%
Observer experience in practice		
High	3; 33.3%	4; 57.1%
Not reported	6; 66.7%	3; 42.9%
Observer experience with RCM		
High	6; 66.7%	5; 71.4%
Not reported	3; 33.3%	2; 28.6%
Reference Standard		
Histology alone	8; 88.9%	6; 85.7%
Histology and clinical follow-up	-	1; 14.3%
Histology and expert diagnosis	1; 11.1%	-

Footnotes

RCM - reflectance confocal microscopy; NR - not reported.

3 Comparison of RCM with Dermoscopy

Test	Studies	Participants	DOR (95% CI)	Specificity at 90% sensitivity	Relative DOR (95% CI)	P-value[1] (DOR)	P-value[2] (HSROC models)
'Any lesion suspicious for melanoma' studies (all studies)							
RCM	9	1452	57.5 (18.5, 179.4)	82%	4.82 (2.16, 10.8)	0.0001	<0.001
Dermoscopy	3	451	14.4 (2.7, 77.6)	42%			
'Any lesion suspicious for melanoma' studies (direct comparisons)							
RCM	3	451	251.3 (5.7, 11050)	93%	4.96 (1.1, 21.5)	0.03	<0.001
Dermoscopy	3	451	50.6 (1.6, 1634)	41%			
Equivocal lesion studies (all studies)							
RCM	7	1177	97.6 (30.3, 313.8)	86%	20.1 (6.6, 61.3)	<0.001	<0.001
Dermoscopy	3	645	3.0 (1.3, 6.8)	49%			
Equivocal lesion studies (direct comparisons)							
RCM	3	645	154.5 (16.4, 1457)	94%	22.1 (1.7, 283.6)	0.03	<0.001
Dermoscopy	3	645	7.0 (2.1, 23.6)	44%			

Footnotes

CI - confidence interval; RCM - reflectance confocal microscopy; DOR - diagnostic odds ratio; HSROC - hierarchical summary receiver operating characteristic curve.

1 The P value assesses whether the observed difference in DOR between RCM and Dermoscopy is explicable by chance

2 The P value is a global test assessing whether the observed differences in all HSROC parameters (accuracy and threshold) between RCM and Dermoscopy is explicable by chance.

4 Pooled sensitivity and specificity for individual algorithms

Person / image	Target condition Test	Studies (n)	Participants (n)	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Detection of invasive melanoma (MM)					
In person	RCM ≥ 3	1	50	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]
Image-based	Segura >-1	1	100	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]
Image-based	Guitera 2-step (significant characteristics for MM)	1	356	0.78 [0.65, 0.89]	0.86 [0.81, 0.90]
Image-based	No algorithm (observer diagnosis)	1	63	0.88 [0.47, 1.00]	0.62 [0.48, 0.75]
Image-based	No algorithm (significant characteristics)	1	140	1.00 [0.85, 1.00]	0.91 [0.85, 0.96]
Image-based	No algorithm (any threshold)	2	203	0.98 [0.27, 1.00]	0.81 [0.52, 0.94]
Detection of invasive melanoma or atypical intraepidermal melanocytic variants (MM+MiS)					
Image-based	RCM ≥ 2	1	351	0.96 [0.92, 0.99]	0.52 [0.45, 0.59]
Image-based	RCM ≥ 3	3	668	0.91 [0.87, 0.94] †	0.67 [0.62, 0.71] †
In person	RCM ≥ 3	1	50	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
In person	RCM unstated but likely ≥ 3	2	366	1.00 [0.88, 1.00]*	0.62 [0.40, 0.80]
Both	RCM ≥ 3 or likely ≥ 3	6	1209	0.92 [0.87, 0.95]	0.72 [0.62, 0.81]
Image-based	RCM ≥ 4	3	604	0.86 [0.76,0.92]	0.73 [0.60, 0.82]
Image-based	Segura >-1	4	863	0.93 [0.76, 0.98]	0.88 [0.72, 0.95]
Image-based	Guitera 2-step (significant characteristics)	1	356	0.78 [0.69, 0.86]	0.84 [0.79, 0.88]
Image-based	Pellacani 2-step	2	130	0.96 [0.72, 1.00]	0.71 [0.61, 0.79]
Image-based	No algorithm (observer diagnosis)	4	578	0.81 [0.65, 0.91]	0.88 [0.78, 0.94]
In person	No algorithm (observer diagnosis)	1	317	0.67 [0.30, 0.93]	0.96 [0.93, 0.98]
Image-based	No algorithm (significant characteristics)	2	331	0.93 [0.78, 0.98]	0.81 [0.63, 0.92]
In person	No algorithm (selected characteristics)	1	125	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Image-based	No algorithm (excise decision)	1	323	1.00 [0.66, 1.00]	0.64 [0.58, 0.69]
In person	No algorithm (excise decision)	1	317	0.89 [0.52, 1.00]	0.52 [0.46, 0.58]
Image-based	RCM computer assisted	1	92	1.00 [0.86, 1.00]	0.24 [0.14, 0.35]
Detection of any skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma (Any)					
In person	RCM ≥ or likely 3	3	541	0.98 [0.91, 0.99]‡	0.75 [0.54, 0.89] †
Image-based	Segura >-1	1	356	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]
Image-based	Pellacani two-step	1	60	0.89 [0.67, 0.99]	0.80 [0.65, 0.91]
Image-based	Guitera 2-step (significant characteristics)	1	356	0.92 [0.86, 0.95]	0.68 [0.61, 0.75]
In person	No algorithm (observer diagnosis)	1	317	0.78 [0.67, 0.87]	0.85 [0.80, 0.89]
Image-based	No algorithm (observer diagnosis)	2	423	0.85 [0.77, 0.90]	0.87 [0.83, 0.90]
In person	No algorithm (excise decision)	1	317	0.85 [0.75, 0.92]	0.61 [0.55, 0.68]
Image-based	No algorithm (excise decision)	1	323	0.90 [0.81, 0.95]	0.79 [0.73, 0.84]

Footnotes

CI - confidence interval; RCM - reflectance confocal microscopy; MM – malignant melanoma; MiS – melanoma *in situ* (or lentigo maligna).

* computed using unstratified data as no false negatives; † computed without correlation between sensitivity and specificity; ‡zero variance assumed for sensitivity random effect

5 Investigations of heterogeneity in RCM accuracy

Subgroup	Studies	Participants	DOR (95% CI)	Specificity at 90% sensitivity	Relative DOR (95% CI)	P-value (DOR)	P-value (HSROC models)
Differences in patient pathway							
Any lesion suspicious for melanoma	9	1452	44.5 (19.8, 99.9)	81%	2.88 (0.80, 10.4)	P = 0.11	P = 0.31
Equivocal lesions	7	1177	147.6 (37.2, 585.7)	94%			
Differences in-person and image based							
Image based	12	1963	54.1 (26.3, 111.1)	84%	4.77 (0.56, 40.8)	P = 0.15	P = 0.13
In person	4	666	257.7 (28.7, 2313)	97%			
Use of a scaling system							
No scale used	6	802	45.7 (16.2, 128.6)	83%	1.81 (0.41, 8.03)	P = 0.43	P = 0.06
Any scale used	10	1663	82.8 (28.9, 236.8)	90%			

Footnotes

CI - confidence interval; DOR - diagnostic odds ratio; HSROC - hierarchical summary receiver operating characteristic curve

References to studies

Included studies

Alarcon 2014

* Alarcon I, Carrera C, Palou J, Alos L, Malvehy J, Puig S. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. British Journal of Dermatology 2014;170(4):802-8. [Other: ER4:17941078; PubMed: 24124911]

Curchin 2011

* Curchin CE, Wurm EM, Lambie DLj, Longo C, Pellacani G, Soyer HP. First experiences using reflectance confocal microscopy on equivocal skin lesions in Queensland. Australasian Journal of Dermatology 2011;52(2):89-97. [Other: ER4:15465900; PubMed: 21605091]

Farnetani 2015

* Farnetani F, Scope A, Braun RP, Gonzalez S, Guitera P, Malvehy J, et al. Skin Cancer Diagnosis With Reflectance Confocal Microscopy: Reproducibility of Feature Recognition and Accuracy of Diagnosis. JAMA Dermatology 2015; 151(10):1075-80. [Other: ER4:25233569; PubMed: 25993262]

Ferrari 2015

* Ferrari B, Pupelli G, Farnetani F, De Carvalho NT, Longo C, Reggiani C, et al. Dermoscopic difficult lesions: an objective evaluation of reflectance confocal microscopy impact for accurate diagnosis. Journal of the European Academy of Dermatology and Venereology 2015;29(6):1135-1140. [DOI: 10.1111/jdv.12769; Other: ER4:20569458; PubMed: 25303304]

Figueroa Silva 2016

* Figueroa-Silva O, Cinotti E, de Almeida Silva T, Moscarella E, Lallas A, Ciardo S, et al. Diagnostic accuracy of reflectance confocal microscopy for lesions typified by dermoscopic island. Journal of the European Academy of Dermatology and Venereology : JEADV 2016;30(9):1594-8. [Other: ER4:25012335; PubMed: 27109574]

Guitera 2009a (Modena)

* Guitera P, Pellacani G, Longo C, Seidenari S, Avramidis M, Menzies SW. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. Journal of Investigative Dermatology 2009;129(1):131-8. [Other: ER4:15465945; PubMed: 18633444]

Guitera 2009b (Sydney)

* Guitera P, Pellacani G, Longo C, Seidenari S, Avramidis M, Menzies SW. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. Journal of Investigative Dermatology 2009;129(1):131-8. [PubMed: 18633444]

Guitera 2012

* 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 two-step method: analysis of 710 consecutive clinically equivocal cases. Journal of Investigative Dermatology 2012;132(10):2386-94. [Other: ER4:15465942; PubMed: 22718115]

Koller 2011

* Koller S, Wiltgen M, Ahlgrimm-Siess V, Weger W, Hofmann-Wellenhof R, Richtig E, et al. In vivo reflectance confocal microscopy: automated diagnostic image analysis of melanocytic skin tumours. Journal of the European Academy of Dermatology and Venereology : JEADV 2011;25(5):554-8. [Other: ER4:15465979; PubMed: 20735518]

Langley 2007

* Langley RG, Walsh N, Sutherland AE, Propperova I, Delaney L, Morris SF, et al. The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: a prospective study. Dermatology 2007;215(4):365-72. [Other: ER4:15465985; PubMed: 17912001]

Longo 2013

* Longo C, Farnetani F, Ciardo S, Cesinaro AM, Moscarella E, Ponti G, et al. Is confocal microscopy a valuable tool in diagnosing nodular lesions? A study of 140 cases. British Journal of Dermatology 2013;169(1):58-67. [Other: ER4:15465992; PubMed: 23374159]

Lovatto 2015

* Lovatto L, Carrera C, Salerni G, Alos L, Malvehy J, Puig S. In vivo reflectance confocal microscopy of equivocal melanocytic lesions detected by digital dermoscopy follow-up. Journal of the European Academy of Dermatology and Venereology : JEADV 2015;29(10):1918-25. [Other: ER4:25012311; PubMed: 25752663]

Pellacani 2007

* Pellacani G, Guitera P, Longo C, Avramidis M, Seidenari S, Menzies S. The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions. Journal of Investigative Dermatology 2007;127(12):2759-65. [Other: ER4:15466047; PubMed: 17657243]

Pellacani 2012

* Pellacani G, Farnetani F, Gonzalez S, Longo C, Cesinaro AM, Casari A, et al. In vivo confocal microscopy for detection and grading of dysplastic nevi: a pilot study. Journal of the American Academy of Dermatology 2012; 66(3):e109-21. [Other: ER4:15466043; PubMed: 21742408]

Pellacani 2014a (cons)

Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. British Journal of Dermatology 2014;171(5):1044-1051. [PubMed: 24891083]

Pellacani 2014b (doc)

* Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. British Journal of Dermatology 2014;171(5):1044-1051. [Other: ER4:20569486; PubMed: 24891083]

Pupelli 2013

* Pupelli G, Longo C, Veneziano L, Cesinaro AM, Ferrara G, Piana S, et al. Small-diameter melanocytic lesions: morphological analysis by means of in vivo confocal microscopy. British Journal of Dermatology 2013;168(5):1027-33. [Other: ER4:15466070; PubMed: 23301553]

Rao 2013

* Rao BK, Mateus R, Wassef C, Pellacani G. In vivo confocal microscopy in clinical practice: comparison of bedside diagnostic accuracy of a trained physician and distant diagnosis of an expert reader. Journal of the American Academy of Dermatology 2013;69(6):e295-300. [Other: ER4:15466076; PubMed: 24035553]

Segura 2009

* Segura S, Puig S, Carrera C, Palou J, Malvehy J. Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy. Journal of the American Academy of Dermatology 2009;61(2):216-29. [Other: ER4:20569494; PubMed: 19406506]

Stanganelli 2015

* Stanganelli I, Longo C, Mazzoni L, Magi S, Medri M, Lanzanova G, et al. Integration of reflectance confocal

microscopy in sequential dermoscopy follow-up improves melanoma detection accuracy. British Journal of Dermatology 2015;172(2):365-371. [Other: ER4:20569496; PubMed: 25154446]

Excluded studies

Agero 2006

Agero AL, Busam KJ, Benvenuto-Andrade C, Scope A, Gill M, Marghoob AA, et al. Reflectance confocal microscopy of pigmented basal cell carcinoma. Journal of the American Academy of Dermatology 2006;54(4):638-43. [PubMed: 16546585]

Ahlgrimm-Siess 2010

Ahlgrimm-Siess V, Cao T, Oliviero M, Hofmann-Wellenhof R, Rabinovitz HS, Scope A. The vasculature of nonmelanocytic skin tumors in reflectance confocal microscopy: vascular features of basal cell carcinoma. Archives of Dermatology 2010; 146(3):354.

Ahlgrimm-Siess 2011

Ahlgrimm-Siess V, Cao T, Oliviero M, Hofmann-Wellenhof R, Rabinovitz HS, Scope A. The vasculature of nonmelanocytic skin tumors in reflectance confocal microscopy: vascular features of squamous cell carcinoma in situ. Archives of Dermatology 2011;147(2):264.

Alarcon 2014a

Alarcon I, Carrera C, Turegano P, Malvehy J, Puig S. Basal cell carcinoma with spontaneous regression: added value of reflectance confocal microscopy when the dermoscopic diagnosis is uncertain. Journal of the American Academy of Dermatology 2014;71(1):e7-9. [PubMed: 24947714]

Amjadi 2011

Amjadi M, Coventry BJ, Greenwood JE. Reflectance confocal microscopy in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: a blinded prospective trial. Internet Journal of Plastic Surgery 2011;7(2):1-6.

Bassoli 2012

Bassoli S, Rabinovitz HS, Pellacani G, Porges L, Oliviero MC, Braun RP, et al. Reflectance confocal microscopy criteria of lichen planus-like keratosis. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26(5):578-90. [PubMed: 21605173]

Benati 2015

Benati E, Argenziano G, Kyrgidis A, Moscarella E, Ciardo S, Bassoli S, et al. Melanoma and naevi with a globular pattern: confocal microscopy as an aid for diagnostic differentiation. British Journal of Dermatology 2015;173(5):1232-8. [PubMed: 26212145]

Braga 2009

Braga JC, Scope A, Klaz I, Mecca P, Gonzalez S, Rabinovitz H, et al. The significance of reflectance confocal microscopy in the assessment of solitary pink skin lesions. Journal of the American Academy of Dermatology 2009;61(2):230-41. [PubMed: 19398144]

Carrera 2015

Carrera C. High-risk melanoma patients: can unnecessary naevi biopsies be avoided? British Journal of Dermatology 2015; 172(2):313-5. [PubMed: 25660675]

Castro 2015

* Castro RP, Stephens A, Fraga-Braghiroli NA, Oliviero MC, Rezze GG, Rabinovitz H, et al. Accuracy of in vivo confocal microscopy for diagnosis of basal cell carcinoma: a comparative study between handheld and wide-probe confocal imaging. Journal of the European Academy of Dermatology and Venereology 2015;29(6):1164-1169. [DOI: 10.1111/jdv.12780; Other: ER4:20569441]

de Carvalho 2015

de Carvalho N, Farnetani F, Ciardo S, Ruini C, Witkowski AM, Longo C, et al. Reflectance confocal microscopy correlates of dermoscopic patterns of facial lesions help to discriminate lentigo maligna from pigmented nonmelanocytic macules. British Journal of Dermatology 2015;173(1):128-33. [PubMed: 25413382]

de Carvalho 2016

de Carvalho N, Guida S, Abraham LS, Cesinaro AM, Farnetani F, Bonamonte D, et al. Pink melanocytic and non-melanocytic lesions: how reflectance confocal microscopy can help in differential diagnosis. Journal of the European Academy of Dermatology and Venereology : JEADV 2016;30(6):1026-9. [PubMed: 25753043]

Edwards 2016

Edwards SJ, Mavranezouli I, Osei-Assibey G, Marceniuk G, Wakefield V, Karner C. VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2016;20(58):1-260. [PubMed: 27483991]

Eichert 2010

Eichert S, Mohrle M, Breuninger H, Rocken M, Garbe C, Bauer J. Diagnosis of cutaneous tumors with in vivo confocal laser scanning microscopy. Journal der Deutschen Dermatologischen Gesellschaft 2010;8(6):400-10.

Gareau 2009

Gareau DS, Karen JK, Dusza SW, Tudisco M, Nehal KS, Rajadhyaksha M. Sensitivity and specificity for detecting basal cell carcinomas in Mohs excisions with confocal fluorescence mosaicing microscopy. Journal of Biomedical Optics 2009; 14(3):034012. [PubMed: 19566305]

Gerger 2005

Gerger A, Koller S, Kern T, Massone C, Steiger K, Richtig E, et al. Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors. Journal of Investigative Dermatology 2005;124(3):493-8. [PubMed: 15737188]

Gerger 2006

Gerger A, Kerl H, Samonigg H, Langsenlehner U, Krippl P, Smolle J. Sensitivity and specificity of confocal laser scanning microscopy for in vivo diagnosis of malignant skin tumors. Journal of Investigative Dermatology 2006;126(Suppl 3):s114.

Gerger 2008a

Gerger A, Wiltgen M, Langsenlehner U, Richtig E, Horn M, Weger W, et al. Diagnostic image analysis of malignant melanoma in in vivo confocal laser-scanning microscopy: a preliminary study. Skin Research & Technology 2008; 14(3):359-63. [PubMed: 19159384]

Gerger 2008b

Gerger A, Hofmann-Wellenhof R, Langsenlehner U, Richtig E, Koller S, Weger W, et al. In vivo confocal laser scanning microscopy of melanocytic skin tumours: diagnostic applicability using unselected tumour images. British Journal of Dermatology 2008;158(2):329-33. [Other:]

Giambrone 2015

Giambrone D, Alamgir M, Masud A, Bronsnick T, Rao B. The diagnostic accuracy of in vivo confocal microscopy in clinical practice. Journal of the American Academy of Dermatology 2015;73(2):317-9. [PubMed: 26183976]

Gill 2014

Gill M, Longo C, Farnetani F, Cesinaro AM, Gonzalez S, Pellacani G. Non-invasive in vivo dermatopathology: identification of reflectance confocal microscopic correlates to specific histological features seen in melanocytic neoplasms. Journal of the European Academy of Dermatology and Venereology : JEADV 2014;28(8):1069-78. [PubMed: 24147614]

Gonzalez 2002

Gonzalez S, Tannous Z. Real-time in vivo confocal reflectance microscopy of basal cell carcinoma. Journal of the American Academy of Dermatology 2002;47(6):869-74. [PubMed: 12451371]

Gonzalez 2013

Gonzalez S. Should reflectance confocal microscopy be the gold standard for basal cell carcinoma diagnosis? Imaging in Medicine 2013;5(4):299-301. [DOI: 10.2217/IIM.13.36]

Guida 2015

Guida S, Longo C, Casari A, Ciardo S, Manfredini M, Reggiani C, et al. Update on the use of confocal microscopy in melanoma and non-melanoma skin cancer. Giornale Italiano di Dermatologia e Venereologia 2015;150(5):547-63. [PubMed: 26140397]

Guitera 2010

Guitera P, Pellacani G, Crotty KA, Scolyer RA, Li LX, Bassoli S, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. Journal of Investigative Dermatology 2010;130(8):2080-91. [PubMed: 20393481]

Guitera 2013

Guitera P, Moloney FJ, Menzies SW, Stretch JR, Quinn MJ, Hong A, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. JAMA Dermatology 2013;149(6):692-8. [PubMed: 23553208]

Haenssle 2006

Haenssle HA, Krueger U, Vente C, Thoms KM, Bertsch HP, Zutt M, et al. Results from an observational trial: digital epiluminescence microscopy follow-up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. Journal of Investigative Dermatology 2006;126(5):980-5. [PubMed: 16514414]

Hennessy 2010

Hennessy R, Jacques S, Pellacani G, Gareau D. Clinical feasibility of rapid confocal melanoma feature detection. In: Kollias N, Choi B, Zeng H, Malek RS, Wong BJF, Ilgner JFR, et al, editors(s). Proceedings of SPIE. Photonic Therapeutics and Diagnostics VI edition. Vol. 7548. March 02, 2010. [DOI: 10.1117/12.842824]

Hoogedoorn 2014

Hoogedoorn L, Peppelman M, Van Erp PEJ, Gerritsen MJP. The use of in vivo reflectance confocal microscopy in clinical practice: prospective differentiation of difficult to distinguish nodular basal cell carcinomas and intradermal nevi. Nederlands Tijdschrift voor Dermatologie en Venereologie 2014;24(1):48. [EMBASE: 71623025]

Hoogedoorn 2015

Hoogedoorn L, Peppelman M, Blokx WA, van Erp PE, Gerritsen MJ. Prospective differentiation of clinically difficult to distinguish nodular basal cell carcinomas and intradermal nevi by non-invasive reflectance confocal microscopy: a case series study. Journal of the European Academy of Dermatology and Venereology : JEADV 2015;29(2):330-6. [PubMed: 24841762]

Humphrey 2006

Humphrey S, Walsh NM, Delaney L, Propperova I, Langley RG. Prognostic significance of vascularity in cutaneous melanoma: Pilot study using in vivo confocal scanning laser microscopy. Journal of Cutaneous Medicine and Surgery 2006; 10(3):122-7. [PubMed: 17241587]

Incel 2015

Incel P, Gurel MS, Erdemir AV. Vascular patterns of nonpigmented tumoral skin lesions: confocal perspectives. Skin Research and Technology 2015;21(3):333-9.

Kadouch 2015

Kadouch DJ, Schram ME, Leeflang MM, Limpens J, Spuls PI, de Rie MA. In vivo confocal microscopy of basal cell carcinoma: a systematic review of diagnostic accuracy. Journal of the European Academy of Dermatology and Venereology : JEADV 2015;29(10):1890-7. [PubMed: 26290493]

Kadouch 2015a

Kadouch DJ, Wolkerstorfer A, Elshot Y, Zupan-Kajcovski B, Crijns MB, Starink MV, et al. Treatment of basal cell carcinoma using a one-stop-shop with reflectance confocal microscopy: study design and protocol of a randomized controlled multicenter trial. JMIR Research Protocols 2015;4(3):e109. [PubMed: 26362616]

Kose 2014

Kose K, Cordova M, Duffy M, Flores ES, Brooks DH, Rajadhyaksha M. Video-mosaicing of reflectance confocal images for examination of extended areas of skin in vivo. British Journal of Dermatology 2014;171(5):1239-41. [PubMed: 24720744]

Langley 2001

Langley RG, Rajadhyaksha M, Dwyer PJ, Sober AJ, Flotte TJ, Anderson RR. Confocal scanning laser microscopy of benign and malignant melanocytic skin lesions in vivo. Journal of the American Academy of Dermatology 2001;45(3):365-76. [PubMed: 11511832]

Langley 2006

Langley RG, Burton E, Walsh N, Propperova I, Murray SJ. In vivo confocal scanning laser microscopy of benign lentigines: Comparison to conventional histology and in vivo characteristics of lentigo maligna. Journal of the American Academy of Dermatology 2006;55(1):88-97. [PubMed: 16781299]

Losi 2014

Losi A, Longo C, Cesinaro AM, Benati E, Witkowski A, Guitera P, et al. Hyporeflective pagetoid cells: a new clue for amelanotic melanoma diagnosis by reflectance confocal microscopy. British Journal of Dermatology 2014;171(1):48-54. [PubMed: 24329036]

Maier 2013

Maier T, Sattler EC, Braun-Falco M, Korting HC, Ruzicka T, Berking C. Reflectance confocal microscopy in the diagnosis of partially and completely amelanotic melanoma: report on seven cases. Journal of the European Academy of Dermatology and Venereology : JEADV 2013;27(1):e42-52. [PubMed: 22324783]

Malvehy 2012

Malvehy J, Hanke-Martinez M, Costa J, Salerni G, Carrera C, Puig S. Semiology and pattern analysis in nonmelanocytic lesions. In: Reflectance Confocal Microscopy for Skin Diseases. Berlin, Heidelberg: Springer, 2012:239-252. [DOI: 10.1007/978-3-642-21997-9_18]

Menge 2016

Menge TD, Hibler BP, Cordova MA, Nehal KS, Rossi AM. Concordance of handheld reflectance confocal microscopy (RCM) with histopathology in the diagnosis of lentigo maligna (LM): A prospective study. Journal of the American Academy of Dermatology 2016;74(6):1114-20. [PubMed: 26826051]

Miller 2011

Miller JH, Chrisler WB, Wang X, Sowa MB. Confocal microscopy for modeling electron microbeam irradiation of skin. Radiation & Environmental Biophysics 2011;50(3):365-9. [PubMed: 21604000]

Nobre 2011

Nobre Moura F, Dalle S, Depaepe L, Durupt F, Balme B, Thomas L. Melanoma: early diagnosis using in vivo reflectance confocal microscopy. Clinical and Experimental Dermatology 2011;36(2):209-11. [PubMed: 20659120]

Nori 2004

* Nori S, Rius-Diaz F, Cuevas J, Goldgeier M, Jaen P, Torres Abel, et al. Sensitivity and specificity of reflectance-mode confocal microscopy for in vivo diagnosis of basal cell carcinoma: a multicenter study. Journal of the American Academy of Dermatology 2004;51(6):923-30. [Other: ER4:15466027; PubMed: 15583584]

Pellacani 2005

Pellacani G, Cesinaro AM, Seidenari S. Reflectance-mode confocal microscopy of pigmented skin lesions--improvement in melanoma diagnostic specificity. Journal of the American Academy of Dermatology 2005;53(6):979-85. [PubMed: 16310058]

Pellacani 2007a

Pellacani G, Bassoli S, Longo C, Cesinaro AM, Seidenari S. Diving into the blue: in vivo microscopic characterization of the dermoscopic blue hue. Journal of the American Academy of Dermatology 2007;57(1):96-104. [PubMed: 17485141]

Pellacani 2008

Pellacani G, Longo C, Malvehy J, Puig S, Carrera C, Segura S, et al. In vivo confocal microscopic and histopathologic correlations of dermoscopic features in 202 melanocytic lesions. Archives of Dermatology 2008;144(12):1597-608. [PubMed: 19075142]

Pellacani 2009

Pellacani G, Vinceti M, Bassoli S, Braun R, Gonzalez S, Guitera P, et al. Reflectance confocal microscopy and features of melanocytic lesions: an internet-based study of the reproducibility of terminology. Archives of Dermatology 2009; 145(10):1137-43. [PubMed: 19841401]

Peppelman 2013

Peppelman M, Wolberink EA, Blokx WA, van de Kerkhof PC, van Erp PE, Gerritsen MJ. In vivo diagnosis of basal cell carcinoma subtype by reflectance confocal microscopy. Dermatology 2013;227(3):255-62. [PubMed: 24158236]

Peppelman 2015

Peppelman M, Nguyen KP, Hoogedoorn L, van Erp PE, Gerritsen MJ. Reflectance confocal microscopy: non-invasive distinction between actinic keratosis and squamous cell carcinoma. Journal of the European Academy of Dermatology and Venereology 2015;29(7):1302-9. [PubMed: 25357235]

Peppelman 2016

Peppelman M, Nguyen KP, Alkemade HA, Maessen-Visch B, Hendriks JC, van Erp PE, et al. Diagnosis of basal cell carcinoma by reflectance confocal microscopy: study design and protocol of a randomized controlled multicenter trial. JMIR Research Protocols 2016;5(2):e114. [PubMed: 27363577]

Puig 2012

Puig S, Di Giacomo TB, Serra D, Cabrini F, Alos L, Palou J, et al. Reflectance confocal microscopy of blue nevus. European Journal of Dermatology 2012;22(4):552-3. [PubMed: 22735078]

Reggiani 2015

Reggiani C, Manfredini M, Mandel VD, Farnetani F, Ciardo S, Bassoli S, et al. Update on non-invasive imaging techniques in early diagnosis of non-melanoma skin cancer. Giornale Italiano di Dermatologia e Venereologia 2015;150(4):393-405. [PubMed: 26184797]

Rishpon 2009

Rishpon A, Kim N, Scope A, Porges L, Oliviero MC, Braun RP, et al. Reflectance confocal microscopy criteria for squamous cell carcinomas and actinic keratoses. Archives of Dermatology 2009;145(7):766-72. [PubMed: 19620557]

Röwert-Huber 2007

Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. British Journal of Dermatology 2007;156(Suppl 3):8-12. [PubMed: 17488400]

Salerni 2011

Salerni G, Lovatto L, Carrera C, Palou J, Alos L, Puig-Butille JA, et al. Correlation among dermoscopy, confocal reflectance microscopy, and histologic features of melanoma and basal cell carcinoma collision tumor. Dermatologic Surgery 2011; 37(2):275-9. [PubMed: 21281387]

Scope 2009

Scope A, Mecca PS, Marghoob AA. skINsight lessons in reflectance confocal microscopy: rapid diagnosis of pigmented basal cell carcinoma. Archives of Dermatology 2009;145(1):106-7. [PubMed: 19153366]

Scope 2014

Scope A, Longo C. Recognizing the benefits and pitfalls of reflectance confocal microscopy in melanoma diagnosis. Dermatology Practical & Conceptual 2014;4(3):67-71. [DOI: 10.5826/dpc.0403a13]

Soyer 2013

Soyer HP, Prow TW. Reflectance confocal microscopy in the diagnosis of nodular skin lesions. British Journal of Dermatology 2013;169(1):4. [PubMed: 23834114]

Steiner 1992

Steiner A, Pehamberger H, Binder M, Wolff K. Pigmented Spitz nevi: improvement of the diagnostic accuracy by epiluminescence microscopy. Journal of the American Academy of Dermatology 1992;27(5 Pt 1):697-701. [PubMed: 1430390]

Stephens 2013

Stephens A, Fraga-Braghiroli N, Oliviero M, Rabinovitz H, Scope A. Spoke wheel-like structures in superficial basal cell carcinoma: a correlation between dermoscopy, histopathology, and reflective confocal microscopy. Journal of the American Academy of Dermatology 2013;69(5):e219-21. [PubMed: 24124839]

Stevenson 2013

Stevenson AD, Mickan S, Mallett S, Ayya M. Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. Dermatology Practical & Conceptual 2013;3(4):19-27. [DOI: 10.5826/dpc.0304a05]

Tannous 2009

Tannous Z, Al-Arashi M, Shah S, Yaroslavsky AN. Delineating melanoma using multimodal polarized light imaging. Lasers in Surgery & Medicine 2009;41(1):10-6. [PubMed: 19143015]

Willard 2011

Willard K, Warschaw KE, Swanson DL. Use of reflectance confocal microscopy to differentiate hidrocystoma from basal cell carcinoma. Dermatologic Surgery 2011;37(3):392-4. [PubMed: 21314800]

Witkowski 2016

* Witkowski AM, Ludzik J, DeCarvalho N, Ciardo S, Longo C, DiNardo A, et al. Non-invasive diagnosis of pink basal cell carcinoma: how much can we rely on dermoscopy and reflectance confocal microscopy? Skin Research and Technology 2016;22(2):230-7. [Other: ER4:25012281; PubMed: 26338448]

Xiong 2016

Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. Journal of the European Academy of Dermatology and Venereology : JEADV 2016;30(8):1295-302. [PubMed: 27230832]

Yelamos 2016

Yelamos O, Nehal KS. Integrating clinical information, dermoscopy and reflectance confocal microscopy to improve the diagnostic accuracy and confidence of amelanotic and lightly pigmented melanomas. British Journal of Dermatology 2016; 175(6):1147-8. [PubMed: 27996145]

Studies awaiting classification

Borsari 2016

Borsari S, Pampena R, Lallas A, Kyrgidis A, Moscarella E, Benati E, et al. Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis. JAMA Dermatology 2016;152(10):1093-98. [PubMed: 27580185]

Guitera 2016

Guitera P, Menzies SW, Argenziano G, Longo C, Losi A, Drummond M, et al. Dermoscopy and in vivo confocal microscopy are complementary techniques for diagnosis of difficult amelanotic and light-coloured skin lesions. British Journal of Dermatology 2016;175(6):1311-19. [PubMed: 27177158]

Jain 2017

Jain M, Pulijal SV, Rajadhyaksha M. The bedside diagnostic accuracy of a novice reflectance confocal microscopy reader for skin cancer detection in vivo in real-time: understanding challenges and potential pitfalls. In: Alfano RR, Demos SG, editors(s). Proceedings of SPIE. Optical Biopsy XV: Toward Real-Time Spectroscopic Imaging and Diagnosis edition. Vol. 10060. March 24, 2017. [DOI: 10.1117/12.2255685]

Ludzik 2016

Ludzik J, Witkowski AM, Roterman-Konieczna I, Bassoli S, Farnetani F, Pellacani G. Improving diagnostic accuracy of dermoscopically equivocal pink cutaneous lesions with reflectance confocal microscopy in telemedicine settings: double reader concordance evaluation of 316 cases. PloS One 2016;11(9):e0162495. [PubMed: 27606812]

Ongoing studies

Other references

Additional references

Abaffy 2010

Abaffy T, Duncan R, Riemer DD, Tietje O, Elgart G, Milikowski C, et al. Differential volatile signatures from skin, naevi and melanoma: a novel approach to detect a pathological process. PLoS One 2010;5(11):e13813. [PubMed: 21079799]

Altamura 2008

Altamura D, Avramidis M, Menzies SW. Assessment of the optimal interval for and sensitivity of short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma. Archives of Dermatology 2008;144(4):502-6. [PubMed: 18427044]

Annessi 2007

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. [PubMed: 17316894]

Argenziano 1998

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. [PubMed: 9875194]

Argenziano 2001

Argenziano G, Soyer HP. Dermoscopy of pigmented skin lesions--a valuable tool for early diagnosis of melanoma. Lancet Oncology 2001;2(7):443-9. [PubMed: 11905739]

Argenziano 2012

Argenziano G, Albertini G, Castagnetti F, De Pace B, Di Lernia V, Longo C, et al. Early diagnosis of melanoma: what is the impact of dermoscopy? Dermatologic Therapy 2012;25(5):403-9. [PubMed: 23046019]

Arnold 2014

Arnold M, Holterhues C, Hollestein LM, Coebergh JW, Nijsten T, Pukkala E, 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 2014;28(9):1170-8. [PubMed: 23962170]

Balch 2001

Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. Journal of Clinical Oncology 2001;19(16):3622-34. [PubMed: 11504744]

Balch 2009

Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. Journal of Clinical Oncology 2009;27(36):6199-206. [PubMed: 19917835]

Beer 2011

Beer J, Xu L, Tschandl P, Kittler H. Growth rate of melanoma in vivo and correlation with dermatoscopic and dermatopathologic findings. Dermatology Practical and Conceptual 2011;1(1):59-67. [PubMed: 24396722]

Binder 1997

Binder M, Schwarz M, Steiner A, Kittler H, Muellner M, Wolff K, et al. Epiluminescence microscopy of small pigmented skin lesions: short-term formal training improves the diagnostic performance of dermatologists. Journal of the American Academy of Dermatology 1997;36(2 Pt 1):197-202. [PubMed: 9039168]

Boring 1994

Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics, 1994. CA: a Cancer Journal for Clinicians 1994; 44(1):7-26. [PubMed: 8281473]

Bossuyt 2015

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527. [DOI: 10.1136/bmj.h5527; PubMed: 26511519]

Cancer Research UK 2017a

Cancer Research UK. Skin cancer statistics. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer#heading-One (accessed prior to 19 July 2017).

Cancer Research UK 2017b

Cancer Research UK. Skin cancer incidence statistics. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/incidence (accessed prior to 1 November 2017).

Chao 2013

Chao D, London Cancer (North and East). Guidelines for Cutaneous Malignant Melanoma Management August 2013. www.londoncancer.org/media/76373/london-cancer-melanoma-guidelines-2013-v1.0.pdf (accessed 25 February 2015).

Chapman 2011

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. New England Journal of Medicine 2011;364(26):2507-16. [PubMed: 21639808]

Chapman 2012

Chapman PB, Hauschild A, Robert C, Larkin J, Haanen JB, Ribas A, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. Journal of Clinical Oncology 2012;30(15 Suppl 1):8502. [EMBASE: 71004853]

Cho 2014

Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer survival mean progress? The insight from population incidence and mortality. Journal of the National Cancer Institute. Monographs 2014;2014(49):187-97. [PubMed: 25417232]

Chu 2006

Chu H, Cole SR. Bivariate meta-analysis for sensitivity and specificity with sparse data: a generalized linear mixed model approach (comment). Journal of Clinical Epidemiology 2006;59(12):1331-2. [PubMed: 17098577]

Church 2001

Church J, Williams H. Another sniffer dog for the clinic? Lancet 2001;358(9285):930. [PubMed: 11575380]

D'Amico 2008

D'Amico A, Bono R, Pennazza G, Santonico M, Mantini G, Bernabei M, et al. Identification of melanoma with a gas sensor array. Skin Research & Technology 2008;14(2):226-36. [PubMed: 18412567]

Debarbieux 2013

Debarbieux S, Depaepe L, Poulalhon N, Balme B, Dalle S, Thomas L. Reflectance confocal microscopy accurately discriminates between benign and malignant melanocytic lesions exhibiting a 'dermoscopic island'. Journal of the European Academy of Dermatology and Venereology 2013;27(2):159-65. [PubMed: 22486883]

Deeks 2005

Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. Journal of Clinical Epidemiology 2005;58(9):882-93. [PubMed: 16085191]

Dinnes 2018

Dinnes J, Chuchu N, Matin RN, Thompson D, Wong KY, Aldridge BJ, et al. The accuracy of dermoscopy as an addition to visual inspection for the diagnosis of cutaneous melanoma in adults. Cochrane Database of Systematic Reviews (in press).

Dummer 2014

Dummer R, Arenberger P, Ascierto PA, De Groot JW, Hallmeyer S, Lotem M, et al. 1130TiP-NEMO: a phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with advanced NRAS-mutant melanoma who are untreated or have progressed after any number of immunotherapy regimens. Annals of Oncology 2014;25(suppl_4):iv392. [PubMed: 28171154]

Efron 1983

Efron B. Estimating the error rate of a prediction rule: improvement on cross-validation. Journal of the American Statistical Association 1983;78(382):316-31. [DOI: 10.1080/01621459.1983.10477973]

Eggermont 2007

Eggermont AM, Gore M. Randomized adjuvant therapy trials in melanoma: surgical and systemic. Seminars in Oncology 2007;34(6):509-15. [PubMed: 18083374]

Erdmann 2013

Erdmann F, Lortet-Tieulent J, Schuz J, Zeeb H, Greinert R, Breitbart EW, 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. [PubMed: 22532371]

Esteva 2017

Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542(7639):115-118. [PubMed: 28117445]

Ferlay 2015

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 2015;136(5):E359-86. [PubMed: 25220842]

Ferris 2012

Ferris LK, Harris RJ. New diagnostic aids for melanoma. Dermatologic Clinics 2012;30(3):535-45. [PubMed: 22800557]

Friedman 1985

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. [PubMed: 3921200]

Gallagher 2008

Gallagher M, Wysocki CJ, Leyden JJ, Spielman AI, Sun X, Preti G. Analyses of volatile organic compounds from human skin. British Journal of Dermatology 2008;159(4):780-91. [PubMed: 18637798]

Garbe 2016

Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. European Journal of Cancer 2016;63:201-17. [PubMed: 27367293]

Gereli 2010

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. [PubMed: 20465608]

Grob 1998

Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Archives of Dermatology 1998;134(1):103-4. [PubMed: 9449921]

Guitera 2009

Guitera P, Pellacani G, Longo C, Seidenari S, Avramidis M, Menzies SW. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. Journal of Investigative Dermatology 2009;129(1):131-8. [PubMed: 18633444]

Guitera 2017

Guitera P, Menzies S, Chamberlain A, Soyer P, Cancer Council Australia Melanoma Guidelines Working Party. What is the role of confocal microscopy in melanoma diagnosis? [Clinical practice guidelines for the Diagnosis and Management of Melanoma]. wiki.cancer.org.au/australiawiki/index.php?oldid=158690 (accessed 18 May 2017).

Haenssle 2010

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. [PubMed: 20226567]

Hamid 2013

Hamid O, Sosman JA, Lawrence DP, Sullivan RJ, Ibrahim N, Kluger HM, et al. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM). Journal of Clinical Oncology 2013;31(15 Suppl 1):9010. [EMBASE: 71099860]

Hauschild 2014

Hauschild A, Chen SC, Weichenthal M, Blum A, King HC, Goldsmith J, et al. To excise or not: impact of MelaFind on German dermatologists' decisions to biopsy atypical lesions. Journal der Deutschen Dermatologischen Gesellschaft 2014; 12(7):606-14. [PubMed: 24944011]

Hodi 2010

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine 2010;363(8):711-23. [PubMed: 20525992]

Hodi 2016

Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncology 2016;17(11):1558–1568. [DOI: 10.1016/S1470-2045(16)30366-7; PubMed: 27622997]

Kasprzak 2015

Kasprzak JM, Xu YG. Diagnosis and management of lentigo maligna: a review. Drugs in Context 2015;4:212281. [PubMed: 26082796]

Kittler 2002

Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy [Review]. Lancet Oncology 2002; 3(3):159-65. [PubMed: 11902502]

Kittler 2011

Kittler H, Rosendahl C, Cameron A, Tschandl P. Dermatoscopy. An algorithmic method based on pattern analysis. Austria: Facultas.WUV, 2011. [Other: ISBN-10: 3708907175]

Kokolakis 2012

Kokolakis A, Zacharakis G, Krasagakis K, Lasithiotakis K, Favicchio R, Spiliopoulos G, et al. Prehistological evaluation of benign and malignant pigmented skin lesions with optical computed tomography. Journal of Biomedical Optics 2012; 17(6):066004. [PubMed: 22734760]

Korn 2008

Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. Journal of Clinical Oncology 2008;26(4):527-34. [PubMed: 18235113]

Kwak 2013

Kwak J, Gallagher M, Ozdener MH, Wysocki CJ, Goldsmith BR, Isamah A, et al. Volatile biomarkers from human melanoma cells. Journal of Chromatography B: Analytical Technologies in the Biomedical & Life Sciences 2013;931:90-6. [PubMed: 23770738]

Kyrgidis 2015

Kyrgidis A, Tzellos T, Mocellin S, Apalla Z, Lallas A, Pilati P, et al. Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD010307 DOI: 10.1002/14651858.CD010307.pub2.

Larkin 2014

Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. New England Journal of Medicine 2014;371(20):1867-76. [PubMed: 25265494]

Larkin 2015

Larkin J, Lao CD, Urba WJ, McDermott DF, Horak C, Jiang J, et al. Efficacy and safety of nivolumab in patients with BRAF V600 Mutant and BRAF wild-type advanced melanoma: a pooled analysis of 4 clinical trials. JAMA Oncology 2015; 1(4):433-40. [PubMed: 26181250]

Leff 2008

Leff B, Finucane TE. Gizmo idolatry. JAMA 2008;299(15):1830-2. [PubMed: 18413879]

Longo 2011

Longo C, Rito C, Beretti F, Cesinaro AM, Piñeiro-Maceira J, Seidenari S, et al. De novo melanoma and melanoma arising from pre-existing nevus: in vivo morphologic differences as evaluated by confocal microscopy. Journal of the American Academy of Dermatology 2011;65(3):604-14. [PubMed: 21715047]

MacKie 1985

MacKie RM, English J, Aitchison TC, Fitzsimons CP, Wilson P. The number and distribution of benign pigmented moles (melanocytic naevi) in a healthy British population. British Journal of Dermatology 1985;113(2):167-74. [PubMed: 4027184]

MacKie 1990

MacKie RM. Clinical recognition of early invasive malignant melanoma. BMJ 1990;301(6759):1005-6. [PubMed: 2249043]

Maio 2015

Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. Journal of Clinical Oncology 2015; 33(10):1191-6. [PubMed: 25713437]

Maley 2014

Maley A, Rhodes AR. Cutaneous melanoma: preoperative tumor diameter in a general dermatology outpatient setting. Dermatologic Surgery 2014;40(4):446-54. [PubMed: 24479783]

Malvehy 2014

Malvehy J, Hauschild A, Curiel-Lewandrowski C, Mohr P, Hofmann-Wellenhof R, Motley R, et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. British Journal of Dermatology 2014;171(5):1099-107. [PubMed: 24841846]

Marsden 2010

Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH, et al. BAD Guidelines: Revised UK guidelines for the management of cutaneous melanoma 2010. British Journal of Dermatology 2010;163(2):238-56. [PubMed: 20608932]

Menzies 1996

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. [PubMed: 8859028]

Mistry 2011

Mistry M, Parkin DM, Ahmad AS, Sasieni P. Cancer incidence in the United Kingdom: projections to the year 2030. British Journal of Cancer 2011;105(11):1795-803. [PubMed: 22033277]

Mocellin 2013

Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008955 DOI: 10.1002/14651858.CD008955.pub2.

Moncrieff 2002

Moncrieff M, Cotton S, Claridge E, Hall P. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions. British Journal of Dermatology 2002;146(3):448-57. [PubMed: 11952545]

Monheit 2011

Monheit G, Cognetta AB, Ferris L, Rabinovitz H, Gross K, Martini M, et al. The performance of MelaFind: a prospective multicenter study. Archives of Dermatology 2011;147(2):188-94. [PubMed: 20956633]

Moreau 2013

Moreau JF, Weissfeld JL, Ferris LK. Characteristics and survival of patients with invasive amelanotic melanoma in the USA. Melanoma Research 2013;23(5):408-13. [PubMed: 23883947]

Morton 2014

Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. New England Journal of Medicine 2014;370(7):599-609. [PubMed: 24521106]

Nachbar 1994

Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions. Journal of the American Academy of Dermatology 1994; 30(4):551-9. [PubMed: 8157780]

NICE 2012a

National Institute for Health and Care Excellence. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. www.nice.org.uk/guidance/ta268 (accessed prior to 19 July 2017).

NICE 2012b

National Institute for Health and Care Excellence. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. www.nice.org.uk/guidance/ta269 (accessed prior to 19 July 2017).

NICE 2014a

National Institute for Health and Care Excellence. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. www.nice.org.uk/guidance/ta321 (accessed prior to 19 July 2017).

NICE 2014b

National Institute for Health and Care Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. www.nice.org.uk/guidance/ta319 (accessed prior to 19 July 2017).

NICE 2015a

National Institute for Health and Care Excellence. Melanoma: assessment and management. www.nice.org.uk/guidance/ng14 (accessed prior to 19 July 2017).

NICE 2015b

National Institute for Health and Care Excellence. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. www.nice.org.uk/guidance/ta366 (accessed prior to 19 July 2017).

NICE 2015c

National Institute for Health and Care Excellence. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. www.nice.org.uk/guidance/ta357 (accessed prior to 19 July 2017).

NICE 2015d

National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral. www.nice.org.uk/guidance/ng12 (accessed prior to 19 July 2017).

NICE 2016a

National Institute for Health and Care Excellence. Nivolumab in combination with ipilimumab for treating advanced melanoma. www.nice.org.uk/guidance/ta400 (accessed prior to 19 July 2017).

NICE 2016b

National Institute for Health and Care Excellence. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. www.nice.org.uk/guidance/ta396 (accessed prior to 19 July 2017).

NICE 2017

National Institute for Health and Care Excellence. Skin cancer. www.nice.org.uk/guidance/conditions-and-diseases/cancer/skin-cancer (accessed prior to 1 November 2017).

Norman 2009

Norman G, Barraclough K, Dolovich L, Price D. Iterative diagnosis. BMJ 2009;339:b3490. [PubMed: 19773326]

Pasquali 2014

Pasquali S, Kefford R, Chiarion Sileni V, Nitti D, Rossi CR, Pilati P, et al. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD011123 DOI: 10.1002/14651858.CD011123.

Pehamberger 1987

Pehamberger H, Steiner A, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. I. Pattern analysis of pigmented skin lesions. Journal of the American Academy of Dermatology 1987;17(4):571-83. [PubMed: 3668002]

Pehamberger 1993

Pehamberger H, Binder M, Steiner A, Wolff K. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. Journal of Investigative Dermatology 1993;100(3):356S-62S. [PubMed: 8440924]

Pellacani 2009a

Pellacani G, Scope A, Ferrari B, Pupelli G, Bassoli S, Longo C, et al. New insights into nevogenesis: in vivo characterization and follow-up of melanocytic nevi by reflectance confocal microscopy. Journal of the American Academy of Dermatology 2009;61(6):1001-13. [PubMed: 19833408]

Pellacani 2014

Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. British Journal of Dermatology 2014;171(5):1044-51. [PubMed: 24891083]

Rajadhyaksha 1995

Rajadhyaksha M, Grossman M, Esterowitz D, Webb RH, Anderson RR. In vivo confocal scanning laser microscopy of human skin: melanin provides strong contrast. Journal of Investigative Dermatology 1995;104(6):946-52. [PubMed: 7769264]

Rajadhyaksha 2017

Rajadhyaksha M, Marghoob A, Rossi A, Halpern AC, Nehal KS. Reflectance confocal microscopy of skin in vivo: from bench to bedside. Lasers in Surgery and Medicine 2017;49(1):7-19. [PubMed: 27785781]

Rajpara 2009

Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. [Review] [95 refs]. British Journal of Dermatology 2009;161(3):591-604. [PubMed: 19302072]

Reitsma 2005

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 [Review]. Journal of Clinical Epidemiology 2005; 58(10):982-90. [PubMed: 16168343]

Ruocco 2011

Ruocco E, Brunetti G, Del Vecchio M, Ruocco V. The practical use of cytology for diagnosis in dermatology [Review]. Journal of the European Academy of Dermatology & Venereology 2011;25(2):125-9. [PubMed: 20553359]

Rutjes 2005

Rutjes AW, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PM. Case-control and two-gate designs in diagnostic accuracy studies [Review]. Clinical Chemistry 2005;51(8):1335-41. [PubMed: 15961549]

Rutjes 2006

Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias and variation in diagnostic accuracy studies. CMAJ 2006;174(4):469-76. [PubMed: 16477057]

Rutter 2001

Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Statistics in Medicine 2001;20(19):2865-84. [PubMed: 11568945]

SAS 2012

SAS 2012 [Computer program]. Version 9.3. Cary, NC, USA: SAS Institute Inc., 2012.

Scope 2007

Scope A, Benvenuto-Andrade C, Agero AL, Malvehy J, Puig S, Rajadhyaksha M, et al. In vivo reflectance confocal microscopy imaging of melanocytic skin lesions: consensus terminology glossary and illustrative images. Journal of the American Academy of Dermatology 2007;57(4):644-58. [PubMed: 17630045]

Scotto di Santolo 2015

Scotto di Santolo M, Sagnelli M, Mancini M, Scalvenzi M, Delfino M, Schonauer F, et al. High-resolution color-Doppler ultrasound for the study of skin growths. Archives of Dermatological Research 2015;307(7):559-66. [PubMed: 25604691]

SEER 2017

SEER. Cancer Stat Facts: Melanoma of the Skin (the Surveillance, Epidemiology, and End Results (SEER) Program). www.seer.cancer.gov/statfacts/html/melan.html (accessed prior to 01 November 2017).

Shaikh 2012

Shaikh WR, Xiong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. Archives of Dermatology 2012;148(1):30-6. [PubMed: 21931016]

SIGN 2017

Scottish Intercollegiate Guidelines Network. Cutaneous Melanoma. www.sign.ac.uk/sign-146-melanoma.html (accessed prior to 19 July 2017).

Sladden 2009

Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, et al. Surgical excision margins for primary cutaneous melanoma. Cochrane Database of Systematic Reviews 2009, Issue 10. Art. No.: CD004835 DOI: 10.1002/14651858.CD004835.pub2.

Slater 2014

Slater D, Walsh M. Standards and datasets for reporting cancers: Dataset for the histological reporting of primary cutaneous malignant melanoma and regional lymph nodes, May 2014. www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G125_DatasetMaligMelanoma_May14.pdf (accessed 29 July 2015).

Sobarun 2015

Sobarun P. Reflectance confocal microscopy. www.dermnetnz.org/topics/reflectance-confocal-microscopy/ (accessed 18 May 2017).

Sober 1979

Sober AJ, Fitzpatrick TB, Mihm MC, Wise TG, Pearson BJ, Clark WH, et al. Early recognition of cutaneous melanoma. JAMA 1979;242(25):2795-9. [PubMed: 501893]

Steiner 1987

Steiner A, Pehamberger H, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. II. Diagnosis of small pigmented skin lesions and early detection of malignant melanoma. Journal of the American Academy of Dermatology 1987; 17(4):584-91. [PubMed: 3668003]

Stolz 1994

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. [EMBASE: 24349113]

Sznol 2013

Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clinical Cancer Research 2013;19(5):1021-34. [PubMed: 23460533]

Takwoingi 2010

Takwoingi Y, Deeks J. MetaDAS: a SAS macro for meta-analysis of diagnostic accuracy studies. User Guide Version 1.3. 2010. www.methods.cochrane.org/sites/methods.cochrane.org.sdt/files/public/uploads/MetaDAS%20Readme%20v1.3%20May%202

(accessed prior to 17 July 2017).

Takwoingi 2013

Takwoingi Y, Leeflang MM, Deeks JJ. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. Annals of Internal Medicine 2013;158(7):544-54. [PubMed: 23546566]

Takwoingi 2015

Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Statistical Methods in Medical Research 2015;24:1-19. [DOI: 10.1177/0962280215592269]

Terushkin 2012

Terushkin V, Dusza SW, Scope A, Argenziano G, Bahadoran P, Cowell L, et al. Changes observed in slow-growing melanomas during long-term dermoscopic monitoring. British Journal of Dermatology 2012;166(6):1213-20. [DOI: 10.1111/j.1365-2133.2012.10846.x]

Themstrup 2015

Themstrup L, Jemec GB. Optical coherence tomography and its role for delineating the thickness of keratinocyte dysplasia and neoplasia. Current Problems in Dermatology 2015;46:95-100. [PubMed: 25561212]

Thomas 1998

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. [PubMed: 9693179]

Villanueva 2010

Villanueva J, Vultur A, Lee JT, Somasundaram R, Fukunaga-Kalabis M, Cipolla AK, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 2010;18(6):683-95. [PubMed: 21156289]

Wachsman 2011

Wachsman W, Morhenn V, Palmer T, Walls L, Hata T, Zalla J, et al. Noninvasive genomic detection of melanoma. British Journal of Dermatology 2011;164(4):797-806. [PubMed: 21294715]

Walter 2012

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 2012;345:e4110. [PubMed: 22763392]

Wells 2012

Wells R, Gutkowicz-Krusin D, Veledar E, Toledano A, Chen SC. Comparison of diagnostic and management sensitivity to melanoma between dermatologists and MelaFind: a pilot study. Archives of Dermatology 2012;148(9):1083-4. [PubMed: 22986873]

Whiting 2011

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine 2011;155(8):529-36. [PubMed: 22007046]

Williams 1989

Williams H, Pembroke A. Sniffer dogs in the melanoma clinic? Lancet 1989;1(8640):734. [PubMed: 2564551]

Zemelman 2014

Zemelman VB, Valenzuela CY, Sazunic I, Araya I. Malignant melanoma in Chile: different site distribution between private and state patients. Biological Research 2014;47(1):34. [PubMed: 25204018]

Other published versions of this review

Dinnes 2015a

Dinnes J, Wong KY, Gulati A, Chuchu N, Leonardi-Bee J, Bayliss SE, et al. Tests to assist in the diagnosis of keratinocyte skin cancers in adults: a generic protocol. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD011901 DOI: 10.1002/14651858.CD011901.

Dinnes 2015b

Dinnes J, Matin RN, Moreau JF, Patel L, Chan SA, Wong KY, et al. Tests to assist in the diagnosis of cutaneous melanoma in adults: a generic protocol. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD011902 DOI: 10.1002/14651858.CD011902.

Classification pending references

AB 2016), 168 lesions (from 128 cases) were imaged with RCM to determine BCC and or melanoma in dermoscopically equivocal lesions. To evaluate the learning curve of the novice reader, diagnostic accuracy

was evaluated at the end of 15 months, as well as during the first half (8 months) and latter half (seven months) of the study. Histopathological diagnosis was available in 95/168 lesions, including 38 melanocytic lesions (ML: 13 melanomas and 25 nevi) and 57 non-melanocytic lesions (NML: 26 BCCs, 4 SCCs and 27 benign). The remaining 73/168 lesions (43.45%) were not biopsied (received topical treatment, monitoring). On RCM, 22/26 (84.61%) BCCs and 11/13 (84.61%) melanomas were correctly diagnosed. BCC was missed in 3/26 (11.53%) lesions and melanoma in 2/13 (15.38%) lesions; these lesions were diagnosed mostly as superficial BCCs and focal epidermal changes overlying deeply situated melanoma nodule on histopathology, respectively. False positive diagnosis of BCC was obtained in 7/23 (30.4%) lesions and of melanoma in 2/22 (4.5%) lesions

AB - Reflectance confocal microscopy (RCM) is a non-invasive device that images skin lesions in vivo at a cellular resolution to guide management of patient care. We assessed the diagnostic potential of a novice RCM reader, in clinical settings, at the bedside. Over a period of 15 months (August 2015- November 2016), 168 lesions (from 128 cases) were imaged with RCM to determine BCC and or melanoma in dermoscopically equivocal lesions. To evaluate the learning curve of the novice reader, diagnostic accuracy was evaluated at the end of 15 months, as well as during the first half (8 months) and latter half (seven months) of the study. Histopathological diagnosis was available in 95/168 lesions, including 38 melanocytic lesions (ML: 13 melanomas and 25 nevi) and 57 non-melanocytic lesions (NML: 26 BCCs, 4 SCCs and 27 benign). The remaining 73/168 lesions (43.45%) were not biopsied (received topical treatment, monitoring). On RCM, 22/26 (84.61%) BCCs and 11/13 (84.61%) melanomas were correctly diagnosed. BCC was missed in 3/26 (11.53%) lesions and melanoma in 2/13 (15.38%) lesions; these lesions were diagnosed mostly as superficial BCCs and focal epidermal changes overlying deeply situated melanoma nodule on histopathology, respectively. False positive diagnosis of BCC was obtained in 7/23 (30.4%) lesions and of melanoma in 2/22 (4.5%) lesions;these were diagnosed mostly as benign inflamed keratosis and moderately atypical dysplastic nevus on histopathology, respectively. In 7 lesions BCC or melanoma could not be ruled out. A marked increase in the sensitivity and specificity was noticed between the two halves of the study. An overall high diagnostic accuracy of 80.28% with high sensitivity and specificity of 80.68% and 80.8%, respectively in diagnosing skin cancers was obtained. Based on this study, we identified some current limitations and potential pitfalls of RCM. The fact that the diagnostic accuracy of the novice reader increased with time, indicates a learning curve reading RCM images. Additionally, current technical limitations of RCM such as inability to differentiate various cell types, sampling error, and, shallow depth of imaging also lead to false diagnosis. Efforts are ongoing to overcome these challenges by building US based teaching-training program and through a multimodal imaging approach for better diagnosis and patient care..

AB 2016), 168 lesions (from 128 cases) were imaged with RCM to determine BCC and or melanoma in dermoscopically equivocal lesions. To evaluate the learning curve of the novice reader, diagnostic accuracy was evaluated at the end of 15 months, as well as during the first half (8 months) and latter half (seven months) of the study. Histopathological diagnosis was available in 95/168 lesions, including 38 melanocytic lesions (ML: 13 melanomas and 25 nevi) and 57 non-melanocytic lesions (NML: 26 BCCs, 4 SCCs and 27 benign). The remaining 73/168 lesions (43.45%) were not biopsied (received topical treatment, monitoring). On RCM, 22/26 (84.61%) BCCs and 11/13 (84.61%) melanomas were correctly diagnosed. BCC was missed in 3/26 (11.53%) lesions and melanoma in 2/13 (15.38%) lesions; these lesions were diagnosed mostly as superficial BCCs and focal epidermal changes overlying deeply situated melanoma nodule on histopathology, respectively. False positive diagnosis of BCC was obtained in 7/23 (30.4%) lesions and of melanoma in 2/22 (4.5%) lesionsa

AB - Reflectance confocal microscopy (RCM) is a non-invasive device that images skin lesions in vivo at a cellular resolution to guide management of patient care. We assessed the diagnostic potential of a novice RCM reader, in clinical settings, at the bedside. Over a period of 15 months (August 2015- November 2016), 168 lesions (from 128 cases) were imaged with RCM to determine BCC and or melanoma in dermoscopically equivocal lesions. To evaluate the learning curve of the novice reader, diagnostic accuracy was evaluated at the end of 15 months, as well as during the first half (8 months) and latter half (seven months) of the study. Histopathological diagnosis was available in 95/168 lesions, including 38 melanocytic lesions (ML: 13 melanomas and 25 nevi) and 57 non-melanocytic lesions (NML: 26 BCCs, 4 SCCs and 27 benign). The remaining 73/168 lesions (43.45%) were not biopsied (received topical treatment, monitoring). On RCM, 22/26 (84.61%) BCCs and 11/13 (84.61%) melanomas were correctly diagnosed. BCC was missed in 3/26 (11.53%) lesions and melanoma in 2/13 (15.38%) lesions; these lesions were diagnosed mostly as superficial BCCs and focal epidermal changes overlying deeply situated melanoma nodule on histopathology, respectively. False positive diagnosis of BCC was obtained in 7/23 (30.4%) lesions and of melanoma in 2/22 (4.5%) lesions;these were diagnosed mostly as benign inflamed keratosis and moderately atypical dysplastic nevus on histopathology, respectively. In 7 lesions BCC or melanoma could not be ruled out. A marked increase in the sensitivity and specificity was noticed between the two halves of the study. An overall high diagnostic accuracy of 80.28% with high sensitivity and specificity of 80.68% and 80.8%, respectively in diagnosing skin cancers was obtained. Based on this study, we identified some current limitations and potential pitfalls of RCM. The fact that the diagnostic accuracy of the novice reader increased with time, indicates a learning curve reading RCM images. Additionally, current technical limitations of RCM such as inability to differentiate various cell types, sampling error, and, shallow depth of imaging also lead to false diagnosis. Efforts are ongoing to overcome these challenges by building US based teaching-training program and through a multimodal imaging approach for better diagnosis and patient care..

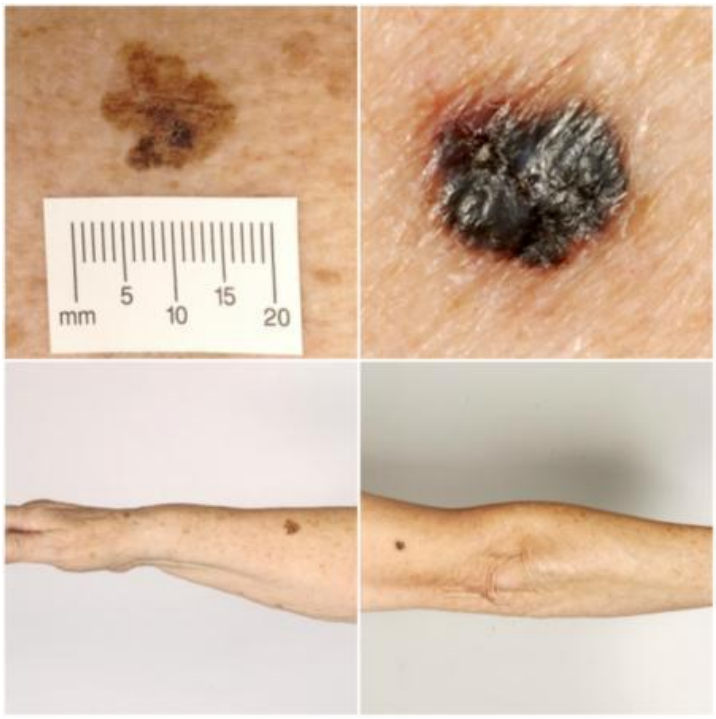
Data and analyses

Data tables by test

Test	Studies	Participants
1 RCM in any lesion suspicious for melanoma (MM)	3	506
2 RCM in studies of other lesion types (MM)	2	203
3 RCM in any lesion suspicious for melanoma (MM+MiS)	9	1452
4 RCM in equivocal lesion studies (MM+MiS)	7	1177
5 RCM in studies of other lesion types (MM+MiS)	2	159
6 Dermoscopy in any lesion suspicious for melanoma (MM+MiS)	3	451
7 Dermoscopy in equivocal lesion studies (MM+MiS)	3	645
8 Dermoscopy in studies of other lesion types (MM+MiS)	1	96
9 RCM in any lesion suspicious for melanoma (Any)	4	912
10 RCM in equivocal lesion studies (Any)	3	468
11 RCM score at ≥ 3 (MM)	1	50
12 Segura algorithm at >-1 (MM)	1	100
13 Guitera Two-step alg (significant characteristics) (MM)	1	356
14 No algorithm (observer diagnosis) (MM)	1	63
15 No algorithm (significant characteristics) (MM)	1	140
16 RCM score at ≥ 2 (MM+MiS)	1	351
17 RCM score at ≥ 3 (MM+MiS)	4	718
18 RCM score at threshold NR (likely ≥ 3) (MM+MiS)	2	491
19 RCM score at ≥ 4 (MM+MiS)	3	579
20 Segura algorithm at >-1 (MM+MiS)	4	863
21 Guitera Two-step alg (significant chars for MM) (MM+MiS)	1	356
22 Pellacani Two step algorithm (dysplastic-MM) image-based (MM+MiS)	2	130
23 RCM CAD algorithm (MM+MiS)	1	92
24 No algorithm (significant characteristics) (MM+MiS)	2	331
25 No algorithm (selected characteristics) (MM+MiS)	1	125
26 No algorithm (observer diagnosis) (MM+MiS)	4	578
27 No algorithm (observer diagnosis) paired in-person (MM+MiS)	1	317
28 No algorithm (excise decision) (MM+MiS)	1	323
29 No algorithm (excise decision) paired in-person (MM+MiS)	1	317
30 RCM score at ≥ 3 (Any)	1	50
31 RCM score at threshold NR (likely ≥ 3) (Any)	2	491
32 Segura algorithm at >-1 (Any)	1	356
33 Pellacani Two step algorithm (dysplastic-MM) (Any)	1	60
34 Guitera Two-step alg (significant characteristics) (Any)	1	356
35 No algorithm (observer diagnosis) (Any)	2	423
36 No algorithm (observer diagnosis) paired in-person (Any)	1	317
37 No algorithm (excise decision) (Any)	1	323
38 No algorithm (excise decision) paired in-person (Any)	1	317
39 Observer experience high - any lesion suspicious for melanoma (MM)	2	456
40 Observer experience low - any lesion suspicious for melanoma (MM)	1	50
41 MM1 observer experience high other	1	140
42 MM1 observer experience NR other	1	63
43 Observer experience high - any lesion suspicious for melanoma (MM+MiS)	8	1402
44 Observer experience low - any lesion suspicious for melanoma (MM+MiS)	2	368
45 Observer experience high - equivocal lesion studies (MM+MiS)	6	1113
46 Observer experience low - equivocal lesion studies (MM+MiS)	1	100
47 Observer experience NR - equivocal lesion studies (MM+MiS)	1	64
48 Observer experience NR - other study populations (MM+MiS)	2	159
49 Observer experience high - equivocal lesion studies (Any)	3	468
50 Observer experience low - equivocal lesion studies (Any)	1	100
51 Observer experience high - any lesion suspicious for melanoma (Any)	3	862
52 Observer experience low - any lesion suspicious for melanoma (Any)	2	368
53 MM2 any scale	16	2465

Figures

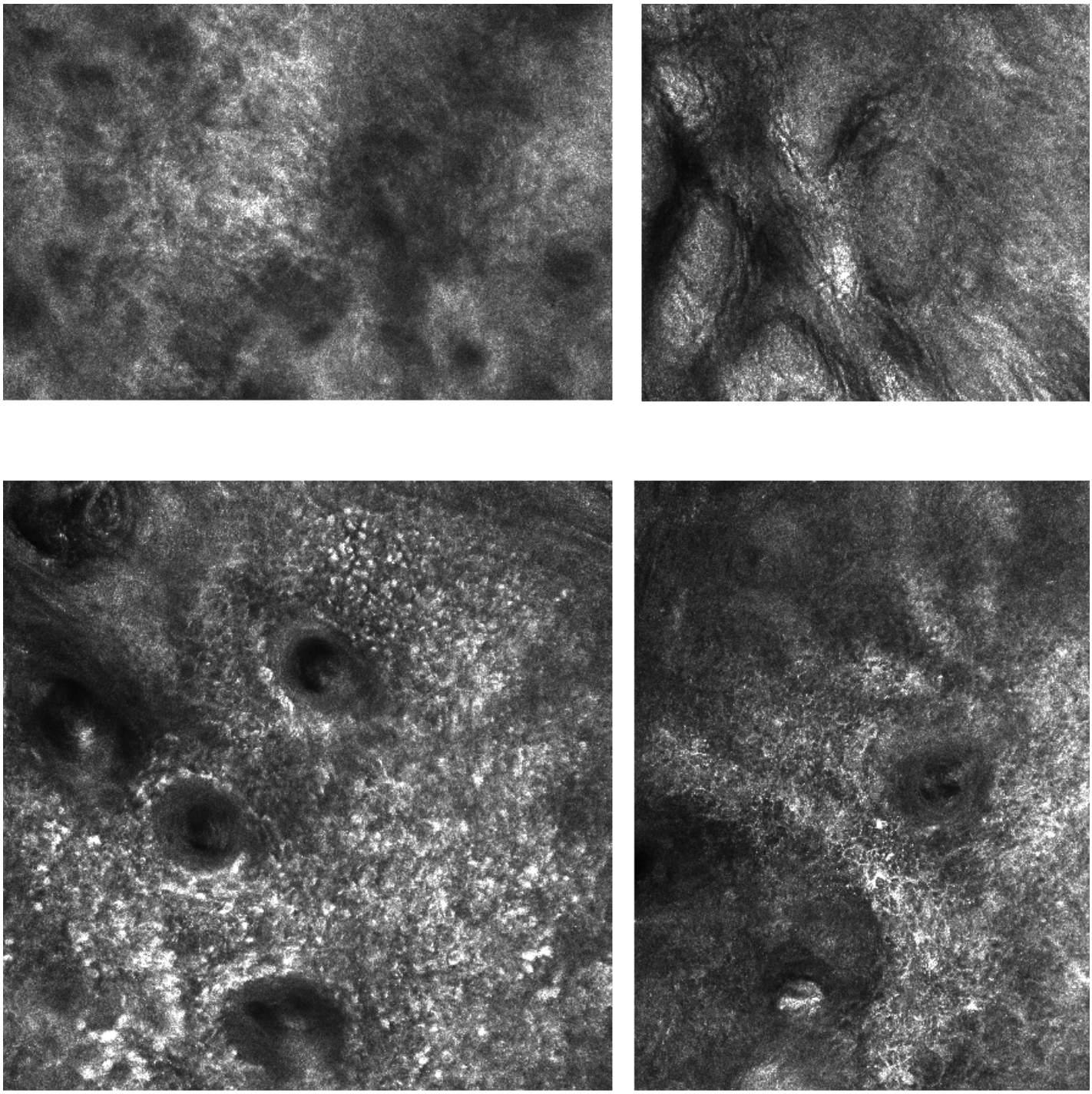
Figure 1



Caption

Sample photographs of superficial spreading melanoma (left) and nodular melanoma (right)

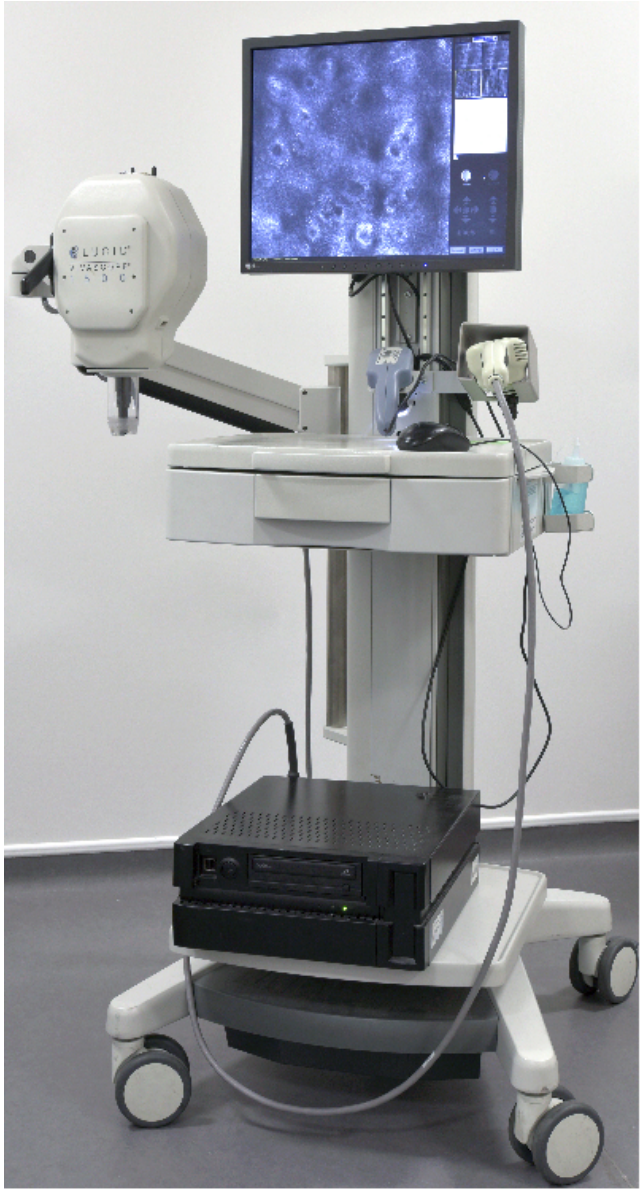
Figure 2



Caption

RCM images of normal skin (top) and of lentigo maligna (bottom)

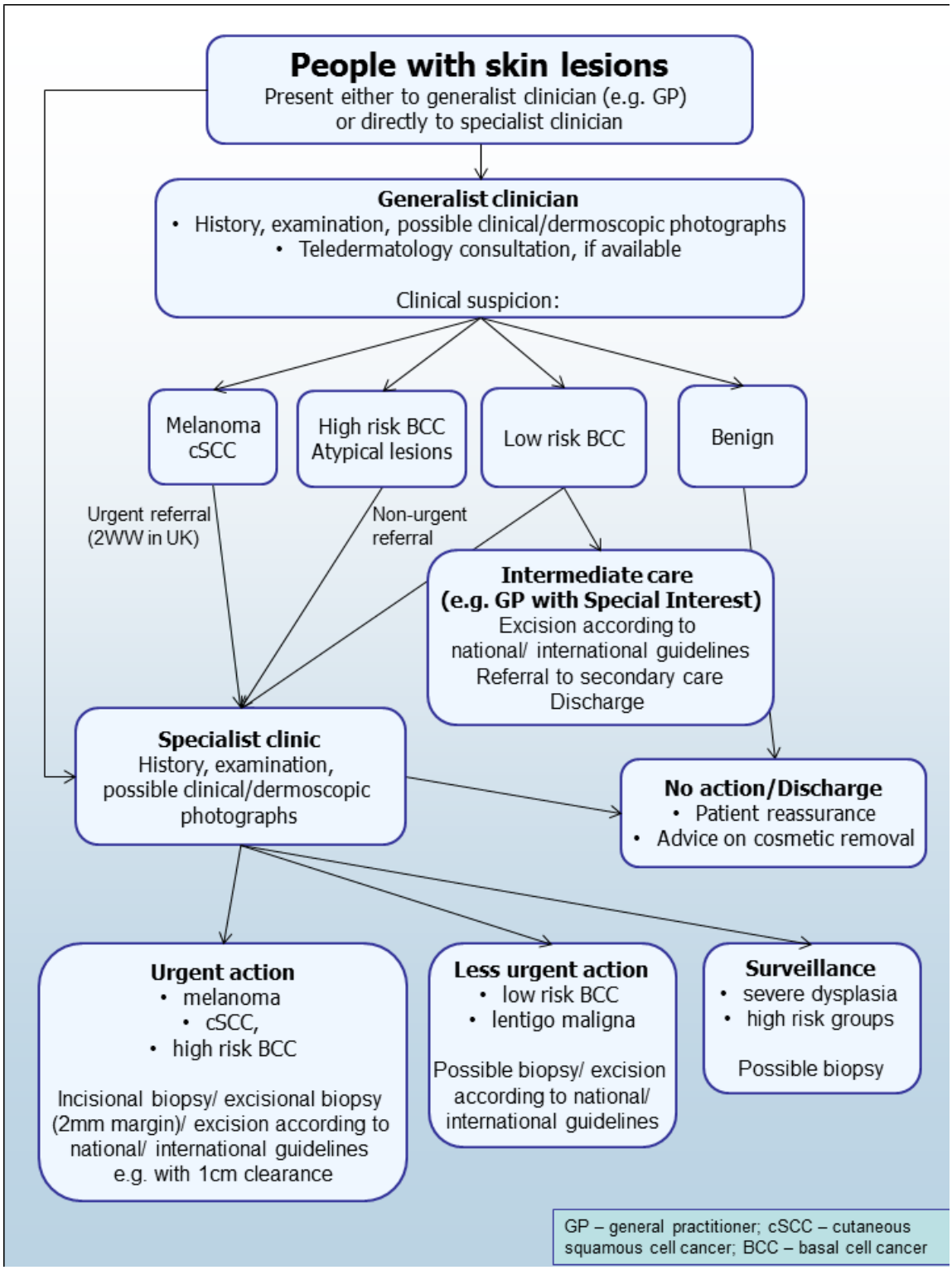
Figure 3



Caption

Caliber ID Vivascope 1500 with 3000 attachment

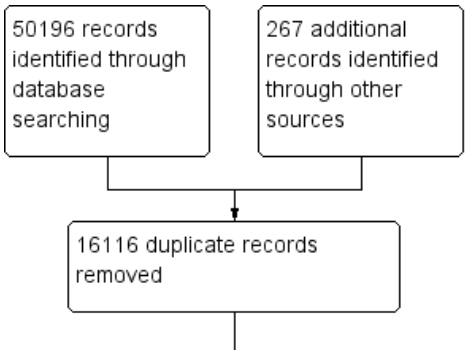
Figure 4

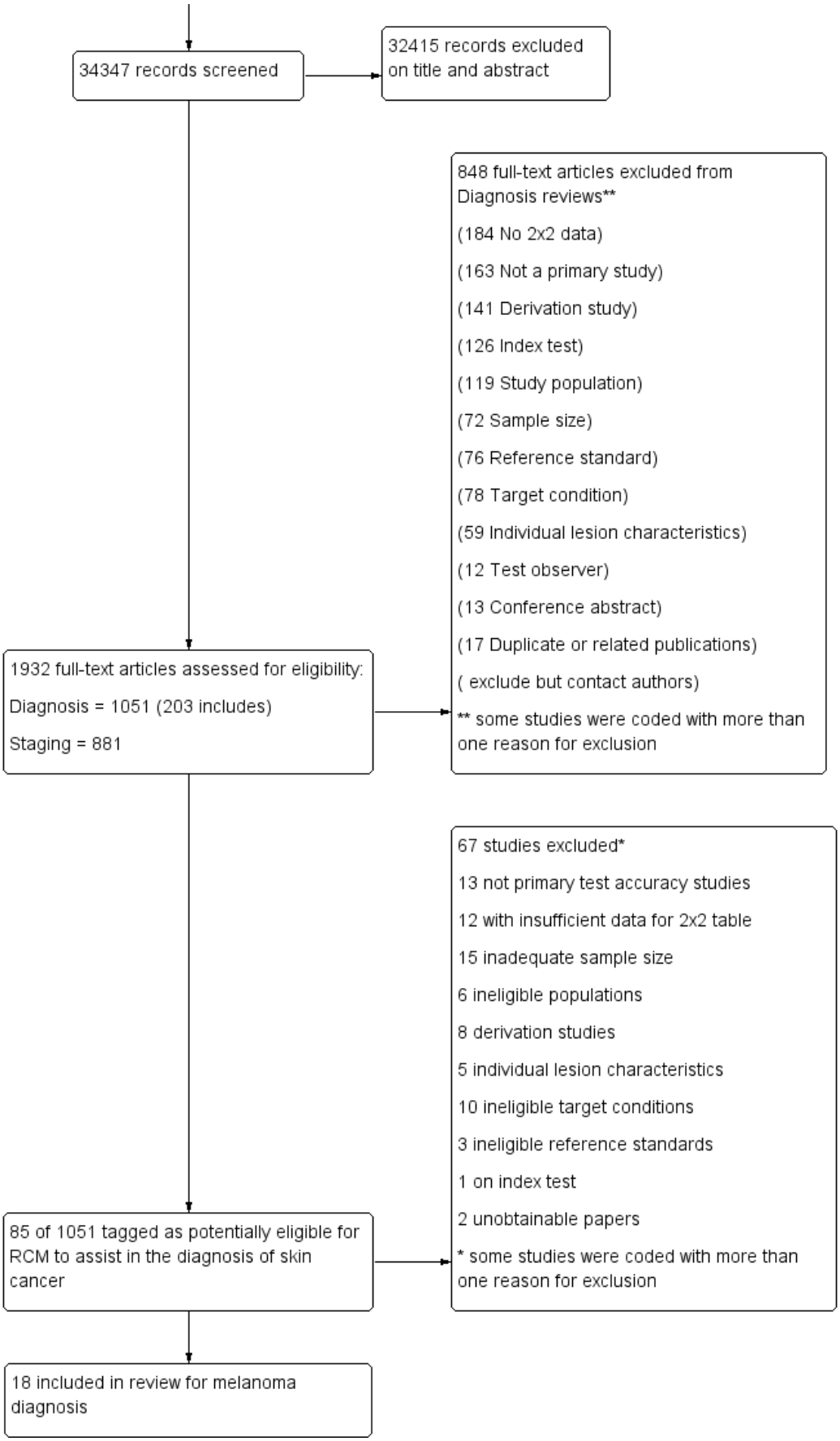


Caption

Current clinical pathway for people with skin lesions

Figure 5

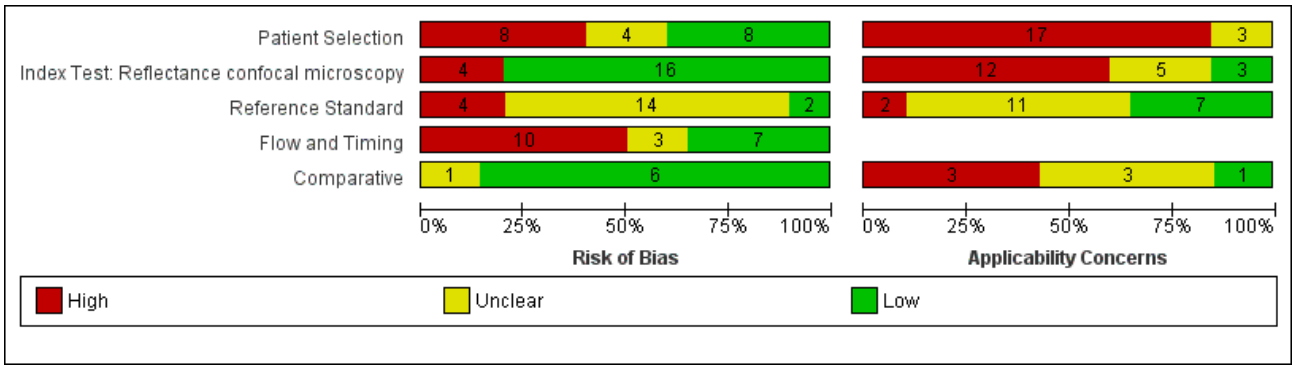




Caption

PRISMA flow diagram.

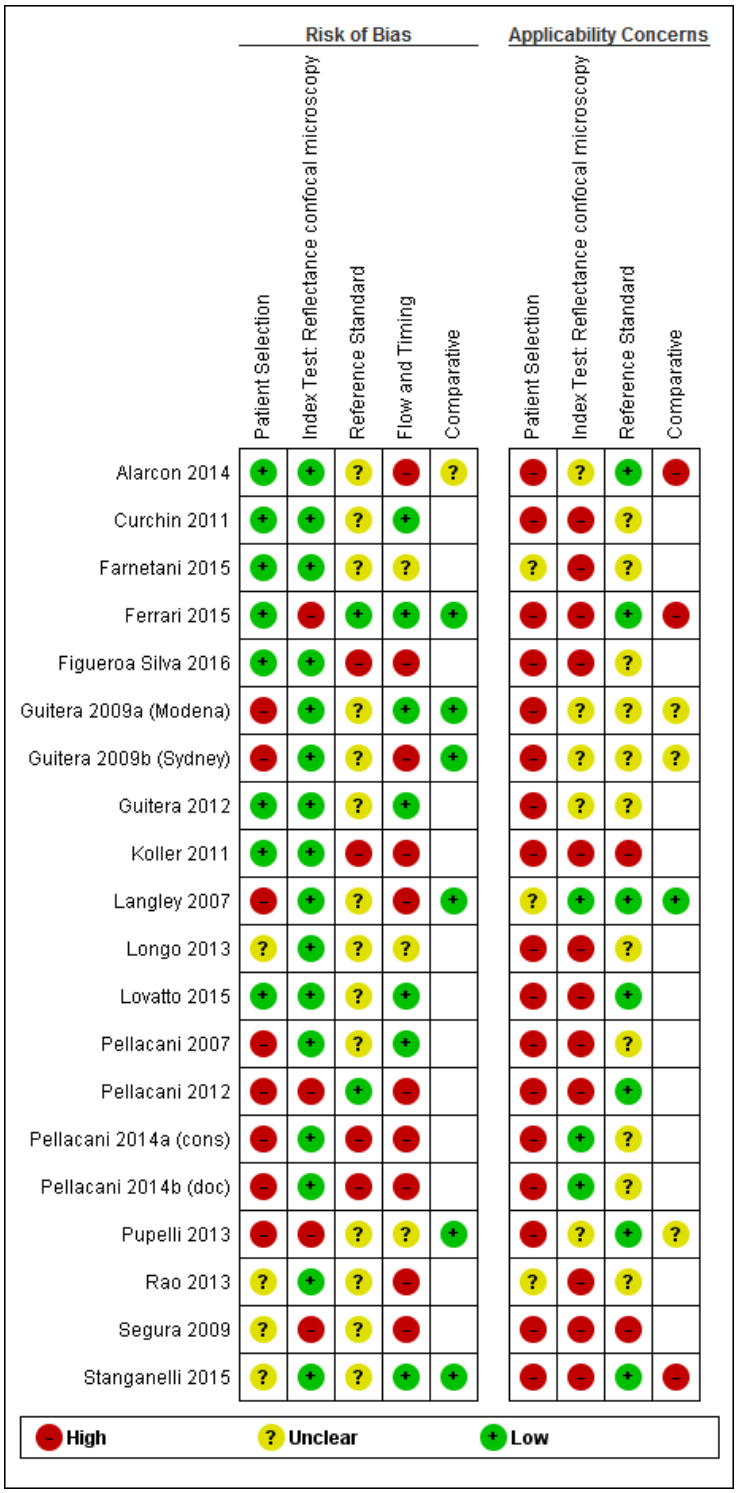
Figure 6



Caption

Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

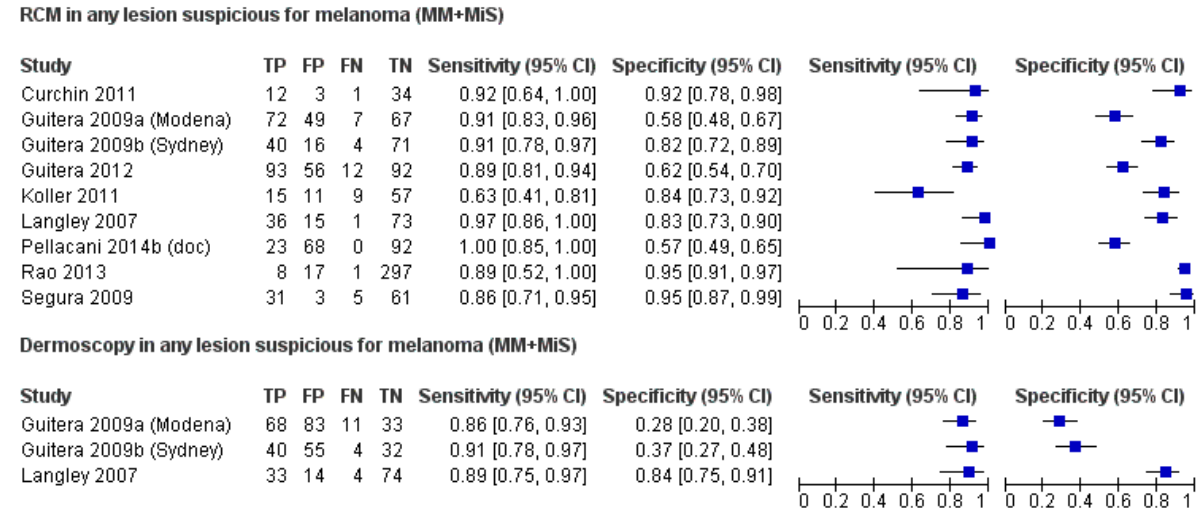
Figure 7



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

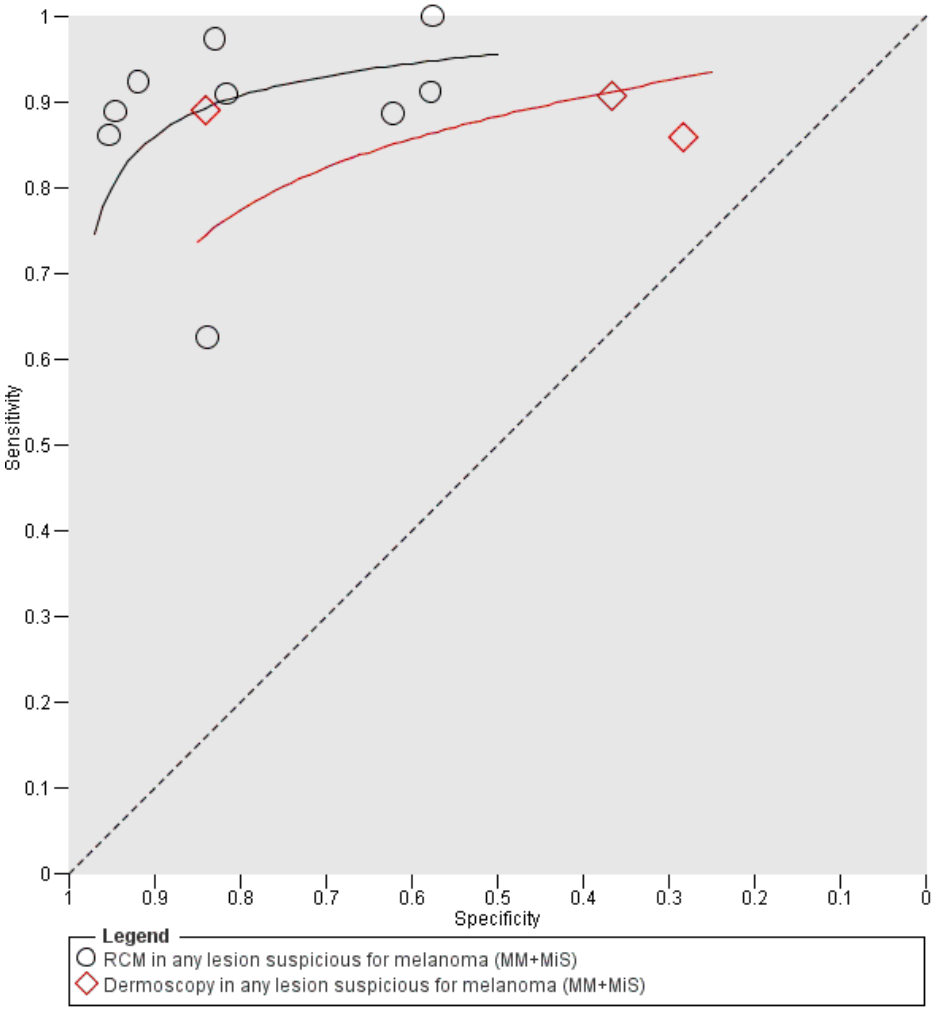
Figure 8 (Analysis 3)



Caption

Forest plot of tests: RCM and dermoscopy data in any lesion suspicious for melanoma for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

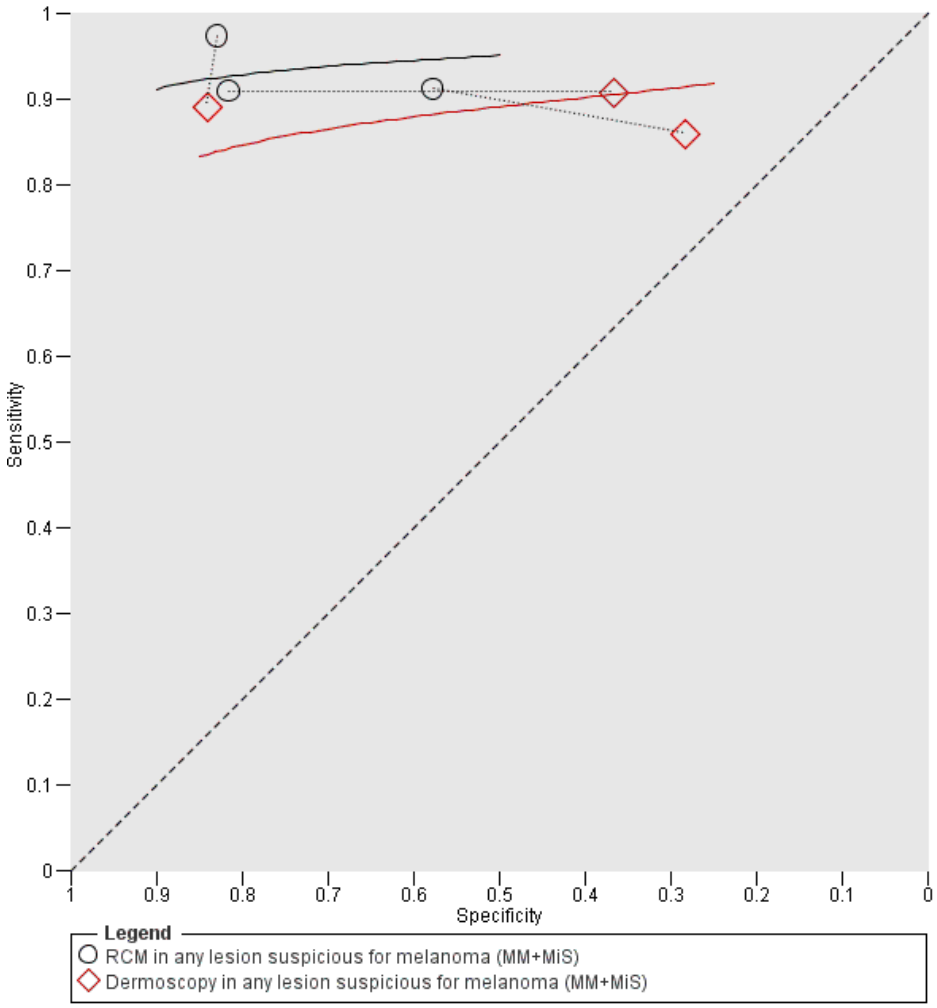
Figure 9 (Analysis 3)



Caption

Summary ROC comparing RCM and Demoscopy in all lesions suspected of melanoma for detection of invasive melanoma or atypical intraepidermal melanocytic variants (MM+MiS).

Figure 10 (Analysis 4)



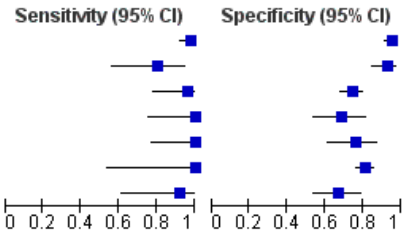
Caption

Summary ROC of paired comparisons of RCM and Demoscopy in all lesions suspected of melanoma for detection of invasive melanoma or atypical intraepidermal melanocytic variants (MM+MiS)

Figure 11 (Analysis 5)

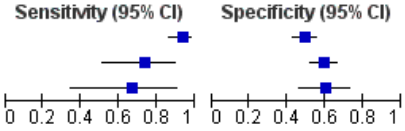
RCM in equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	Image based	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Farnetani 2015	16	6	4	74	Image based	0.80 [0.56, 0.94]	0.93 [0.84, 0.97]
Ferrari 2015	22	54	1	155	Image based	0.96 [0.78, 1.00]	0.74 [0.68, 0.80]
Lovatto 2015	13	16	0	35	Image based	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Pellacani 2012	14	11	0	35	Image based	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Pellacani 2014a (cons)	6	56	0	246	In person	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Stanganelli 2015	11	19	1	39	Image based	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]



Dermoscopy in equivocal lesion studies (MM+MiS)

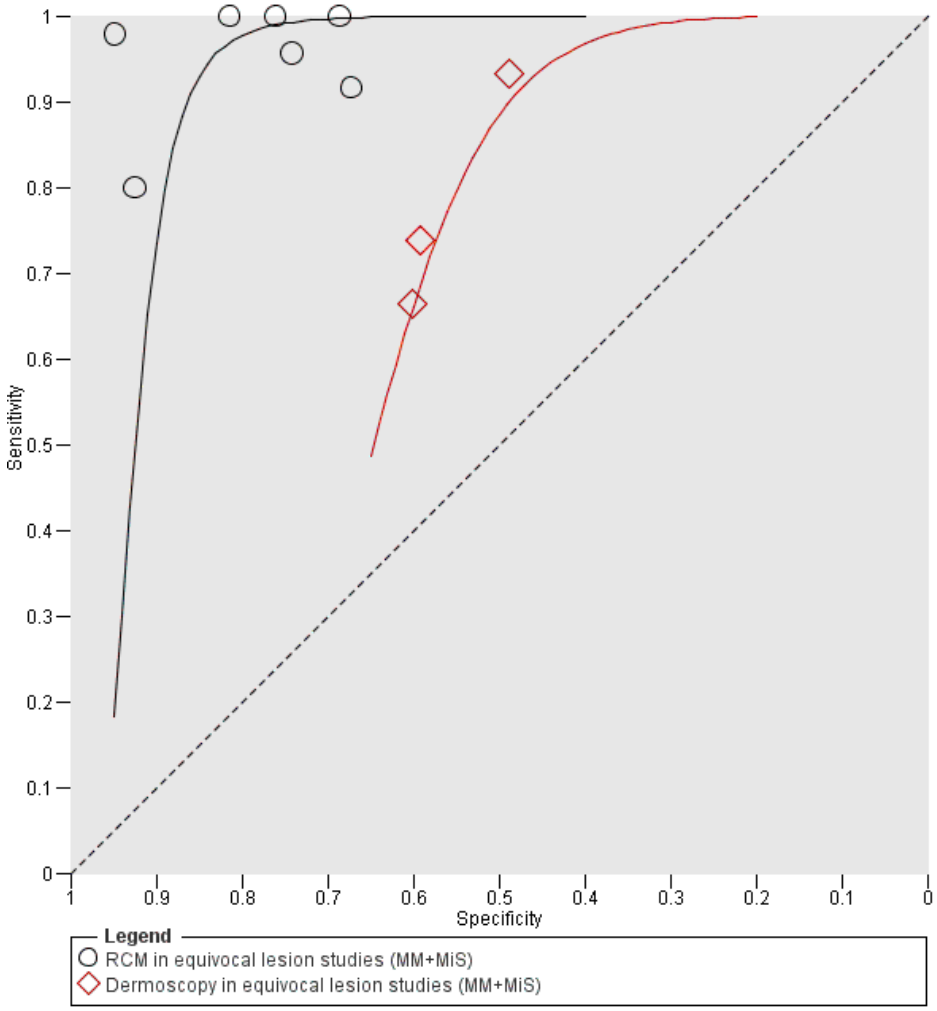
Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	86	128	6	123	image_based	0.93 [0.86, 0.98]	0.49 [0.43, 0.55]
Ferrari 2015	17	85	6	124	image_based	0.74 [0.52, 0.90]	0.59 [0.52, 0.66]
Stanganelli 2015	8	23	4	35	image_based	0.67 [0.35, 0.90]	0.60 [0.47, 0.73]



Caption

Forest plot of tests: RCM and Dermoscopy in equivocal lesion populations for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

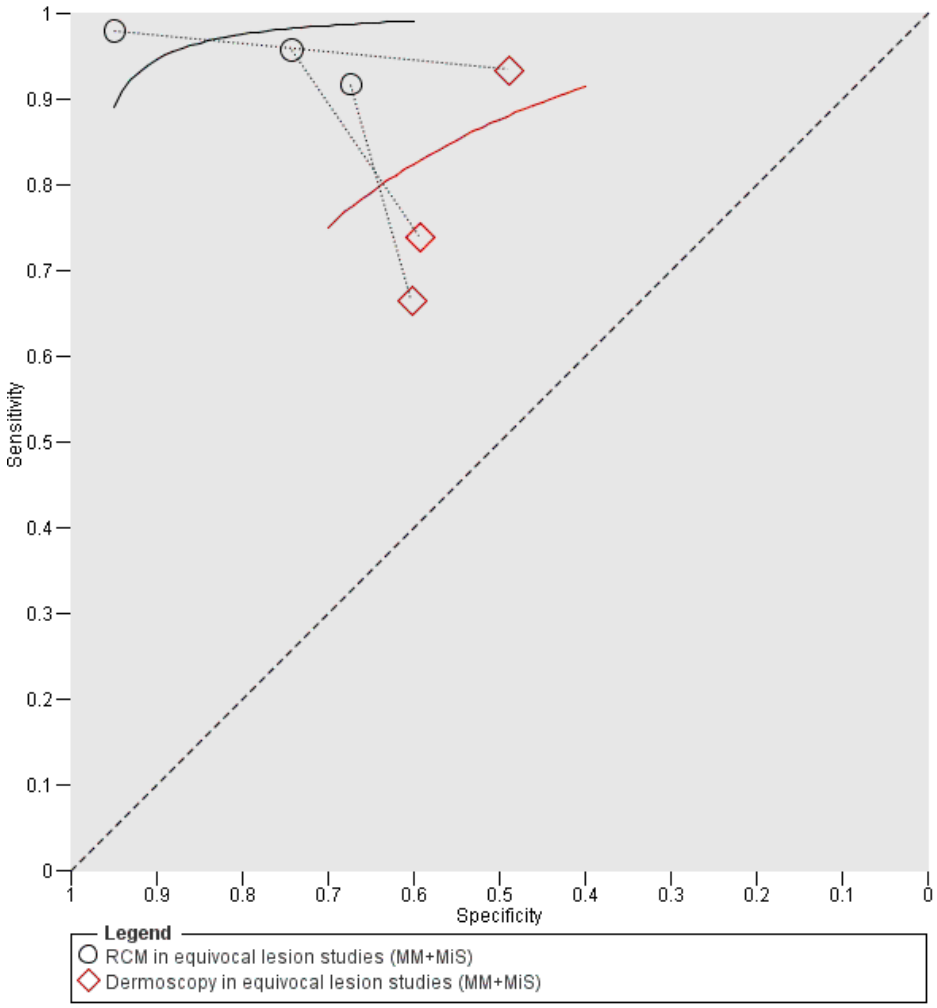
Figure 12 (Analysis 5)



Caption

Summary ROC comparing RCM and Demoscopy in equivocal lesion populations for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

Figure 13 (Analysis 6)



Caption

Summary ROC for paired comparisons of RCM and Dermoscopy in equivocal lesion populations for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

Figure 14 (Analysis 9)

RCM score at ≥ 2 (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2007	131	103	5	112	Image based	Equivocal	0.96 [0.92, 0.99]	0.52 [0.45, 0.59]

RCM score at ≥ 3 (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	1	34	In person	all comers	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Guitera 2012	93	56	12	92	Image based	all comers	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Lovatto 2015	13	16	0	35	Image based	equivocal	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Pellacani 2007	125	66	11	149	Image based	Equivocal	0.92 [0.86, 0.96]	0.69 [0.63, 0.75]

RCM score at threshold NR (likely ≥ 3) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2014a (cons)	6	56	0	246	In person	equivocal	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Pellacani 2014b (doc)	23	68	0	92	In person	equivocal	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]

RCM score at ≥ 4 (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2009a (Modena)	72	49	7	67	Image based	all comers	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	Image based	all comers	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Guitera 2012	81	34	24	114	Image based	all comers	0.77 [0.68, 0.85]	0.77 [0.69, 0.84]

Segura algorithm at >-1 (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	Image based	equivocal	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]

Guitera 2012	80	59	25	192	Image based	all comers	0.76 [0.67, 0.84]	0.76 [0.71, 0.82]
Lovatto 2015	13	16	0	35	Image based	equivocal	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Segura 2009	31	3	5	61	Image based	all comers	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]

Guitera Two-step alg (significant chars for MM) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	82	40	23	211	Image based	all comers	0.78 [0.69, 0.86]	0.84 [0.79, 0.88]

Pellacani Two step algorithm (dysplastic-MM) image-based (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2012	14	11	0	35	Image based	equivocal	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Stanganelli 2015	11	19	1	39	Image based	equivocal	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]

RCM CAD algorithm (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Koller 2011	24	52	0	16	Confocal images - CAD	all comers	1.00 [0.86, 1.00]	0.24 [0.14, 0.35]

No algorithm (significant characteristics) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Ferrari 2015	22	62	1	147	Image based	equivocal	0.96 [0.78, 1.00]	0.70 [0.64, 0.76]
Pupelli 2013	24	7	3	65	Image based	other	0.89 [0.71, 0.98]	0.90 [0.81, 0.96]

No algorithm (selected characteristics) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Langley 2007	36	15	1	73	In person	all comers	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]

No algorithm (observer diagnosis) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	16	20	4	60	Image based	equiv	0.80 [0.56, 0.94]	0.75 [0.64, 0.84]
Figueroa Silva 2016	24	4	3	32	Image based	other	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]
Koller 2011	15	11	9	57	Image based	all comers	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Rao 2013	8	17	1	297	Image based	all comers	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]

No algorithm (observer diagnosis) paired in-person (MM+MiS)

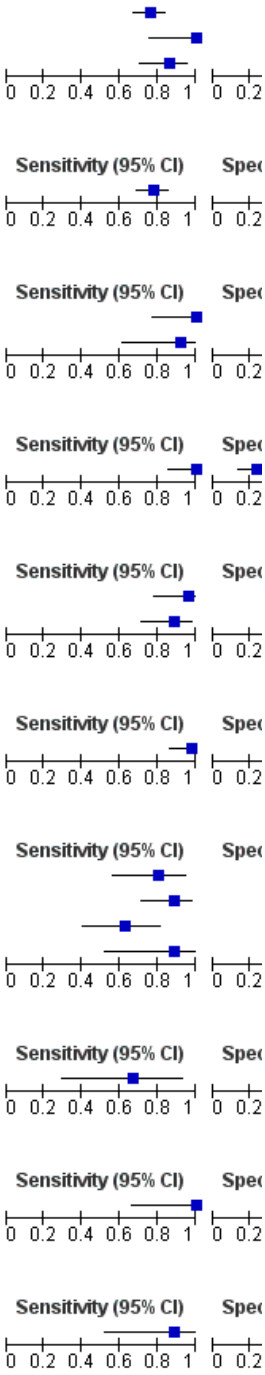
Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	6	13	3	295	In person	all comers	0.67 [0.30, 0.93]	0.96 [0.93, 0.98]

No algorithm (excise decision) (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	9	113	0	201	Image based	all comers	1.00 [0.66, 1.00]	0.64 [0.58, 0.69]

No algorithm (excise decision) paired in-person (MM+MiS)

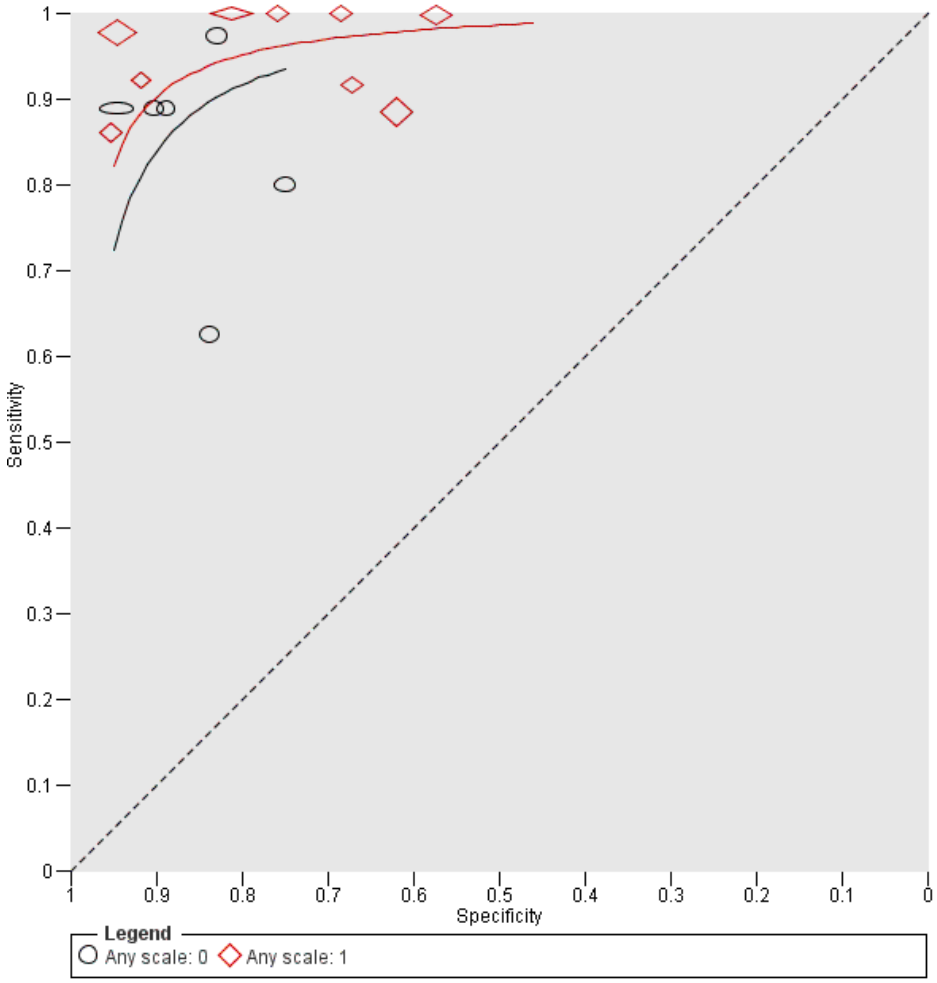
Study	TP	FP	FN	TN	Method of diagnosis	Lesion suspicion	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	8	148	1	160	In person	all comers	0.89 [0.52, 1.00]	0.52 [0.46, 0.58]



Caption

Forest plot : RCM results by algorithm, threshold and number of observers for diagnosis of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

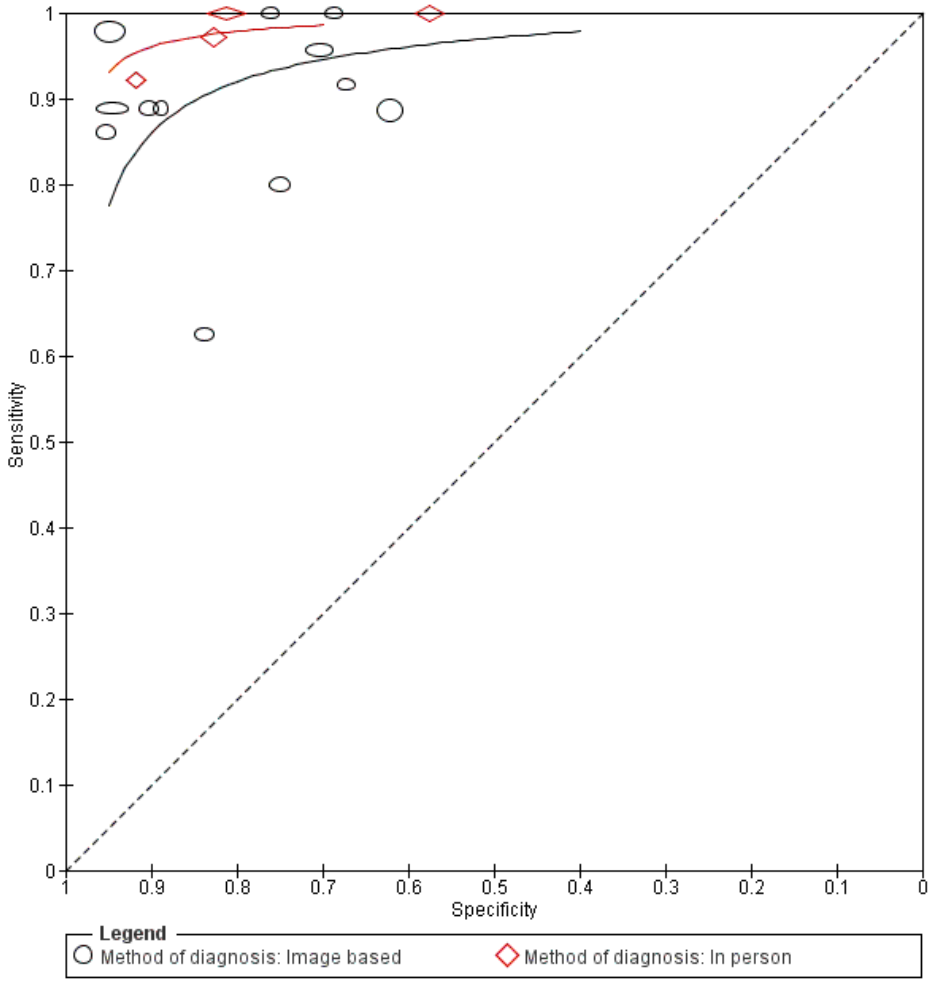
Figure 15 (Analysis 8)



Caption

Summary ROC Plot comparing studies which used and did not use an algorithm or scale to assist RCM diagnosis (0=none, 1=tool used) [outcome is detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)]

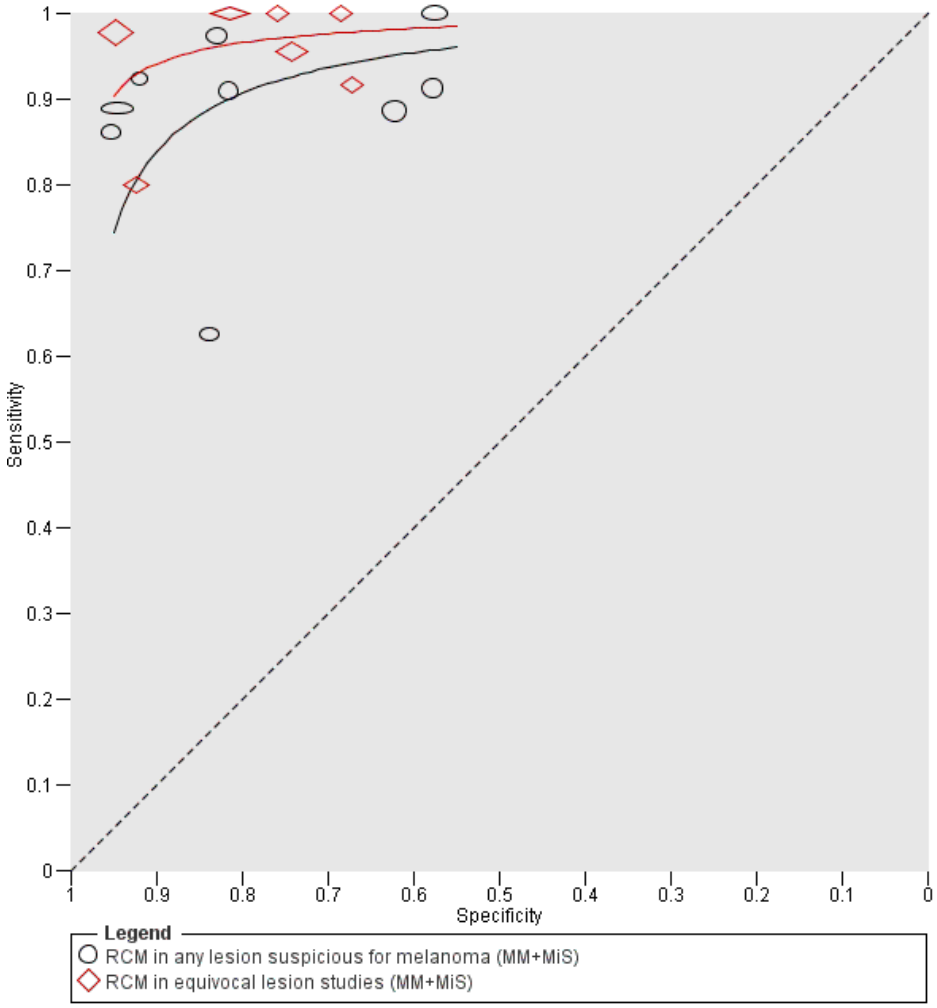
Figure 16 (Analysis 7)



Caption

Summary ROC Plot - Comparison of in-person and Image based studies of RCM for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS)

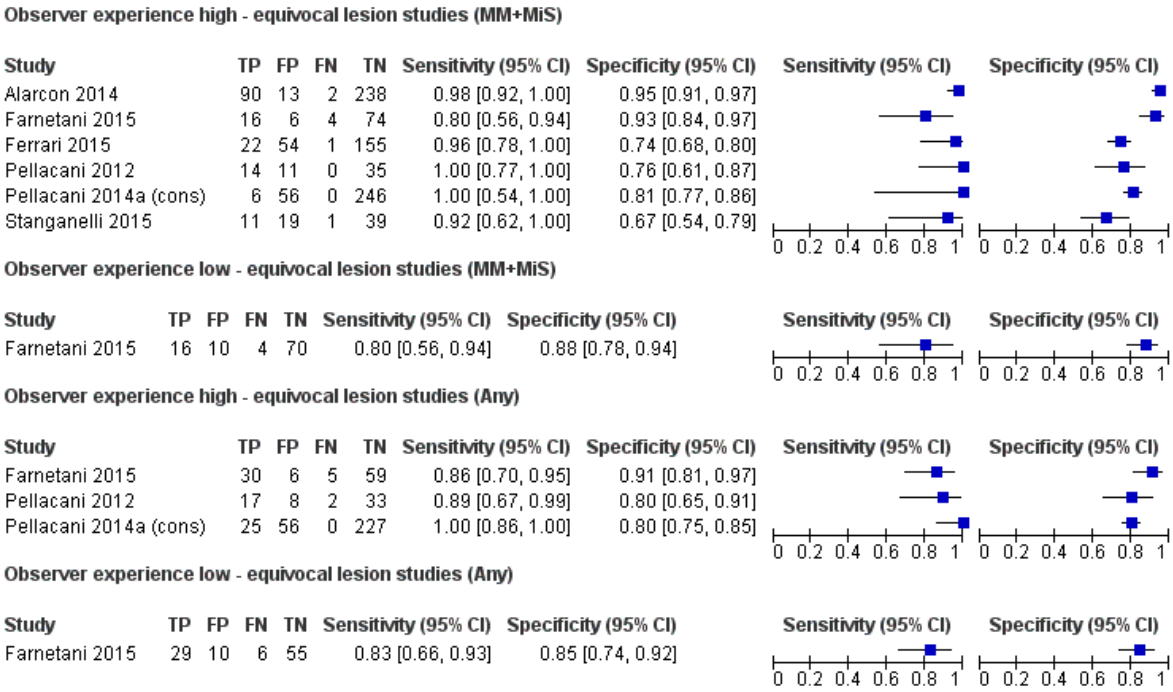
Figure 17 (Analysis 2)



Caption

Summary ROC Plot comparing RCM performance in studies of all lesions suspected of melanoma with those in patients with equivocal lesions (for detection of invasive melanoma (MM) and atypical intraepidermal melanocytic variants (or melanoma in situ, MiS))

Figure 18 (Analysis 13)



Caption

Forest plot: RCM diagnosis in studies of patients with equivocal lesions by observer experience, for the detection of invasive melanoma (MM), of invasive melanoma and atypical intraepidermal melanocytic variants (or melanoma in situ) (MM+MiS), and of any potential skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma (Any)

Figure 19 (Analysis 12)

Observer experience high - any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	40	43	11	262	0.78 [0.65, 0.89]	0.86 [0.81, 0.90]
Segura 2009	22	12	1	65	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]

Observer experience low - any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	0	35	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]

Observer experience high - any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2009a (Modena)	72	49	7	67	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Guitera 2012	93	56	12	92	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Koller 2011	15	11	9	57	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Langley 2007	36	15	1	73	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Pellacani 2014b (doc)	23	68	0	92	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]
Rao 2013	8	17	1	297	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]
Segura 2009	31	3	5	61	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]

Observer experience low - any lesion suspicious for melanoma (MM+MiS)

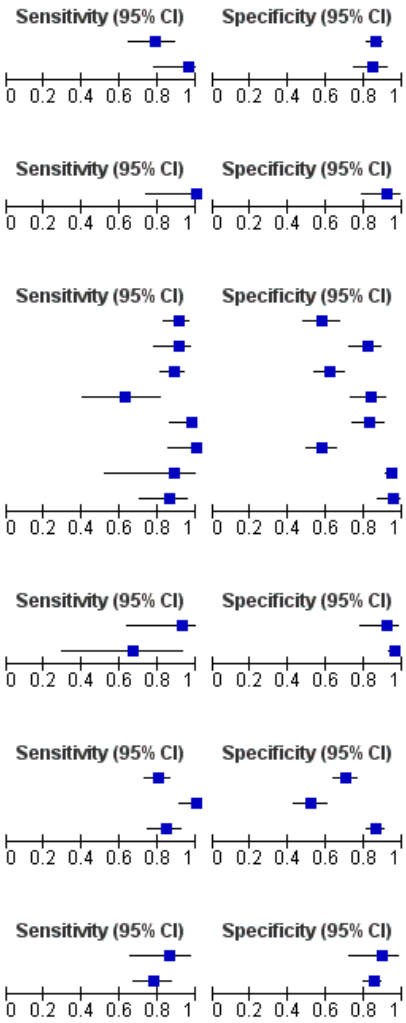
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Rao 2013	6	13	3	296	0.67 [0.30, 0.93]	0.96 [0.93, 0.98]

Observer experience high - any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	126	59	31	140	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]
Pellacani 2014b (doc)	42	68	0	73	1.00 [0.92, 1.00]	0.52 [0.43, 0.60]
Rao 2013	66	34	12	211	0.85 [0.75, 0.92]	0.86 [0.81, 0.90]

Observer experience low - any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	19	3	3	25	0.86 [0.65, 0.97]	0.89 [0.72, 0.98]
Rao 2013	57	37	16	208	0.78 [0.67, 0.87]	0.85 [0.80, 0.89]



Caption

Forest plot: RCM diagnosis in studies of all lesions suspected of melanoma by observer experience, for the detection of invasive melanoma (MM), of invasive melanoma and atypical intraepidermal melanocytic variants (or melanoma in situ) (MM+MiS), and of any potential skin cancer (melanoma or other skin cancer) or skin lesion with a high risk of progression to melanoma (Any)

Figure 20 (Analysis 1)

RCM in any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Segura 2009	22	12	1	65	Image based	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]
Guitera 2012	40	40	11	265	Image based	0.78 [0.65, 0.89]	0.87 [0.83, 0.90]
Curchin 2011	12	3	0	35	In person	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]

RCM in studies of other lesion types (MM)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	7	21	1	34	Image based	0.88 [0.47, 1.00]	0.62 [0.48, 0.75]
Longo 2013	23	10	0	107	Image based	1.00 [0.85, 1.00]	0.91 [0.85, 0.96]

RCM in any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Segura 2009	31	3	5	61	Image based	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]
Rao 2013	8	17	1	297	Image based	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]
Guitera 2012	93	56	12	92	Image based	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Koller 2011	15	11	9	57	Image based	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Guitera 2009a (Modena)	72	49	7	67	Image based	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	Image based	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Pellacani 2014b (doc)	23	68	0	92	In person	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]
Langley 2007	36	15	1	73	In person	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Curchin 2011	12	3	1	34	In person	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]

RCM in equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	Image based	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Ferrari 2015	22	54	1	155	Image based	0.96 [0.78, 1.00]	0.74 [0.68, 0.80]
Farnetani 2015	16	6	4	74	Image based	0.80 [0.56, 0.94]	0.93 [0.84, 0.97]
Pellacani 2012	14	11	0	35	Image based	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Lovatto 2015	13	16	0	35	Image based	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Stanganelli 2015	11	19	1	39	Image based	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]
Pellacani 2014a (cons)	6	56	0	246	In person	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]

RCM in studies of other lesion types (MM+MiS)

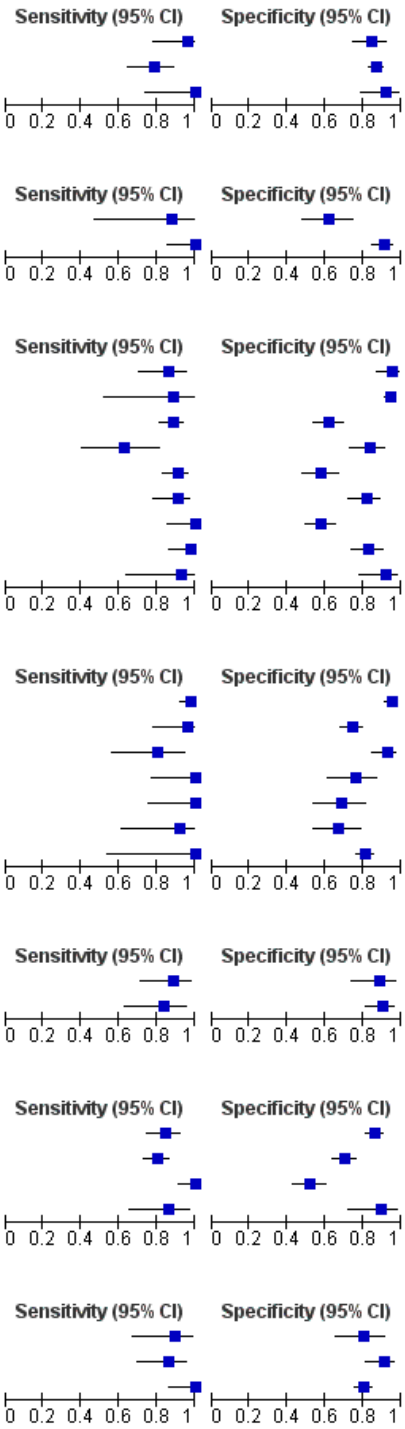
Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	24	4	3	32	Image based	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]
Pupelli 2013	20	7	4	65	Image based	0.83 [0.63, 0.95]	0.90 [0.81, 0.96]

RCM in any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	66	34	12	211	Image based	0.85 [0.75, 0.92]	0.86 [0.81, 0.90]
Guitera 2012	126	59	31	140	Image based	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]
Pellacani 2014b (doc)	42	68	0	73	In person	1.00 [0.92, 1.00]	0.52 [0.43, 0.60]
Curchin 2011	19	3	3	25	In person	0.86 [0.65, 0.97]	0.89 [0.72, 0.98]

RCM in equivocal lesion studies (Any)

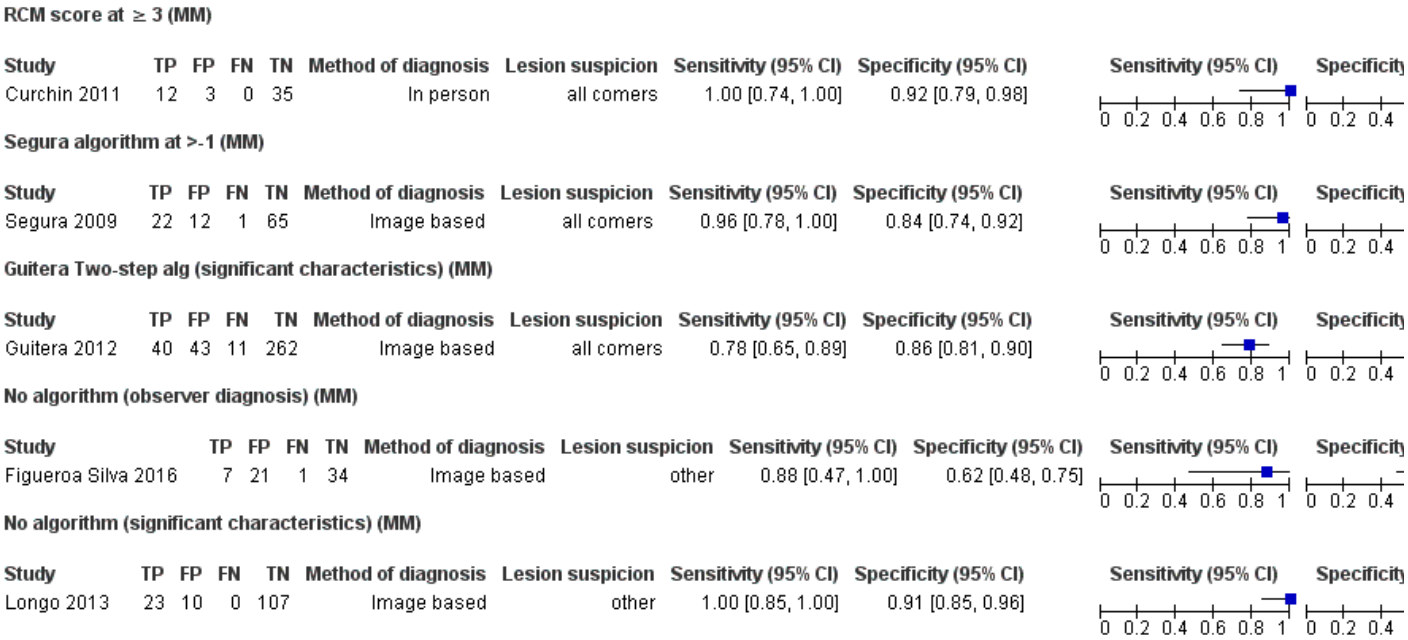
Study	TP	FP	FN	TN	Method of diagnosis	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2012	17	8	2	33	Image based	0.89 [0.67, 0.99]	0.80 [0.65, 0.91]
Farnetani 2015	30	6	5	59	Image based	0.86 [0.70, 0.95]	0.91 [0.81, 0.97]
Pellacani 2014a (cons)	25	56	0	227	In person	1.00 [0.86, 1.00]	0.80 [0.75, 0.85]



Caption

Forest plot of RCM performance by study group and target condition definition (invasive melanoma alone (MM), invasive melanoma and atypical intraepidermal melanocytic variants, or melanoma in situ (MM+MiS), and for any skin cancer or or skin lesion with a high risk of progression to melanoma (Any))

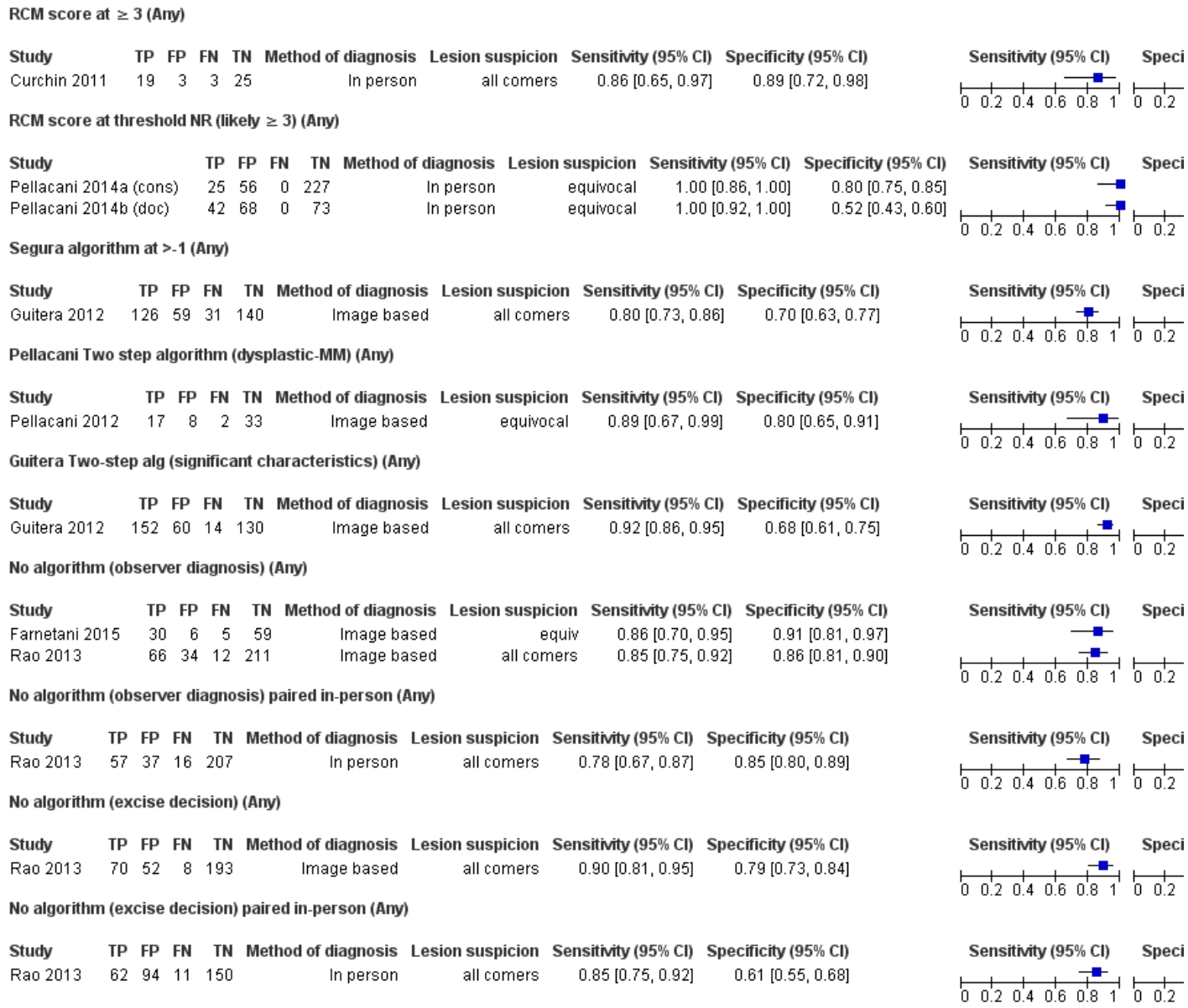
Figure 21 (Analysis 10)



Caption

Forest plot: RCM results by algorithm and threshold for diagnosis of invasive melanoma (MM)

Figure 22 (Analysis 11)



Caption

Forest plot: RCM results by algorithm and threshold for diagnosis of any skin cancer or skin lesion with a high risk of progression to melanoma (Any)

Sources of support

Internal sources

- No sources of support provided

External sources

- NIHR Systematic Review Programme, UK
- The National Institute for Health Research (NIHR), UK
  The NIHR, UK, is the largest single funder of the Cochrane Skin Group

Feedback

Appendices

1 Current content and structure of the Programme Grant

List of reviews	Estimated number of studies
Diagnosis of melanoma	
1. Visual inspection versus visual inspection plus dermoscopy	120
2. Teledermatology	12
3. Mobile phone applications	2
4. Computer-aided diagnosis – dermoscopy-based and spectroscopy-based techniques	37
5. Reflectance confocal microscopy	19
6. High frequency ultrasound	3
7. Overview: Comparing the accuracy of tests for which sufficient evidence is identified either alone or in combination	
Diagnosis of keratinocyte skin cancer (BCC and cSCC)	
8. Visual inspection +/- dermoscopy	22
9. Computer-aided diagnosis – dermoscopy-based and spectroscopy-based techniques	3
10. Optical coherence tomography	6
11. Reflectance confocal microscopy	9
12. High frequency ultrasound	1
13. Exfoliative cytology	5
14. Overview: Comparing the accuracy of tests for which sufficient evidence is identified either alone or in combination	
Staging of melanoma	
15. Ultrasound	25 to 30
16. CT	5 to 10
17. PET or PET-CT	20 to 25
18. MRI	5
19. Sentinel lymph node biopsy +/- high frequency ultrasound	70
20. Overview: Comparing the accuracy of tests for which sufficient evidence is identified either alone or in combination	
Staging of cSCC	
21. Imaging tests review	10 to 15
22. Sentinel lymph node biopsy +/- high frequency ultrasound	15 to 20

2 Final search strategies

Melanoma Search strategies to August 2016

Database: Ovid MEDLINE(R) 1946 to August Week 3 2016

Search Strategy:

1 exp melanoma/

2 exp skin cancer/

3 exp basal cell carcinoma/

4 basalioma$1.ti,ab.

5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.

6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

8 nmsc.ti,ab.

9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

10 (BCC or CSCC or NMSC).ti,ab.

11 keratinocy$.ti,ab.

12 Keratinocytes/

13 or/1-12

14 dermoscop$.ti,ab.

15 dermatoscop$.ti,ab.

16 photomicrograph$.ti,ab.

17 exp epiluminescence microscopy/

18 (epiluminescence adj2 microscop$).ti,ab.

19 (confocal adj2 microscop$).ti,ab.

20 (incident light adj2 microscop$).ti,ab.

21 (surface adj2 microscop$).ti,ab.

22 (visual adj (inspect$ or examin$)).ti,ab.

23 ((clinical or physical) adj examin$).ti,ab.

24 3 point.ti,ab.

25 three point.ti,ab.

26 pattern analys$.ti,ab.

27 ABCD$.ti,ab.

28 menzies.ti,ab.

29 7 point.ti,ab.

30 seven point.ti,ab.

31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.

32 artificial intelligence.ti,ab.

33 AI.ti,ab.

34 computer assisted.ti,ab.

35 computer aided.ti,ab.

36 neural network$.ti,ab.

37 exp diagnosis, computer-assisted/

38 MoleMax.ti,ab.

39 image process$.ti,ab.

40 automatic classif$.ti,ab.

41 image analysis.ti,ab.

42 SIAscop$.ti,ab.

43 Aura.ti,ab.

44 (optical adj2 scan$).ti,ab.

45 MelaFind.ti,ab.

46 SIMSYS.ti,ab.

47 MoleMate.ti,ab.

48 SolarScan.ti,ab.

49 VivaScope.ti,ab.

50 (high adj3 ultraso$).ti,ab.

51 (canine adj2 detect$).ti,ab.

52 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.

53 smartphone$.ti,ab.

54 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.

55 Mole Detective.ti,ab.

56 Spot Check.ti,ab.

57 (mole$1 adj2 map$).ti,ab.

58 (total adj2 body).ti,ab.

59 exfoliative cytolog$.ti,ab.

60 digital analys$.ti,ab.

61 (image$1 adj3 software).ti,ab.

62 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.

63 (optical coherence adj (technolog$ or tomog$)).ti,ab.

64 (computer adj2 diagnos$).ti,ab.

65 exp sentinel lymph node biopsy/

66 (sentinel adj2 node).ti,ab.

67 nevisense.mp. or HFUS.ti,ab.

68 electrical impedance spectroscopy.ti,ab.

69 history taking.ti,ab.

70 patient history.ti,ab.

71 (naked eye adj (exam$ or assess$)).ti,ab.

72 (skin adj exam$).ti,ab.

73 physical examination/

74 ugly duckling.mp. or UD.ti,ab.

75 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.

76 ABCDE.mp. or VOC.ti,ab.

77 clinical accuracy.ti,ab.

78 Family Practice/ or Physicians, Family/ or clinical competence/

79 (confocal adj2 microscop$).ti,ab.

80 diagnostic algorithm$1.ti,ab.

81 checklist$.ti,ab.

82 virtual imag$1.ti,ab.

83 volatile organic compound$1.ti,ab.

84 dog$1.ti,ab.

85 gene expression analy$.ti,ab.

86 reflex transmission imag$.ti,ab.

87 thermal imaging.ti,ab.

88 elastography.ti,ab.

89 or/14-88

90 (CT or PET).ti,ab.

91 PET-CT.ti,ab.

92 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

93 exp Deoxyglucose/

94 deoxy-glucose.ti,ab.

95 deoxyglucose.ti,ab.

96 CATSCAN.ti,ab.

97 exp Tomography, Emission-Computed/

98 exp Tomography, X-ray computed/

99 positron emission tomograph$.ti,ab.

100 exp magnetic resonance imaging/

101 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

102 exp echography/

103 Doppler echography.ti,ab.

104 sonograph$.ti,ab.

105 ultraso$.ti,ab.

106 doppler.ti,ab.

107 magnetic resonance imag$.ti,ab.

108 or/90-107

109 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

110 "Sensitivity and Specificity"/

111 exp cancer staging/

112 or/109-111

113 108 and 112

114 89 or 113

115 13 and 114

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 29, 2016

Search Strategy:

1 basalioma$1.ti,ab.

2 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.

3 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

4 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

5 nmsc.ti,ab.

6 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

7 (BCC or CSCC or NMSC).ti,ab.

8 keratinocy$.ti,ab.

9 or/1-8

10 dermoscop$.ti,ab.

11 dermatoscop$.ti,ab.

12 photomicrograph$.ti,ab.

13 (epiluminescence adj2 microscop$).ti,ab.

14 (confocal adj2 microscop$).ti,ab.

15 (incident light adj2 microscop$).ti,ab.

16 (surface adj2 microscop$).ti,ab.

17 (visual adj (inspect$ or examin$)).ti,ab.

18 ((clinical or physical) adj examin$).ti,ab.

19 3 point.ti,ab.

20 three point.ti,ab.

21 pattern analys$.ti,ab.

22 ABCD$.ti,ab.

23 menzies.ti,ab.

24 7 point.ti,ab.

25 seven point.ti,ab.

26 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.

27 artificial intelligence.ti,ab.

28 AI.ti,ab.

29 computer assisted.ti,ab.

30 computer aided.ti,ab.

31 neural network$.ti,ab.

32 MoleMax.ti,ab.

33 image process$.ti,ab.

34 automatic classif$.ti,ab.

35 image analysis.ti,ab.

36 SIAscop$.ti,ab.

37 Aura.ti,ab.

38 (optical adj2 scan$).ti,ab.

39 MelaFind.ti,ab.

40 SIMSYS.ti,ab.

41 MoleMate.ti,ab.

42 SolarScan.ti,ab.

43 VivaScope.ti,ab.

44 (high adj3 ultraso$).ti,ab.

45 (canine adj2 detect$).ti,ab.

46 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.

47 smartphone$.ti,ab.

48 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.

49 Mole Detective.ti,ab.

50 Spot Check.ti,ab.

51 (mole$1 adj2 map$).ti,ab.

52 (total adj2 body).ti,ab.

53 exfoliative cytolog$.ti,ab.

54 digital analys$.ti,ab.

55 (image$1 adj3 software).ti,ab.

56 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.

57 (optical coherence adj (technolog$ or tomog$)).ti,ab.

58 (computer adj2 diagnos$).ti,ab.

59 (sentinel adj2 node).ti,ab.

60 nevisense.mp. or HFUS.ti,ab.

61 electrical impedance spectroscopy.ti,ab.

62 history taking.ti,ab.

63 patient history.ti,ab.

64 (naked eye adj (exam$ or assess$)).ti,ab.

65 (skin adj exam$).ti,ab.

66 ugly duckling.mp. or UD.ti,ab.

67 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.

68 ABCDE.mp. or VOC.ti,ab.

69 clinical accuracy.ti,ab.

70 (Family adj (Practice or Physicians)).ti,ab.

71 (confocal adj2 microscop$).ti,ab.

72 clinical competence.ti,ab.

73 diagnostic algorithm$1.ti,ab.

74 checklist$.ti,ab.

75 virtual imag$1.ti,ab.

76 volatile organic compound$1.ti,ab.

77 dog$1.ti,ab.

78 gene expression analy$.ti,ab.

79 reflex transmission imag$.ti,ab.

80 thermal imaging.ti,ab.

81 elastography.ti,ab.

82 or/10-81

83 (CT or PET).ti,ab.

84 PET-CT.ti,ab.

85 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

86 deoxy-glucose.ti,ab.

87 deoxyglucose.ti,ab.

88 CATSCAN.ti,ab.

89 positron emission tomograph$.ti,ab.

90 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

91 Doppler echography.ti,ab.

92 sonograph$.ti,ab.

93 ultraso$.ti,ab.

94 doppler.ti,ab.

95 magnetic resonance imag$.ti,ab.

96 or/83-95

97 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

98 96 and 97

99 82 or 98

100 9 and 99

Database: Embase 1974 to 2016 August 29

Search Strategy:

1 *melanoma/

2 *skin cancer/

3 *basal cell carcinoma/

4 basalioma$.ti,ab.

5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$ or adenoma$ or epithelioma$ or lesion$ or malignan$ or nodule$)).ti,ab.

6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.

8 nmsc.ti,ab.

9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.

10 (BCC or cscc).mp. or NMSC.ti,ab.

11 keratinocyte.ti,ab.

12 keratinocy$.ti,ab.

13 or/1-12

14 dermoscop$.ti,ab.

15 dermatoscop$.ti,ab.

16 photomicrograph$.ti,ab.

17 *epiluminescence microscopy/

18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 MoleMax.ti,ab.
38 exp diagnosis, computer-assisted/
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 (optical adj2 scan$).ti,ab.
44 Aura.ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 confocal microscop$.ti,ab.
51 (high adj3 ultraso$).ti,ab.
52 (canine adj2 detect$).ti,ab.
53 ((mobile or cell$ or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
54 smartphone$.ti,ab.
55 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
56 Spot Check.ti,ab.
57 Mole Detective.ti,ab.
58 (mole$1 adj2 map$).ti,ab.
59 (total adj2 body).ti,ab.
60 exfoliative cytolog$.ti,ab.
61 digital analys$.ti,ab.
62 (image$1 adj3 software).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.

64 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$).mp. or tele-dermatoscop$.ti,ab.

65 (computer adj2 diagnos$).ti,ab.

66 *sentinel lymph node biopsy/

67 (sentinel adj2 node).ti,ab.

68 nevisense.ti,ab.

69 HFUS.ti,ab.

70 electrical impedance spectroscopy.ti,ab.

71 history taking.ti,ab.

72 patient history.ti,ab.

73 (naked eye adj (exam$ or assess$)).ti,ab.

74 (skin adj exam$).ti,ab.

75 *physical examination/

76 ugly duckling.ti,ab.

77 UD sign$.ti,ab.

78 ((physician$ or clinical or physical) adj (exam$ or recog$ or triage)).ti,ab.

79 ABCDE.ti,ab.

80 clinical accuracy.ti,ab.

81 *general practice/

82 (confocal adj2 microscop$).ti,ab.

83 clinical competence/

84 diagnostic algorithm$.ti,ab.

85 checklist$1.ti,ab.

86 virtual image$1.ti,ab.

87 volatile organic compound$1.ti,ab.

88 VOC.ti,ab.

89 dog$1.ti,ab.

90 gene expression analys$.ti,ab.

91 reflex transmission imaging.ti,ab.

92 thermal imaging.ti,ab.

93 elastography.ti,ab.

94 dog$1.ti,ab.

95 gene expression analys$.ti,ab.

96 reflex transmission imaging.ti,ab.

97 thermal imaging.ti,ab.

98 elastography.ti,ab.

99 or/14-93

100 PET-CT.ti,ab.

101 (CT or PET).ti,ab.

102 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.

103 exp Deoxyglucose/

104 CATSCAN.ti,ab.

105 deoxyglucose.ti,ab.

106 deoxy-glucose.ti,ab.

107 *positron emission tomography/

108 *computer assisted tomography/

109 positron emission tomograph$.ti,ab.

110 *nuclear magnetic resonance imaging/

111 (MRI or fMRI or NMRI or scintigraph$).ti,ab.

112 *echography/

113 Doppler.ti,ab.

114 sonograph$.ti,ab.

115 ultraso$.ti,ab.

116 magnetic resonance imag$.ti,ab.

117 or/100-116

118 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.

119 "Sensitivity and Specificity"/

120 *cancer staging/

121 or/118-120

122 117 and 121

123 99 or 122

124 13 and 123

Database: Cochrane Library (Wiley) 2016 searched 30 August 2016 CDSR issue 8 of 12 2016 CENTRAL Issue 7 of 12 2016 HTA Issue 3 of 4 July 2016 DARE Issue 3 of 4 2015

Search strategy:

#1 melanoma* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyte*

#2 MeSH descriptor: [Melanoma] explode all trees

#3 "skin cancer*"

#4 MeSH descriptor: [Skin Neoplasms] explode all trees

#5 skin near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

#6 nmsc

#7 "squamous cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*) near/2 (skin or epiderm* or cutaneous)

#8 "basal cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

#9 pigmented near/2 (lesion* or nevus or mole* or naevi or naevus or nevi or skin)

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 dermoscop*

#12 dermatoscop*

#13 Photomicrograph*

#14 MeSH descriptor: [Dermoscopy] explode all trees

#15 confocal near/2 microscop*

#16 epiluminescence near/2 microscop*

#17 incident next light near/2 microscop*

#18 surface near/2 microscop*

#19 "visual inspect*"

#20 "visual exam*"

#21 (clinical or physical) next (exam*)

#22 "3 point"

#23 "three point"

#24 "pattern analys*"

#25 ABDC

#26 menzies

#27 "7 point"

#28 "seven point"

#29 digital near/2 (dermoscop* or dermatoscop*)

#30 "artificial intelligence"

#31 "AI"

#32 "computer assisted"

#33 "computer aided"

#34 AI

#35 "neural network*"

#36 MoleMax

#37 "computer diagnosis"

#38 "image process*"

#39 "automatic classif*"

#40 SIAscope

#41 "image analysis"

#42 "optical near/2 scan*"

#43 Aura

#44 MelaFind

#45 SIMSYS

#46 MoleMate

#47 SolarScan

#48 Vivascope

#49 "confocal microscopy"

#50 high near/3 ultraso*

#51 canine near/2 detect*

#52 Mole* near/2 map*

#53 total near/2 body

#54 mobile* or smart near/2 phone*

#55 cell next phone*

#56 smartphone*

#57 "mitotic index"

#58 DermoScan or SkinVision or DermLink or SpotCheck

#59 "Mole Detective"

#60 "Spot Check"

#61 mole* near/2 map*

#62 total near/2 body

#63 "exfoliative cytolog*"

#64 "digital analys*"

#65 image near/3 software

#66 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatolog*

#67 "optical coherence" next (technolog* or tomog*)

#68 computer near/2 diagnos*

#69 sentinel near/2 node*

#70 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69

#71 ultraso*

#72 sonograph*
#73 MeSH descriptor: [Ultrasonography] explode all trees
#74 Doppler
#75 CT or PET or PET-CT
#76 "CAT SCAN" or "CATSCAN"
#77 MeSH descriptor: [Positron-Emission Tomography] explode all trees
#78 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#79 MRI
#80 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#81 MRI or fMRI or NMRI or scintigraph*
#82 "magnetic resonance imag*"
#83 MeSH descriptor: [Deoxyglucose] explode all trees
#84 deoxyglucose or deoxy-glucose
#85 "positron emission tomograph*"
#86 #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85
#87 stage* or staging or metasta* or recurrence or sensitivity or specificity or "false negative*" or thickness*
#88 MeSH descriptor: [Neoplasm Staging] explode all trees
#89 #87 or #88
#90 #89 and #86
#91 #70 or #90
#92 #10 and #91
#93 BCC or CSCC or NMCS
#94 keratinocy*
#95 #93 or #94
#96 #10 or #95
#97 nevisense
#98 HFUS
#99 "electrical impedance spectroscopy"
#100 "history taking"
#101 "patient history"
#102 naked next eye near/1 (exam* or assess*)
#103 skin next exam*
#104 "ugly duckling" or (UD sign*)
#105 MeSH descriptor: [Physical Examination] explode all trees
#106 (physician* or clinical or physical) near/1 (exam* or recog* or triage*)
#107 ABCDE
#108 "clinical accuracy"
#109 MeSH descriptor: [General Practice] explode all trees
#110 confocal near microscop*
#111 "diagnostic algorithm*"
#112 MeSH descriptor: [Clinical Competence] explode all trees
#113 checklist*
#114 "virtual image*"
#115 "volatile organic compound*"
#116 dog or dogs
#117 VOC
#118 "gene expression analys*"

#119 "reflex transmission imaging"

#120 "thermal imaging"

#121 elastography

#122 #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121

#123 #70 or #122

#124 #96 and #123

#125 #96 and #90

#126 #125 or #124

#127 #10 and #126

Database : CINAHL Plus (EBSCO) 1937- 30 August 2016

Search strategy:

S1 (MH "Melanoma") OR (MH "Nevi and Melanomas+")

S2 (MH "Skin Neoplasms+")

S3 (MH "Carcinoma, Basal Cell+")

S4 basalioma*

S5 (basal cell) N2 (cancer* or carcinoma* or mass or masses or tumor* or tumour* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)

S6 (pigmented) N2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin)

S7 melanom* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt*

S8 nmsc

S9 TX BCC or cscc or NMSC

S10 (MH "Keratinocytes")

S11 keratinocyt*

S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

S13 dermoscop* or dermatoscop* or photomicrograph* or (3 point) or (three point) or ABCD* or menzies or (7 point) or (seven point) or AI or Molemax or SIASCOP* or Aura or MelaFind or SIMSYS or MoleMate or SolarScan or smartphone* or DermoScan or SkinVision or DermLink or SpotCheck

S14 (epiluminescence or confocal or incident or surface) N2 (microscop*)

S15 visual N1 (inspect* or examin*)

S16 (clinical or physical) N1 (examin*)

S17 pattern analys*

S18 (digital) N2 (dermoscop* or dermatoscop*)

S19 (artificial intelligence)

S20 (computer) N2 (assisted or aided)

S21 (neural network*)

S22 (MH "Diagnosis, Computer Assisted+")

S23 (image process*)

S24 (automatic classif*)

S25 (image analysis)

S26 SIAScop*

S27 (optical) N2 (scan*)

S28 (high) N3 (ultraso*)

S29 elastography

S30 (mobile or cell or cellular or smart) N2 (phone*) N2 (app or application*)

S31 (mole*) N2 (map*)

S32 total N2 body

S33 exfoliative cytolog*

S34 digital analys*

S35 image N3 software

S36 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatoscop* teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop*

S37 (optical coherence) N1 (technolog* or tomog*)

S38 computer N2 diagnos*

S39 sentinel N2 node

S40 (MH "Sentinel Lymph Node Biopsy")

S41 nevisense or HFUS or checklist* or VOC or dog*

S42 electrical impedance spectroscopy

S43 history taking

S44 "Patient history"

S45 naked eye

S46 skin exam*

S47 physical exam*

S48 ugly duckling

S49 UD sign*

S50 (physician* or clinical or physical) N1 (exam*)

S51 clinical accuracy

S52 general practice

S53 (physician* or clinical or physical) N1 (recog* or triage)

S54 confocal microscop*

S55 clinical competence

S56 diagnostic algorithm*

S57 checklist*

S58 virtual image*

S59 volatile organic compound*

S60 gene expression analys*

S61 reflex transmission imag*

S62 thermal imaging

S63 S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62

S64 CT or PET

S65 PET-CT

S66 FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical*

S67 (MH "Deoxyglucose+")

S68 deoxy-glucose or deoxyglucose

S69 CATSCAN

S70 CAT-SCAN

S71 (MH "Deoxyglucose+")

S72 (MH "Tomography, Emission-Computed+")

S73 (MH "Tomography, X-Ray Computed")

S74 positron emission tomograph*

S75 (MH "Magnetic Resonance Imaging+")

S76 MRI or fMRI or NMRI or scintigraph*

S77 echography

S78 doppler

S79 sonograph*

S80 ultraso*

S81 magnetic resonance imag*

S82 S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81

S83 stage* or staging or metasta* or recurrence or sensitivity or specificity or (false negative*) or thickness

S84 (MH "Neoplasm Staging")

S85 S83 OR S84

S86 S82 AND S85

S87 S63 OR S86

S88 S12 AND S87

Database : Science Citation Index SCI Expanded (Web of Science) 1900 – 30 August 2016

Conference Proceedings Citation Index (Web of Science) 1900 – 1 September 2016

Search strategy:

#1 (melanom* or nonmelanom* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyt*)

#2 (basalioma*)

#3 ((skin) near/2 (cancer* or carcinoma or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#4 ((basal) near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#5 ((pigmented) near/2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin))

#6 (nmsc or BCC or NMSC or keratinocy*)

#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#8 (skin or epiderm* or cutaneous)

#9 #8 AND #7

#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))

#12 ((nevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))

#13 #11 or #12

#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))

#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))

#16 #14 AND #15

#17 #16 OR #13

#18 #10 AND #17

Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

3 Full text inclusion criteria

CRITERION	INCLUSION	EXCLUSION
STUDY DESIGN	For diagnostic and staging reviews • Any study for which a 2x2 contingency table can be extracted, e.g. ◦ diagnostic case-control studies ◦ 'cross sectional' test accuracy study with retrospective or prospective data collection ◦ studies where estimation of test accuracy is not the primary objective but test results for both index and reference standard are available ◦ randomised controlled trials of tests or testing strategies where participants are randomised between index tests and all undergo a reference standard (i.e., accuracy RCTs)	• < 5 melanoma cases (diagnosis reviews) • < 10 participants (staging reviews) • Studies developing new criteria for diagnosis unless a separate 'test set' of images are used to evaluate the criteria (mainly digital dermoscopy) • Studies using 'normal' skin as controls • Letters, editorials, comment papers, narrative reviews • Insufficient data to construct a 2x2 table
TARGET CONDITION	• Melanoma • Keratinocyte skin cancer (or non-melanoma skin cancer) ◦ basal cell carcinoma (BCC) or epithelioma ◦ cutaneous squamous cell carcinoma (cSCC)	• Studies exclusively conducted in children • Studies of non-cutaneous melanoma or SCC
POPULATION	For diagnostic reviews • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms include pigmented skin lesion/nevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC For staging reviews • Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both	• Individuals suspected of other forms of skin cancer • Studies conducted exclusively in children
INDEX TESTS	For diagnosis • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscpoy • Smartphone/mobile phone applications • Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High frequency ultrasound • Canine odour detection • DNA expression analysis/Gene chip analysis • Other For staging • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology FNAC • Sentinel lymph node biopsy +/high frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g., radioisotope used)	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders • Tests to improve histopathology diagnose • Lymph node dissection

CRITERION	INCLUSION	EXCLUSION
REFERENCE STANDARD	For diagnostic studies • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign-appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) For studies of imaging tests for staging • Histopathology (via lymph node dissection or sentinel lymph node biopsy) • Clinical/radiological follow-up • A combination of the above For studies of SLNB accuracy for staging • Lymph node dissection (LND) of both SLN+ and SLNparticipants to identify all diseased nodes • Lymph node dissection of SLN+ participants and follow-up of SLNparticipants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	For diagnostic studies • Exclude if any disease-positive participants have diagnosis unconfirmed by histology • Exclude if more than 50% of disease-negative participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e., comparing referral decision with expert diagnosis, unless evaluations of teledermatology or mobile phone applications

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; CT = computed tomography; DNA = deoxyribonucleic acid; FNAC = fine needle aspiration cytology; LND = lymph node dissection; MRI = magnetic resonance imaging; PET = positron emission tomography; PET-CT = positron emission tomography computed tomography; RCT = randomised controlled trial; SLN+ = positive sentinel lymph node; SLn = negative sentinel lymph node; SLNB = sentinel lymph node biopsy.

4 Quality assessment (based on QUADAS-2)

The QUADAS-2 checklist (Whiting 2011) was tailored to the review topic as follows below.

Patient selection domain (1)

Selective recruitment of study participants can be a key influence on test accuracy. In general terms, all participants eligible to undergo a test should be included in a study, allowing for the intended use of that test within the context of the study. We considered studies that separately sampled malignant and benign lesions to have used a case-control design; and those that supplemented a series of suspicious lesions with additional malignant or benign lesions to be at unclear risk of bias

In terms of exclusions, we considered studies that excluded particular lesion types (e.g. lentigo maligna), particular lesion sites, or that excluded lesions on the basis of image quality or lack of observer agreement (e.g. on histopathology) to be at high risk of bias.

In judging the applicability of patient populations to the review question, we considered restriction to particular lesion populations, such as melanocytic, nodular, high risk or restrictions by size to be of high concern for applicability.

Given that diagnosis of skin cancer is primarily lesion-based, there is the potential for study participants with multiple lesions to contribute disproportionately to estimates of test accuracy, especially if they are at particular risk of having skin cancer. We considered studies that include a high number of lesions in relation to the number of study to be less representative than studies conducted in a more general population participants (i.e., if the difference between the number of included lesions and number of included participants is greater than 5%).

Index test domain (2)

Given the potential for subjective differences in test interpretation for melanoma, the interpretation of the index test blinded to the result of the reference standard is a key means of reducing bias. For prospective studies and retrospective studies that used the original index test interpretation, the diagnosis will by nature be interpreted and recorded before the result of the reference standard is known; however, studies using previously acquired images could be particularly susceptible to information bias. For these studies to be at low risk of bias, we required a clear indication that observers were unaware of the reference standard diagnosis at time of test interpretation. An item was also added to assess the presence of blinding between interpretations of different algorithms, however this item was not included in the overall assessment of risk of bias.

Pre-specification of the index test threshold was considered present if the study clearly reported that the threshold used was not data driven, i.e., was not based on study results. Studies that did not clearly describe the threshold used but that required clinicians to record a diagnosis or management decision for a lesion were considered to be unclear on this criterion. Studies reporting accuracy for multiple numeric thresholds, where ROC analysis was used to select the threshold, or that reported accuracy for the presence of independently significant lesion characteristics with no separate test set of lesions were considered at high risk of bias.

In terms of applicability of the index test to the review question, we required the test to be applied and interpreted as it would be in a clinical practice setting, i.e., in-person or face-to-face with the patient, and by a single observer as opposed to a

consensus decision or average across multiple observers. Image-based studies were considered to be high concern, although RCM image interpretations where the observer was also supplied with a clinical or dermoscopic image of the lesion along with some patient characteristics were considered ‘unclear’.

Despite the often subjective nature of test interpretation, it is also important for study authors to outline the particular lesion characteristics that were considered to be indicative for melanoma, particularly where established algorithms or checklists were not used. Studies were considered of low concern if the threshold used was established in a prior study or sufficient threshold details were presented to allow replication.

The experience of the examiner will also impact on the applicability of study results. We required studies to describe the test interpreter as ‘experienced’ or ‘expert’ in RCM to have low concern about applicability.

Reference standard domain (3)

In an ideal study, consecutively recruited participants should all undergo incisional or excisional biopsy of the skin lesion regardless of level of clinical suspicion of melanoma. In reality, both partial and differential verification bias are likely. Partial verification bias may occur where histology is the only reference standard used, and only those participants with a certain degree of suspicion of malignancy based on the result of the index test undergo verification, the others either being excluded from the study or defined as being disease-negative without further assessment or follow-up, as discussed above.

Differential verification bias will be present where other reference standards are used in addition to histological verification of suspicious lesions. A typical example of verification bias in skin cancer occurs when investigators do not biopsy people with benign-appearing lesions but instead follow them up for a period of time to determine whether any malignancy subsequently develops (these would be false-negatives on the index test). We defined an 'adequate' reference standard as: all disease-positive individuals having a histological reference standard either at the time of application of the index test or after a period of clinical follow-up; and at least 80% of disease-negative participants have received a histological diagnosis, with up to 20% undergoing at least three months' follow-up of benign-appearing lesions.

A further challenge is the potential for incorporation bias, i.e., where the result of the index test is used to help determine the reference standard diagnosis. It is normal practice for the clinical diagnosis (usually by visual inspection or dermoscopy) to be included on pathology request forms and for the histopathologist to use this diagnosis to help with the pathology interpretation. Although inclusion of such clinical information on the histopathology request form is theoretically a form of incorporation bias, blinded interpretation of the histopathology reference standard is not normal practice, and enforcement of such conditions would significantly limit the generalisability of the study results. For studies evaluating RCM, this item was divided into two questions, firstly whether the reference standard was blinded to the index test result (RCM), and secondly whether it was blinded to the clinical diagnosis. Only the response to the first part (i.e. blinding to RCM) was included in our overall assessment of risk of bias for the reference standard domain.

In judging the applicability of the reference standard to our review question, scored studies as high concern around applicability if they used expert diagnosis (with no follow-up) as a reference standard in any patient, or did not report histology interpretation by a dermatopathologist.

Flow and timing domain (4)

In the ideal study, the diagnosis based on the index test and reference standard should be made consecutively or as near to each other in time as possible to avoid changes in lesion over time. For lesions with a histological reference standard, we have defined a one-month period as an appropriate interval between application of the index test and the reference standard. For studies using clinical follow-up, a minimum three-month follow-up period has been defined as at low risk of bias for detecting false-negatives. This interval was chosen based on a study showing that most false-negative melanomas will be diagnosed within three months of the initial negative index test although a small number will be diagnosed up to 12 months subsequently (Altamura 2008).

In assessing whether all patients were included in the analysis, we considered studies at high risk of bias if participants were excluded following recruitment.

Comparative domain

A comparative domain was added to the QUADAS-2 checklist for studies comparing the accuracy of RCM and dermoscopy. Items were included to assess the presence blinding of interpretation between tests, and to specify a maximum of one month interval between application of index tests, as intervals greater than these may be accompanied by changes in tumour characteristics. As it would not be normal practice for RCM to be interpreted blinded to the clinical or dermoscopic diagnosis, the scoring of this item did not contribute to our overall assessment of risk of bias. We also considered whether both tests were applied and interpreted in a clinically applicable manner.

The following tables use text that was originally published in the QUADAS-2 tool by Whiting and colleagues (Whiting 2011 *).*

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
1) Was a consecutive or random sample of participants or images enrolled?	**Yes** – if paper states consecutive or random **No** – if paper describes other method of sampling **Unclear** – if participant sampling not described

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
2) Was a case-control design avoided?	**Yes** – if consecutive or random or case-control design clearly not used **No** – if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** – if not described
3) Did the study avoid inappropriate exclusions, e.g., • 'difficult to diagnose' lesions not excluded • lesions not excluded on basis of disagreement between evaluators	**Yes** if inappropriate exclusions were avoided **No** – if lesions were excluded that might affect test accuracy, e.g., 'difficult to diagnose' lesions, or where disagreement between evaluators was observed **Unclear** – if not clearly reported but there is suspicion that difficult to diagnose lesions may have been excluded
4) For between-person comparative studies only (i.e., allocating different tests to different study participants): • **A)** were the same participant selection criteria used for those allocated to each test? • **B)** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C)** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	<u>For A)</u> • **Yes** – if same selection criteria were used for each index test, **No** – if different selection criteria were used for each index test, **Unclear** – if selection criteria per test were not described, **N/A** – if only 1 index test was evaluated or all participants received all tests <u>For B)</u> • **Yes** – if adequate randomisation procedures are described, **No** – if inadequate randomisation procedures are described, **Unclear** – if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient), **N/A** – if only 1 index test was evaluated or all participants received all tests <u>For C)</u> • **Yes** – if appropriate methods of allocation concealment are described, **No** – if appropriate methods of allocation concealment are not described, **Unclear** – if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required), **N/A** – if only 1 index test was evaluated
Could the selection of participants have introduced bias? <u>For non-comparative and within-person-comparative studies</u> 1. If answers to all of questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': <u>For between-person comparative studies</u> 1. If answers to all of questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	<u>For non-comparative and within-person-comparative studies</u> 1. Risk is low 2. Risk is high 3. Risk unclear <u>For between-person comparative studies</u> 1. Risk is low 2. Risk is high 3. Risk unclear
PARTICIPANT SELECTION (1) CONCERNS REGARDING APPLICABILITY	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
1) Are the included participants and chosen study setting appropriate to answer the review question, i.e., are the study results generalisable? • This item is not asking whether exclusion of certain participant groups might bias the study's results (as in Risk of Bias above), but is asking whether the chosen study participants and setting are appropriate to answer our review question. Because we are looking to establish test accuracy in both primary presentation and referred participants, a study could be appropriate for 1 setting and not for the other, or it could be unclear as to whether the study can appropriately answer either question • For each study assessed, please consider whether it is more relevant for A) participants with a primary presentation of a skin lesion or B) referred participants, and respond to the questions in either A) or B) accordingly. If the study gives insufficient details, please respond **Unclear** to both parts of the question	**A) For studies that will contribute to the analysis of participants with a primary presentation of a skin lesion (i.e., test naive)** **Yes** – if participants included in the study appear to be generally representative of those who might present in a usual practice setting **No** – if study participants appear to be unrepresentative of usual practice, e.g., in terms of severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants **B) For studies that will contribute to the analysis of referred participants (i.e., who have already undergone some form of testing)** **Yes** – if study participants appear to be representative of those who might be referred for further investigation. If the study focuses only on those with equivocal lesions, for example, we would suggest that this is not representative of the wider referred population **No** – if study participants appear to be unrepresentative of usual practice, e.g., if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants
2) Did the study **avoid including** participants with multiple lesions?	**Yes** – if the difference between the number of included lesions and number of included participants is less than 5% **No** – if the difference between the number of included lesions and number of included participants is greater than 5% **Unclear –** if it is not possible to assess
Is there concern that the included participants do not match the review question? 1. If the answer to question 1) or 2) 'Yes': 2. If the answer to question 1) or 2) 'No': 3. If the answer to question 1) or 2) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
INDEX TEST (2) RISK OF BIAS (to be completed per test evaluated)	
1) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	**Yes** – if index test described as interpreted without knowledge of reference standard result or, for prospective studies, if index test is always conducted and interpreted prior to the reference standard **No** – if index test described as interpreted in knowledge of reference standard result **Unclear** – if index test blinding is not described

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
2) Was the diagnostic threshold at which the test was considered positive (i.e., melanoma present) prespecified?	**Yes** – if threshold was prespecified (i.e., prior to analysing study results) **No** – if threshold was not prespecified **Unclear** – if not possible to tell whether or not diagnostic threshold was prespecified
3) For within-person comparisons of index tests or testing strategies (i.e., > 1 index test applied per participant): was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	**Yes** – if all index tests were described as interpreted without knowledge of the results of the others **No** – if the index tests were described as interpreted in the knowledge of the results of the others **Unclear** – if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation **N/A** – if only 1 index test was evaluated
Could the conduct or interpretation of the index test have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to either questions 1) or 2) 'No': 3. If answers to either questions 1) or 2) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), for any index test and 3) 'Yes': 2. If answers to any 1 of questions 1) or 2) for any index test or 3) 'No': 3. If answers to any 1 of questions 1) or 2) for any index test or 3) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
INDEX TEST (2) CONCERN ABOUT APPLICABILITY	
1) Was the diagnostic threshold to determine presence or absence of disease established in a previously published study? E.g., previously evaluated/established • algorithm/checklist used • lesion characteristics indicative of melanoma used • objective (usually numerical) threshold used	**Yes** – if a previously evaluated/established tool to aid diagnosis of melanoma was used or if the diagnostic threshold used was established in a previously published study **No** – if an unfamiliar/new tool to aid diagnosis of melanoma was used, if no particular algorithm was used, or if the objective threshold reported was chosen based on results in the current study **Unclear** – if insufficient information was reported
2) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? Study results can only be reproduced if the diagnostic threshold is described in sufficient detail. This item applies equally to studies using pattern recognition and those using checklists or algorithms to aid test interpretation	**Yes** – If the criteria for diagnosis of melanoma were reported in sufficient detail to allow replication **No** – if the criteria for diagnosis of melanoma were not reported in sufficient detail to allow replication **Unclear** – If some but not sufficient information on criteria for diagnosis to allow replication were provided

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
3) Was the test interpretation carried out by an experienced examiner?	**Yes** – if the test was interpreted by 1 or more speciality-accredited dermatologists, or by examiners of any clinical background with special interest in dermatology and with any formal training in the use of the test **No** – if the test was not interpreted by an experienced examiner (see above) **Unclear** – if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners were described as 'Expert' with no further detail given **N/A** – if system-based diagnosis, i.e., no observer interpretation
Is there concern that the index test, its conduct, or interpretation differ from the review question? 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to questions 1), 2), or 3) 'No': 3. If answers to questions 1), 2), or 3) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
REFERENCE STANDARD (3) RISK OF BIAS	
1) Is the reference standard likely to correctly classify the target condition? A) Disease-positive – 1 or more of the following: • histological confirmation of melanoma following biopsy or lesion excision • clinical follow-up of benign-appearing lesions for at least 3 months following the application of the index test, leading to a histological diagnosis of melanoma B) Disease-negative – 1 or more of the following: • histological confirmation of absence of melanoma following biopsy or lesion excision in at least 80% of disease-negative participants • clinical follow-up of benign-appearing lesions for a minimum of 3 months following the index test in up to 20% of disease-negative participants	A) Disease-positive **Yes** – if all participants with a final diagnosis of melanoma underwent 1 of the listed reference standards **No** – If a final diagnosis of melanoma for any participant was reached without histopathology **Unclear** – if the method of final diagnosis was not reported for any participant with a final diagnosis of melanoma or if the length of clinical follow-up used was not clear or if a clinical follow-up reference standard was reported in combination with a participant-based analysis and it was not possible to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test B) Disease-negative **Yes** – If at least 80% of benign diagnoses were reached by histology and up to 20% were reached by clinical follow-up for a minimum of 3 months following the index test **No** – if more than 20% of benign diagnoses were reached by clinical follow-up for a minimum of 3 months following the index test or if clinical follow-up period was less than 3 months **Unclear** – if the method of final diagnosis was not reported for any participant with benign or non-melanoma diagnosis
2) Were the reference standard results interpreted without knowledge of the results of the index test? Please score this item for all studies even though histopathology interpretation is usually conducted with knowledge of the clinical diagnosis (from visual inspection or dermoscopy or both). We will deal with this by not including the response to this item in the 'Risk of bias' assessment for these tests. For reviews of all other tests, this item will be retained	**Yes** – if the reference standard diagnosis was reached blinded to the index test result **No** – if the reference standard diagnosis was reached with knowledge of the index test result **Unclear** – if blinded reference test interpretation was not clearly reported

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1) 'Yes': 2. If answer to question 1) 'No': 3. If answer to question 1) 'Unclear': **For all other tests** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to questions 1) or 2) 'No': 3. If answers to questions 1) or 2) 'Unclear':	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
REFERENCE STANDARD (3) CONCERN ABOUT APPLICABILITY	
1) Are index test results presented separately for each component of the target condition (i.e., separate results presented for those with invasive melanoma, melanoma in situ, lentigo maligna, severe dysplasia, BCC, and cSCC)?	**Yes –** if index test results for each component of the target condition can be disaggregated **No –** if index test results for the different components of the target condition cannot be disaggregated **Unclear** – if not clearly reported
2) Expert opinion (with no histological confirmation) was not used as a reference standard 'Expert opinion' means diagnosis based on the standard clinical examination, with no histology or lesion follow-up ***do not complete this item for teledermatology studies	**Yes** – if expert opinion was not used as a reference standard for any participant **No** – if expert opinion was used as a reference standard for any participant **Unclear** – if not clearly reported
3) Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	**Yes –** if histology interpretation was reported to be carried out by an experienced histopathologist or dermatopathologist **No –** if histology interpretation was reported to be carried out by a less experienced histopathologist **Unclear** – if the experience/qualifications of the pathologist were not reported
Is there concern that the target condition as defined by the reference standard does not match the review question? 1. If answers to all questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': *****For teledermatology studies only** 1. If answers to all questions 1) and 3) 'Yes': 2. If answers to questions 1) or 3) 'No': 3. If answers to questions 1) or 3) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear *****For teledermatology studies only** 1. Concern is low 2. Concern is high 3. Concern is unclear
FLOW AND TIMING (4): RISK OF BIAS	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) RISK OF BIAS	
1) Was there an appropriate interval between index test and reference standard? **A)** For histopathological reference standard, was the interval between index test and reference standard ≤ 1 month? **B)** If the reference standard includes clinical follow-up of borderline/benign-appearing lesions, was there at least 3 months' follow-up following application of index test(s)?	**A)** **Yes** – if study reports ≤ 1 month between index and reference standard **No** – if study reports > 1 month between index and reference standard **Unclear** – if study does not report interval between index and reference standard **B)** **Yes** – if study reports ≥ 3 months' follow-up **No** – if study reports < 3 months' follow-up **Unclear** – if study does not report the length of clinical follow-up
2) Did all participants receive the same reference standard?	**Yes** – if all participants underwent the same reference standard **No** – if more than 1 reference standard was used **Unclear** – if not clearly reported
3) Were all participants included in the analysis?	**Yes** – if all participants were included in the analysis **No** – if some participants were excluded from the analysis **Unclear**– if not clearly reported
4) **For within-person comparisons of index tests** Was the interval between application of index tests ≤ 1 month?	**Yes** – if study reports ≤ 1 month between index tests **No** – if study reports > 1 month between index tests **Unclear** – if study does not report the interval between index tests
Could the participant flow have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.	

5 Details of RCM algorithms and diagnostic thresholds for diagnosis

RCM algorithms (based on analysis of training set)			
RCM score (Pellacani 2005; Pellacani 2007)	Segura score - two step to id melanocytic first and then melanomas (Segura 2009)	Guitera two-step method for BCC and MM (Guitera 2012)	Pellacani two-step method for dysplastic lesions and then MM (Pellacani 2012)

RCM algorithms (based on analysis of training set)			
Used in: Curchin 2011 (w LM score) Guitera 2009 Guitera 2012 Lovatto 2015 Pellacani 2007 Pellacani 2014	Used in: Alarcon 2014 Guitera 2012 Lovatto 2015 Segura 2009		Used in: Pellacani 2012 Stanganelli 2015
RCM score ≥ 2, ≥ 3, ≥ 4 Presence of two major features (each scoring 2): - non-edged papillae - cellular atypia at dermal–epidermal junction Presence of four minor features (each scored 1) - roundish pagetoid cells, - widespread pagetoid infiltration, - cerebriform nests, - nucleated cells within the papilla	Cutoff of >-1 = 'most probable melanoma' Within melanocytic lesions 2 protective features associated with benign lesions (score -1 each) - typical basal cells and - edged papillae 2 risk features associated with melanoma (score +1 each) - roundish pagetoid cells and - atypical dermal nucleated cells. Lesions were assigned a value from -2 to 2 according to the presence or absence of these factors	Correct id as MM or BCC (based on independently significant features as id from training set) Melanoma: - cerebriform nests, - atypical cobblestone pattern with small nucleated cells in the epidermis, - marked cytological atypia, and - pagetoid cells, and - disarranged epidermal layer with no honey comb - Large inter-papillae spaces filled with honeycomb - Dense nest	Two step algorithm (≥ 3 characteristics present, two at step 1 and one at step 2) Step 1: id dysplastic nevus Presence of cytologic atypia (≥ 1 present) - round pagetoid cells - atypical cells at DEJ and Presence of architectural atypia (≥ 1 present) - irregular junctional nests - short interconnections between junctional nests - nonhomogenous cellularity within junctional nests Step 2: id melanoma from dysplastic nevus (≥ 1 characteristic present) - widespread (≥ 50% of lesional area) round pagetoid cells, - widespread (≥ 50% of lesional area) atypical cells at the DEJ, and - nonedged papillae (≥ 10% of the lesional area)

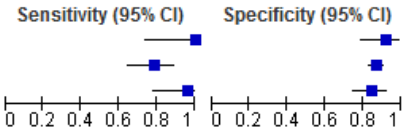
RCM 'no algorithm' (selected lesion characteristics, independently significant characteristics identified, or 'observer diagnosis')		
Langley 2007 (based on Langley 2001)	Ferrari 2015	Koller 2011 (MM) Rao 2013 (MM/BCC/SCC) Farnetani 2015 (MM and BCC)

RCM algorithms (based on analysis of training set)		
≥ 1 characteristic present (selected from prior study) Any one of: - epidermal disarray with loss of the normal honeycomb pattern; - a grainy image; - pagetoid cells in the epidermis; - complex branching dendrites or dendritic cells; - atypical and pleomorphic refractile cells, and the - presence of bright, highly refractile particles	Independently significant features (These four features are referenced to Pellacani 2012 as 'melanoma clues') For featureless lesions (score 0-2 on dermoscopy 7PCL), presence of at least one of: - ≥5 round pagetoid cells - architectural disorder For equivocal lesions (score 3-4 on dermoscopy 7PCL), presence of at least one of: - any number of round pagetoid cells - five or more atypical cells at the junction ≥ 1 characteristic present for each	Observer diagnosis Koller 2011 'diagnoses based on 'expert experience' Rao 2013 (MM/BCC/SCC) Observers gave diagnosis and excise decision (no further details) Farnetani 2015 (MM and BCC) Evaluators completed a 'pattern description' (presence/absence of a number of RCM features) and gave an overall diagnosis of malignant (melanoma or BCC) or benign
RCM 'no algorithm' (developed for specific study populations)		
Longo 2013 Nodular lesions	Pupelli 2013 <=5 mm melanocytic lesions	Figueroa Silva 2016 'Thin' MM with dermoscopic island
Independently significant features - widespread pagetoid distribution (graded as focal, localized, widespread); - many atypical cells; - cerebriform nests.	Independently significant features - presence of at least five pagetoid cells per mm2, - tangled lines within the epidermis, and - atypical roundish cells at the dermoepidermal junction	Overall diagnosis reported; features assessed included: - cobblestone pattern, - pagetoid cells, - architecture type (ringed, meshwork or clod prevalent pattern at DEJ, regular/irregular) - and atypical cells at the DEJ
RCM - reflectance confocal microscopy; DEJ - dermo-epidermal junction; 7PCL - seven point checklist; MM -melanoma; BCC - basal cell carcinoma; SCC; squamous cell carcinoma.		

Graphs

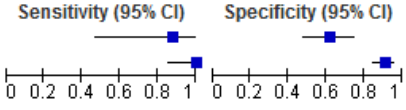
RCM in any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	0	35	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]
Guitera 2012	40	40	11	265	0.78 [0.65, 0.89]	0.87 [0.83, 0.90]
Segura 2009	22	12	1	65	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]



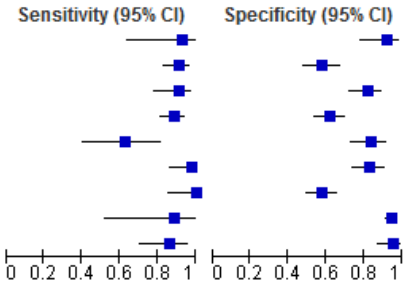
RCM in studies of other lesion types (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	7	21	1	34	0.88 [0.47, 1.00]	0.62 [0.48, 0.75]
Longo 2013	23	10	0	107	1.00 [0.85, 1.00]	0.91 [0.85, 0.96]



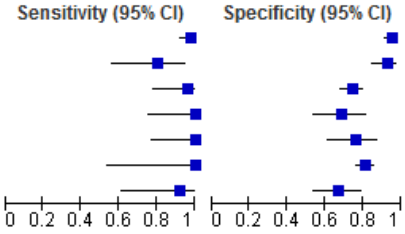
RCM in any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Guitera 2009a (Modena)	72	49	7	67	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Guitera 2012	93	56	12	92	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Koller 2011	15	11	9	57	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Langley 2007	36	15	1	73	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Pellacani 2014b (doc)	23	68	0	92	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]
Rao 2013	8	17	1	297	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]
Segura 2009	31	3	5	61	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]



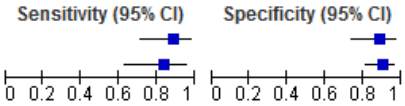
RCM in equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Farnetani 2015	16	6	4	74	0.80 [0.56, 0.94]	0.93 [0.84, 0.97]
Ferrari 2015	22	54	1	155	0.96 [0.78, 1.00]	0.74 [0.68, 0.80]
Lovatto 2015	13	16	0	35	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Pellacani 2012	14	11	0	35	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Pellacani 2014a (cons)	6	56	0	246	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Stanganelli 2015	11	19	1	39	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]



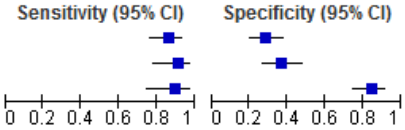
RCM in studies of other lesion types (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	24	4	3	32	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]
Pupelli 2013	20	7	4	65	0.83 [0.63, 0.95]	0.90 [0.81, 0.96]



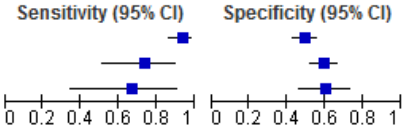
Dermoscopy in any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2009a (Modena)	68	83	11	33	0.86 [0.76, 0.93]	0.28 [0.20, 0.38]
Guitera 2009b (Sydney)	40	55	4	32	0.91 [0.78, 0.97]	0.37 [0.27, 0.48]
Langley 2007	33	14	4	74	0.89 [0.75, 0.97]	0.84 [0.75, 0.91]



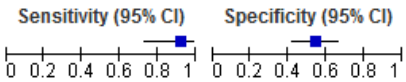
Dermoscopy in equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	86	128	6	123	0.93 [0.86, 0.98]	0.49 [0.43, 0.55]
Ferrari 2015	17	85	6	124	0.74 [0.52, 0.90]	0.59 [0.52, 0.66]
Stanganelli 2015	8	23	4	35	0.67 [0.35, 0.90]	0.60 [0.47, 0.73]



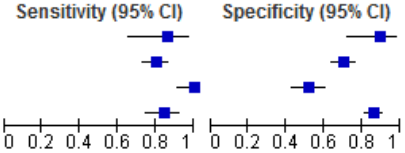
Dermoscopy in studies of other lesion types (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pupelli 2013	22	33	2	39	0.92 [0.73, 0.99]	0.54 [0.42, 0.66]



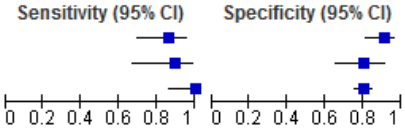
RCM in any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	19	3	3	25	0.86 [0.65, 0.97]	0.89 [0.72, 0.98]
Guitera 2012	126	59	31	140	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]
Pellacani 2014b (doc)	42	68	0	73	1.00 [0.92, 1.00]	0.52 [0.43, 0.60]
Rao 2013	66	34	12	211	0.85 [0.75, 0.92]	0.86 [0.81, 0.90]



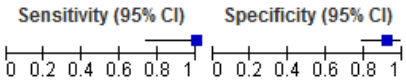
RCM in equivocal lesion studies (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	30	6	5	59	0.86 [0.70, 0.95]	0.91 [0.81, 0.97]
Pellacani 2012	17	8	2	33	0.89 [0.67, 0.99]	0.80 [0.65, 0.91]
Pellacani 2014a (cons)	25	56	0	227	1.00 [0.86, 1.00]	0.80 [0.75, 0.85]



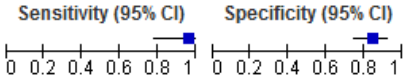
RCM score at ≥ 3 (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	0	35	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]



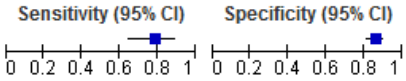
Segura algorithm at >-1 (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Segura 2009	22	12	1	65	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]



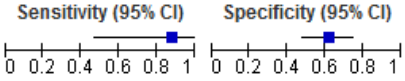
Guitera Two-step alg (significant characteristics) (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	40	43	11	262	0.78 [0.65, 0.89]	0.86 [0.81, 0.90]



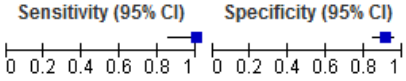
No algorithm (observer diagnosis) (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	7	21	1	34	0.88 [0.47, 1.00]	0.62 [0.48, 0.75]



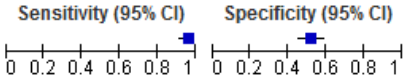
No algorithm (significant characteristics) (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Longo 2013	23	10	0	107	1.00 [0.85, 1.00]	0.91 [0.85, 0.96]



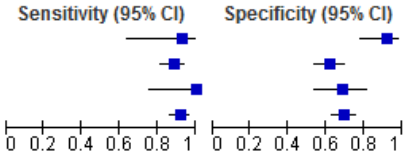
RCM score at ≥ 2 (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2007	131	103	5	112	0.96 [0.92, 0.99]	0.52 [0.45, 0.59]



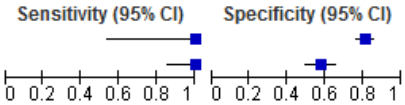
RCM score at ≥ 3 (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Guitera 2012	93	56	12	92	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Lovatto 2015	13	16	0	35	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Pellacani 2007	125	66	11	149	0.92 [0.86, 0.96]	0.69 [0.63, 0.75]



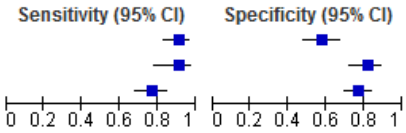
RCM score at threshold NR (likely ≥ 3) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2014a (cons)	6	56	0	246	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Pellacani 2014b (doc)	23	68	0	92	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]



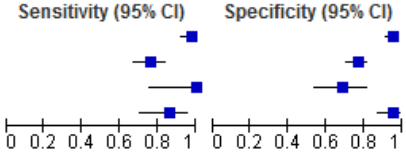
RCM score at ≥ 4 (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2009a (Modena)	72	49	7	67	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Guitera 2012	81	34	24	114	0.77 [0.68, 0.85]	0.77 [0.69, 0.84]



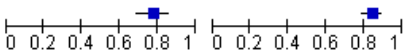
Segura algorithm at >-1 (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Guitera 2012	80	59	25	192	0.76 [0.67, 0.84]	0.76 [0.71, 0.82]
Lovatto 2015	13	16	0	35	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Segura 2009	31	3	5	61	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]



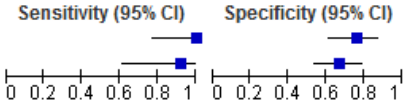
Guitera Two-step alg (significant chars for MM) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	82	40	23	211	0.78 [0.69, 0.86]	0.84 [0.79, 0.88]		



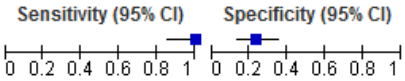
Pellacani Two step algorithm (dysplastic-MM) image-based (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2012	14	11	0	35	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]		
Stanganelli 2015	11	19	1	39	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]		



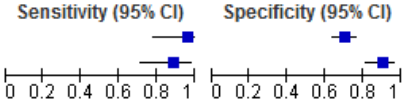
RCM CAD algorithm (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Koller 2011	24	52	0	16	1.00 [0.86, 1.00]	0.24 [0.14, 0.35]		



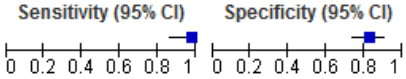
No algorithm (significant characteristics) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ferrari 2015	22	62	1	147	0.96 [0.78, 1.00]	0.70 [0.64, 0.76]		
Pupelli 2013	24	7	3	65	0.89 [0.71, 0.98]	0.90 [0.81, 0.96]		



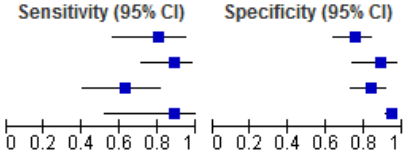
No algorithm (selected characteristics) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Langley 2007	36	15	1	73	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]		



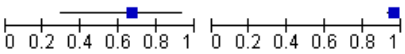
No algorithm (observer diagnosis) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	16	20	4	60	0.80 [0.56, 0.94]	0.75 [0.64, 0.84]		
Figueroa Silva 2016	24	4	3	32	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]		
Koller 2011	15	11	9	57	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]		
Rao 2013	8	17	1	297	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]		



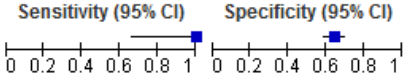
No algorithm (observer diagnosis) paired in-person (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	6	13	3	295	0.67 [0.30, 0.93]	0.96 [0.93, 0.98]		



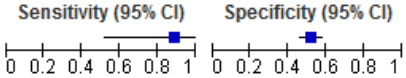
No algorithm (excise decision) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	9	113	0	201	1.00 [0.66, 1.00]	0.64 [0.58, 0.69]		



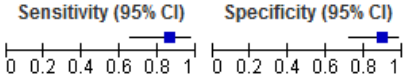
No algorithm (excise decision) paired in-person (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	8	148	1	160	0.89 [0.52, 1.00]	0.52 [0.46, 0.58]		



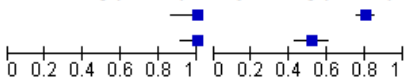
RCM score at ≥ 3 (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	19	3	3	25	0.86 [0.65, 0.97]	0.89 [0.72, 0.98]		



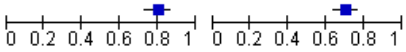
RCM score at threshold NR (likely ≥ 3) (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2014a (cons)	25	56	0	227	1.00 [0.86, 1.00]	0.80 [0.75, 0.85]		
Pellacani 2014b (doc)	42	68	0	73	1.00 [0.92, 1.00]	0.52 [0.43, 0.60]		



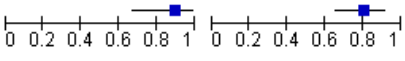
Segura algorithm at >-1 (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	126	59	31	140	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]		



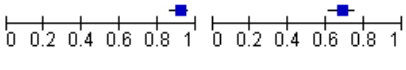
Pellacani Two step algorithm (dysplastic-MM) (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Pellacani 2012	17	8	2	33	0.89 [0.67, 0.99]	0.80 [0.65, 0.91]		



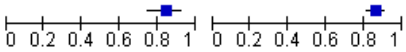
Guitera Two-step alg (significant characteristics) (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	152	60	14	130	0.92 [0.86, 0.95]	0.68 [0.61, 0.75]		



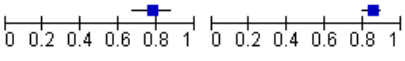
No algorithm (observer diagnosis) (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	30	6	5	59	0.86 [0.70, 0.95]	0.91 [0.81, 0.97]		
Rao 2013	66	34	12	211	0.85 [0.75, 0.92]	0.86 [0.81, 0.90]		



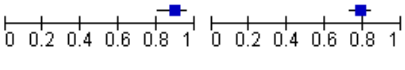
No algorithm (observer diagnosis) paired in-person (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	57	37	16	207	0.78 [0.67, 0.87]	0.85 [0.80, 0.89]		



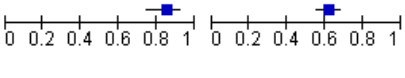
No algorithm (excise decision) (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	70	52	8	193	0.90 [0.81, 0.95]	0.79 [0.73, 0.84]		



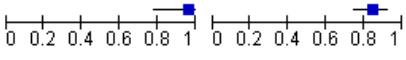
No algorithm (excise decision) paired in-person (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rao 2013	62	94	11	150	0.85 [0.75, 0.92]	0.61 [0.55, 0.68]		



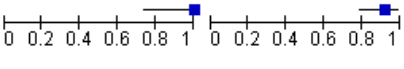
Observer experience high - any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	40	43	11	262	0.78 [0.65, 0.89]	0.86 [0.81, 0.90]		
Segura 2009	22	12	1	65	0.96 [0.78, 1.00]	0.84 [0.74, 0.92]		



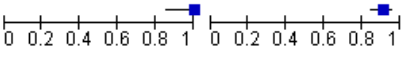
Observer experience low - any lesion suspicious for melanoma (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	0	35	1.00 [0.74, 1.00]	0.92 [0.79, 0.98]		



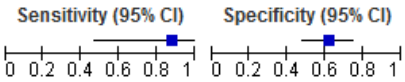
MM1 observer experience high other

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Longo 2013	23	10	0	107	1.00 [0.85, 1.00]	0.91 [0.85, 0.96]		



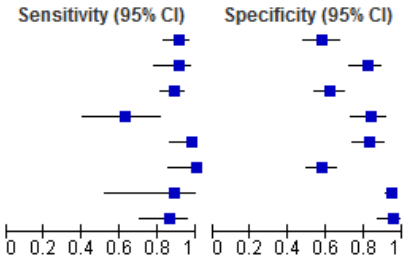
MM1 observer experience NR other

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	7	21	1	34	0.88 [0.47, 1.00]	0.62 [0.48, 0.75]



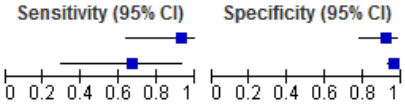
Observer experience high - any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2009a (Modena)	72	49	7	67	0.91 [0.83, 0.96]	0.58 [0.48, 0.67]
Guitera 2009b (Sydney)	40	16	4	71	0.91 [0.78, 0.97]	0.82 [0.72, 0.89]
Guitera 2012	93	56	12	92	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Koller 2011	15	11	9	57	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Langley 2007	36	15	1	73	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Pellacani 2014b (doc)	23	68	0	92	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]
Rao 2013	8	17	1	297	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]
Segura 2009	31	3	5	61	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]



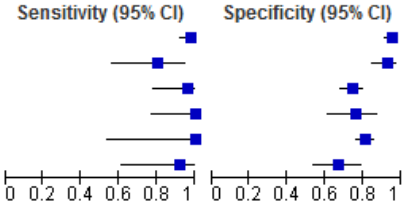
Observer experience low - any lesion suspicious for melanoma (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Rao 2013	6	13	3	296	0.67 [0.30, 0.93]	0.96 [0.93, 0.98]



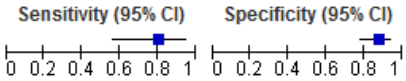
Observer experience high - equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Farnetani 2015	16	6	4	74	0.80 [0.56, 0.94]	0.93 [0.84, 0.97]
Ferrari 2015	22	54	1	155	0.96 [0.78, 1.00]	0.74 [0.68, 0.80]
Pellacani 2012	14	11	0	35	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Pellacani 2014a (cons)	6	56	0	246	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Stanganelli 2015	11	19	1	39	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]



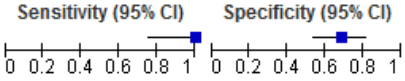
Observer experience low - equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	16	10	4	70	0.80 [0.56, 0.94]	0.88 [0.78, 0.94]



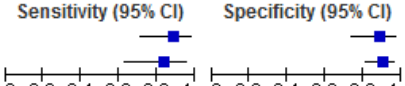
Observer experience NR - equivocal lesion studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lovatto 2015	13	16	0	35	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]



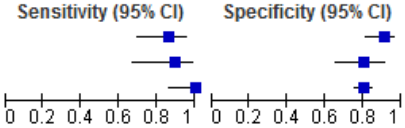
Observer experience NR - other study populations (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Figueroa Silva 2016	24	4	3	32	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]
Pupelli 2013	20	7	4	65	0.83 [0.63, 0.95]	0.90 [0.81, 0.96]



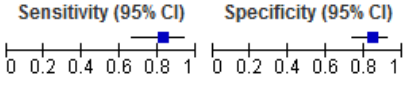
Observer experience high - equivocal lesion studies (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	30	6	5	59	0.86 [0.70, 0.95]	0.91 [0.81, 0.97]
Pellacani 2012	17	8	2	33	0.89 [0.67, 0.99]	0.80 [0.65, 0.91]
Pellacani 2014a (cons)	25	56	0	227	1.00 [0.86, 1.00]	0.80 [0.75, 0.85]



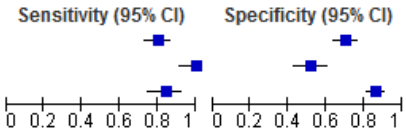
Observer experience low - equivocal lesion studies (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Farnetani 2015	29	10	6	55	0.83 [0.66, 0.93]	0.85 [0.74, 0.92]



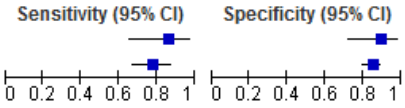
Observer experience high - any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Guitera 2012	126	59	31	140	0.80 [0.73, 0.86]	0.70 [0.63, 0.77]
Pellacani 2014b (doc)	42	68	0	73	1.00 [0.92, 1.00]	0.52 [0.43, 0.60]
Rao 2013	66	34	12	211	0.85 [0.75, 0.92]	0.86 [0.81, 0.90]



Observer experience low - any lesion suspicious for melanoma (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Curchin 2011	19	3	3	25	0.86 [0.65, 0.97]	0.89 [0.72, 0.98]
Rao 2013	57	37	16	208	0.78 [0.67, 0.87]	0.85 [0.80, 0.89]



MM2 any scale

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alarcon 2014	90	13	2	238	0.98 [0.92, 1.00]	0.95 [0.91, 0.97]
Curchin 2011	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]
Farnetani 2015	16	20	4	60	0.80 [0.56, 0.94]	0.75 [0.64, 0.84]
Ferrari 2015	22	62	1	147	0.96 [0.78, 1.00]	0.70 [0.64, 0.76]
Figueroa Silva 2016	24	4	3	32	0.89 [0.71, 0.98]	0.89 [0.74, 0.97]
Guitera 2012	93	56	12	92	0.89 [0.81, 0.94]	0.62 [0.54, 0.70]
Koller 2011	15	11	9	57	0.63 [0.41, 0.81]	0.84 [0.73, 0.92]
Langley 2007	36	15	1	73	0.97 [0.86, 1.00]	0.83 [0.73, 0.90]
Lovatto 2015	13	16	0	35	1.00 [0.75, 1.00]	0.69 [0.54, 0.81]
Pellacani 2012	14	11	0	35	1.00 [0.77, 1.00]	0.76 [0.61, 0.87]
Pellacani 2014a (cons)	6	56	0	246	1.00 [0.54, 1.00]	0.81 [0.77, 0.86]
Pellacani 2014b (doc)	23	68	0	92	1.00 [0.85, 1.00]	0.57 [0.49, 0.65]
Pupelli 2013	24	7	3	65	0.89 [0.71, 0.98]	0.90 [0.81, 0.96]
Rao 2013	8	17	1	297	0.89 [0.52, 1.00]	0.95 [0.91, 0.97]
Segura 2009	31	3	5	61	0.86 [0.71, 0.95]	0.95 [0.87, 0.99]
Stanganelli 2015	11	19	1	39	0.92 [0.62, 1.00]	0.67 [0.54, 0.79]