Computer assisted diagnosis techniques (dermoscopy and spectroscopy-based) for the diagnosis of skin cancer in adults

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Abstract

Background

Early accurate detection of all skin cancer types is essential to guide appropriate management and to improve morbidity and survival. Melanoma and cutaneous squamous cell carcinoma (cSCC) are high risk skin cancers which have the potential to metastasise and ultimately lead to death, whereas basal cell carcinoma (BCC) is usually localised with potential to infiltrate and damage surrounding tissue. Anxiety around missing early curable cases needs to be balanced against inappropriate referral and unnecessary excision of benign lesions. Computer assisted diagnosis (CAD) systems use artificial intelligence to analyse lesion data and arrive at a diagnosis of skin cancer. When used in unreferred settings ('primary care'), CAD may assist GPs or other clinicians to more appropriately triage high risk lesions to secondary care. Used alongside clinical and

dermoscopic suspicion of malignancy, CAD may reduce unnecessary excisions without missing melanoma cases.

Objectives

To determine the accuracy of CAD systems for diagnosing cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, BCC or cSCC in adults, and to compare its accuracy with that of dermoscopy when dermoscopy is also evaluated in CAD studies.

Search methods

We undertook a comprehensive search of the following databases from inception up to 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 CAD alone, or in comparison with dermoscopy, in adults with lesions suspicious for melanoma or BCC or cSCC, and 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 separately by type of CAD system using the bivariate hierarchical model. Comparisons of CAD with dermoscopy were made using a) all available CAD data (indirect comparisons), and b) studies providing paired data for both tests (direct comparisons). The contribution of human decision making to the accuracy of CAD diagnoses was examined in a sensitivity analysis by removing studies that gave CAD results to clinicians to guide diagnostic decision-making.

Main results

In total 42 studies were included, 24 evaluating digital dermoscopy based CAD systems (Derm–CAD) in 23 study cohorts with 9602 lesions (1220 melanomas, at least 83 BCCs, 9 cSCCs), providing 32 datasets for Derm–CAD and 7 for dermoscopy. Eighteen studies evaluated spectroscopy based CAD (Spectro–CAD) in 16 study cohorts with 6336 lesions (934 melanomas, 163 BCC, 49 cSCCs), providing 32 datasets for Spectro–CAD and 6 for dermoscopy. These consisted of 15 studies using multispectral imaging (MSI), 2 studies using electrical impedance spectroscopy (EIS) and 1 study using diffuse reflectance spectroscopy. Studies were incompletely reported and of unclear to high risk of bias across all domains. Included studies inadequately address the review question due to an abundance of low quality studies, poor reporting, and recruitment of highly selected groups of participants.

Across all CAD systems, considerable variation was encountered in the hardware and software technologies used, the types of classification algorithm employed, methods used to train the algorithms, and which lesion morphological features were extracted and analysed across all CAD systems, and even between studies evaluating CAD systems. Meta–analysis found CAD systems had high sensitivity for correct identification of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in highly selected populations, but with low and very variable specificity, particularly for Spectro–CAD systems. Pooled data from 22 studies estimated the sensitivity of Derm–CAD for the detection of melanoma as 90.1% (95% CI: 84.0% to 94.0%) and specificity as 74.3% (95% CI: 63.6% to 82.7%). Pooled data from 8 studies estimated the sensitivity of multispectral imaging CAD (MSI–CAD) as 92.9% (95% CI: 83.7% to 97.1%) and specificity as 43.6% (95% CI: 24.8% to 64.5%). When applied to a hypothetical population of 1000 lesions at the mean observed melanoma prevalence of 20%, Derm–CAD would miss 20 melanomas and would lead to 206 false positive results for melanoma. MSI–CAD would miss 14 melanomas and would lead to 451 false diagnoses for melanoma. Preliminary findings suggest CAD systems are at least as sensitive as assessment of dermoscopic images for the diagnosis of invasive melanoma and atypical intraepidermal melanocytic variants. It is not possible to make summary statements regarding the use of CAD in unreferred populations, or its accuracy in detecting keratinocyte cancers, or its use in any setting as a diagnostic aid, because of the paucity of studies.

Authors' conclusions

In highly selected patient populations all CAD types demonstrate high sensitivity, and could prove useful as a back-up for specialist diagnosis to assist in minimising the risk of missing melanomas. However, the evidence–base is currently too poor to understand whether CAD system outputs translate to different clinical decision–making in practice. Insufficient data are available on the use of CAD in community settings, or for the detection of keratinocyte cancers. The evidence–base for individual systems is too limited to draw conclusions on which might be preferred for practice. Prospective comparative studies are required that evaluate the use of already evaluated CAD systems as diagnostic aids, by comparison to face–to–face dermoscopy, and in participant populations that are representative of those in which the test would be used in practice.

Plain language summary

What is the diagnostic accuracy of computer–assisted diagnosis techniques for the detection of skin cancer in adults?

Why is improving the diagnosis of skin cancer important?

There are a number of different types of skin cancer including melanoma, squamous cell carcinoma (SCC) and basal cell

carcinoma (BCC). Melanoma is one of the most dangerous forms. If it is not recognised early treatment can be delayed and this risks the melanoma spreading to other organs in the body and may lead to eventual death. Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) are considered less dangerous as they are localised (less likely to spread to other parts of the body compared to melanoma). However, cSCC can spread to other parts of the body and BCC can cause disfigurement if not recognised early. Diagnosing a skin cancer when it is not actually present (a false positive result) might result in unnecessary surgery and other investigations and can cause stress and anxiety to the patient. Missing a diagnosis of skin cancer may result in the wrong treatment being used or lead to a delay in effective treatment.

What is the aim of the review?

The aim of this Cochrane Review was to find out how accurate computer–assisted diagnosis (CAD) is for diagnosing melanoma, BCC or cSCC. The review also compared the accuracy of two different types of CAD and compared the accuracy of CAD with diagnosis by a doctor using a handheld illuminated microscope (a dermatoscope or 'dermoscopy'). Researchers in Cochrane included 42 studies to answer these questions.

What was studied in the review?

A number of tools are available to skin cancer specialists which allow a more detailed examination of the skin compared to examination by the naked eye alone. Currently a dermatoscope which magnifies the skin lesion using a bright light source is used by most skin cancer specialists. CAD tests are computer systems that analyse information about skin lesions obtained from a dermatoscope or other techniques that use light to describe the features of a skin lesion (spectroscopy) to produce a result indicating whether skin cancer is likely to be present. CAD systems that get their information from dermoscopic images of lesions (Derm–CAD), or that use data from spectroscopy, were included in this review. Most of the spectroscopy studies used data from multispectral imaging (MSI–CAD) and are the main focus here. Results from CAD systems can be used alone to make a diagnosis of skin cancer (CAD–based diagnosis), or can be used by doctors in addition to their visual inspection examination of a skin lesion to help them reach a diagnosis (CAD–aided diagnosis). Researchers examined how useful CAD systems are to help diagnose skin cancers in addition to visual inspection and dermoscopy.

What are the main results of the review?

The review included 42 studies looking at CAD systems for the diagnosis of melanoma. There was not enough evidence to determine the accuracy of CAD systems for the diagnosis of BCC (3 studies) or cSCC (1 study).

Derm–CAD results for diagnosis of melanoma

The main results for Derm-CAD are based on 22 studies including 8992 lesions.

Applied to a group of 1000 skin lesions, of whom 200 (20%) actually do have melanoma, the results suggest that:

- An estimated 386 people will have a Derm–CAD result suggesting that a melanoma is present and of these 206 (53%) will not actually have a melanoma (false positive result)

- Of the 614 people with a Derm–CAD result indicating that no melanoma is present, 20 (3%) will in fact actually have a melanoma (false negative result)

There was no evidence to suggest that dermoscopy or Derm–CAD was different in its ability to detect or rule out melanoma.

MSI–CAD results for diagnosis of melanoma

The main results for MSI–CAD are based on 8 studies including 2401 lesions. In a group of 1000 people, of whom 200 (20%) actually do have melanoma, then:

- An estimated 637 people will have an MSI–CAD result suggesting that a melanoma is present and of these 451 (71%) will not actually have a melanoma (false positive result)

- Of the 363 people with an MSI–CAD result indicating that no melanoma is present, 14 (4%) will in fact actually have a melanoma (false negative result)

MSI–CAD detects more melanomas, but possibly produces more false positive results (an increase in unnecessary surgery).

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

Incomplete reporting of studies made it difficult for us to judge how reliable they were. Many studies had important limitations. Some studies only included particular types of skin lesions or excluded lesions that were considered difficult to diagnose. Importantly most of the studies only included skin lesions with a biopsy result which means that only a sample of lesions that would be seen by a doctor in practice were included. These characteristics may result in CAD systems appearing more or less accurate than they actually are.

Who do the results of this review apply to?

Studies were largely conducted in Europe (29, 69%) and North America (8, 19%). Mean age (reported in 6/42 studies) ranged from 32–49 years for melanoma. The percentage of people with a final diagnosis of melanoma ranged from 1% to 52%. It was not always possible to tell whether suspicion of skin cancer in study participants was based on clinical examination alone, or both clinical and dermoscopic examination. Almost all studies were done in people with skin lesions who were seen at specialist clinics rather than by doctors in primary care.

What are the implications of this review?

CAD systems appear accurate for identification of melanomas in skin lesions that have been already selected for excision on the basis of clinical examination (visual inspection and dermoscopy). It is possible that some CAD systems identify more

melanomas than doctors using dermoscopy images. However, CAD systems also produced far more false positive diagnoses than dermoscopy and could lead to considerable increases in unnecessary surgery. The performance of CAD systems for detecting BCC and cSCC skin cancers is unclear. More studies are needed to evaluate the use of CAD by doctors for the diagnosis of skin cancer in comparison to face-to-face diagnosis using dermoscopy, in both primary care and in specialist skin cancer clinics.

How up-to-date is this review?

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

*In these studies, biopsy, clinical follow up, or specialist clinician diagnosis were the reference standards.

Background

This review is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers conducted for the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. Table 1 provides a glossary of terms used and a table of acronyms used is provided in Appendix 2.

Target condition being diagnosed

There are three main forms of skin cancer. Melanoma is the most widely known amongst the general population, yet the commonest skin cancers in Caucasian populations are those arising from keratinocytes: basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) (Gordon 2013; Madan 2010). In 2003, the World Health Organization estimated that between two and three million 'non-melanoma' skin cancers (of which BCC and cSCC are estimated to account for around 80% and 16% of cases, respectively) and 132,000 melanoma skin cancers occur globally each year (WHO 2003).

In this diagnostic test accuracy review there are three target conditions of interest (a) melanoma, (b) basal cell carcinoma (BCC), and (c) cutaneous squamous cell carcinoma (cSCC).

Melanoma

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. 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 (see Figure 1). Melanoma *in situ* refers to malignant melanocytes that are contained within the epidermis and have not invaded the dermis, 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 is a '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. Melanoma is one of the most serious forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and bloodstream. It accounts for only a small proportion of skin cancer cases but is responsible for up to 75% deaths (Boring 1994; Cancer Research UK 2017).

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 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 2017). Rates are higher in women than in men; however, the rate of incidence in men is increasing faster than in women (Arnold 2014).The rising incidence in melanoma is thought to be primarily related to an increase in recreational sun exposure and tanning bed use and an increasingly ageing population with higher lifetime recreational ultraviolet (UV) exposure, in conjunction with possible earlier detection (Belbasis 2016; Linos 2009). Putative risk factors are reviewed in detail elsewhere (Belbasis 2016).

A database of over 40,000 US patients from 1998 onwards which assisted the development of the 8th American Joint Committee on Cancer (AJCC) Staging System indicated a five-year survival of 97% to 99% for stage I melanoma, dropping to between 32% and 93% in stage III disease depending on tumour thickness, the presence of ulceration and number of involved nodes (Gershenwald 2017). While these are substantial increases relative to survival in 1975 (Cho 2014), mortality rates have remained static during the same period. This observation coupled with increasing incidence of localised disease, suggests that improvements in survival may be due to earlier detection and heightened vigilance (Cho 2014). 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 (e.g. using BRAF-inhibitors (Chapman 2012; Villanueva 2010) and MEK inhibitors (Dummer 2014; Larkin 2014), and immunomodulation (Chapman 2011; Hamid 2013; Hodi 2010).

Basal cell carcinoma

BCC can arise from multiple stem cell populations, including from the bulge and interfollicular epidermis (Grachtchouk 2011). BCC growth is usually localised, but it can infiltrate and damage surrounding tissue, sometimes causing considerable destruction and disfigurement, particularly when located on the face (Figure 2). The four main subtypes of BCC are superficial, nodular, morphoeic (infiltrative) and pigmented. Lesions typically present as slow-growing, asymptomatic papules, plaques, or nodules which bleed or form ulcers that do not heal (Firnhaber 2012).

The diagnosis is often made incidentally rather than by people presenting with symptoms (Gordon 2013).

BCC most commonly occurs on sun-exposed sites on the head and neck (McCormack 1997) and are more common in men and in people over the age of 40. A rising incidence of BCC in younger people has been attributed to increased recreational sun exposure (Bath-Hextall 2007a; Gordon 2013; Musah 2013). Other risk factors include Fitzpatrick skin types I and II (Fitzpatrick 1975; Lear 1997; Maia 1995), previous skin cancer history, immunosuppression, arsenic exposure, and genetic predisposition such as in basal cell naevus (Gorlin) syndrome (Gorlin 2004; Zak-Prelich 2004). Annual incidence is increasing worldwide; Europe has experienced an average increase of 5.5% per year over the last four decades, the USA 2% per year, while estimates for the UK show incidence appears to be increasing more steeply at a rate of an additional 6 / 100,000 persons per year (Lomas 2012). The rising incidence has been attributed to an ageing population, changes in the distribution of known risk factors, particularly ultraviolet radiation, and improved detection due to the increased awareness amongst both practitioners and the general population (Verkouteren 2017). Hoorens 2016 points to evidence for a gradual increase in the size of BCCs over time, with delays in diagnosis ranging from 19 to 25 months.

According to National Institute for Health and Care Excellence (NICE) guidance (NICE 2010), low risk BCCs that may be considered for excision are nodular lesions occurring in patients older than 24 years old who are not immunosuppressed and do not have Gorlin syndrome. Furthermore, low risk lesions should be located below the clavicle, should be small (< 1 cm) with well-defined margins, not recurrent following incomplete excision and are not difficult to reach surgically or in highly visible locations (NICE 2010). Superficial BCCs are also typically low risk and may be amenable to medical treatments such as photodynamic therapy or topical chemotherapy (Kelleners-Smeets 2017). Assigning BCCs as low or high risk influences the management options (Batra 2002; Randle 1996).

Advanced locally destructive BCC can arise from long-standing untreated lesions or from a recurrence of aggressive basal cell carcinoma after primary treatment (Lear 2012). Very rarely, BCC metastasises to regional and distant sites resulting in death, especially cases of large neglected lesions in those who are immunosuppressed or those with Gorlin syndrome (McCusker 2014). Rates of metastasis are reported at 0.0028% to 0.55% (Lo 1991), with very poor survival rates. It is recognised that basosquamous carcinoma (more like a high risk cSCC in behaviour and not considered a true BCC) is likely to have accounted for many cases of apparent metastases of BCC hence teh spuriously high reported incidence in some studies of up to 0.55% which is not seen in clinical practice (Garcia 2009).

Squamous cell carcinoma of the skin

Primary cSCC arises from the keratinocytes in the epidermis or its appendages. People with cSCC often present with an ulcer or firm (indurated) papule, plaque, or nodule (Griffin 2016) often with an adherent crust (Madan 2010). cSCC can arise in the absence of a precursor lesion or it can develop from pre-existing actinic keratosis (dysplastic epidermis) or Bowen's disease (considered by some to be cSCC *in situ*). The estimated annual risk of progression is <1% to 20% (Alam 2001) and 5% for lesions developing from pre–existing dysplasia (Kao 1986). It remains locally invasive for a variable length of time, but has the potential to spread to the regional lymph nodes or via the bloodstream to distant sites, especially in immunosuppressed individuals (Lansbury 2010). High risk lesions are those arising on the lip or ear, recurrent cSCC, lesions arising on non-exposed sites, scars or chronic ulcers, tumours larger than 20mm in diameter or which have a histological depth of invasion greater than 4mm or poor differentiation status on histopathological examination (Motley 2009).

Chronic ultraviolet light exposure through recreation or occupation is strongly linked to cSCC occurrence (Alam 2001). It is particularly common in people with fair skin and in less common genetic disorders of pigmentation, such as albinism, xeroderma pigmentosum, and recessive dystrophic epidermolysis bullosa (RDEB) (Alam 2001). Other recognised risk factors include immunosuppression; chronic wounds; arsenic or radiation exposure; certain drug treatments, such as voriconazole and BRAF mutation inhibitors; and previous skin cancer history (Baldursson 1993; Chowdri 1996; Dabski 1986; Fasching 1989; Lister 1997; Maloney 1996; O'Gorman 2014). In solid organ transplant recipients, cSCC is the most common form of skin cancer; the risk of developing cSCC has been estimated at 65 to 253 times that of the general population (Hartevelt 1990; Jensen 1999; Lansbury 2010). Overall, local and metastatic recurrence of cSCC at five years is estimated at 8% and 5% respectively. The five-year survival rate of metastatic cSCC of the head and neck is around 60% (Moeckelmann 2018).

Treatment

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

Treatment options for BCC and cSCC include surgery, other destructive techniques such as cryotherapy or electrodesiccation and topical chemotherapy. A Cochrane systematic review of 27 randomised controlled trials (RCTs) of interventions for BCC found very little good quality evidence for any of the interventions used (Bath-Hextall 2007b). Complete surgical excision of primary BCC has a reported five-year recurrence rate of < 2% (Griffiths 2005; Walker 2006), leading to significantly fewer recurrences than treatment with radiotherapy (Bath-Hextall 2007b). After apparent clear histopathological margins (serial vertical sections) after standard excision biopsy with 4mm surgical peripheral margins taken there is a 5-year reported recurrence rate of around 4% (Drucker 2017). Mohs micrographic surgery, whereby horizontal sections of the tumour are microscopically examined intraoperatively and re-excision is undertaken until the margins are tumour-free, can be considered for high risk lesions where standard wider excision margins of

surrounding healthy skin might lead to considerable functional impairment (Bath-Hextall 2007b; Motley 2009; Lansbury 2010; Stratigos 2015). Bath-Hextall and colleagues (Bath-Hextall 2007b) found a single trial comparing Mohs micrographic surgery with standard excision in BCC (Smeets 2004); the update at 10 years follow-up showed no statistically significant difference in recurrence with Mohs micrographic surgery (4.4% compared to 12.2% after surgical excision, P = 0.10) (van Loo 2014).

The main treatments for high risk BCC are wide local excision, Mohs micrographic surgery and radiotherapy. For low risk or superficial subtypes of BCC, or for small and or multiple BCCs at low risk sites (Marsden 2010), destructive techniques other than excisional surgery may be used (e.g. electrodesiccation and curettage or cryotherapy (Alam 2001; Bath-Hextall 2007b)). Alternatively non-surgical (or non-destructive) treatments may be considered (Bath-Hextall 2007a; Drew 2017; Kim 2014), including topical chemotherapy such as imiquimod (Williams 2017), 5-fluorouracil (Arits 2013), ingenol mebutate (Nart 2015) and photodynamic therapy (Bath-Hextall 2007b; Roozeboom 2016). Although non-surgical techniques are increasingly used, they do not allow histological confirmation of tumour clearance, and their use is dependent on accurate characterisation of the histological subtype and depth of tumour. The 2007 systematic review of BCC interventions found limited evidence from very small RCTs for these approaches (Bath-Hextall 2007b), which have only partially been addressed by subsequent studies (Bath-Hextall 2014; Kim 2014; Roozeboom 2012). Most BCC trials have compared interventions within the same treatment class, and few have compared medical versus surgical treatments (Kim 2014).

Vismodegib, a first-in-class Hedgehog signalling pathway inhibitor is now available for the treatment of metastatic or locally advanced BCC based on the pivotal study ERIVANCE BCC (Sekulic 2012). It is licensed for use in these patients where surgery or radiotherapy is inappropriate, e.g. for treating locally advanced periocular and orbital BCCs with orbital salvage of patients who otherwise would have required exenteration (Wong 2017). However, NICE has recently recommended against the use of vismodegib based on cost effectiveness and uncertainty of evidence (NICE 2017).

A systematic review of interventions for primary cSCC found only one RCT eligible for inclusion (Lansbury 2010). Current practice therefore relies on evidence from observational studies, as reviewed in Lansbury 2013, for example. Surgical excision with pre-determined margins is usually the first-line treatment (Motley 2009; Stratigos 2015). Estimates of recurrence after Mohs micrographic surgery, surgical excision, or radiotherapy, which are likely to have been evaluated in higher risk populations, have shown pooled recurrence rates of 3%, 5.4% and 6.4%, respectively with overlapping confidence intervals; the review authors advise caution when comparing results across treatments (Lansbury 2013).

Index test(s)

Computer–aided diagnosis (CAD) describes a range of artificial intelligence-based techniques that automate the diagnosis of skin cancer by using a computer to analyse lesion images, and determine the likelihood of malignancy, or need for excision. Each CAD system has a data collection component, which collects imaging or non-visual data (e.g. electrical impedance measurements) from the suspicious lesion and feeds it to the data processing component, which then performs a series of analyses to arrive at a diagnostic classification.

Images are acquired using a number of different techniques, though most commonly by digital dermoscopy (Derm–CAD) which creates digital subsurface images of the skin using a computer coupled with a dermatoscope, videocamera and digital television (Rajpara 2009; Esteva 2017). Commercially available systems include the DB–MIPS® (DB–Dermo MIPS) (Biomips Engineering SRL, Sienna Italy), MicroDERM (Visiomed AG, Germany), SolarScan (Polartechnics Ltd, Australia) and MoleExpert (DermoScan GmbH, Germany), all of which are hand–held digital or video dermatoscopes that communicate with CAD analysis software (see Figure 3).

Other systems use spectroscopy (Spectro-CAD), whereby information on cell characteristics (such as cell shape or size) is gathered by measuring how electromagnetic waves pass through skin lesions. This information is most commonly acquired using multispectral imaging (MSI–CAD) that enable computer–generated graphic representations of lesion morphology to be produced from detecting light reflected at several wavelengths across the lesion. By far the most common of these is diffuse reflectance spectrophotometry imaging (DRSi), which uses light that diffusely penetrates the skin to a depth of 2–2.5mm beneath the surface to produce light reflectance images at a number of specific wavelengths across the visible – near infrared light spectrum (approximately 400–1000nm) to capture variations in light attenuation and scattering from melanin, collagen and blood vessel structures.

DRSi developed from diffuse reflectance spectroscopy, a non-visual spectroscopic technique which uses optical reflectance to distinguish between lesion types based on spectral shape and calibrated level of reflected light for wavelengths continuously varying from the ultraviolet (320 nm) to the near infrared (1100 nm) with a high spectral resolution (4 nm) (e.g. Marchesini 1992; Wallace 2000b). Commercially available DRSi computer aided diagnosis (CAD) systems include the SIAscope™ (MedX Health Corp, Canada), a hand–held unit that communicates with CAD analysis software (Figure 3). The MelaFind® system (Strata Skin Sciences (formerly Mela Sciences Inc), Horsham, PA, USA) was FDA approved; however, it no longer appears to be commercially available.

The Nevisense™ system (SciBase III, Sweden; Figure 3) is also commercially available, but is based on electrical impedance spectroscopy (EIS), a non-optical method which seeks to provide information on cellular features by measuring the feedback from an electrical current once it has passed through the intended tissue. With Nevisense™, an alternating applied voltage (electrical current) is passed by a probe through a skin lesion and the current that is bounced back is measured by the same probe, which measures a combination of tissue resistance and capacitance. At high frequencies, conduction occurs easily through all tissue components, including cells, but at low frequencies current tends to flow only

through the extracellular space. The spectral shape is therefore sensitive to cellular components and dimensions, internal structure and cellular arrangements. The Nevisense™ EIS system measures at 4 multiple depths and at 35 frequencies logarithmically distributed from 1.0 kHz to 2.5 MHz using a 5 x 5 mm area electrode covered in tiny pins that penetrate into the stratum corneum.

Other non-visual sources of lesion data include Raman spectroscopy, in which a laser is used to excite vibrations in molecules which then impart wavelength shifts to some of the scattered light waves, creating spectral patterns that are related to the molecular structure of lesions (Maglogiannis 2009), and fluorescence spectroscopy which uses a laser to excite electrons, causing molecules to absorb and then re-emit light in spectral patterns that are also related to the molecular structure of lesions (Rallan 2004).

All CAD systems use machine learning, where a classification algorithm learns features of groups of lesions (i.e. diagnostic types) by exposure to a 'training set' of lesions of known histological diagnosis. This process creates a model which is designed to distinguish between these lesion types in future observations. Examples of machine learning algorithms include discriminant analysis, decision trees, neural networks, fuzzy logic, nearest k-neighbours, logistic regression and support vector machines (SVMs), and all use different mathematical equations to set out how observed features relate to a given diagnosis (Maglogiannis 2009; Masood 2013). Model outputs also vary, in part according to the type of data used to acquire lesion information, and can take the form of binary outputs indicating the presence of malignancy versus benignity (e.g. the Melafind® system), risk scores which can be used at varying thresholds (e.g. the DANAOS system used by MicroDerm), or graphical representations of the CAD pattern analysis which highlight areas of concern within a lesion (e.g. the SIAgraphs produced by SIAscope™). Artificial intelligence systems using continuous learning algorithms, where computer systems continuously develop their classification algorithm as each new case is examined, and do not stop learning at the end of a training period, are not addressed in this review.

Clinical Pathway

The diagnosis of skin lesions occurs in primary, secondary, and tertiary care settings by both generalist and specialist healthcare providers. In the UK, people with concerns about a new or changing lesion will present to their general practitioner rather than directly to a specialist in secondary care. A general practitioner with clinical concerns usually refers a patient to a specialist in secondary care – usually a dermatologist but sometimes to a surgical specialist such as a plastic surgeon or an ophthalmic surgeon. Suspicious skin lesions may also be identified in a referral setting, for example by a general surgeon, and referred for a consultation with a skin cancer specialist (Figure 4). Skin cancers identified by other specialist surgeons (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon will usually be diagnosed and treated without further referral.

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 or cSCC should be referred for appropriate specialist assessment within two weeks (Chao 2013; Marsden 2010; NICE 2015). Evidence is emerging, however, to suggest that excision of melanoma by GPs is not associated with increased risk compared with outcomes in secondary care (Murchie 2017). In the UK, low risk BCC are usually recommended for routine referral, with urgent referral for those in whom a delay could have a significant impact on outcomes, for example due to large lesion size or critical site (NICE 2015). Appropriately qualified generalist care providers increasingly undertake management of low risk BCC in the UK, such as by excision of low risk lesions (NICE 2010). Similar guidance is in place in Australia (CCAAC Network 2008).

For referred lesions, the specialist clinician will use history-taking, visual inspection of the lesion (in conjunction with other skin lesions), palpation of the lesion and associated lymph nodes in conjunction with dermoscopic examination to inform a clinical decision. If melanoma is suspected, then urgent 2mm excision biopsy is recommended (Lederman 1985; Lees 1991); for cSCC predetermined surgical margin excision or a diagnostic biopsy may be considered. BCC and pre-malignant lesions potentially eligible for nonsurgical treatment may undergo a diagnostic biopsy before initiation of therapy if there is diagnostic uncertainty. Equivocal melanocytic lesions for which a definitive clinical diagnosis cannot be reached may undergo surveillance to identify any lesion changes that would indicate excision biopsy or reassurance and discharge for those lesions that remain stable over a period of time.

Theoretically, teledermatology consultations may aid appropriate triage of lesions into urgent referral; non-urgent secondary care referral (e.g. for suspected basal cell carcinoma); or where available, referral to an intermediate care setting, e.g. clinics run by GPs with a special interest in dermatology. The distinction between setting and examiner qualifications and experience is important as specialist clinicians might work in primary care settings (for example, in the UK, general practitioners (GPs) with a special interest in dermatology and skin surgery who have undergone appropriate training), and generalists might practice in secondary care settings (for example, plastic surgeons who do not specialise in skin cancer). The level of skill and experience in skin cancer diagnosis will vary for both generalist and specialist care providers and will also impact on test accuracy.

Prior test(s)

Although smartphone applications and community-based teledermatology services can increasingly be directly accessed by people who have concerns about a skin lesion (Chuchu 2018b), visual inspection of a suspicious lesion by a clinician is usually the first in a series of tests to diagnose skin cancer. In the UK this usually takes place in primary care, however in many countries people with suspicious lesions can present directly to a specialist setting.

A range of technologies have emerged to aid skin cancer diagnosis, both to ensure that malignancies (especially melanoma) are not missed, and at the same time minimising unnecessary surgical procedures. Dermoscopy

using a hand-held microscope has become the most widely used tool for clinicians to improve diagnostic accuracy of pigmented lesions, in particular for melanoma (Argenziano 1998; Argenziano 2012; Haenssle 2010; Kittler 2002), although it is less well established for the diagnosis of BCC or cSCC. Dermoscopy is frequently combined with visual inspection of a lesion in secondary care settings, and is also increasingly used in primary care, particularly in countries such as Australia (Youl 2007).The diagnostic accuracy, and comparative accuracy, of visual inspection and dermoscopy have been evaluated in a further three reviews in this series (Dinnes 2018a; Dinnes 2018b; Dinnes 2018c).

Consideration of the degree of prior testing that study participants have undergone is key to interpretation of test accuracy indices, as these are known to vary according to the disease spectrum (or case-mix) of included participants (Lachs 1992; Moons 1997; Leeflang 2013; Usher-Smith 2016). Spectrum effects are often observed when tests that are developed further down the referral pathway have lower sensitivity and higher specificity when applied in settings with participants with limited prior testing (Usher-Smith 2016). Studies of individuals with suspicious lesions at the initial clinical presentation stage ('test naïve') are likely to have a wider range of differential diagnoses and include a higher proportion of people with benign diagnoses compared with studies of participants who have been referred for a specialist opinion on the basis of visual inspection (with or without dermoscopy) by a generalist practitioner. Furthermore, studies in more specialist settings may focus on equivocal or difficult to diagnose lesions rather than lesions with a more general level of clinical suspicion. However this direction of effect is not consistent across tests and diseases, the mechanisms in action often being more complex than prevalence alone and can be difficult to identify (Leeflang 2013). A simple categorisation of studies according to primary, secondary or specialist setting therefore may not always adequately reflect these key differences in disease spectrum that can affect test performance.

Role of index test(s)

Skin cancer diagnosis, whether by visual inspection alone or with the use of dermoscopy 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. In the hands of experienced dermatologists, dermoscopy has been shown to enhance the accuracy of skin cancer detection (especially melanoma) when compared to unaided visual examination (Dinnes 2018b; Dinnes 2018c). The subjectivity involved in interpreting lesion morphology is thought to underlie the decrease in accuracy that occurs when the dermatoscope is used by less experienced clinicians (Binder 1995).

The addition of computer–based diagnosis to these investigations has potential to increase the detection of melanomas by reducing the clinicians’ reliance on subjective information, which is necessarily interpreted using their experience of past cases. The additive value of CAD systems is also likely to vary with differences in setting, prior testing and selection of participants, as previously discussed (Prior test(s)). CAD systems could therefore fulfil three different roles in clinical practice: 1) to help GPs, or other clinicians working in unreferred settings, to appropriately triage lesions for referral; 2) as part of a remote diagnostic service; or 3) as an expert–level second–opinion to specialists in referral settings. All three roles would rely on CAD being as sensitive for the diagnosis of melanoma as experienced dermatologists. On the other hand, the specificity required for CAD to add value differs for each of these three situations, as discussed below.

If sensitive enough, use of CAD in primary care could allow more appropriate triage of higher risk lesions to secondary care by increasing the early detection of potentially malignant lesions. However, although a relatively lower specificity (higher false positive rate) may be acceptable in a primary care setting, limiting false–positive diagnoses would create health service benefits by avoiding unnecessary referral, and alleviating patient anxiety more promptly. Similarly, the remote use of CAD could inform the need for referral, by sending images or other diagnostic data to specialist clinics, or even to commercial organisations, for remote interpretation, much as teledermatology is already used. In this circumstance, a relatively high specificity would be required in order to avoid unacceptable increases in rates of referral to specialist centres.

Finally, when used in referral settings as a complement to in-person diagnosis by a specialist, even if CAD could be shown pick up difficult to diagnose melanomas that might be missed on VI or dermoscopy, the specificity of the system would be need to be very high so as not to inordinately increase the burden of skin surgery. False-positive diagnoses not only cause unnecessary scarring from a biopsy or excision procedure, but also increase patient anxiety whilst they await the definitive histological results and increase healthcare costs as the number needed to remove to yield one melanoma diagnosis increases. Pigmented lesions are common, so the resource implication for even a small 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 lesions that are not excised turn out to be benign. The use of CAD to detect melanoma in specialist clinics would only be advantageous if it could be shown to detect skin cancers that would otherwise be missed, or to decrease unnecessary surgical intervention (i.e. removal of false–positive lesions) with no loss of sensitivity.

Delay in diagnosis of a BCC as a result of a false-negative test is not as serious as for melanoma because BCCs are usually slow-growing and very unlikely to metastasise, nevertheless delayed diagnosis can result in larger and more complex surgical procedures with consequent greater morbidity. Very sensitive diagnostic tests for BCC, however may compromise on lower specificity leading to a higher false positive rate and an increased burden of skin surgery such that a balance between sensitivity and specificity is needed. The greatest potential advantage of CAD in the management of BCC is likely to lie in its ability to perform rapid, non–invasive assessments of multiple lesions (common in BCC patients, Lear 1997).

The situation for cSCC is more similar to melanoma, in that the consequences of falsely reassuring a person that they do not have skin cancer can be serious and potentially fatal given that removal of an early cSCC is usually curative. Thus, a good diagnostic test for cSCC should demonstrate high sensitivity and a corresponding high negative predictive value. A test that can also reduce false positive clinical diagnoses without missing true cases of cSCC has patient and resource benefits.

Alternative test(s)

A number of other tests which may have a role in the diagnosis of skin cancer in a specialist setting have been reviewed as part of our series of systematic reviews, including reflectance confocal microscopy (Dinnes 2018d Dinnes 2018e), optical coherence tomography (Ferrante di Ruffano 2018a), high frequency ultrasound (Dinnes 2018f) and exfoliative cytology (Ferrante di Ruffano 2018b). Other tests with a role in earlier settings include teledermatology (Chuchu 2018a) and smart–phone applications (Chuchu 2018b). Reviews on the accuracy of gene expression testing and volatile organic compounds could not be performed as planned due to an absence of relevant studies. 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.

We also considered and excluded a number of tests from this review such as tests used for screening (e.g. total body photography of those with large numbers of typical or atypical naevi) or monitoring (e.g. CAD systems used to monitor the progression of suspicious skin lesions).

Lastly, we did not assess the accuracy of histopathological confirmation following lesion excision because it 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 skin cancer 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 diagnostic and treatment decisions. With increasing rates of melanoma and basal cell carcinoma and a trend to adopt dermoscopy and other high resolution image analysis in primary care, the anxiety around missing early malignant lesions needs to be balanced against the risk of too many unnecessary referrals, and to avoid sending too many people with benign lesions for a specialist opinion. It is questionable whether all skin cancers identified by sophisticated techniques, even in specialist settings, help to reduce morbidity and mortality. It is also a concern that newer technologies incur 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 little or 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).

The central premise underlying CAD is that it uses quantitative, objective and expert–level assessments of lesion features, which lessens the need for specialist training and lengthy experience in test use. Given the reliance on specialist training and experience to make accurate skin cancer diagnosis using dermoscopy, CAD diagnosis has the potential to improve the health of patients by widening access to specialist diagnostic capabilities in primary and secondary care. If sensitive enough, introducing CAD could increase the early detection of skin cancers, which for melanoma and cSCC in particular, is critical to improving outcomes. As with any technology requiring significant investment, a full understanding of the benefits including patient acceptability and cost-effectiveness compared with usual practice should be obtained before such an approach can be recommended; establishing the accuracy of diagnosis and referral accuracy is one of the key components.

We identified four published systematic reviews focussing on the accuracy of CAD, two synthesising the performance of Derm–CAD systems (Ali 2012; Rajpara 2009), and two reviewing both Derm–CAD and Spectro–CAD systems (Rosado 2003; Vestergaard 2008). All are limited by out–of–date search periods (Ali 2012 up to 2011, Rajpara 2009 and Vestergaard 2008 up to 2007, Rosado 2003 up to 2002), which is a key concern in the rapidly advancing field of machine learning. Another concern for Ali 2012, Rajpara 2009 and Rosado 2003 is their inclusion of studies which are ineligible for the current Cochrane review due to the absence of an independent validation set, a methodological feature likely to inflate the apparent accuracy of predictive models (Altman 2009). Rosado 2003 also selected datasets on the basis of highest performance, and pooled accuracy estimates for Derm–CAD with Spectro–CAD which we consider to be two different diagnostic tests. There is therefore a need for an up-to-date and rigorous review of the accuracy of dermoscopy–based CAD and of spectroscopy–based CAD which explicitly considers the following key characteristics .

Because CAD models are created by analysing patterns in archived datasets, the degree to which they are likely to make accurate classifications of new observations in real life clinical situations relies on the generalisability of the training sets used to develop them (Horsch 2011). Training sets that contain few lesions, or a restricted range of the differential diagnoses encountered in clinical practice, are likely to produce models that misclassify new observations due to inadequate learning. Other important attributes thought to influence diagnostic ability are the segmentation process (how the lesion's border is detected by the computer), which features are selected for analysis (akin to the selection of features for analysis in the algorithms used in ELM dermoscopy, e.g. ABCD or 7–point), the algorithm used, and the type of information produced by the CAD system (e.g. binary outputs indicating presence of malignancy, or visual images of lesions such as macro– or microscopic photographs or graphical representations of highlighting suspect structures).

This review follows a generic protocol which covers the full series of Cochrane DTA reviews for the diagnosis of melanoma (Dinnes 2015a) and for the diagnosis of keratinocyte cancers (Dinnes 2015b). The Background and Methods sections of this review therefore use some text that was originally published in these protocols (Dinnes 2015a; Dinnes 2015b) and text that overlaps some of our other reviews (Dinnes 2018a; Dinnes 2018b; Ferrante di Ruffano 2018a).

Objectives

To determine the accuracy of CAD systems for diagnosing cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults, and to compare the accuracy of CAD systems with that of clinician diagnosis using

dermoscopy when dermoscopy is also evaluated in CAD studies.

To determine the accuracy of CAD systems for diagnosing BCC in adults, and to compare the accuracy of CAD systems with that of clinician diagnosis using dermoscopy when dermoscopy is also evaluated in CAD studies.

To determine the accuracy of CAD systems for diagnosing cSCC in adults, and to compare the accuracy of CAD systems with that of clinician diagnosis using dermoscopy when dermoscopy is also evaluated in CAD studies.

Secondary objectives

- i. To determine the accuracy of CAD systems for diagnosing invasive melanoma alone in adults, and to compare the accuracy of CAD systems with that of clinician diagnosis using dermoscopy
- ii. To determine the accuracy of CAD systems for identifying any lesion requiring excision (due to any skin cancer or high–grade dysplasia) in adults, and to compare the accuracy of CAD systems with that of clinician diagnosis using dermoscopy

For each of the primary target conditions, to:

- iii. To compare the diagnostic accuracy of CAD systems to clinician diagnosis using dermoscopy, where both tests have been evaluated in the same studies (direct comparisons);
- iv. To determine the diagnostic accuracy of individual CAD systems;
- v. To compare the accuracy of CAD–based diagnosis to CAD–assisted diagnosis (CAD results used by clinicians as a diagnostic aid)
- vi. Where CAD systems are used as a diagnostic aid, to determine the effect of observer experience on diagnostic accuracy.

Investigation of sources of heterogeneity

We set out to investigate a range of potential sources of heterogeneity across our series of reviews, as outlined in our generic protocols (Dinnes 2015a; Dinnes 2015b) and described in Appendix 3; however, our ability to investigate these was prevented by the available data on each individual test reviewed.

Methods

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that assessed the result of the index test against that of a reference standard, including the following:

- studies where all participants received a single index test and a reference standard;
- studies where all participants received more than one index test and reference standard;
- studies where participants were 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 recruited 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 recruited diseased and non-diseased groups (see Rutjes 2005), however we did not include studies that compared results for malignant lesions to those for healthy skin (i.e. with no lesion present)
- 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 or derive 2x2 contingency data of the number of true positives, false positives, false negatives and true negatives, or if studies included fewer than five skin cancer cases or fewer than five benign lesions. Although the size threshold of five is arbitrary, such small studies are likely to give unreliable estimates of sensitivity or specificity, and may be biased like small randomised controlled trials of treatment effects.

Participants

We included studies in adults with pigmented or non–pigmented skin lesions considered to be suspicious for melanoma or an intraepidermal melanocytic variant or a keratinocyte skin cancer (BCC or cSCC). Studies examining adults at high risk of developing skin cancer, including those with a family history or previous history of skin cancer, atypical or dysplastic naevus syndrome, or genetic cancer syndromes were also eligible for inclusion.

We excluded studies that recruited only participants with malignant diagnoses.

We excluded studies conducted in children or which clearly reported inclusion of more than 50% of participants aged 16 and under.

Index tests

Studies reporting accuracy data for tests using automated diagnosis were eligible for inclusion, whether diagnosis was produced independently by the CAD system (system–based diagnosis), or by a clinician using a CAD system as a diagnostic aid (computer–assisted diagnosis). CAD systems using any type of data capture were eligible, including imaging and non–imaging modalities. All machine learning algorithms were included.

Studies developing new algorithms or methods of diagnosis (i.e. derivation studies) were **included** if they evaluated the new

approach using a separate 'test set' of participants or images.

Studies were **excluded** if they:

- evaluated a new statistical model or algorithm in the same participants or images as those used to train the model (i.e. absence of an independent test set);
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983); or
- evaluated the accuracy of the presence or absence of individual lesion characteristics or morphological features, with no overall diagnosis of malignancy.

Although primary care clinicians can in practice be specialists in skin cancer, we considered primary care physicians as generalist practitioners and dermatologists as specialists. Within each group, we extracted any reporting of special interest or accreditation in skin cancer.

Target conditions

The primary target conditions were defined as the detection of:

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

Two additional target conditions were considered in secondary analyses, namely the detection of:

- any form of invasive cutaneous melanoma alone
- any skin lesion requiring excision: all forms of skin cancer listed above, as well as melanoma *in situ*, lentigo maligna, and lesions with severe melanocytic dysplasia.

Reference standards

The ideal reference standard is histopathological diagnosis 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 this 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 is unlikely to be carried out for all benign-appearing lesions within a representative population sample. Therefore to reflect what happens in reality, 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).

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 skin cancer 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 (Appendix 4), 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 29 August 2016 for relevant published studies:

- MEDLINE via OVID (from 1946);
- MEDLINE In-Process & Other Non-Indexed Citations via OVID; and
- EMBASE via OVID (from 1980).

We searched the following bibliographic databases to 30 August 2016 for relevant published studies:

- the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7, 2016, in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR) Issue 8, 2016 in the Cochrane Library;
- Cochrane Database of Abstracts of Reviews of Effects (DARE) Issue 2, 2015;
- CRD HTA (Health Technology Assessment) database Issue 3, 2016;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960).

We searched the following databases for relevant unpublished studies:

- CPCI (Conference Proceedings Citation Index) via Web of Science™ (from 1990);
- Zetoc (from 1993)
- 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 (http://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.

Searching other resources

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 was 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 5) were applied independently by both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JDi, NC or LFR) 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 final lesion diagnoses or diagnostic threshold were missing. In particular, invasive cSCC (included as disease positive for one of our secondary objectives) is not always differentiated from '*in situ*' variants such as Bowens disease (which we did not consider as disease positive for any of our definitions of the target condition).

Authors of conference abstracts published from 2013 to 2015 were contacted to ask whether full data were available. Conference abstracts were marked as 'pending' and we 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 6). 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

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. Where multiple CAD models or algorithms were assessed in an individual study, one was selected at random using a random number generator. Where studies evaluated CAD as a diagnostic aid by clinicians with varying degrees of experience, the dataset reporting the highest degree of clinical experience was selected. These selections were conducted without reference to the corresponding accuracy data.

Accuracy of dermoscopy was estimated separately according to whether the diagnosis recorded was based on a face–to–face (in-person) encounter or based on remote (image-based) assessment. Where multiple algorithms were assessed in an individual study, dermoscopy 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. ABCD algorithm (or derivatives of)

iv. 7-point checklist (also referred to as Glasgow/Mackie checklist)

v. Menzies algorithm

vi. 3-point checklist

As for CAD, dermoscopy datasets reporting the highest degree of clinical experience were preferentially selected from studies reporting multiple results using clinicians of varying experience.

CAD study data were pooled for systems using similar methods of data acquisition; thus all studies using digital dermoscopy based CAD (Derm-CAD) were considered similar and pooled, however spectroscopy-based CAD (Spectro-CAD) systems analyse different data types and so were only pooled in these subgroups: multispectral imaging studies (MSI-CAD), electrical impedance spectroscopy (EIS-CAD), and diffuse reflectance spectroscopy (DRS-CAD). 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. CAD thresholds are created by complex statistical algorithms and a threshold is difficult to define. Therefore, we assumed results were binary for the purpose of pooling results across similar CAD systems. We estimated summary operating points (summary sensitivities and specificities) with 95% confidence and prediction regions using the bivariate model (Chu 2006; Reitsma 2005). Where inadequate data were available for the analysis to converge, the model was simplified, first by assuming no correlation between estimates of sensitivity and specificity and secondly by setting variance terms to zero if little or no heterogeneity was observed on SROC plots (Takwoingi 2015).

Data on the accuracy of dermoscopy were extracted from all included studies that performed both CAD and dermoscopy in the same patients. We performed test comparisons using two analytic strategies. First we performed indirect comparisons by using all studies of the two tests. Second we made direct comparisons of CAD and dermoscopy by including only comparative studies that assessed the accuracy of both tests in the same study population to enable a robust comparison (Takwoingi 2013). To minimize the risk of bias in the direct comparison, studies that performed either CAD or dermoscopy on a subsample of the total analysed population were excluded. In the comparative meta-analyses of indirect and direct comparisons, we compared summary points by using a bivariate meta-regression model that included test type as a covariate. Covariate terms were included for sensitivity and specificity. Model fit was assessed using likelihood ratio tests to compare nested models. We computed estimates of absolute differences in sensitivity and specificity using the bivariate model parameters and 95% confidence intervals were obtained using the delta method. P values for the absolute differences were obtained using Wald tests. Univariate random-effects logistic regression models incorporating test type as a covariate were fitted when there were few studies or a bivariate meta-regression analysis did not converge.

For illustration of the meta-analytic findings in the summary of findings tables, we computed the numbers of true positives, false positives, false negatives and true negatives, using the summary estimates of sensitivity and specificity together with the lower quartile, median and upper quartile of the prevalence observed in the studies included in the meta-analysis.

Bivariate models were fitted using the xtmelogit command in STATA 15.

Investigations of heterogeneity

We examined heterogeneity between studies by visually inspecting the forest plots of sensitivity and specificity and summary ROC plots. Due to limited data availability, we were unable to formally investigate heterogeneity using meta-regression.

Sensitivity analyses

The primary analysis included both CAD–based diagnoses and CAD–aided diagnoses. Sensitivity analyses excluding studies of CAD–aided diagnoses were undertaken.

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), we did not perform tests to detect publication bias.

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 (see Figure 5 PRISMA flow diagram of search and eligibility results).

Of the 227 studies tagged as potentially eligible for this review of CAD (166 for Derm–CAD, 61 for Spectro–CAD), 42 publications were included (24 Derm–CAD and 18 Spectro–CAD). Exclusions were mainly due to the absence of a 'test' set of lesions used to evaluate CAD's performance independently of the computer algorithm's development (Derm–CAD n = 76, Spectro-CAD n = 17); inability to construct a 2x2 contingency table based on the data presented (Derm–CAD n = 24, Spectro-CAD n = 8); the use of ineligible index tests (Derm–CAD n = 18, Spectro-CAD n = 5) (for example: computers used to measure lesions but not to diagnose them, e.g. Seidenari 2012); or not meeting our requirements for an eligible reference standard (Derm–CAD n = 13, Spectro-CAD n = 9). Other reasons for exclusion included ineligible definition of the target condition (Derm–CAD n = 10, Spectro-CAD n = 3) and CAD systems based on evaluating the presence of a single lesion characteristic (Derm–CAD n = 17) (for example, a CAD system analysing the colour balance of a lesion). A list of the 185 publications 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 separate pdf.

The authors of 10 publications were contacted to provide additional detail on published 2x2 data for the accuracy of CAD, with responses regarding four publications received to date. These did not result in the inclusion of any additional studies, however did permit the inclusion of one additional dataset in an already–included study (Mollersen 2015). One response highlighted an alternative publication that was independently ascertained by the project search, and was included (Serrao 2006); two replies were unable to provide the information requested in relation to two study publications, both of which were subsequently excluded due to incomplete 2x2 data. Attempts to contact authors of six publications failed, resulting in the exclusion of those six studies from review. In addition to these 10 attempted contacts, authors of one other publication (Walter 2012) were contacted as part of another review in this series, the accuracy of visual inspection for the diagnosis of melanoma (Dinnes 2018a), to provided clarifications on methods used; the author response enabled it to be included.

The 42 included studies reported on 39 cohorts of lesions and provided 63 datasets with 13,445 lesions and 2452 malignancies. The majority of studies (n = 24, 57%) contributed data on the diagnostic accuracy of digital dermoscopy–based CAD systems (Derm–CAD), of which seven also compared the diagnostic accuracy of Derm–CAD with dermoscopic diagnosis. The remaining 18 studies contributed data on the diagnostic accuracy of spectroscopy–based CAD (Spectro-CAD), of which five provided comparative accuracy data with dermoscopy. A cross-tabulation of studies by CAD type, reported comparisons and target conditions is provided in Table 2.

Studies were case series (n = 27, 64%), case control (n = 10, 24%), randomised controlled trial (n = 1, 2%), or of unclear design (n = 4, 10%). Lesion selection was most commonly retrospective (n = 22, 52%) or prospective (n = 15, 36%), though was unclear in five studies (12%). Studies included only pigmented (n = 29, 69%) or melanocytic lesions (n = 6, 14%), only suspected melanomas (n = 4, 10%), or any lesions suspected of malignancy (n = 2, 5%). Patient characteristics such as age and gender were reported by 15/42 studies.

Methodological quality of included studies

The majority of included studies were of methodological concern primarily due to lack of applicability to the current review question, but also due to a high or unclear risk of bias in their design. Since there were no major differences in quality according to CAD type, we provide an overview of the quality and applicability of all included studies regardless of CAD type. The methodological quality of studies according to CAD type (Derm–CAD or spectroscopy–based CAD) is summarized in Figure 6 and Figure 7.

The risk of participant selection bias was judged as high in 17 (40%) studies, due to the selection of lesions according to their final diagnosis (case–control studies: n = 10, 24%), and/or to the inappropriate exclusion of lesions with particular prognostic characteristics (n = 8, 19%), such as high-grade dysplastic lesions (Ferris 2015) or small/large lesions (Malvehy 2014; Monheit 2011). Study eligibility criteria and participant exclusions were not reported clearly enough to ascertain the risk of selection bias in 17 studies (40%); this meant that we could not determine whether consecutive or random samples of lesions were recruited (n = 22, 52%), whether participants had been selected according to their final diagnoses (use of 'case–control' selection, n = 5, 12%), or whether participant exclusions were appropriate (n = 22, 52%).

A single study (Sgouros 2014) was of low concern for the applicability of its participant sample to the current review question: it included unexcised lesions and did not recruit participants with multiple lesions. All others (n = 41, 98%) were of high concern due to the use of restricted participant groups and settings (n = 40, 95%), with study populations limited to lesions selected for excision based on the clinical or dermoscopic diagnosis or selected retrospectively from histopathology databases (n = 36, 84%). Six studies did not restrict inclusion to excised lesions, however in three of these the non–excised lesions could not be extracted due to the absence of clinical follow–up in

at least 50% of benign cases (Boldrick 2007; Bono 1996; Sgouros 2014). Fourteen studies were also of concern due to their recruitment of participants with multiple lesions (including over 5% more lesions than participants). One of these, Dreiseitl 2009, provided patient–based 2x2 data as well as lesion–based data for the accuracy of a Derm–CAD system. These 2 analyses of the same population highlight the distortion that can occur in study populations that include multiple lesions per patient: lesion–based sensitivity was lower than patient based sensitivity (74% versus 89%), however lesion–based specificity was far higher (84% versus 48%) due to the inclusion of many disease negative lesions per patient.

Twenty–two (52%) studies did not report the number of participants included (precluding assessment of the inclusion of multiple lesions). Of the 18 studies including model derivation, 6 (33%) used a wide range of skin conditions to train the classification algorithm. Two (11%) used an inadequately narrow range (absence of non–dysplastic benign conditions), while the remaining 10 (56%) provided inadequate detail of diagnoses included in the training set.

Over half the studies were at high (n = 14, 33%) or unclear (n = 10, 24%) risk of bias due to the methods used to undertake the index test. Most studies (n = 40, 95%) blinded CAD results to the reference standard diagnosis though almost half (n = 20, 48%) failed to clearly pre–specify the diagnostic threshold, of which 13 (30%) were threshold–finding studies that provided accuracy data for the best threshold possible once index test results had been examined. Most studies (n = 35, 83%) evaluated CAD in an independent population to that used to train the classification algorithm, either by external validation (n = 23, 55%) or internal validation (randomised division of a single study group into training and test sets: n = 12, 29%). An additional six (14%) studies used internal validation, but failed to specify whether division of the study group was made randomly (i.e. not selected according to diagnosis), while one study was at risk of bias by selecting which diagnoses to place in the train and test sets (Tomatis 2003).

Of the 18 studies that included CAD model derivation (training of the classification algorithm), eight (44%) accounted for model overfitting by using a Support Vector Machine algorithm (Gilmore 2010; Mohr 2013; Stanganelli 2005), performing a jack–knife calculation (Binder 1994; Burroni 2004), or another method (Rubegni 2002; Tomatis 2003; Tomatis 2005). One study specified that model optimisation was not incorporated (Garcia Uribe 2012) and 9 (50%) did not discuss overfitting. The majority of studies (n = 32, 76%) were of high concern regarding the applicability of the index test, due to their evaluation of an unestablished threshold (n = 23), lack of detail regarding the diagnostic threshold used (n = 16), and/or the use of non–expert clinicians (n = 2) in studies evaluating CAD as a diagnostic aid (n = 7).

Almost all studies reported use of an acceptable reference standard (n = 37, 88%), and around half (n = 19, 45%) clearly reported blinding of the reference standard to the CAD result. For the applicability of the reference standard, four reported using expert diagnosis for some lesions (high concern) and 30 (71%) were unclear as to whether histopathology had been interpreted by an experienced histopathologist or dermatopathologist.

Reporting of study flow and timing was generally poor with an unclear risk of bias in 28 (67%) studies, largely due to ambiguity regarding the interval between the application of the index test and reference standard (excision for histology or first follow–up visit) (n = 28). Thirteen (30%) studies were at a high risk of bias because they used different reference standards according to diagnosis (differential verification) (n = 6) and/or did not include all participants in the analysis (n = 10), primarily due to technical difficulties with the CAD system (n = 6).

Eleven of the 15 studies comparing CAD with dermoscopy were at high (n = 2) or unclear (n = 9) risk of bias. Six reported blinding between tests, two reported no blinding and seven were unclear. Half (n = 8) did not clearly report the interval between tests.

Findings

The 24 studies evaluating a Derm–CAD system reported 23 cohorts of lesions providing 32 CAD datasets with 9602 lesions including 1313 malignancies of which 1220 were melanomas, at least 83 BCCs (number not specified in one study, Menzies 1996), and 9 cSCCs. The total number of study participants with suspicious lesions cannot be estimated due to lack of reporting in study publications (reported in only 10 studies (with 2400 participants). Two publications provided data for one cohort of lesions (Seidenari 1998; Seidenari 1999), the larger of the two studies (Seidenari 1999) was included in the primary analysis with data from Seidenari 1998 contributing only to the direct comparison of Derm–CAD with dermoscopy. A total of 17 different systems were evaluated, 3 by multiple independent studies: Microderm (Barzegari 2005; Boldrick 2007; Serrao 2006), DB–MIPS (also called DB–Dermo MIPS) (Bauer 2000; Burroni 2004; Rubegni 2002; Seidenari 1998; Seidenari 1999; Stanganelli 2005; Wollina 2007), and Skin View (Cascinelli 1992; Cristofolini 1997). The 17 systems differ in terms of the type of dermoscopy used to acquire images, the storage devices used, features analysed and statistical classifier used (summarised in Table 3). The approach to computer–assisted support also differed, with 21 studies (88%) evaluating a stand–alone automated diagnosis ('system–based diagnosis'), and 3 studies using Derm–CAD as a diagnostic aid to assist clinical decision–making.

The 18 publications evaluating a Spectro–CAD system reported 16 cohorts of lesions contributing 32 datasets with 6336 lesions including 1084 malignancies of which 934 were melanomas, 163 BCCs and 49 cSCCs. The total number of study participants with suspicious lesions cannot be estimated due to lack of reporting in study publications (reported in only 8 studies totaling 4484 participants). Four publications provided data for two patient cohorts (Bono 2002; Tomatis 2003 and Hauschild 2014; Monheit 2011), the larger studies (Monheit 2011; Tomatis 2003) were included in the primary analysis, with data from Bono 2002 (same population as Tomatis 2003) and Hauschild 2014 (same population as Monheit 2011) contributing only to the direct comparison of Spectro–CAD with dermoscopy. These 18 studies reported on 5 different multispectral systems using DRSi: SpectroShade (Ascierto 2010; Tomatis 2005), Melafind (Friedman 2008; Gutkowicz Krusin 1997; Hauschild 2014; Monheit 2011; Wells 2012; Winkelmann 2016), SIAscope (Glud 2009; Terstappen

2013), and 'Telespectrophotometric System' (Bono 1996; Tomatis 2003). One study evaluated a non–imaging diffuse reflectance spectroscopy system: OIDRS (Garcia Uribe 2012), which used analysis of data from incidentally reflected diffuse light. Nevisense was the only system to use electrical impedance spectroscopy (EIS), and was evaluated in two large prospective studies; these had overlapping recruitment periods and study centres, thus the possibility of overlap in analysed participants cannot be ruled out (Malvehy 2014; Mohr 2013). As for the Derm–CAD systems, the Spectro–CAD systems differ in terms of the image acquisition and storage devices used, features analysed, statistical classifier used, and the approach to computer–assisted support (i.e. whether used as a stand–alone automated diagnosis, or as information to assist a clinician's diagnostic decision) (Table 4).

Study results are summarised below according to target condition with forest plots of available study data provided in Figures 8-23. Results of meta–analysis are provided in Table 5 and Table 6.

Target condition: invasive melanoma and atypical intraepidermal melanocytic variants

The diagnostic accuracy of CAD assessment for the detection of invasive cutaneous melanoma or intraepidermal variants was reported by 36 studies with a total of 14,451 lesions including 1889 melanomas. Of these, 23 studies evaluated a Derm–CAD system (total 9082 lesions with 1094 melanomas) and 13 studies evaluated a Spectro-CAD system (total 5369 lesions with 795 melanomas).

Derm-CAD

Twenty–two studies were included in a meta–analysis to estimate the accuracy of dermoscopy–based CAD systems in referral settings, regardless of the system manufacturer, algorithm used, or whether CAD was used as a stand–alone automated diagnosis or as a diagnostic aid (Barzegari 2005; Bauer 2000; Binder 1994; Binder 1998; Blum 2004b; Boldrick 2007; Burroni 2004; Cascinelli 1992; Cristofolini 1997; Dreiseitl 2009; Ferris 2015; Gilmore 2010; Maglogiannis 2015; Menzies 2005; Mollersen 2015; Piccolo 2002; Piccolo 2014; Rubegni 2002; Seidenari 1999; Serrao 2006; Stanganelli 2005; Wollina 2007). One additional study was excluded from this analysis (Seidenari 1998) due to suspected population overlap with an included study (Seidenari 1999). These 22 studies provided 23 datasets for meta–analysis (Mollersen 2015 evaluated two CAD systems, Nevus Doctor and MoleExpert, in the same lesion population). Eleven studies were model derivation studies, eight evaluating the resulting classification algorithm in an independent population (random division of one study group into training and test sets: Binder 1994; Binder 1998; Blum 2004b; Burroni 2004; Ferris 2015; Maglogiannis 2015; Menzies 2005; Stanganelli 2005), and three providing insufficient details to determine the independence of the test population (Cascinelli 1992; Gilmore 2010; Rubegni 2002). The remaining 11 studies were external validation studies with prospective (Bauer 2000; Cristofolini 1997; Dreiseitl 2009; Wollina 2007), retrospective (Piccolo 2002; Piccolo 2014; Seidenari 1999; Serrao 2006), or unclear (Barzegari 2005; Boldrick 2007; Mollersen 2015) recruitment designs. Only one study did not use excision as an eligibility criterion (Dreiseitl 2009).

Across the 23 datasets, sensitivity ranged from 17% to 100% and specificity from 20% to 98%. A total of 8992 lesions including 1063 melanomas were pooled, giving summary sensitivity of 90.1% (95% CI 84.0% to 94.0%) and summary specificity of 74.3% (95% CI 63.6% to 82.7%) (Table 5 and Figure 8, Figure 9).

The prevalence of melanoma ranged from 1% (Dreiseitl 2009) to 52% (Gilmore 2010; Maglogiannis 2015), and the number of melanomas missed ranged from 0 (Barzegari 2005; Piccolo 2014; Seidenari 1999) to 16 (Maglogiannis 2015) (not reported in 4 studies). Clear identification of the target condition was not provided in 10 of the 22 studies (Binder 1994; Blum 2004b; Cascinelli 1992; Cristofolini 1997; Dreiseitl 2009; Gilmore 2010; Maglogiannis 2015; Piccolo 2002; Rubegni 2002; Stanganelli 2005), and the inclusion of melanoma *in situ* lesions as disease positive was assumed on the basis that the disease positive group was described as 'melanoma' and not as 'invasive melanoma' or 'malignant melanoma'. Of the 12 studies that clearly reported including *in situ* lesions (Barzegari 2005; Bauer 2000; Binder 1998; Boldrick 2007; Burroni 2004; Ferris 2015; Menzies 2005; Mollersen 2015; Piccolo 2014; Seidenari 1999; Serrao 2006; Wollina 2007), the percentage of the disease positive group (invasive melanoma and atypical intraepidermal melanocytic variants) described as being *in situ* ranged from 12–50%. The number of missed *in situ* lesions was reported in 7 studies, with no missed lesions in 3 studies (Barzegari 2005; Piccolo 2014; Seidenari 1999) and between 7% (1 of 14, Ferris 2015) and 100% (3 of 3, Boldrick 2007) of *in situ* lesions misdiagnosed by the remaining studies.

Some studies reported difficulties in excluding a malignancy from clinically benign lesions, particularly non-melanocytic pigmented lesions such as seborrhoeic keratoses which were reported as an included lesion by five studies (Barzegari 2005; Cascinelli 1992; Ferris 2015; Menzies 2005; Mollersen 2015). Four of these provided lesion diagnoses by CAD result, finding 41 of 61 seborrhoeic keratoses (67%) to have been falsely identified as malignant, while a fifth study highlighted their problematic misclassification of this lesion by both Derm–CAD systems (Mollersen 2015). Other notable false positive diagnoses include dysplastic melanocytic nevi (Binder 1994; Binder 1998; Cascinelli 1992; Ferris 2015; Seidenari 1999), actinic keratosis (Barzegari 2005), dermatofibroma (Barzegari 2005; Menzies 2005) and haemangioma (Menzies 2005).

One dataset from one study contributed data for the accuracy of a Derm–CAD system in self–referring patients seeking advice for pigmented naevi (Wollina 2007) (Table 7). This prospective study evaluated the DB–MIPS system, a fully integrated dermoscopy unit with internal stereomicroscope, storage database and pattern analysis software, giving it to clinicians to use as a diagnostic aid. Although 3541 lesions (1308 patients) were examined, only the excised lesions (n = 466) were analysed by the authors, of which 357 were recruited in primary care clinics. These included 19 melanomas, and 283 dysplastic melanocytic naevi. The authors reported a sensitivity of 89.0% (95% CI 68.6% to 97.1%) and specificity of 84.0% (95% CI 79.7% to 87.5%).

Derm–CAD versus Dermoscopy

Seven studies (32%) reported accuracy data comparing Derm–CAD with dermoscopy for the detection of invasive melanoma and atypical intraepidermal melanocytic variants, providing 7 datasets (4104 lesions including 226 melanomas and no other malignancies). A further 4 studies reported accuracy data for dermoscopy in a subsample of the total study population, and so were excluded from analysis (Blum 2004b; Ferris 2015; Menzies 2005; Stanganelli 2005).

Five of the seven studies compared Derm–CAD to diagnosis by expert dermoscopists using dermoscopic images alone (Binder 1994; Gilmore 2010; Piccolo 2014; Seidenari 1998) or alongside clinical images (Piccolo 2002) in 765 lesions (153 melanomas). Two studies compared face-to-face dermoscopic diagnosis by an expert dermatologist with Derm–CAD systems DB–MIPS (Bauer 2000) and Image J (Dreiseitl 2009).

The accuracy of Derm-CAD was compared with the accuracy of dermoscopy using:

(a) all 22 Derm-CAD studies (8992 lesions and 1063 melanomas) and the 5 image-based dermoscopy studies (765 lesions and 153 melanomas) in an indirect comparison (Figure 10 and Figure 11), and

(b) direct comparisons in the subset of 5 studies that evaluated both Derm-CAD and image-based dermoscopy (765 lesions and 153 melanomas; Figure 12, Appendix 7).

In both comparisons similar sensitivities were observed but with lower specificity for CAD compared to dermoscopy, however none of the observed differences were statistically significant (Table 6). For the indirect comparison, the difference (95% CI) in summary sensitivities (Derm-CAD 90.1% versus dermoscopy 93.3%) was -3.21% (-11.2% to 4.79%), P = 0.43; the difference (95% CI) in summary specificities (Derm CAD 74.3% versus dermoscopy 88.5%) was -14.1% (-34.4% to 6.06%), P = 0.17. For the direct comparison the difference (95% CI) in summary sensitivities (Derm–CAD 94.1% versus dermoscopy 93.9%) was 0.17% (-6.61% to 6.95%), P = 0.96; the difference (95% CI) in summary specificities (CAD-Derm 80.8% versus dermoscopy 88.3%) was -7.44% (-28.4% to 13.6%), P = 0.49.

Contrasting differences in accuracy were produced by the two studies comparing Derm–CAD with face–to–face dermoscopic diagnosis by an expert (Bauer 2000; Dreiseitl 2009; Table 8), however these differences were imprecise.

Spectro-CAD

Eight datasets were meta–analysed to estimate the accuracy of MSI-CAD systems in referral settings, regardless of the system make, algorithm used, or whether CAD was used as a stand–alone automated diagnosis or as a diagnostic aid (Friedman 2008; Glud 2009; Gutkowicz Krusin 1997; Monheit 2011; Tomatis 2003; Tomatis 2005; Wells 2012; Winkelmann 2016). One other dataset (Hauschild 2014) was excluded from this analysis due to being a subgroup of Monheit 2011. Four were model derivation studies (Friedman 2008; Gutkowicz Krusin 1997; Tomatis 2003; Tomatis 2005), two of which validated the resulting classification algorithm in an independent population (Friedman 2008; Tomatis 2005), and the remaining four were prospective (Glud 2009; Monheit 2011) or retrospective (Wells 2012; Winkelmann 2016) external validation studies. Melanoma prevalence ranged from 7% (Monheit 2011 to 49% (Friedman 2008; Wells 2012). These eight datasets evaluated 2537 excised lesions with 296 melanomas, with sensitivities ranging from 76% (Tomatis 2003) to 100% (Glud 2009; Gutkowicz Krusin 1997), and specificities ranging from 8% (Wells 2012) to 77% (Tomatis 2005). The pooled sensitivity was 92.9% (95% CI 83.7% to 97.1%) and specificity was 43.6% (95% CI 24.8% to 64.5%) (Table 5, Figure 13 and Figure 14). The number of melanomas missed ranged from 0 (Glud 2009; Gutkowicz Krusin 1997) to 9 (Tomatis 2003), though the reporting of false positive diagnoses was poor so data could not be analysed.

One study evaluated a Spectro–CAD system based on the analysis of diffuse reflectance spectroscopy data, a non–imaging CAD system called OIDRS (Garcia Uribe 2012). This model derivation study prospectively recruited 136 pigmented skin lesions with a melanoma prevalence of 7% (final diagnosis determined by histology following biopsy). OIDRS was found to operate with a sensitivity of 90.0% (95% CI 59.6% to 98.2%) and specificity of 89.7% (95% CI 83.2% to 93.9%) (Table 9).

The two studies evaluating Nevisense, a CAD system using electrical impedance spectroscopy (EIS), included one internal validation study (Mohr 2013) and one external validation study (Malvehy 2014) (Table 10). Pooling 2389 lesions with 368 melanomas, the summary sensitivity was estimated as 97% (95% CI 94.7% to 98.3%) and specificity was 33.6% (95% CI 31.6% to 35.7%) (Table 5). Both studies reported considerable difficulties in the ability of Nevisense to identify seborrhoeic keratoses, with 69/73 (95%) such lesions falsely identified as malignant. Other notable false positive diagnoses included dysplastic melanocytic nevi, actinic keratoses and dermatofibroma.

One study evaluated the accuracy of an MSI–CAD system in an unreferred population (Walter 2012). A series of participants with pigmented skin lesions who were presenting for a first clinical assessment were prospectively recruited and imaged by GPs, using a SIAscope™ coupled with MoleMate, a multispectral imaging device with viewing platform and integrated Primary Care Scoring Algorithm (developed by Emery 2010). Originally an RCT comparing patient referrals by GPs using MSI–CAD (experimental arm) with GP clinical assessment only (control arm), we extracted the experimental arm data as a prospective case series evaluating MSI–CAD against histology or clinical follow-up of at least 3 months for lesions considered benign, as well as expert diagnosis without follow-up for some benign lesions. Overall 36 melanomas were identified and an additional 209 false diagnoses made amongst 766 included lesions; MSI–CAD sensitivity was 100% (95% CI 82.4% to 100%) and specificity was 72% (95% CI 68.7% to 75.2%) (Table 7).

Spectro–CAD versus Dermoscopy

Six MSI–CAD studies (67%) also evaluated the accuracy of dermoscopy, providing 6 datasets (684 lesions and 229

malignancies comprising 220 melanomas, 8 BCCs and no cSCCs). One of these compared Derm–CAD to in–person dermoscopic diagnosis (Bono 2002), and five studies evaluated dermoscopy using expert dermoscopists (Friedman 2008; Glud 2009; Hauschild 2014) or dermatologists of unreported expertise (Wells 2012; Winkelmann 2016) to interpret stored dermoscopic images of 371 lesions, including 154 melanomas. Four studies also provided additional diagnostic information to clinicians in the form of clinical examination notes (Friedman 2008; Hauschild 2014; Wells 2012) or clinical images (Winkelmann 2016).

The accuracy of MSI-CAD was compared with the accuracy of dermoscopy using:

(a) all 8 MSI-CAD studies (2401 lesions and 286 melanomas) and the 5 image-based dermoscopy studies (371 lesions and 154 melanomas) in an indirect comparison (Figure 15 and Figure 16), and

(b) direct comparisons in the subset of 5 studies that evaluated both MSI-CAD and image-based dermoscopy (371 lesions and 154 melanomas; Figure 17, Appendix 7).

In both comparisons MSI–CAD was significantly more sensitive with lower specificity, though differences in specificity were only significant for (b), the direct comparison (Table 6). For the indirect comparison (a), the difference (95% CI) in summary sensitivities (MSI–CAD 92.9% versus dermoscopy 74.0%) was 18.9% (9.58, 28.2%), P = 0.003; the difference (95% CI) in summary specificities (MSI–CAD 43.6% versus dermoscopy 58.7%) was -15.0% (-40.7% to 10.6%), P = 0.26. For the direct comparison (b), the difference (95% CI) in summary sensitivities (MSI–CAD 96.8% versus dermoscopy 74.0%) was 22.7% (15.2% to 30.2%), P < 0.001; the difference (95% CI) in summary specificities (MSI–CAD 29.8% versus dermoscopy 58.7%) was -28.9% (-56.3% to -1.48%), P = 0.039.

Four of the five image–based dermoscopy studies used the MelaFind system (Friedman 2008; Hauschild 2014; Wells 2012; Winkelmann 2016), with the same impact on sensitivity (MelaFind 96.5% versus dermoscopy 72.5%; difference (95% CI) of 23.9% (16.0% to 31.9%), P < 0.001) and specificity (MelaFind 22.8% versus dermoscopy 50.7%; difference (95% CI) –27.9% (-50.1% to -5.66%), P = 0.014) (Table 6).

One study compared the accuracy of MSI–CAD to in–person diagnosis by an expert dermatologist (Bono 2002), and results are presented in Table 8.

Derm–CAD versus Spectro–CAD

None of the studies directly compared the accuracy of Derm-CAD and MSI-CAD. An indirect comparison of MSI–CAD (8 studies) and Derm–CAD (22 studies), demonstrated similar sensitivities (Derm–CAD 90.1% versus MSI–CAD 92.9%) with a difference (95% CI) of 2.83% (-5.04% to 10.7%), P = 0.48. However, specificity was lower for MSI–CAD (43.6%) compared to Derm-CAD (74.3%) with a difference of -30.7% (-53.8% to -7.64%), P = 0.009 (Table 6).

Secondary analyses for the detection of invasive melanoma and atypical intraepidermal melanocytic variants

Accuracy of individual Derm–CAD systems

Our ability to compare the accuracy of individual CAD systems was limited by lack of data. A sufficient number of datasets to allow separate pooling was available only for the DB-MIPS system. Six studies evaluated the DB–MIPS system, using varying classification algorithms, in a total of 1903 lesions including 502 melanomas (Bauer 2000; Burroni 2004; Rubegni 2002; Seidenari 1999; Stanganelli 2005; Wollina 2007; a seventh study, Seidenari 1998, was excluded from this analysis due to population overlap with Seidenari 1999). Three were external validation studies (Bauer 2000; Seidenari 1999; Wollina 2007), and all six included only excised lesions. Summary estimates of sensitivity were 95.2% (95% CI 89.5% to 97.9%) and specificity 89.1% (95% CI 78.7% to 94.8%) (Table 5, Figure 8 and Figure 18).

Three external validation studies evaluated the MicroDERM system in a total of 793 lesions with 54 melanomas. However, due to the limited number of studies and substantial variability between studies, we did not perform meta-analysis. Sensitivities ranged from 17% (95% CI 0% to 64%) to 86% (95% CI 42% to 100%) and specificities from 50% (95% CI 46% to 54%) to 90% (95% CI 83% to 95%) (Barzegari 2005; Boldrick 2007; Serrao 2006). These represent accuracy for thresholds using DANAOS scores of ≥ 6.5 (Serrao 2006), ≥ 7 (Boldrick 2007) and ≥ 7.34 (Barzegari 2005). The outlying sensitivity of 17% observed in Boldrick 2007 is likely due to a skewed sample of lesions since of the 1000 PSLs assessed in the study, only 18 received an eligible reference standard (histology, clinical follow–up was not reported) and so could be included. The vast majority of the original sample (982/1000) were clinically diagnosed as benign lesions not requiring excision.

Two studies evaluated the Skin View system in 220 excised lesions with 45 melanomas (Cascinelli 1992; Cristofolini 1997). The earlier publication included a model validation phase using internal validation (Cascinelli 1992), while Cristofolini 1997 performed an external validation only. Summary estimates of sensitivity were 80.0% (95% CI 65.8% to 89.3%) and specificity 47.4% (95% CI 40.1% to 54.8%) (Table 5 and Figure 8).

Accuracy of individual Spectro–CAD systems

Five MSI–CAD studies evaluated the MelaFind system in a total of 1798 lesions including 196 melanomas (Friedman 2008; Gutkowicz Krusin 1997; Monheit 2011; Wells 2012; Winkelmann 2016). Summary estimates of sensitivity were 97.1% (95% CI 91.9% to 98.9%) and specificity 29.8% (95% CI 12.3% to 56.3%) (Table 5, Figure 11 and Figure 19).

Both EIS–CAD studies reported above evaluated the Nevisense system, in a total of 2389 lesions with 368 melanomas, giving a summary sensitivity of 97.0% (95% CI 94.7% to 98.3%) and specificity of 33.6% (95% CI 31.6% to 35.7%).

CAD–only performance versus CAD–aided performance

In sensitivity analyses, we excluded studies that used CAD as a diagnostic aid. Three of the 22 Derm–CAD studies

evaluated the Derm–CAD system as a diagnostic aid in referral settings (Bauer 2000; Piccolo 2014; Wollina 2007). Two of the six DB–MIPS studies (both prospective, external validation studies) assessed the system as a diagnostic aid. For MSI–CAD, one of the eight studies used CAD as a diagnostic aid in a referral setting (MelaFind, Winkelmann 2016). The results of the sensitivity analyses are shown in Appendix 8. The results indicate very similar findings to the main analyses.

Direct evidence was available from one study (Dreiseitl 2009) which compared Derm–CAD computer diagnoses (CAD–only) with diagnoses produced by clinicians using Derm–CAD as a diagnostic aid (CAD–aided). In an external validation study, Dreiseitl 2009 compared CAD–only performance of MoleMax II analysed with the Image J software programme (using a neural network classifier), with CAD–aided diagnosis performed by dermatologists with high experience, low experience, and a third cohort with mixed experience. In this prospective study, 458 consecutive participants who were referred to a secondary care centre for further investigation of 3021 suspicious pigmented skin lesions were included. While lesion–based results were reported for the CAD–only diagnosis, only patient–based results were provided for its comparison to CAD–aided diagnoses; it is notable that the lesion–based sensitivity and specificity for CAD-only diagnosis differ substantially from the patient–based estimates for CAD-only diagnosis (74% versus 89% sensitivity, 84% versus 48% specificity), which is to be expected when many more lesions were free of disease (true negatives n = 2512) than were patients (n = 207). The within–study comparison to CAD-aided diagnosis are reported in Table 8.

A case–control reader study (Hauschild 2014) undertaken in a referred setting was the only direct comparison of an MSI CAD–only diagnosis with MSI CAD–aided diagnosis. The study included 65 melanomas and 65 benign pigmented skin lesions that had been excised to evaluate the ability of MelaFind to accurately recommend biopsy in pigmented skin lesions. The study sample was a randomly selected subset of the consecutively recruited, prospective Monheit 2011 population. Differences (95% CI) are reported in Table 8.

Target Condition: Basal Cell Carcinoma (BCC)

Derm–CAD

Four study populations from referred settings included BCC lesions (Cascinelli 1992; Ferris 2015; Menzies 1996; Mollersen 2015), however two did not provide adequate data to derive 2x2 data (Menzies 1996; Mollersen 2015) and one included fewer than the minimum of five lesions to meet our inclusion criteria for this question (Cascinelli 1992). The remaining study evaluated 11 BCCs amongst 173 dermoscopically atypical lesions using the output of an unnamed CAD system (CAD–based diagnosis), in a retrospective case series. Three BCCs were missed giving a sensitivity of 73% (95% CI 43.4% to 90.3%) with 108 false positives giving a specificity of 33% (95% CI 26.5% to 40.9%) for the detection of BCC (Ferris 2015). The study used dermoscopic images of skin lesions excised on the basis of clinical suspicion of malignancy, and also included melanomas, cSCCs, seborrhoeic keratosis and benign melanocytic lesions. The very low specificity was as a result of misclassification of seborrhoeic keratoses (7/11), low–grade dysplastic naevi (27/47) and lentigo (8/10) as malignant lesions.

Spectro–CAD

Two studies evaluated the ability of a Spectro–CAD system to detect BCC lesions, both using the EIS–CAD Nevisense system in patients with suspected melanoma referred for excision (Malvehy 2014; Mohr 2013) (Table 10). Of 2389 analysed lesions, all 69 BCCs were identified giving a summary sensitivity of 100% (95% CI 94.7% to 100%) and very low specificity of 26.3% (95% CI 24.5% to 28.1%). Since both populations were recruited to rule out melanoma, few benign keratotic lesions were included (including lichenoid keratosis (n = 4), seborrhoeic keratosis (n = 73) and actinic keratosis (n = 8)), a factor which may have contributed to the very low specificity.

Target Condition: Cutaneous Squamous Cell Carcinoma (cSCC)

The only study to evaluate the performance of a CAD system to detect cSCC used the EIS–based Nevisense system in referred patients, identifying all 7 cSCCs amongst 1943 lesions to give a sensitivity of 100% (95% CI 59.0% to 100%) and specificity of 43.4% (95% CI 41.2% to 45.6%) (Malvehy 2014) (Table 10). The high sensitivity could have been influenced by the study's melanoma–focused recruitment selection which resulted in very few benign differential diagnoses being included (lichenoid keratosis (n = 4), seborrhoeic keratosis (n = 51) and actinic keratosis (n = 8)).

Secondary target conditions: invasive melanoma alone

The diagnostic accuracy of CAD assessment for the detection of invasive cutaneous melanoma alone was reported by seven studies for a total of 1336 lesions with 236 invasive melanomas.

Of these, two studies evaluated Derm–CAD systems (total 950 lesions with 120 invasive melanomas): SolarScan (Menzies 2005) and an unnamed system (Menzies 1996), both of which included model derivation within the same population (Menzies 1996 did not report the method of dividing lesions into train and test sets). Both also included pigmented skin lesions referred for excision (Menzies 1996; Menzies 2005) of which one may have included BCCs amongst the target disease negative group (Menzies 1996 included 18 BCCs in the full study population but did not report how many were included in the independent test set). Melanoma prevalence was 10% in Menzies 2005 and 27% in Menzies 1996. Meta–analysis of these studies provided a summary sensitivity estimate of 90.8% (95% CI 84.2% to 94.9%) and summary specificity of 63.5% (95% CI 60.2% to 66.7%) (Table 5). Menzies 2005 also reported data for the primary target condition, invasive melanoma and atypical intraepidermal melanocytic variants, with little difference in sensitivity (92.0% invasive melanoma only versus 91.0%, –1.0% difference (95% CI –8.7% to 8.2%)) or specificity (61.5% invasive melanoma only versus 65.1%, –3.6% difference (95% CI -8.7% to 1.5%)). Despite *in situ* lesions making up 39% (47/122) of disease positives, similar proportions of *in situ* (5/47) and invasive lesions (6/75) were missed by the SolarScan.

One Derm–CAD study, retrospective with uncertain design, also allowed a comparison with image–based dermoscopy in 164 lesions containing 45 invasive melanomas (Menzies 1996). Observer experience was not reported. Accuracy estimates were similar and are reported in Table 8.

Five studies evaluated an MSI-CAD system (total 386 lesions with 116 invasive melanomas), regardless of the system make, algorithm used, or whether CAD was used as a stand–alone automate diagnosis or as a diagnostic aid. All were conducted in lesions referred for excision, four solely in pigmented skin lesions (Ascierto 2010; Bono 1996; Friedman 2008; Hauschild 2014) and the fifth in any lesion clinically suspected of being a melanoma (Terstappen 2013). Systems evaluated were MelaFind (Friedman 2008; Hauschild 2014), SpectroShade (Ascierto 2010), Telespectrophotometric System (Bono 1996) and SIAscope, version V (Terstappen 2013).

Sensitivities ranged from 24% (Terstappen 2013) to 100% (Friedman 2008) and specificities from 29% (Friedman 2008) to 84% (Terstappen 2013). The study producing the highest sensitivity and lowest specificity, Friedman 2008, excluded all high grade dysplastic lesions and therefore included only melanomas, BCCs (n = 2), low grade dysplastic nevi (n = 32) and other benign melanocytic lesions (n = 14). The lowest sensitivity and highest specificity were produced by Terstappen 2013 who further selected their population of clinically suspicious lesions to include only lesions with a positive CAD result (SIAscope). Both datasets that evaluated the MelaFind system (Hauschild 2014; Friedman 2008) generated high sensitivities (81% and 100%) and low specificities (39% and 29%). These five studies (386 lesions including 116 invasive melanomas) gave a summary sensitivity estimate of 76.5% (95% CI 43.0% to 93.3%) and summary specificity of 60.7% (95% CI 38.5% to 79.2%) (Figure 20; Figure 21; Table 5).

In sensitivity analyses, we excluded one study that used CAD as a diagnostic aid, in a referral setting (Hauschild 2014). The results of the sensitivity analysis are shown in Appendix 8. The results indicate very similar findings to the main analysis.

One study compared MSI–CAD (MelaFind) to diagnosis by expert dermoscopists using dermoscopic images in 99 lesions including 21 invasive melanomas, finding Melafind's sensitivity to be higher (100% versus 81%) and specificity lower (29% versus 45%) than dermoscopy (Friedman 2008) (Table 8).

One other study compared MSI–CAD (SpectroShade) to face–to–face diagnosis by expert dermatologists in 54 lesions with 12 invasive melanomas, finding SpectroShade's sensitivity to be lower (67% versus 100%) and specificity higher (76% versus 45%) than dermoscopy (Ascierto 2010) (Table 8).

The two studies evaluating the EIS–based Nevisense system produced accuracy data for 2389 lesions with 226 invasive melanomas, giving a summary sensitivity of 98.2% (95% CI 95.4% to 99.3%) and specificity of 38.0% (95% CI 36.0% to 40.1%) (Mohr 2013, Malvehy 2014) (Table 5).

A single study contributed data for the accuracy of detecting invasive melanoma in an unreferred setting, reporting the use of MoleMate with SIAscope by GPs in 766 lesions with 14 invasive melanomas (Walter 2012). No melanomas were missed: sensitivity 100% (95% CI 77.4% to 100%); although false positive findings were high giving a specificity of 72% (95% CI 68.3% to 74.8%) (Table 7).

Secondary target conditions: any lesion requiring excision

Derm–CAD

Four datasets from three studies (Cascinelli 1992; Ferris 2015; Mollersen 2015) provided data to evaluate the accuracy of Derm–CAD to detect any skin cancer or other atypical lesion requiring excision in referred settings. Two were retrospective derivation studies using stored dermoscopic images to train either the Skin View system in clinically suspect pigmented skin lesions referred for excision (Cascinelli 1992), or an unnamed system in lesions suspected of malignancy also referred for excision (Ferris 2015). The third study conducted a head–to–head external validation comparison of two systems, in a case series of pigmented and nonpigmented (if melanoma, BCC, or SCC was a potential differential diagnosis) skin lesions scheduled for excision (Mollersen 2015). The Nevus Doctor system was the subject of evaluation as a system still in development, being compared against the commercially available Mole Expert. The three studies provided a total of 1087 lesions, the 186 malignancies included 83 BCCs, 9 cSCCs and 1 adnexal carcinoma (Mollersen 2015). Sensitivities were high, ranging from 83% (Cascinelli 1992) to 98% (Mollersen 2015, Nevus Doctor), while specificities were low and more varied ranging from 12% (Mollersen 2015 Nevus Doctor) to 59% (Cascinelli 1992). The lowest specificities (Nevus Doctor 12%, Mole Expert 13%) were produced by the study with the lowest disease prevalence (14%, Mollersen 2015). Mollersen 2015 also produced the highest sensitivity and was the only study to include clinically obvious melanomas amongst its lesions.

These accuracy estimates did not differ substantially from those for the detection of the individual target conditions reported above.

No data were available to compare these results with the use of standard dermoscopy to detect any skin cancer.

Spectro–CAD

Two datasets evaluated the performance of DRS–CAD systems in referred settings, both from one study (Garcia Uribe 2012) evaluating the performance of the Oblique Incidence Diffuse Reflectance Spectrometry (OIDRS) system in two cohorts of lesions (i.e. CAD algorithms trained separately in each cohort). Amongst 136 pigmented skin lesions including 25 lesions to be excised (10 melanoma, 15 severe dysplastic lesions) OIDRS gave a sensitivity of 92% (95% CI 74.0% to 98.8%) and specificity 86% (95% CI 78.9% to 91.6%); amongst 89 non–pigmented skin lesions including 64 lesions to be excised (39 BCC, 25 cSCC) OIDRS gave a sensitivity of 92% (95% CI 83.0% to 96.6%) and specificity 92% (95% CI 74.0% to 98.8%). However, caution must be used to interpret these estimates as the spread of disease was different to that intended by our

target condition definition of all malignancies: no malignancies other than melanoma were included in the pigmented population, and no melanomas were included in the non–pigmented population.

The two EIS–CAD studies conducted in referred settings produced accuracy data for 2389 lesions with 644 malignancies or highly dysplastic lesions, giving a summary sensitivity of 93.5% (95% CI 91.3% to 95.1%) and specificity of 32.6% (95% CI 30.4% to 34.8%) (Malvehy 2014; Mohr 2013) (Table 5). In addition to the malignancies described above, one Merkel cell carcinoma was included (Malvehy 2014) and detected by Nevisense.

Two datasets provided data for the use of MSI–CAD in unreferred settings (Sgouros 2014; Walter 2012) (Table 7). While both used a SIAscope™ device, Walter 2012 used the MoleMate analysis system incorporating the 'primary care scoring algorithm' to analyse lesion images and arrive at a diagnosis (Walter 2012), while Sgouros 2014 also used the primary care scoring algorithm but did not report how images were interpreted. Sensitivity was slightly higher in Walter 2012 study (92% versus 84% in Sgouros 2014) and specificity substantially so (72% versus 46% Sgouros 2014). In addition to the probable use of different analysis software, this difference is likely explained by two factors, firstly CAD test results were used in different ways, as a diagnostic aid to GPs (after a period of training) by Walter 2012 and as the diagnostic output for a CAD–based diagnosis in Sgouros 2014. Second, our exclusion of 144 benign cases with no reference standard diagnosis from Sgouros 2014 has created a highly selected (excised only) and unrepresentative study population in this study (low sample size, n = 44, and high prevalence of malignancy, 70%). Of the 153 lesions considered benign after clinico-dermoscopic assessment (of which nine were later excised), 122 were diagnosed as naevi, 23 as seborrhoeic keratoses, seven as dermatofibroma and one as cherry angioma. SIAscopy gave a negative score (< 6) in 100 of these 153 lesions.

Discussion

Summary of main results

Computer–assisted diagnosis has been evaluated using a wide range of computer systems that analyse lesion images obtained by digital dermoscopy, lesion images obtained by multispectral imaging, or that analyse non–visual data from electrical impedance or diffuse reflectance spectroscopy. These computer systems have employed a variety of classification algorithms to scrutinise diverse selections of features. CAD sensitivity estimates were generally high, though with highly variable specificity.

We present six main findings from our review:

1) Included studies inadequately address the review question due to an abundance of low quality studies, poor reporting, and recruitment of highly selected groups of participants

This review aimed to assess the accuracy of computer–assisted diagnosis for detecting melanoma, BCC or cSCC in adults. Most included studies focused on its use for detecting or ruling out melanoma in lesions scheduled for excision. Therefore these studies do not reveal CAD's ability to detect clinically missed melanomas, since most have excluded lesions clinically diagnosed as benign. Only three studies, all of Derm–CAD systems, examined lesions not recommended for excision (and thus potentially missed melanomas) using an adequate reference standard in clinically benign lesions.

Studies were poorly reported and generally of unclear to high risk of bias across all domains, particularly with regard to the selection of study participants, the timing of CAD diagnosis in relation to the reference standard diagnosis, and pre–specification of CAD thresholds. Most studies used restricted groups of participants and failed to provide details of diagnostic thresholds sufficient for their reproducibility, leading to an almost universally poor clinical applicability of studies.

Poor reporting in the primary studies also hindered attempts to assess sources of heterogeneity, particularly with regard to the lack of reporting CAD results according to the final diagnosis. A substantial number of included studies (half of Derm–CAD studies and a third of Spectro–CAD studies) evaluated experimental versions of CAD systems, in which classification algorithms were trained alongside preliminary assessments of test performance within the same source population. The frequency of these internal validation studies causes high concern for the reliability of accuracy estimates, chiefly because models are likely to give overly–optimistic results when training and testing datasets are very similar in the spread of lesion types and severity, as is the case when the same source population is used (Altman 2009). In addition, great caution should be employed when considering the applicability of these results to current clinical practice, since the generalisability of a new model can only be estimated in *external validation* studies that recruit new groups of patients from entirely new source populations.

Most study populations were restricted to excised lesions. Since lesions which are not excised are more likely to be benign, and without an atypical morphological pattern that could be mistaken for a malignancy, their absence from datasets may have reduced CAD specificity estimates from their likely performance in populations where CAD tests would be used in clinical practice, namely those being referred for specialist assessment. Including the appropriate spectrum of benign conditions is key to establishing the accuracy of any test (Lijmer 1999). Spectrum effects are often observed when tests that are developed further down the referral pathway have lower sensitivity and higher specificity when applied in settings with participants with limited prior testing (Usher-Smith 2016). However, this direction of effect is not consistent across tests and diseases as Leeflang 2013 clearly demonstrates; the mechanisms in action are often more complex than prevalence alone and can be difficult to identify. It is therefore crucial that tests are evaluated in lesions that are representative of those in which the test will be used in practice. For tests such as CAD that use machine learning, a representative participant population is vital for both training the algorithm and testing its validity. If a narrow range of benign conditions is used to train a computer algorithm, the resulting CAD system is likely to struggle in discriminating new, previously unseen benign lesions at the validation stage. Unfortunately, very poor reporting of the spectrum of conditions included in studies prevents any assessment of whether mismatches have occurred between training and validation

populations.

Limited data regarding the use of CAD as a diagnostic aid further limits the applicability of study results. Although CAD systems are designed to be used as diagnostic aids, the majority of studies did not evaluate how CAD outputs were interpreted and acted upon by clinicians in their diagnostic decision–making, but instead evaluated the accuracy of the CAD system outputs as stand–alone tests.

2) CAD systems correctly identify melanoma in highly selected populations, but their low and very variable specificity suggest they are unreliable as stand–alone diagnostic tests, especially in less selected populations

Reflecting the design aims of system developers, the vast majority of studies sought to evaluate the ability of CAD to identify melanomas. The Summary of findings table 1 presents key results for the primary target condition of cutaneous invasive melanoma or atypical intraepidermal melanocytic variants. For digital dermoscopy CAD systems, pooled results from 22 studies (8992 lesions, 1063 melanomas) provided a sensitivity of 90.1% (95% CI 84.0% to 94.0%) and specificity of 74.3% (95% CI 63.6% to 82.7%). The Summary of findings table 1 illustrates how these estimates would affect diagnoses in a hypothetical cohort of 1000 lesions clinically suspected of being melanomas. At the median melanoma prevalence of 20% that might occur in a highly specialised melanoma referral clinic, digital dermoscopy CAD systems would on average miss 20 out of 200 melanomas and would result in 206 false positive diagnoses. At the lower and upper quartile melanoma prevalence of 7% and 40%, 7 and 40 melanomas would be missed, with 239 and 154 false positive diagnoses respectively.

For multispectral imaging CAD systems, pooled results from 8 studies (2401 lesions, 286 melanomas) provided a sensitivity of 92.9% (95% CI 83.7% to 97.1%) and specificity of 43.6% (95% CI 24.8% to 64.5%). In a hypothetical cohort of 1000 lesions clinically suspected of being melanomas with melanoma prevalence of 20%, MSI–CAD systems would on average miss 14 out of 200 melanomas and would result in 451 false positive diagnoses (Summary of findings table 1). At the lower and upper quartile melanoma prevalence of 7% and 40%, 5 and 28 melanomas would be missed, with 525 and 338 false positive diagnoses respectively.

These results demonstrate a consistently high sensitivity for the detection of invasive melanoma and atypical intraepidermal melanocytic variants by CAD, regardless of type (Derm–CAD versus Spectro–CAD). However, specificity tends to be low and varies considerably between studies, particularly for MSI–based systems. The evidence certainly indicates that some benign lesions are more difficult to distinguish from malignancy using both Derm–CAD and Spectro–CAD systems, particularly seborrhoeic keratoses which proved problematic for Derm–CAD and EIS–CAD systems. However the reporting of benign diagnoses by CAD result was very poor, and omitted in 29 of the 42 included studies. As a result, the performance of MSI–CAD systems with regard to these lesions remains uncertain. This difficulty in ruling melanoma out from seborrhoeic keratoses is also encountered when visual examination and dermoscopy are employed, and for CAD systems is equally likely to be due to similarities in the morphological appearance of these non-melanocytic pigmented lesions and melanomas (Menzies 2005; Mollersen 2015).

Poor reporting of other aspects of study conduct also limit our interpretation of the heterogeneity in specificity, however likely causes include a wide variation in the spread of disease negative conditions included in study populations (both for training algorithms and for validating them), as well as considerable variation in CAD system characteristics.

3) There is insufficient evidence to assess the accuracy of CAD systems in primary care settings

Insufficient data were available from primary care populations to draw firm conclusions, particularly for Derm–CAD with only one included study which restricted inclusion to excised lesions only. For MSI–CAD, some suggestion of high sensitivity was found, though the evidence–based was limited to 2 studies evaluating differing target conditions and with differing approaches to the use of CAD results (CAD–based versus CAD–aided diagnosis). Limiting study populations to excised lesions is particularly problematic in such settings, since the frequency and distribution of disease is far removed from the range one would expect to see in patients who have received limited prior testing, such as those self–referring to specialist pigmented lesion clinics. Only one study examined all individuals presenting to generalist settings that had lesions which could not immediately be diagnosed as benign (Walter 2012). A second study also included all such lesions (Sgouros 2014), however failed to provide non–excised lesions with any clinical follow–up and so these lesions had to be excluded from our analysis.

4) Preliminary findings suggest CAD systems are at least as sensitive as assessment of dermoscopic images for the diagnosis of invasive melanoma and atypical intraepidermal melanocytic variants

MSI–CAD was found to be significantly more sensitive than image-based dermoscopy (92.9% versus 74%, P = 0.003), while direct comparisons indicate that it is also significantly less able to rule out truly benign lesions (29.8% versus 58.7%, P = 0.039). However indirect comparisons did not confirm this difference (43.6% versus 58.7%, P = 0.26) (Table 6). Conversely, our evidence suggests Derm–CAD may not differ significantly from dermoscopy in its ability to identify melanomas. However, we caution against drawing firm conclusions from these comparisons in the absence of sufficient data from studies evaluating face–to–face dermoscopy, on the basis that another review in this series has found such studies to demonstrate significantly higher accuracy for dermoscopy than those relying on review of dermoscopic images (Dinnes 2018b).

5) The evidence–base for individual systems is too limited to draw conclusions on which might be preferred for practice

Despite the large number of included studies, the evidence–base for the accuracy of individual systems to detect the primary target condition of the detection (invasive melanoma and atypical intraepidermal melanocytic variants) remains low with

meta–analysis possible for only two Derm–CAD systems (DB–MIPS and Skin View), one MSI–CAD system (MelaFind) and one EIS–CAD system (Nevisense). Only one of these, DB–MIPS, demonstrated a high specificity (89.1%) alongside high sensitivity (95.2%). Even though they evaluated the same CAD system, the six studies that were pooled for this estimate of DB-MIPS were very varied in the classification algorithm used (ANN, SVM, K–NN, discriminant analysis, Euclidean distances), disease prevalence (5% to 45%), use of CAD results (two studies evaluated DB–MIPS as a diagnostic aid and four evaluated the DB–MIPS computer output) and range of disease negative conditions included (poorly reported, with a mixture of common naevus, dysplastic naevus, and only one study including seborrhoeic keratoses). The clinical settings to which this estimate applies therefore remains unclear.

We observed considerable variation in test characteristics across all CAD systems, such as hardware and software technologies used, the types of classification algorithm employed, methods used to train the algorithms, and which lesion morphological features were extracted and analysed. Wide variations in technology specifications were observed even within the same CAD systems; for example the four studies evaluating the SIAscope (a commercially available MSI–CAD system) captured between 4 and 8 optical reflectance images at varying wavelengths to inform the final image (not reported in 2 studies), using different SIAscopes (versions II and V, not reported in 2 studies) coupled to different software programmes (the MoleMate™ in 2 studies, and not reported in 2 studies) utilising 2 different thresholds (the Moncrieff 2002 and Emery 2010 methods). This variation in CAD method, alongside limited reporting of important technological variables, was encountered in all CAD systems evaluated in this review.

6) Evidence of the ability of CAD to detect keratinocyte cancers is very limited and studies are confined to specialist settings

Only 3 studies included sufficient numbers of BCC cases for analysis; the one small retrospective study evaluating Derm–CAD is insufficient to draw any conclusions. For EIS–CAD, the two large prospective studies were designed to evaluate Nevisense's ability to detect melanoma, thus neither recruited populations clinically applicable for keratinocyte cancer detection, casting doubt on the generalisability of pooled estimates to clinical practice. Similarly, evidence for the accuracy of cSCC detection is limited to one Nevisense study, of unlikely clinical applicability to the target condition.

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 focusing on estimating incremental gains in accuracy was adopted. A detailed and replicable analysis of methodologic quality was undertaken.

In comparison with the four main existing systematic reviews, our review extends the time period searched for eligible studies (from 2002 in Rosado 2003, from 2007 in Rajpara 2009 and Vestergaard 2008, and from 2011 in Ali 2012), includes all eligible studies regardless of language (Ali 2012; Rosado 2003), the presence of melanocytic lesions (Rajpara 2009), or use of a histological reference standard (Rajpara 2009). Although Vestergaard 2008 reviewed studies evaluating multispectral imaging CAD, electrical impedance spectroscopy CAD, and digital dermoscopy–based CAD systems, ours is the first review to meta-analyse data and provide pooled accuracy estimates for each of these three types of CAD system. Ours is also the first review to include keratinocyte cancers as a target condition.

Our stringent application of review inclusion criteria meant that some studies included in previous reviews were excluded. For example, those developing CAD systems and training new algorithms ('derivation studies') without assessing their performance in an independent population were not included. Of the 30 studies included in Rosado 2003, we excluded 23 studies including 17 derivation studies without independent test sets (16 Derm–CAD studies (Andreassi 1999; Binder 2000; Elbaum 2001; Ercal 1994; Ganster 2001; Green 1991; Green 1994; Hintz-Madsen 2001; Horsch 1997; Kahofer 2002; Pompl 2000; Rubegni 2001a; Sboner 2001; Schindewolf 1994; Schmid-Saugeon 2003; Smith 2000) and one MSI–CAD study, Farina 2000). Three others were excluded for lack of clarity on the 2x2 contingency table (Schindewolf 1993), evaluating the diagnostic ability of a single feature (shape, Claridge 1992), and unclear reporting on CAD type and eligibility of the reference standard (Lefevre 2000). Two others were conference abstracts, and so were not eligible for analysis. Of the 12 Derm–CAD studies included in Rajpara, we excluded 4 derivation studies without independent test sets (Green 1994; Manousaki 2006; Rubegni 2002a; Sboner 2001). Similarly, we excluded four of the nine Derm-CAD studies in Ali 2012 due to the absence of independent test sets in derivation studies (Iyatomi 2006; Iyatomi 2008a; Iyatomi 2008b; Iyatomi 2010a), and another that did not evaluate diagnosis of the presence of skin cancer (Abbas 2011a). Vestergaard 2008 also required studies to evaluate CAD systems in an independent test set, and consequently only one of the nine studies included in Vestergaard 2008 was excluded, due to the absence of a reference standard test in selected participants (Jamora 2003).

Our stringent exclusion of studies without an independent test population has resulted in the exclusion of all studies evaluating non–imaging diffuse reflectance spectroscopy (DRS) systems (e.g. Wallace 2002). This class of technologies used high spectral sampling to achieve a much higher resolution of spectral information from pigmented skin lesions than is found in the included DRSi (multispectral imaging) studies, giving an apparent strong performance for the detection of melanoma (Wallace 2000a; Wallace 2000b). Whether these promising results were overly–optimistic due to their study design, or are genuine indicators diagnostic ability cannot be assessed by this review. However, as technology improves we are likely to see systems with both imaging capability and high spectral sampling, making further carefully-planned evaluation worthwhile.

The main concerns for the review are a result of the poor reporting of primary studies, limiting our assessment of methodological quality, and in particular limiting an understanding of which malignant and benign conditions were correctly

and incorrectly identified by the CAD systems. The poor reporting is of particular concern given the clear heterogeneity in all aspects of study design, and consequently the clinical applicability of results is difficult to determine. Poor reporting also precludes our ability to identify those studies that may have been well designed, but did not document their design and conduct adequately.

Clear identification of the target condition was not provided in 9/22 Derm–CAD datasets or in 4/8 MSI–CAD datasets included in our primary analyses for detection of invasive melanoma or atypical intraepidermal melanocytic variants. These studies may or may not have included melanoma *in situ* lesions. 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.

Our review is limited to studies published up to August 2016, and since computer–assisted diagnosis is a rapidly developing field of technology, the review will have missed some important and more recent developments in the field of machine learning with an application to the detection of skin cancer. Deep learning algorithms (Esteva 2017; Han 2018) are one example where recent advances in computation have been applied to the development of new CAD systems for the detection of skin cancer. In future, it is also probable that CAD systems using continuous machine learning algorithms (where the CAD model continues to refine itself with exposure to clinical cases) will be developed.

Applicability of findings to the review question

The majority of data included in this review are unlikely to be applicable to the current clinical settings of primary care and dermatology clinics that exist in many developed countries. The predominance of highly selected lesion groups, scarce documentation of prior testing and frequency of internally validated derivation studies are likely to restrict the applicability of accuracy estimates to clinical practice. Poor documentation of the final diagnoses used to train CAD systems prevents any conclusion regarding the ideal target patient group, while very limited reporting of CAD results by final diagnosis does not allow for recommendations to be made as to which CAD is most and least likely to perform well, further restricting the transferability of results in practice.

Authors' conclusions

Implications for practice

The utility of CAD for the primary diagnosis of melanoma in patients referred to specialist care remains largely unknown, since most included studies used CAD to detect malignancy in lesions already scheduled for surgical excision, most commonly with a high clinical suspicion of melanoma. For the detection of melanoma in patients with clinically suspicious lesions, the evidence consistently shows all CAD types to have high sensitivity. CAD systems could therefore by useful as a back-up by specialists to assist in minimising the risk of missing melanomas. However, the evidence–base is currently too poor to understand whether CAD system outputs translate to different clinical decision–making in practice, and our sensitivity analysis suggests sensitivity may actually decrease when CAD is used as a diagnostic aid to triage unreferred patients. In addition, any projected gains in the early detection of melanomas must be set against the costs and practicality of implementing new systems.

Our evidence suggests MSI–CAD *may* be significantly more sensitive than dermoscopy. Given the paucity of data to allow comparison with in–person dermoscopy studies, this finding should be considered as exploratory.

Insufficient data are available to provide conclusive comments on the accuracy of CAD in community settings, or its accuracy to detect BCC and cSCC in any setting.

Implications for research

Further prospective evaluation of the added value of CAD systems is warranted. Given the technological complexity and variation of CAD systems, it is certainly challenging to evaluate them in a rigorous manner. Nonetheless studies are needed to evaluate CAD in its intended position in the patient care pathway in comparison to routine clinical examination and dermoscopy. For its use in specialist referral settings, studies should prospectively recruit *all* consecutive participants that have been referred for investigation of potential malignancy; for melanoma this should include all pigmented skin lesions, and for keratinocyte cancers any lesion at suspicion of being a BCC or cSCC. These studies should include lesions that are clinically determined to be benign and not excised, using specialist follow–up of *at least 6 months* as the accuracy reference standard. Comparisons with dermoscopy should consist of in–person diagnosis by dermatologists with expertise in dermoscopy. In community care settings, studies should prospectively recruit all participants presenting to clinic with lesions about which the clinician cannot clearly rule out malignancy, with clinical follow–up of all lesions which are not excised. To understand the clinical validity of CAD systems, studies should further evaluate on how CAD system outputs are used to alter clinical decision making in real world practice settings.

Future studies must also report CAD test results according to their final diagnosis so that its ability to distinguish between morphologically difficult lesions can be established. Crucially, studies must report the full technological specifications of their CAD systems, including which features were analysed as well as the diagnostic criteria and thresholds used to determine the presence of malignancy. Information on the distribution of lesions used to train the CAD system in previous studies would also be a welcome addition that would enable an interpretation of the system’s accuracy.

In terms of the development of new systems, or refinement of existing ones, cohorts of lesions should be selected so that training sets contain the range of benign and malignant lesions that would be encountered in routine clinical practice. Full

descriptions of included lesions should be reported, together with an indication of how diagnostic thresholds have been selected. Validation of preliminary results should be assessed in independent populations, ideally from a different source to that used for model development.

Any future research study needs to be clear about the diagnostic pathway followed by study participants, and should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

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Contributions of authors

JDi was the contact person with the editorial base.
LFR co-ordinated contributions from the co-authors and wrote the final draft of the review.
JDi, NC, LFR screened papers against eligibility criteria.
LFR, JDi, NC, appraised the quality of papers.
LFR, JDi, NC, AG, SAC, AD extracted data for the review
LFR sought additional information about papers.
LFR, JDi entered data into RevMan.
YT, LFR analysed and interpreted data.
LFR, JDi, YT worked on the methods sections.
LFR drafted the clinical sections of the background and responded to the clinical comments of the referees.
LFR responded to the methodology and statistics comments of the referees.
CO, KG were the consumer co-authors and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
JDi is the guarantor of the update.

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Declarations of interest

Lavinia Ferrante di Ruffano: The NIHR funded the project but to my knowledge did not influence its planning or conduct.
Yemisi Takwoingi: nothing to declare.
Jac Dinnes: nothing to declare.
Naomi Chuchu: nothing to declare.
Susan E Bayliss: 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).
Rubeta N Matin: nothing to declare.
Kathie Godfrey: I have received reimbursement of travel expenses incurred by attending meetings.
Colette O'Sullivan: nothing to declare.
Abha Gulati: nothing to declare.
Sue Ann Chan: nothing to declare.
Alana Durack: nothing to declare.
Susan O'Connell: nothing to declare.
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NIHR Biomedical Research Centre and the Royal Marsden NHS Foundation Trust and Institute of Cancer Research, and the Cancer Research UK Imaging Centre Grant to the Institute of Cancer Research. There was no involvement of grant funders or other sponsors in the study whatsoever.
Jonathan J Deeks: 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

Reviews on the accuracy of gene expression testing and volatile organic compounds could not be performed as planned due to an absence of relevant studies.

For this review, inclusion criteria were 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" and "at high risk of developing BCC or cSCC, including those with a family history or previous history of skin cancer or genetic cancer syndromes, such as basal cell naevus (Gorlin) syndrome" as these are not target populations for CAD use.

One of the primary objectives and primary target conditions has been changed from diagnosing "cutaneous invasive melanoma alone", to diagnosing "cutaneous invasive melanoma and atypical intraepidermal melanocytic variants", as the latter is more clinically relevant to the practicing clinician. The diagnosis of the target condition of invasive melanoma alone has instead been included as a secondary objective.

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:

"Studies developing new algorithms or methods of diagnosis (i.e. derivation studies) were **included** if they evaluated the new approach using a separate 'test set' of participants or images.

Studies were **excluded** if they:

- evaluated a new statistical model or algorithm in the same participants or images as those used to train the model (i.e. absence of an independent test set)
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983)"

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.

Due to lack of data, we could not perform the following analyses: restriction to analysis of per patient data, or comparison of accuracy using diagnosis of stored images (image–based) with in–person diagnosis.

Upon closer review of the topic, but before examination of study data, we planned 4 additional secondary analyses than those listed in the protocol: estimation of diagnostic accuracy for individual CAD systems; comparison of the accuracy of CAD to dermoscopy where both tests have been evaluated in the same studies (direct comparisons); the comparison of CAD–based diagnosis to CAD–assisted diagnosis (CAD results used by clinicians as a diagnostic aid); and where CAD systems are used as a diagnostic aid, to determine the effect of observer experience on diagnostic accuracy.

We planned 3 additional heterogeneity investigations relating to population characteristics than those listed in the protocol (Patient population: primary/secondary/specialist unit; Lesion type: any pigmented/melanocytic; Inclusion of multiple lesions per participant), however we could not perform these investigations due to insufficient data.

Published notes

Characteristics of studies

Characteristics of included studies

Ascierto 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Not reported (states in a period of 1 year) **Country** Italy **Test set derived:** The training set consisted of 78 PSL images, comprising 19 MMs and 59 naevi of comparable size. The test set consisted of 383 lesions, including 18 MMs thinner than 0.75 mm (8 in situ).The 59 naevi belonging to the training set were randomly selected from routine material, whereas the 424 naevi of the test set represented consecutive cases.
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:** Clinically relevant cutaneous pigmented lesions, undergoing dermoscopy and excision; only melanocytic lesions meeting at least two clinical ABCDE criteria underwent dermoscopy **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 54/ No. included: 54 **Sample size (lesions):** 54 **Participant characteristics:** **Age (yrs):** - Median: 41/ Range: 19-73 years **Gender:** - Male: 19 males **Lesion characteristics** NR
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1.Dermoscopy** **Method of diagnosis:** - In person diagnosis **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** - Qualitative - Very high risk - Lesion with a pigment network and any of the classical ELM features specific for melanoma (pseudopods, radial streaming, blue-gray veil, atypical vessel, etc.)High risk - Lesion with a pigment network and subtle newELM features that may suggest melanoma but often are also seen in atypical nevi. **Diagnosis based on:** Unclear NR; evaluations made by expert dermatologists Number of examiners Not reported **Observer qualifications:** - Dermatologist **Experience in practice:** - High experience or 'Expert' **Experience with index test:** - High experience /'Expert' users 'expert dermatologists' **2.Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SpectroShade (MHT, Verona Italy) (classifier not reported) **System details:** The system provides information including a series of 15 multispectral images into the near infrared bandwidth. Three spectral areas play a major role in quantification of parameters: 584 nm, 650-750 nm, 750-950 nm. **No derivation aspect (external validation study)** **Lesion characteristics assessed:** Seven parameters: mean reflectans, MR; variegation, V; area, A; dark area ratio, DAR; dark island reflectance, DA; dark distribution factor, DDF **Additional predictors included:** - No further information used **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - Clinical examination and/or case notes - Dermoscopy **CAD output:** - Diagnostic category: 1 no melanoma, 2 doubtful melanoma, 3 suspected melanoma, 4 probable melanoma **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone Disease positive: 12 MM; Disease negative: 42 TARGET CONDITION (Final diagnoses) Melanoma (in situ and invasive, or not reported): 12 'Benign' diagnoses: 42
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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 reported Time interval to reference test: "Before surgery, all patients were investigated by clinical and epiluminescence microscopy (ELM) screenings" Time interval between index test(s): As above
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
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Barzegari 2005

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported **Period of data collection** NR **Country** Iran
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:** Pigmented skin lesions with a clinical diagnosis of melanocytic lesion <=15mm diameter referred to dermatology clinic for diagnostic evaluation or cosmetic reasons **Setting:** Secondary (general dermatology) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion - Patient request for evaluation/excision **Setting for prior testing:** Not reported **Exclusion criteria:** >15mm **Sample size (patients):** No. included: 91 **Sample size (lesions):** No. included: 122 **Participant characteristics:** **Age (yrs):** - Mean: 32.3/ Range: 6-94 **Gender:** - Male: 30; 33% **Lesion characteristics** NR
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD: microDERM (DANAOS software, ANN classifier) **System details:** The system consists of a special camera, which had ability to take images at ×15, ×20, ×30, and ×50 magnifications and contains a 752 × 582 pixel chargecoupled device. The image analysis software was Visiomed AG (Ver. 3.50) based on an ANN that was trained using images collected in a Europe-wide multicenter study (DANAOS). **No derivation aspect (external validation study)** **Lesion characteristics assessed:** - Lesion features analysed not described **Additional predictors included:** - No further information used **Method of diagnosis:** - In person diagnosis – CAD-based diagnosis **Prior/other test data:** - Clinical examination and/or case notes **CAD Output:** The software produces a score per lesion ranging from 0 to 10. **Diagnostic threshold:** - 2x2 data for more than one diagnostic threshold - Threshold determined based on ROC analysis; threshold chosen on basis of similarity to other microDERM studies: 7.34

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone Disease positive: 6; Disease negative: 116 **Target condition (Final diagnoses)** Melanoma (invasive): 3; Melanoma (in situ): 3 Sebhorrheic keratosis: 2; Benign naevus: 104; Dysplastic naevus 7 DF 1 AK
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	1. Excluded participants: None; 3. Time interval between index test(s): Consecutive
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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Bauer 2000

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported. Appears retrospective? But refers to a "campaign for the early diagnosis of cutaneous melanoma (CM) by three dermatologists according to the ABCD system and using ELM evaluation (Stanganelli 1995) **Period of data collection** January 1996 to February 1997 **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?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented skin lesions examined during a campaign for the early diagnosis of cutaneous melanoma (CM) **Setting:** Secondary (general dermatology) From authors' institution **Prior testing:** Not reported "campaign for the early diagnosis of cutaneous melanoma (CM)" **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** No. included: 311 **Sample size (lesions):** No. included: 315 **Participant characteristics:** NR **Lesion characteristics** NR **Thickness/depth:** 14 <0.75 mm, 10 0.75 to 1.5 mm, and 6 >1.5 mm (n=42 melanoma)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm possibly Pattern analysis **Method of diagnosis:** - In person diagnosis **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** - Qualitative - Presence of malignancy; threshold not detailed but ELM parameters included irregular and multi component pigmentary network pattern, peripheral dark network patches, sharp network margin, pseudopods, radial streaming, blue-grey areas, pigment dots (blotches, black dots, brown globules), black dots at periphery, whitish veil, depigmentation and hypopigmented areas, erythema, telangiectasia, comedo-like openings, milia-like cysts, red-blue areas. (ABCD appears to related to naked eye exam) **Diagnosis based on:** Consensus (3 observers) "the evaluation was uniform as the diagnosis was made by consensus amongst the dermatologists (Stanganelli 2005).When they disagreed a fourth dermatologist, an expert in the diagnosis of PSLs, was consulted." Number of examiners 3 **Observer qualifications:** - Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described Any other detail The dermatologists had all been trained in the recognition of PSLs during a training course on the clinical diagnosis of naevi and melanomas **2. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB–MIPS (Biomips engineering, Italy) (ANN classifier) **System details:** DBDermoMIPS (Dell'Eva-Burroni), which consists of a stereomicroscope (magnification ranging from 36 to340), a high resolution 3CCD RGB video cameraand a 486/33 MHz personal computer equippedwith a 300 Mb hard disk and 16 Mb of RAM. Thedigital images of the lesions, shown on a secondRGB video monitor, are framed at 768 3 576 truecolour pixels and saved onto a 230 Mb magnetooptic removable disk. **derivation aspect (study type)** **Lesion characteristics assessed:** - Once the borders of the lesion have been automatically detected, the system evaluates 38 variables (grouped into geometries, colours and Burroni's islands of colours). Suspect areas of the lesion are highlighted by means of a proper algorithm called `Burroni's islands filter' based on a local histogram equalization to produce a new enhanced image in which the darker areas have been enhanced and the shades in the green-blue dominant areas (when present) are more evident. **Additional predictors included:** - No further information used **Method of diagnosis:** - Dermoscopic images - CAD-aided diagnosis (test operator not reported) **Prior/other test data:** - No further information used **CAD output:** - Diagnosis suggested (e.g. melanoma, benign melanocytic nevus) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Disease positive: 42; Disease negative: 273 **TARGET CONDITION (Final diagnoses)** Melanoma (invasive): 30; Melanoma (in situ): 12 Severe dysplasia: 25 'atypical' dysplastic; 212 Benign naevus; 36 nonmelanocytic (SK, thrombosed angioma)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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 After dermoscopy and CAD, all lesions excised and examined histologically Time interval between index test(s): consecutive Time interval to reference standard: 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Binder 1994

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** not reported **Country** Austria **Test set derived** From a sample of 200 PSL, two databases were randomly created for learning and testing purposes. The database was also provided with the histological diagnosis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Images of pigmented skin lesions randomly selected from a pigmented skin lesion image database. **Setting:** Secondary (general dermatology) **Prior testing:** - Selected for excision (no further detail) **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** NR **Sample size (lesions):** 200 included (100 test set) **Participant characteristics:** **Lesion characteristics:** NR
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1.Dermoscopy** (Modified) pattern analysis **Method of diagnosis:** - Dermoscopic images **Prior test data:** No further information used **Diagnostic threshold:** - Qualitative - **Diagnosis based on:** Consensus (2 observers) Number of examiners 3 **Observer qualifications:** - Dermatologist **Experience in practice:** - High experience or 'Expert' **Experience with index test:** - High experience /'Expert' users Any other detail The images were obtained by photographing the PSL on 24x36 mm colour slide film, with oil immersion, using a Wild binocular stereomicroscope M 650 (Wild Heerbrugg AG, Switzerland) at a final magnification of x16 using flashlight illumination. **2. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: name not reported (ANN classifier) **System details:** Computer analysis of stored images captured using digital stereomicroscope **Derivation study (internal validation)** Approach to feature selection An input layer of nodes represented external data (ELM characteristics), an output layer represented the class identity (diagnoses). The network processed data by accepting input patterns (the value 0 for "ELM criterion not present") and the value 1 for "ELM criterion present" into the input layer. During the learning process each input pattern (ELM pattern) had a known output pattern (histological diagnosis as the gold standard of truth) the network was expected to produce. **Lesion characteristics assessed:** – Features analysed as present or absent (pattern analysis): Pigment network, brown globules, radial streaming, pseudopods, black dots, margin, pigmentation, depigmentation **Additional predictors included:** - Unclear **Method of diagnosis:** - dermoscopic images - CAD-based diagnosis **Prior/other test data:** - NR **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Disease positive: 40; Disease negative: 60 **TARGET CONDITION (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 40 Benign naevus: 60 (30 CN, 30 DN)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Binder 1998

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:** Austria **Test set derived:** Computer generated random numbers split data into learning and testing sets; relative proportion of cases in each set was "about 80% and 20%, respectively".
Was a consecutive or random sample of patients enrolled?	Yes
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:** Pigmented skin lesions with available oil immersion dermoscopic images **Setting:** - Secondary (general dermatology) **Prior testing:** - Selected for excision (no further detail) **Setting for prior testing:** - Unspecified **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** NR **Sample size (lesions):** 120 (29 test set) - No. included: 120 **Participant characteristics:** NR **Thickness/depth:** - Other: median 0.72mm (range 0.3 to 1.4mm) for 39 melanomas
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: IBAS 2000 workstation (Zeiss, Oberkochen, Germany) (ANN classifier) **System details:** Digital image analysis workstation attached to Wild binocular stereomicroscope M 650 (Wild Heerbrugg AG, Switzerland). The images were obtained by photographing the PSLs on 24 X 36 mm colour slide film using a Wild binocular stereomicroscope M 650 (Wild Heerbrugg AG, Switzerland) at a final magnification of 16X or 25 X using flashlight illumination. **Derivation study (internal validation)** Approach to feature selection: A three-layer, feed-forward neural-network with 16 input nodes and three hidden nodes was trained with a back propagation algorithm. Each morphological input feature was assigned a numerical value that was scaled so that each input ranged from 0 to 1. The network was trained to yield a value from 0 to 1 in the output nodes. The node yielding the greatest numerical output was then used as the classification result (the winning node). - artificial neural networks Two different ANNs were trained: the first classified between CN and DN as benign lesions versus MM as a malignant lesion in a dichotomized model, whereas the second classified between the three entities of PSL examined, i.e. CN versus DN versus MM. Data for only the first ANN have been extracted **Lesion characteristics assessed:** – Analysis of 16 morphometric parameters from the lesion and the border image: lesion area and perimeter: minimum polar distance, maximum polar distance, aspect ratio, circularity shape factor, variances of grey, number different colours, range different colours. Border features and area: maximum and minimum border width, ratio of border area to lesion area, ratio of border perimeter to lesion perimeter. **Additional predictors included:** - No further information used **Method of diagnosis:** - dermoscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - Dichotomous decision: MM vs. Benign (CN or DN). **Diagnostic threshold:** - The network was trained to yield a value from 0 to 1 in the output nodes. The node yielding the greatest numerical output was then used as the classification result.

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (not further described)* - No. patients/lesions: 29/120 lesions included in test set - Disease positive: 10 - Disease negative: 19 TARGET CONDITION (Final diagnoses) - Melanoma (in situ and invasive, or not reported): 39 in whole dataset; 5 in situ10 MM in test test; number in situ not reported - Other: common naevi and dysplastic naevi: 19
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	Exclusion of lesions from analysis: 6 lesions excluded due to incorrect segmentation results Time interval to reference test: NR; "after photography"
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?	No
Could the patient flow have introduced bias?	High risk

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Blum 2004b

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective Period of data collection 11 Nov 1998 - 2 Mar 2000 Country Germany **Test set derived** For validation of a new CAD procedure the complete collection (837 melanocytic lesions) was divided into two equal random subgroups n1 (training set) and n2(test set).
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 imaged prospectively at the Pigmented Lesion Clinic of the Department of Dermatology, University of Tuebingen, Germany. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Not reported **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** images from mucous membrane areas were excluded **Sample size (patients):** NR **Sample size (lesions):** No. eligible: 837/ No. included: 837 (test set 418) **Participant characteristics:** NR **Lesion characteristics** **Thickness/depth:** - ≤1mm: Median breslow thickness for all melanomas 0.78mm (range 0.10-3.50)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** 7FFM 7 point checklist ABCD Menzies criteria **Method of diagnosis:** - Dermoscopic images. **Prior test data:** No further information used **Diagnostic threshold:** Not reported **Diagnosis based on:** - Single observer Number of examiners 1 **Observer qualifications:** - Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described Any other detail The colour video camera MediCam 400 with Y/C 1signal exit had a 1/4-inch charged-couple device shooting element with 470 000 pixels (picture elements). The focal area for the dermoscopic pictures was defined from 3.5 cm diameter up to infinity. The focal area for the dermoscopic pictures could be positioned continuously by zoom from 3.2 mm to approx. 1.0 cm, corresponding to a x20–70 magnification on a 17-inch monitor. Lesions ≤12 mm diameter could be imaged completely. The glass plate contacting the skin was always moistened with disinfectant spray According to the established dermoscopic classification rules (ABCD rule, Menzies' score, seven-point checklist and seven features for melanoma) the lesions were prospectively classified as benign or malignant melanocytic lesions by the principal investigator(A.B.).27–30 **2.Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD: System name NR (Vision algebra classifiers) **System details:** Computer analysis of stored images captured using digital microscope **Derivation study (internal validation)** The analytical parameters of the digital dermoscopy analysis were reduced by means of a factor analysis. In a second step, the impact of the different parameters was examined by logistic regression analysis. The number of parameters included in the multi-variate analysis was limited in relation to the number of malignant melanomas: in the sample of large, partially imaged lesions it was restricted to six parameters and for small, completely imaged lesions it was limited to three parameters. **Lesion characteristics assessed:** - Analysis of 64 analytical parameters including: a large number of morphological parameters such as margin, geometric parameters (surface area, extent, largest diameter and largest orthogonal diameter), invariant moments, symmetry, colours (red, green, blue and grey value), texture (energy, entropy, correlation, inverse difference moment and inertia), number of regions, focus and difference of the lesion and its convex cover. **Additional predictors included:** - Unclear **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis plus follow up *Histology* Disease positive: 84; Disease negative: 185 *Clinical FU plus histology of suspicious lesions* - unexcised lesions were analysed independently by two of the investigators 2-3 times in 6 months on the basis of dermoscopic criteria. These lesions were classified as benign without any suspicion of malignancy by dermoscopic criteria, and follow-up records for at least 6 months showed no evidence of malignancy. Disease negative: 568 **TARGET CONDITION (Final diagnoses)** Melanoma (invasive): 71; Melanoma (in situ): 9; Lentigo maligna 4 'Benign' diagnoses: 766
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 likely to correctly classify the target condition (disease negative)?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: none reported Time interval to reference test: not reported
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
Could the patient flow have introduced bias?	High risk

Notes

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Boldrick 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** - Case series **Data collection:** - Prospective - Retrospective CAD Period of data collection January 2002 and August 2005 Country USA
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:** Study inclusion criteria Patients >=18years of age **Setting:** - Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** - Clinical and/or dermatoscopic suspicion **Setting for prior testing:** - Unspecified **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** - No. eligible: 83 - No. included: 12 **Sample size (lesions):** - No. eligible: 1000 - No. included: 18 **Participant characteristics:** Participant characteristics
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** CAD-Derm-Other MicroDerm/DANAOS Derm-CAD system: MicroDERM (DANAOS software, ANN classifier) **System details:** Dermoscopy unit with internal camera containing DANAOS analysis system. T The hand unit contained a miniature charged coupled device (3CCD) with a camera with a resolution of 768 3 576 (440,000) pixels. Digital images were stored and compresed using JPEG format. **No derivation aspect (external validation study)** **Lesion characteristics assessed:** – Dermoscopic features of PSLs based on the ABCD rule **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - DANAOS score indicating risk of malignancy **Diagnostic threshold:** - DANAOS score – 2x2 data for more than one diagnostic threshold - Per patient data reported. Threshold selected on basis of similarity to other microDERM studies: DANAOS score of ≥7

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (biopsy)* - No. patients/lesions: 18PSL - Disease positive: 6 MM - Disease negative: 12 TARGET CONDITION (Final diagnoses) - Melanoma (invasive): 3 - Melanoma (in situ): 2 - Lentigo maligna 1 - Severe dysplasia: 1 - Mild/moderate dysplasia: 6 - Benign naevus: 5
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	Exclusion of lesions from analysis: Review team - only 18 lesions had an adequate reference standard; 982 clinically dx benign lesions without a reference standard were not extracted. interval between index test and reference standard: NR
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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Bono 1996

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Unclear **Data collection:** Not reported **Period of data collection** between March 1993 and Oct 1994 **Country** Italy
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
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:** Pigmented skin lesions at the Instituto Nazionale Tumori of Milan. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) Instituto Nazionale Tumori of Milan **Prior testing:** Not reported **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 45 **Sample size (lesions):** No. eligible: 54/ No. included: 43 **Participant characteristics:** NR **Lesion characteristics:** Site - Face/Ears: 3 (6%)/ Trunk: 39 (72%)/ Limbs: 12(22%); 10 MM ≤1mm depth; median size: 10mm (4 to 40mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: Telespectrophotometric System (Linear discriminant classifier) **System details:** Digital camera coupled with an illumination system with interference filters and computer for storage and analysis of multispectral images **No derivation aspect (external validation study)** Described in prior study Marchesini 1995 **Lesion characteristics assessed:** – From each spectral image, three parameters, i.e. mean reflectance, variegation index and lesion area; were derived at the corresponding wavelength **Additional predictors included:** - None reported **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis - Disease positive: 18; Disease negative: 25 *Expert opinion* - Disease negative: 11 **TARGET CONDITION (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 18 Mild/moderate dysplasia: 8 dysplactic nevi Benign naevus: 17 common melanocytic 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?	Unclear
Were the reference standard results likely to correctly classify the target condition (disease negative)?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: only 43 lesions had complete clinical and histological information. 11 lesions not surgically removed had only clinical diagnosis (benign) and were not included in the final accuracy analysis 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?	No
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	

Bono 2002

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** June 1998-March 2000 **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:** Cutaneous pigmented lesions with clinical and/or dermatoscopic features that suggetsed a more or less important suspcion for CM **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** - Location/site of lesion Awkwardly situated lesions eg interdigital space, ears, nose or eyelids. Lesions on scalp excluded due to hair interference with reflectance - lesion size obvious large, thick melanomas **Sample size (patients):** No. included: 298 **Sample size (lesions):** No. included: 313 **Participant characteristics:** Mean age: 40y (10-86y); Male: 122; 41% **Lesion characteristics:** Lesion site: Head/Neck: 3%; Trunk: 61%; Limbs: 36%; Thickness ≤1mm: 70% (46/66); for 55 invasive MM: median thickness 0.64mm, range 0.17-3.24mm. Median diameter: 11mm (3-31mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1.Visual inspection (VI)** No algorithm (Training in the unit is based on ABCD but subjective experience of the clinician used for diagnosis) **Method of diagnosis:** - In person diagnosis **Prior test data:** N/A in person diagnosis **Diagnostic threshold:** Clinical diagnostic criteria based on subjective experience; emphasise lesion colour over dimensions. Diagnosis of suspect CM made when the level of suspicion was 'roughly 50% or more'.ABCD (asymmetry, border, colour, dimension) criteria have been the basis of training at the unit, but is not implemented in diagnosis; preferred emphasis on colour rather than dimensional character **Diagnosis based on:** - Single observer (n=1) **Observer qualifications:** Surgical oncologists **Experience in practice:** - High experience or 'Expert'; over 5 years **2.Dermoscopy** No algorithm **Method of diagnosis:** - In person diagnosis **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** Presence of at least one of the following criterion: radial streaming, pseudopods, grey-blue veil, regression and erythema, whitish veil, black dots at the periphery (if network present), thick irregular network or milky-red background with red dots. Test observers as described for Visual Inspection (above) **Experience with index test:** - Experience (years) over 5 years **Any other detail** Dermatoscopy performed by a hand-held monocular microscope equipped with an achomatic lens permitting a magnification of x10 (Heine Delta 10). **3.Computer Assisted Diagnosis - Spectroscopy based** CAD-Spect-Other Described as; referenced to MSI-CAD system: 'telespectrophotometry' (Linear discriminant classifier) **System details:** The TS consists mainly of a charge-coupled device camera that is provided with a set of 17 interference filters and a personal computer to allow imaging of cutaneous pigmented lesions at selected wavelengths from 420 to 1040nm. The acquired 17 spectral images are stored in the personal computer for offline processing. Intensity levels as well as the dimensions of the image picture elements (pixels) were calibrated according to aset of four reflectance standards and a geometric reference frame, respectively. Details on the system's feautres have been reported elsewhere (Marchini 1995). **No derivation aspect (external validation study)** Derivation described in Marchesini 1995 **Lesion characteristics assessed:** – For each spectral image, five parameters (lesion descriptors) based on ABCD and related to colour and shape of the imaged lesion were evaluated: mean reflectance, variegation index, roundness, border irregularity. **Additional predictors included:** - No further information used **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - None **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone **TARGET CONDITION (Final diagnoses)** Melanoma (invasive): 55; Melanoma (in situ): 11; BCC: 6 'Benign' diagnoses: 241;151 compound naevus, 24 junctional naevus, 12 dermal naevus, 12 lentigo simplex, 10 dysplastic naevus, 8 spindle-cell naevus, 8 sebhorrheic keratosis, 5 blue naevus, 3 spitz naevus, 8 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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 lesions from analysis: none reported Intervals between tests: Appears consecutive but not fully clear
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Burroni 2004

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** - Case control **Data collection:** - Retrospective image selection / Prospective interpretation **Period of data collection** 1999-2003 **Country** Italy Test set derived For the 3 linear classifiers: lesions from each centre (Rome and Siena) were randomly allocated to training and test sets. Linear classifier 1 was constructed from the Rome tarining set and tested on all lesions from Siena; Linear classifier 2 was constructed on the Siena training set and tested on all lesions from Rome; Linear classifier 3 was constructed on training sets from both centres and tested on test sets from both centers. For the K-nearest-neighbour (K-nn) classifiers, a separate trianing set of lesions were selected from the image databases of several institutions that iused the same ELM instrumentation, i.e., IDI-Rome; Siena University Dermatology Clinic; IDI-Capranica; and the Italian Cancer League Clinics of Grosseto, Livorno, Arezzo, Trento, and Siena. It was then tested on all lesions from both centers as described above.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Study inclusion criteria All melanomas undergoing ELM and excision at the two centers (1999-2003) and random sample of surgically removed benign melanocytic lesions, inlcuding 85 histologically atypical nevi. **Setting:** - Secondary (general dermatology) Dept Dermatology, University of Siena - Specialist unit (skin cancer/pigmented lesions clinic) Instituto Dermatopatico dell'Immacolata (IDI), a research hospital for skin diseases in Rome **Prior testing:** - Selected for excision (no further detail) **Setting for prior testing:** - Secondary (general dermatology) Siena - Specialist unit (skin cancer/pigmented lesions clinic) Rome **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** NR **Sample size (lesions):** - No. included: 821 (475 from Siena; 346 from Rome) **Participant characteristics:** Participant characteristics **Thickness/depth:** - Other: 178 (48% of 372 MM) <=0.75mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**3. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB-Mips system (KNN and Linear discrimination classifiers) Classifier selected at random for analysis in review: KNN **System details:** dermoscopy unit, internal steromicroscope, internal DB, pattern analysis system **Derivation study (internal validation)** Linear classifier 3 was constructed on training sets from both centres and tested on test sets from both centers. For the K-nearest-neighbour (K-nn) classifiers, a separate trianing set of lesions were selected from the image databases of several institutions that iused the same ELM instrumentation, i.e., IDI-Rome; Siena University Dermatology Clinic; IDI-Capranica; and the Italian Cancer League Clinics of Grosseto, Livorno, Arezzo, Trento, and Siena. It was then tested on all lesions from both centers as described above. Discriminant analysis used to identify features for which there was a significant (t test) difference between melanomas and non-melanomas and, within these diagnostic classes, no significant difference between centers. Details provided. Selected variables were: geometric variables - area*, variance of contour symmetry*, fractality of borders*color variables - mean skin-lesion gradient*, variance of border gradient*, and border interruptions*. texture variables - mean contrast and entropy* of lesionislands of color variables - dark area*, blue-gray area*, transition region imbalance* **Lesion characteristics assessed:** 38 parameters belonged to four categories (referenced to Soyer 2000): geometries; colors; textures; and islands of color (i.e., color clusters inside the lesion). These were all described in detail. **Additional predictors included:** - No further information used **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - Diagnosis suggested (e.g. melanoma, benign melanocytic nevus) **Diagnostic threshold:** - Threshold not reported The method of receiver operating characteristic curves was used to identify the threshold value for a fixed sensitivity of 95% The prevalence of melanomas among the first 100 closest neighbors was determined, and the lesion was assigned to the melanoma group if the prevalence was higher than a threshold value T 100 . The method of receiver operating characteristic curves was used to identify the T 100 value necessary for a sensitivity of 98%"

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (excision)* - No. patient/lesions: 821 (475 Siena; 346 Rome) - Disease positive: 372 (217 Siena; 155 Rome) - Disease negative: 449 (258 Siena; 191 Rome) TARGET CONDITION (Final diagnoses) - Melanoma (invasive): 302 - Melanoma (in situ): 70 (higher % at Siena than in Rome) - Severe dysplasia: 85 (architectural disorder and melanocytic atypia) - Benign naevus: 364
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	Participant exclusions: none Intervals between tests: 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Cascinelli 1992

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** - Case series **Data collection:** - Prospective - Not reported **Period of data collection** Mar-Dec 1991 **Country** Italy **Test set derived:** Derivation of tets set not described.Training set: 169 lesions; 124 benign and 45 malignant lesions, Test series: 44 images, 33 benign lesions and 12 malignant, of which 10 were melanoma.
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:** Study inclusion criteria Training set: Pigmented cutaneous lesions were referred to Institute for a second opinionTest set: not described **Setting:** - Secondary (general dermatology) Surgical Oncology **Prior testing:** - Describe if other Training set: Referred for second opinion; basis not reportedTest set: not described **Setting for prior testing:** - Unspecified **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** - No. included: Training set: 165, Test set: not described **Sample size (lesions):** - No. included: Training set: 169, Test set: 44 **Participant characteristics:** Participant characteristics **Age (yrs):** - Other Training set: 17 aged <20; 59 aged 21-40; 66 aged 41-60; 23 aged >61Test set: not described **Gender:** - Male: Training set: 70; 42%Test set: not described **Lesion site:** - Head/Neck: Training set: 7.7% - Trunk: Training set: 45.5% - Limbs: Training set: 46.7%
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: Skin View (classifier NR) **System details:** Computerised image analysis system, digital television, videocamera. Connection with the computer is through a digitizing board able to process colour images **Derivation study (internal validation)** **Lesion characteristics assessed:** – Features of ABCD system plus clinical data (anatomic site, months of growth, size, shape, colour, ulceration or regression) – 8 binary indicators generated: shape, clinical data, size, colour, darkness, saturation, border, and texture (all described). **Additional predictors included:** - Predictors included clinical data, which takes into account anamnestic data provided by the clinician (change in size, change in colour) and an objective evaluation made by the clinician (presence of regression, presence of ulceration); **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - none reported **CAD output:** - CAD–based diagnosis **Diagnostic threshold:** - Malignant lesion -≥2 positive indicators

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (excision)* - No. patient/lesions: Test set only: 44 - Disease positive: 12 - Disease negative: 32 TARGET CONDITION (Final diagnoses) - Melanoma (in situ and invasive, or not reported): 10 - BCC: 2 - 'Benign' diagnoses: 32
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: NR Time interval to reference test: 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?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Cristofolini 1997

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Nov 1992 to Sept 1993 **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?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with small and flat common and atypical pigmented skin lesions recruited during a health campaign for the early diagnosis of CM underwent clinical diagnosis, computerized analysis by SVS and subsequent skin biopsy. **Setting:** Secondary (general dermatology) **Prior testing:** No prior testing **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** None reported **Sample size (patients):** 176 included **Sample size (lesions):** 176 included **Participant characteristics:** NR **Lesion characteristics:** NR
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: Skin View (classifier NR) **System details:** Computerised image analysis system, digital television, videocamera. Connection with the computer is through a digitizing board able to process colour images **No derivation aspect (external validation)** **Lesion characteristics assessed:** – Features of ABCD system plus clinical data (anatomic site, months of growth, size, shape, colour, ulceration or regression) : 1 shape (asymmetry); 2 clinical data (changes through time, regression, ulceration); 3 size (mm); 4 colour (distribution of hue); 5 darkness (percent of black mixed with the hue); 6 saturation (percent of white mixed with the hue); 7 border (sharpness of transition between lesion and healthy skin; 8 texture. **Additional predictors included:** - Clinical data **Method of diagnosis:** - dermoscopy images - CAD-based diagnosis **Prior/other test data:** - none reported **CAD output:** - CAD–based diagnosis **Diagnostic threshold:** - ≥2 of 8 binary (on/off) indicators indicates malignancy

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone - Disease positive: 35 - Disease negative: 141 **TARGET CONDITION (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 35 Other: 141 melanocytic 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?	Unclear
Were the reference standard results likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: 'subsequent skin biopsy'
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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Dreiseitl 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Test set: Feb-Nov 2004 **Country** Austria **Test set derived** Study focuses on test set but gives detail of separate study in which classifier was trained
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:** Patients presenting at pigmented skin lesion clinic at Dept Dermatology which serves as a secondary and tertiary referral centre **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) The pigmented skin lesion unit of the Department of Dermatology at the Medical University of Vienna serves as a secondary and tertiary referral center. **Prior testing:** Not reported **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 511; No. included: 458 with complete information **Sample size (lesions):** No. eligible: 3827; No. included: 3021 **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?	No
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** No algorithm **Method of diagnosis:** In person diagnosis **Prior test data:** Clinical examination and/or case notes **Diagnostic threshold:** Not reported **Diagnosis based on:** Single observer (n=1) **Observer qualifications:** Expert dermatologist **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' users **3. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: Image J (NIH, Bethesda, USA) (ANN classifier) **System details:** image analysis coupled with dermoscope MoleMax II **No derivation aspect (external validation)** Described in prior study Hable 2004 (PhD thesis) **Lesion characteristics assessed:** 29 Features analysed from 38 extracted features describing shape, form and colour. Approach to feature selection Prior study: A stepwise feature selection method used to identify 29 features relevant for the classification process. **Additional predictors included:** - No further information used **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis – CAD–aided diagnosis **Test observers:** - Single observer Number of examiners 6 **Observer qualifications:** - Other (describe) The educational training of the 6 participating physicians ranged from no training in dermatology to 4 years training in dermatology. **Experience in practice:** - Mixed experience (low and high experience combined) educational training of the 6 participating physicians ranged from no training in dermatology to 4 years training in dermatology. **Experience with index test:** - Mixed experience (low and high experience combined) No physician was specifically trained in dermatoscopy. **Prior/other test data:** - Clinical examination and/or case notes **CAD output:** - 2 outputs: 1) Visual rendering of analysis showing coloured areas. 2) Excision vs. no excision decision (system considers the green zone of the scale as benign (0 to 0.1), the yellow zone suspicious (0.1 to 0.4), and the red zone malignant (0.4 to 1)). **Diagnostic threshold:** - scale 0–1: 0–0.1 = benign, 0.1–4 = suspicious, >0.4 = malignant

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	No
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis plus follow up *Histology (excision);* No. patient/lesions: Not reported *Clinical FU plus histology of suspicious lesions* Length of FU: 6 months; No. patients: Not reported **TARGET CONDITION (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 27 patients; 31 lesions 'Benign' diagnoses: 431 patients; 2990 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?	Yes
Were the reference standard results likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: 806 lesions (53 patients) with inadequate follow-up Intervals between tests: not reported
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
Could the patient flow have introduced bias?	High risk

Notes

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Ferris 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Unclear Some dermoscopic images were collected prospectively and some were obtained from collection of existing images; selection process not described. **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** not reported **Country** USA **Test set derived** Some dermoscopic images used to train the classifier were obtained from publicly available or purchased image libraries, these were not included in the reader study or used to test the performance of the classifier. The image set was randomly divided into 2 by diagnosis, with half used for training and half used for testing, with the exception that all high-grade dysplastic nevi were exclusively assigned to the training set to increase the representation of dermoscopic features that could be present in melanoma. Results are presented only for the test set.
Was a consecutive or random sample of patients enrolled?	No
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:** Dermoscopic images of skin lesions excised on the basis of clinical suspicion of malignancy, with available histologic diagnoses **Setting:** Secondary (general dermatology) **Prior testing:** Clinical and/or dermatoscopic suspicion; Selected for excision (no further detail) **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** high-grade dysplastic nevi were not included in the test set **Sample size (patients):** No. eligible: not reported; No. included: not reported **Sample size (lesions):** No. eligible: 473 (includes 273 randomised to training set and 27 non-biopsied lesions); No. included: CAD- Derm- test set 173 lesions; Dermscopy- 65 lesions **Participant characteristics:** None reported **Lesion characteristics:** Test set: mean lesion thickness 0.76 mm, median 0.5 mm, range 0.2-2.98 mm); Reader study: mean 0.93 mm, median 0.74 mm, range 0.2 to 2.98 mm.
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: name NR (Digital forest classifier) **System details:** Computer analysis of stored images captured using different dermoscopy/camera combinations **Derivation study (internal validation)** **Lesion characteristics assessed:** –54 features analysed, such as border irregularity, eccentricity, length of major and minor axes, and colour histogram properties. Variations of some features described in Zortea et al (2014) were included. **Additional predictors included:** - unclear **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - Severity score (the fraction of decision trees (n=1000) in which the path ends in ‘‘malignant’’. Lesion classified as malignant if its image traced a path to a malignant node in at least 40% of the trees) **Diagnostic threshold:** - 0.4; a lesion was classified as malignant if its image traced a path to a malignant node in at least 40% of the decision trees.

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Details: All lesions were biopsied based on clinical suspicion of malignancy. All histologic diagnoses were rendered by at least 1board-certified dermatopathologist and were used as the reference standard for diagnosis Disease positive: Derm 25MM; CAD 39MM / Disease negative: Derm=40; CAD= 134 **Target condition (Final diagnoses)** Melanoma (invasive): Derm = 15; CAD = 25; Melanoma (in situ): Derm = 10; CAD = 14; BCC: CAD= 11; cSCC: CAD=3 Mild/moderate dysplasia: CAD = 47; Derm= 16. Sebhorrheic keratosis: CAD=11; Derm=4. Benign naevus: CAD=42; Derm= 14.Other: CAD=10 lentigines, 5 blue nevi, 2 Spitz nevi, 2 angiomas, and 1 dermatofibroma; Derm = 2 blue nevi, 4 lentigines
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	1. Excluded participants: none reported 2. Time interval to reference test: 'Dermoscopic images of skin lesions were collected before biopsy'
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Friedman 2008

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective image selection / Prospective interpretation Period of data collection NR; lesions selected in July 2005 Country US **Test set derived** MelaFind data randomly split into training and test sets however Melafind has previously been evaluated, the only difference here being that only small lesions were included. Would argue that full dataset can reasonably be included here rather than test set only
Was a consecutive or random sample of patients enrolled?	No
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	**!nclusion criteria:** A database of images of pigmented skin lesions <=6mm was used to sample images of melanoma and non melanoma lesions; high-grade dysplastic nevi were excluded. **Setting:** A digital dermoscopic database acquired by Electro-Optical Sciences Inc for the development and testing of MelaFind; 26 clinical sites have contributed **Prior testing:** Selected for excision (no further detail) All lesions excised or underwent shave biopsy **Setting for prior testing:** Not reported **Exclusion criteria:** High-grade dysplastic nevi were excludedPreviously biopsied, ulcerated, or bleeding lesions also excluded, as were those on mucosal surfaces and lesions that contained foreign matter (eg, tattoos). **Sample size (patients):** No. included: 94 **Sample size (lesions):** No. eligible: 1977; No. included: 99 **Participant characteristics:** None reported **Lesion characteristics** 21 invasive MM: median thickness 0.32mm (0.10, 1.40mm). Lesion size: Range: 2mm to 22mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** No algorithm **Method of diagnosis:** Dermoscopic images **Prior test data:** Clinical examination and/or case notes sex, age, and lesion location **Diagnostic threshold:** Not reported. 2x2 reported for: diagnostic sensitivity and specificity, i.e melanoma vs not melanoma and biopsy sensitivity and specificity, i.e excise lesion vs not excise. Each reader had to answer the question: “Is this lesion a melanoma?” and “Would you biopsy/excise this lesion?” with a reason for biopsy. If readers indicated that they would biopsy the lesion because they were sure it was melanoma or to rule out melanoma, then the case was considered true positive (TP) **Diagnosis based on:** Average; mean and median reported (n=10) **Observer qualifications:** 9 dermatologists; 1 nurse practitioner specializing in dermatology **Experience in practice:** High experience or ‘Expert’ **Experience with index test:** High experience /‘Expert’ users **2. Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: MelaFind (EO Sciences, USA) (6 constrained linear classifiers) **System details:** Multispectral imaging system with integrated image analysis software; device takes images in vivo **External validation study** Derivation described in prior study Gutkowicz-Krusin 1997; Elbaum 2001; Gutkowicz-Krusin 2000. **Lesion characteristics assessed:** – NR **Additional predictors included:** - None reported **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - Binary output: excise or follow–up **Diagnostic threshold:** A lesion is recommended for biopsy to rule out melanoma only if all scores are above the threshold value. - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Disease positive: 49; Disease negative: 50 **Target condition (Final diagnoses)** Melanoma (invasive): 21; Melanoma (in situ): 28; BCC: 2 Mild/moderate dysplasia: 32 low grade dysplastic; Sebhorrheic keratosis: 2; 14 other benign
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: none reported Interval between tests: 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Garcia Uribe 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** - Case series **Data collection:** - Prospective **Period of data collection** not reported **Country** USA Test set derived Of the 407 pigmented skin lesions, 271 were used for the training sets of ANN classifiers (Tables 1 and 2) to separate malignant melanoma from varieties of nevi. The remaining 136 data sets were used to test the efficacy of the ANN classifiers. The nonpigmented lesions consisted of BCCs, SCCs, benign actinic keratoses, and seborrheic keratoses. Among the 266 nonpigmented lesions, 177 were used to train the ANN classifier and the remaining 89 were used for testing
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:** Study inclusion criteria not reported **Setting:** - Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** - Not reported **Setting for prior testing:** - Unspecified **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** NR **Sample size (lesions):** 136 included **Participant characteristics:** - Pigmented (%): 407 pigmented lesions (60%) - Non-pigmented (%): 266 nonpigmented (40%)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** DRS-CAD system: OIDRS (ANN classifier) **System details:** Light probe coupled to imaging spectrograph, camera, and computer to store images. The system was built onto a portable cart; it was easily moved to the patient examination rooms. To target both small and large skin lesions, we constructed an optical fi ber probe using micromachining technology. The probe consisted of 3 source fibers and 2 linear arrays of 12 collection fibers within an area of 2. The collection fibers were coupled to an imaging spectrograph that generated an optical spectrum from 455 to 765 nm for the collection channel. A charge-coupled device (CCD) camera collected the spectral images, which were stored on a com- puter for data analysis. The data collection took less than 5 minutes, and it did not interfere with the standard health care provided to the patients **Derivation study (internal validation)** A physician identified the lesion(s) to be measured before the scheduled biopsy. To average out the effect of structural anisotropy of the skin tissue, the measurement of each lesion was repeated 4 times to obtain images from different orientations. To provide self-references, the same measurements were also repeated on the neighboring healthy skin tissues. The anisotropy is defined as the variation of the measurements when conducted in different directions. After the measurements were completed, a biopsy was carried out for each skin lesion and submitted for histopathologic analysis. **Lesion characteristics assessed:** – NR **Additional predictors included:** - Unclear **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - Diagnostic category (e.g. CN, MM, DN, BCC, cSCC) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone TARGET CONDITION (Final diagnoses) - Melanoma (in situ and invasive, or not reported): 10 - Severe dysplasia: 15 - Mild/moderate dysplasia: 83 - Benign naevus: common nevi 28
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: Biopsy was done after the CAD-OIDRS measurements were taken
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?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Gilmore 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** 2003-2008 **Country** Austria **Test set derived:** Not reported. Training set: 65 melanomas and 65 dysplastic naevi, Test set:36 melanomas and 33 dysplastic naevi.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Polarised dermoscopic images of atypical melanocytic lesions were obtained from the Department of Dermatology at the Medical University of Graz in Austria; describes database as a "database may be considered a random, but representative, cohort" but does not describe method of selection **Setting:** Secondary (general dermatology) **Prior testing:** Clinical and/or dermatoscopic suspicion atypical melanocytic lesions. **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** No. included: NR **Sample size (lesions):** No. included: 199: Derivation set n=130 Test set n= 69 **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?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Dermoscopy** No algorithm; dermoscopic method of diagnosis not reported **Method of diagnosis:** Dermoscopic images **Prior test data:** No further information used **Diagnostic threshold:** Not reported - subjective impression; excise or not **Diagnosis based on:** Single observer (n=1) **Observer qualifications:** Dermatologist **Experience in practice:** High experience or 'Expert' **Experience with index test:** High experience /'Expert' Any other detail images captured using a DermLite FOTO lens (3Gen LLC; Dana Point, CA, USA) coupled to a digital camera (Nikon CoolPix4500; Nikon Corporation, Tokyo, Japan) without flash using the camera's auto setting **Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: name NR (SVM classifier) **System details:** Computer analysis of stored images captured using digital microscope **Derivation study (internal validation)** "Feature data from the training set were first normalised to zeromean and unit variance. We then reduced the dimensionality of this set by taking the first three principal components, corresponding to the points to the left and including the infection point of the hyperbolic eigenvalue curve." Training set (p832): "At each step, corresponding to a unique parameter regime, we took 60 random data points (30 of each class) from our 130 training data points to derive a model, and then we tested that model on 30 randomly chosen data points from the same data set. To assess the effectiveness of the model in classification, we performed a tenfold cross-vali- dation. Because we are using only a subset of the total training set to derive each model Ð this is loosely analo- gous to the subset selection procedure known as chunking - finding the optimal solution is computationally fast. Each tenfold cross-validation took approximately 200 s using Mathematica 6.0 on a Macintosh G4 with 4MB of RAM." **Lesion characteristics assessed:** – 14 features investigated: 1. Asymmetry 1 (mean int.)*2. Asymmetry 2 (mean int.) *3. Asymmetry 3 (variance red) *4. Asymmetry 4 (variance red) *5. Variance red *6. Variance green*7. Variance blue *8. Mean red *9. Mean green *10. Mean blue*11. Mean intensity *12. Range red intensity*13. Range green intensity*14. Range blue intensity* **Additional predictors included:** - No further information used **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - unclear **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	No
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Details: ""All lesions were excised and examined microscopically by expert dermatopathologists using standard histopathologic diagnostic criteria" Disease positive: 36=test set and 65=derivation set Disease negative: 33=test set and 65=derivation set **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 36 test set and 65 derivation set Dysplastic naevi 33 test set and 65 derivation set
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: none reported Intervals between tests: 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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Glud 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection** Jan to Apr 2007 **Country** Denmark
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:** Patients referred for excision biopsy of pigmented lesions where the diagnosis of melanoma could not be excluded on clinical investigation **Setting:** Secondary (other); Dept Plastic Surgery and Burn Unit **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Secondary (not further specified); Department of Plastic Surgery and Burn Unit **Exclusion criteria:** None reported **Sample size (patients):** No. included: 65 **Sample size (lesions):** No. included: 83 **Participant characteristics:** Median age 47 yrs (18 to 90y); Male - 29; 45% **Lesion characteristics:** melanoma thickness 0.29 mm to 2.18mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm **Method of diagnosis:** Dermoscopic images **Prior test data:** No further information used **Diagnostic threshold:** Not reported -"dermoscopic images were examined by an experienced dermatologist" **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 Any other detail The dermoscopic and SIAgraphic images were obtained by SIAscope II (Amon Clinica, Cambridge, UK) and stored using the proprietary Dermetrics software (Astron Clinica). **2. Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SIAscope II (**Astron Clinica, UK**)(classifier NR) **System details:** Skin lesion is interrogated with light of different wavelengths and the reflection spectra are analyzed by proprietary algorithms showing distribution, position and quantity of melanin, blood , and collagen within the papillary dermis (the SIAgraphs). **No derivation aspect (external validation)** Derivation described in prior study – See Moncrieff 2002, Govindan 2007 **Lesion characteristics assessed:** – Analysis of dermal melanin, erythematous blush, lesion asymmetry, collagen 'holes', blood commas, or irregularities in the collagen **Additional predictors included:** - None **Method of diagnosis:** - Spectroscopic images, SIAgraphic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - Binary (based on Australian Scoring System): 'strong chance of melanoma' or 'low risk of melanoma' **Diagnostic threshold:** Australian Scoring System - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone (excision biopsy) Details: Breslow thickness and Clark level were determined by standard histopathologic examination. Tumor staging was performed as described by Balch et al according to the 2001 melanoma staging system. Disease positive: 12; Disease negative: 71 **Target condition (Final diagnoses)** Melanoma (invasive): 7; Melanoma (in situ): 5; 1 melanoma metastasis (incl as benign) Sebhorrheic keratosis: 1; Benign naevus: 57; 'Benign' diagnoses: bowens 1 haemangioma 1 lentigo simplex 2 epidermal naevi 2 DF 6
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	Participant excluded from analysis: none reported Interval between tests: not reported Interval to reference standard: Images taken prior to biopsy
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Gutkowicz Krusin 1997

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** - Unclear **Data collection:** - Retrospective image selection / Prospective interpretation Period of data collection NR Country US (from authors' institution) Test set derived NR. The "classifier was then tested blindly on an independentset of 28 images of melanocytic lesions on slides provided by Dr. A. w. Kopf."
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
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:** Study inclusion criteria Lesions suspected of early melanoma or atypical melanocytic nevus **Setting:** - Secondary (general dermatology) From authors' institution **Prior testing:** - Selected for excision (no further detail) No details; all lesions excised **Setting for prior testing:** - Unspecified **Exclusion criteria:** Study exclusion criteria: None reported **Sample size (patients):** - No. included: NR **Sample size (lesions):** - No. included: 104; 76 training; 28 test set **Participant characteristics:** Participant characteristics
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: MelaFind precurser (Multiparametric linear classifier) **System details:** Digital camera and illumination assembly coupled to a computer, with separate image analysis **Derivation study (internal validation)** **Lesion characteristics assessed:** – Lesion asymmetry, border, gradient, centroid, texture, colour **Additional predictors included:** - No further information used **Method of diagnosis:** - spectroscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (not further described)* - No. patients/lesions: 28 in test set - Disease positive: 5 - Disease negative: 23 TARGET CONDITION (Final diagnoses) - Melanoma (in situ and invasive, or not reported): 5 - Benign naevus: 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?	Yes
Were the reference standard results likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: NR Time interval to reference test: NR
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Hauschild 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control; all lesions in this study were imaged and analysed by MelaFind in a previous study (Monheit 2011). **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** NR **Country** US-data from Monheit 2011 study
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Subset of pigmented skin lesions evaluated in the Monheit et al trial; melanoma and non-melanoma randomly selected; none were ulcerated, non-pigmented, or located on excluded anatomic sites. **Setting:** Lesions sampled from Monheit trial "Seven clinical sites with 23 investigators participated in this trial. Three sites were academic institutions (University of Pittsburgh, Duke University, and Northwestern University), and 4 sites were dermatologic practices highly experienced in managing PLs." **Prior testing:** - Selected for excision (no further detail) **Setting for prior testing:** Not reported **Exclusion criteria:** ulcerated, non-pigmented, or located on excluded anatomic sites **Sample size (patients):** No. included: 130 **Sample size (lesions):** No. eligible: 1632 lesions in Monheit trial; No. included: 130 **Participant characteristics:** None reported **Lesion characteristics:** site - Head/Neck: 22.3%; - Trunk: 41.5%; - Upper limbs/shoulder: 20%; - Lower limbs/hip: 16.2%. Median thickness (melanomas) 0.39mm (range 0.12 to 1.2mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm **Method of diagnosis:** Clinical photographs and dermoscopic images **Prior test data:** Clinical examination and/or case notes. Lesion images consisted of a clinical overview at 53 cm/21 inches, a clinical close-up at 20 cm/8 inches, and a dermatoscopic image. Clinical exam information consisted of 24 items regarding patient demographics and risk factors for melanoma such as: personal or family history of melanoma, number of atypical nevi, Fitzpatrick skin type, number of severe sunburns before and after age 20, etc. **Diagnostic threshold:** Not reported. Responses to the questions regarding whether or not the dermatologist would biopsy the lesion and reason for biopsy were used to determine dermatologist sensitivity and specificity **Diagnosis based on:** Average (Arm 1: 101 board certified dermatologists; Arm 2 (MelaFind): further 101 board certified dermatologists; Arm 3: 9 Pigmented Skin Lesion (PSL)) **Observer qualifications:** Dermatologist (Experts (Arm 3) prospectively identified by the Principal Investigator based on field standing prior to participant recruitment) **Experience in practice:** High experience or 'Expert'; >90% had more than 10 years experience in practice **Experience with index test:** High experience /'Expert' users. All except 6 were trained in dermoscopy use; 155/202 always or almost always used dermoscopy for PSLs **2. Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: MelaFind (classifier NR) **System details:** Multispectral imaging system with integrated image analysis software; device takes images in vivo **No derivation aspect (reader study)** **Lesion characteristics assessed:** – NR **Additional predictors included:** - None reported **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - Clinical examination and/or case notes Study presents system based diagnosis plus MelaFind combined with dermatologist decision which was also infomred by clinical exam info **CAD output:** - Binary output: (1) positive, (lesion should be considered for biopsy to rule out melanoma); and (2) negative (lesion should be considered for later evaluation) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone *Histology (not further described).* Disease positive: 65; Disease negative: 65 **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 65 'Benign' diagnoses: 65
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	participants excluded from analysis: none Time interval between index tests: unclear Time interval to reference standard: unclear
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Maglogiannis 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** case-control **Data collection:** retrospective **Period of data collection:** Not reported **Country:** Greece Random division of 208 lesions into train and test sets (equal numbers)
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** lesions excised (no further details) **Setting: Specialist -** Department of Plastic Surgery and Dermatology (Athens) **Prior testing:** lesions excised (no further details) **Setting for prior testing:** Not specified **Exclusion criteria:** none reported **Sample size (patients):** NR **Sample size (lesions):** 208 lesions, **Participant characteristics:** Participant characteristics
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: name NR (SVM polykernel c=5 classifier, selected at random for this review) **System details:** Computer analysis of digital dermoscopy images captured using the Molemax II dermatoscope **Derivation study (internal validation)** Five classifiers trained: Multilayer perceptron, kNN, Random forest, SVM polykernel c=5, SVM PUK kernel. **Lesion characteristics assessed:** – features corresponding to the number, size and asymmetry of dots: (a)Number of dots, (b) Total Number of pixels in dots, (c) mean number of pixels in dots, (d) variance of num. pixels in dots ,(e) fraction of lesion area occupied by dark dots. Asymmetry: radial, angular, primary axis. **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone Disease positive: 50 MM; Disease negative: 54 TARGET CONDITION (Final diagnoses) Melanoma (in situ and invasive, or not reported): 50 'Benign' diagnoses (not further specified): 54
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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 reported Time interval to reference test: No details 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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Malvehy 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective; dermoscopic images assessed remotely from the patient **Period of data collection:** March 2010 and November 2011 **Country:** conducted at five American and 17 European investigational sites (Sweden, Germany, Austria, Hungary, U.K. and Spain);
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 patients with skin lesions selected for total excision to rule out melanoma; dermatologists were encouraged to enrol a mix of lesions with an even distribution of low-, medium and high-risk lesions. **Setting:** Secondary; authors institutions primarily listed as Dept Dermatology with one "Dermatology Clinical Research Center" **Prior testing:** Selected for excision **Exclusion criteria:** lesions < 2 mm or > 20 mm and those located: on acral skin, e.g. sole or palm; areas of scars, crusts, psoriasis, eczema or similar skin conditions; hair-covered areas, e.g. scalp, beards, moustaches or whiskers; genitalia; in an area that has been previously biopsied or subjected to any kind of surgical intervention or trauma; mucosal surfaces; with foreign matter, e.g. tattoo or splinter; acute sunburn; or skin surface not measurable, e.g. lesion on a stalk; surface not accessible, e.g. inside ears, under nails or not intact (measurement area), **Sample size (patients):** No. eligible: 1951; No. included: 1611 **Sample size (lesions):** No. eligible: 2416; No. included: 1943 **Participant characteristics:** For Nevisense sample: median age: 48y (range 18 to 91); male 47.5%; 97.5% of white ethnicity. Fitzpatrick skin types: I (7.3%); II (48.6%); III (37%); IV (9.8%); V (1.4%); VI (0.1%) **Lesion characteristics:** median Breslow thickness of 0.57 mm (153 invasive melanomas);
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** EIS-CAD system: Nevisense (SciBase III, Sweden) (SVM classifier) **System details:** Electrical Impedance spectroscopy imaging system with integrated image analysis software. The system measures the overall electrical resistance and reactance at 35 different frequencies **derivation aspect (study type)** **Lesion characteristics assessed:** – NR **Additional predictors included:** - None reported **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - None considered by CAD for diagnosis **CAD output:** - The system computes both a score (0–10) and a dichotomous output (EIS negative/positive) at a fixed cut-off. **Diagnostic threshold:** - Score: The fixed threshold is set at 4, i.e. scores < 4 are EIS negative and scores of ≥ 4 are EIS positive. – Prior study (Mohr 2013) used dichotomous outcome but recommended score output

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Visual inspection

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Lesions were excised and underwent usual histopathology at investigational site. A further histopathological evaluation was undertaken for study purposes by a panel of three experienced histopathologists who evaluated each lesion independently; blinded from the investigational site's original histopathology diagnosis. If they agreed, the diagnosis was considered as the histopathological gold standard (HGS); if there was significant disagreement regarding malignancy the slides were submitted to two additional experts whose diagnosis was then chosen as the HGS if they reached agreement. In case of disagreement by the two additional reviewers, the corresponding lesion was excluded from the efficacy analysis. Disease positive: 478; Disease negative: 1440 **Target condition (Final diagnoses)** 153 invasive melanomas, 112 melanoma in situ, 48 BCC, 1 invasive cSCC; 1 Merkel cell carcinoma 157 severely dysplastic, 988 mild to moderate dysplasia, 352 benign nevi, 5 spitz nevi, 51 seborrheic keratosis, 6 cSCC in situ; 8 AK; 61 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Participant exclusions:** 473 excluded from Nevisense analysis; all reasons listed; primary reason was investigator oversight or the inability to render a final histopathological diagnosis; 74 exclusions were device-related (60 with inadequate reference measurement quality and 14 to device failure). **Index test to reference standard interval:** Appears consecutive; prospective recruitment with imaging and then "eligible and evaluable lesions were excised and subjected to the investigational site's histopathology evaluation and managed accordingly." "A postprocedure follow-up either by a telephone call or at a participant's visit to the investigational site was conducted at 7 +/- 3 days after the Nevisense evaluation, at which time the patient was evaluated for any adverse events."
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?	No
Could the patient flow have introduced bias?	High risk

Notes

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Menzies 1996

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Unclear Describes including melanomas and randomly selected clinically atypical nonmelanoma lesions **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** NR **Country** Australia **Test set derived** NR; describes 'division' into a training set and a test set.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
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:** Pigmented skin lesions from the Sydney Melanoma Unit with dermoscopic images and histological diagnoses; melanomas and randomly selected clinically atypical nonmelanoma lesions were included. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) From authors' institution **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** unequivocal nonmelanoma excluded **Sample size (patients):** No. included: NR **Sample size (lesions):** No. included: 385 (training set 221, test set 164) **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?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** Menzies criteria **Method of diagnosis:** Dermoscopic images **Prior test data:** No further information used **Diagnostic threshold:** Two negative features of melanoma (i.e. cannot be found).Point and axial symmetry of pigmentation Presence of only a single colourNine positive features of melanoma were used (at least one feature found). Multiple (5-6) colors Blue-white veil Multiple brown dots Multiple blue/gray Peripheral black dots or globules A broadened network Pseudopods Radial streaming Scarlike **Diagnosis based on:** Unclear (n=NR) **Observer qualifications:** Not reported likely dermatologists **Experience in practice:** Not described **Experience with index test:** Not described **2. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: Name not reported (CART classifier) **System details:** Computer analysis of stored images captured using digital microscope. Pigmented skin lesions were photographed in vivo by means of immersion oil and a camera (Dermaphot, Heine Ltd). The surface microscopic images were studied on a viewer (Kodak Ektagraphic Viewer, Model 575AF, Eastman Kodak Co, Rochester, NY). **Derivation study (Internal validation)** **Lesion characteristics assessed:** Approach to feature selection A classification and regression tree constructed on the training set produced a 7-node tree Negative Features: Point and axial symmetry of pigmentation Presence of only a single colour. Positive Features: Blue-white, veil, Multiple brown dots, Pseudopods, Radial streaming, Scarlike depigmentatlon, Peripheral black dots/globules, Multiple (5-6) colors, Multiple blue/gray dots, Broadened network **Additional predictors included:** - Unclear **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - NR **Diagnostic threshold:** - Presence of indicative features (Melanoma = 0/2 morphologically negative features AND at least 1/9 positive morphological features)

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone *Histology (not further described);* Disease positive: 107; Disease negative: 278 **Target condition (Final diagnoses)** Melanoma (invasive): 107; BCC: 18 ?Ephilis lentigo 17; Sebhorrheic keratosis: 23; Benign acquired nevi - 58; Dysplastic nevi - 105; Blue nevi 11; Spiz nevi 6; spindle cell nevus 2; dermatofibroma 2; hemangioma 13; solar keratosis 9; other 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** none 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?	No
Could the patient flow have introduced bias?	High risk

Notes

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Menzies 2005

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** June 1998 to September 2003 **Country** Multicentre (Australia, US, Germany) **Test set derived:** study population divided at ratio 2:1 for training:test sets; divison randomised but stratified by diagnostic category and Breslow.
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:** Pigmented skin lesions imaged using SolarScan at 9 different clinical centers including specialist referral centers and private skin cancer clinics; only the 78 lesions from the Sydney Melanoma Unit included in the VI/Dermoscopy evaluation. In all but 1 clinic site, the sole indication for imaging was that the pigmented lesion was to be excised, usually because of a clinical suspicion **Setting:** Private skin cancer clinics in Australia staffed by general practitioners **Prior testing:** In 8/9 clinics, included lesions were to be excised, usually because of a clinical suspicion. "However, clinics were inconsistent in imaging excised lesions from their own practices, with some clinics obtaining images of lesions with a predominately high probability of melanoma." **Setting for prior testing:** Private care **Exclusion criteria:** awkwardly situated lesions (eg, eyelids, some parts of the pinna, some genital sites, and perianal and mucosal surfaces); acral lesions; non-pigmented pure amelanotic lesions (based on dermoscopy imaging); benign non melanocytic lesions excluded from one classifier. Poor quality index test image - lesions outside the field of view (24x18 mm), contamination of calibration surfaces, or excess artifacts (hair, air bubbles, or movement artifacts). Ulcerated lesions, or diagnosed as pigmented basal cell carcinoma, pigmented Bowen disease, or squamous cell carcinoma **Sample size (patients):** No. included: NR **Sample size (lesions):** No. eligible: 2430/ No. included: 1644 training; 786 test set **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?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Visual inspection (VI)** **Method of diagnosis:** **Prior test data:** **Diagnostic threshold:** **Diagnosis based on:** Number of examiners **Observer qualifications:** **Experience in practice:** **Experience with index test:** **2. Dermoscopy** No algorithm **Method of diagnosis:** Dermoscopic images **Prior test data:** Clinical examination and/or case notes clinical photographs and patient histories **Diagnostic threshold:** Not reported. No details on lesion characteristics used; data can be extracted at two thresholds:- correct diagnosis of melanoma (in situ or invasive) - excise decision **Diagnosis based on:** Average (n=13) **Observer qualifications:** GP 3; Dermatology registrar 3; Dermatologist 4 (one local practising dermatologists (Sydney), plus 3 international dermoscopy experts who headed pigmented lesion clinics) **Experience in practice:** Mixed experience (low and high experience combined) **Experience with index test:** Mixed experience Any other detail had clinical and dermoscopy photographic images (taken with a Heine Dermaphot camera, Heine Ltd, Herrsching, Germany) **3. Computer Assisted Diagnosis – Dermoscopy based** Derm-CAD system: SolarScan (Polartechnics Lts, Australia) (Linear discriminant analysis classifier) **System details:** Dermoscopy video unit with internal algorithm for image analysis. The algorithm model used by SolarScan is an optimized set offixed discriminant variables with associated weighting factors and relationships features (Australian Patent application No.20022308395 and Australian Patent No. 2003905998). **Derivation study (internal validation)** Described in prior study Menzies 2001, referenced. Various properties of color, pattern, and geometry were extracted from the segmented lesion images.The patient history features (see below) and 103 image analysis variables, in combination with the diagnostic weights (based on a linear representation (range, 0.25-20) of correctly classifying the lesion as benign or melanoma), were used in the training set to model 2 diagnostic algorithms. **Lesion characteristics assessed:** 103 automated image analysis variables extracted: consisting of various properties of colour, pattern, and geometry. Number analysed not reported. **Additional predictors included:** - Predictors included whether the lesion had, within the previous 2 years, bled without being scratched, changed in colour or pattern, or increased in size **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - Probability of melanoma, with cut–off (not provided) for benign vs. melanoma **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis plus follow up *Histology (not further described)*: 71% of total dataset (n = 1725), presumably including all disease positive *Clinical FU plus histology of suspicious lesions*; Length of FU: 3 mo. 26% of full dataset (n = 632) *Expert opinion*. 3% of image set were diagnosed clinically but not excised **Target condition (Final diagnoses).** All numbers are for complete dataset Melanoma (invasive): 238; Melanoma (in situ): 144 Benign naevus: 1835 benign melanocytic; Other: 213 benign nonmelanocytic, incl 140 SK
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 likely to correctly classify the target condition (disease negative)?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **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?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	High risk

Notes

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Mohr 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective; dermoscopic images assessed remotely from the patient **Period of data collection:** January 2009 to November 2010* **Country:** conducted at 19 private and/or academic dermatological centres located in Germany, Hungary, Sweden, Switzerland, and U.K. * some overlap in study population with Malvehy 2014 possible (no author reply), as ascertained by similar recruitment centres and overlapping periods of data collection. **Test set derived:** Data randomised into train set (approximately 40% of data) and test set (approximately 60%).
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:** Adults of any ethnic group, aged at least 18, with one or more primary skin lesion(s), at least 2 mm in diameter, located on normal uninflamed skin and requiring full excision for histopathological analysis. **Setting:** Secondary; authors institutions primarily listed as Dept Dermatology with one "Division of Imaging and Technology" **Prior testing:** Selected for excision **Exclusion criteria:** > 8 lesions per patient; metastatic or recurrent; patients with lesions under finger and toe nails, in sites where the electrode could not reach, e.g. between toes, those lesions with abnormal reference areas (usually inflammatory skin disease like eczema and psoriasis), those with lesion in scars or striae, crusted lesions and those previously subjected to any surgical procedure. **Sample size (patients):** No. eligible: NR; No. included: 1134 **Sample size (lesions):** No. eligible: NR; No. included: 1300 **Participant characteristics:** NR **Lesion characteristics:** median Breslow thickness of 0.43 mm (67 invasive melanomas);
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** EIS-CAD system: Nevisense predecessor (SciBase, Sweden) (SVM classifier) **System details:** Electrical impedance was measured with the SciBase III electrical impedance spectrometer, equipped with a spring-loaded probe and a disposable five-bar electrode. The system measures bio-impedance of the skin at 35 different frequencies, logarithmically distributed from 1.0 kHz to 2.5 MHz, at four different depths utilizing 10 permutations. **Derivation study (internal validation)** Classification algorithm calibration and testing was conducted in two stages. In the first stage of development, the data were randomized into two cohorts for calibration and verification, utilizing 40% and 0% of the available data respectively. In the second stage approximately 55% of the data were used for calibration and the whole data set was used for verification (second algorithm, not extracted). **Lesion characteristics assessed:** The electrical impedance data obtained from each measurement represented a very large data set consisting of the complex ratio of voltage to current, composed of the magnitude and phase shift at 35 frequencies for 10 permutations yielding a data set of 700 variables for each measurement. By combining permutations and frequencies, a large EIS feature space could be constructed. The features' ability to differentiate between melanoma and benign cutaneous lesions was then ranked and, by means of cross-validation, the optimum number of features was extracted. **Additional predictors included:** - None reported **Method of diagnosis:** - Stored EIS measurements - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - Dichotomous outcome: malignant vs. benign **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Lesions were excised and underwent usual histopathology at investigational site. A further histopathological evaluation was undertaken for study purposes by a panel of three experienced histopathologists who evaluated each lesion independently using information from clinical diagnosis and histopathology referral reason; blinded from the investigational site's original histopathology diagnosis. If they agreed, the diagnosis was considered as the histopathological gold standard (HGS); Disease positive: 166 Disease negative: 280 (TOTAL 446 in test set, after exclusions from analysis) **Target condition (Final diagnoses)** 67 invasive melanomas, 30 melanoma in situ, 21 BCC, 4 cSCC 38 severely dysplastic, 185 moderate dysplasia, 64 benign nevi, 22 seborrheic keratosis, 9 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Participants exclusions from analysis:** 549/1300 lesions excluded from analysis, mainly due to poor reference measurement quality (n=290). Other reasons were: Screening failure 2, Protocol violations 72, No measurements performed 35, Unable to map lesions with measurements 9, Lesion not excised 18, Poor histopathology 11, No consensus diagnosis reached by pathologists 20. Expanded Exclusions: Bleeding, traumatized or ulcerated lesion 38 Lesion located on acral skin 11, Surface area not measurable 34, Insufficiently covered with measurements 2, No clinical suspicion of melanoma 5, Hair-bearing areas 2. An additional 6 lesions excluded by review team: 6 undefined thickness mel excluded from MM1 to give total sample of 446–6=440 **Time interval to reference test:** Consecutive, excision within 2 weeks of EIS measurements; prospective recruitment: "After obtaining informed consent from each patient, eligible lesions destined for excision were measured with the SciBase III electrical impedance spectrometer (SciBase AB, Stockholm, Sweden). After a maximum of 14 days the lesions were surgically excised and subjected to histopathological evaluation."
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
Could the patient flow have introduced bias?	High risk

Notes

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Mollersen 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Unclear **Period of data collection:** March to December 2013 **Country:** Germany
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:** Adult patients scheduled for excision of a pigmented skin lesion and those with nonpigmented skin lesions if melanoma, BCC, or SCC was a potential differential diagnosis. The presence of hairs and bubbles, lesion size, inadequate segmentation, etc. were not used as exclusion criteria. **Setting:** Private dermatology practice **Prior testing:** Scheduled for excision on basis of clinical diagnosis, because of concern about malignancy or when requested by the patient for other reasons (no further details) **Setting for prior testing:** Unspecified **Exclusion criteria:** None reported **Sample size (patients):** Eligible NR, Included 516 **Sample size (lesions):** Eligible NR, Included 877 **Participant characteristics:** median age: 53y (range 18 to 93); male 53% **Lesion characteristics:** median Breslow thickness of 0.50 mm (23 invasive melanomas); maximum Breslow thickness 2.25mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Computer Assisted Diagnosis – Dermoscopy based** Derm-CAD system: Nevus Doctor (classifier NR) **System details:** Computerised image analysis system coupled to digital dermoscope. ND takes a dermoscopic image from the Canon/DermLite device as input and classifies the lesion. ND is still in an experimental phase. All skin lesions were photographed prior to excision with a digital camera (Canon G10, Canon Inc., Tokyo, Japan) with an attached dermoscope (DermLite FOTO, 3Gen LLC, California, USA) and with a videodermoscope (DermoGenius ultra, DermoScan GmbH, Regensburg,Germany). **No derivation aspect (external validation study)** Described in previous study Mollersen 2015 in press, reference #37 **Lesion characteristics assessed:** – NR **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Clinical diagnosis **CAD output:** - Probability of malignancy **Diagnostic threshold:** - CAD system tuned to 95% melanoma sensitivity **2. Computer Assisted Diagnosis – Dermoscopy based** Derm-CAD system: MoleExpert (classifier NR) **System details:** ME (MoleExpert micro Version 3.3.30.156) takes a dermoscopic image from the DermoGenius device as input. ME is intended for use on melanocytic lesions only. All skin lesions were photographed prior to excision with a digital camera (Canon G10, Canon Inc., Tokyo, Japan) with an attached dermoscope (DermLite FOTO, 3Gen LLC, California, USA) and with a videodermoscope (DermoGenius ultra, DermoScan GmbH, Regensburg,Germany). **No derivation aspect (external validation study)** No information provided (ME is a commercial system developed by others and used as a comparator in this study) **Lesion characteristics assessed:** – Features of ABCD system plus other features (not listed), e.g. color variation and gray veil. **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Clinical diagnosis **CAD output:** - Number between −5.00 and 5.00, where high values indicate suspicion of melanoma **Diagnostic threshold:** - CAD system tuned to 95% melanoma sensitivity

Computer-assisted diagnosis

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone **Details:** All excised lesions were examined by a dermatopathologist. In the case of a malignant diagnosis, a second dermatopathologist examined the excised lesion and a consensus diagnosis was set. Disease positive: 107; Disease negative: 278 **Target condition (Final diagnoses)** Melanoma: invasive 25, in situ 19; BCC: 70, cSCC 6, adnexal carcinoma 1 Benign diagnoses: 38 benign non melanocytic; 13 collision tumours; 13 AK; 11 Bowen's disease; 79 Sebhorrheic keratosis; 595 benign nevus
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** one lesion lacking clinical diagnosis; of 875 lesions with histopathological diagnosis, four were excluded because ME did not give an output (one naevus, one seborrheic keratosis, one BCC, and one SCC) and one was excluded because the Canon/DermLite image was lost (melanoma in situ) **Time interval to reference test:** Not reported **Time interval between index test(s):** Appears consecutive
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?	No
Could the patient flow have introduced bias?	High risk

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Monheit 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** January 2007 to July 2008 **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?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented skin lesions scheduled for biopsy in toto, with diameter >=2mm **Setting:** Specialist unit (skin cancer/pigmented lesions clinic). Three sites were academic institutions and 4 sites were dermatologic practices highly experienced in managing PLs. **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Unspecified **Exclusion criteria:** Difficult to diagnose lesions; Location/site of lesion anatomic site of pigmented lesion not accessible to the device; within 1 cm of the eye; or on palmar, plantar, or mucosal (eg, lips, genitals) surface or under nails; lesion size diameter <2 mm or >22 mm excluded Previous history of skin cancer/ prior treatment at site lesion previously biopsied, excised, or traumatized Other characteristic known allergy to isopropyl alcohol; skin not intact (eg, open sores, ulcers, bleeding); in an area of visible scarring; or containing foreign matter (eg, tattoo ink, splinter, marker). **Sample size (patients):** Eligible: 1383, Included 1257 **Sample size (lesions):** Eligible: 1831, Included 1632 **Participant characteristics:** Median age 46y (Range 7-97y); Male 575 (45.7%); Ethnicity: White 1232 (98%), Black or African American 2 (0.2%), Asian 17 (1.4%), Other 6 (0.5%). **Thickness/depth:** ≤1mm: 69/70 invasive MM (99%), 1.01-2.00mm: 1/70 (1%). Median Breslow 0.36 mm (70 invasive MM)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	MSI-CAD system: MelaFind (EO Sciences, USA) (classifier NR) **System details:** Multispectral imaging system with integrated image analysis software; device takes images in vivo. MelaFind takes images at 10 spectral bands, between 430–950nm. **No derivation aspect (external validation study)** The properties of these images as well as image analysis methods have been previously described.15-21 (Gutkowicz-Krusin 1997, 2000, 2007 and Elbaum 2001) **Lesion characteristics assessed:** –NR **Additional predictors included:** - None **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - Binary output: (1) positive, (lesion should be considered for biopsy to rule out melanoma); and (2) negative (lesion should be considered for later evaluation) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (not further described)* - No. patients/lesions: 1632 Disease positive: 175, Disease negative: 1457 **Target condition** (Final diagnoses) Melanoma: invasive 70, in situ 57; BCC: 23; cSCC: 10, Severe dysplasia: 43 Benign diagnoses: 998 Mild/moderate dysplasia; 93 Sebhorrheic keratosis, 217 Benign naevus, 5 atypical melanocytic hyperplasia (AMH) or atypical melanocytic proliferation (AMP), 16 actinic keratosis, 10 other keratosis, 76 lentigo, 14 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** 20 lesions with the prebiopsy dermatologic diagnosis of melanoma were excluded from the primary MelaFind analysis; 1 withdrew, 3 clinician deemed inelig, 14 dermatopath deemed inelig, 19 missing/inad histol slides, 162 imaging failed (operator errors, too many bubbles, lesion not centred), 36 MelaFind or camera malfunction, 61operator or MelaFind error (lesion too small to visualise, automatic segmentation falied). **Time interval to reference test:** Unclear
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?	No
Could the patient flow have introduced bias?	High risk

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Piccolo 2002

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** NR; 6-month period **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?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented lesions excised because of equivocal dermoscopic findings or at the patient's request **Setting:** Secondary (general dermatology); from authors' institution **Prior testing:** Dermatoscopic suspicion; Patient request for evaluation/excision **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** No. included: 289 **Sample size (lesions):** No. included: 341 **Participant characteristics:** Mean age 33.6y, range 3–83y; Male gender: 127 (43.9%); Fitzpatrick phototype I to II (31.4%); Type III (42.2%); Type IV-V (26.4%) **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm **Method of diagnosis:** Clinical photographs and dermoscopic images Cases were clinically and dermoscopically evaluated on a high-resolution colour monitor, in a random sequence **Prior test data:** Unclear Not specifically described but appears to be images only **Diagnostic threshold:** Not reported **Diagnosis based on:** Single observer (n=2) **Observer qualifications:** Dermatologist; Resident clinician with minimal training in PSLs **Experience in practice:** High experience or 'Expert' 5 years of experience; Low experience or recently qualified minimal training in PSLs (6 months of experience, comprising 8 h of specialized training on three consecutive days and 2h per week in the routine of dermoscopy) **Experience with index test:** Mixed **Any other detail:** stereomicroscope with magnifications varying from x 6 to x 40 **2. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DEM-MIPS (Digital Epi Microscopy Melanoma Image Processing Software; Biomips SRL, Siena, Italy) (ANN classifier) **System details:** DEM-MIPS is designed to evaluate different colorimetric and geometric parameters of a lesion automatically in real time. All digital images of PSLs were collected in a Truevision Advanced Graphic Array format file with a size of 887 kB for each image. Digital dermoscopic images were framed at x 16 magnification before analysis with DEM-MIPS **No derivation aspect (External validation study)** Described in prior study "DEM-MIPS is based on an ANN trained with 100 PSLs (50non-melanomas and 50 melanomas) and is designed toevaluate different colorimetric and geometric parametersof a lesion automatically in real time." No citation given **Lesion characteristics assessed:** – Evaluates colorimetric and geometric features (not reported). **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability	

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone *Histology (not further described);* Disease positive: 13; Disease negative: 328 **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 13 Sebhorrheic keratosis: 3; Benign naevus: 316; Other: 7 dermatofibromas, 2 angiomas
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	Time interval to reference test: nr
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
Could the patient flow have introduced bias?	Unclear risk

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Piccolo 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection:** September 2010 and October 2013 **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?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Dermoscopically atypical pigmented skin lesions selected from the archives of the Dermatology Department at the University of L'Aquila, Italy. **Setting:** Secondary (general dermatology) **Prior testing:** Not reported **Setting for prior testing:** Not reported **Exclusion criteria:** Location/site of lesion - acral sites and the face **Sample size (patients):** No. included: 165 **Sample size (lesions):** No. included: 165 **Participant characteristics:** Mean age 43.5 yrs (range 12 to 84 years); Male gender: 59.4% **Lesion characteristics:** lesion site - upper extremities 18 (11%); lower extremities 53 (32.1%); 62 (37.5%) on the back; 32 (19.4%) on the chest. Melanoma thickness 87.9% (29/33) <0.75mm; 12.1% (4/33) >1.5 mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

	1. Visual inspection (VI) **Method of diagnosis:** **Prior test data:** **Diagnostic threshold:** **Diagnosis based on:** Number of examiners **Observer qualifications:** **Experience in practice:** **Experience with index test:** **2. Dermoscopy** ABCD **Method of diagnosis:** Dermoscopic images **Prior test data:** No further information used **Diagnostic threshold:** Semi-quantitative. Total dermoscopic score is calculated (TDS) - a PSL with a TDS <4.75 benign, TDS 4.75 to 5.45 suspicious of malignancy, TDS >5.45 highly suggestive of melanoma. **Diagnosis based on:** Single observer (n=4)

Index tests	**Observer qualifications:** 3 dermatologists and 1 GP with different degrees of dermoscopic experience **Experience in practice:** Mixed **Experience with index test:** Experience scored using following criteria: Following criteria assessed: number of years specializing in dermoscopy (score: 1, 0-1 year; 2, 2-5 years; 3, >5 years); number of pigmented skin lesions assessed by dermoscopy on a daily basis (1,<10 lesions/day; 2, 11-20 lesions; 3, 21-30 lesions; 4, >30 lesions); number of relevant workshops/ seminars attended (1, 0-1 workshops/seminars; 2, 2-5 workshops/seminars; 2, >5 workshops/seminars); and the number of authored publications on dermoscopy (1, 0-1publications; 2, 2-5 publications; 3, 6-10 publications; 4, >10 publications). Observer 4 considered low experience (underwent dermoscopic training by studying an interactive atlas of dermoscopy between T0 and T1); Observer 1 High experience /'Expert'; Observers 2 and 3); moderately experienced **3. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: Nevuscreen ® **(Arkè s.a.s., Avezzano, Italy)** (classifier NR) **System details:** Digital database containing image analysis software, coupled to digital dermoscope. Nevuscreen software automatically analyses ABCD features **No derivation aspect (external validation study)** **Lesion characteristics assessed:** –ABCD features. After image scanning, each pixel is classified in accordance with the main dermoscopic colour to which it is closest. Once the different colour regions are identified, DDA can also calculate asymmetry by considering the overall asymmetry parameter.**Differential dermoscopic structures Pigment network, Globules, Streaks, Black dots and Structureless areas represent notable criteria in dermoscopic evaluation. Various digital filters (median filters, essentially)are used to obtain a morphological analysis for recognizing particles of various dimensions, which are subsequently evaluated for size and shape and compared to numerous sample images. Once the different structures have been recognized, their asymmetry is calculated as a contribution to the overall asymmetry parameter **Additional predictors included:** - Clinicians use CAD output to assist their diagnosis **Method of diagnosis:** - In person diagnosis - CAD-aided diagnosis **Prior/other test data:** 4 test operators 4 **Operator qualifications:** - GP - Dermatologist **Experience in practice:** - Mixed experience (low and high experience combined) **Experience with index test:** - Mixed experience (low and high experience combined) **CAD output:** - TDS **Diagnostic threshold:** -Total Dermoscopy Score: <4.75 benign, 4.75–5.45 suspicious, >5.45 highly suggestive of melanoma

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	No
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone **Target condition (Final diagnoses)** Melanoma (invasive): 23; Melanoma (in situ): 10 Benign naevus: 105 Clark nevi; 19 Spitz/Reed nevi; 5 blue nevi; 3 dermal 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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:** reference test conducted first not clear what the time interval is between this and the current index test(s) **Time interval between index test(s):** not clear- looks like it was simultaneous
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
Could the patient flow have introduced bias?	Unclear risk

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Rubegni 2002

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection:** 1996 to 2001 **Country:** Italy **Test set derived:** NR "To train the SLP-ANN, 550 of the 588 available cases were used (30 nevi and 200 melanomas in 550 sessions, each with 2 subsets); 549 cases were used for training, and 1 case at a time was used to check overfitting and stepwise feature selection. A third small, independent subset consisting of the other 17 melanomas and 21 nevi was used to test SLP-ANN diagnostic performance on data not used in the training process."
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:** Excised PSL, clinically atypical (asymmetrical with variegated color), flat and impalpable. All were difficult to diagnose and therefore suitable for morphologic and parametric evaluation of early melanoma. **Setting:** Secondary (general dermatology) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion; Selected for excision (no further detail) Described as clinically atypical and difficult to diagnose **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** Difficult to diagnose lesions: Location/site of lesion acral, lesion size only 0.4–1 cm in diameter were included; non-melanocytic appearance pink skin lesions (amelanotic melanoma and classical Spitz nevi); Blue nevi were excluded, as were lentigo maligna, lentigo maligna melanoma **Sample size (patients):** No. included: 588 included (one per pt) **Sample size (lesions):** No. eligible: 4200 PSL excised; No. included: 588 included (38 in test set) **Participant characteristics:** Mean age 49y (+/- 15y); Male: 40% (of full sample; n=588); 100% Pigmented. Median Breslow 0.4 mm (157 invasive melanomas)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB-Mips (Biomips Engineering, Italy) (ANN classifier) **System details:** Dermoscopy unit, internal stereomicroscope, internal DB, pattern analysis system. Lesions were imaged by ELM at a magnification of 16 with the DBDermo-Mips apparatus. **Derivation study (internal validation)** Described in prior study Andreassi 1999 **Lesion characteristics assessed:** – Approach to feature selection: Computer-aided stepwise technique to choose the number of discriminant features for optimum generalization. The parameters, as previously described,19 belonged to 4 categories: geometries, colors, textures and islands of color. Geometric: area, maximum and minimum* diameters, radius, variance of contour symmetry, circularity*, fractality of borders and ellipsoidality. Color: mean values of red*, green and blue inside the lesion; mean values of red, green* and blue of healthy skin around the lesion; deciles of red*, green and blue inside the lesion; quartiles of red, green and blue* inside the lesion, mean skin-lesion gradient*, variance of the border gradient, border homogeneity and interruptions of the border. Texture: mean contrast* and entropy of lesion as well as contrast and entropy fractality. Islands of color: peripheral dark regions*; dark area; imbalance of dark region; green area; red area; dominant green region imbalance; blue-gray area; blue-gray regions; transition area*; transition region imbalance*; background area*; background region imbalance*; red, green and blue multicomponent; and number of red, green and blue percentiles inside the lesion. **Additional predictors included:** - No further information used **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - Diagnosis suggested (e.g. melanoma, benign melanocytic nevus) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Unclear
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone *Histology (not further described)* - Details: Histopathologic diagnosis of melanoma and nevi was made according to the criteria of the NIH Consensus Conference (1992). Histopathologic diagnosis discordance was c9%. These were classified as melanoma or nevi when at least 2 of 3 dermopathologists agreed on the diagnosis. No. patients/lesions: 588, 38 in test set Disease positive: 17; Disease negative: 21 **Target condition** (Final diagnoses) Melanoma (in situ and invasive, or not reported): 17 Benign diagnoses: 21 (not further specified)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None reported **Time interval to reference test:** NR but appears consecutive
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
Could the patient flow have introduced bias?	Unclear risk

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Seidenari 1998

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** NR; 4 year period **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?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Melanomas and benign pigmented skin lesions from a larger series of pigmented skin lesions used to develop a new automated classifier; all melanomas with x20 magnification images were included plus a random sample of benign lesions with the same magnification. For the larger series, lesions were referred by dermatologists or general physicians because of one or more PSL that were difficult to interpret on clinical grounds alone, numerous PSLs, or because the patients were at increased risk for melanoma or had had a malignant PSL in the past. **Setting:** Secondary **Prior testing:** Clinical suspicion of malignancy **Setting for prior testing:** Primary; Secondary (general dermatology) **Exclusion criteria:** None reported **Sample size (patients):** Not reported **Sample size (lesions):** No. eligible: 917; No. included: 100 **Participant characteristics:** None reported **Lesion characteristics:** Melanoma thickness: ≤1mm : 70.8% (n=46), <1 mm 58.5% (n=38). mean thickness 0.73 ± 0.69 mm;
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm **Method of diagnosis:** Dermoscopic images; (obtained via videomicroscopy) **Prior test data:** No further information used; "Images appeared in a random sequence on the computer screen, and no information about the patient (such as history, skin site, age of the patient, evolution of the lesion) was given to the evaluators" **Diagnostic threshold:** Clinical diagnosis **Diagnosis based on:** Single observer (n=2) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with dermoscopy:** Low - one 'untrained' dermatologist; High - one routinely used videomicroscopy **Any other detail** For instrumental examination a 10- (39 cases), 20- (501 cases), or 50-fold–magnification (377 cases) was chosen according to the size of the lesion, enabling the whole lesion to be seen on the monitor. For the study, the 31 MM with x20 magnification were selected plus a random sample of 59 benign **2. Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB–MIPS (Biomips Engineering, Italy) (Multivariate discriminant analysis classifier) **System details:** Digital videomicroscope equipped with a dedicated program for the diagnosis of melanocytic PSL by evaluating digital features referring to benign and malignant PSL images. For this study an NTSC VMS-110A videomicroscope (Scalar, Mitsubishi, Tama-shi, Tokyo, Japan) was used. **No derivation aspect (external validation study)** **Lesion characteristics assessed:** – Radius, area and perimeter of the lesion, symmetry and circularity, fractality (shape), texture analysis, colour expressed as red, green and blue components, skin lesion gradient, 'dark areas' inside the lesion. All described in detail. **Additional predictors included:** - Unclear – For each patient personal data and information such as the site of the lesion, the magnification , the clinical and the histological diagnosis were recorded. Unclear how these were used **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear, not reported **CAD output:** - Graphical output and numerical output of features provided. Diagnosis suggested (e.g. melanoma, benign melanocytic nevus) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone Details: describes using "conventional histopathologic criteria." Disease positive: 31; Disease negative: 59 **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 31 'Benign' diagnoses: 59 "nonmelanoma cases consisted of nevi including dysplastic 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Participant exclusions:** None reported **Index test to reference standard interval:** Not described
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Seidenari 1999

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection:** NR **Country:** Italy **Test set derived:** Not clearly reported but appears that the training set was randomly sampled, but the melanomas in the training set were supplemented with images of lesions of comparable size but thicker than 0.75 mm, randomly selected from other melanoma images.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented skin lesions with 20x magnification images **Setting:** Secondary (general dermatology) From authors' institution **Prior testing:** Selected for excision (no further detail) **Setting for prior testing:** Unspecified **Exclusion criteria:** None reported **Sample size (patients):** NR **Sample size (lesions):** No. eligible: 461; No. included: 383 in test set, 78 in train set **Participant characteristics:** thickness ≤1mm: 18 (100%) <0.75 mm (eight in situ)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB–MIPS (Biomips Engineering, Italy) (Multivariate discriminant analysis classifier) **System details:** Dermoscopy unit, internal stereomicroscope, internal DB, DB–MIPS pattern analysis system – integrated database stores the patient's data and the description of the lesion along with the image icons. 38 features analysed (grouped into geometries, colours and Burroni's islands of colours). **Derivation study (internal validation)** **Lesion characteristics assessed:** – The borders of the lesion were automatically identified, plus estimation of radius, area and perimeter of the lesion, symmetry and circularity, fractality (shape) , texture analysis, colour expressed as red, green and blue components, skin lesion gradient, 'dark areas' inside the lesion. All described in detail – Approach to feature selection DBDermo-MIPS software. Discriminant analysis enables the identification of variables that are important for distinguishing between the groups in the training set in order to develop a procedure for predicting group membership for new cases in which group membership is undetermined (test set). Using the training set data, a threshold score was established that enabled the attribution of each malignant lesion to the right group (100% sensitivity). The same value was employed for discriminating benign and malignant lesions belonging to the test set. **Additional predictors included:** - Unclear For each patient personal data and information such as the site of the lesion, the magnification , the clinical and the histological diagnosis were recorded. Unclear how these were used **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - NR **Diagnostic threshold:** - Threshold not reported. Using the training set data, a threshold score was established that enabled the attribution of each malignant lesion to the right group (100% sensitivity). The same value was employed for discriminating benign and malignant lesions belonging to the test set.

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (not further described)* - No. patients/lesions: 461 (383 in training set) - Disease positive: 18 - Disease negative: 365 **Target condition** (Final diagnoses): Melanoma: invasive 10, in situ 8 'Benign' diagnoses: 365 non-melanoma cases consisted of benign naevi including common naevi and clinically dysplastic naevi (> 5 mm in diameter, irregular or ill-defined border, irregular pigmentation)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **Time interval to reference test:** 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Serrao 2006

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective **Period of data collection:** September 2002 to September 2005 **Country:** Portugal
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 from patients with multiple atypical naevi, personal/familiar melanoma history or doubtful cases on clinical inspection who were referred to a Dermoscopy Unit **Setting:** Specialist dermatoscopy unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion. Mixed population; high risk and/or clinically suspicious **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** Unequivocal appearance/diagnosis. All clearly benign lesions by clinical examination were not referred **Sample size (patients):** No. eligible: 1186; No. included: 344 **Sample size (lesions):** No. included: 652 **Participant characteristics:** Mean age 40 years (SD± 14), age range: 11 to 84 years; 49% in the 35-64 age group, 33% aged 25 to 34 years old, 3% aged under 18; Male: 33% (114); **High risk characteristics:** History of melanoma/skin cancer (%) 19%, Family history of melanoma (%) 3%, 24% history of dysplastic nevi; **Lesion site:** Trunk: back 56% chest 20%, Lower limbs/hip: 13%; **Thickness/depth:** ≤1mm: 29/41 plus 8 in situ; >1mm: 3
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: microDERM (Visiomed AG, Germany) (ANN classifier) **System details:** Dermoscopy unit with internal camera containing analysis system. DANAOS software combines analytical system based on ABCD with database of 21,000 PSLs. The system has an integrated filter that reduces influence of hairs in the analysis of lesions. **No derivation aspect (external validation study)** Described in prior study Fidalgo 2003 **Lesion characteristics assessed:** – lesions assessed for about 50 parameters (geometrical, colour and internal pattern) **Additional predictors included:** - None reported **Method of diagnosis:** - Dermoscopic images - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - DANAOS score indicating risk of malignancy **Diagnostic threshold:** - High risk DANAOS score (> 6.5); data also presented for score of >7.5

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone Details: *C*riteria used for excision were: · Dermoscopic suspicious lesions, irrespective of the DANAOS score. · All lesions with high risk DANAOS score (> 6.5) · Significant dermoscopic or clinical architectural change, irrespective of the DANAOS score. Disease positive 41; Disease negative 611 **Target condition** (Final diagnoses) Melanoma: invasive 32; in situ 9 Benign diagnoses: 472 Benign naevus, 139 dysplastic naevus
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **Time interval to reference test:** Unclear; CAD performed in advance of histology
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Sgouros 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** 3 mo period; dates not specified **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?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented skin tumours, clinically suspicious for the diagnosis of melanoma, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) and the inability to establish a definite diagnosis on clinical grounds only. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 180 **Sample size (lesions):** No. eligible: 188; No. included: 44 excised (authors included remaining 144 non-excised lesions but these only received expert diagnosis with no FU so not eligible for our review) **Participant characteristics:** Mean age 43yrs (range: 2 to 95) (n = 188); Male: 97 (51.6%).
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	Yes
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SIAscope (MedX Health Corp, Canada) (classifier NR) **System details:** Spectrophotometric imaging system with hand–held skin probe (SIAscope, version NR) and integrated software **No derivation aspect (external validation study)** Derivation described in prior study Moncrieff 2002 **Lesion characteristics assessed:** Analysis of dermal melanin, erythematous blush, lesion asymmetry, collagen 'holes', blood commas, or irregularities in the collagen **Additional predictors included:** - None **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - Clinical examination and/or case notes - Dermoscopy **CAD output:** - SIAgraph and PCSA (see below) **Diagnostic threshold:** - Primary care scoring algorithm (PCSA) (Emery 2010); score >= 6 regarded as suspicious.

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** Histological diagnosis alone *Histology (excision)* No. patient/lesions: 44 Disease positive: 31; Disease negative: 13 **Target condition** (Final diagnoses) Melanoma (in situ and invasive, or not reported): 18 BCC: 10, cSCC: 3 'Benign' diagnoses: 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?	Unclear
Were the reference standard results likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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:** 144 with only expert final diagnosis (excluded by Review team) **Time interval between index test(s):** Appears consecutive
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
Could the patient flow have introduced bias?	Unclear risk

Notes

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Stanganelli 2005

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Dataset previously used in Stanganelli 2000 **Period of data collection** NR **Country** Italy **Test set derived** A training set of 22 melanomas and 218 melanocytic nevi was randomised from the dataset. The test set was formed by the complement (the remaining 20 melanomas and 217 nevi). A further subset of images from the original dataset, consisting of 31 melanomas and 103 nevi, was used for the comparison between observers and CAD; derivation of the subset not reported.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
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:** Melanocytic lesions from patients referred to the Skin Cancer Unit and undergoing clinical and dermoscopic evaluation. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 1556 referred / No. included: NR **Sample size (lesions):** No. eligible: 3274 / No. included: 477 melanocytic lesions; 237 in test set and 134 in comparison between CAD and human operators **Participant characteristics:** None reported **Lesion characteristics:** Melanoma thickness 61.2% <0.75mm
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB–MIPS (Biomips Engineering, Italy) (SVM classifier) **System details:** Dermoscopy unit, internal steromicroscope, internal DB, pattern analysis system. Automatic Data Analysis for Melanoma early detection (ADAM) software which analyses boundary shape, texture and colour distribution **Derivation study (internal validation)** see also Stanganelli 1995 and Stanganelli 2000 **Lesion characteristics assessed:** – (ADAM) software is based on a quite recent mathematical technique of shape representation: the Size Functions. "These are very general invariants designed to capture, in a formal and quantitative way, the essential behaviour of some specified aspects (the so called measuring functions) of a signal (27, 28). In the present case, the examined signal is the image of a melanocytic lesion, and the aspects concerned are: boundary shape, texture and color distribution. Size Functions are standardized objects, easy to compute, to store and to compare. So the study is performed on the Size Function instead of the original image. Thisyields a great simplification and, above all, a greatly focussed analysis. The Size Function obtained from a curve with the distance from point C as measuring function is shown in Figure 1" **Additional predictors included:** - No further information used **Method of diagnosis:** - Dermoscopy images - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - Low risk, intermediate risk or high risk of melanoma **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis plus cancer registry All included lesions underwent histology but some were identified using a cancer-registry-based follow-up of benign diagnoses. **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 42 in full sample; 31 in CAD vs human observer interp and 20 in test set 'Benign' diagnoses: 435 melanocytic nevi; 103 in CAD-observer comp and 217 in test set
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 likely to correctly classify the target condition (disease negative)?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the reference standard?	Unclear
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	**Exclusions from analysis:** None **Time interval to reference test:** Not reported
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
Could the patient flow have introduced bias?	High risk

Notes

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Terstappen 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported **Period of data collection:** NR **Country:** Sweden
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:** Study inclusion criteria Lesions clinically suspicious for melanoma and showing positive SIAscopic findings **Setting:** Secondary (general dermatology) (details from Authors' institution) **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion, showing positive SIAscopic findings **Setting for prior testing:** Secondary (general dermatology) **Exclusion criteria:** Poor quality index test image: 9 lesions excluded due to technical problems **Sample size (patients):** No. eligible: 69; No. included: 60 **Sample size (lesions):** No. eligible: 69; No. included: 60 **Participant characteristics:** ≤1mm thickness: 17/29 melanomas; 8/29 melanomas Breslow thickness <0.76 mm (Clark II-III) and 9/29 Breslow thickness 0.76− ≤ 1.0 mm (Clark II-III) and 12 lesions Breslow thickness ≥1.1 (Clark III-V).
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SIAscope (**Astron Clinica, UK**) (classifier NR) **System details:** Spectrophotometric imaging system with hand–held skin probe (SIAscope V) and integrated software (Dermetrics Version 2.0, Astron Clinica Ltd., Great Britain). **No derivation aspect (external validation study)** **Lesion characteristics assessed:** – Dermal melanin, blood displacement, collagen holes, erythematous blush **Additional predictors included:** - No further information used **Method of diagnosis:** - In person spectroscopic images (SIAgraphs) - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** The instrument generates four images depicting the concentration of haemoglobin, melanin, collagen and dermal melanin. **Diagnostic threshold:** - "SIAscopic findings indicating melanoma were applied using the method described by Moncrieff (2002)" Results described for: "the combined features (presence of blood displacement with erythematous blush, collagen holes and presence of dermal melanin)" NB Moncrieff 2002 is a derivation study for SIAscope and suggests a number of combinations of features indicative of melanoma, the same features investigated here

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard:** Histological diagnosis alone Details: The excised specimens were routinely processed and the histological sections, 4 µm thick, were stained with haematoxylin and eosin. Before cutting the specimen in slices, the lesion was oriented and the positions of the SIAscopic areas of interest were outlined by comparisons with the overview clinical photo of the lesion No. patients/lesions: 60 Disease positive: 29; Disease negative: 31 **Target condition** (Final diagnoses) Melanoma: invasive 29, in situ 13 (included as D-) BCC: 2 Benign diagnoses: 2 Sebhorrheic keratosis; 4 melanocytic lesions; 10 dysplastic naevi
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?	No
Were the reference standard results likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** 9/69 lesions (2 invasive melanoma, two melanoma in situ, and five benign lesions) had to be excluded due to technical problems. **Time interval to reference test:** 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?	No
Could the patient flow have introduced bias?	High risk

Notes

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Tomatis 2003

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection:** Jan 1995 to Mar 2000 (test set Apr 1999 to Mar 2000) **Country:** Italy **Test set derived:** Chronological; acquired in last year of recruitment. Study population not randomised (training set enriched with melanomas)
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:** Cutaneous pigmented lesions that required a surgical biopsy for diagnosis **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) tumour institute of milan **Prior testing:** Selected for excision (no further detail) **Setting for prior testing:** Unspecified **Exclusion criteria:** "Difficult to diagnose" lesions, thick and/or large melanomas and awkwardly situated lesions. like those placed at the interdigital spaces, on ears, nose, eyelids, etc.; lesions on the scalp due to hair interference; **Sample size (patients):** No. eligible NR; No. included: 534 **Sample size (lesions):** No. eligible NR; No. included: 573 **Participant characteristics:** Median age 36 y (range 10-95y); 59.7% Male; thickness ≤1mm: 91/132 MM (68.9%); thickness 0.16 to 3.24 mm. Median Breslow 0.68mm; Mean diameter: 10mm (range 3 to 39mm)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: Telespectrophotometric system (ANN classifier; Linear discriminant classifier also trained and reported, ANN selected at random for review) **System details:** Digital camera coupled with an illumination system with interference filters and computer for storage and analysis of multispectral images. The Telespectrophotometric System consists of a CCD camera, a set of 17 interference filters. a PC. and an illumination system composed by two halogen (2 X 100 W) and two lamps (2X 150 W) with emission in the infrared region . **Derivation study (internal validation)** The train set is required for the instruction of the classifiers whose diagnostic performances are evaluated against an independent verify set. the considerable fraction of cases devoted to the classifier training was selected to include an adequate number of positives Derivation described in **prior studies** Marchesini 1995, Tomatis 1998, Furina 2000 **Lesion characteristics assessed:** – For each spectral image, five parameters (lesion descriptors) based on ABCD and related to colour and shape of the imaged lesion were evaluated: mean reflectance, variegation index, roundness, border irregularity. **Additional predictors included:** - No further information used **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - None reported **CAD output:** - NR **Diagnostic threshold:** - Threshold selected by authors using ROC analysis. No further information provided

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	No
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone *Histology (not further described)* - No. patients/lesions: 573 (210 in test set) - Disease positive: 132 (37 in test set) - Disease negative: 441 (136 in test set) **Target condition** (Final diagnoses) - Melanoma (in situ and invasive, or not reported): 37 (test set) - 'Benign' diagnoses: 136 (test set)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **Time interval to reference test:** Appears consecutive: 'images acquired in vivo before surgey'. Interval 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
Could the patient flow have introduced bias?	Unclear risk

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Tomatis 2005

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** September 2002 to April 2004 **Country:** Italy **Test set derived:** The study population was split into three sets: train, verify and test. The cases were randomly assigned to the above sets among all the 1391 lesions with histology.
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:** Study inclusion criteria Cutaneous pigmented lesions with clinical and/or dermoscopicfeatures that supported a suspicion for cutaneous melanoma and therefore eligible for excision. A further of lesions all diagnosed as clearly benign common nevi at both clinical and dermoscopic evaluations that did not undergo excision, data for these have not been included as >50% of benign group must undergo histology or active follow-up. **Setting:** Specialist unit (skin cancer/pigmented lesions clinic) **Prior testing:** Clinical and/or dermatoscopic suspicion **Setting for prior testing:** Specialist unit (skin cancer/pigmented lesions clinic) **Exclusion criteria:** Difficult to diagnose lesions, Poor quality index test image incorrectly acquired or not correctly segmented by the system **Sample size (patients):** No. eligible: 1359 patients **Sample size (lesions):** No. eligible: 1485; No. included: 1391 excised [94 excluded: lesions out of focus, 46 cases, 3%, or system failure to correctly segment the lesion border (48 cases, 3%)]. **Participant characteristics:** Median age 36y (range 5 to 88y); Male: 597 (43.9% of 1359); Pigmented (%): 100%; Located on: Head/Neck: 2.9%, Trunk: 66.2%, Upper limbs/shoulder: 9.1%, Lower limbs/hip: 17%, Limbs: 4.8% **Thickness/depth:** ≤1mm: 140/164 (85%) invasive MM; median thickness 0.58 mm, (0.1 mm to 2.7 mm), for 164 invasive MM. Median size: 9 mm in maximum diameter; <=6 mm in 44 cases (24%).
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SpectroShade (MHT, Verona, Italy) (ANN classifier) **System details:** Illumination assembly located inside a PC and an external detection device placed in a hand-held probe, with integrated image analysis software **Derivation study (internal validation)** The train group (696 cases, including 90 melanomas) was used to optimize the inner fitting weights of the neural network by means of a training algorithm. The verify set (348 cases, including 53 melanomas) was used to properly stop the training process preventing the so-called overlearning, i.e., a drop in the generalization capabilities of the classifier which would otherwise fit the noise pattern of the data instead of defining a proper boundary between malignant and benign moles. The test set (347 cases, including 41 melanomas) was used to confirm, by independent data, the discrimination performances of the system as obtained from the previous data sets. Also described in prior studies Marchesini et al 1995, Tomatis et al 1998, 2003 **Lesion characteristics assessed:** – Features analysed: (i) reflectance (R); (ii) variegation (V); (iii) area (A); (iv) dark area ratio (DAR); (v) dark island reflectance (DIR); (vi) dark distribution factor (DDF); (vii) dark permanence (D PER) **Additional predictors included:** - No further information used **Method of diagnosis:** - Spectroscopic images - CAD-based diagnosis **Prior/other test data:** - No further information used **CAD output:** - NR **Diagnostic threshold:** - Threshold set to produce sensitivity of 80%

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	No
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone Data provided for subgroup (test set) that all underwent excision *Histology (not further described)* - No. patients/lesions: 1391 (347 in test set) - Disease positive: 184 (41 in test set) - Disease negative: 1207 (306 in test set) **Target Condition** (Final diagnoses) Melanoma (invasive): 164 (full sample, number in test set NR) - Melanoma (in situ): 20 (full sample, number in test set NR) - Melanoma (in situ and invasive, or not reported): 41 (test set only) - BCC: 7 (full sample, number in test set NR) - Sebhorrheic keratosis: 27 (full sample, number in test set NR) - 'Benign' diagnoses: 280 dysplastic naevus, rest various benign (893)
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: Not reported "Before surgery, images of the 1485 pigmented lesions were acquired in vivo."
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
Could the patient flow have introduced bias?	Unclear risk

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Walter 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Randomised controlled trial, only experimental group included **Data collection:** Prospective **Period of data collection** March 2008 to May 2010 **Country** UK
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:** Adults with any suspicious pigmented skin lesion, i.e. any lesion presented by a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured. **Setting:** Primary 15 general practices in eastern England **Prior testing:** Clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing:** Primary **Exclusion criteria:** Those unable to give informed consent or considered inappropriate to include by their family doctor. **Sample size (patients):** No. eligible: 1297; No. included: 1293 in RCT, 643 in experimental group **Sample size (lesions):** No. eligible: 1580; No. included: 1583 in RCT, 788 in experimental group **Participant characteristics (whole population):** Mean age: 44.6y (SD 16.8). Male: 465 (36%). Ethnicity: White 1214 (93.9%); Mixed 45 (3.5%); Missing: 34 (2.6%) **Lesion characteristics.** Lesion thickness ≤1mm: in 'more than half' of MM
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: SIAscope + MoleMate (classifier NR) **System details:** SIAscopy with MoleMate (software image management system) viewing platform and integrated primary care scoring algorithm **No derivation aspect (external validation study)** **Lesion characteristics assessed:** – Lesion characteristics not described **Additional predictors included:** - None reported **Method of diagnosis:** - In person diagnosis, spectroscopic images (SIAgraphs) - CAD-aided diagnosis **Prior/other test data:** - Clinical history and naked eye examination **Operators:** 28 clinicians **Operator qualifications:** - GP - Other (describe) 2 nurse practitioners **Experience in practice:** - Mixed experience (low and high experience combined) as previously recorded **Experience with index test:** - Low experience / novice users **CAD output:** - SIAgraphs and Lesion score using Primary Care Scoring Algorithm **Diagnostic threshold:** Primary Care Scoring Algorithm (6 or more points regarded as suspicious)

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis plus FU and Epxert opinion *Histology (not further described)* 215 (histology result missing in further 4) Disease positive: 35; Disease negative: 180 *Clinical FU plus histology of suspicious lesions:* 22 of the 411 referred patients were monitored (not further described); 566 of the 1162 not referred underwent expert review and were then re-assessed at 3-6 months Disease positive: 1; Disease negative: 588 *Expert opinion.* Reviewed by two dermatology experts using the recorded clinical history and examination, a digital photograph, and MoleMate image where available. Disease positive: 0; Disease negative: 725 **Target condition (Final diagnoses)** Melanoma (invasive): 30; Melanoma (in situ): 6; BCC: 10 'Benign' diagnoses: 1306
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?	No
Were the reference standard results likely to correctly classify the target condition (disease negative)?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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: 417 withdrew from control group after randomisation - 10 did not attend for dermatology assessment; 19 excluded; 1 died; 4 missing histology (in referred group; included as benign?); plus 12 with unknown outcome (in non-referred group, assumed benign and included)
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
Could the patient flow have introduced bias?	High risk

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Wells 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective - MelaFind diagnoses from acquisition study were used Retrospective image selection / Prospective interpretation - Clinical and dermoscopic images **Period of data collection** NR **Country** US
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Pigmented lesions cases selected from a repository of lesions amassed during an acquisition study conducted by MELA Sciences Inc for the US Food and Drug Administration **Setting:** Company database (MELA Sciences Inc) of lesion images amassed during an acquisition study for the FDA **Prior testing:** Selected for excision (no further detail) **Setting for prior testing:** Not reported **Exclusion criteria:** None reported **Sample size (patients):** NR **Sample size (lesions):** No. eligible NR; No. included: 47 **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?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Dermoscopy** No algorithm **Method of diagnosis:** Dermoscopic images **Prior test data:** Clinical images and detailed clinical history **Diagnostic threshold:** Not reported; Decision to biopsy the lesion / Melanoma or not **Diagnosis based on:** Average (n=39) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described **2. Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: MelaFind (EO Sciences, USA) (classifier NR) **System details:** Multispectral imaging system with integrated image analysis software; device takes images in vivo **No derivation aspect (external validation study)** Described in prior study Monheit 2011 **Lesion characteristics assessed:** – NR **Additional predictors included:** - None reported **Method of diagnosis:** - In person diagnosis - CAD-based diagnosis **Prior/other test data:** - Unclear **CAD output:** - Binary output: (1) positive, (lesion should be considered for biopsy to rule out melanoma); and (2) negative (lesion should be considered for later evaluation) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Unclear
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)	**Reference standard** Histological diagnosis alone Disease positive: 23 / Disease negative: 24 **Target condition (Final diagnoses)** Melanoma (in situ and invasive, or not reported): 23 'Benign' diagnoses: 24
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **Time interval to reference test:** NR; Images taken prior to biopsy
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
Could the patient flow have introduced bias?	Unclear risk

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Winkelmann 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control **Data collection:** Retrospective image selection / Prospective interpretation **Period of data collection** not reported **Country** Not reported
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Images of pigmented skin lesions previously analysed by a digital classifier MSDSLA; method of selection of the 12 not reported **Setting:** Dermoscopy conference **Prior testing:** Not reported **Setting for prior testing:** Unspecified **Exclusion criteria:** None reported **Sample size (patients):** NR **Sample size (lesions):** No. eligible No. included: 12 **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?	Unclear
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**1. Visual inspection (VI)** No algorithm **Method of diagnosis:** Clinical photographs **Prior test data:** Unclear **Diagnostic threshold:** Not reported - biopsy decision **Diagnosis based on:** Average (n=70) **Observer qualifications:** Dermatologist **Experience in practice:** Not described **Experience with index test:** Not described **Other detail:** Any other detail practitioners with a particular interest in skin cancer or technology may have chosen to attend this conference and/or self-selected to take part in the study. **2. Dermoscopy** No algorithm **Method of diagnosis:** dermoscopic images **Prior test data:** clinical images **Diagnostic threshold:** Not reported - biopsy decision **Test observers** as described for Visual Inspection (above) **3. Computer Assisted Diagnosis - Spectroscopy based** MSI-CAD system: MelaFind (EO Sciences, USA) (Logistic regression classifier) **System details:** Multispectral imaging system with integrated image analysis software; device takes images in vivo **No derivation aspect (reader study)** **Lesion characteristics assessed:** – NR **Additional predictors included:** - None **Method of diagnosis:** - Spectroscopic images - CAD-aided diagnosis **Prior/other test data:** - clinical and dermoscopic images **CAD output:** Binary output: (1) positive, (lesion should be considered for biopsy to rule out melanoma); and (2) negative (lesion should be considered for later evaluation) **Diagnostic threshold:** - Threshold not reported

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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
Was the CAD model evaluated in an independent study population?	
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No
Was the test interpretation carried out by an experienced examiner?	Yes
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	
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)	**Reference standard** Histological diagnosis alone Disease positive: 5 / Disease negative: 7 **Target condition (Final diagnoses)** Melanoma (invasive): 3 / Melanoma (in situ): 2 Mild/moderate dysplasia: 7 low grade dysplastic 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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the reference standard?	Unclear
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	**Exclusions from analysis:** None **Time interval to reference test:** Not reported
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

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Wollina 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Not reported **Period of data collection:** Jan 2003 to Oct 2004 **Country:** Germany (Dresden); Switzerland (Locarno and Lugarno)
Was a consecutive or random sample of patients enrolled?	Yes
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:** Pigmented skin lesions **Setting:** Secondary (general dermatology) Dept Dermatology, Dresden; Primary (private clinic), Locarno and Lugano **Prior testing:** - No prior testing Lugano and Locarno (described as representing 'a sort of first-screening check) - Clinical and/or dermatoscopic suspicion Dresden (described as having many patients referred for a second level control) **Setting for prior testing:** Unspecified **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 1308, No. included: NR **Sample size (lesions):** No. eligible: 3541, No. included: 466 **Participant characteristics:** Male: 566; 43.2% (full sample) **Thickness/depth:** ≤1mm: 38 (incl 8 in situ) Dresden: 22 (incl 4 in situ) Locarno: 7 (incl 2 in situ)Lugano 9 (incl 2 in situ)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Was an adequate spectrum of cases used to train the algorithm?	
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Computer Assisted Diagnosis - Dermoscopy based** Derm-CAD system: DB-MIPs (Biomips Engineering, Italy) (Euclidian distances classifier) **System details:** Dermoscopy unit, internal steromicroscope, internal DB, pattern analysis system. DDA software analysis – analyses 50 parameters subdivided into three categories, i.e. geometries, colours, and textures and islands of colours (Burroni islands) **No derivation aspect (external validation study)** **Lesion characteristics assessed:** – characteristics included 35 variables including: variance of symmetry, maximum diameter, border's gradient, skin red average, red average, red tenth, unbalance, dark areas towards periphery, dishomogeneity, blue dominant, transition, unbalance of transition **Additional predictors included:** - No further information used **Method of diagnosis:** - in person diagnosis - CAD-aided diagnosis **Operator qualifications:** - Not reported **Experience in practice:** - Not described **Experience with index test:** - Not described. States that test operators do not need a special training **Prior/other test data:** - CAD used as part of clinical analysis **CAD output:** - Not specified **Diagnostic threshold:** - The automated diagnosis was run at similprob=45 and similprob=75 thresholds, the latter being more sensitive but less specific. Similprob=75 threshold selected at random for review.

Computer-assisted diagnosis

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
Was the CAD model evaluated in an independent study population?	Yes
Was model overfitting accounted for during model development?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Was the diagnostic threshold to determine presence or absence of disease established in a previously published study?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Visual inspection

A. Risk of Bias

B. Concerns regarding applicability

Dermoscopy

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Reference standard** - Histological diagnosis alone Unclear whether data relate to compariaon with histology alone or to whoel set of lesions, in which case the reference standard is not reported for the majority of benign lesions although the 'decision to follow-up' is mentioned *Histology (not further described)* - No. patients/lesions: 466 - Disease positive: 52 (incl 8 in situ) - Disease negative: Either 414 or 3489 **Target condition** (Final diagnoses) - Melanoma (invasive): 44 - Melanoma (in situ): 8 - 'Benign' diagnoses: 414
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 likely to correctly classify the target condition (disease negative)?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Was the use of expert opinion (with no histological confirmation) avoided as the 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	**Exclusions from analysis:** None **Time interval to reference test:** CAD performed during clinical diagnosis, before histopathology. Interval to surgery 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
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Footnotes

Included studies: Two quality assessment items could not be evaluated for all studies, and so were left blank:

Patient Selection: Concerns regarding applicability: “Was an adequate spectrum of cases used to train the algorithm? (training set)” (Could only be answered if the study included a derivation aspect)**CAD Risk of Bias**: "Was model overfitting accounted for during model development?" (Could only be answered if the study included a derivation aspect)

Index test - CAD: Concerns regarding applicability: "Was the test interpretation carried out by an experienced examiner? (Could only be answered if the study gave computer generated CAD results to clinicians to make a diagnosis [CAD–aided diagnosis])"

Characteristics of excluded studies

Abbas 2010

Reason for exclusion	EXCLUDE on target condition *border detection not diagnosis*

Abbas 2011a

Reason for exclusion	• EXCLUDE on index test *test used to determine border* • EXCLUDE if derivation study

Abbas 2011b

Reason for exclusion	EXCLUDE on target condition *border detection not diagnosis*

Abbas 2012

Reason for exclusion	EXCLUDE if derivation study *Reports training on 20% and testing on 80% of images but results presented only for whole dataset* • EXCLUDE but contact authors *Reports training on 20% and testing on 80% of images but results presented only for whole dataset. Author responded - cannot help*

Abbas 2013a

Reason for exclusion	EXCLUDE on target condition *border detection not diagnosis*

Abbas 2013b

Reason for exclusion	EXCLUDE if individual lesion characteristics *seems to focus on border detection* • EXCLUDE if derivation study

Abuzaghleh 2015

Reason for exclusion	EXCLUDE if derivation study • EXCLUDE but contact authors *In the experiments, 75% of the database images are used for training and 25% are used for testing. No breakdown of D+/D- in the test set, cannot back calculate from the sensitivity and specificity values given*

Afonso 2012

Reason for exclusion	• EXCLUDE on index test *Not used to differentiate malignant from benign lesions*

Alfed 2015

Reason for exclusion	• EXCLUDE if derivation study *no independent test set used*

Ali 2012

Reason for exclusion	• EXCLUDE not a primary study

Altamura 2008

Reason for exclusion	EXCLUDE on index test *study of optimal surveillance/appropriate follow-up times not initial diagnosis*

Andreassi 1999

Reason for exclusion	EXCLUDE if derivation study *I think derivation? Uses jack knife validation*

Armengol 2011

Reason for exclusion	• EXCLUDE on index test • EXCLUDE if derivation study

Arroyo 2011

Reason for exclusion	EXCLUDE if individual lesion characteristics • EXCLUDE if derivation study

Ballerini 2012

Reason for exclusion	EXCLUDE on target condition *D+ includes AK*

Barata 2012a

Reason for exclusion	EXCLUDE if derivation study

Barata 2012b

Reason for exclusion	EXCLUDE if derivation study

Barata 2013

Reason for exclusion	EXCLUDE if derivation study

Barata 2015a

Reason for exclusion	EXCLUDE if derivation study *USes LOO procedure*

Barata 2015b

Reason for exclusion	EXCLUDE if derivation study *uses 10-fold classification*

Barata 2015c

Reason for exclusion	EXCLUDE if derivation study *uses 10-fold classification*

Binder 2000

Reason for exclusion	• EXCLUDE if derivation study *no independent test set*

Bjerring 2001

Reason for exclusion	• EXCLUDE not a primary study *leaflet*

Blum 2004

Reason for exclusion	EXCLUDE overlapping sudy population (Blum 2004b)

Boden 2013

Reason for exclusion	EXCLUDE if derivation study *uses leave-one-out method; no independent test set*

Bono 1999

Reason for exclusion	EXCLUDE if derivation study • EXCLUDE on 2x2 data *LFR: not a test accuracy study*

Borlu 2008

Reason for exclusion	EXCLDUE not a primary study - not test accuracy; no patient data in this study

Brown 2000

Reason for exclusion	EXCLUDE not a primary study *systematic review* • systematic review

Carrara 2007

Reason for exclusion	• EXCLUDE on reference standard <50% benign lesions had histology or clinical follow-up

Celebi 2008

Reason for exclusion	EXCLUDE if derivation study *this is a derivation study. From what I can deduce it seems like they used a sample of 100 images as a training set and test set. They then used the outcome of this to test out the technique on all the 545 images from the study sample. Their outcome is recorded as: "The performance of this decision tree on the entire image set (545 images) was a sensitivity of 69.35% and a specificity of 89.97%."*

Chen 2003

Reason for exclusion	EXCLUDE if individual lesion characteristics *investigates colour only* • EXCLUDE if derivation study • EXCLUDE on 2x2 data

Cheng 2012

Reason for exclusion	EXCLUDE if individual lesion characteristics *only telengiectasia used to evaluate whether a BCC or not. No other characteristics are evaluated* • EXCLUDE if derivation study

Cheng 2013

Reason for exclusion	EXCLUDE if derivation study • EXCLUDE on 2x2 data

Christensen 2010

Reason for exclusion	EXCLUDE if derivation study

Claridge 1992

Reason for exclusion	EXCLUDE if individual lesion characteristics *appears to be looking at the shape of the lesion*

Cukras 2013

Reason for exclusion	EXCLUDE not a primary study

Day 2001

Reason for exclusion	• EXCLUDE on reference standard *16/73 excised; 9 were melanoma*

Debeir 1999

Reason for exclusion	• EXCLUDE if derivation study

Di 2010

Reason for exclusion	EXCLUDE if derivation study *primarily derivations study with small paragraph on a validation study; limited details given* • EXCLUDE on 2x2 data *se/sp given for validation study for individual characteristics but not for overall se/sp of the system. [**could contact authors]* • EXCLUDE but contact authors *For the test database of 200 images do you have se/sp or 2x2 for the overall aability of the classifier to detect melanoma? Table 2 provides data for indivudal lesoin characteristcis only*

Ding 2015

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

Dreiseitl 2005

Reason for exclusion	EXCLUDE on index test *not test accuracy and the CDSS recommendations were simulated*

Durg 1993

Reason for exclusion	EXCLUDE on target condition *detection of variegated colouring*

Elbaum 2001

Reason for exclusion	• EXCLUDE if derivation study *uses LOO procedure*

Emery 2010

Reason for exclusion	• EXCLUDE on reference standard *only 111/1211 lesions were excised and the others did not have any reported follow-up.*

Engin 2016

Reason for exclusion	• EXCLUDE on sample size • EXCLUDE on reference standard

Ercal 1994

Reason for exclusion	EXCLUDE if derivation study

Faal 2013

Reason for exclusion	EXCLUDE if derivation study *The 436 images were split into 60% training and 40% test sets. They combined the results of the training and tests sets as an average of the performace of the test, no breakdown of the classifer rate according to the test and training images.*

Farina 2000

Reason for exclusion	EXCLUDE if derivation study - no test set

Ferris 2016

Reason for exclusion	EXCLUDE not a primary study

Fidalgo 2003

Reason for exclusion	EXCLUDE on 2x2 data • EXCLUDE duplicate or related publication *Appears to be superseded by* Serrao 2006 • EXCLUDE but contact authors *Paper provides % of MM and of DN with DNAOS scores of >=5.5 and >7, is it possible for you to provide the same information for the remaining 127 lesions in the study? Also can you advise as to whether any of the 247 lesions included in this study overlap with the 652 reported in* Serrao 2006 *(#1144)?*

Fikrle 2007

Reason for exclusion	EXCLUDE on reference standard *follow up study need >=50% of participants to have their lesion excised.*

Fikrle 2013

Reason for exclusion	• EXCLUDE on reference standard *Follow up study <50% of study participants have their final diagnosis reached by histopathology.*

Fruhauf 2012

Reason for exclusion	EXCLUDE on reference standard *35/219 underwent histology; 13 followed-up; 171 expert clinical Dx*

Fueyo-Casado 2009

Reason for exclusion	EXCLUDE on reference standard *<50% of the study population recieved histology as a test. No information given on those who were followed up.*

Ganster 2001

Reason for exclusion	EXCLUDE if derivation study *Use leave one out methods for cross validation Seem like they have a "test set" for the automated diagnosis but it is not clear whether data given in table 1 incorporates data from the training set as well. It is likely that there is some crossover.*

Garcia 2014

Reason for exclusion	EXCLUDE on target condition *test aims to detect presence of pigment network, is not an evaluation of detection of MM*

Garcia-Uribe 2004

Reason for exclusion	• EXCLUDE on index test *reflectance spectrometry/spectroscopy* • EXCLUDE if derivation study **[very difficult to classify given mention of training/test sets of images, however all images appear to have come from same sample of lesions, all of which were used to develop the classifiers. Even though new images were obtained from same lesions, I still think this is derivation]*

Garcia-Uribe 2010

Reason for exclusion	• EXCLUDE on 2x2 data *only give the values for sensitivity and specificity but do not give a breakdown of D+/D- numbers in the test set so not able to populate the 2x2 table.* • EXCLUDE but contact authors *Paper provides sensitivity and specificity for the test set but does not give a breakdown of numbers D+/D- to allow us to populate the 2x2 table.*

Garnavi 2012

Reason for exclusion	EXCLUDE on reference standard *not properly defined the reference standard, it could be the images were sampled from a database of histopathologically diagnosed lesions but this is not very clear from the paper*

Gerger 2003

Reason for exclusion	EXCLUDE on reference standard *no reference standard in 133 nevi, unclear whether these were in the test set. Training sets (n=2) and test set must overlap as total number of lesions (n=423) add up to more than total included lesions (n=136).*

Glotsos 2015

Reason for exclusion	EXCLUDE if derivation study *uses LOO procedure*

Gniadecka 2004

Reason for exclusion	• EXCLUDE on index test *Raman spectroscopy* • EXCLUDE if derivation study *Seems like a derivation study; although methods do report use of a 'test set', this is not further described* • EXCLUDE on 2x2 data

Govindan 2007

Reason for exclusion	• EXCLUDE on reference standard *"Six hundred and twenty seven (71%) lesions were diagnosed as benign and were discharged from the PLC" "As the patients who were clinically diagnosed as having benign lesions did not undergo biopsy of their lesions, the false negative rate for the consultant could not be determined. None of the patients with benign lesions from this study have reported back to the PLC with any concern about their lesions and none have had excision biopsy of their lesions."*

Green 1991

Reason for exclusion	EXCLUDE if derivation study - no test set

Green 1994

Reason for exclusion	EXCLUDE if derivation study *CAD - no independent test set*

Guerra-Rosas 2015

Reason for exclusion	EXCLUDE if derivation study *no test set* • EXCLUDE on 2x2 data *no se/sp presented*

Guillod 1996

Reason for exclusion	EXCLUDE if derivation study

Gutkowicz-Krusin 2000

Reason for exclusion	EXCLUDE on sample size *2 melanoma* • EXCLUDE if derivation study

Hacioglu 2013

Reason for exclusion	Does not provide 2x2 data for an investigated outcome

Haenssle 2004

Reason for exclusion	• EXCLUDE on target condition *this reads very much like a follow up paper- not sure it is really relevant to our reviews.*

Haenssle 2010

Reason for exclusion	EXCLUDE on 2x2 data *Does not report specificity* • EXCLUDE duplicate or related publication *same patients as Haenssle 2010 #191*

Haniffa 2007

Reason for exclusion	EXCLUDE on reference standard *looks like approximately 20% of patients recieved a final diagnosis by histology. 179 biopsies were performed. Total sample was 881 lesions*

Hintz-Madsen 2001

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

Hoffmann 2003

Reason for exclusion	EXCLUDE if derivation study *Uses LOO procedure* • EXCLUDE on 2x2 data *Only giving ROC values not able to extract a 2x2 table*

Horsch 1997

Reason for exclusion	EXCLUDE if derivation study

Huang 1996

Reason for exclusion	EXCLUDE if individual lesion characteristics *Border irregularity not overall dx* • EXCLUDE on 2x2 data

Ikuma 2013

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

Isasi 2011

Reason for exclusion	EXCLUDE if derivation study

Iyatomi 2006

Reason for exclusion	EXCLUDE if derivation study *uses LOO procedure and same lesions and tumour extraction method as* Iyatomi 2006 • EXCLUDE on 2x2 data

Iyatomi 2008a

Reason for exclusion	• EXCLUDE if derivation study

Iyatomi 2008b

Reason for exclusion	• EXCLUDE if derivation study

Iyatomi 2008c

Reason for exclusion	EXCLUDE if derivation study *the performance was evaluated by averaging both combinations (training and test sets) they did not present the data separately; uses LOO procedure* • EXCLUDE on 2x2 data *Not test accuracy; compares automated with manual extraction of tumour area*

Iyatomi 2010a

Reason for exclusion	EXCLUDE if individual lesion characteristics • EXCLUDE on 2x2 data *not a test accuracy study*

Iyatomi 2010b

Reason for exclusion	• EXCLUDE on target condition *differentiates melanocytic from non-melanocyitc lesinos and not malignant from benign*

Iyatomi 2011

Reason for exclusion	EXCLUDE on index test *colour calibration rather than MM detection* • EXCLUDE if individual lesion characteristics • EXCLUDE on 2x2 data *not a test accuracy study*

Jain 2015

Reason for exclusion	• EXCLUDE not a primary study

Jakovels 2013

Reason for exclusion	EXCLUDE on reference standard *reference standard test not reported*

Jamora 2003

Reason for exclusion	EXCLUDE on reference standard *no referene standard for index test negatives*

Jaworek-Korjakowska 2016a

Reason for exclusion	• EXCLUDE if derivation study *no separate test set*

Jaworek-Korjakowska 2016b

Reason for exclusion	• EXCLUDE if derivation study *uses cross-validation with no separate test set* • EXCLUDE on 2x2 data *only gives accuracy, not se/sp*

Jeddi 2016

Reason for exclusion	• EXCLUDE on study population *unclear whether data for BCC inlcudes only those with lesions actually suspicious for BCC* • EXCLUDE on index test *limited details* • EXCLUDE on reference standard *appears to be expert Dx*

Kahofer 2002

Reason for exclusion	• EXCLUDE if derivation study *Lesions not split into training/test*

Kaur 2015

Reason for exclusion	EXCLUDE on reference standard *% of benign with histology versus expert dx not reported* • EXCLUDE on 2x2 data *Only gives AUC and not se/sp* • EXCLUDE but contact authors *1. reference standard in benign group 2. se/sp for model using all four features needed Dr WV Stoeker e-mail: wvs@mst.edu*

Korotkov 2012

Reason for exclusion	• EXCLUDE not a primary study *narrative review*

Kuzmina 2011

Reason for exclusion	EXCLUDE if derivation study • EXCLUDE on reference standard *reference standard test not reported*

Landau 1999

Reason for exclusion	• EXCLUDE if derivation study *No indication that system has previously been evaluated*

LeAnder 2010

Reason for exclusion	• EXCLUDE if derivation study *no separate 2x2 data for training set and test set*

Lefevre 2000

Reason for exclusion	• EXCLUDE on index test *Limited test detail; cannot tell whether clinical or dermoscopic images used even* • EXCLUDE on reference standard *No details of reference standard*

Lihacova 2013

Reason for exclusion	EXCLUDE if derivation study *No test set*

Liu 2012

Reason for exclusion	EXCLUDE if derivation study *asymmetry detection; 10-fold cross validation* • EXCLUDE on 2x2 data

Machado 2015

Reason for exclusion	EXCLUDE on target condition *detection of reticular pattern not MM*

Maglogiannis 2004

Reason for exclusion	• EXCLUDE if derivation study • EXCLUDE on 2x2 data

Maglogiannis 2006

Reason for exclusion	EXCLUDE if derivation study *They incorporated the training set population together with the test set as shown below "A training set of 500 cases was randomly selected from the dataset of the total cases. The accuracy of the classification algorithm was examined using a test set consisted of the full set of 1041 cases."*

Manousaki 2006

Reason for exclusion	EXCLUDE if derivation study - Training set only

Marchesini 1992

Reason for exclusion	EXCLUDE if derivation study - no independent data set

Masood 2013

Reason for exclusion	EXCLUDE if derivation study

Menzies 1999

Reason for exclusion	• EXCLUDE not a primary study

Mete 2011

Reason for exclusion	• EXCLUDE if derivation study • EXCLUDE on 2x2 data *Not test accuracy*

Mhaske 2013

Reason for exclusion	• EXCLUDE if derivation study • EXCLUDE on 2x2 data *Not test accuracy*

Moncrieff 2002

Reason for exclusion	EXCLUDE if derivation study - no independent test set

Morrow 2010

Reason for exclusion	• EXCLUDE not a primary study *narrative review*

Nagaoka 2012

Reason for exclusion	EXCLUDE on 2x2 data *they did not give the number of lesions in test set, they state The sensitivity of 90% and specificity of 84% was obtained by applying this threshold value to the validation set. Cannot see how to work out the 2x2 data from this information* • EXCLUDE but contact authors *Can you provide us with the number of lesions in the test set, with a breakdown of number of melanoma vs other lesions? We can then use the sensitivity of 90% and specificity of 84% provided to work out the 2x2.*

Nagaoka 2013

Reason for exclusion	EXCLUDE if derivation study *index was developed on nonglabrous skin and is being applied to acral skin for first time which makes it a derviation study?* • EXCLUDE on reference standard *No reference standard reported for D-*

Nagaoka 2015

Reason for exclusion	EXCLUDE on reference standard • EXCLUDE but contact authors reference standard *not clearly reported - "Lesions that were clinically judged benign were not biopsied because of ethical reasons." T. Nagaoka e-mail: nagaoka@aoni.waseda.jp **Previous contact for prior studies was unsuccessful*

Noroozi 2016

Reason for exclusion	EXCLUDE on index test

Oka 2004

Reason for exclusion	• EXCLUDE not a primary study *letter*

Oka 2004a

Reason for exclusion	• EXCLUDE if derivation study *uses LOO procedure*

Oka 2006

Reason for exclusion	EXCLUDE not a primary study *letter*

Pellacani 2004a

Reason for exclusion	• EXCLUDE if individual lesion characteristics

Pellacani 2004b

Reason for exclusion	EXCLUDE if individual lesion characteristics *this paper seems to be examing colours in melanocytic lesion (ML) images. which I think means it is only looking at an individual lesion characteristic. However they do have a test set so based on this it would be an include?*

Pellacani 2006

Reason for exclusion	EXCLUDE if derivation study *looks at detection of asymmetry between clinicians and computer* • EXCLUDE on 2x2 data *2x2 could be derived for overall asymmetry or border cut-off but not overall diagnosis*

Perrinaud 2007

Reason for exclusion	• EXCLUDE on sample size *CAD - fewer than 5 melanomas (not including 'typical' melanomas)* • EXCLUDE on index test *Does not provide data for visual inspection alone*

Pompl 2000

Reason for exclusion	EXCLUDE if derivation study *Train set (60 mel and 60 benign) reincluded for model evaluation*

Rajpara 2009

Reason for exclusion	EXCLUDE not a primary study *Systematic review* • systematic review

Rastgoo 2015

Reason for exclusion	• EXCLUDE if derivation study *Difficult one as it does describe splitting each set of 180 lesions into 70% for training, 15% for validation and 15% for testing (n=27?). But it's difficult to follow what the results actually relate to, especially as the classifier is repeated 10 times with different sets of dysplastic lesions but the same melanoma cases*

Rigel 2012

Reason for exclusion	EXCLUDE duplicate or related publication *CAD - all lesions included in* Monheit 2011

Rosado 2003

Reason for exclusion	• EXCLUDE not a primary study *Systematic Review* • systematic review

Rubegni 2001a

Reason for exclusion	EXCLUDE not a primary study *letter*

Rubegni 2001b

Reason for exclusion	EXCLUDE if derivation study *paper states that the accuracy estimates (sensitivity, specificty) are given using the leave one out method but they have not given a breakdown of the actually number. its not possible to tell if they used the whole study sample.*

Rubegni 2002a

Reason for exclusion	EXCLUDE if derivation study *the training and test data not given separately.*

Rubegni 2005

Reason for exclusion	• EXCLUDE not a primary study *Editorial*

Rubegni 2010

Reason for exclusion	EXCLUDE if derivation study *uses LOO procedure* • EXCLUDE on 2x2 data

Rubegni 2013

Reason for exclusion	• EXCLUDE if derivation study

Sadeghi 2013

Reason for exclusion	• EXCLUDE if individual lesion characteristics *irregular streaks* • EXCLUDE on 2x2 data *Only given the AUC values not possible to work out 2x2 from this.*

Safi 2011

Reason for exclusion	EXCLUDE if derivation study

Salerni 2012

Reason for exclusion	EXCLUDE on index test *test used for surveillance*

Sboner 2001

Reason for exclusion	EXCLUDE duplicate or related publication *same data as Sboner 2004*

Sboner 2003

Reason for exclusion	• EXCLUDE if derivation study *derivation? but describes 10-fold cross-validation rpocess for training/testing classifier. Check w statistician Also could include dermatologists diagnosis (via dermoscopic mages?) if read Se/Sp pairs from plot*

Sboner 2004

Reason for exclusion	EXCLUDE if derivation study *Uses LOO method with no independent test set for validation* *[the whole set of cases is divided in 10 disjoint sets, which are used as test cases. For each test set, the remaining nine sets are used to train the classifiers (training set). The final results are the average values computed on the ten test sets.]*

Schindewolf 1993

Reason for exclusion	EXCLUDE on 2x2 data *not given enough information to populate 2x2 data*

Schindewolf 1994

Reason for exclusion	EXCLUDE on index test *evaluates CAD not VI* • EXCLUDE if derivation study *uses cross-validation*

Schmid-Saugeon 2003

Reason for exclusion	EXCLUDE if derivation study *no separate test set for validation*

Schumacher 2016

Reason for exclusion	• EXCLUDE not a primary study *comment paper*

Seidenari 1995

Reason for exclusion	EXCLUDE on index test *comparing two ways of attaining videomicroscope images no accuracy data provided* • EXCLUDE on 2x2 data

Seidenari 2005

Reason for exclusion	• EXCLUDE on reference standard *All D+ were excised (n=95) but only 45% of benign group were excised (76 AN plus 30% of BN (86/288)) and methods of estabishing final diagnosis was not reported for the remainder.* • EXCLUDE but contact authors *We would like to include test accuracy results from this study, however in order to do so we would need some further information on how the final diagnosis was reached for thos lesions that were not excised. We have noted that all D+ lesions were excised (n=95) and 45% of benign lesions were excised (76 atypical naevi plus 30% of benign (86/288)). Can you advise us as to how the final diagnosis was reached for the remaining 126 benign lesions?*

Seidenari 2007

Reason for exclusion	• EXCLUDE if individual lesion characteristics *CAD only - CAD system based on single characteristic*

Seidenari 2012

Reason for exclusion	EXCLUDE on index test *CAD ONLY - does not evaluate a CAD system* • EXCLUDE if individual lesion characteristics *looks at indvdl lesion chars to distinguish Mel in situ, also gives mean ABCD and seven point scores* • EXCLUDE on 2x2 data • EXCLUDE but contact authors *Table 3 provides mean ABCD and seven point checklist scores, are you able to provide us with a cross tabulation of results with each checklist at 'standard' thresholds against final diagnosis? e.g. ABCD >4.75 and >5.45 for MIS and benoign groups 7-point checklist: presence >=2 chars and >=3 chars?*

Shakya 2012

Reason for exclusion	EXCLUDE on target condition *SCC in situ is not inlcuded in target condition*

She 2007

Reason for exclusion	EXCLUDE if derivation study

She 2013

Reason for exclusion	• EXCLUDE if derivation study *no separate data for training and test set. used leave-one-out technique*

Shimizu 2012

Reason for exclusion	• EXCLUDE if derivation study *The performance was evaluated under the leave-one-out cross-validation test.*

Skrovseth 2010

Reason for exclusion	EXCLUDE not a primary study *Statistical paper for developing a new algorithm*

Smith 2000

Reason for exclusion	EXCLUDE if derivation study

Sober 1994

Reason for exclusion	• EXCLUDE if individual lesion characteristics *Reports separately for shape, radii and border but not overall classification; note these sare results for one centre taking part in a larger multi-centre study*

Stanganelli 1995

Reason for exclusion	• EXCLUDE on index test *aim of study is to assess the intraobserver agreement*

Stanley 2007

Reason for exclusion	EXCLUDE if individual lesion characteristics • EXCLUDE if derivation study

Stanley 2008

Reason for exclusion	EXCLUDE if derivation study *cross validation study (check eligibility);*

Stoecker 2005

Reason for exclusion	EXCLUDE if individual lesion characteristics • EXCLUDE if derivation study

Swanson 2010

Reason for exclusion	EXCLUDE on index test *reflectance spectroscopy* • EXCLUDE if derivation study *This looks like an include as they mention a pilot study of 47 initial patients. There is an additional 47 patients included, however it seems that they have combined the data so for this reason it would be an excluded if derivation study-as the training data and test data are combined.*

Tehrani 2006

Reason for exclusion	EXCLUDE if derivation study **[Borderline exclude - 4 features of NMSC identifed in pilot study and re-examined in larger sample here; diagnostic model then created based on signiicaince of characteristics and se/sp data give. No test set presented]*

Terstappen 2007

Reason for exclusion	• EXCLUDE on study population *Includes only BCC - looking for BCC chars on Siascope* • EXCLUDE if derivation study *Derivation study; first application of Siascope to pigmented BCC; 21/25 lesions were BCCs*

Varol 2006

Reason for exclusion	• EXCLUDE not a primary study *Link to study with correction "Error in Byline. In the the Study by Menzies et al titled "The Performance of SolarScan: An Automated Dermoscopy Image Analysis Instrument for the Diagnosis of Primary Melanoma," published in the November 2005 issue of the ARCHIVES (2005;141:1388-1396), the name of the one of the authors was misspelled. The author's name is Alexandra Varol, B Med."*

Vestergaard 2008

Reason for exclusion	• EXCLUDE not a primary study *systematic review* • systematic review

Wallace 2000a

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

Wallace 2000b

Reason for exclusion	EXCLUDE on 2x2 data

Wallace 2002

Reason for exclusion	EXCLUDE if derivation study - Uses LOO cross-validation

Walter 2010

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

Watson 2009

Reason for exclusion	EXCLUDE on 2x2 data *Not test accuracy; training in MoleMate*

Wazaefi 2012

Reason for exclusion	• EXCLUDE if derivation study *no separate independent test set they used a 20 folds cross-validation*

Wells 2011

Reason for exclusion	• EXCLUDE not a primary study *see* Wells 2012 • EXCLUDE duplicate or related publication *see* Wells 2012

Wilson 2013

Reason for exclusion	EXCLUDE on 2x2 data *this study is an economic evaluation of a SIAscopy, which itself was trialled in another paper - not enough data to populate 2x2 table*

Winkelmann 2015a

Reason for exclusion	EXCLUDE duplicate or related publication

Winkelmann 2015b

Reason for exclusion	EXCLUDE on target condition *D+ incldues 15 lesions with moderate dysplasia* • EXCLUDE on sample size *only 1 MM*

Winkelmann 2015c

Reason for exclusion	EXCLUDE on sample size

Winkelmann 2015d

Reason for exclusion	• EXCLUDE duplicate or related publication

Winkelmann 2016a

Reason for exclusion	EXCLUDE on index test *aim of the test to to investigate correlation with clinical histology features (development of new CAD system?)*

Wood 2008

Reason for exclusion	EXCLUDE on 2x2 data *Not test accuracy - acceptability etc*

Yoo 2015

Reason for exclusion	EXCLUDE conference abstract

Zagrouba 2004

Reason for exclusion	• EXCLUDE on reference standard *No reference standard details provided* • EXCLUDE but contact authors *Contacted re reference standard Author responded - can't help*

Zhou 2010a

Reason for exclusion	• EXCLUDE if derivation study

Zhou 2010b

Reason for exclusion	EXCLUDE if individual lesion characteristics

Zortea 2014

Reason for exclusion	• EXCLUDE if derivation study *Although data are divided into training and test sets, the test set data is used more than once over 20 realisations of each model, especailly th emalanomas, for which the same 10 are used in each realisation*

Zouridakis 2004

Reason for exclusion	• EXCLUDE on study population • EXCLUDE on sample size • EXCLUDE if derivation study

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of results tables

1 Summary of findings table

Question:	**What is the diagnostic accuracy of computer-assisted diagnosis for the detection of: i) cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, ii) BCC, or iii) cSCC in adults?**				
Population:	Adults with lesions suspicious for skin cancer, including: • Any lesion referred for specialist investigation due to suspicion of skin cancer, and • Any lesion excised due to suspicion of skin cancer				
Index test:	Computer-assisted diagnosis (CAD)				
Comparator test:	Dermoscopy				
Target condition:	Cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, or basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC)				
Reference standard:	Histology with or without long term follow-up				
Action:	If accurate, positive results of CAD will identify skin cancers that could otherwise be missed, while negative results will stop patients having unnecessary excision of skin lesions				
Quantity of evidence					
Number of studies	**42[a]**	**Total lesions with test results**	**13,445**	**Total with target condition**	**2452**
Limitations					
Risk of bias:	Patient selection methods were poorly reported with some concern (34/42) due to use of case-control designs, exclusion of difficult to diagnose types of lesion, and inadequate reporting to assess risk of bias. CAD was generally evaluated in independent populations (35/42). Some concern as it was not clear that the reference standard was interpreted blind to the CAD results in 19/42 studies. Differential verification was used in 6/42 studies, participants were excluded in 10/42, primarily due to technical difficulties with CAD. Timing of tests was not mentioned in 28/42.				

Question:	**What is the diagnostic accuracy of computer-assisted diagnosis for the detection of: i) cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, ii) BCC, or iii) cSCC in adults?**					
Applicability of evidence to question:	High concern for poor clinical applicability of included studies. Almost all studies recruited narrowly defined populations (41/42) and/or multiple lesions per patient (14/42) and may not be representative of populations eligible for CAD. Studies provided little information regarding the thresholds used for presence of malignancy (16/42) and often evaluated unestablished thresholds (23/42). Studies performing training of algorithms provided scarce information on the range of conditions included in training sets. model derivation gave Little information was given concerning the expertise of the histopathologist.					
FINDINGS: All analyses are undertaken on subgroups of the studies						
All included studies considered the detection of melanoma, three of which also looked at the detection of BCC and 1 at the detection of cSCC. There is therefore not sufficient data to make summary statements regarding the accuracy of CAD for the detection of BCC or cSCC. All results below consider the detection of the primary target condition: cutaneous invasive melanoma and atypical intraepidermal melanocytic variants.						
Test: Digital-dermoscopy based CAD (all systems)						
Quantity of evidence	Number of studies	**22**	Total lesions with test results	**8992**	Total with melanoma	**1063**
Sensitivity (95% CI): 90.1% (84.0, 94.0) **Specificity (95% CI):** 74.3% (63.6, 82.7)				**Numbers observed in a cohort of 1000 people being tested[b]**		
Consistency	Sensitivity estimates consistent. Some heterogeneity in specificity between studies.	**Consequences**		**Prevalence**		
				7%	**20%**	**40%**
		True positives	**Receive necessary excision**	63	180	360
		False positives	**Receive unnecessary excision**	239	206	154
		False negatives	**Do not receive required excision**	7	20	40
		True negatives	**Appropriately do not receive excision**	691	594	446
		PPV		21%	46%	70%
		NPV		99%	97%	92%
Test: Multispectral imaging based CAD (all systems)						
Quantity of evidence	Number of studies	**8**	Total lesions with test results	**2401**	Total with melanoma	**286**
Sensitivity (95% CI): 92.9% (83.7, 97.1) **Specificity (95% CI):** 43.6% (24.8, 64.5)				**Numbers observed in a cohort of 1000 people being tested**		

Question:	What is the diagnostic accuracy of computer-assisted diagnosis for the detection of: i) cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, ii) BCC, or iii) cSCC in adults?					
Consistency	Sensitivity estimates consistent. High heterogeneity in specificity between studies.	Consequences		Prevalence		
				7%	20%	40%
		True positives	Receive necessary excision	65	186	372
		False positives	Receive unnecessary excision	525	451	338
		False negatives	Do not receive required excision	5	14	28
		True negatives	Appropriately do not receive excision	405	349	262
		PPV		12%	29%	52%
		NPV		99%	96%	90%

Footnotes

[a]six studies with overlapping lesions (Seidenari 1998 & Seidenari 1999; Tomatis 2003 & Bono 2002; Monheit 2011 & Hauschild 2014)

[b]Numbers estimated at 25th, 50th (median) and 75% percentiles of invasive melanoma and atypical intraepidermal melanocytic variants prevalence, observed across 42 studies reporting evaluations of CAD.

BCC - Basal cell carcinoma; CAD - computer-assisted diagnosis; CI - confidence interval; cSCC - cutaneous squamous cell carcinoma; NPV - negative predictive value; PPV - positive predicitive value

Additional tables

1 Glossary of terms

Term	Definition
Artificial intelligence	Computer systems undertaking tasks that normally require human intelligence, such as decision–making or visual perception
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma *in situ* and lentigo maligna
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin
Basaloid cells	Cells in the skin that look like those in epidermal basal layer
BRAF V600 mutation	BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. BRAF mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs.
BRAF inhibitors	Therapeutic agents which inhibit the serine-threonine protein kinase BRAF mutated metastatic melanoma.
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour.
Congenital naevi	A type of mole found on infants at birth
Dermoscopy	Whereby a handheld microscope is used to allow more detailed, magnified, examination of the skin compared to examination by the naked eye alone
Dermo-epidermal junction	The area where the lower part of the epidermis and top layer of the dermis meet
Dermis	Layer of skin below the epidermis, composed of living tissue and containing blood capillaries, nerve endings, sweat glands, hair follicles and other structures
Desmoplastic subtypes of SCC	An aggressive squamous cell carcinoma variant characterised by a proliferation of fibroblasts and formation of fibrous connective tissue
Electrodesiccation	The use of high frequency electric currents to cut, destroy or cauterise tissue. It is performed with the use of a fine needle-shaped instrument

Term	Definition
Electrical impedance spectroscopy	The measurement of electrical current properties as they pass through skin tissues, to retrieve information on cellular structures
Epidermis	Outer layer of the skin
False negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.
False positive	An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease.
Histopathology/Histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope.
Incidence	The number of new cases of a disease in a given time period.
Index test	A diagnostic test under evaluation in a primary study
Interferometry	The measurement of waves of light or sound after interference in order to extract information
Lentigo maligna	Unusual area of darker pigmentation contained within the epidermis which includes malignant cells but with no invasive growth. May progress to an invasive melanoma
Lymph node	Lymph nodes filter the lymphatic fluid (clear fluid containing white blood cells) that travels around the body to help fight disease; they are located throughout the body often in clusters (nodal basins).
Melanocytic naevus	An area of skin with darker pigmentation (or melanocytes) also referred to as ‘moles’
Meta-analysis	A form of statistical analysis used to synthesise results from a collection of individual studies.
Metastases/metastatic disease	Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system.
Morbidity	Detrimental effects on health.
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1000, 10,000 or 100,000 people.
Multidisciplinary team	A team with members from different healthcare professions and specialties (e.g. urology, oncology, pathology, radiology, and nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.
Naevus	A mole or collection of pigment cells (plural: naevi or nevi)
Optical coherence tomography (OCT)	Based on the same principle as ultrasound, OCT uses a handheld probe to measure the optical scattering of near-infrared (1310 nm) light waves (rather than sound waves) from under the surface of the skin
Prevalence	The proportion of a population found to have a condition.
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it which might affect the patient’s prognosis.
Receiver operating characteristic (ROC) plot	A plot of the sensitivity and 1 minus the specificity of a test at the different possible thresholds for test positivity; represents the diagnostic capability of a test with a range of binary test results
Receiver operating characteristic (ROC) analysis	The analysis of a ROC plot of a test to select an optimal threshold for test positivity
Recurrence	Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.
Reference Standard	A test or combination of tests used to establish the final or ‘true’ diagnosis of a patient in an evaluation of a diagnostic test
Reflectance confocal microscopy (RCM)	A microscopic technique using infrared light (either in a handheld device or a static unit) that can create images of the deeper layers of the skin
Resolution	Resolution in an imaging system refers to its ability to distinguish two points in space as being separate points; resolution is measured in two directions: axial and lateral.

Term	Definition
Sensitivity	In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test
Specificity	The proportion of individuals without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Spectroscopy	Study of the interaction between matter and electromagnetic radiation
Spindle subtypes of SCC	A squamous cell carcinoma variant characterised by poorly differentiated spindle cells surrounded by collagenous stroma
Staging	Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.
Stratum corneum	The outermost layer of the epidermis. This layer is the most superficial layer of skin, which is composed of flattened skin cells organised like a brick wall. In normal conditions cells are not nucleated at this layer
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination.

Footnotes

2 A cross-tabulation of studies by CAD type, reported comparisons and target conditions

Study	CAD type	CAD system	CAD diagnosis	Comparison with dermoscopy	Target conditions[a]
Bauer 2000	Derm–CAD	DB-MIPs	CAD diagnostic aid	in–person dermoscopy	1
Wollina 2007	Derm–CAD	DB-MIPs	CAD diagnostic aid	No	1
Burroni 2004	Derm–CAD	DB-MIPs	CAD only	No	1
Rubegni 2002	Derm–CAD	DB-MIPs	CAD only	No	1
Seidenari 1998	Derm–CAD	DB-MIPs	CAD only	image–based assessment	1
Seidenari 1999	Derm–CAD	DB-MIPs	CAD only	No	1
Stanganelli 2005	Derm–CAD	DB-MIPs	CAD only	No	1
Piccolo 2002	Derm–CAD	DEM-MIPS	CAD only	image–based assessment	1
Binder 1998	Derm–CAD	IBAS 2000	CAD only	No	1
Barzegari 2005	Derm–CAD	MicroDERM	CAD only	No	1
Boldrick 2007	Derm–CAD	MicroDERM	CAD only	No	1
Serrao 2006	Derm–CAD	MicroDERM	CAD only	No	1
Dreiseitl 2009	Derm–CAD	Image J (MoleMax II)	CAD only	in–person dermoscopy	1
Maglogiannis 2015	Derm–CAD	System name NR (MoleMax II)	CAD only	No	1
Mollersen 2015	Derm–CAD	Nevus Doctor Mole Expert	CAD only	No	1,5
Piccolo 2014	Derm–CAD	Nevuscreen	CAD diagnostic aid	image–based assessment	1
Cascinelli 1992	Derm–CAD	Skin View	CAD only	No	1,5
Cristofolini 1997	Derm–CAD	Skin View	CAD only	No	1
Menzies 2005	Derm–CAD	SolarScan	CAD only	Excluded (different sample sizes)	1,4
Binder 1994	Derm–CAD	System name NR	CAD only	image–based assessment	1
Blum 2004b	Derm–CAD	System name NR	CAD only	Excluded (different sample sizes)	1

Study	CAD type	CAD system	CAD diagnosis	Comparison with dermoscopy	Target conditions[a]
Ferris 2015	Derm–CAD	System name NR	CAD only	Excluded (different sample sizes)	1,2,5
Gilmore 2010	Derm–CAD	System name NR	CAD only	image–based assessment	1
Menzies 1996	Derm–CAD	System name NR	CAD only	image–based assessment	4
Hauschild 2014	MSI–CAD	MelaFind	CAD diagnostic aid	image–based assessment	1,4
Winkelmann 2016	MSI–CAD	MelaFind	CAD diagnostic aid	image–based assessment	1
Friedman 2008	MSI–CAD	MelaFind	CAD only	image–based assessment	1,4
Monheit 2011	MSI–CAD	MelaFind	CAD only	No	1
Wells 2012	MSI–CAD	MelaFind	CAD only	image–based assessment	1
Sgouros 2014	MSI–CAD	Siascope (version NR)	CAD only	No	5
Glud 2009	MSI–CAD	Siascope II	CAD only	image–based assessment	1
Terstappen 2013	MSI–CAD	Siascope V	CAD only	No	4
Walter 2012	MSI–CAD	Siascope V (MoleMate)	CAD diagnostic aid	No	1,4,5
Tomatis 2005	MSI–CAD	Spectroshade	CAD only	No	1
Ascierto 2010	MSI–CAD	Spectroshade	CAD only	in–person dermoscopy	4
Gutkowicz Krusin 1997	MSI–CAD	System name NR	CAD only	No	1
Tomatis 2003	MSI–CAD	Telespectrophotometric system	CAD only	No	1
Bono 1996	MSI–CAD	Telespectrophotometric System	CAD only	No	4
Bono 2002	MSI–CAD	Telespectrophotometric System	CAD only	in–person dermoscopy	1
Garcia Uribe 2012	DRS–CAD	OIDRS	CAD only	No	1,5
Malvehy 2014	EIS–CAD	Nevisense	CAD only	Excluded (different sample sizes)	1,2,3,4,5
Mohr 2013	EIS–CAD	Nevisense	CAD only	No	1,2,4,5

Footnotes

Key: Derm-CAD – Dermoscopy based computer–assisted diagnosis; DRS–CAD – diffuse reflectance spectroscopy computer–assisted diagnosis; EIS-CAD - Electrical impedance based computer assisted diagnosis; MSI-CAD - Multispectral imaging based computer–assisted diagnosis; NR – Not reported; OIDRS - oblique incidence reflectance spectroscopy.

[a]1 – Invasive melanoma and atypical intraepidermal melanocytic variants, 2 – Basal cell carcinoma, 3 – cutaneous Squamous cell carcinoma, 4 – Invasive melanoma alone, 5 – Any skin cancer or lesion requiring excision

3 Characteristics of included digital dermoscopy-based CAD (Derm–CAD) systems

Derm-CAD processing machine	Role of machine	Image analysis	Classifier	CAD output	Studies
MicroDERM (Visiomed AG, Germany)	dermoscopy unit with internal camera containing analysis system	DANAOS software combines analytical system based on ABCD with database of 21,000 PSLs.	ANN	DANAOS score indicating risk of malignancy	Barzegari 2005 Serrao 2006 Boldrick 2007

Derm-CAD processing machine	Role of machine	Image analysis	Classifier	CAD output	Studies
DB–Dermo MIPS (Biomips Engineering, Italy)	dermoscopy unit, internal stereomicroscope, internal DB, pattern analysis system	DB–MIPS pattern analysis system – integrated database stores the patient's data and the description of the lesion along with the image icons. 38 features analysed (grouped into geometries, colours and Burroni's islands of colours).	ANN	Diagnosis suggested (e.g. melanoma, benign melanocytic nevus)	Bauer 2000 Rubegni 2002
		Automatic Data Analysis for Melanoma early detection (ADAM) software which analyses boundary shape, texture and colour distribution	SVM	Low risk, intermediate risk or high risk of melanoma	Stanganelli 2005
		DB–MIPS pattern analysis system	Multivariate discriminant analysis	Graphical output and numerical output of features provided. Diagnosis suggested (e.g. melanoma, benign melanocytic nevus)	Seidenari 1998 Seidenari 1999
		DB–MIPS pattern analysis system	KNN	Diagnosis suggested (e.g. melanoma, benign melanocytic nevus)	Burroni 2004
		DB–MIPS pattern analysis system	Linear discrimination	Diagnosis suggested (e.g. melanoma, benign melanocytic nevus)	Burroni 2004
		DDA software analysis – analyses 50 parameters subdivided into three categories, i.e. geometries, colours, and textures and islands of colours (Burroni islands)	Euclidian distances	Not specified	Wollina 2007
DEM–MIPS (Biomips SRL, Siena, Italy)	Commercially available software coupled to stereomicroscope Wild M-650 (Leica), video camera, computer, colour monitor.	DEM-MIPS software (Digital Epi Microscopy Melanoma Image Processing Software; Biomips SRL, Siena, Italy). Evaluates colorimetric and geometric features (not reported).	ANN	Not specified	Piccolo 2002

Derm-CAD processing machine	Role of machine	Image analysis	Classifier	CAD output	Studies
Skin View	Computerised image analysis system, digital television, videocamera. Connection with the computer is through a digitising board able to process colour images	Features of ABCD system plus clinical data (anatomic site, months of growth, size, shape, colour, ulceration or regression)	NR	≥2 of 8 binary (on/off) indicators indicates malignancy: 1 shape (asymmetry); 2 clinical data (changes through time, regression, ulceration); 3 size (mm); 4 colour (distribution of hue); 5 darkness (percent of black mixed with the hue); 6 saturation (percent of white mixed with the hue); 7 border (sharpness of transition between lesion and healthy skin; 8 texture.	Cascinelli 1992 Cristofolini 1997
Nevus Doctor	Computerised image analysis system coupled to digital dermatoscope	ND takes a dermoscopic image from the Canon/DermLite device as input and classifies the lesion. Features not reported	NR	Probability of malignancy	Mollersen 2015
MoleExpert (DermoScan GmbH, Germany)	(micro Version 3.3.30.156). Computerised image analysis with output giving probability of malignancy	Features of ABCD system plus other features (not listed), e.g. colour variation and grey veil.	NR	Number between −5.00 and 5.00, where high values indicate suspicion of melanoma	Mollersen 2015
Image J (NIH, Bethesda, USA)	Image segmentation, feature extraction, image analysis coupled with dermatoscope MoleMax II	29 Features analysed from 38 extracted features describing shape, form and colour.	ANN	2 outputs: 1) Visual rendering of analysis showing coloured areas. 2) Excision vs. no excision decision (system considers the green zone of the scale as benign (0 to 0.1), the yellow zone suspicious (0.1 to 0.4), and the red zone malignant (0.4 to 1)).	Dreiseitl 2009
IBAS 2000 workstation (Zeiss, Oberkochen, Germany)	Digital image analysis workstation attached to Wild binocular stereomicroscope M 650 (Wild Heerbrugg AG, Switzerland)	Analysis of 16 morphometric parameters from the lesion and the border image: lesion area and perimeter: minimum polar distance, maximum polar distance, aspect ratio, circularity shape factor, variances of grey, number different colours, range different colours. Border features and area: maximum and minimum border width, ratio of border area to lesion area, ratio of border perimeter to lesion perimeter.	ANN	Dichotomous decision: MM vs. Benign (CN or DN). The network was trained to yield a value from 0 to 1 in the output nodes. The node yielding the greatest numerical output was then used as the classification result.	Binder 1998

Derm-CAD processing machine	Role of machine	Image analysis	Classifier	CAD output	Studies
Nevuscreen ® (Arkè s.a.s., Avezzano, Italy)	Digital database containing image analysis software, coupled to digital dermatoscope	Nevuscreen software automatically analyses ABCD features	NR	TDS score: <4.75 benign, 4.75–5.45 suspicious, >5.45 highly suggestive of melanoma	Piccolo 2014
SolarScan (Polartechnics Lts, Australia)	dermoscopy video unit with internal algorithm for image analysis	103 automated image analysis variables extracted: consisting of various properties of colour, pattern, and geometry. Number analysed not reported.	linear discriminant analysis	Probability of melanoma, with cut–off (not provided) for benign vs. melanoma	Menzies 2005
Name not reported	Computer analysis of stored images captured using different dermoscopy/camera combinations	54 features analysed, such as border irregularity, eccentricity, length of major and minor axes, and colour histogram properties	Digital forest classifier	Severity score (the fraction of decision trees (n = 1000) in which the path ends in ‘‘malignant’’. Lesion classified as malignant if its image traced a path to a malignant node in at least 40% of the trees)	Ferris 2015
Name not reported	Computer analysis of stored images captured using digital stereomicroscope	Features analysed as present or absent (pattern analysis): Pigment network, brown globules, radial streaming, pseudopods, black dots, margin, pigmentation, depigmentation	ANN	NR	Binder 1994
Name not reported	Computer analysis of digital dermoscopy images (Molemax II)	features corresponding to the number, size and asymmetry of dots: (a)Number of dots, (b) Total Number of pixels in dots, (c) mean number of pixels in dots, (d) variance of num. pixels in dots ,(e) fraction of lesion area occupied by dark dots. Asymmetry: radial, angular, primary axis.	Comparison of 5 classifiers: Multilayer perceptron kNN Random forest SVM polykernel c=5* SVM PUK kernel	NR	Maglogiannis 2015
Name not reported	Computer analysis of stored images captured using digital microscope	14 features investigated: 4 asymmetry features, colour variance (red, green, blue), mean colour (red, green, blue, intensity), range colour (red, green, blue).	SVM (principal components analysis)	NR	Gilmore 2010

Derm-CAD processing machine	Role of machine	Image analysis	Classifier	CAD output	Studies
Name not reported	Computer analysis of stored images captured using digital microscope	Negative Features: Point and axial symmetry of pigmentation Presence of only a single colour. Positive Features: Blue-white, veil, Multiple brown dots, Pseudopods, Radial streaming, Scarlike depigmentation, Peripheral black dots/globules, Multiple (5-6) colours, Multiple blue/grey dots, Broadened network	Classification and regression tree	Presence of indicative features (Melanoma = 0/2 morphologically negative features AND at least 1/9 positive morphological features)	Menzies 1996
Name not reported	Computer analysis of stored images captured using digital microscope	Analysis of 64 analytical parameters including: a large number of morphological parameters such as margin, geometric parameters (surface area, extent, largest diameter and largest orthogonal diameter), invariant moments, symmetry, colours (red, green, blue and grey value), texture (energy, entropy, correlation, inverse difference moment and inertia), number of regions, focus and difference of the lesion and its convex cover.	Vision algebra methods	NR	Blum 2004b

Footnotes

*(classifier selected at random for inclusion in review)

Key: ANN – artificial neural network; CN – common naevus; DN – dysplastic naevus; KNN – K–nearest neighbour; NR – not reported; MM – malignant melanoma; SVM – support vector machine; TDS – total dermoscopic score

4 Characteristics of included Spectroscopy-based CAD (Spectro-CAD) systems

Spectro–CAD system [spectroscopy type]	Role of machine	Image analysis	Classifier	CAD Output	Studies
SpectroShade (MHT, Verona Italy) **[MSI–CAD]**	Illumination assembly located inside a PC and an external detection device placed in a hand-held probe, with integrated image analysis software	Features analysed: (i) reflectance (R); (ii) variegation (V); (iii) area (A); (iv) dark area ratio (DAR); (v) dark island reflectance (DIR); (vi) dark distribution factor (DDF); (vii) dark permanence (D PER)	ANN (multilayer perceptron)	NR	Tomatis 2005
	SpectroShade coupled with a MoleMax II dermatoscope		NR	Diagnostic category: 1 no melanoma, 2 doubtful melanoma, 3 suspected melanoma, 4 probable melanoma	Ascierto 2010

Spectro–CAD system [spectroscopy type]	Role of machine	Image analysis	Classifier	CAD Output	Studies
MelaFind (early predecessor) **[MSI-CAD]**	Digital camera and illumination assembly coupled to a computer, with separate image analysis	Features analysed: Lesion asymmetry, border, gradient, centroid, texture, colour	Multiparametric linear classifier	NR	Gutkowicz Krusin 1997
MelaFind (STRATA Skin Sciences [formerly Mela Sciences Inc], Horsham, PA, USA) **[MSI-CAD]**	Multispectral imaging system with integrated image analysis software; device takes images in vivo	MelaFind image analysis	NR	Binary output: (1) positive, (lesion should be considered for biopsy to rule out melanoma); and (2) negative (lesion should be considered for later evaluation)	Monheit 2011
			6 constrained linear classifiers	Binary output: excise or follow–up	Friedman 2008
			NR	Monheit 2011	Wells 2012
			Logistic regression	Monheit 2011	Winkelmann 2016
			NR	Monheit 2011	Hauschild 2014
Telespectrophotometric system [MSI–CAD]	Digital camera coupled with an illumination system with interference filters and computer for storage and analysis of multispectral images	From each spectral image, three parameters, i.e. mean reflectance, variegation index and lesion area; were derived at the corresponding wavelength.	Linear discriminant	NR	Bono 1996
		For each spectral image, five parameters (lesion descriptors) based on ABCD and related to colour and shape of the imaged lesion were evaluated: mean reflectance, variegation index, roundness, border irregularity.	Linear discriminant vs. ANN*	NR	Tomatis 2003
			Linear discriminant	NR	Bono 2002

Spectro–CAD system [spectroscopy type]	Role of machine	Image analysis	Classifier	CAD Output	Studies
SIAscopy ™ (Astron Clinica, UK) **[MSI–CAD]**	Spectrophotometric imaging system with hand–held skin probe (SIAscope II) and integrated software	Analysis of dermal melanin, erythematous blush, lesion asymmetry, collagen 'holes', blood commas, or irregularities in the collagen	NR	SIAgraphs and Binary output (based on Australian Scoring System): 'strong chance of melanoma' or 'low risk of melanoma'	Glud 2009
	Spectrophotometric imaging system with hand–held skin probe (SIAscope V) and integrated software (software Dermetrics Version 2.0, Astron Clinica Ltd., Great Britain)		NR	SIAgraphs (no further information)	Terstappen 2013
SIAscope (MedX Health Corp, Canada) **[MSI–CAD]**	Spectrophotometric imaging system with hand–held skin probe (SIAscope, version NR) and integrated software		NR	SIAgraphs and lesion score using Primary Care Scoring Algorithm (6 or more points regarded as suspicious)	Sgouros 2014
SIAscope (MedX Health Corp, Canada) **[MSI–CAD]**	SIAscopy with MoleMate (software image management system) viewing platform and integrated primary care scoring algorithm		NR	SIAgraphs and lesion score using Primary Care Scoring Algorithm (6 or more points regarded as suspicious)	Walter 2012
Oblique Incidence Diffuse Reflectance Spectroscopy [DRS–CAD]	Light probe coupled to imaging spectrograph, camera, and computer to store images.	NR	ANN	Diagnostic category (e.g. CN, MM, DN, BCC, cSCC)	Garcia Uribe 2012
Nevisense (SciBase III, Sweden) **[EIS–CAD]**	Electrical Impedance spectroscopy imaging system with integrated image analysis software	The system measures the overall electrical resistance and reactance at 35 different frequencies	SVM (non-probabilistic binary linear classifier)	The system computes both a score (0–10) and a dichotomous output (EIS negative/positive) at a fixed cut-off. The fixed threshold is set at 4, i.e. scores < 4 are EIS negative and scores of ≥ 4 are EIS positive.	Mohr 2013 Malvehy 2014

Footnotes

* Classifier excluded at random

Key: ANN – artificial neural network; BCC – basal cell carcinoma; cSCC – cutaneous squamous cell carcinoma; CAD - computer-assisted diagnosis; CN – common naevus; DN – dysplastic naevus; EIS - electrical impedance spectroscopy; KNN – K–nearest neighbour; NR – not reported; MM – malignant melanoma; MSI – multispectral imaging; SVM – support vector machine.

5 Summary estimates of sensitivity and specificity for CAD according to target condition

Index test, target condition	Studies	Cases/Number of participants	Summary sensitivity (95% CI) %	Summary specificity (95% CI) %
Main analyses: Invasive melanoma and atypical intraepidermal melanocytic variants				
Derm–CAD	22	1063/8992	90.1 (84.0, 94.0)	74.3 (63.6, 82.7)
MSI–CAD	8	286/2401	92.9 (83.7, 97.1)	43.6 (24.8, 64.5)
EIS–CAD (Nevisense*)	2	368/2389	97.0 (94.7, 98.3)	33.6 (31.6, 35.7)
Individual CAD systems: Invasive melanoma and atypical intraepidermal melanocytic variants				
DB–MIPS (Derm–CAD)	6	502/1903	95.2 (89.5, 97.9)	89.1 (78.7, 94.8)
Skin View (Derm–CAD)	2	45/220	80.0 (65.8, 89.3)	47.4 (40.1, 54.8)
MelaFind (MSI–CAD)	5	196/1798	97.1 (91.9, 98.9)	29.8 (12.3, 56.3)
Main analyses: Basal cell carcinoma				
EIS–CAD (Nevisense*)	2	69/2389	100 (94.7, 100)	26.3 (24.5, 28.1)
Secondary target condition: invasive melanoma alone				
Derm–CAD	2	120/950	90.8 (84.2, 94.9)	63.5 (60.2, 66.7)
MSI–CAD	5	116/386	76.5 (43.0, 93.3)	60.7 (38.5, 79.2)
EIS–CAD (Nevisense*)	2	226/2389	98.2 (95.4, 99.3)	38.0 (36.0, 40.1)
Secondary target condition: any skin cancer or lesions requiring excision				
EIS–CAD (Nevisense*)	2	644/2389	93.5 (91.3, 95.1)	32.6 (30.4, 34.8)

Footnotes

* For EIS-CAD the only evidence available was for one system

Key: CAD - computer-assisted diagnosis; CI - confidence interval; Derm-CAD - digital dermoscopy based computer-assisted diagnosis; EIS-CAD - electrical impedance spectroscopy based computer-assisted diagnosis; MSI-CAD - multispectral imaging based computer-assisted diagnosis.

6 Comparisons of CAD with dermoscopy for detection of the primary target condition: invasive melanoma and atypical intraepidermal melanocytic variants

Test	Number of studies	Number of cases	Number of patients	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
Derm–CAD versus image–based dermoscopy – indirect comparison					
Derm–CAD	22	1063	8992	90.1 (84.0, 94.0)	74.3 (63.6, 82.7)
Image-based dermoscopy	5	153	765	93.3 (83.4, 97.5)	88.5 (57.3, 97.8)
Difference (95% CI), P value				-3.21 (-11.2, 4.79), P = 0.43	-14.1 (-34.4, 6.06), P = 0.17
Derm–CAD versus image–based dermoscopy – direct comparison					
Derm–CAD	5	153	765	94.1 (89.1, 96.9)	80.8 (68.2, 89.3)
Image-based dermoscopy	5	153	765	93.9 (85.1, 97.7)	88.3 (56.5, 97.8)
Difference (95% CI), P value				0.17 (-6.61, 6.95), P = 0.96	-7.44 (-28.4, 13.6), P = 0.49
MSI–CAD versus image-based dermoscopy – indirect comparison					
MSI–CAD	8	286	2401	92.9 (83.7, 97.1)	43.6 (24.8, 64.5)
Image-based dermoscopy	5	154	371	74.0 (66.5, 80.3)	58.7 (43.5, 72.4)
Difference (95% CI), P value				18.9 (9.58, 28.2), P = 0.003	-15.0 (-40.7, 10.6), P = 0.26
MSI–CAD versus image-based dermoscopy – direct comparison					
MSI–CAD	5	154	371	96.8 (92.4, 98.6)	29.8 (12.4, 56.1)
Image-based dermoscopy	5	154	371	74.0 (66.5, 80.3)	58.7 (43.5, 72.4)
Difference (95% CI), P value				22.7 (15.2, 30.2), P < 0.001	-28.9 (-56.3, -1.48), P = 0.039
Melafind (MSI–CAD) versus Image–based dermoscopy – indirect comparison					
MelaFind	5	196	1798	97.4 (94.0, 98.9)	29.3 (12.1, 55.6)
Image-based dermoscopy	4	142	288	72.5 (64.6, 79.2)	50.7 (42.6, 58.7)
Difference (95% CI), P value				24.5 (16.5, 32.4), P < 0.001	-20.9 (-45.5, 3.75), P = 0.10
Melafind (MSI–CAD) versus Image–based dermoscopy – direct comparison					
MelaFind	4	142	288	96.5 (91.8, 98.5)	22.8 (8.38, 48.9)
Image-based dermoscopy	4	142	288	72.5 (64.6, 79.2)	50.7 (42.6, 58.7)
Difference (95% CI), P value				23.9 (16.0, 31.9), P < 0.001	-27.9 (-50.1, -5.66), P = 0.014
Derm–CAD versus MSI–CAD - indirect comparison					
Derm–CAD	22	1063	8992	90.1 (84.0, 94.0)	74.3 (63.6, 82.7)
MSI–CAD	8	286	2401	92.9 (83.7, 97.1)	43.6 (24.8, 64.5)
Difference (95% CI), P value				2.83 (-5.04, 10.7), P = 0.48	-30.7 (-53.8, -7.64), P = 0.009

Footnotes

Key: CAD - computer-assisted diagnosis; CI - confidence interval; Derm-CAD - digital dermoscopy based computer-assisted diagnosis; MSI-CAD - multispectral imaging based computer-assisted diagnosis; P - probability.

7 Sensitivity and Specificity of CAD systems in Unreferred Populations

Derm-CAD								
CAD System	**Study**	**Target condition**	**TP**	**FP**	**FN**	**TP**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
DB-MIPS	Wollina 2007	MM+Mis	31	16	2	60	0.89 [0.67, 0.99]	0.84 [0.80, 0.88]
MSI-CAD								
CAD System	**Study**	**Target condition**	**TP**	**FP**	**FN**	**TP**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
MoleMate SIAscope	Walter 2012	MM+Mis	18	209	0	539	1.00 [0.81, 1.00]	0.72 [0.69, 0.75]
MoleMate SIAscope	Walter 2012	MM	14	213	0	539	1.00 [0.77, 1.00]	0.72 [0.68, 0.75]
MoleMate SIAscope	Walter 2012	Any*	23	204	2	537	0.92 [0.74, 0.99]	0.72 [0.69, 0.76]
SIAscope	Sgouros 2014	Any*	26	7	5	6	0.84 [0.66, 0.96]	0.46 [0.19, 0.75]

Footnotes

Any - any skin cancer or lesion requring excision (secondary objective); CI - confidence interval; Derm-CAD - digital dermoscopy based computer-assisted diagnosis; FN - false negative; FP - false positive; MSI-CAD - multispectral imaging based computer-assisted diagnosis; MM - invasive melanoma only (secondary objective); MM+Mis - invasive melanoma and atypical intraepidermal melanocytic variants (primary objective); TN - true negative; TP - true positive.

8 Direct comparisons of single CAD studies with dermoscopy for diagnosis of melanoma and other types of skin cancer

Study	Sensitivity (true positives/cases) %		Difference (95% CI)	Specificity (true negatives/non cases) %		Difference (95% CI)
MSI–CAD study comparisons: invasive melanoma and atypical intraepidermal melanocytic variants						
	MSI–CAD	*In–person dermoscopy*		*MSI–CAD*	*In–person dermoscopy*	
Bono 2002	80.3 (53/66)	90.9 (60/66)	-10.6 (-22.8, 1.58)	49.0 (121/247)	74.5 (184/247)	-25.5 (-33.5, -17.0)
MSI–CAD study comparisons: Invasive melanoma						
	MSI–CAD	*In–person dermoscopy*		*MSI–CAD*	*In–person dermoscopy*	
Ascierto 2010	66.7 (8/12)	100 (12/12)	-33.3 (-60.9, -2.20)	76.2 (32/42)	45.2 (19/42)	31.0 (10.1, 48.4)
	MelaFind (MSI–CAD)	*Image-based dermoscopy*		*Melafind (MSI–CAD)*	*Image-based dermoscopy*	
Friedman 2008	100 (21/21)	81.0 (17/21)	19.1 (-0.15, 40.0)	29.5 (23/78)	44.9 (35/78)	-15.4 (-29.6, -0.23)
Derm–CAD comparisons: invasive melanoma and atypical intraepidermal melanocytic variants						
	Derm–CAD	*In–person dermoscopy*		*Derm–CAD*	*In–person dermoscopy*	
Bauer 2000	92.9 (39/42)	78.6 (33/42)	14.3 (-1.06, 29.5)	97.8 (267/273)	96.3 (263/273)	1.47 (-1.55, 4.64)
Dreiseitl 2009 *	88.9 (24/27)	96.3 (26/27)	-7.41 (-24.6, 8.88)	48.0 (207/431)	71.9 (310/431)	-23.9 (-30.1, -17.4)
	Unnamed system Derm–CAD	*Image-based dermoscopy*		*Unnamed system Derm–CAD*	*Image-based dermoscopy*	
Menzies 1996	88.9 (40/45)	91.1 (41/45)	-2.22 (-15.7, 11.2)	75.6 (90/119)	70.6 (84/119)	5.04 (-6.21, 16.1)
	DB-MIPS (Derm–CAD)	*In–person dermoscopy*		*DB-MIPS (Derm–CAD)*	*In–person dermoscopy*	
Bauer 2000	92.9 (39/42)	78.6 (33/42)	14.3 (-1.06, 29.5)	97.8 (267/273)	96.3 (263/273)	1.47 (-1.55, 4.64)
	DB-MIPS (Derm–CAD)	*Image-based dermoscopy*		*DB-MIPS (Derm–CAD)*	*Image-based dermoscopy*	
Seidenari 1998	93.5 (29/31)	80.6 (25/31)	12.9 (-4.62, 30.5)	94.9 (56/59)	94.9 (56/59)	0.00 (-9.44, 9.44)
CAD–based diagnosis vs. CAD–aided diagnosis: invasive melanoma and atypical intraepidermal melanocytic variants						
	CAD–based diagnosis	CAD–aided diagnosis		CAD–based diagnosis	CAD–aided diagnosis	
Dreiseitl 2009 *	88.9 (24/27)	74.1 (20/27)	14.8 (-6.4, 34.9)	48.0 (207/431)	81.9 (353/431)	-33.9 (39.6, -27.7)
Hauschild 2014	96.9 (63/65)	78.5 (51/65)	18.5 (7.3, 30.1)	9.2 (6/65)	46.2 (30/65)	-36.9 (-49.9, -22.0)

Footnotes

* Patient-based analysis unlike other studies in the table which were lesion-based.

Key: CAD - computer-assisted diagnosis; CI - confidence interval; Derm-CAD - digital dermoscopy based computer-assisted diagnosis; MSI-CAD - multispectral imaging based computer-assisted diagnosis.

9 Sensitivity and Specificity of Oblique Incidence Diffuse Reflectance Spectrometry CAD (OIDRS–CAD) studies for primary target condition: invasive melanoma and atypical intraepidermal melanocytic variants

Index test, target condition	True positives	False positives	False negatives	True negatives	Sensitivity (95% CI) %	Specificity (95% CI) %
Garcia Uribe 2012	9	13	1	113	90.0 (59.6, 98.2)	89.7 (83.2, 93.9)

Footnotes

10 Sensitivity and Specificity of Electrical Impedance Spectroscopy CAD (EIS–CAD) studies for each primary target condition

Index test, target condition	True positives	False positives	False negatives	True negatives	Sensitivity (95% CI) %	Specificity (95% CI) %
Invasive melanoma and atypical intraepidermal melanocytic variants						
Mohr 2013	101	246	2	97	98.1 (93.2, 99.5)	28.3 (23.8, 33.3)
Malvehy 2014	256	1095	9	583	96.6 (93.7, 98.2)	34.7 (32.5, 37.1)
Basal cell carcinoma						
Mohr 2013	21	351	0	74	100 (84.5, 100)	17.4 (14.1, 21.3)
Malvehy 2014	48	1359	0	536	100 (92.6, 100)	28.3 (26.3, 30.4)
Cutaneous Squamous cell carcinoma						
Malvehy 2014	7	1095	0	841	100 (59.0, 100)	43.3 (41.3, 45.7)

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Classification pending references

Data and analyses

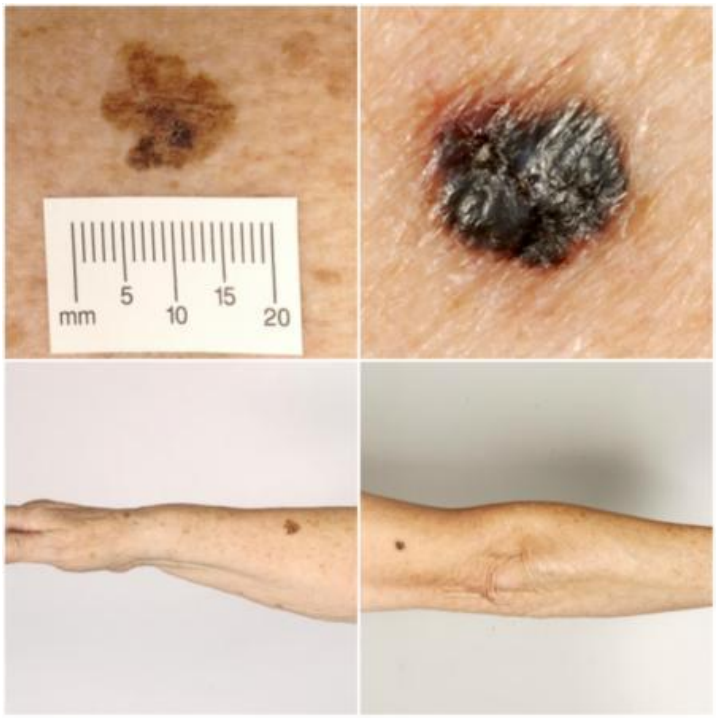
Data tables by test

Test	Studies	Participants
1 Derm-CAD Microderm (MM+MiS)	3	793
2 Derm-CAD DBMIPS (MM+MiS)	6	1903
3 Derm-CAD DBMIPS vs Dermoscopy (MM+MiS)	2	405
4 Derm-CAD DEMMIPS (MM+MiS)	1	341
5 Derm-CAD SkinView (MM)	0	0
6 Derm-CAD SkinView (MM+MiS)	2	220
7 Derm-CAD SkinView (Any)	1	44
8 Derm-CAD NevusDr (MM+MiS)	1	870
9 Derm-CAD NevusDr (Any)	1	870
10 Derm-CAD ImageJ (MM+MiS)	1	3021
11 Derm-CAD IBAS2000 (MM+MiS)	1	29
12 Derm-CAD Nevuscreen (MM+MiS)	1	165
13 Derm-CAD SolarScan (MM)	1	786
14 Derm-CAD SolarScan (MM+MiS)	1	786
15 Derm-CAD No name (MM)	1	164
16 Derm-CAD No name (MM+MiS)	5	864
17 Derm-CAD No name (Any)	1	173
18 Derm-CAD No name (BCC)	1	173
19 Derm-CAD DBMIPS_UNREF (MM+MiS)	1	357
20 MSI-CAD SIAscope_UNREF (MM)	1	766
21 MSI-CAD SIAscope_UNREF (MM+MiS)	1	766
22 MSI-CAD SIAscope_UNREF (Any)	1	766
23 MSI-CAD SpectroShade (MM)	1	54
24 MSI-CAD SpectroShade (MM+MiS)	1	347
25 EIS-CAD-Nevisense (MM)	2	2389
26 EIS-CAD-Nevisense (MM+MiS)	2	2389
27 EIS-CAD-Nevisense (Any)	2	2389
28 EIS-CAD-Nevisense (BCC)	2	2389
29 EIS-CAD-Nevisense (cSCC)	1	1943

Test	Studies	Participants
30 MSI-CAD Melafind (MM)	2	229
31 MSI-CAD Melafind (MM+MiS)	5	1798
32 MSI-CAD Melafind vs Dermoscopy (MM+MiS)	4	288
33 MSI-CAD Melafind (Any)	0	0
34 MSI-CAD SIAscopy (MM)	1	60
35 MSI-CAD SIAscopy (MM+MiS)	1	83
36 MSI-CAD SIAscope Only_UNREF (Any)	1	44
37 DRS-CAD OIDRS (MM+Mis)	1	136
38 DRS-CAD OIDRS (Any + dysplastic)	1	136
39 DRS-CAD OIDRS (Any)	1	89
40 MSI-CAD TS (MM)	1	43
41 MSI-CAD TS (MM+MiS)	1	173
42 CAD–DRS–TS vs Dermoscopy (MM+MiS)	1	313
43 MSI-CAD OTHER (MM+MiS)	0	0
44 MSI-CAD NR_ML (MM+MiS)	0	0
45 Derm-CAD OTHER (MM)	0	0
46 PersonDERM-DigidermDBMIPS (MM+MiS)	1	315
47 ImageDERM-DigidermDBMIPS (MM+MiS)	1	90
48 ImageDERM-DigidermDEMMIPS (MM+MiS)	1	341
49 PersonDerm-DigidermImageJ (MM+MiS)	1	458
50 ImageDerm-DigidermNevuscreen (MM+MiS)	1	165
51 ImageDerm-DigidermNR (MM)	1	164
52 ImageDerm-DigidermNR (MM+MiS)	2	169
53 PersonDERM-DRS-SpectroShade (MM)	1	54
54 ImageDERM-DRSMelafind (MM)	1	99
55 ImageDERM-DRSMelafind (MM+MiS)	4	288
56 ImageDERM-DRSSIA (MM+MiS)	1	83
57 PersonDERM-DRSTS (MM+MiS)	1	313
58 Derm-CAD (direct comparison only) (MM+MiS)	10	2233
59 Image-based Dermoscopy (for Derm-CAD comparison) (MM+MiS)	5	765
60 In-person based Dermoscopy - Derm-CAD studies (MM+MiS)	2	773
61 MSI-CAD (direct comparison only) (MM+MiS)	8	1059
62 Image-based Dermoscopy (for MSI-CAD comparison) (MM+MiS)	5	371
63 MSI-CAD All systems (MM+MiS)	8	2401
64 Derm-CAD All systems (MM+MiS)	22	8992
65 Derm-CAD MoleExpert (Any)	1	870
66 Derm-CAD All systems (MM)	2	950
67 Image-based Dermoscopy - Derm-CAD studies (MM)	1	164
68 MSI-CAD All (Melafind) (MM+MiS), CAD + Clinician (diagnostic aid) only	2	142
69 MSI-CAD All (MM+MiS), CAD only	6	777
70 MSI-CAD Melafind (MM+MiS), CAD only	3	174
71 Derm-CAD All (MM+MiS), CAD + Clinician (diagnostic aid) only	3	589
72 Derm-CAD All (MM+MiS), CAD only	19	8403

Figures

Figure 1



Caption

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

Figure 2

Caption

Sample photographs of BCC (left) and cSCC (right)

Figure 3

(A) MoleExpertMicro (DermoScan GmbH, Germany)

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(B) Nevisense™ (SciBase III, Sw

Copyright © 2018 SciBase III: re permission.

(C) SIAscope V (MedX Corp, Canada)

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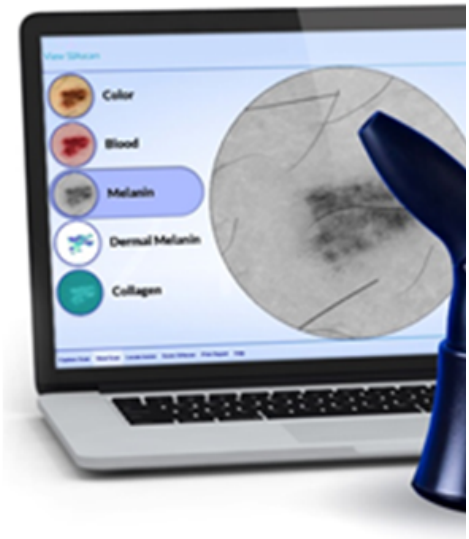
(D) MoleMate™ SIAscope V (M



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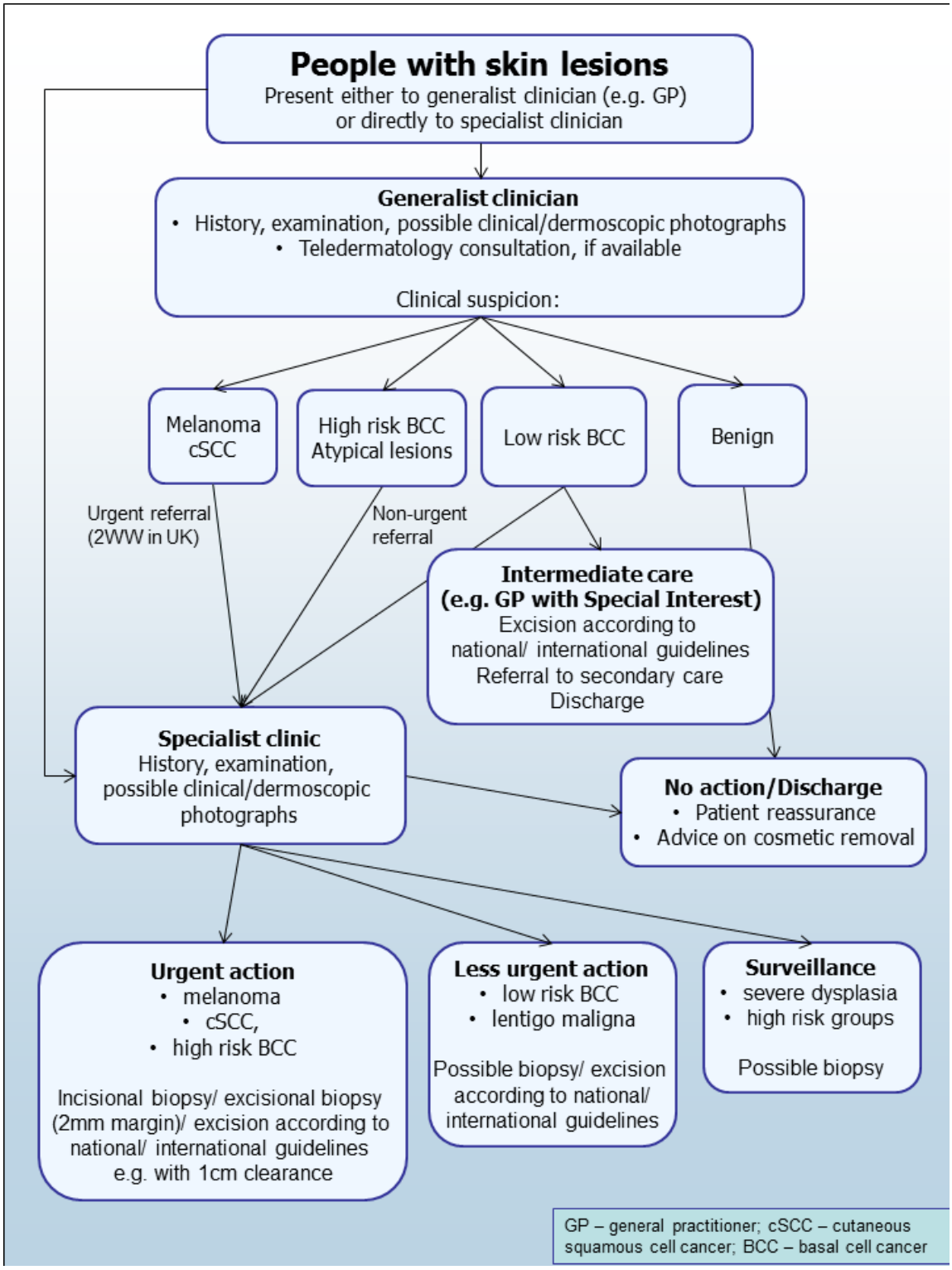
Caption

Examples of commercially available CAD systems using digital dermoscopy (A), electrical impedance spectroscopy (B) and multispectral imaging (C and D). Reproduced with permission of the manufacturers. Copyright © [2018] [MedX Corp,

Canada; DermoScanGmbH, Germany; SciBase III, Sweden]: reproduced with permission.

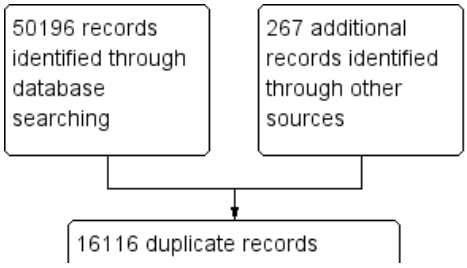
Figure 4

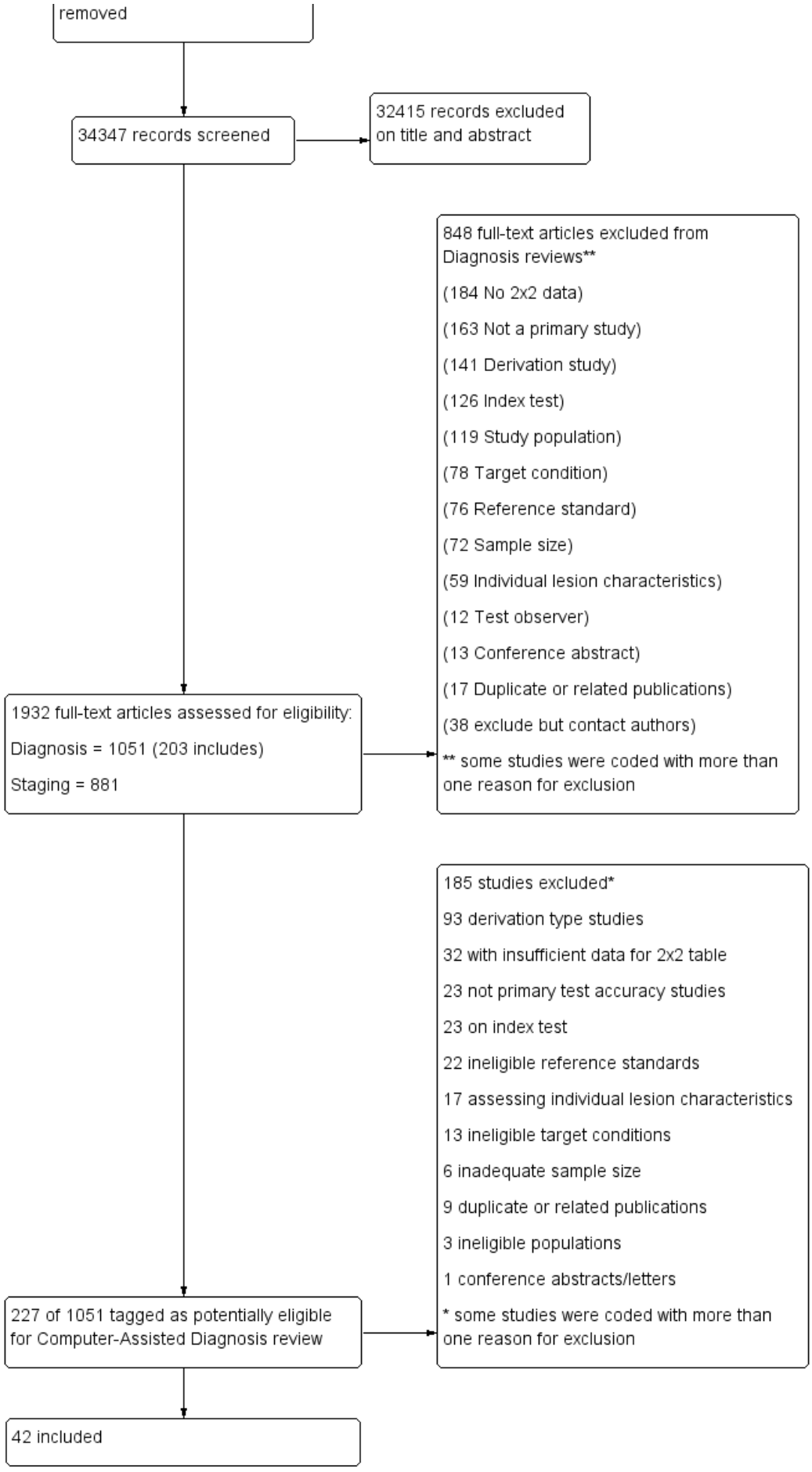


Caption

Current clinical pathway for people with skin lesions

Figure 5

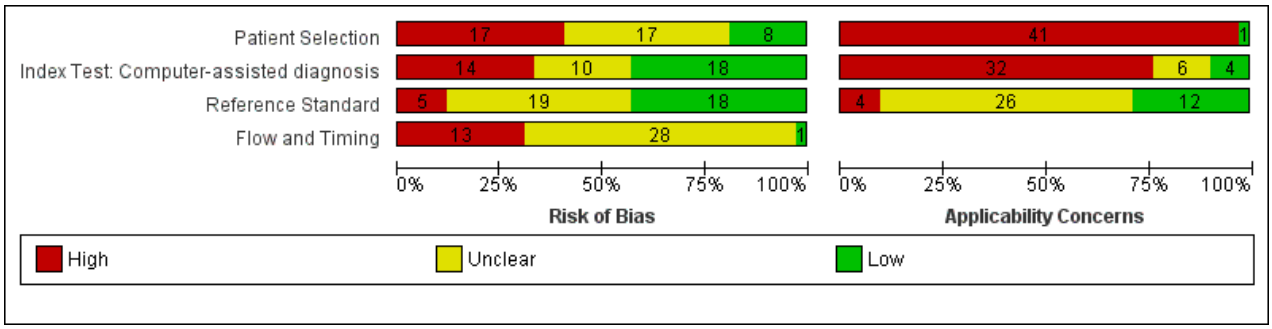




Caption

PRISMA flow diagram.

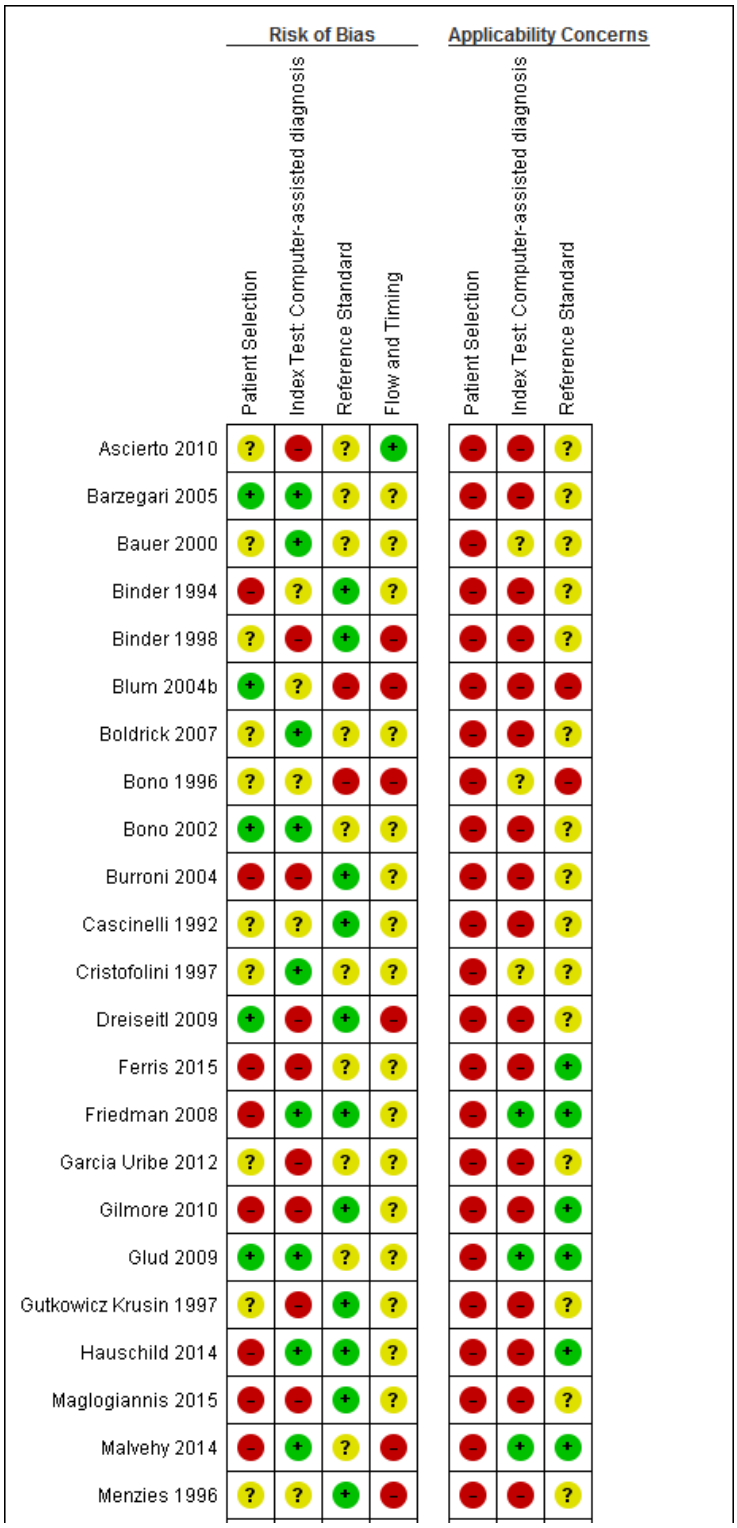
Figure 6

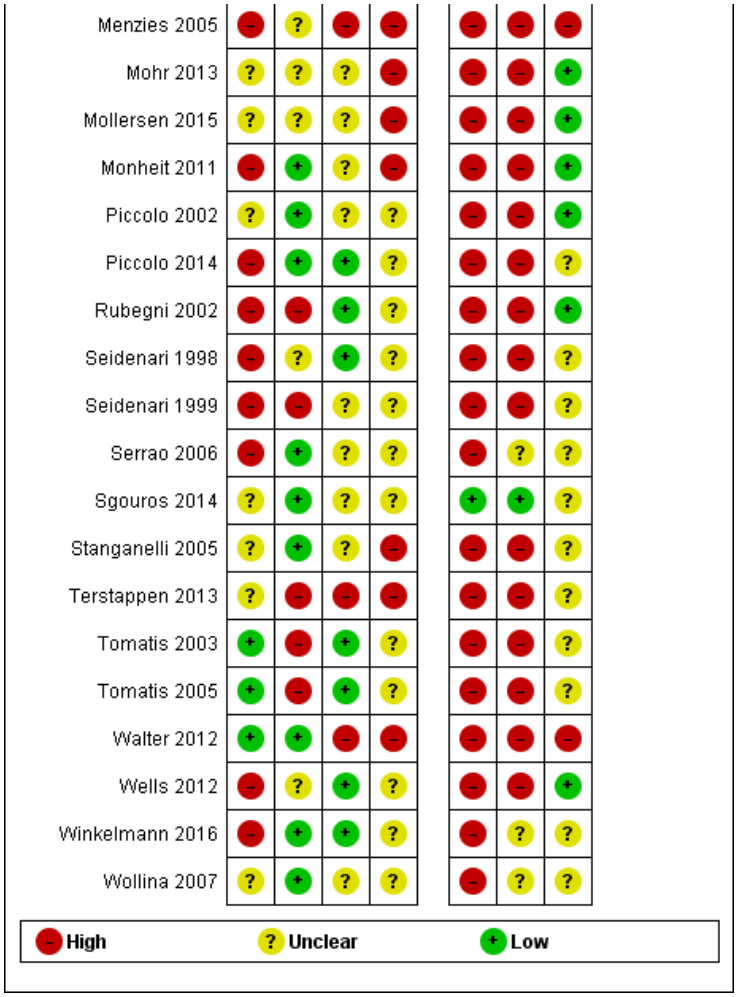


Caption

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

Figure 7

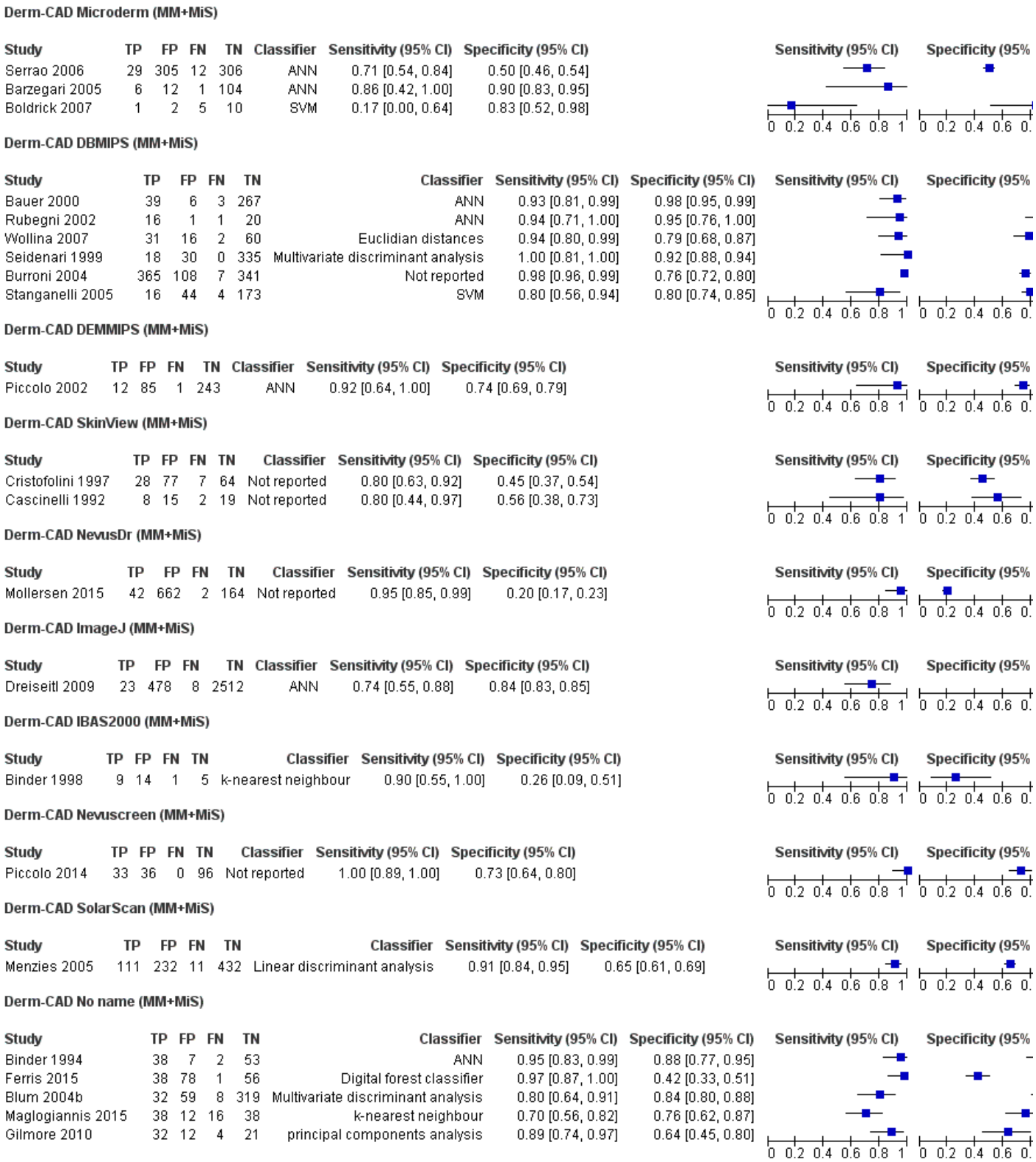




Caption

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

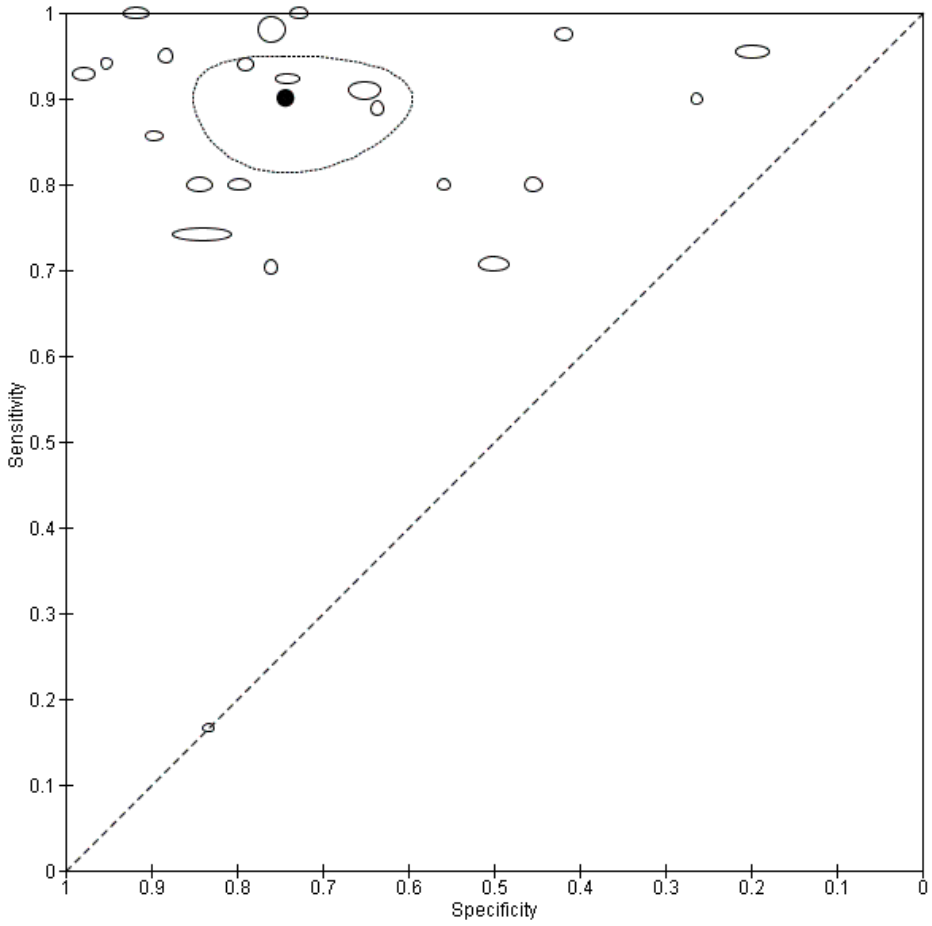
Figure 8 (Analysis 11)



Caption

Forest plot of different types of digital dermoscopy CAD systems (DermCAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

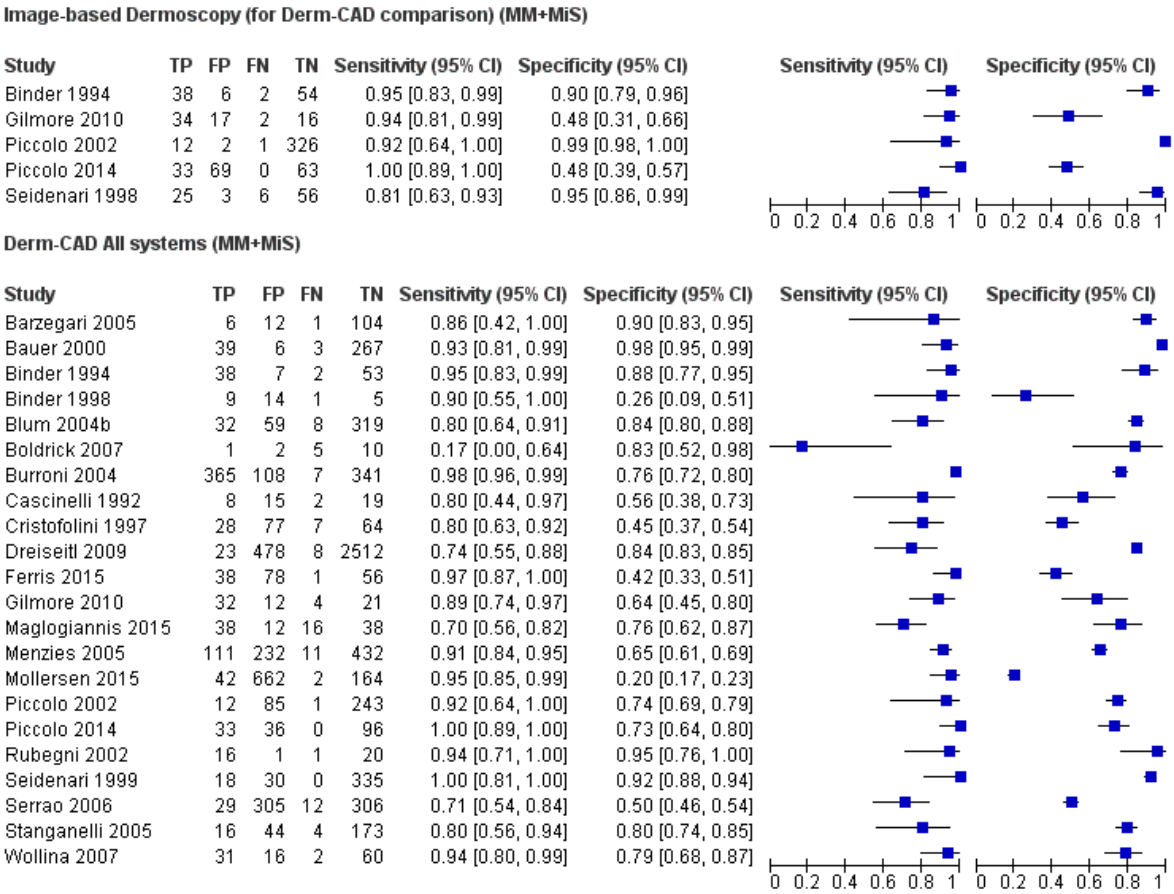
Figure 9 (Analysis 10)



Caption

Summary plot of digital dermoscopy CAD systems (Derm-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

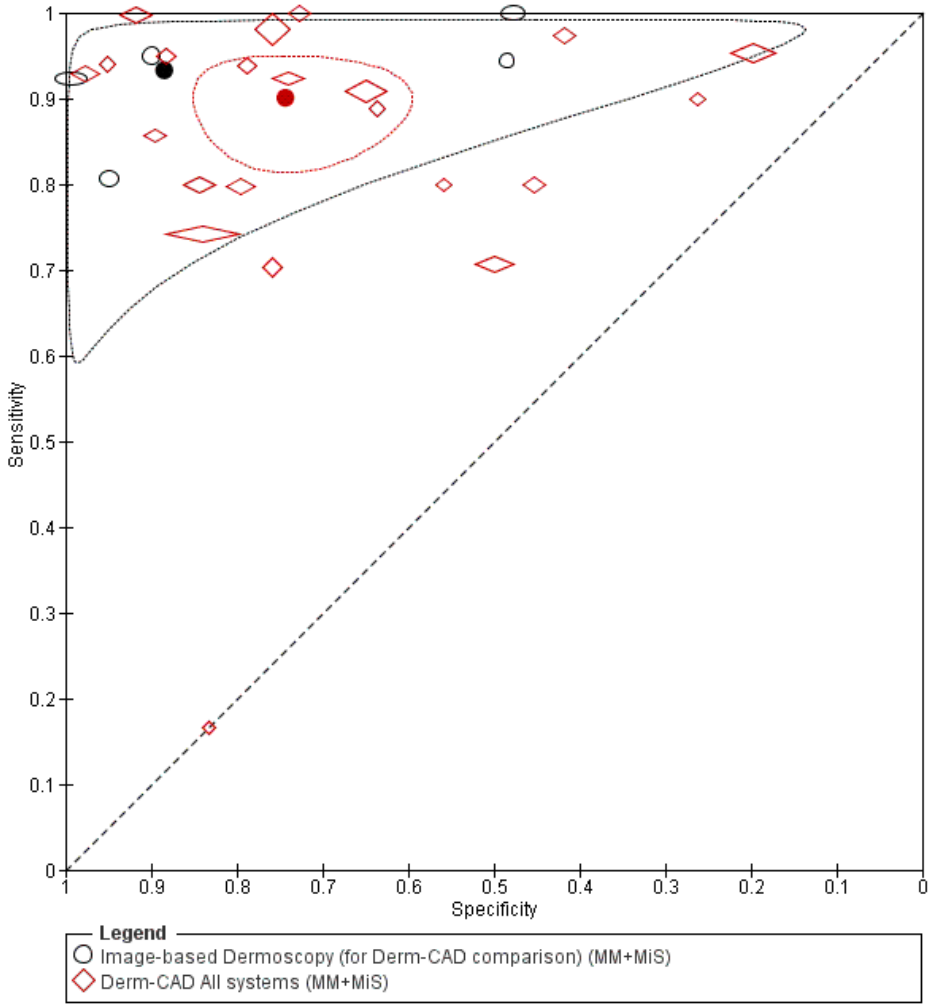
Figure 10 (Analysis 38)



Caption

Forest plot of data for image-based dermoscopy diagnosis and digital dermoscopy CAD systems (Derm-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

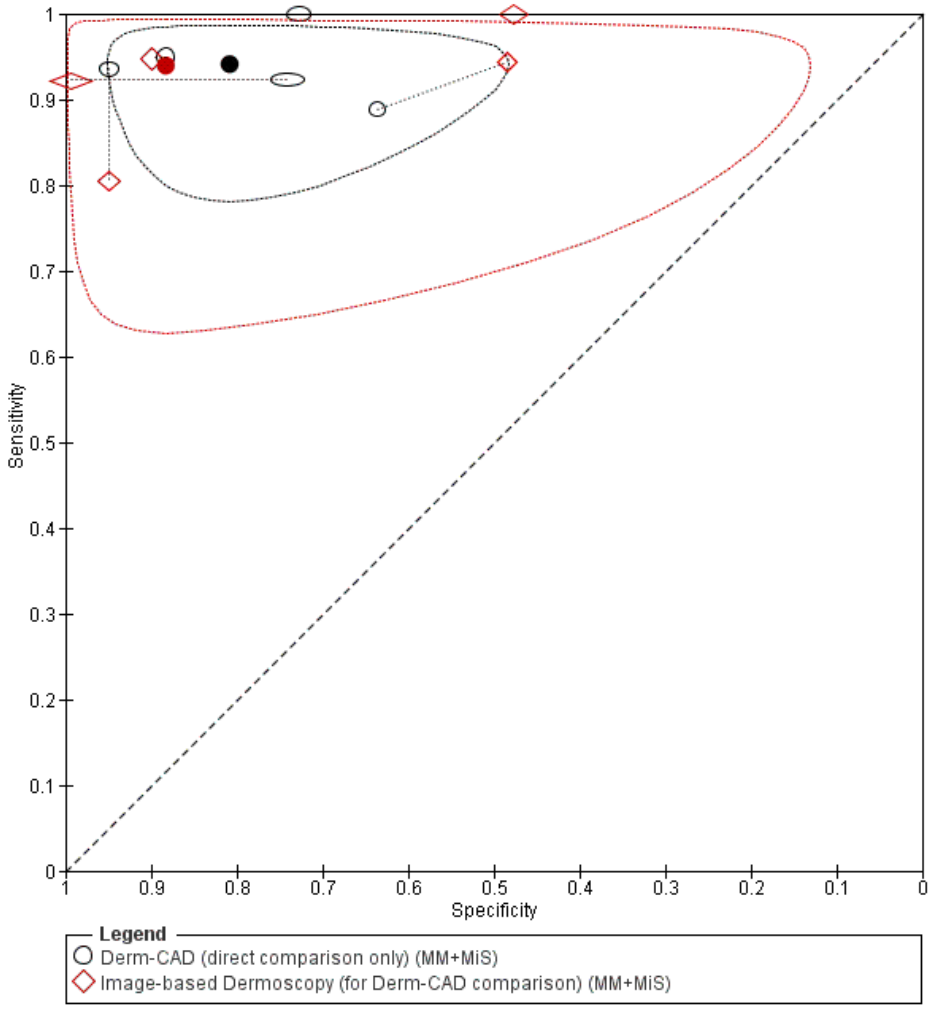
Figure 11 (Analysis 38)



Caption

Summary plot of image-based dermoscopy diagnosis versus digital dermoscopy CAD systems (Derm-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

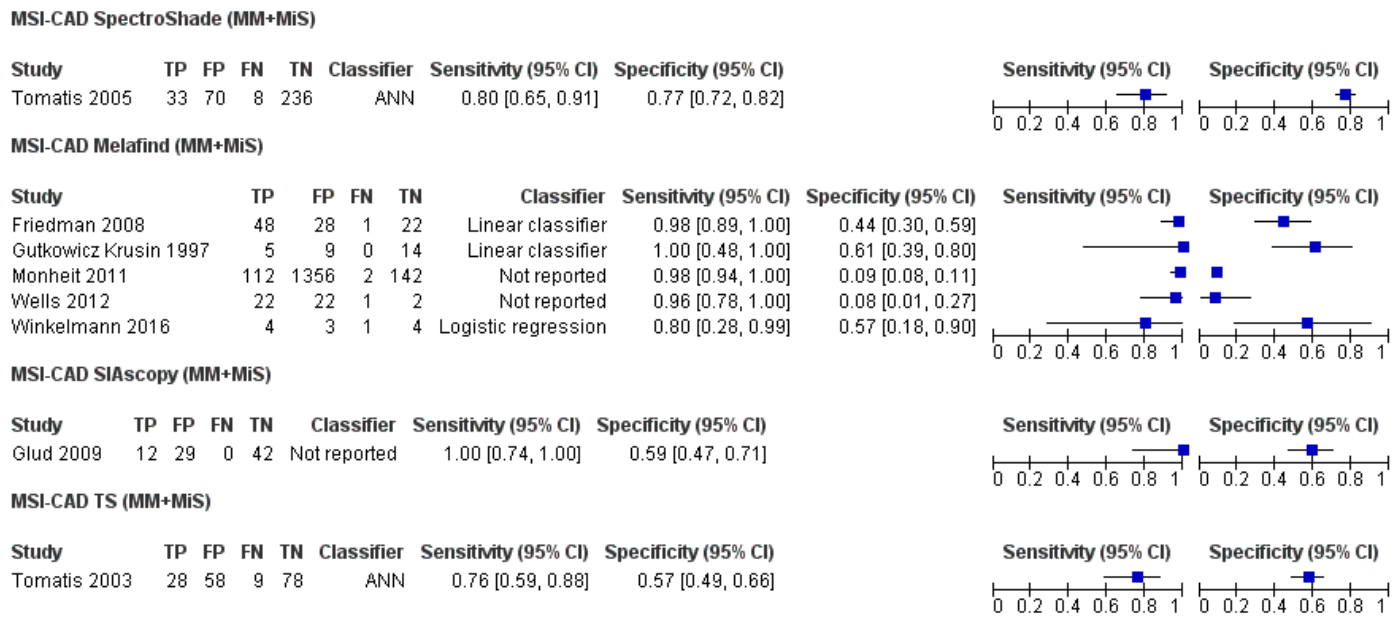
Figure 12 (Analysis 15)



Caption

Summary plot of direct comparisons between image-based dermoscopy diagnosis versus digital dermoscopy CAD systems (Derm-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

Figure 13 (Analysis 1)

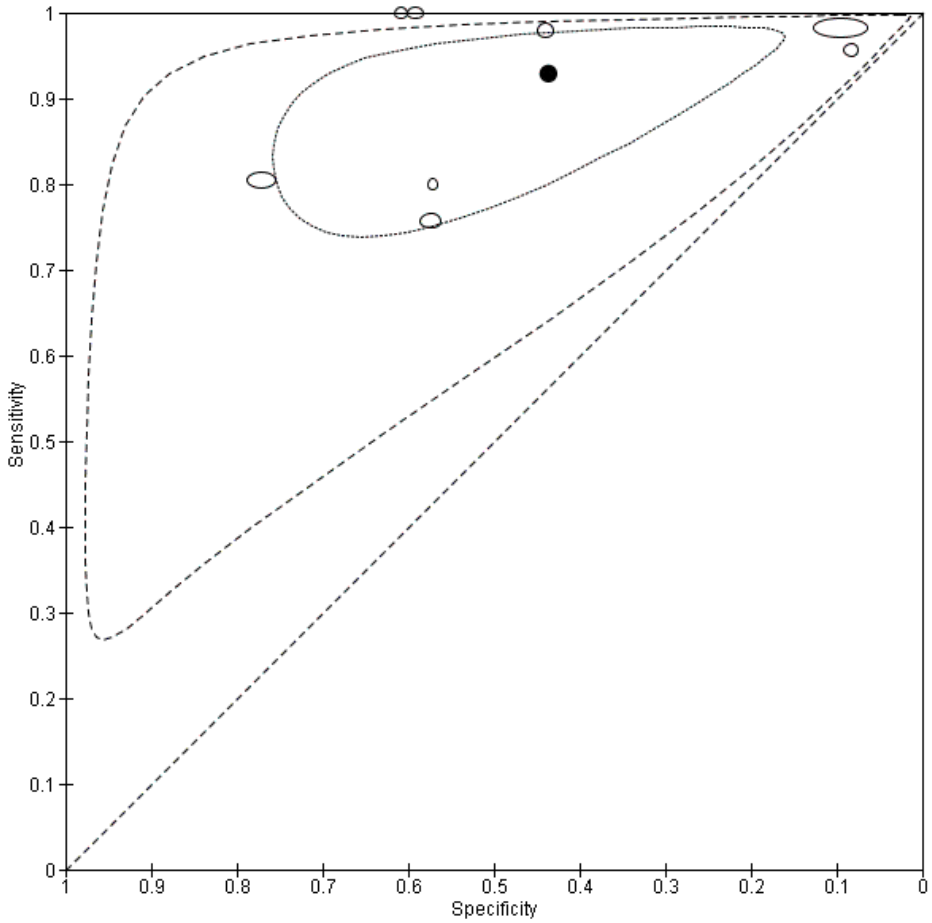


Caption

Forest plot of different types of multi-spectral imaging CAD (MSI-CAD) for the detection of invasive melanoma or

intraepidermal melanocytic variants (MM+MiS)

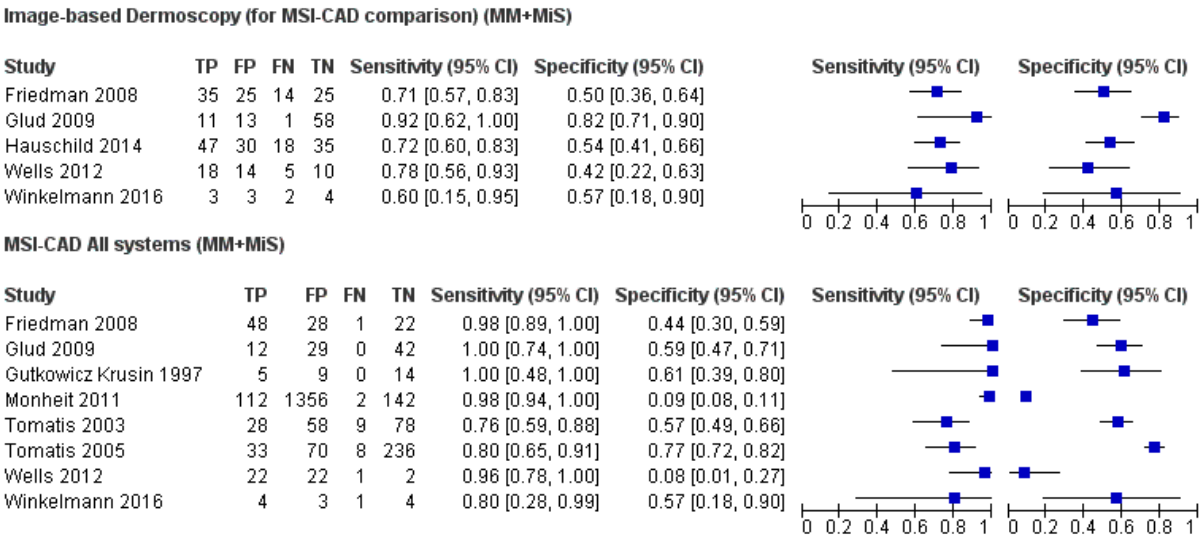
Figure 14 (Analysis 4)



Caption

Summary plot of multi-spectral imaging CAD (MSI-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

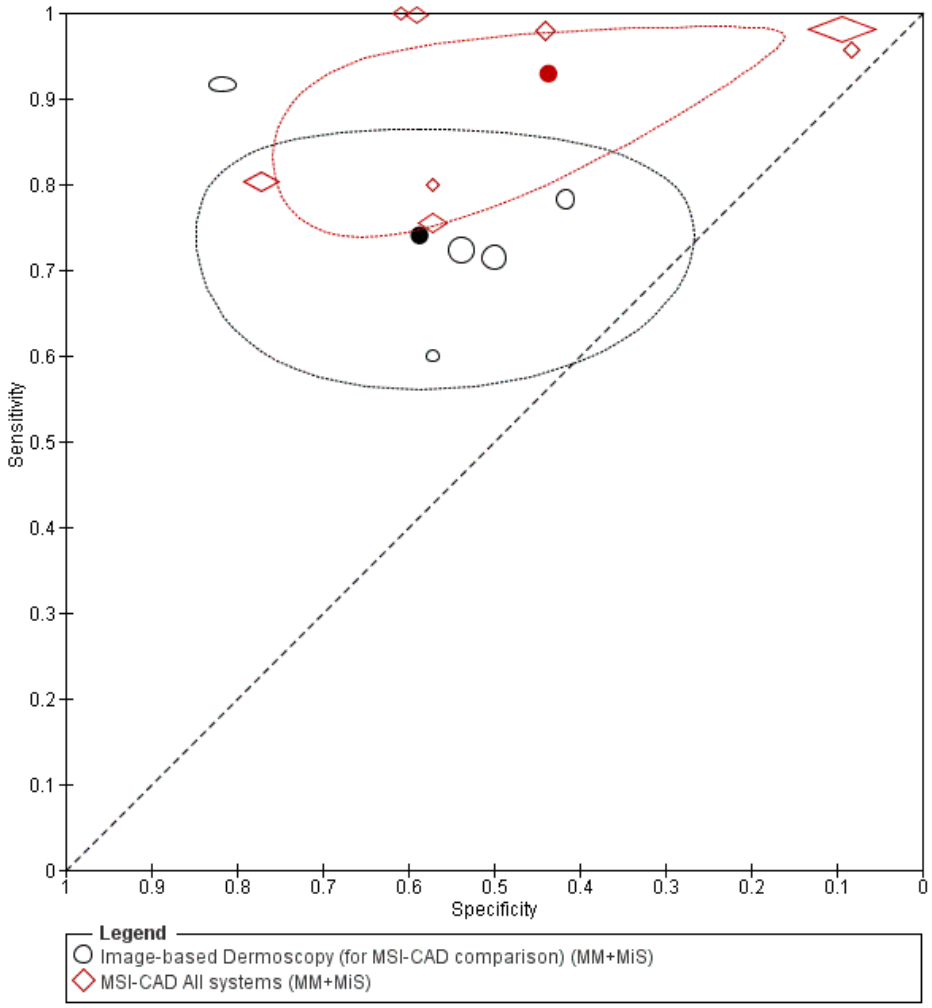
Figure 15 (Analysis 37)



Caption

Forest plot of data for image-based dermoscopy diagnosis and multi-spectral imaging CAD systems (MSI-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

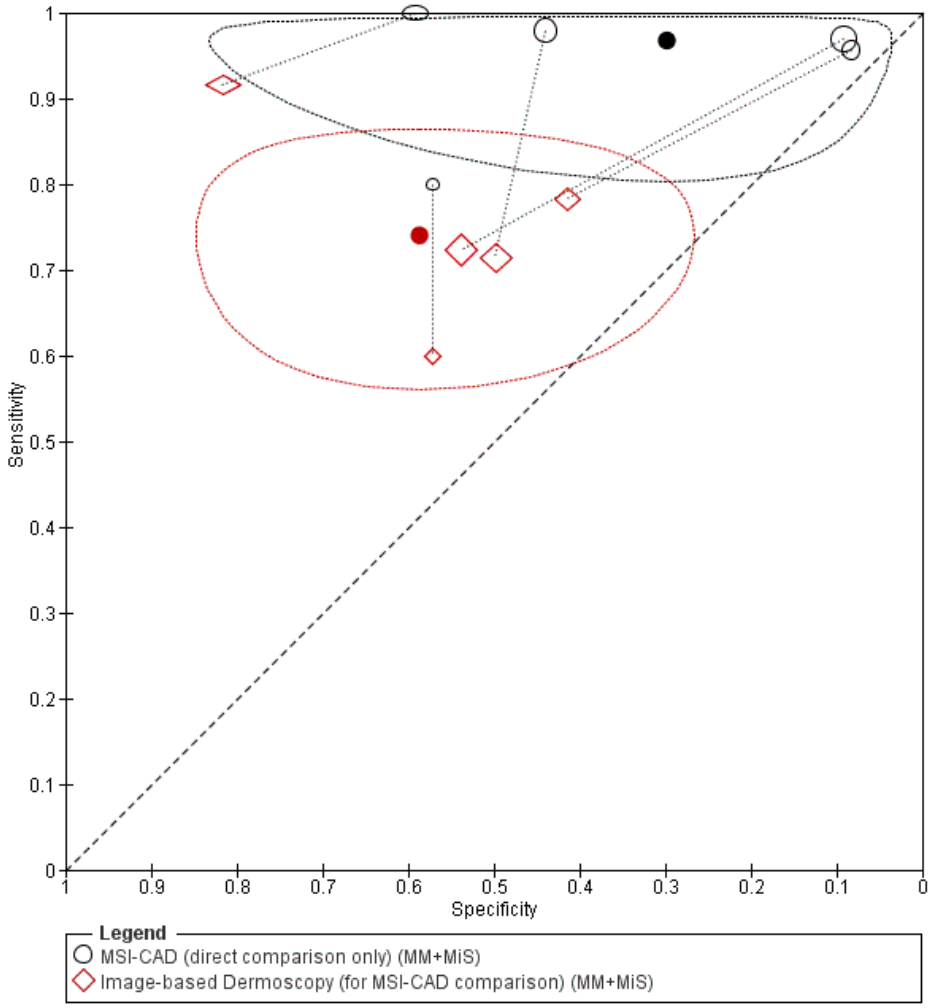
Figure 16 (Analysis 37)



Caption

Summary plot of image-based dermoscopy diagnosis versus multi-spectral imaging CAD systems (MSI-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

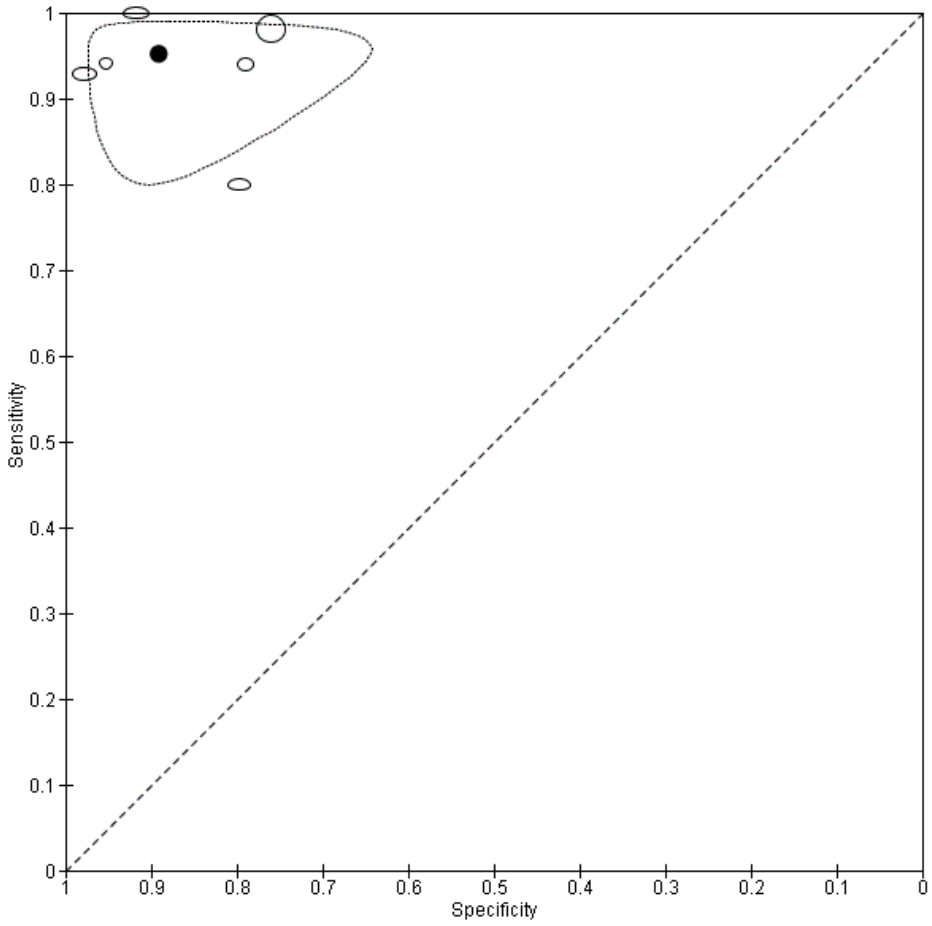
Figure 17 (Analysis 8)



Caption

Summary plot of direct comparisons between image-based dermoscopy diagnosis versus multi-spectral imaging CAD systems (MSI-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

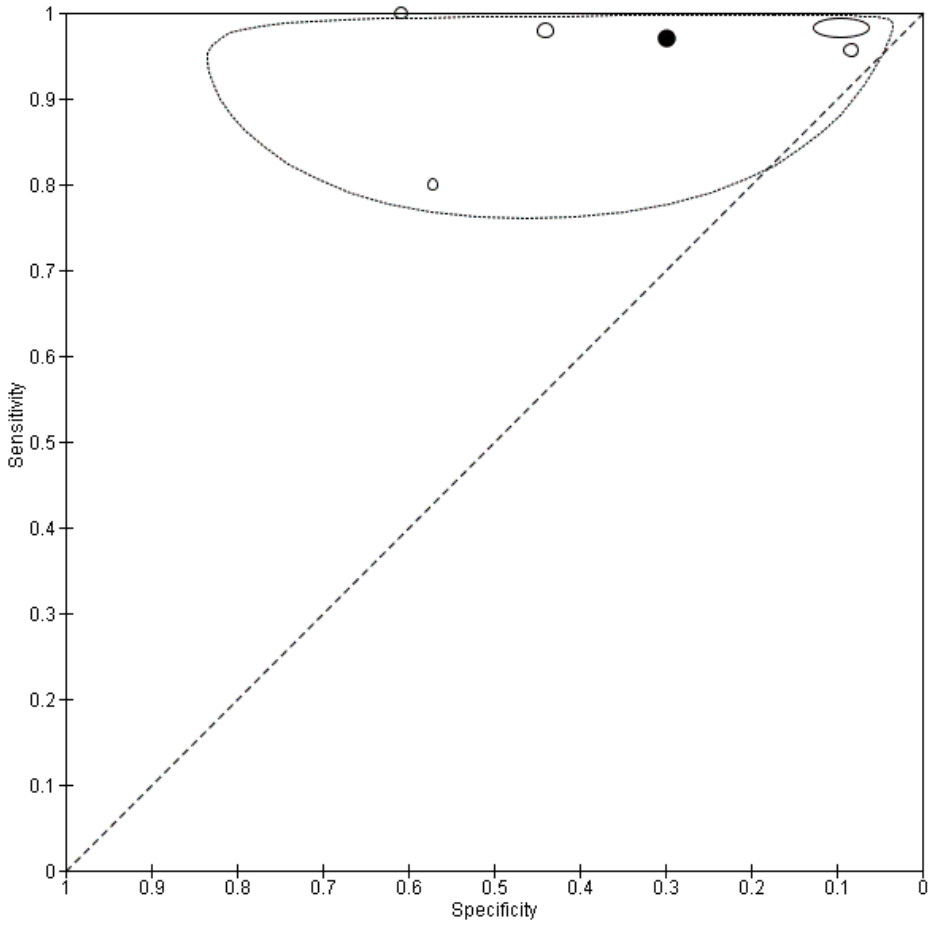
Figure 18 (Analysis 18)



Caption

Summary plot for the multi-spectral imaging CAD system (MSI-CAD) DBMIPS for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

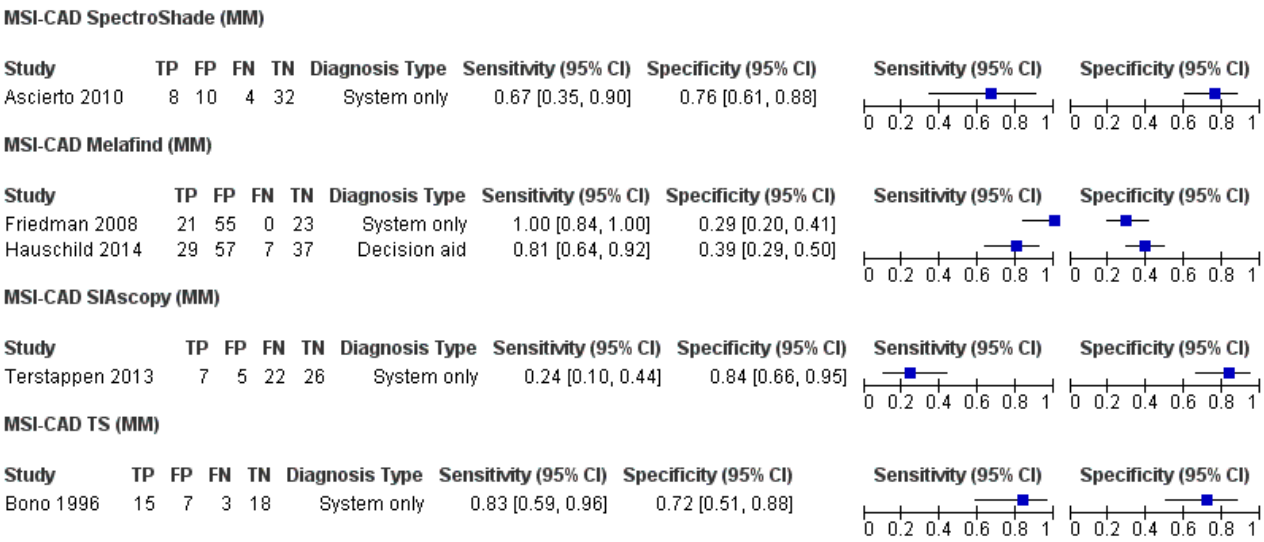
Figure 19 (Analysis 21)



Caption

Summary plot for the multi-spectral imaging CAD system (MSI-CAD) MelaFind for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

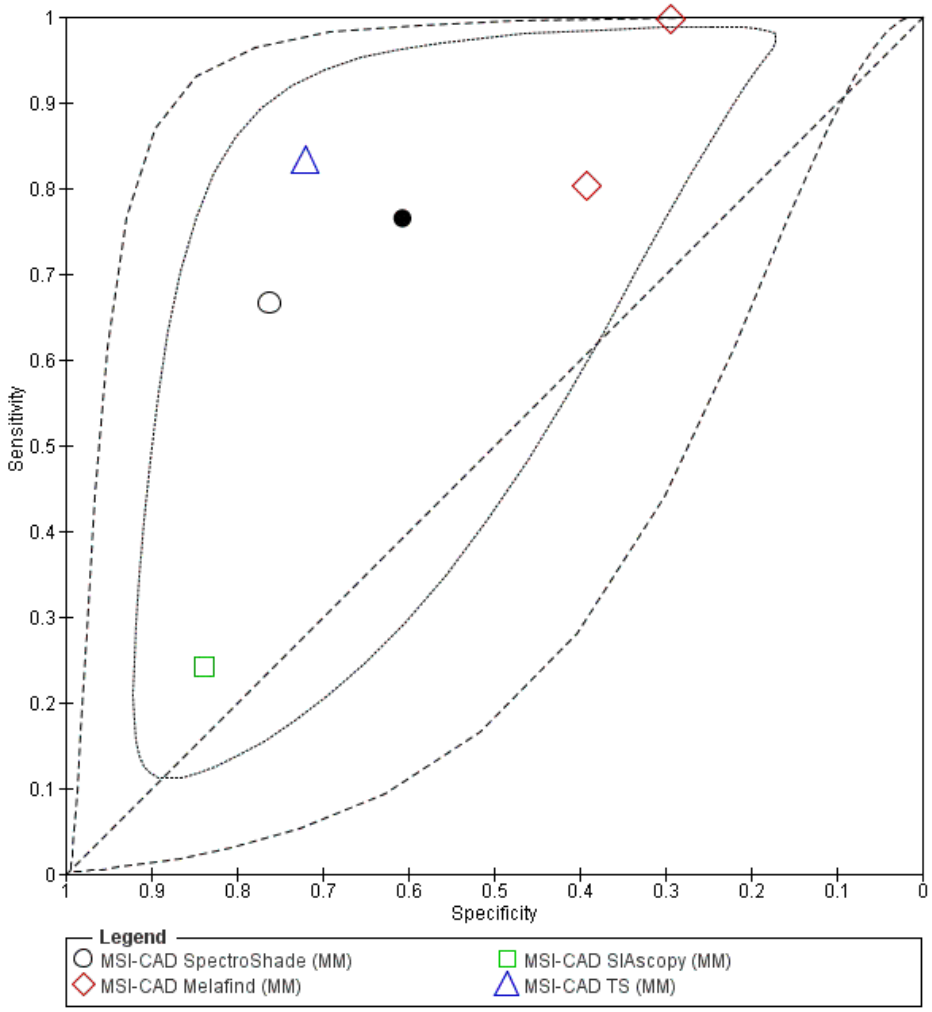
Figure 20 (Analysis 32)



Caption

Forest plot of different types of multi-spectral imaging CAD system(MSI-CAD) for the detection of invasive melanoma alone (MM)

Figure 21 (Analysis 32)



Caption

Summary plot of different types of multi-spectral imaging CAD (MSI-CAD) for the detection of invasive melanoma alone (MM)

Figure 22 (Analysis 8)

MSI-CAD (direct comparison only) (MM+MiS)

Study	TP	FP	FN	TN	Diagnosis Type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hauschild 2014	63	59	2	6	Decision aid	0.97 [0.89, 1.00]	0.09 [0.03, 0.19]		
Winkelmann 2016	4	3	1	4	Decision aid	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]		
Friedman 2008	48	28	1	22	System only	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]		
Glud 2009	12	29	0	42	System only	1.00 [0.74, 1.00]	0.59 [0.47, 0.71]		
Wells 2012	22	22	1	2	System only	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]		

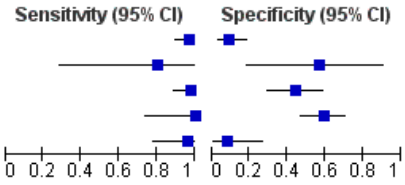
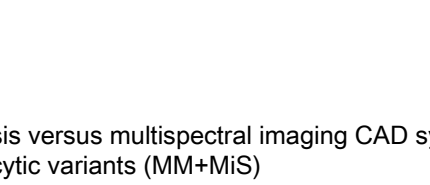


Image-based Dermoscopy (for MSI-CAD comparison) (MM+MiS)

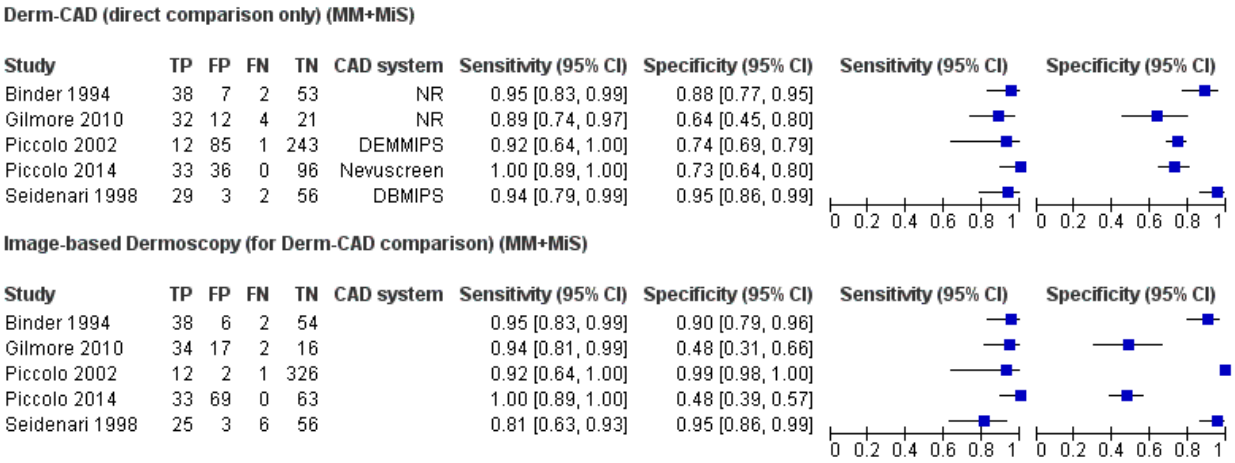
Study	TP	FP	FN	TN	Diagnosis Type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hauschild 2014	47	30	18	35	Decision aid	0.72 [0.60, 0.83]	0.54 [0.41, 0.66]		
Winkelmann 2016	3	3	2	4	Decision aid	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]		
Friedman 2008	35	25	14	25	System only	0.71 [0.57, 0.83]	0.50 [0.36, 0.64]		
Glud 2009	11	13	1	58	System only	0.92 [0.62, 1.00]	0.82 [0.71, 0.90]		
Wells 2012	18	14	5	10	System only	0.78 [0.56, 0.93]	0.42 [0.22, 0.63]		



Caption

Forest plot of direct comparisons between image-based dermoscopy diagnosis versus multispectral imaging CAD systems (MSI-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

Figure 23 (Analysis 15)



Caption

Forest plot of direct comparisons between image-based dermoscopy diagnosis versus digital dermoscopy CAD systems (Derm-CAD) for the detection of invasive melanoma or intraepidermal melanocytic variants (MM+MiS)

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 was identified either alone or in combination	–
Diagnosis of keratinocyte skin cancer (basal cell carcinoma and cutaneous squamous cell carcinoma)	
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 was identified either alone or in combination	–
Staging of melanoma	
15. Ultrasound	25 to 30
16. Computer tomography	5 to 10
17. Positron emission tomography or positron emission tomography-computer tomography	20 to 25
18. Magnetic resonance imaging	5
19. Sentinel lymph node biopsy ± high frequency ultrasound	70
20. Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination	–
Staging of cutaneous squamous cell carcinoma	
21. Imaging tests review	10 to 15
22. Sentinel lymph node biopsy ± high frequency ultrasound	15 to 20

2 Acronyms

Acronym	Definition
µm	micrometre
AK	actinic keratosis
ANN	artificial neural network
BCC	basal cell carcinoma
BD	Bowen's disease
BPC	between person comparison (of tests)
CAD	computer assisted diagnosis
CCS	case control study
CS	case series
cSCC	cutaneous squamous cell carcinoma

Acronym	Definition
D-	disease negative
D+	disease positive
Derm–CAD	Digital dermoscopy based computer assisted diagnosis
DF	dermatofibroma
DRS	diffuse reflectance spectroscopy
DRSi	diffuse reflectance spectroscopy imaging
Dx	diagnosis
EIS	electrical impedance spectroscopy
FN	false negative
FP	false positive
FU	Follow- up
GP	general practitioner
H&E	haematoxylin and eosin stain
HFUS	high frequency ultrasound
Hz	hertz
KHz	kilohertz
K–NN	k nearest neighbour
MHz	megahertz
MiS	melanoma in situ (or lentigo maligna)
MM	malignant melanoma
mm	millimetre
MSI	multispectral imaging
N/A	not applicable
NC	non comparative
nm	nanometre
NPV	negative predictive value
NR	not reported
P	prospective
PPV	positive predictive value
PSL	pigmented skin lesion
R	retrospective
RCM	reflectance confocal microscopy
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SD	standard deviation
se	sensitivity
sp	specificity
spectro–CAD	spectroscopy based computer–assisted diagnosis
SK	seborrhoeic keratosis
SSM	superficial spreading melanoma
SVM	Support vector machine
TN	true negative

Acronym	Definition
TS	Telespectrophotometry System
VI	visual inspection
UNREF	Unreferred population
WPC	within person comparison (of tests)
WPC-algs	within person comparison (of algorithms)

3 Proposed sources of heterogeneity

i. Population characteristics

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

ii. Index test characteristics

- the nature of and definition of criteria for test positivity
- observer experience with the index test
- approaches to lesion preparation (e.g., the use of oil or antiseptic gel for dermoscopy)

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

4 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 29 August 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 29 August 2016

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 to 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 to 30 August 2016

Conference Proceedings Citation Index (Web of Science) 1900 to 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)

5 Full text inclusion criteria

Criterion	Inclusion	Exclusion

Study design	For diagnostic and staging reviews
	• Any study for which a 2×2 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 was not the primary objective but test results for both index and reference standard were available
	  ◦ RCTs of tests or testing strategies where participants were 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 were 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 2×2 table

Target condition	• Melanoma
	• Keratinocyte skin cancer (or non-melanoma skin cancer)
	  ◦ BCC or epithelioma
	  ◦ 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	• People 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 • SLNB +/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 • LND

Criterion	Inclusion	Exclusion
Reference standard	<u>For diagnostic studies</u> • 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) <u>For studies of imaging tests for staging</u> • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above <u>For studies of SLNB accuracy for staging</u> • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	<u>For diagnostic studies</u> • Exclude if any disease positive participants have diagnosis unconfirmed by histology • Exclude if > 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; 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; SCC: squamous cell carcinoma; SLN+: positive sentinel lymph node; SLn: negative sentinel lymph node; SLNB: sentinel lymph node biopsy.		

6 Quality assessment (based on QUADAS-2)

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
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

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
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?	**For A)** • **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 **For B)** • **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 **For C)** • **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? **For non-comparative and within person-comparative studies** 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': **For between-person comparative studies** 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':	**For non-comparative and within person-comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear **For between-person comparative studies** 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 generalisable to the patient population who will receive the test in practice? (Test set) • 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
3) Was an adequate spectrum of cases used to train the algorithm? (training set)	**For melanoma studies:** **Yes** – if all PSLs, main types of melanoma all present (nodular, SSM, Mis), main types of dysplasia present, and a range of benign diagnoses included. **For keratinocyte cancer studies:** **Yes** - if the main malignant diagnoses are included (BCC, cSCC), as well as main types of atypia/dysplasia and a range of benign differential diagnoses (AK, SK, BD). **No** - if study participants appear to be unrepresentative of usual practice, for example with a specific focus on certain lesions groups, e.g. melanoma and common nevus only **Unclear** – insufficient details to determine generalisability of study participants **N/A** - algorithm trained in a previous study

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
Is there concern that the included participants do not match the review question? 1. If the answer to question 1) and 2) and 3) 'Yes': 2. If the answer to question 1) or 2) or 3) 'No': 3. If the answer to question 1) or 2) or 3) '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
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) Was the CAD classification algorithm evaluated in an independent patient population?	**Yes** – Test set only study (validated in previous study) **OR** validated within–study in a test set using in a different group of participants recruited from a different source (external validation) **OR** validated within–study in a test set comprising a randomised subset of one larger participant population also used for model training **No** – Algorithm developed and evaluated within the same study (internal validation) where training and test sets use the same population which is not divided randomly **Unclear** – The relationship between training and tests sets is not reported clearly
4) Was model overfitting accounted for?	**Yes** – a shrinkage method was applied, e.g. bootstrapping for calibration in the large, calibration in the small, overoptimisation, optimisation, use of a verify set to optimise stopping. **No** – study clearly reports that no method was applied **Unclear** – overfitting not discussed or corrected **N/A** - study does not contain a derivation element
Could the conduct or interpretation of the index test have introduced bias? 1. If answers to questions 1) and 2) and 3) and 4) 'Yes' or 'N/A': 2. If answers to any of questions 1) or 2) or 3) or 4) 'No': 3. If answers to any of questions 1) or 2) or 3) or 4) 'Unclear':	1. Risk is low 2. Risk is high 3. Risk is unclear
INDEX TEST (2) - CONCERN ABOUT APPLICABILITY	
1) 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	
2) 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
3) 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
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

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
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
Could the reference standard, its conduct, or its interpretation have introduced bias? 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':	1. Risk is low 2. Risk is high 3. Risk is unclear
REFERENCE STANDARD (3) - CONCERN ABOUT APPLICABILITY	
1) 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	**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
2) 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) and 2), 'Yes': 2. If answers to any 1 of questions 1) or 2) 'No': 3. If answers to any 1 of questions 1) or 2) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
FLOW AND TIMING (4): 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

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
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
Could the participant flow have introduced bias? 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':	1. Risk is low 2. Risk is high 3. Risk is unclear
BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.	

7 Forest plots for the direct comparison of CAD systems vs. image-based dermoscopy

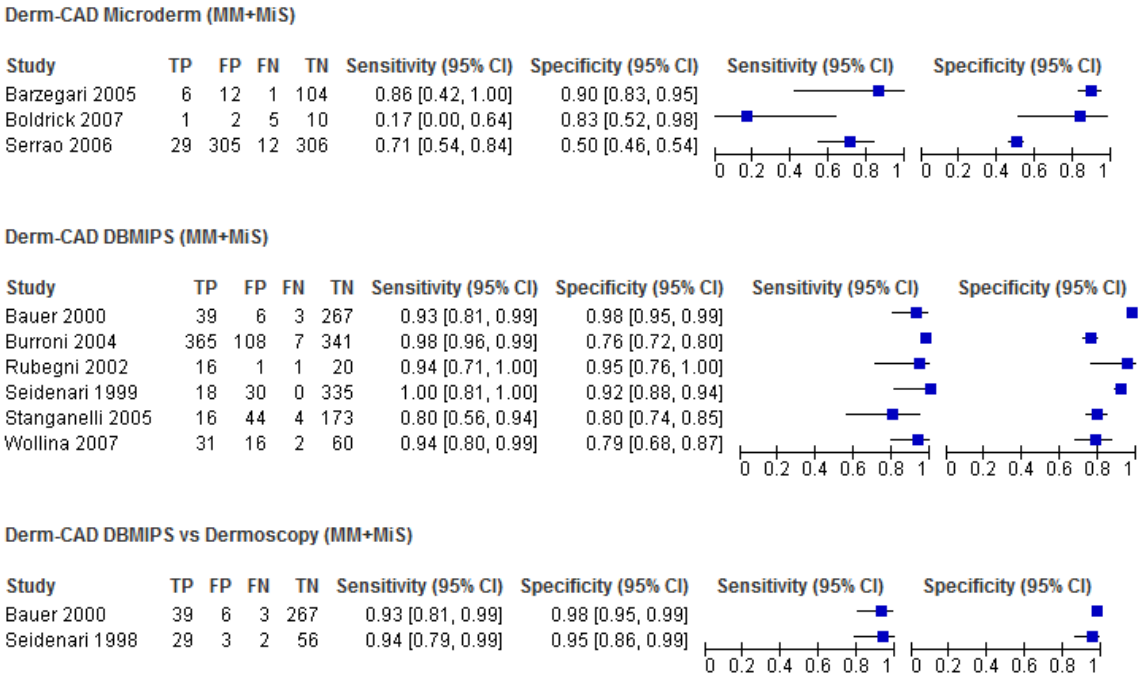
Figure 22; Figure 23

8 Results of sensitivity analysis for CAD systems (excludes diagnostic aid studies)

Index test	Studies	Cases/Number of participants	Summary sensitivity (95% CI) %	Summary specificity (95% CI) %
Primary target condition: Invasive melanoma and atypical intraepidermal melanocytic variants				
MSI-CAD	7	281/2389	93.7 (83.9, 97.7)	41.7 (22.0, 64.6)
Derm-CAD	19	955/8403	88.5 (81.3, 93.1)	71.3 (60.0, 80.4)
DB–MIPS	4	427/1479	96.4 (84.9, 99.2)	85.5 (75.7, 91.7)
MelaFind	4	191/1786	97.9 (94.6, 99.2)	24.8 (8.82, 52.9)
Secondary target condition: Invasive melanoma alone				
MSI-CAD	4	80/256	83.1 (26.5, 98.5)	66.9 (41.6, 85.1)

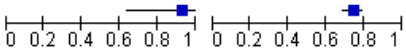
9 Forest plots for diagnosis of MM+Mis and MM in unreferred populations

Graphs



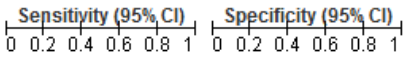
Derm-CAD DEMMIPS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Piccolo 2002	12	85	1	243	0.92 [0.64, 1.00]	0.74 [0.69, 0.79]		



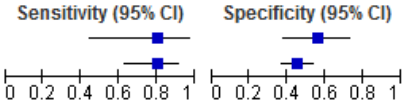
Derm-CAD SkinView (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)



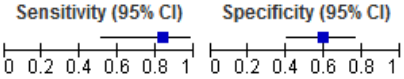
Derm-CAD SkinView (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cascinelli 1992	8	15	2	19	0.80 [0.44, 0.97]	0.56 [0.38, 0.73]		
Cristofolini 1997	28	77	7	64	0.80 [0.63, 0.92]	0.45 [0.37, 0.54]		



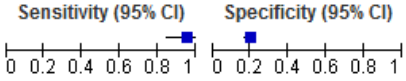
Derm-CAD SkinView (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cascinelli 1992	10	13	2	19	0.83 [0.52, 0.98]	0.59 [0.41, 0.76]		



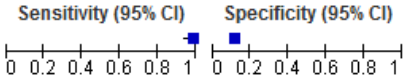
Derm-CAD NevusDr (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mollersen 2015	42	662	2	164	0.95 [0.85, 0.99]	0.20 [0.17, 0.23]		



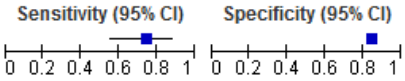
Derm-CAD NevusDr (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mollersen 2015	119	662	2	87	0.98 [0.94, 1.00]	0.12 [0.09, 0.14]		



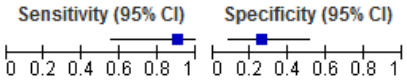
Derm-CAD ImageJ (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dreiseitl 2009	23	478	8	2512	0.74 [0.55, 0.88]	0.84 [0.83, 0.85]		



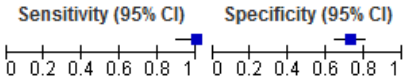
Derm-CAD IBAS2000 (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Binder 1998	9	14	1	5	0.90 [0.55, 1.00]	0.26 [0.09, 0.51]		



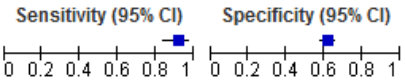
Derm-CAD Nevuscreen (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Piccolo 2014	33	36	0	96	1.00 [0.89, 1.00]	0.73 [0.64, 0.80]		



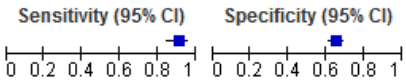
Derm-CAD SolarScan (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 2005	69	274	6	437	0.92 [0.83, 0.97]	0.61 [0.58, 0.65]		



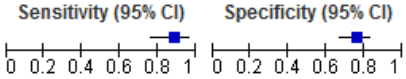
Derm-CAD SolarScan (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 2005	111	232	11	432	0.91 [0.84, 0.95]	0.65 [0.61, 0.69]		



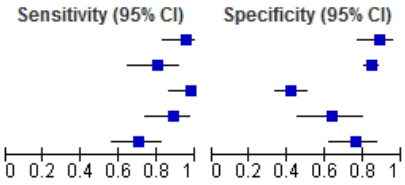
Derm-CAD No name (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 1996	40	29	5	90	0.89 [0.76, 0.96]	0.76 [0.67, 0.83]		



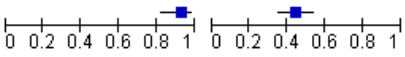
Derm-CAD No name (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Binder 1994	38	7	2	53	0.95 [0.83, 0.99]	0.88 [0.77, 0.95]		
Blum 2004b	32	59	8	319	0.80 [0.64, 0.91]	0.84 [0.80, 0.88]		
Ferris 2015	38	78	1	56	0.97 [0.87, 1.00]	0.42 [0.33, 0.51]		
Gilmore 2010	32	12	4	21	0.89 [0.74, 0.97]	0.64 [0.45, 0.80]		
Maglogiannis 2015	38	12	16	38	0.70 [0.56, 0.82]	0.76 [0.62, 0.87]		



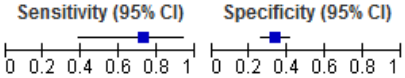
Derm-CAD No name (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ferris 2015	49	67	4	53	0.92 [0.82, 0.98]	0.44 [0.35, 0.54]		



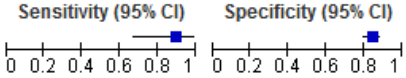
Derm-CAD No name (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ferris 2015	8	108	3	54	0.73 [0.39, 0.94]	0.33 [0.26, 0.41]		



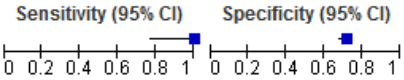
Derm-CAD DBMIPS_UNREF (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wollina 2007	17	54	2	284	0.89 [0.67, 0.99]	0.84 [0.80, 0.88]		



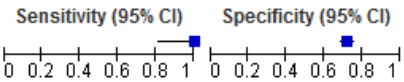
MSI-CAD SIAscope_UNREF (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Walter 2012	14	213	0	539	1.00 [0.77, 1.00]	0.72 [0.68, 0.75]		



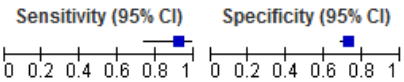
MSI-CAD SIAscope_UNREF (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Walter 2012	18	209	0	539	1.00 [0.81, 1.00]	0.72 [0.69, 0.75]		



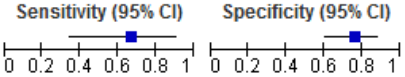
MSI-CAD SIAscope_UNREF (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Walter 2012	23	204	2	537	0.92 [0.74, 0.99]	0.72 [0.69, 0.76]		



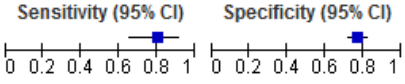
MSI-CAD SpectroShade (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ascierto 2010	8	10	4	32	0.67 [0.35, 0.90]	0.76 [0.61, 0.88]		



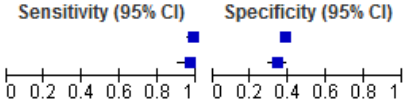
MSI-CAD SpectroShade (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Tomatis 2005	33	70	8	236	0.80 [0.65, 0.91]	0.77 [0.72, 0.82]		



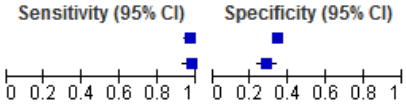
EIS-CAD-Nevisense (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Malvehy 2014	151	1095	2	695	0.99 [0.95, 1.00]	0.39 [0.37, 0.41]		
Mohr 2013	71	246	2	127	0.97 [0.90, 1.00]	0.34 [0.29, 0.39]		



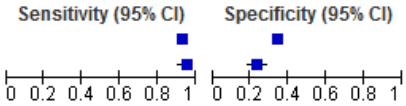
EIS-CAD-Nevisense (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malvehy 2014	256	1095	9	583	0.97 [0.94, 0.98]	0.35 [0.32, 0.37]
Mohr 2013	101	246	2	97	0.98 [0.93, 1.00]	0.28 [0.24, 0.33]



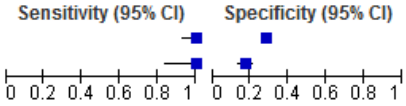
EIS-CAD-Nevisense (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malvehy 2014	444	963	34	502	0.93 [0.90, 0.95]	0.34 [0.32, 0.37]
Mohr 2013	158	214	8	66	0.95 [0.91, 0.98]	0.24 [0.19, 0.29]



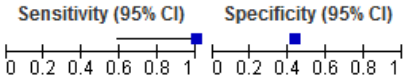
EIS-CAD-Nevisense (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malvehy 2014	48	1359	0	536	1.00 [0.93, 1.00]	0.28 [0.26, 0.30]
Mohr 2013	21	351	0	74	1.00 [0.84, 1.00]	0.17 [0.14, 0.21]



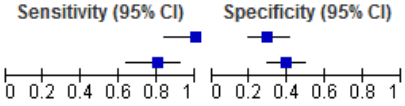
EIS-CAD-Nevisense (cSCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malvehy 2014	7	1095	0	841	1.00 [0.59, 1.00]	0.43 [0.41, 0.46]



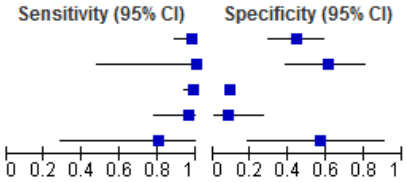
MSI-CAD Melafind (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	21	55	0	23	1.00 [0.84, 1.00]	0.29 [0.20, 0.41]
Hauschild 2014	29	57	7	37	0.81 [0.64, 0.92]	0.39 [0.29, 0.50]



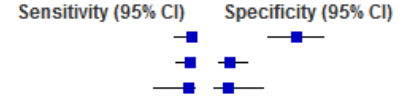
MSI-CAD Melafind (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Gutkowicz Krusin 1997	5	9	0	14	1.00 [0.48, 1.00]	0.61 [0.39, 0.80]
Monheit 2011	112	1356	2	142	0.98 [0.94, 1.00]	0.09 [0.08, 0.11]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]
Winkelmann 2016	4	3	1	4	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]



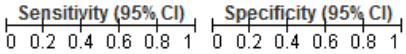
MSI-CAD Melafind_vs Dermoscopy (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Hauschild 2014	63	59	2	6	0.97 [0.89, 1.00]	0.09 [0.03, 0.19]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]
Winkelmann 2016	4	3	1	4	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]



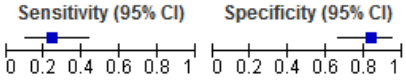
MSI-CAD Melafind (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)



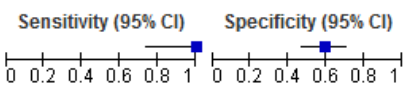
MSI-CAD SIAscopy (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Terstappen 2013	7	5	22	26	0.24 [0.10, 0.44]	0.84 [0.66, 0.95]



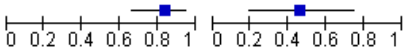
MSI-CAD SIAscopy (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Glud 2009	12	29	0	42	1.00 [0.74, 1.00]	0.59 [0.47, 0.71]



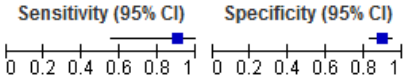
MSI-CAD SIAscope Only_UNREF (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Sgouros 2014	26	7	5	6	0.84 [0.66, 0.95]	0.46 [0.19, 0.75]		



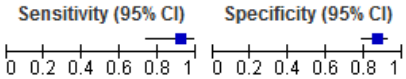
DRS-CAD OIDRS (MM+Mis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Garcia Uribe 2012	9	13	1	113	0.90 [0.55, 1.00]	0.90 [0.83, 0.94]		



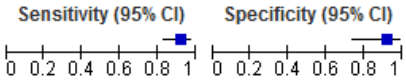
DRS-CAD OIDRS (Any + dysplastic)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Garcia Uribe 2012	23	15	2	96	0.92 [0.74, 0.99]	0.86 [0.79, 0.92]		



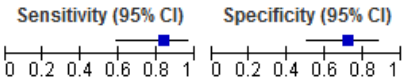
DRS-CAD OIDRS (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Garcia Uribe 2012	59	2	5	23	0.92 [0.83, 0.97]	0.92 [0.74, 0.99]		



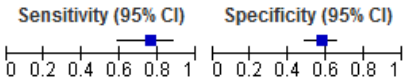
MSI-CAD TS (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bono 1996	15	7	3	18	0.83 [0.59, 0.96]	0.72 [0.51, 0.88]		



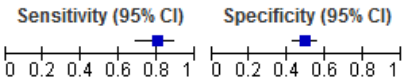
MSI-CAD TS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Tomatis 2003	28	58	9	78	0.76 [0.59, 0.88]	0.57 [0.49, 0.66]		



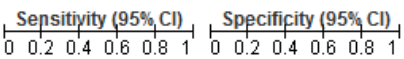
CAD-DRS-TS vs Dermoscopy (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bono 2002	53	126	13	121	0.80 [0.69, 0.89]	0.49 [0.43, 0.55]		



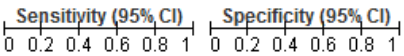
MSI-CAD OTHER (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)



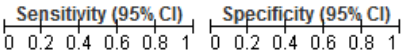
MSI-CAD NR_ML (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)



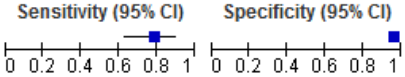
Derm-CAD OTHER (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)



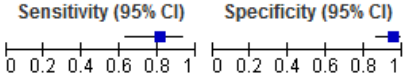
PersonDERM-DigidermDBMIPS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bauer 2000	33	10	9	263	0.79 [0.63, 0.90]	0.96 [0.93, 0.98]		



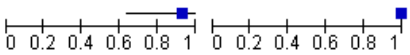
ImageDERM-DigidermDBMIPS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Seidenari 1998	25	3	6	56	0.81 [0.63, 0.93]	0.95 [0.86, 0.99]		



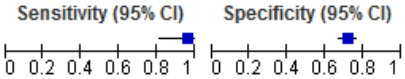
ImageDERM-DigidermDEMMIPS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Piccolo 2002	12	2	1	326	0.92 [0.64, 1.00]	0.99 [0.98, 1.00]		



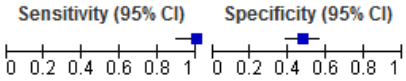
PersonDerm-DigidermImageJ (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dreiseitl 2009	26	121	1	310	0.96 [0.81, 1.00]	0.72 [0.67, 0.76]		



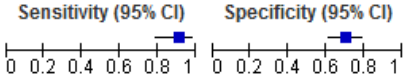
ImageDerm-DigidermNevuscreen (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Piccolo 2014	33	69	0	63	1.00 [0.89, 1.00]	0.48 [0.39, 0.57]		



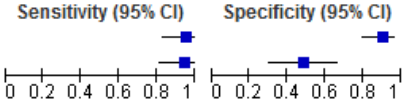
ImageDerm-DigidermNR (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 1996	41	35	4	84	0.91 [0.79, 0.98]	0.71 [0.62, 0.79]		



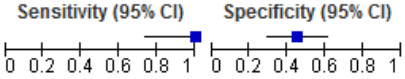
ImageDerm-DigidermNR (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Binder 1994	38	6	2	54	0.95 [0.83, 0.99]	0.90 [0.79, 0.96]		
Gilmore 2010	34	17	2	16	0.94 [0.81, 0.99]	0.48 [0.31, 0.66]		



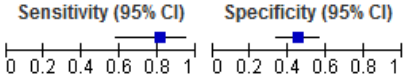
PersonDERM-DRS-SpectroShade (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ascierto 2010	12	23	0	19	1.00 [0.74, 1.00]	0.45 [0.30, 0.61]		



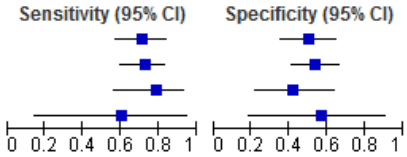
ImageDERM-DRSMelafind (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	17	43	4	35	0.81 [0.58, 0.95]	0.45 [0.34, 0.57]		



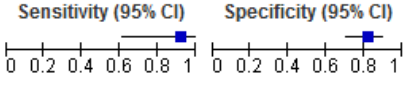
ImageDERM-DRSMelafind (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	35	25	14	25	0.71 [0.57, 0.83]	0.50 [0.36, 0.64]		
Hauschild 2014	47	30	18	35	0.72 [0.60, 0.83]	0.54 [0.41, 0.66]		
Wells 2012	18	14	5	10	0.78 [0.56, 0.93]	0.42 [0.22, 0.63]		
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]		



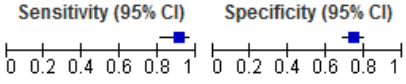
ImageDERM-DRSSIA (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Glud 2009	11	13	1	58	0.92 [0.62, 1.00]	0.82 [0.71, 0.90]		



PersonDERM-DRSTS (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bono 2002	60	63	6	184	0.91 [0.81, 0.97]	0.74 [0.69, 0.80]		



Derm-CAD (direct comparison only) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bauer 2000	39	6	3	267	0.93 [0.81, 0.99]	0.98 [0.95, 0.99]
Binder 1994	38	7	2	53	0.95 [0.83, 0.99]	0.88 [0.77, 0.95]
Blum 2004b	32	59	8	319	0.80 [0.64, 0.91]	0.84 [0.80, 0.88]
Dreiseitl 2009	24	224	3	207	0.89 [0.71, 0.98]	0.48 [0.43, 0.53]
Ferris 2015	38	78	1	56	0.97 [0.87, 1.00]	0.42 [0.33, 0.51]
Gilmore 2010	32	12	4	21	0.89 [0.74, 0.97]	0.64 [0.45, 0.80]
Maglogiannis 2015	38	12	16	38	0.70 [0.56, 0.82]	0.76 [0.62, 0.87]
Piccolo 2002	12	85	1	243	0.92 [0.64, 1.00]	0.74 [0.69, 0.79]
Piccolo 2014	33	36	0	96	1.00 [0.89, 1.00]	0.73 [0.64, 0.80]
Seidenari 1998	29	3	2	56	0.94 [0.79, 0.99]	0.95 [0.86, 0.99]

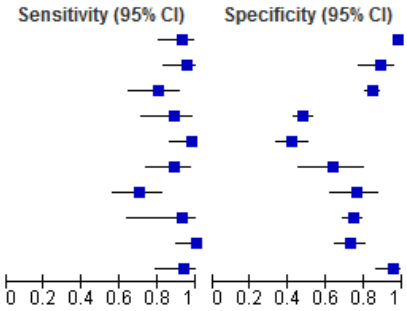
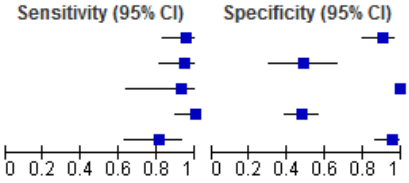


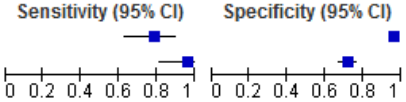
Image-based Dermoscopy (for Derm-CAD comparison) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Binder 1994	38	6	2	54	0.95 [0.83, 0.99]	0.90 [0.79, 0.96]
Gilmore 2010	34	17	2	16	0.94 [0.81, 0.99]	0.48 [0.31, 0.66]
Piccolo 2002	12	2	1	326	0.92 [0.64, 1.00]	0.99 [0.98, 1.00]
Piccolo 2014	33	69	0	63	1.00 [0.89, 1.00]	0.48 [0.39, 0.57]
Seidenari 1998	25	3	6	56	0.81 [0.63, 0.93]	0.95 [0.86, 0.99]



In-person based Dermoscopy - Derm-CAD studies (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bauer 2000	33	10	9	263	0.79 [0.63, 0.90]	0.96 [0.93, 0.98]
Dreiseitl 2009	26	121	1	310	0.96 [0.81, 1.00]	0.72 [0.67, 0.76]



MSI-CAD (direct comparison only) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bono 2002	53	126	13	121	0.80 [0.69, 0.89]	0.49 [0.43, 0.55]
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Glud 2009	12	29	0	42	1.00 [0.74, 1.00]	0.59 [0.47, 0.71]
Gutkowicz Krusin 1997	5	9	0	14	1.00 [0.48, 1.00]	0.61 [0.39, 0.80]
Hauschild 2014	63	59	2	6	0.97 [0.89, 1.00]	0.09 [0.03, 0.19]
Tomatis 2005	33	70	8	236	0.80 [0.65, 0.91]	0.77 [0.72, 0.82]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]
Winkelmann 2016	4	3	1	4	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]

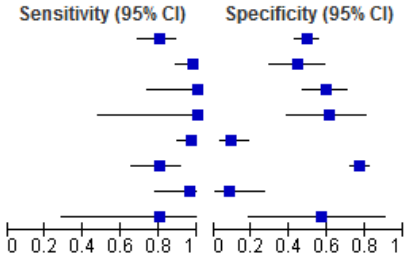
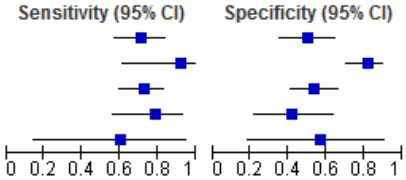


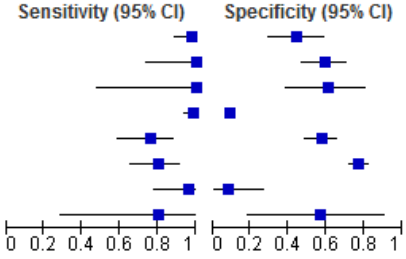
Image-based Dermoscopy (for MSI-CAD comparison) (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	35	25	14	25	0.71 [0.57, 0.83]	0.50 [0.36, 0.64]
Glud 2009	11	13	1	58	0.92 [0.62, 1.00]	0.82 [0.71, 0.90]
Hauschild 2014	47	30	18	35	0.72 [0.60, 0.83]	0.54 [0.41, 0.66]
Wells 2012	18	14	5	10	0.78 [0.56, 0.93]	0.42 [0.22, 0.63]
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]



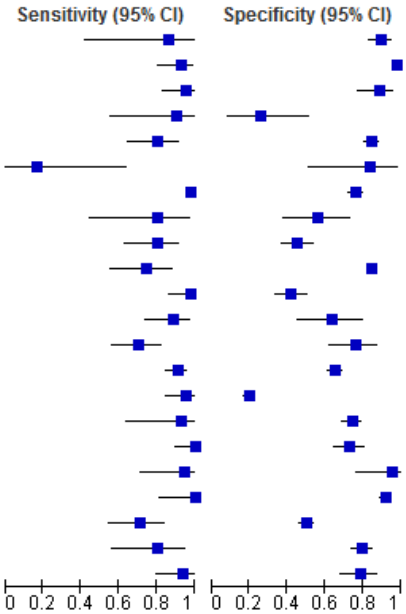
MSI-CAD All systems (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Glud 2009	12	29	0	42	1.00 [0.74, 1.00]	0.59 [0.47, 0.71]
Gutkowicz Krusin 1997	5	9	0	14	1.00 [0.48, 1.00]	0.61 [0.39, 0.80]
Monheit 2011	112	1356	2	142	0.98 [0.94, 1.00]	0.09 [0.08, 0.11]
Tomatis 2003	28	58	9	78	0.76 [0.59, 0.88]	0.57 [0.49, 0.66]
Tomatis 2005	33	70	8	236	0.80 [0.65, 0.91]	0.77 [0.72, 0.82]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]
Winkelmann 2016	4	3	1	4	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]



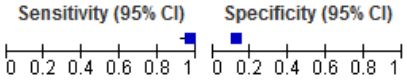
Derm-CAD All systems (MM+MiS)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barzegari 2005	6	12	1	104	0.86 [0.42, 1.00]	0.90 [0.83, 0.95]
Bauer 2000	39	6	3	267	0.93 [0.81, 0.99]	0.98 [0.95, 0.99]
Binder 1994	38	7	2	53	0.95 [0.83, 0.99]	0.88 [0.77, 0.95]
Binder 1998	9	14	1	5	0.90 [0.55, 1.00]	0.26 [0.09, 0.51]
Blum 2004b	32	59	8	319	0.80 [0.64, 0.91]	0.84 [0.80, 0.88]
Boldrick 2007	1	2	5	10	0.17 [0.00, 0.64]	0.83 [0.52, 0.98]
Burroni 2004	365	108	7	341	0.98 [0.96, 0.99]	0.76 [0.72, 0.80]
Cascinelli 1992	8	15	2	19	0.80 [0.44, 0.97]	0.56 [0.38, 0.73]
Cristofolini 1997	28	77	7	64	0.80 [0.63, 0.92]	0.45 [0.37, 0.54]
Dreiseitl 2009	23	478	8	2512	0.74 [0.55, 0.88]	0.84 [0.83, 0.85]
Ferris 2015	38	78	1	56	0.97 [0.87, 1.00]	0.42 [0.33, 0.51]
Gilmore 2010	32	12	4	21	0.89 [0.74, 0.97]	0.64 [0.45, 0.80]
Maglogiannis 2015	38	12	16	38	0.70 [0.56, 0.82]	0.76 [0.62, 0.87]
Menzies 2005	111	232	11	432	0.91 [0.84, 0.95]	0.65 [0.61, 0.69]
Mollersen 2015	42	662	2	164	0.95 [0.85, 0.99]	0.20 [0.17, 0.23]
Piccolo 2002	12	85	1	243	0.92 [0.64, 1.00]	0.74 [0.69, 0.79]
Piccolo 2014	33	36	0	96	1.00 [0.89, 1.00]	0.73 [0.64, 0.80]
Rubegni 2002	16	1	1	20	0.94 [0.71, 1.00]	0.95 [0.76, 1.00]
Seidenari 1999	18	30	0	335	1.00 [0.81, 1.00]	0.92 [0.88, 0.94]
Serrao 2006	29	305	12	306	0.71 [0.54, 0.84]	0.50 [0.46, 0.54]
Stanganelli 2005	16	44	4	173	0.80 [0.56, 0.94]	0.80 [0.74, 0.85]
Wollina 2007	31	16	2	60	0.94 [0.80, 0.99]	0.79 [0.68, 0.87]



Derm-CAD MoleExpert (Any)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mollersen 2015	117	652	4	97	0.97 [0.92, 0.99]	0.13 [0.11, 0.16]



Derm-CAD All systems (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 1996	40	29	5	90	0.89 [0.76, 0.96]	0.76 [0.67, 0.83]
Menzies 2005	69	274	6	437	0.92 [0.83, 0.97]	0.61 [0.58, 0.65]

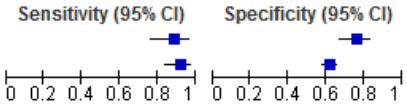
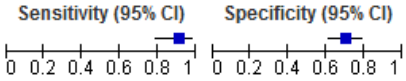


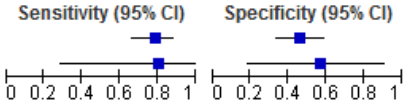
Image-based Dermoscopy - Derm-CAD studies (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 1996	41	35	4	84	0.91 [0.79, 0.98]	0.71 [0.62, 0.79]



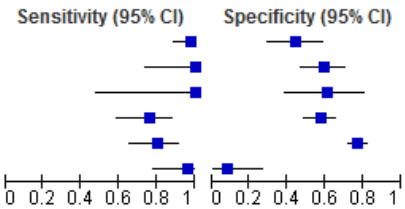
MSI-CAD All (Melafind) (MM+MiS), CAD + Clinician (diagnostic aid) only

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hauschild 2014	51	35	14	30	0.78 [0.67, 0.88]	0.46 [0.34, 0.59]
Winkelmann 2016	4	3	1	4	0.80 [0.28, 0.99]	0.57 [0.18, 0.90]



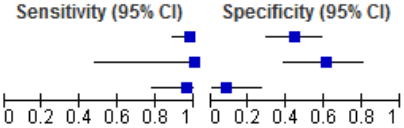
MSI-CAD All (MM+MiS), CAD only

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Glud 2009	12	29	0	42	1.00 [0.74, 1.00]	0.59 [0.47, 0.71]
Gutkowicz Krusin 1997	5	9	0	14	1.00 [0.48, 1.00]	0.61 [0.39, 0.80]
Tomatis 2003	28	58	9	78	0.76 [0.59, 0.88]	0.57 [0.49, 0.66]
Tomatis 2005	33	70	8	236	0.80 [0.65, 0.91]	0.77 [0.72, 0.82]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]



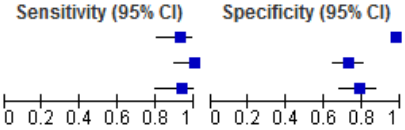
MSI-CAD Melafind (MM+MiS), CAD only

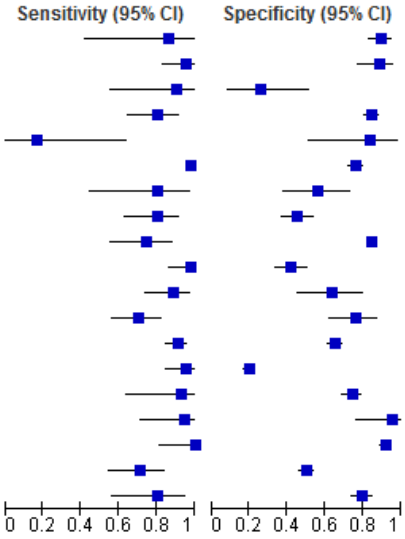
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedman 2008	48	28	1	22	0.98 [0.89, 1.00]	0.44 [0.30, 0.59]
Gutkowicz Krusin 1997	5	9	0	14	1.00 [0.48, 1.00]	0.61 [0.39, 0.80]
Wells 2012	22	22	1	2	0.96 [0.78, 1.00]	0.08 [0.01, 0.27]



Derm-CAD All (MM+MiS), CAD + Clinician (diagnostic aid) only

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bauer 2000	39	6	3	267	0.93 [0.81, 0.99]	0.98 [0.95, 0.99]
Piccolo 2014	33	36	0	96	1.00 [0.89, 1.00]	0.73 [0.64, 0.80]
Wollina 2007	31	16	2	60	0.94 [0.80, 0.99]	0.79 [0.68, 0.87]



Derm-CAD All (MM+MiS), CAD only

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barzegari 2005	6	12	1	104	0.86 [0.42, 1.00]	0.90 [0.83, 0.95]
Binder 1994	38	7	2	53	0.95 [0.83, 0.99]	0.88 [0.77, 0.95]
Binder 1998	9	14	1	5	0.90 [0.55, 1.00]	0.26 [0.09, 0.51]
Blum 2004b	32	59	8	319	0.80 [0.64, 0.91]	0.84 [0.80, 0.88]
Boldrick 2007	1	2	5	10	0.17 [0.00, 0.64]	0.83 [0.52, 0.98]
Burroni 2004	365	108	7	341	0.98 [0.96, 0.99]	0.76 [0.72, 0.80]
Cascinelli 1992	8	15	2	19	0.80 [0.44, 0.97]	0.56 [0.38, 0.73]
Cristofolini 1997	28	77	7	64	0.80 [0.63, 0.92]	0.45 [0.37, 0.54]
Dreiseitl 2009	23	478	8	2512	0.74 [0.55, 0.88]	0.84 [0.83, 0.85]
Ferris 2015	38	78	1	56	0.97 [0.87, 1.00]	0.42 [0.33, 0.51]
Gilmore 2010	32	12	4	21	0.89 [0.74, 0.97]	0.64 [0.45, 0.80]
Maglogiannis 2015	38	12	16	38	0.70 [0.56, 0.82]	0.76 [0.62, 0.87]
Menzies 2005	111	232	11	432	0.91 [0.84, 0.95]	0.65 [0.61, 0.69]
Mollersen 2015	42	662	2	164	0.95 [0.85, 0.99]	0.20 [0.17, 0.23]
Piccolo 2002	12	85	1	243	0.92 [0.64, 1.00]	0.74 [0.69, 0.79]
Rubegni 2002	16	1	1	20	0.94 [0.71, 1.00]	0.95 [0.76, 1.00]
Seidenari 1999	18	30	0	335	1.00 [0.81, 1.00]	0.92 [0.88, 0.94]
Serrao 2006	29	305	12	306	0.71 [0.54, 0.84]	0.50 [0.46, 0.54]
Stanganelli 2005	16	44	4	173	0.80 [0.56, 0.94]	0.80 [0.74, 0.85]