

Optical coherence tomography for the diagnosis of skin cancer in adults

Review information

Review type: Diagnostic test accuracy

Review number: #165e

Authors

Lavinia Ferrante di Ruffano¹, Jacqueline Dinnes¹, Jonathan J Deeks¹, Naomi Chuchu¹, Susan E Bayliss¹, Clare Davenport¹, Yemisi Takwoingi¹, Kathie Godfrey², Colette O'Sullivan², Rubeta N Matin³, Hamid Tehrani⁴, Hywel C Williams⁵, Cochrane Skin Cancer Diagnostic Test Accuracy Group¹

¹Institute of Applied Health Research, University of Birmingham, Birmingham, UK

²c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK

³Department of Dermatology, Churchill Hospital, Oxford, UK

⁴Department of Plastic and Reconstructive Surgery, Whiston Hospital, Liverpool, UK

⁵Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK

Citation example: Ferrante di Ruffano L, Dinnes J, Deeks JJ, Chuchu N, Bayliss SE, Davenport C, Takwoingi Y, Godfrey K, O'Sullivan C, Matin RN, Tehrani H, Williams HC, Cochrane Skin Cancer Diagnostic Test Accuracy Group. Optical coherence tomography for the diagnosis of skin cancer in adults. Cochrane Database of Systematic Reviews , Issue . Art. No.: . DOI: .

Contact person

Jacqueline Dinnes

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

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

Dates

Assessed as Up-to-date: 29 August 2016

Date of Search: 29 August 2016

Next Stage Expected: Not provided

Protocol First Published: Not specified

Review First Published: Not specified

Last Citation Issue: Not specified

What's new

Date	Event	Description
------	-------	-------------

History

Date	Event	Description
------	-------	-------------

Abstract

Background

Early accurate detection of all skin cancer types is essential to guide appropriate management and to improve morbidity and survival. Melanoma and squamous cell carcinoma (SCC) 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 cases needs to be balanced against inappropriate referral and unnecessary excision of benign lesions. Optical coherence tomography (OCT) is a microscopic imaging technique, which magnifies the surface of a skin lesion using near-infrared light. Used in conjunction with clinical or dermoscopic examination of suspected skin cancer, or both, OCT may offer additional diagnostic information compared to other technologies.

Objectives

To determine the diagnostic accuracy of OCT for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC) in adults.

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 evaluating OCT in adults with lesions suspicious for invasive melanoma and atypical intraepidermal melanocytic variants, BCC or cSCC, compared with a reference standard of 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). Our unit of analysis was lesions. Where possible, we estimated summary sensitivities and specificities using the bivariate hierarchical model.

Main results

Five studies including 529 cutaneous lesions (273 malignant lesions) were included, providing nine datasets for OCT, two for visual inspection alone, and two for visual inspection plus dermoscopy. Studies were of moderate to poor quality using data driven thresholds for test positivity and giving poor accounts of reference standard interpretation and blinding. Studies may not be representative of populations eligible for OCT in practice, for example due to high disease prevalence in study populations, and may not reflect how OCT is used in practice, for example by using previously acquired OCT images.

It is not possible to make summary statements regarding accuracy of detection of melanoma or of cSCC because of the paucity of studies, small sample sizes, and for melanoma differences in the OCT technologies used (high-definition versus conventional resolution OCT), and differences in the degree of testing performed prior to OCT (i.e. visual inspection alone or visual inspection plus dermoscopy).

Pooled data from two studies using conventional swept-source OCT alongside visual inspection and dermoscopy for the detection of BCC estimated the sensitivity and specificity of OCT as 95% (95% CI: 91, 97%) and 77% (95% CI: 69, 83%), respectively.

When applied to a hypothetical population of 1000 lesions at the mean observed BCC prevalence of 60%, OCT would miss 31 BCCs (91 fewer than would be missed by visual inspection alone and 53 fewer than would be missed by visual inspection and dermoscopy), and OCT would lead to 93 false positive results for BCC (a reduction in unnecessary excisions of 159 compared to using visual inspection alone and of 87 compared to visual inspection and dermoscopy).

Authors' conclusions

Insufficient data are available on the use of OCT for the detection of melanoma or cSCC. Initial data suggests conventional OCT may have a role for the diagnosis of BCC in clinically challenging lesions, our meta-analysis showing a higher sensitivity and higher specificity when compared to visual inspection and dermoscopy. However the small number of studies and varying methodological quality means implications to guide practice cannot currently be drawn.

Appropriately designed prospective comparative studies are required, given the paucity of data comparing OCT with dermoscopy and indeed other similar diagnostic aids such as reflectance confocal microscopy.

Plain language summary

What is the diagnostic accuracy of optical coherence tomography (OCT), an imaging test, 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. Melanoma is one of the most dangerous forms, and it is important that it is recognised early so that it can be removed. If it is not recognised (also known as a false negative test result), treatment can be delayed, and this risks the melanoma spreading to other organs in the body, which may lead to eventual death. Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) are usually localised (i.e. limited to a certain part of the body) skin cancers, although 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) may result in unnecessary surgery and other investigations and can cause stress and anxiety to the patient. Making the correct diagnosis is important, and mistaking one skin cancer for another can lead to 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 optical coherence tomography (OCT) is for diagnosing skin cancer. Researchers in Cochrane included five studies to answer this question. Two studies were concerned with the diagnosis of melanoma and three with the diagnosis of BCC.

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 is used by most skin cancer specialists, which magnifies the skin lesion using a bright light source. OCT magnifies the surface of a skin lesion to the level of that seen using a microscope using near-infrared light. It is quick to perform but is more expensive compared to dermoscopy and requires specialist training. Researchers examined how useful OCT is to help diagnose skin cancers when used after visual inspection or visual inspection and dermoscopy.

What are the main results of the review?

The review included five studies: two studies with a total of 97 participants with 133 skin lesions suspected of being melanoma, and three studies with a total of 314 participants with 396 lesions suspected of being BCC of which one (50 lesions) also analysed cSCCs (9 lesions).

The studies investigating the accuracy of OCT for diagnosing melanoma were small and too different from each other to allow a reliable estimate of the accuracy of OCT for melanoma to be made. Similarly, only one small, low-quality study investigated the accuracy of OCT for diagnosing cSCC.

For identifying BCC, two studies show the effects of skin specialists using OCT after visual inspection alone, or visual inspection with dermoscopic examination. These two studies indicate that in theory, if OCT were to be used in a group of 1000 people with skin lesions that are particularly difficult to diagnose, of whom 600 (60%) actually have BCC, then:

- An estimated 662 people will have an OCT result confirming that a BCC is present and of these 93 (14%) will not actually have a BCC (false positive result)
- Of the 338 people with an OCT result indicating that no BCC is present, 31 (9%) will in fact actually have a BCC (false negative result)

Compared to making a diagnosis of BCC using visual inspection and dermoscopy, the addition of OCT in this group would reduce the number of false positive results by 87 (thus reducing unnecessary surgical procedures) and would miss 53 fewer BCCs.

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

In all included studies, the diagnosis of skin cancer was made by lesion biopsy (OCT/dermoscopy positive) (a biopsy involves taking a sample of body cells and examining them under a microscope), and the absence of skin cancer was confirmed by biopsy (OCT/dermoscopy negative)*. This is likely to have been a reliable method for deciding whether patients really had skin cancer. However, the small number of studies included in this review, and variability between them, reduces the reliability of findings. Included studies also had important limitations, in particular study participants were from more restricted groups than would be eligible for an OCT scan in practice (for example all studies included people with skin lesions that had already been selected for surgical removal), while the way in which OCT was used may not reflect real life situations.

Who do the results of this review apply to?

Studies were conducted in Europe and the US only. Mean age (reported in only two studies) was 46 years for melanoma and 63 years for BCC. The percentage of people with a final diagnosis of melanoma was 23% and 27% (in two studies), ranged from 58% to 61% for BCC (three studies), and was 18% for cSCC (one study). For the diagnosis of BCC, the results apply to people with 'pink' and non-pigmented skin lesions that the clinician considers particularly difficult to diagnose by the naked eye alone.

What are the implications of this review?

Not enough research has been done regarding the use of OCT in detecting skin cancers. The results of this review suggest that OCT might help to diagnose BCC when it is difficult to distinguish it from benign skin lesions, but it is not yet clear whether it can adequately distinguish between BCC, cSCC and melanoma skin cancers. More studies are needed comparing OCT to dermoscopy and to other microscopic techniques (such as reflectance confocal microscopy) in well-described groups of people with suspicious skin lesions.

How up-to-date is this review?

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

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

Background

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.

Target condition being diagnosed

There are three main forms of skin cancer. Melanoma has the highest skin cancer mortality ([Cancer Research UK 2017](#)), however the commonest skin cancers in Caucasian populations are those arising from keratinocyte cells: 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, the target conditions of interest are: (a) melanoma, (b) basal cell carcinoma, and (c) cutaneous squamous cell carcinoma. We will also examine accuracy for the target condition of (d) any skin cancer or other lesion requiring excision, including melanoma or atypical intraepidermal melanocytic variants, keratinocyte skin cancer, any other skin cancer, and severely dysplastic melanocytic lesions.

Melanoma

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. Melanoma can occur in any organ that contains melanocytes, including mucosal surfaces, the back of the eye, and lining around the spinal cord and brain, but most commonly arises in the skin. 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](#)) ([SIGN 2017](#)). Melanoma in situ refers to malignant melanocytes that are contained within the epidermis and have not yet 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. Melanoma in situ and lentigo maligna are both atypical intraepidermal melanocytic variants. All forms of melanoma in situ can progress to invasive melanoma if its growth breaches the dermo-epidermal junction during a vertical growth phase, although malignant transformation is both lower and slower for lentigo maligna 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 dangerous forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and blood stream. It accounts for only a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths ([Boring 1994](#); [Cancer Research UK 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](#)). The highest incidence is observed in Australia with 11,405 new cases of melanoma of the skin ([ACIM 2014](#)) and in New Zealand with 2,341 registered cases ([HPA and MelNet NZ 2014](#)) in 2010. For 2014 in the USA, the predicted incidence was 73,870 per annum and the predicted number of deaths 9,940 ([Siegel 2015](#)). The highest rates in Europe are seen in north-western Europe and the Scandinavian countries, with highest incidence reported in Switzerland of 25.8 per 100,000 in 2012. Rates in the UK have trebled from 4.6 and 6.0 per 100,000 in men and women, respectively in England in 1990, to 18.6 and 19.6 per 100,000 in 2012 ([EUCAN 2012](#)). In the UK, melanoma has one of the fastest rising incidence rates of any cancer, and has had the biggest projected increase in incidence between 2007 and 2030 ([Mistry 2011](#)). In the decade leading up to 2013, age standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2459 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 ([Linos 2009](#); [Belbasis 2016](#)). Putative risk factors including eye and hair colour, skin type and density of freckles, history of melanoma, sunburn, and presence of particular lesion types 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](#)), increasing incidence between 1975 and 2010 means that mortality rates have reportedly remained static. 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 ([Pasquali 2018](#)).

Basal cell carcinoma

BCC can arise from multiple stem cell populations, including from the follicular bulge and interfollicular epidermis ([Grachtchouk 2011](#)). Growth is usually localised, but it can infiltrate and damage surrounding tissue, which if left untreated can cause considerable destruction and disfigurement, particularly when located on the face ([Figure 2](#)). The four main types of BCC are superficial, nodular, morphoeic or infiltrative, and pigmented. Lesions typically present as slow-growing asymptomatic papules, plaques, or nodules which may bleed or form ulcers that do not heal ([Firnhaber 2012](#)). People with a BCC often present themselves to health care professionals with a non-healing lesion rather than specific symptoms such as pain. Many lesions are diagnosed incidentally ([Gordon 2013](#)).

BCC most commonly occurs on sun-exposed areas of 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 are nodular lesions occurring in people older than 24 years old who are not immunosuppressed and do not have Gorlin's syndrome. Furthermore, lesions should be located below the clavicle; should be small (< 1 cm) with clinically well-

defined margins; not recurrent following incomplete excision or other treatment; and not in awkward or highly visible locations ([NICE 2010](#)). Superficial BCCs are also typically low risk and may be amenable to medical treatments such as cryotherapy, photodynamic therapy or topical immunomodulatory therapy e.g. 5% Imiquimod cream ([Kelleners-Smeets 2017](#)). Assigning BCCs as low or high risk influences the management options ([Batra 2002](#); [Randle 1996](#)).

Advanced locally destructive BCC can be found on the H-area of the face ([Lear 2014](#)), can arise from long-standing untreated lesions, or from a recurrence of aggressive basal cell carcinoma after primary treatment ([Lear 2012](#)). Very rarely, BCC may metastasise to regional and distant sites resulting in death; this is particularly true for 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% with very poor survival rates ([Lo 1991](#)). 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 the 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 keratinising cells of the epidermis or its appendages. cSCC typically presents with an ulcer or firm (indurated) papule, plaque, or nodule ([Griffin 2016](#)) often with an adherent crust ([Madan 2010](#)) ([Figure 2](#)). cSCC can arise in the absence of a precursor lesion, or may develop from pre-existing actinic keratosis or Bowen's disease (considered by some to be cSCC in situ); the estimated annual risk of progression being <1% to 20% for newly arising lesions ([Alam 2001](#)) and 5% for pre-existing lesions ([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, within scars or chronic ulcers, tumours more than 20mm in diameter and those with a histological depth of invasion exceeding 4mm, and poor differentiation status on pathological examination ([Motley 2009](#)). Perineural nerve invasion of PNI of at least >0.1 mm in diameter is a further documented risk factor for high risk cSCC ([Carter 2013](#)).

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 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 2015a](#); [Garbe 2016](#); [SIGN 2017](#)). Recommended surgical margins vary according to tumour thickness ([Garbe 2016](#)) and stage of disease at presentation ([NICE 2015a](#)). Following histological confirmation of diagnosis, the lesion is staged according to the American Joint Committee on Cancer (AJCC) Staging System to guide treatment ([Balch 2009](#)). Stage 0 refers to melanoma in situ; stages I to II indicate localised melanoma; stage III occurs where there is regional metastasis; and stage IV indicates distant metastasis ([Balch 2009](#)). The main prognostic indicators can be divided into histological and clinical factors. Histologically, Breslow thickness is the single most important predictor of survival, as it is a quantitative measure of tumour invasion which correlates with the propensity for metastatic spread ([Balch 2001](#)). Microscopic ulceration, mitotic rate, microscopic satellites, regression, lymphovascular invasion, and nodular (rapidly growing) or amelanotic (lacking in melanin pigment) subtypes ([Moreau 2013](#); [Shaikh 2012](#)) are also associated with worse prognosis. Independent of tumour thickness, prognosis is worse in: older people, males, those with recurrent lesions, and in those with distant lymph node involvement (micro or macroscopic) and/or metastatic disease at the time of primary presentation. There is debate regarding the prognostic effect from primary lesion site, with some evidence suggesting a worse prognosis for truncal lesions or those on the scalp or neck ([Zemelman 2014](#)).

Treatment for BCC and cSCC can be different to melanoma, in that there are a range of primary treatment options that 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 excised specimen are microscopically examined intraoperatively, and re-excision is undertaken until the margins are tumour-free, can be considered for high-risk lesions such as on the centre of the face where standard wider excision margins might lead to incomplete excision or considerable functional and/or cosmetic impairment ([Bath-Hextall 2007b](#); [Lansbury 2010](#); [Motley 2009](#); [Stratigos 2015](#)). Bath-Hextall and colleagues ([Bath-Hextall 2007b](#)) found a single trial comparing Mohs micrographic surgery with a 3mm surgical margin excision in BCC ([Motley 2009](#)), showing non-significantly lower

recurrence at 10 years with Mohs micrographic surgery (4.4% compared to 12.2% after surgical excision, $P = 0.10$) ([van Loo 2014](#)).

[Bath-Hextall 2007b](#) 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 2007b](#); [Drew 2017](#); [Kim 2014](#)), including topical chemotherapy such as imiquimod ([Williams 2017](#)), 5-fluorouracil (5-FU) ([Arits 2013](#)), ingenol mebutate ([Nart 2015](#)) and photodynamic therapy (PDT) ([Roozeboom 2016](#)). Non-surgical treatments are most frequently used for superficial forms of BCC, with one head to head trial suggesting topical imiquimod is superior to PDT and 5-FU ([Jansen 2018](#)). Although non-surgical techniques are increasingly used, they do not allow histological confirmation of tumour clearance, and their efficacy is dependent on accurate characterisation of the histological subtype and depth of tumour and so a baseline diagnostic biopsy can be helpful. 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 filled 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](#)).

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 predetermined margins is usually the first-line treatment ([Motley 2009](#); [Stratigos 2015](#)). Observational studies suggest low recurrence rates for small, low risk lesions treated with cryotherapy or curettage and electrodesiccation (recurrence rates $< 2\%$). Estimates of recurrence after Mohs microsurgery, 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)

Optical coherence tomography (OCT) is a non-invasive technology that was first applied to the diagnosis of skin lesions in 1997 ([Welzel 1997](#)). The technique uses a handheld probe based on the same principle as ultrasound, but instead of using sound waves, it uses low-coherence interferometry to measure the optical scattering of near-infrared (1310 nm) light waves from under the surface of the skin; an image similar to a sonograph is created based on multiple parallel scans ([Hussain 2015](#); [Olsen 2015](#)) ([Figure 3](#) and [Figure 4](#)). Both 2D and 3D images can be created. There are a number of different types of OCT, the most commonly used in dermatological research is frequency domain or swept source OCT where several scans are taken using a rotating optical mirror to construct multi-slice scans; these can create vertical cross-sectional slices of skin, or 'en-face' images of horizontal layers (as with Reflectance Confocal Microscopy, RCM).

A challenge for any imaging device is the trade-off between high resolution (clearer image) and depth of penetration of the layers of the skin ([Olsen 2015](#)). Conventional OCT devices can achieve penetration depths of up to 2 mm, with respective axial and lateral resolutions of up to 7.5µm and 5µm ([Hussain 2015](#); [Olsen 2015](#)). Skin features that can be visualised include the epidermis, the dermal-epidermal junction (DEJ), the upper or papillary dermis, the lower or reticular dermis, blood vessels travelling through the upper dermis, skin appendages, such as hair follicles and sebaceous glands, and the nail unit and nail plate ([DermNet New Zealand 2013](#)). High-definition OCT can achieve axial and lateral resolutions of 3µm (thereby allowing single cells to be visualised) at a depth of up to 0.57mm ([Boone 2015](#); [Hussain 2015](#); [Olsen 2015](#)).

OCT is not routinely used in current practice ([NICE 2015a](#)). It is considered to be of particular potential for the differentiation of non-pigmented lesions as pigmented lesions demonstrate regular scattering patterns that inhibit the differentiation of malignant from benign lesions ([Gambichler 2015b](#); [Olsen 2015](#)). Preliminary work using HD OCT in melanocytic lesions suggests that pagetoid cells, fusion of rete ridges, and junctional or dermal nests with atypical cells, or both, are more prevalent in melanomas compared to benign nevi ([Gambichler 2015a](#)). A recent review suggests that eight characteristics associated with BCC have been variously reported for conventional OCT including: disruption of layering, hypo-reflective rounded areas surrounded by a hyper-reflective halo ('honeycomb' structures), palisading at margin, dilated vessels, well-circumscribed black/signal poor areas, intact DEJ with underlying dark rounded areas, thinning of the epidermis, horizontal signal intense cords ([Figure 5](#)) ([Hussain 2015](#)). While there are no data to suggest that conventional OCT can discriminate between BCC subtypes ([Calin 2013](#); [Hussain 2015](#)), HD OCT has been advocated as a tool to do so, however results to date have been conflicting ([Boone 2012](#); [Gambichler 2014](#); [Hussain 2015](#)). Features thought to describe cSCC lesions by conventional OCT include destruction of the epidermis and thickened epidermal layer, however these are also visualised in actinic keratosis and so are not thought to be adequately discriminating ([Reggiani 2015](#)). Features thought to be useful for identifying cSCC by HD OCT include disruption of the DEJ, disarranged epidermal pattern in the absence of honeycomb structures ([Boone 2015](#)), and very bright irregularly broadened cell outlines masking the nucleus, which are thought to represent atypical keratinocytes ([Reggiani 2015](#)).

Internationally, there are a large number of companies producing different commercially available OCT devices, across a range of medical specialties; [Gambichler 2015b](#) lists nine different devices applied in dermatology. Imaging can reportedly be undertaken by clinicians or technicians, taking around 30 seconds to scan a lesion, with results immediately available for review and discussion with patients. No information on the cost of OCT was identified.

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 either present to their general practitioner or directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, general surgeon or other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist ([Figure 6](#)). 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 revised seven-point checklist ([Mackie 1990](#)); lesions suspected to be melanoma ([Chao 2013](#); [Marsden 2010](#); [NICE 2015b](#)) or cSCC ([London Cancer Alliance 2013](#)) should be referred for appropriate specialist assessment within two weeks. Generalist care providers increasingly carry out management of low-risk BCC ([CCAAC Network 2008](#)).

The specialist clinician will use history-taking, visual inspection of the lesion (in comparison with other lesions on the skin), and usually dermoscopy to inform a clinical decision. If melanoma or cSCC is suspected, then urgent excision is recommended. Lesions such as BCC may be referred for a diagnostic biopsy, followed by appropriate treatment or further surveillance or reassurance and discharge.

Prior test(s)

Fundamental to the diagnosis of skin cancer is history-taking and clinical examination. In the UK, this is typically done at two decision points – first in the GP surgery where a decision is made to refer or not to refer, and then a second time by a dermatologist or other professional in secondary care where a decision is made to biopsy or not. However, a range of technologies have emerged to aid diagnosis to reduce the number of biopsies. Dermoscopy in particular has become the most widely used tool for clinicians to try to obtain an accurate assessment of melanoma following visual inspection ([Argenziano 1998](#); [Argenziano 2012](#); [Haenssle 2010](#); [Kittler 2002](#)), although is less well established for BCC or cSCC diagnosis ([Dinnes 2018a](#)).

Visual inspection of the skin is undertaken iteratively, using both implicit pattern recognition (non-analytical reasoning) and more explicit 'rules' based on conscious analytical reasoning ([Norman 2009](#)), the balance of which will vary according to experience and familiarity with the diagnostic question. Various attempts have been made to formalise the "mental rules" involved in analytical pattern recognition for melanoma, ranging from a setting out of lesion characteristics that should be considered ([Friedman 1985](#); [Sober 1979](#)) to formal scoring systems with explicit numerical thresholds. The revised seven-point checklist, for example, assesses change in lesion size, shape, colour, inflammation, crusting or bleeding, sensory change, or diameter ≥ 7 mm ([Mackie 1990](#)). Other available tools include the ABCD(E) approach (presence of features: asymmetry, border, colour, diameter, evolution) ([Friedman 1985](#); [Thomas 1998](#)) and 'ugly duckling' sign ([Grob 1998](#)). For keratinocyte skin cancers, visual inspection relies primarily on pattern recognition and accuracy has been shown to vary according to the expertise of the clinician. Primary care physicians have been found to miss over half of BCC ([Offidani 2002](#)) and to inappropriately diagnose one third of BCC ([Gerbert 2000](#)). In contrast, an Australian study found that trained dermatologists were able to detect 98% of BCC, but with a specificity of only 45% ([Green 1988](#)).

Dermoscopy is a non-invasive, in vivo technique that uses a hand-held microscope and incident light (with or without oil immersion) to reveal subsurface images of the skin at increased magnification of $\times 10$ to $\times 100$ ([Kittler 2011](#)). Although widely used, the accuracy of dermoscopy largely depends on the experience and training of the examiner ([Binder 1997](#); [Kittler 2002](#); [Kittler 2011](#)). Pattern analysis ([Pehamberger 1987](#); [Steiner 1987](#)) is thought to be the most specific and reliable technique to aid dermoscopy interpretation when used by specialists ([Maley 2014](#)); however, dermoscopic histological correlations have been established and diagnostic algorithms have been developed to improve melanoma diagnosis, using features based on colour, aspect, pigmentation pattern, and skin vessels, including the ABCD rule for dermoscopy ([Nachbar 1994](#); [Stolz 1994](#)), the Menzies approach ([Menzies 1996](#)), the seven-point dermoscopy checklist ([Annessi 2007](#); [Argenziano 1998](#); [Argenziano 2001](#); [Gereli 2010](#)), and the three-point checklist ([Gereli 2010](#)). Similar algorithms have been developed to aid in the detection of BCC ([Menzies 2000](#); [Navarrete-Dechent 2016](#)).

The accuracy, and comparative accuracy, of visual inspection and dermoscopy and their associated scoring systems for the detection of both melanoma and keratinocyte skin cancers is summarised in three reviews in this series ([Dinnes 2018a](#); [Dinnes 2018b](#); [Dinnes 2018c](#)).

Role of index test(s)

Used in conjunction with clinical or dermoscopic suspicion of malignancy, or both, OCT may provide a means of reducing the number of false positive diagnoses and therefore reduce unnecessary biopsies in suspected BCC ([Gambichler 2015b](#); [Hussain 2015](#); [Reggiani 2015](#)). OCT is said to lie within the 'imaging gap' between high resolution ultrasound and RCM in terms of depth of penetration of the skin and resolution of the resulting image ([Olsen 2015](#); [Themstrup 2015](#)). OCT has a lower depth of penetration but higher resolution in comparison to ultrasound. Compared to RCM, OCT uses a longer wavelength (830nm as opposed to 1305nm for OCT), has considerably deeper penetration (RCM < 300 μm ; OCT < 2 mm) meaning it can visualise deeper into the dermis, has a greater depth of focus (RCM 3-5 μm ; OCT 1 mm), and wider basic field of view (RCM basic 500 x 500 μm in the horizontal plane; OCT basic 6 x 6 mm). However OCT has lower lateral resolution in comparison to RCM (RCM 1 μm , cellular; OCT 7.5 μm , near cellular), although newer high definition OCT reportedly has the capacity to visualise most RCM features ([Olsen 2015](#)). Both OCT and RCM have fields of view that are extendible by mechanical scanning and image mosaicking, although for equivalent fields of view 3D imaging is much faster with OCT (RCM for mosaicked field of view and stack > 10 min; OCT 6 cross-sectional frames per

second, < 2 min for 6 x 6 x 2mm volume). OCT may therefore be well placed to provide a combination of diagnostic information that cannot be retrieved with either confocal microscopy or ultrasound alone. Furthermore, the speed of OCT imaging allows rapid assessment of multiple lesions potentially obviating the need for multiple biopsies. In addition to diagnosis, OCT has the potential to inform therapeutic decisions for patients with a diagnosis of BCC, by determining the thickness of lesions, and when using HD OCT potentially also establishing the subtype of BCC. Once diagnosed, superficial BCC can be treated using nonsurgical treatments (listed in [Target condition being diagnosed](#)), which could be advantageous for multiple lesions or those arising on cosmetically critical sites e.g. face ([Powell 2000](#)). Excisional surgery and Mohs micrographic surgery are the most successful treatments for nodular / infiltrative BCC, although smaller nodular BCCs in low risk areas can also be treated with topical treatments ([Williams 2017](#)). Therefore the ability to confirm the subtype of BCC in these patients using a fast and non-invasive approach is attractive since it could reduce treatment-related morbidity, and possibly reduce the cost of management.

The potential role of OCT to diagnose melanomas is less clear, given that its resolution is insufficient to visualise melanocytes, a key feature for the diagnosis of melanoma. However, OCT has been suggested to allow the identification of architectural characteristics that are useful for differentiating malignant from benign melanocytic lesions ([Gambichler 2007](#)). Although the primary aim in diagnosing potentially life-threatening conditions such as melanoma is to minimise false negative diagnoses (to avoid delay to diagnosis and even death), a test that can reduce false positive clinical diagnoses without missing true cases of disease has patient and resource benefits. False-positive clinical diagnoses not only cause unnecessary morbidity from the biopsy, but also increase patient anxiety. Pigmented lesions are common so the resource implication for even a slight increase in the threshold to excise lesions in populations where melanoma rates are increasing, will avoid a considerable healthcare burden to both patient and healthcare provider, as long as such lesions turn out to be harmless.

A delay in the diagnosis of BCC as a result of a false-negative test is usually not as serious as for melanoma because BCC is usually slow-growing and very unlikely to metastasise. However, delayed diagnosis can result in a larger and more complex excision. Very sensitive tests for BCC, which compromise on lower specificity leading to a high false-positive rate, are likely to result in an enormous burden of skin surgery because BCC is so common, which the National Health Service (NHS) will struggle to cope with, so a balance between sensitivity and specificity is needed. With the greater potential for cSCC to metastasise, delayed diagnosis can be a much more serious problem, ultimately impacting on long-term prognosis. A test that can accurately distinguish between BCC, cSCC and melanoma could reduce the time to diagnosis, better inform appropriate treatment decisions in those who need it, and could avoid unnecessary surgical procedures.

OCT has also been investigated for its ability to identify lesion thickness, define tumour margins, and to assist in Mohs surgery, reducing the number of layers needed to remove the lesion ([De Carvalho 2018](#); [Gambichler 2015b](#); [Hussain 2015](#); [Olsen 2015](#)); however, these applications are not considered in this review.

Alternative test(s)

Several other non-invasive diagnostic technologies that are not routinely used in practice may also have a role for the diagnosis of skin cancer in a specialist setting, and these are being reviewed as part of our series of Cochrane DTA reviews on the diagnosis of melanoma and keratinocyte cancers: visual inspection and dermoscopy ([Dinnes 2018a](#); [Dinnes 2018b](#); [Dinnes 2018c](#)), reflectance confocal microscopy (RCM) ([Dinnes 2018d](#); [Dinnes 2018e](#)), high-frequency ultrasound (HFUS) ([Dinnes 2018f](#)), and computer-aided diagnosis (CAD) techniques that make use of dermoscopic or spectroscopic images, or other spectroscopic data ([Ferrante di Ruffano 2018a](#)).

RCM in particular is emerging as a potential alternative or adjunct to dermoscopy for the diagnosis of skin cancer ([Edwards 2016](#)), and can be used to visualise horizontally sectioned images of the skin at a cellular lateral resolution of ~1 micron, in vivo to the depth of the upper dermis. The contrast for the monochrome images produced is achieved by the variation of the optical properties within the skin when illuminated by a near-infrared light (830 nm); the greatest contrast is achieved from melanin, so that RCM is advocated as being particularly useful for assessing pigmented lesions ([Dinnes 2018e](#)).

Computer-assisted diagnosis (CAD) or artificial intelligence-based techniques analyse either dermoscopic or spectroscopic images, or other forms of spectroscopic data (such as diffuse reflectance or electrical impedance measurements), using predefined algorithms to process and manipulate acquired images to identify the features that discriminate malignant from benign lesions ([Esteve 2017](#); [Rajpara 2009](#)). A variety of spectroscopy-based tests have been developed and evaluated in both primary and secondary care settings, including SIAscopy™ ([Moncrieff 2002](#); [Walter 2012](#)), MelaFind® ([Hauschild 2014](#); [Monheit 2011](#); [Wells 2012](#)), and Nevisense™ ([Malveyhy 2014](#)). Ultrasound relies on the measurement of sound wave reflections from the tissues of the body. At lower frequencies, the deeper structures of the body such as the internal organs can be visualised, while high frequency ultrasound (HFUS) with transducer frequencies of at least 20MHz has a much lower depth of tissue penetration but produces a higher resolution image of tissues and structures closer to the skin surface. HFUS may therefore offer additional diagnostic information compared to other technologies, however evidence to date is scarce and of generally poor quality ([Dinnes 2018f](#)).

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.

Alternative tests identified as potential candidates for review but for which no eligible studies were found include volatile organic compounds (including canine odour detection) ([Abaffy 2010](#); [Church 2001](#); [D'Amico 2008](#); [Gallagher 2008](#);

[Kwak 2013](#); [Williams 1989](#)), and gene expression analysis ([Ferris 2012](#); [Wachsman 2011](#)).

We also considered and excluded a number of tests from this review including tests used in the context of monitoring people, such as total body photography of those with large numbers of typical or atypical naevi, and histopathological confirmation following lesion excision. The latter is the established reference standard for melanoma diagnosis and will be one of the standards against which the index tests are evaluated in these reviews.

Rationale

Our series of reviews of diagnostic tests used to assist the clinical diagnosis of melanoma and of the keratinocyte skin cancers BCC and cSCC, aims to identify the most accurate approaches to diagnosis and provide clinical and policy decision-makers with the highest possible standard of evidence on which to base decisions. With increasing rates of melanoma incidence and the push towards the use of dermoscopy and other high resolution image analysis in primary care, the anxiety around missing early cases needs to be balanced in order to avoid referring too many people with benign lesions for a specialist opinion. For keratinocyte skin cancers, the increasing availability of a wider range of tests means these technologies must be evaluated for their ability to differentiate and appropriately triage keratinocyte skin cancers, to avoid sending too many people with benign or low risk lesions for a specialist opinion and possible excision or biopsy, whilst not missing those people who have lesions that require treatment. It is questionable whether all skin cancers picked up by sophisticated techniques, even in specialist settings, help to reduce morbidity and mortality or whether newer technologies run the risk of increasing false-positive diagnoses. It is also possible that use of some technologies, e.g. widespread use of dermoscopy in primary care with no training, could actually result in harm by missing skin cancers 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](#)).

Despite having been first applied to skin lesions in the 1990s, OCT - and particularly HD-OCT - is a fast developing novel technology, that if accurate enough could have considerable potential to assist in the non-invasive diagnosis of skin cancers. Existing systematic reviews of OCT focus on the important question of synthesising the histological and imaging correlates of skin cancer diagnoses; however this emphasis means their selection and presentation of test accuracy evidence is not as rigorous and comprehensive as would be expected in systematic reviews of diagnostic test accuracy. In addition, none reported undertaking any assessment of quality assessment or attempted meta-analysis ([Calin 2013](#); [Gambichler 2015b](#); [Hussain 2015](#); [Olsen 2015](#)), and all are limited by out of date searches (the most recent finishing in May 2015, [Olsen 2015](#)). In this rapidly advancing field, there is a need for an up-to-date analysis of the accuracy of OCT for the diagnosis of melanoma and keratinocyte skin cancer.

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 skin cancers ([Dinnes 2015b](#)). The Background and Methods sections of this review therefore use some text that was originally published in the protocol ([Dinnes 2015a](#); [Dinnes 2015b](#)) and text that overlaps some of our other reviews ([Dinnes 2018d](#); [Dinnes 2018e](#); [Dinnes 2018f](#); [Ferrante di Ruffano 2018a](#); [Ferrante di Ruffano 2018b](#)).

Objectives

To determine the diagnostic accuracy of OCT for the detection of cutaneous invasive melanoma and intraepidermal melanocytic variants, basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC) in adults.

Secondary objectives

To determine the diagnostic accuracy of OCT in comparison to standard diagnostic practice for the detection of either cutaneous invasive melanoma and intraepidermal melanocytic variants, basal cell carcinoma, or cutaneous squamous cell carcinoma in adults.

To determine the diagnostic accuracy of OCT for the detection of invasive melanoma alone.

Investigation of sources of heterogeneity

We set out to address a range of potential sources of heterogeneity for investigation across our series of reviews, as outlined in our generic protocol ([Dinnes 2015a](#); [Dinnes 2015b](#)); however, our ability to investigate these and other sources of heterogeneity is necessarily limited by the data available for each reviewed test.

i. Population characteristics

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

ii. Index test characteristics

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

iii. Reference standard characteristics

- reference standard used

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

iv. Study quality

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

Methods

Criteria for considering studies for this review

Types of studies

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

- studies where all participants receive a single index test and a reference standard;
- studies where all participants receive more than one index test(s) and reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests and all receive a reference standard (between-person comparative studies (BPC));
- studies that recruit series of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (see [Rutjes 2005](#)), 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 2x2 contingency data or if they included fewer than five disease positive or five disease negative cases. The size threshold of five is arbitrary. However such small studies are unlikely to add precision to estimate of accuracy.

Participants

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

We excluded studies that recruited only participants with malignant diagnoses. We excluded studies with more than 50% of participants aged 16 and under.

Index tests

Studies evaluating optical coherence tomography alone, or optical coherence tomography in comparison to visual inspection or dermoscopy, or both, were included.

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

No exclusions were made according to test observer.

Target conditions

The target conditions were defined as the detection of:

- any form of invasive cutaneous melanoma or atypical melanocytic intraepidermal variants (i.e. including melanoma in situ, or lentigo maligna, which has a risk of progression to invasive melanoma)
- basal cell carcinoma (all types)
- cutaneous squamous cell carcinoma (invasive)
- any skin cancer or other lesion requiring excision (including melanoma or atypical intraepidermal melanocytic variants, severely dysplastic melanocytic lesions, keratinocyte skin cancer, and any other skin cancer).

Reference standards

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

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

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

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

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

Search methods for identification of studies

Electronic searches

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

We searched the following bibliographic databases to 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. Update searches will be time and resource dependent.

Searching other resources

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

Data collection and analysis

Selection of studies

Titles and abstracts were screened by at least one author (JD or NC), with any queries discussed and resolved by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. Primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC were included at initial screening. Inclusion criteria ([Appendix 3](#)) were applied independently by both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JD or NC) to all full text articles, disagreements were resolved by consensus or by a third party (JJD, 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 (JD, 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 (JJD, CD, HW, and RM).

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

Dealing with multiple publications and companion papers

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

Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the QUADAS-2 checklist ([Whiting 2011](#)), tailored to the review topic (see [Appendix 4](#) for full details of items, responses and summary judgement criteria). 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 (JD, NC or LFR) independently assessed quality for the remaining studies; any disagreement was resolved by consensus or by a third party where necessary (JJD, CD, HW, and RM).

Statistical analysis and data synthesis

Due to paucity of data and differences in thresholds used to define test positivity, no meta-analysis was undertaken for the diagnosis of melanoma or for the diagnosis of cSCC. Statistical pooling was undertaken for the diagnosis of BCC.

For the diagnosis of cSCC at each threshold, any other skin cancers (i.e. BCC) that were included in the study and that were incorrectly identified as cSCCs (i.e. positive on OCT) were considered as true negative test results rather than as false positives, on the basis that excision of such lesions may still have been appropriate for the participants concerned. For the diagnosis of BCC however, any other skin cancers (for example melanomas or cSCCs) in the 'disease negative' group that were incorrectly identified by OCT as BCCs were kept as false positive results. This decision was taken on the basis that the clinical management of a lesion considered to be a BCC (for example, initiation of Mohs micrographic surgery, destructive techniques or non-surgical treatments) could be quite different to that for a melanoma or cSCC and could potentially lead to a negative outcome for those concerned.

Estimates of sensitivity and specificity were plotted on coupled forest plots for each threshold under consideration. 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.

To allow statistical pooling where multiple thresholds per algorithm were reported ([Wahrlich 2015](#)), we analysed data separately using each threshold. For tests where commonly used thresholds were reported we estimated summary operating points (summary sensitivities and specificities) with 95% confidence and prediction regions using the bivariate hierarchical model ([Chu 2006](#); [Reitsma 2005](#)). Where inadequate data were available for the model to converge

the model was simplified by assuming no correlation between estimates of sensitivity and specificity ([Takwoingi 2017](#)).

Data on the accuracy of visual inspection and/or dermoscopy was included to allow comparisons of tests, but only if reported in the included studies of OCT due to the known substantial unexplained heterogeneity in all studies of the accuracy of dermoscopy ([Dinnes 2018b](#)). The bivariate model was extended by addition of covariates to allow for differences in sensitivity and specificity between OCT and visual inspection and/or dermoscopy, with the significance of differences being assessed using a single likelihood ratio test comparing models with and without the covariates.

Investigations of heterogeneity

We examined heterogeneity between studies by visually inspecting the forest plots of sensitivity and specificity. Insufficient numbers of studies were identified to allow meta-regression to investigate potential sources of heterogeneity.

Sensitivity analyses

No sensitivity analyses were done.

Assessment of reporting bias

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

Results

Results of the search

A total of 34,347 unique references were identified and screened for inclusion. Of these, 1051 full text papers were reviewed for eligibility for any one of the suite of reviews of tests to assist in the diagnosis of melanoma or keratinocyte skin cancer. [Figure 7](#) documents a PRISMA flow diagram of search and eligibility results. Of the 1051 studies assessed, exclusions were due to lack of test accuracy data (184 studies), or because they were derivation studies (141 studies), evaluated an ineligible index test (126 studies), included ineligible populations (83 studies), assessed an ineligible target condition (78 studies), had fewer than 5 malignant cases (72 studies) or did not meet our requirements for eligible reference standards (i.e. at least 50% of all participants with benign lesions had to have either a histological diagnosis or clinical follow up to determine the final diagnosis (76 studies)). A total of 43 studies were tagged as potentially eligible for this review; ultimately 5 publications (reporting 5 studies) were included. A list of the 38 studies excluded from this review with reasons for exclusion is provided in [Characteristics of excluded studies](#), with a list of all studies excluded from the full series of reviews available as a separate pdf.

Across all skin cancer DTA reviews, the corresponding authors of 86 studies were contacted and asked to supply further information to allow study inclusion (n = 37) to clarify diagnostic thresholds (n = 18) or target condition definition (n = 30).

Characteristics of included studies

This review reports on a total of 5 cohorts of participants with lesions suspected of skin cancer, published in 5 study publications, and providing 9 datasets for OCT, two for visual inspection and two for dermoscopy. A description of thresholds used for diagnosis across the studies is provided in [Table 2](#) and summary study details are presented in [Appendix 5](#).

The five included studies consisted of four prospective case series and one study in which the design was unclear ([Wahrlich 2015](#)). Three were conducted in Germany ([Gambichler 2015](#); [Ulrich 2015](#); [Wahrlich 2015](#)), one in the Netherlands ([Wessels 2015](#)), and one in the US ([Markowitz 2015](#)). Three studies were funded by OCT manufacturers ([Gambichler 2015](#); [Markowitz 2015](#); [Ulrich 2015](#)), in [Wahrlich 2015](#) the OCT device was provided by the manufacturer, and no company funding was reported in [Wessels 2015](#). Two studies were conducted in participants with pigmented ([Wessels 2015](#)) or melanocytic lesions ([Gambichler 2015](#)) and focused on identification of melanomas. The remaining three studies ([Markowitz 2015](#); [Ulrich 2015](#); [Wahrlich 2015](#)) studied series of non-pigmented lesions ([Markowitz 2015](#) focused on head and neck lesions), two focusing on 'pink' lesions suspected of being BCCs ([Markowitz 2015](#); [Ulrich 2015](#)) and the third selecting nonpigmented lesions according to their histological diagnosis ([Wahrlich 2015](#)). All five studies analysed lesions selected for excision or biopsy, two of which focused on clinically challenging lesions ([Markowitz 2015](#); [Ulrich 2015](#)). The studies also varied in the degree of testing performed prior to study inclusion and performance of the OCT scan: the two melanoma studies included participants with clinical suspicion of melanoma and either prior dermoscopy in all ([Gambichler 2015](#)) or some ([Wessels 2015](#)) study participants. All three studies of non-pigmented lesions reported visual inspection as a prior test, with the case-control study also reporting dermoscopy and histology ([Wahrlich 2015](#)), while the two prospective studies performed dermoscopy and histology during the study ([Markowitz 2015](#); [Ulrich 2015](#)).

A total of 402 participants with 529 lesions were included, the numbers included in each study ranging from 33 to 164 participants and 40 to 256 lesions. The prevalence of disease was 23% ([Wessels 2015](#)) and 27% ([Gambichler 2015](#)) in the two melanoma studies (both of which included only benign nevi in the disease negative group), and disease prevalence ranged from 58% ([Wahrlich 2015](#)) to 61% ([Markowitz 2015](#)) in the studies of BCC. Of the three BCC studies, one did not describe diagnoses in the disease negative group ([Markowitz 2015](#)); one included participants with cSCC, Bowen's disease, and actinic keratosis only ([Wahrlich 2015](#)); while [Ulrich 2015](#) included participants with Bowen's disease, actinic keratosis, and inflammatory diseases such as psoriasis and eczema amongst others (no cSCC lesions were included). One of these, [Wahrlich 2015](#), provided the only dataset available for the detection of cSCC, with a prevalence of 18%.

Four studies evaluated conventional swept source OCT (all with similar resolutions and tissue penetration

capacities), and one evaluated high-definition (HD) OCT for diagnosis of melanoma ([Gambichler 2015](#)). A number of different thresholds for test positivity were assessed across the studies ([Table 2](#)). For the detection of melanoma, [Gambichler 2015](#) developed a new scoring system based on the presence or absence of risk features and protective features as derived from existing literature; the method of selection of the numeric cut-off for test positivity was not described, and [Wessels 2015](#) derived the optimal attenuation coefficient for detection of melanoma using Youden's index. For the diagnosis of BCC, two studies described a number of OCT characteristics considered indicative of BCC, which were used by observers to form an overall clinical impression of BCC or not BCC ([Markowitz 2015](#); [Ulrich 2015](#)). Both studies also reported accuracy for in person visual examination alone and for visual examination plus dermoscopic diagnosis. [Wahrlich 2015](#) assessed similar OCT characteristics ([Table 2](#)), assigning a score to each based on the clarity of visualisation of each feature (named the 'Berlin Score'). Scores based on a separate training set of lesions were used to identify limit values (T1,T2) to differentiate BCCs from cSCCs, actinic keratosis and Bowen's disease ([Wahrlich 2015](#)).

Four studies reported image-based diagnosis with OCT (i.e. diagnosis based on OCT scans interpreted remotely from the patient concerned); with only [Ulrich 2015](#) describing OCT scans interpreted in real-time following clinical examination and then dermoscopy of the lesions. One study ([Wahrlich 2015](#)) described observer qualifications (with interpretation by a dermatopathologist), and three described observers as experienced or regular users of an OCT device ([Gambichler 2015](#); [Ulrich 2015](#); [Wahrlich 2015](#)). Only [Wahrlich 2015](#) described any test failures (see [Methodological quality of included studies](#)). In all studies the reference standard diagnosis was made by histology alone.

Methodological quality of included studies

Overall study quality was moderate or unclear, with considerable concerns regarding the clinical applicability of results ([Figure 8](#) and [Figure 9](#)).

Three of the five studies were at low risk of bias for participant selection; the remaining two did not clearly describe consecutive patient recruitment and one may have used a case-control type design. All studies were judged as having high concern for applicability of the patient selection; all scored high concern on both QUADAS items apart from one recruiting a representative range of non-pigmented lesions ([Ulrich 2015](#)), and one ([Wahrlich 2015](#)) which avoided recruitment of participants with multiple lesions. All studies included only lesions selected for excision, however.

Two studies were at low risk of bias in the index test domain ([Markowitz 2015](#); [Ulrich 2015](#)). Of the remaining three, one did not enforce blinded interpretation of the index test (OCT interpretation by the dermatopathologist following histology ([Wahrlich 2015](#))), one used a data driven threshold ([Wessels 2015](#)) and one did not describe the approach to selection of the numeric threshold used ([Gambichler 2015](#)).

Four studies were at high concerns around the applicability of the index test. All studies reported the thresholds used to define test positivity; however, in four studies the application of the test was judged as not clinically applicable due to the use of image-based diagnosis remote from the study participants. The expertise of the clinician interpreting the OCT scan was not reported in two studies ([Markowitz 2015](#); [Wessels 2015](#)), Furthermore, one reported blinding to all other clinical information ([Gambichler 2015](#)), and two did not clearly describe what information was provided to test observers ([Wessels 2015](#); [Markowitz 2015](#)).

All studies reported the use of an acceptable reference standard, but not one clearly reported blinding of the reference standard either to the OCT result or to the referral diagnosis, based on clinical examination or dermoscopy (although the latter did not contribute to overall judgements of applicability). For the applicability of the reference standard, no study reported using expert diagnosis to provide the final diagnosis of any lesion but only one reported histopathology interpretation by an experienced dermatopathologist; the remainder scored as unclear concerns regarding applicability of the reference standard.

Three studies were judged at low risk of bias in the flow and timing domain apart; [Ulrich 2015](#) reported the exclusion of lesions with missing histology and [Wahrlich 2015](#) described exclusion of three participants due to awkward lesion site, different scan 'heights' and shadow artefacts in the discussion section of the paper. None of the other studies described any failure to successfully image a lesion, raising the possibility that such cases occurred but were not reported.

For the two studies comparing OCT with visual inspection and dermoscopy, both reported consecutive diagnoses using each of the three and blinding between tests was not enforced in either (this did not contribute to the overall assessment of risk of bias). The clinical applicability of the application of the tests was of low concern in [Ulrich 2015](#). The same item was scored as unclear [Markowitz 2015](#) where visual inspection and dermoscopy diagnoses were both undertaken in person and OCT interpretation was done remotely with no indication as to whether the diagnosis was undertaken by the same test observer nor whether clinical or dermoscopic images were provided to assist OCT diagnosis.

Findings

All results below refer to the detection of skin cancer in lesions, not in participants (see [Statistical analysis and data synthesis](#)).

Detection of invasive melanoma or melanoma in situ

Two studies analysed 133 lesions for the detection of 36 melanomas ([Figure 10](#)). The single study evaluating conventional swept source OCT for the detection of melanoma or intraepidermal melanocytic variants in 40 lesions selected for excision reported sensitivity of 89% (95% CI: 52, 100%) and specificity of 61% (95% CI: 42, 78%) at an attenuation coefficient of 5.4mm^{-1} ([Wessels 2015](#)). In their discussion, the authors reported an inability to visualise some architectural features (such as brown globules, rete ridges or vertical icicle-shaped structures) useful to making a melanoma

diagnosis, due to the insufficient resolution provided by the conventional OCT system.

Using HD OCT and their own scoring system for the presence of recognised OCT characteristics in a sample of 93 lesions, [Gambichler 2015](#) reported sensitivity of 74% (95% CI: 54, 89%) and specificity of 92% (95% CI: 83, 97%) for the detection of melanoma or atypical intraepidermal melanocytic variants at a score of ≥ -1 and < -1.5 , with sensitivity increasing to 80% (95% CI: 59, 93%) and specificity to 93% (95% CI: 84, 98%) for the detection of invasive melanoma alone; both melanoma *in situ* lesions included in the study were misclassified as negative on OCT.

Detection of BCC

All three studies used conventional swept source OCT for the detection of 237 BCCs in 396 analysed lesions. [Wahrlich 2015](#)'s quantitative scoring of OCT characteristics resulted in a sensitivity of 97% (95% CI: 82, 100%) and specificity 76% (95% CI: 53, 92%) at a Berlin score of ≥ 8 , with lower sensitivity (66% (95% CI: 46, 82%)) and higher specificity (86% (95% CI: 64, 97%)) at the higher score of ≥ 12 ([Figure 10](#)). Four of the five false positive results at ≥ 8 and all three at ≥ 12 were cSCC lesions.

[Markowitz 2015](#) and [Ulrich 2015](#) both reported observer diagnosis of BCC based on the subjective judgement of the presence of specified OCT features ([Table 2](#)), in clinically challenging non-pigmented 'pink' lesions, and compared this to diagnosis by visual inspection alone and by visual inspection plus dermoscopy ([Figure 11](#)). Meta-analysis of the 346 lesions (including 273 BCCs) produced a pooled sensitivity for OCT of 95% (95% CI: 91, 97%) and pooled specificity of 77% (95% CI: 69, 83%). Neither study reported including any cSCC lesions (benign diagnoses not described in [Markowitz 2015](#)) owing to the fact that both studies limited participant inclusion to erythematous / pink lesions which are uncommon presentations for invasive cSCC.

OCT was significantly more accurate for the diagnosis of BCC in comparison to visual inspection alone ($P = 0.007$; [Figure 11](#) and [Figure 12](#)); visual inspection showing a pooled sensitivity of 80% (95% CI: 55, 93%) and specificity 37% (95% CI: 24, 52%). OCT was also significantly more accurate for the diagnosis of BCC in comparison to visual inspection with the addition of dermoscopy ($P < 0.001$; [Figure 11](#), [Figure 13](#)); visual inspection and dermoscopy having a pooled sensitivity of 86% (95% CI: 76, 92%) and specificity of 55% (95% CI: 46, 63%).

Detection of cSCC

One study reported OCT results for the diagnosis of 9 cSCCs amongst a group of 50 lesions consisting of BCCs (29), actinic keratoses (5) and Bowen's disease (7) ([Wahrlich 2015](#)). Using the quantitative scoring of conventional swept source OCT characteristics reported above, sensitivity was 56% (95% CI: 21, 86%) and specificity was 100% (91, 100%) at a score of ≥ 8 , with a lower sensitivity using a score of ≥ 12 (33%, 95% CI: 7, 70%) ([Figure 10](#)). BCC lesions with positive OCT results were considered as true negatives (not as false positives) as explained in the [Statistical analysis and data synthesis](#) section above.

Investigations of heterogeneity

We were unable to undertake formal investigations of heterogeneity due to insufficient study numbers.

Discussion

Summary of main results

This review aimed to assess the accuracy of optical coherence tomography as an aid to diagnosing melanoma, BCC, or cSCC in adults. We included five studies evaluating optical coherence tomography, two of which also evaluated visual inspection and visual inspection combined with dermoscopy ([Summary of findings table 1](#)).

Studies were generally of moderate to unclear methodological quality, and poor in terms of the applicability of their results to a clinical setting. For risk of bias, there was a lack of clarity of description of a number of different items across the studies including: recruitment methods, study design, threshold selection and particularly blinding of the reference standard to the index test result. Applicability concerns were almost universally high for participants and index test, due to unrepresentative samples and the use of image-based OCT interpretation undertaken remotely from study participants. Limited information was provided regarding the qualifications of the clinicians undertaking and interpreting the tests. The final diagnoses were established by histology in all studies; however, reference standard interpretation was poorly described.

For the detection of melanoma, a paucity of studies, small sample sizes, and differences in the tests make summary statements regarding accuracy impossible. Conventional OCT using a data driven threshold in a sample with a high prior history of melanoma (61%) produced a sensitivity of 89% (95% CI: 52, 100%) and specificity 61% (95% CI: 42, 78%); however, low resolution was reported as problematic. High definition OCT using a scoring system based on OCT characteristics misclassified the two included melanoma *in situ* lesions as OCT negative, leading to a sensitivity of 74% (95% CI: 54, 89%) and specificity of 92% (95% CI: 83, 97%) for the detection of melanoma or intraepidermal melanocytic variants. No data were found that compared OCT to standard diagnostic practice for the detection of melanoma.

For the detection of BCC, two studies evaluated observer diagnosis with conventional OCT using the same diagnostic criteria, in similar populations of participants. Meta-analysis of the 346 lesions resulted in pooled sensitivity of 95% (95% CI: 91, 97%) and specificity 77% (95% CI: 69, 83%). In both studies, OCT was found to be statistically significantly more sensitive and more specific compared to visual inspection alone (sensitivity 15% higher and specificity 40% higher) and to visual inspection combined with dermoscopy (sensitivity 9% higher and specificity 22% higher). The [Summary of findings table 1](#) translates these estimates to a hypothetical cohort of 1000 lesions at the mean prevalence of BCC of 60%. A sensitivity for OCT of 95% would miss 31 BCCs; a reduction from those that would be missed by using visual inspection

alone in these lesions of 91 and a reduction from those that would be missed by visual inspection and dermoscopy of 53 BCCs. A specificity of 77% for OCT would result in 93 false positive results; a reduction in unnecessary excisions of 159 compared to using visual inspection alone and of 87 compared to using visual inspection and dermoscopy. Both studies analysed clinically challenging 'pink' lesions; however, BCC prevalence was very high.

One further study which developed an OCT score (Berlin score) to determine the presence of BCC reported similar sensitivity and specificity in at least one threshold but it is unclear whether these results would be reproducible. Producing the only evidence for the detection of cSCC, this study suggests that OCT is poor in its ability to discriminate between BCC and cSCC when the 'Berlin score' is used. However, the study included few cSCC cases that were retrospectively selected as 'controls' against the detection of BCC cases, and so is at high risk of having produced biased results. No studies evaluated high definition OCT technology for the detection and discrimination of keratinocyte skin cancers.

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 was planned to allow test accuracy in different study populations to be estimated and a detailed and replicable analysis of methodologic quality was undertaken.

The main concerns for the review regard the clinical applicability of study findings to a normal practice setting, both in terms of using more highly selected study populations than are encountered in practice and commonly interpreting OCT scans remotely from the patient. While OCT could be used in clinical practice to examine several lesions in a single patient, studies that did so were downgraded in quality appraisal due to the potential bias introduced by including patients with many lesions ([Appendix 4](#)). This was compounded by poor reporting of study conduct, especially with regard to the reference standard and lack of clear pre-specification of the diagnostic threshold for test positivity. The inability of the 'Berlin score' to differentiate BCC from cSCC and the lack of inclusion of cSCC lesions in the two studies of observer diagnosis without the aid of the score raises questions over the ability of observers to discriminate between these lesion types using OCT. Furthermore, no study reported the presence or absence of index test failures, for example due to inadequate imaging quality or inaccessibility of lesions, and so it is unclear how frequently one would encounter uninterpretable scans when OCT is used in clinical practice.

Many of the studies excluded from this review were derivation studies or assessed the accuracy of individual OCT characteristics rather than the overall ability of the test to diagnose a particular skin cancer. This is indicative of the relatively novel nature of the test and its application to skin cancer diagnosis.

Applicability of findings to the review question

The data included in this review are unlikely to be generally applicable to the clinical setting. Narrow definitions of the eligible study populations, high disease prevalence, the use of remote image-based test interpretation, and lack of description of the reference standards used may restrict applicability and transferability of results in practice.

Authors' conclusions

Implications for practice

Insufficient data are available to determine the accuracy of OCT for the detection of melanoma or cSCC. For the detection of BCC, initial data on OCT shows potential increased sensitivity and specificity compared with visual inspection and dermoscopy; however, the small number of studies and varying methodological quality means that no implications to guide clinical practice can currently be drawn.

Implications for research

Further prospective evaluation of optical coherence tomography is warranted in populations with a clinical suspicion of melanoma, and in populations with a clinical suspicion of keratinocyte skin cancer. For melanoma, these studies should evaluate HD OCT in comparison to visual inspection and dermoscopy alone, in a standard healthcare setting and with a clearly defined and representative population of participants with a range of different lesion types to whom study results can be applied in practice. For a full and proper evaluation of the ability of OCT to detect keratinocyte skin cancers, similar comparisons should recruit study populations that include sufficient numbers of participants with suspected BCC and cSCC in order to assess whether the test is able to discriminate adequately between the different forms of skin cancer.

Given that RCM is likely the closest direct 'competitor' test to OCT, a comparison with RCM in lesions that are equivocal following visual inspection and dermoscopy may also be warranted.

The clinical pathway, or referral process, for study eligibility must be clearly described in order to establish the participant groups to whom study results can be applied in practice. A multi-centred approach would allow confirmation that results are replicable across centres and that the technology can be implemented across a health service. Prospective recruitment of a consecutive series of participants, with test interpretation blinded to the reference standard diagnosis and using pre-specified and clearly defined diagnostic thresholds for determining test positivity, are easily achieved. In order to be generalisable to clinical practice, studies should perform OCT scans within the clinical pathway, with interpretation made in the presence of patients and by clinicians experienced with skin cancer diagnosis and OCT. Points-based 'rules' to assist diagnosis require proper validation in an appropriate clinical setting and would allow a standardised approach to diagnosis. Clear identification of the qualifications and level of observer training and experience needed to achieve good results is also required. Systematic follow-up of non-excised lesions avoids over-reliance on a histological reference standard and allows results to be more

generalisable to routine practice. Any future research study needs to be clear about the diagnostic pathway followed by study participants prior to study enrolment, and reporting should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline ([Bossuyt 2015](#)).

Acknowledgements

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

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

Thanks also to Dr Rakesh Patalay for providing images of OCT equipment and imaging scans.

The Cochrane Skin Group editorial base wishes to thank Robert Dellavalle, who was the Dermatology Editor for this review, and the clinical referees, Julia Welzel and Nathalie de Carvalho. We also wish to thank the Cochrane DTA editorial base and colleagues.

Contributions of authors

LFR was the contact person with the editorial base.

JD co-ordinated contributions from the co-authors and wrote the final draft of the review.

LFR, JD and NC screened papers against eligibility criteria.

LFR, JD and NC obtained data on ongoing and unpublished studies.

LFR, JD and NC appraised the quality of papers.

LFR, JD and NC extracted data for the review and sought additional information about papers.

LFR, JD and NC entered data into RevMan.

JD and JJD analysed and interpreted data.

JD, JJD, NC and LFR worked on the methods sections.

JD, LFR, HT, RNM and HCW drafted the clinical sections of the background and responded to the clinical comments of the referees.

LFR, JD, JJD, YT and CD responded to the methodology and statistics comments of the referees.

KG and CO were the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.

JD is the guarantor of the update.

Disclaimer

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

Declarations of interest

Lavinia Ferrante di Ruffano: nothing to declare.

Jac Dinnes: I am employed by the University of Birmingham under a NIHR Cochrane Programme Grant to produce the reviews.

Jonathan J Deeks: Funding was provided to the University of Birmingham from a Cochrane Programme Grant to complete this review and other linked reviews.

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 programme grant awarded to Jac Dinnes, the PI.

Yemisi Takwoingi: nothing to declare.

Kathie Godfrey: I have received reimbursement of travel expenses incurred by attending meetings.

Colette O'Sullivan: nothing to declare.

Rubeta N Matin: nothing to declare.

Hamid Tehrani: Reimbursement of travel expenses was received for review group meetings.

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.

Clinical referees:

Julia Welzel: "I am one of the authors of one of the cited studies ([Welzel 1998](#), excluded). This study was supported in part by Michelson Diagnostics. I participated for some years in an advisory board of Michelson Diagnostics, one of the suppliers of OCT systems."

Nathalie de Carvalho is an author of a study awaiting classification ([Olsen 2016](#)).

Differences between protocol and review

Due to the small number of studies available, a single review has been produced that evaluates the accuracy of OCT in all skin cancers; this replaces the two reviews intended in the protocols to address cutaneous melanoma and keratinocyte cancers.

For the detection of melanomas, primary objectives and primary target condition have been changed from detection of cutaneous invasive melanoma alone, to the detection of cutaneous invasive melanoma and intraepidermal melanocytic variants, as the latter is more clinically relevant to the practicing clinician. These are reported alongside the original primary objectives and primary target conditions for the review of keratinocyte cancers. The detection of the target condition of invasive melanoma alone has instead been included as a secondary objective.

Inclusion criteria amended to remove inclusion of participants: "at high risk of developing melanoma, including those with a family history or previous history of melanoma skin cancer, atypical or dysplastic naevus syndrome, or genetic cancer syndromes" 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 OCT use.

Studies using cross-validation, such as 'leave-one-out' cross-validation, were *excluded* rather than included as these methods are not sufficiently robust and are likely to produce unrealistic estimates of test accuracy. To improve clarity of methods, this text from the protocol: "*We will include studies developing new algorithms or methods of diagnosis (i.e. derivation studies) if they use a separate independent 'test set' of participants or images to evaluate the new approach. We will also include studies using other forms of cross validation, such as 'leave-one-out' cross-validation (Efron 1983). We will note for future reference (but not extract) any data on the accuracy of lesion characteristics individually, e.g. the presence or absence of a pigment network or detection of asymmetry.*" has been replaced with: "*All established algorithms or checklists to assist diagnosis were included. Studies developing new algorithms or methods of diagnosis (i.e. derivation studies) were included if they used a separate independent 'test set' of participants or images to evaluate the new approach. Studies that did not report data for a separate test set of patients or images were included only if the lesion characteristics investigated had previously been suggested as associated with melanoma, BCC, or with cSCC, and the study reported accuracy based on the presence or absence of particular combinations of characteristics. Studies using a statistical model to produce a data driven equation, or algorithm based on multiple diagnostic features, with no separate test set were excluded. Studies using cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983) were excluded.*"

We proposed to supplement the database searches by searching the annual meetings of appropriate organisations (e.g. British Association of Dermatologists Annual Meeting, American Academy of Dermatology Annual Meeting, European Academy of Dermatology and Venereology Meeting, Society for Melanoma Research Congress, World Congress of Dermatology, European Association of Dermato Oncology), however due to volume of evidence retrieved from database searches and time restrictions we were unable to do this.

For quality assessment, the QUADAS-2 tool was further tailored according to the review topic.

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

We planned three 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

Gambichler 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Study design: Case series Data collection: Prospective Period of data collection: NR Country: Germany Funding: Agfa Healthcare
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: Patients scheduled for melanocytic skin lesion excision because of cosmetic reasons or suspicion of CM Setting: Secondary (Dermato-oncology) Prior testing: Clinical inspection + dermoscopy Exclusion criteria: Presence of frank ulceration, marked hyperkeratosis, histopath confirmation of non-melanocytic skin lesion Sample size (patients): No. eligible: NR; No. included: 64 Sample size (lesions): No. eligible: NR; No. included: 93 Participant characteristics: None reported Lesion characteristics: Mean Breslow thickness of correctly identified melanoma (all invasive) 1.2 (SD 1.1mm); n=20. Mean Breslow thickness of missed melanoma (false negatives) 0.29 (SD 0.23mm) for 5 invasive MM, plus melanoma <i>in situ</i>
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	<p>Optical Coherence Tomography - High definition (Skintell; Agfa, Belgium); resolution 3µm lateral by 5µm axial; tissue penetration 570µm; centre wavelength 1300nm; the 3D images of the scans showing the best quality (i.e. no artefacts) were chosen.</p> <p>Diagnostic threshold: New scoring system based on previously described micromorphological HD-OCT correlates of melanocytic skin lesions (Boone 2014; Picard 2013) and from RCM (Segura 2009) and conventional OCT studies (Gambichler 2007); A score ≥ -1 indicated melanoma, a score ≥ -1.5 indicated benign melanocytic skin lesion, i.e. melanoma present if score ≥ -1 and < -1.5.</p> <p>Method of diagnosis: Image-based</p> <p>Prior test data available: None; blinded to clinical exam and dermoscopy</p> <p>Diagnosis based on: Single (n = 1)</p> <p>Observer qualifications: NR; presumed dermatologist</p> <p>Experience in practice: NR</p> <p>Experience with index test: High; described as "OCT-experienced investigator"</p> <p>Any other detail: OCT scoring based on "predominant presence of the following risk (+) and/or protective (-) features ... (i) HD-OCT en-face mode - typical basal cells/clusters (-1), edged papillae (-1), honeycomb/cobblestone pattern (-1), large roundish pagetoid cells (+1), atypical cell clusters in the dermoepidermal junction (DEJ) (+1), totally disarranged epidermal/ dermal pattern (+1); (ii) HD-OCT slice mode - clearly demarcated DEJ (-0.5), finger-shaped elongated rete ridges (-0.5), bright bizarre dermal horizontal streaks (+0.5), large vertical icicle- shaped structures (+0.5). The total score is the sum of the aforementioned sub-scores for the various particular criteria."</p>
-------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

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

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

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)	<p>Type of reference standard: Histology alone</p> <p>Details: Lesions completely excised and processed for routine haematoxylin and eosin staining, plus immunohistochemistry for S100 and MART/ Melan-A.</p> <p>Disease positive: 27; Disease negative: 66</p> <p>Target condition (Final diagnoses):</p> <p>Invasive melanoma: 25; Melanoma in situ: 2</p> <p>Benign nevi: 66 (23 compound naevi, 20 junctional naevi, 10 dermal naevi, 9 dysplastic naevi, 2 nevoid lentigo and 2 blue naevi)</p>
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (Does not contribute to Risk of Bias judgement)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	Index test to reference standard interval: Consecutive; "after HD-OCT assessments, the tumours were completely excised" Interval between index tests: N/A Exclusions: None reported
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
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias
Comparative
B. Concerns regarding applicability

Notes

Notes	
-------	--

Markowitz 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Study design: Case series Data collection: Prospective Period of data collection not reported Country USA Funding: study was sponsored by Michelson Diagnostics
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	<p>Inclusion criteria: Consecutive patients with clinically challenging pink lesions on the head or neck and that were suspicious for basal cell carcinoma and therefore to be biopsied to rule BCC in or out; also required to be eligible for Mohs surgery; maximum of three lesions per patient</p> <p>Setting: Secondary (general dermatology)</p> <p>Prior testing: Clinical or dermoscopic suspicion of malignancy; decision to perform diagnostic biopsy was made following clinical, dermoscopic and OCT evaluation</p> <p>Setting for prior testing: Secondary (general dermatology)</p> <p>Exclusion criteria: Previous history of skin cancer/ prior treatment at site; history of evidence of metastases, topical actinic therapy within 8 weeks prior to evaluation, other skin conditions within lesion</p> <p>Sample size (patients): No. included: 100</p> <p>Sample size (lesions): No. included: 115</p> <p>Participant characteristics: None reported</p> <p>Lesion characteristics: All head and neck</p>
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Visual inspection (VI): No algorithm
	Method of diagnosis: In person diagnosis
	Prior test data: N/A in person diagnosis
	Diagnostic threshold: Observer diagnosis of BCC; clinically challenging lesions defined as "lesions that did not have the usual characteristics of BCC, such as ulceration, bleeding, crusting, isolated pink scaly patches, or pearly papules"; also took into account patient's clinical history of a nonhealing area of concern or the clinician's inability to rule out BCC"
	Diagnosis based on: Unclear; likely in clinic diagnoses (n=NR)
	Observer qualifications: Not described; likely dermatologist
	Experience in practice: Not described
	Experience with index test: Not described
	Dermoscopy: 2 step algorithm referenced to Marghoob 2010 and Malveyh 2002 .
	Method of diagnosis: In person diagnosis
	Prior test data: N/A in person diagnosis
	Diagnostic threshold: Dermoscopic features consistent with BCC: arborized vessels, pink white shiny background, blue/grey ovoid nests, ash leaf pattern, dot-globular-like pattern, spoke wheel, and crystalline-like structures
	Test observers as described for Visual Inspection (above)
	OCT: No algorithm; - Multi-beam swept-source frequency domain (VivoSight; Michelson Diagnostics, UK); resolution axial 10µm, lateral 7.5µm; tissue penetration 2000µm; centre wavelength 1305nm; "multi-1" setting automatically provided 60 lateral scans of 6mm length every 100µm.
	Method of diagnosis: Image-based; OCT scans obtained at time of visual inspection and dermoscopic diagnoses and read within a week of the diagnostic biopsy
	Prior test data: Unclear; clinical and dermoscopic images obtained but not clear whether provided to OCT interpreter
	Diagnostic threshold: Observer diagnosis based on features described in previous studies (Ulrich 2015 ; Wahrlich 2015 ; Maier 2013): "epidermis was analysed for protrusions into the dermis with shadowing; the epidermal-dermal junction for lack of definition or rupturing; and the dermis for signal-poor ovoid structures, dark rims, ovoid structures with bright centres, dilated vessels, black areas or cysts, bright stroma, and/or small ovoid signal-poor structures ("fish shoal")"
	Test observers: Not described

Optical coherence tomography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

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
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Dermoscopy

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

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Unclear
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Reference standard Histological diagnosis alone Details: None reported Disease positive: 70 BCC; Disease negative: 45 Target condition (Final diagnoses) BCC: 70; 'Benign' diagnoses: 45 (not further described)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (Does not contribute to Risk of Bias judgement)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	Excluded participants: none reported Time interval to reference test: Appears consecutive; Figure 2 describes the OCT scans undertaken at the time of clinical examination and dermoscopy; diagnostic biopsy is then performed and the "OCT scan is read within a week, prior to obtaining the results of the diagnostic biopsy"
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias	
Comparative	Time interval between index test(s): Consecutive; clinical, dermoscopic and OCT images taken at the same time; clinical and dermoscopic diagnoses made at the time of taking the images while OCT scans were read within a week.
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	No
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk

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

Notes

Notes	
-------	--

Ulrich 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Study design: Case series Data collection: Prospective Period of data collection April 2013 to March 2014 Country Germany Funding: study was funded by Michelson Diagnostics Ltd (MDL)
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	<p>Inclusion criteria: Patients with non-pigmented pink lesions with clinical suspicion of BCC requiring biopsy for diagnostic confirmation. Pink lesions defined as clinically unclear erythematous papule or plaque; either reddish macules, patches or small papules with or without scale. [only lesions with histology included]</p> <p>Setting: Multicentre study; authors' institutions included Dermatology departments (n=4) and private dermatology offices (n=3)</p> <p>Prior testing: Inclusion was based on clinical assessment alone, without the assistance of dermoscopy</p> <p>Setting for prior testing: Unspecified</p> <p>Exclusion criteria: Unequivocal appearance/diagnosis - Lesions with the typical clinical appearance of BCC on clinical examination (such as the presence of a pearly border, central ulceration and obvious telangiectasias), as well as pigmented lesions, were excluded from the protocol. Patients with unstable or uncontrolled clinically significant medical conditions were excluded. Lesions with missing histology also excluded (n=21)</p> <p>Sample size (patients): No. eligible: 164; No. included: 155</p> <p>Sample size (lesions): No. eligible: 256; No. included: 235 (different sets of 231 lesions were available for each test)</p> <p>Participant characteristics: Median age: 70y (33-90y)</p> <p>Lesion characteristics Head/Neck: 41%; Upper body 48.8%</p>
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Visual inspection (VI): No algorithm
	Method of diagnosis: In person diagnosis
	Prior test data: N/A in person diagnosis
	Diagnostic threshold: Observer diagnosis of BCC; pink or red lesions that could be either macules, patches or small papules with or without scale.
	Diagnosis based on: Single observer; (n=NR; 6 centres participated)
	Observer qualifications: but probably dermatologists given authors institutions
	Experience in practice: Not described
	Experience with index test: Not described
	Dermoscopy: No algorithm
	Method of diagnosis: In person diagnosis
	Prior test data: Clinical examination and/or case notes
	Diagnostic threshold: Observer diagnosis; "A scattered vascular global pattern with loose haphazard distribution. Shiny white to red structures with or without chrysalis-like structures. Small fine telangiectasias appearing as fine, kinked vessels of small calibre, with length < 1 mm in superficial BCC and larger arborizing vessels in more invasive BCC (nodular/infiltrative)"; referenced to Marghoob 2012 .
	Test observers as described for Visual Inspection (above)
	Any other detail: After clinical examination dermoscopy was carried out using a DermLite ProHr (3Gen Inc., San Juan Capistrano, CA, U.S.A.), attached to a Sony Cybershot DSC-W710 camera (Sony, Tokyo, Japan) (supplied by MDL). As polarized light was used, no preparation of the area under examination was necessary
	OCT: No algorithm; Multi-beam swept-source frequency domain; Vivosight (MDL); resolution axial 10µm, lateral 7.5µm; tissue penetration 2000µm; centre wavelength 1305nm; the function 'multi-1' setting automatically provided 60 lateral scans of 6mm length every 100 µm.
	Method of diagnosis: In person; OCT images were assessed following dermoscopy by naked eye for features affecting the epidermis, the dermoepidermal junction and the dermis.
	Prior test data available: Clinical exam and dermoscopy
	Diagnostic threshold: Observer diagnosis; based on "Epidermis: protrusions into the dermis with shadowing; dermoepidermal junction: lack of definition or rupturing; and dermis: signal-poor ovoid structures, dark rims, ovoid structures with bright centres, dilated vessels, black areas or cysts, bright stroma and small ovoid signal-poor structures ('fish shoal')." Paper cites Boone 2012 as having been published since the study was designed.
	Observers: As above. All centres described as regular users of OCT, with at least 3 months of practical experience with the device. Nonetheless, all centres received training before participating in the study.

Optical coherence tomography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

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
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Dermoscopy

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	Yes
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Yes
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Reference standard Histological diagnosis alone Details: a biopsy or excision of the lesion was taken Disease positive: 141; Disease negative: 94 Target condition (Final diagnoses) BCC: 141 'Benign' diagnoses: 94 (32 actinic keratosis, 17 Bowen's disease, 6 seborrhoeic keratoses, 6 inflammatory diseases (psoriasis,eczema etc), 34 other including sebaceous hyperplasia, dermal naevus, microcystic adnexal carcinoma NB: different sets of 231 lesions were recorded for each test, therefore the number diseased per 2x2 varies
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (Does not contribute to Risk of Bias judgement)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk
B. Concerns regarding applicability	
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	<p>Excluded participants: Histology was missing for 21 lesions, and one case was found to have a combination of both BCC and SK or AK, leaving 235 lesions for analysis in the ITT group</p> <p>Time interval to reference test: consecutively done after index test "All diagnostic steps had to be completed before histological confirmation was made."</p>
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
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias	
Comparative	Time interval between index test(s): Consecutive
Was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	No
Was the interval between application of the index tests less than one month?	Yes
Are there any concerns that the test comparison could have introduced bias?	Low risk
B. Concerns regarding applicability	
Were all tests applied and interpreted in a clinically applicable manner?	Yes
Are there concerns that the test comparison differs from the review question?	Low concern

Notes

Notes	
-------	--

Wahrlich 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	<p>Study design: Unclear</p> <p>Data collection: Retrospective</p> <p>Period of data collection: Sept 2011 to Jun 2012</p> <p>Country: Germany</p> <p>Funding: None; OCT device provided by Michelson Diagnostics</p>
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	<p>Inclusion criteria: Participants with non-melanoma skin cancer including BCC or other skin lesions; phase 1 of study excluded as student observers</p> <p>Setting: Secondary (Dermatology)</p> <p>Prior testing: Unclear</p> <p>Exclusion criteria: pre-operated or ulcerated lesions.</p> <p>Sample size (patients): No. eligible: NR; No. included: 50</p> <p>Sample size (lesions): No. eligible: 50; No. included: 50</p> <p>Participant characteristics: mean age 62.8y; 46% male</p> <p>Lesion characteristics: None reported</p>
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	<p>OCT: 'Berlin score', developed by authors 'prior to the start of the study' based on data from other study groups; Multi-beam swept-source frequency domain; Vivosight (MDL); resolution axial 10µm, lateral 7.5µm; tissue penetration 2000µm; centre wavelength 1305nm; performed using free-run and multi-slice functions on an area of 6 x 6 x 2 mm. Affected areas were shaved (hairy areas) or pre-treated with Sellotape (scaly lesions) as required</p> <p>Diagnostic threshold: Two thresholds assessed, Berlin score ≤ 8 (T1 limit) and of ≤ 12 (T2 limit)</p> <p>Method of diagnosis: Unclear</p> <p>Prior test data available: Unclear; appears that following histological diagnosis the histologist then retrospectively examined the OCT images</p> <p>Diagnosis based on: Single (n = 1)</p> <p>Observer qualifications: Dermatopathologist; described as "dermatological specialist/dermatopathologist and expert familiar with OCT</p> <p>Experience in practice: High</p> <p>Experience with index test: High</p> <p>Other detail: BCC features subdivided into major (dark borders underneath the tumour, hyporeflexive nests and ovoid structures) and minor criteria (disruption of dermal-epidermal junction (DEJ) and cysts). Presence of feature classed between 0 (absent) and 3 (clearly recognizable structure); visible (2) and less visible (1) structures could not clearly be allocated. Criteria were added to a cumulative score with a maximum of 24 points. Binary logistic regression identified limit values (T1,T2) to differentiate BCC from 'others' using phase 1 of the study (100 BCC and 30 'other' skin diseases; using student observers). Main diagnostic features based on already existing data of other study groups (Khandwala 2010; Mogensen 2009; Sabban 2004; Vogt 2003; Zhao 2008).</p>
-------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Optical coherence tomography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	
Could the conduct or interpretation of the index test have introduced bias?	High risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
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
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)	Type of reference standard: Histology alone Details: Biopsy or excision Disease positive: 29; Disease negative: 21 Target condition (Final diagnoses): BCC 29; cSCC 9 Bowen's disease 7; Actinic keratosis 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 interpreted without knowledge of the referral diagnosis? (Does not contribute to Risk of Bias judgement)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability

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

Flow and Timing

A. Risk of Bias

Flow and timing	Index test to reference standard interval: Consecutive; OCT described as followed by excision or biopsy Exclusions: Discussion reports exclusion of 3 participants due to anatomical position, different scan 'heights' and shadow artefacts.
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
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	High risk

Comparative

A. Risk of Bias

Comparative

B. Concerns regarding applicability

Notes

Notes	
-------	--

Wessels 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Study design: Case series Data collection: Prospective Period of data collection: Nov 2011 – April 2012 Country: Netherlands Funding: None declared
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk
B. Concerns regarding applicability	
Patient characteristics and setting	Inclusion criteria: Consecutive patients with pigmented (melanocytic) lesions with clinical suspicion of melanoma during routine skin cancer screening, from whom an excision had to be taken in the outpatient clinic of the Netherlands Cancer Institute in Amsterdam. Setting: Secondary; outpatient clinic Prior testing: Clinical assessment during routine skin cancer screening Exclusion criteria: None reported Sample size (patients): No. eligible: NR; No. included: 33 Sample size (lesions): No. eligible: NR; No. included: 40 Participant characteristics: Mean age 46y (SD 16); 42% Male; History of melanoma (20, 61%); Lesion characteristics: All lesions rated as clinically suspicious on naked eye and 19 also had dermoscopic suspicion; Lesion site - Trunk and Neck (28, 70%), arms and legs (12, 30%); Fitzpatrick type 1 (2,6%), type 2 (15,46%), type 3 (15,46%), type 4 (1,3%). Mean attenuation coefficient of benign lesions was 5.49 mm ⁻¹ and 4.28 mm ⁻¹ for melanomas.
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	<p>OCT: No algorithm; Swept-source OCT (Santec Inner Vision 2000); resolution axial 10µm, lateral 20µm; tissue penetration 2000µm; centre wavelength 1300nm; for each lesion 5 2D and one 3D OCT scans were recorded, plus 5 2D scans from healthy skin next to the lesion. Attenuation coefficient could not be identified in 20 2D OCT scans due to thin layer thickness.</p> <p>Diagnostic threshold: Investigated accuracy of two morphological features on 3D scans (absence of clear dermoepidermal junction and no lower boundary of lesion visible) and attenuation coefficient based on 2D scans 5.4mm⁻¹ (optimal threshold estimated via Youden index)</p> <p>Method of diagnosis: Image-based</p> <p>Prior test data available: Unclear; "All scans were stored to be analysed at a later date by one investigator (RW) blinded for the pathology report."</p> <p>Diagnosis based on: Single (n=1)</p> <p>Observer qualifications: Unclear; investigator institution Dept of Surgery</p> <p>Experience in practice: Not described</p> <p>Experience with index test: Not described</p> <p>Other detail: epidermal layer thickness and the attenuation coefficient (µopt mm⁻¹) were measured. "The attenuation coefficient is the decrease in light intensity per millimetre; measurement was performed as described before (Faber 2004) using custom written software (LabVIEW 2011; National Instruments, Austin, TX, USA).</p>
-------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Optical coherence tomography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk
B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	No
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes
Was the test interpretation carried out by an experienced examiner?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

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)	Type of reference standard: Histology alone Details: Excision; All stained sections were reviewed by one pathologist. Disease positive: 9; Disease negative: 31 Target condition (Final diagnoses): Invasive melanoma 7; Melanoma in situ 2 Benign nevi: 31 (24 compound nevi, 5 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?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis? (Does not contribute to Risk of Bias judgement)	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	Index test to reference standard interval: Consecutive; "After OCT-imaging, excision was performed" Exclusions: None reported
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
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	
Could the patient flow have introduced bias?	Low risk

Comparative

A. Risk of Bias	
Comparative	
B. Concerns regarding applicability	

Notes

Notes	-
-------	---

Footnotes

AK - actinic keratosis; BCC - basal cell carcinoma; BD - Bowens disease; CM - cutaneous melanoma; cSCC - cutaneous squamous cell carcinoma; DEJ - dermoepidermal junction; HD-OCT - high definition optical coherence tomography; ITT - intention-to-test; MM - malignant melanoma; N/A - not applicable; NR - not reported; NS - not specified; OCT - optical coherence tomography; SD - standard deviation; SK - seborrhoeic keratosis.

Characteristics of excluded studies

Alawi 2013

Reason for exclusion	EXCLUDE on index test <i>OCT used to determine surgical margins</i>
Bechara 2004	
Reason for exclusion	EXCLUDE on sample size <i>only 3 BCCs</i> EXCLUDE if individual lesion characteristics
Boone 2014	
Reason for exclusion	EXCLUDE if individual lesion characteristics
Boone 2015	
Reason for exclusion	EXCLUDE on study population <i>includes healthy volunteers; also pre-selected AK and SCC</i> EXCLUDE if derivation study <i>study developed a diagnostic algorithm for HD-OCT (no independent test population)</i>
Boone 2015a	
Reason for exclusion	EXCLUDE if derivation study EXCLUDE on 2x2 data
Boone 2016	
Reason for exclusion	EXCLUDE if derivation study <i>appears to be first study assessing optical properties of HD-OCT rather than dx by morphological characteristics</i>
Brudermanns 2008	
Reason for exclusion	EXCLUDE not a primary study <i>Comment on Gambichler 2007</i>
Calin 2013	
Reason for exclusion	EXCLUDE not a primary study systematic review
Coleman 2013	
Reason for exclusion	EXCLUDE on study population <i>no results for benign lesions</i>
Cunha 2011	
Reason for exclusion	EXCLUDE on study population <i>all BCC cases (no benign lesions)</i>
de Boer 2016	

Reason for exclusion	EXCLUDE not a primary study <i>systematic review (not addressing OCT)</i>
----------------------	------------------------------------------------------------------------------

de Giorgi, 2005

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

Evans 2014

Reason for exclusion	EXCLUDE not a primary study <i>Editorial review</i>
----------------------	--------------------------------------------------------

Forsea 2010

Reason for exclusion	EXCLUDE on sample size EXCLUDE if derivation study
----------------------	-------------------------------------------------------

Gambichler 2007

Reason for exclusion	EXCLUDE if derivation study <i>First study of OCT in skin cancer; Looking at features of OCT and comparing with histology.</i> EXCLUDE on 2x2 data <i>not enough data to populate 2x2 table</i>
----------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Gambichler 2014

Reason for exclusion	EXCLUDE on study population <i>BCCs only included</i>
----------------------	----------------------------------------------------------

Gambichler 2015a

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

Hinz 2011

Reason for exclusion	EXCLUDE on target condition <i>assesses tumour thickness only</i>
----------------------	----------------------------------------------------------------------

Hussain 2015

Reason for exclusion	EXCLUDE not a primary study systematic review
----------------------	--------------------------------------------------

Hussain 2016

Reason for exclusion	EXCLUDE on study population <i>Patients undergoing FU for recurrent BCC</i> EXCLUDE on target condition <i>recurrent BCC</i>
----------------------	---------------------------------------------------------------------------------------------------------------------------------------

Jorgensen 2008

Reason for exclusion	EXCLUDE on index test <i>Machine learning OCT</i>
----------------------	------------------------------------------------------

Maier 2013

Reason for exclusion	EXCLUDE on study population– <i>BCCs only included (no disease negative included)</i>
----------------------	---------------------------------------------------------------------------------------

Marneffe 2016

Reason for exclusion	EXCLUDE on study population <i>AK - SCC - normal skin</i>
----------------------	--------------------------------------------------------------

Meyer 2014

Reason for exclusion	EXCLUDE on target condition <i>detection of lesion thickness only</i>
----------------------	--------------------------------------------------------------------------

Mogensen 2009

Reason for exclusion	EXCLUDE on study population <i>Differentiating NMSC from normal skin</i> EXCLUDE on reference standard <i>not clearly reported; described as 'clinically diagnosed'</i>
----------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Mogensen 2009a

Reason for exclusion	EXCLUDE not a primary study <i>review/opinion paper</i>
----------------------	------------------------------------------------------------

Mogensen 2009b

Reason for exclusion	EXCLUDE on target condition <i>precision of tumour size measurements</i>
----------------------	-----------------------------------------------------------------------------

Moraes 2015

Reason for exclusion	EXCLUDE if individual lesion characteristics
----------------------	----------------------------------------------

Olmedo 2006

Reason for exclusion	EXCLUDE on study population - <i>BCCs only included (no disease negative included)</i>
----------------------	----------------------------------------------------------------------------------------

Olsen 2015

Reason for exclusion	EXCLUDE not a primary study <i>systematic review</i>
----------------------	---------------------------------------------------------

Picard 2013

Reason for exclusion	EXCLUDE not a primary study <i>case report</i>
----------------------	---------------------------------------------------

Reggiani 2015

Reason for exclusion	EXCLUDE not a primary study <i>systematic review</i>
----------------------	---------------------------------------------------------

Strasswimmer 2004

Reason for exclusion	EXCLUDE on sample size <i>2 cases presented</i> EXCLUDE if derivation study
----------------------	-----------------------------------------------------------------------------------

Ulrich 2014

Reason for exclusion	EXCLUDE conference abstract <i>included full paper (Ulrich 2015)</i>
----------------------	-------------------------------------------------------------------------------------------

Welzel 1998

Reason for exclusion	EXCLUDE on 2x2 data <i>Not test accuracy; preliminary study of OCT</i>
----------------------	---------------------------------------------------------------------------

Wessels 2013

Reason for exclusion	EXCLUDE conference abstract <i>included full paper (Wessels 2015)</i>
----------------------	--------------------------------------------------------------------------------------------

Zakharov 2014

Reason for exclusion	EXCLUDE conference abstract
----------------------	-----------------------------

Zakharov 2015

Reason for exclusion	EXCLUDE on index test <i>ex-vivo diagnosis not relevant to the review</i>
----------------------	------------------------------------------------------------------------------

Footnotes

Characteristics of studies awaiting classification

Cheng 2016

Patient Sampling	Consecutive group of patients at moderate to very high risk of melanoma presenting to Melanoma Institute Australia from April 2014 - March 2015 with possible sBCC based on clinical and dermoscopic findings.
Patient characteristics and setting	168 lesions; 52% were sBCC, 26% were other BCC variants and the remaining lesions were actinic keratosis, squamous cell carcinoma in situ, other benign inflammatory processes and two other malignant tumours.
Index tests	Visual examination, dermoscopy, optical coherence tomography
Target condition and reference standard(s)	BCC, histology (punch biopsy)
Flow and timing	Biopsy performed immediately after OCT scanning
Comparative	No
Notes	Comparison of 3 observers with varying levels of OCT experience. Confidence in the diagnosis also recorded

Olsen 2016

Patient Sampling	Retrospective study of image bank from scans performed 2010 - 2015.
Patient characteristics and setting	142 Good quality OCT images of BCC, AK and normal skin (good quality defined as: minimal shadowing artefacts from hairs, hyperkeratosis and crustae)
Index tests	OCT
Target condition and reference standard(s)	BCC, Histology
Flow and timing	Not reported
Comparative	No
Notes	Published August 2016 but not id in update search; awaiting author communication to allow inclusion (contacted 07-06-17)

Footnotes

AK - actinic keratosis; BCC - basal cell carcinoma; OCT - optical coherence tomography.

Characteristics of ongoing studies**Footnotes****Summary of results tables****1 Summary of Findings**

Question	What is the diagnostic accuracy of optical coherence tomography for the diagnosis of skin cancer in adults?
Population:	Adults with skin lesions suspicious for melanoma (2/5) or for BCC (3/5). No studies recruited sufficient numbers of cases of cSCC for inclusion.
Prior testing and prevalence:	All studies included lesions selected for excision or biopsy. There was some requirement for clinical suspicion of malignancy (1/2 in melanoma) and for recruitment of only clinically challenging lesions (2/3 in BCC). The prevalence of melanoma was 23 to 27%; prevalence of BCC ranged from 58 to 61%.
Settings:	Secondary care and specialist cancer clinics.
Target condition(s):	Invasive melanoma and atypical intraepidermal melanocytic variants (2); basal cell carcinoma (3).

Question	What is the diagnostic accuracy of optical coherence tomography for the diagnosis of skin cancer in adults?						
Index test:	Conventional and high density optical coherence tomography (OCT); diagnostic thresholds based on subjective assessment of OCT features with (2) and without (2) associated scoring, and quantitative assessment of attenuation (1).						
Reference standard:	Histology						
Action:	If accurate, positive results of OCT could help to appropriately select lesions for excision and reduce multiple biopsies in those with suspected BCC.						
Limitations							
Risk of bias:	Patient selection methods unclear (3/5) due to lack of description of recruitment methods (2) or study design (1). High risk of bias for the index test due to lack of blinding (1/5) and clearly (1/5) or possibly (1/5) data driven thresholds. Reference standard blinding was not described (5/5). Timing of index and reference standards was not reported. Exclusions due to test failures were not reported (3/5) or their final diagnoses were not described (1/5). Low risk of bias for flow and timing apart from exclusions due to missing histology (1/5) and failure to adequately image lesions (1/5). No other index test failures mentioned.						
Applicability of evidence to question:	High (3/5) or unclear (1/5) concerns about applicability of participants due to unrepresentative participant samples or multiple lesions per participant (1/5). High concerns about applicability of index test due to image-based diagnosis (4/5) with blinding to all other clinical information (1/5) or unclear information provided to test observers (2/5). Reference standard interpretation by experienced histopathologists not described (4/5).						
Quantity of evidence							
Number of studies	5	Total participants with test results ^a	402	Total lesions with test results ^a	529	Total melanoma lesions	36
						Total BCC lesions	240
						Total cSCC lesions	9
Detection of invasive melanoma and atypical intraepidermal melanocytic variants							
Number of studies	Total lesions with test results		Total lesions with melanoma				
	2		133				
Findings	36 (32 invasive, 4 melanoma <i>in situ</i>)						
	Two studies evaluated invasive melanoma and melanoma in situ: <ul style="list-style-type: none">Conventional OCT at an attenuation coefficient of 5.4mm⁻¹: sensitivity 89% (95% CI: 52, 100%) and specificity 61% (95% CI: 42, 78%); (1/2)HD OCT sensitivity 74% (95% CI: 54, 89%) and specificity 92% (95% CI: 83, 97%) using scoring system based on OCT characteristics (1/2); both melanoma <i>in situ</i> lesions misclassified as negative on OCT.						
Detection of BCC [pooled analysis ^b]							
Number of studies	Total lesions with test results		Total lesions with BCC				
	3 [2]		396 [346]				
Pooled analyses	237 [208]		Numbers observed in a cohort of 1000 lesions being tested (at mean prevalence 60%) ^c				

Question		What is the diagnostic accuracy of optical coherence tomography for the diagnosis of skin cancer in adults?					
2 studies of observer diagnosis with VI alone, VI plus dermoscopy, and with OCT (total n = 346; melanoma n = 208)	Sensitivity (95% CI)	Specificity (95% CI)	True Positive	False Positive	False Negative	True Negative	
			(receive necessary excision)	(receive unnecessary excision)	(do not receive required excision)	(appropriately not excised)	
VI alone:	80% (55, 93)	37% (24, 52)	478	252	122	148	
VI plus dermoscopy:	86% (76, 92)	55% (46, 63)	516 (↑38)	180 (↓72)	84 (↓38)	220 (↑72)	
OCT:	95% (91, 97)	77% (69, 83)	569 (↑53)	93 (↓87)	31 (↓53)	307 (↑87)	
Findings	Pooled studies - results consistent between studies; conducted in clinically equivocal populations. Other studies (n = 1) - Similar results for OCT obtained using Berlin score at ≥ 8 (sensitivity 97% (95% CI: 82, 100%) and specificity 76% (95% CI: 53, 92%)) with lower sensitivity (66% (95% CI: 46, 82%)) and higher specificity (86% (95% CI: 64, 97%)) at the higher score of ≥ 12. Unclear whether this would be replicated in usual practice setting.						
Detection of cSCC							
Findings	One case-control study with 9 cSCCs, total number of lesions = 50: <ul style="list-style-type: none">Poor sensitivity for OCT obtained using Berlin score at ≥ 8 (sensitivity 56% (95% CI: 21, 86%) and specificity 100% (95% CI: 91, 100%)) with lower sensitivity (33% (95% CI: 7, 70%)) and the same specificity (100%) at the higher score of ≥ 12. Unclear whether this would be replicated in usual practice setting.						

Footnotes

^aAll results use lesions as the unit of analysis

^bSquared brackets indicate numbers used in pooled analysis

^cNumbers estimated at 25th, 50th (median) and 75% percentiles of basal cell carcinoma prevalence observed across 2 datasets reporting evaluations of OCT added to dermoscopy and visual inspection

BCC - basal cell carcinoma; cSCC - cutaneous squamous cell carcinoma; CI - confidence interval; HD - high definition; OCT - optical coherence tomography; VI - visual inspection

Additional tables

1 Glossary of terms

Term	Definition
Acantholytic subtypes	An uncommon squamous cell carcinoma variant characterised by acantholysis, which is the marked disruption of intercellular connections and resulting separation of epidermal cells
Arborizing blood vessels	Blood vessels in the skin that form a tree-like branching appearance. They can be a sign of basal cell carcinomas
Atypical honeycombing	This pattern arises from variation in size and shape of keratinocytic nuclei and irregular cell borders of keratinocytes in the spinous-granular epidermal layer. It is a feature of actinic keratosis and squamous cell carcinoma on optical coherence tomography and on reflective confocal microscopy examination
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma <i>in situ</i> and lentigo maligna
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin

Term	Definition
Atypical pleomorphic keratinocytes	Abnormal skin cells of different shapes and sizes, a feature visible on histopathology
Axial resolution	Axial resolution describes the ability of an OCT system to distinguish between two points in space that lie in the direction parallel to the light beam
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
Dermal nests	Collections of pigment cells that are bunched together in the dermis
Dermal papilla	Small projections of the dermis into the overlying epidermis giving an undulating pattern and visible as "fingerprints" in hands and feet
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
Electrodessication	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
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.
Fibrotic septa	Excess fibrous connective tissue formation separating other parts of tissue
Grey-blue ovoid nests and globules	Grey-blue coloured oval shaped areas seen under dermoscopy that may represent basal cell carcinomas
Histopathology/Histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope.
Hypertrophic actinic keratosis	Precancerous scaly patches of skin that are particularly thickened
Hypoechoic	Displaying lower echogenicity reflecting and appears darker on ultrasonography
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
Inflammatory dermatoses	Skin conditions where the main disease process is inflammatory, often involving immune cells, as apposed to malignant or infectious processes. The inflammatory process may be due to internal or external factors
Interferometry	The measurement of waves of light or sound after interference in order to extract information
Interfollicular epidermis	The part of the epidermis that lies in between the hair follicles
Junctional nests	Collections of pigment cells bunched up around the junction between the epidermis and dermis
Lateral resolution	Lateral resolution describes the ability of an OCT system to distinguish between two points in space that lie in a perpendicular direction to the light beam
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

Term	Definition
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.
Micrometastases	Micrometastases are metastases so small that they can only be seen under a microscope.
Mitotic activity	Relates to the presence of proliferating cells and used as an index of tumour aggressiveness
Mitotic rate	Microscopic evaluation of number of cells actively dividing in a tumour.
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)
Nuclear dysplasia and mitoses	A histopathological term referring to abnormal nuclei with increased mitotic activity and nuclear size associated with disordered nuclear dysplasia and mitoses cell growth
Nucleated	The presence of a nuclei within a cell, which contain most of the cell's genetic material
Pagetoid cells	Abnormal pigment cells that spread upwards through the epidermis
Papillary dermis	Also called the 'upper dermis', this is the uppermost layer of the dermis that connects to the dermal-epidermal junction
Peripheral palisading	A histopathological term referring to the wall-like appearance of cells around a central focus
Pleomorphic	Variability in size or shape
Polygonal cells	Skin cells that appear to have many sides, such as taking up a pentagonal, hexagonal or octagonal appearance
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.
Rete ridges	Also called 'epidermal ridges' or 'epidermal pegs', they represent downward projections of the epidermis into underlying connective tissue
Reticular dermis	Also called the 'lower dermis', the reticular dermis is the lower layer of the dermis, located under the papillary dermis

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
Spindle subtypes of SCC	A squamous cell carcinoma variant characterised by poorly differentiated spindle cells surrounded by collagenous stroma
Spinous-granular layer	One of several layers of the epidermis, which is the outermost layer of skin. The nuclei of keratinocytes, which contain most of the cell's genetic material are found here
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
Stromal reaction	Change in connective tissue microenvironment
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination.
Superficial fine telangiectasia	Fine dilated blood vessels of small/varying diameter located in the superficial dermis
Targetoid hair follicles	The presence of yellow keratotic follicular plugs surrounded by a white rim on dermoscopy, more frequently known as 'white circle', which can be a characteristic of squamous cell carcinoma

Footnotes

2 Description of diagnostic thresholds used by optical coherence tomography for the detection of all target conditions

Study	Threshold	Threshold detail
Melanoma		
Gambichler 2014 HD-OCT	Score ≥ -1 MM; score of ≥ -1.5 benign MSL, based on sum of sub-scores for various OCT characteristics	New scoring system based on previously described micromorphological HD-OCT correlates of melanocytic skin lesions (Boone 2014 ; Picard 2013) and from RCM (Segura 2009) and conventional OCT studies (Gambichler 2007) OCT scoring based on "predominant presence of the following risk (+) and/or protective (-) features ... (i) HD-OCT en-face mode - typical basal cells/clusters (-1), edged papillae (-1), honeycomb/cobblestone pattern (-1), large roundish pagetoid cells (+1), atypical cell clusters in the dermoepidermal junction (DEJ) (+1), totally disarranged epidermal/ dermal pattern (+1); (ii) HD-OCT slice mode - clearly demarcated DEJ (-0.5), finger-shaped elongated rete ridges (-0.5), bright bizarre dermal horizontal streaks (+0.5), large vertical icicle- shaped structures (+0.5). The total score is the sum of the aforementioned sub-scores for the various particular criteria."
Wessels 2015 SS-OCT	Attenuation coefficient 5.4mm^{-1}	Based on 2D scans: "The attenuation coefficient is the decrease in light intensity per millimetre; measurement was performed as described before (Faber 2004) using custom written software (LabVIEW 2011; National Instruments, Austin, TX, USA)." The optimal attenuation coefficient of 5.4mm^{-1} was estimated using Youden's index. (Attenuation refers to the loss of signal by scattering and absorption of light; scattering is caused by the nature of cellular structures, while absorption is caused by skin tissue's biochemical composition. The 'attenuation coefficient (μ_{opt})' plots OCT signal decay by its penetration depth. The authors hypothesise that this tracks morphological and physiological changes in tissue.) Study also investigated accuracy of two morphological features on 3D scans (absence of clear dermoepidermal junction and no lower boundary of lesion visible) but these were excluded from review
BCC		
Markowitz 2015 SS-OCT	Diagnostic judgement (BCC present/absent)	Observer diagnosis was based on features described in previous studies (Maier 2013 ; Ulrich 2015 ; Wahrlich 2015): "epidermis was analyzed for protrusions into the dermis with shadowing; the epidermal-dermal junction for lack of definition or rupturing; and the dermis for signal-poor ovoid structures, dark rims, ovoid structures with bright centers, dilated vessels, black areas or cysts, bright stroma, and/or small ovoid signal-poor structures ('fish shoal')"
Ulrich 2015 SS-OCT	Diagnostic judgement (BCC present/absent)	Observer diagnosis; based on "Epidermis: protrusions into the dermis with shadowing; dermoepidermal junction: lack of definition or rupturing; and dermis: signal-poor ovoid structures, dark rims, ovoid structures with bright centres, dilated vessels, black areas or cysts, bright stroma and small ovoid signal-poor structures ('fish shoal')." Paper cites Boone 2012 's identification of features for BCC as having been published since the study was designed.
Wahrlich 2015 SS-OCT	1. Berlin score ≥ 8 2. Berlin score ≥ 12	BCC features subdivided into major (dark borders underneath the tumour, hyporeflexive nests and ovoid structures) and minor criteria (disruption of dermal-epidermal junction (DEJ) and cysts). The presence of each feature was classed between 0 (absent) and 3 (clearly recognizable structure); visible (2) and less visible (1) structures could not clearly be allocated. Criteria were added to a cumulative score with a maximum of 24 points. Binary logistic regression identified limit values (T1,T2) to differentiate BCC from 'others' using lesions in phase 1 of the study (100 BCC and 30 'other' skin diseases; using student observers). T1 threshold identified as ≥ 8 and T2 ≥ 12 . Main diagnostic features were based on already existing data from other study groups (Khandwala 2010 ; Mogensen 2009 ; Sabban 2004 ; Vogt 2003 ; Zhao 2008).

Footnotes

BCC - basal cell carcinoma; DEJ - dermoepidermal junction; HD-OCT - high definition optical coherence tomography; MM - malignant melanoma; OCT - optical coherence tomography; RCM - reflectance confocal microscopy; SS-OCT - swept-source optical coherence tomography.

References to studies

Included studies

[Gambichler 2015](#)

Gambichler T, Schmid-Wendtner MH, Plura I, Kampilafkos P, Stucker M, Berking C, et al. A multicentre pilot study investigating high-definition optical coherence tomography in the differentiation of cutaneous melanoma and melanocytic naevi. *Journal of the European Academy of Dermatology and Venereology* : JEADV 2015;29(3):537-41. [[PubMed: 25073788](#)]

Markowitz 2015

* Markowitz O, Schwartz M, Feldman E, Bienenfeld A, Bieber AK, Ellis J, et al. Evaluation of optical coherence tomography as a means of identifying earlier stage basal cell carcinomas while reducing the use of diagnostic biopsy. *Journal of Clinical and Aesthetic Dermatology* 2015;8(10):14-20. [Other: ER4:25012306; [PubMed: 26557214](#)]

Ulrich 2015

* Ulrich M, von Braunmuehl T, Kurzen H, Dirschka T, Kellner C, Sattler E, et al. The sensitivity and specificity of optical coherence tomography for the assisted diagnosis of nonpigmented basal cell carcinoma: an observational study. *British Journal of Dermatology* 2015;173(2):428-35. [Other: ER4:25012284; [PubMed: 25904111](#)]

Wahrlich 2015

Wahrlich C, Alawi SA, Batz S, Fluhr JW, Lademann J, Ulrich M. Assessment of a scoring system for Basal Cell Carcinoma with multi-beam optical coherence tomography. *Journal of the European Academy of Dermatology and Venereology* : JEADV 2015;29(8):1562-9. [[PubMed: 25640145](#)]

Wessels 2015

Wessels R, de Bruin DM, Relyveld GN, Faber DJ, Vincent AD, Sanders J, et al. Functional optical coherence tomography of pigmented lesions. *Journal of the European Academy of Dermatology and Venereology* : JEADV 2015;29(4):738-44. [[PubMed: 25175118](#)]

Excluded studies

Alawi 2013

Alawi SA, Kuck M, Wahrlich C, Batz S, McKenzie G, Fluhr JW, et al. Optical coherence tomography for presurgical margin assessment of non-melanoma skin cancer - a practical approach. *Experimental Dermatology* 2013;22(8):547-51. [[PubMed: 23879814](#)]

Bechara 2004

Bechara FG, Gambichler T, Stücker M, Orlikov A, Rotterdam S, Altmeyer P, et al. Histomorphologic correlation with routine histology and optical coherence tomography. *Skin Research and Technology* 2004;10(3):169-73. [[PubMed: 15225266](#)]

Boone 2014

Boone MA, Norrenberg S, Jemec GB, Del Marmol V. High-definition optical coherence tomography imaging of melanocytic lesions: a pilot study. *Archives of Dermatological Research* 2014;306(1):11-26. [[PubMed: 23832144](#)]

Boone 2015

Boone MA, Marneffe A, Suppa M, Miyamoto M, Alarcon I, Hofmann-Wellenhof R, et al. High-definition optical coherence tomography algorithm for the discrimination of actinic keratosis from normal skin and from squamous cell carcinoma. *Journal of the European Academy of Dermatology and Venereology* : JEADV 2015;29(8):1606-15. [[PubMed: 25656269](#)]

Boone 2015a

Boone MA, Suppa M, Pellacani G, Marneffe A, Miyamoto M, Alarcon I, et al. High-definition optical coherence tomography algorithm for discrimination of basal cell carcinoma from clinical BCC imitators and differentiation between common subtypes. *Journal of the European Academy of Dermatology and Venereology*: JEADV 2015;29(9):1771-80. [[PubMed: 25712021](#)]

Boone 2016

Boone MA, Suppa M, Dhaenens F, Miyamoto M, Marneffe A, Jemec GB, et al. In vivo assessment of optical properties of melanocytic skin lesions and differentiation of melanoma from non-malignant lesions by high-definition optical coherence tomography. *Archives of Dermatological Research* 2016;308(1):7-20. [[PubMed: 26563265](#)]

Brudermanns 2008

Brudermanns B. Characterization of melanocytic skin lesions using optical coherence tomography [Melanozytäre Hautläsionen - Charakterisierung mittels Kohärenztomografie]. *RoFo Fortschritte auf dem Gebiet der Röntgenstrahlen und der Bildgebenden Verfahren* 2008;180(5):388-9. [DOI: 10.1055/s-2008-1075121]

Calin 2013

Calin MA, Parasca SV, Savastru R, Calin MR, Dontu S. Optical techniques for the noninvasive diagnosis of skin cancer. *Journal of Cancer Research and Clinical Oncology* 2013;139(7):1083-104. [[PubMed: 23552870](#)]

Coleman 2013

Coleman AJ, Richardson TJ, Orchard G, Uddin A, Choi MJ, Lacy KE. Histological correlates of optical coherence tomography in non-melanoma skin cancer. *Skin Research and Technology* 2013;19(1):10-9. [[PubMed: 22738357](#)]

Cunha 2011

Cunha D, Richardson T, Sheth N, Orchard G, Coleman A, Mallipeddi R. Comparison of ex vivo optical coherence tomography with conventional frozen-section histology for visualizing basal cell carcinoma during Mohs micrographic surgery. *British Journal of Dermatology* 2011;165(3):576-80. [[PubMed: 21797838](#)]

de Boer 2016

de Boer E, Moore LS, Warram JM, Huang CC, Brandwein-Gensler MS, van Dam GM, et al. On the horizon: Optical imaging for cutaneous squamous cell carcinoma. *Head & Neck* 2016;38(Suppl 1):E2204-13. [[PubMed: 25899874](#)]

de Giorgi, 2005

de Giorgi V, Stante M, Massi D, Mavilia L, Cappugi P, Carli P. Possible histopathologic correlates of dermoscopic features in pigmented melanocytic lesions identified by means of optical coherence tomography. *Experimental Dermatology* 2005; 14(1):56-9. [[PubMed: 15660920](#)]

Evans 2014

Evans CL. Peering under the skin: measuring melanoma depth with ultrasound and optical coherence tomography. *British Journal of Dermatology* 2014;171(4):690-1. [[PubMed: 25319422](#)]

Forsea 2010

Forsea AM, Carstea EM, Ghervase L, Giurcaneanu C, Pavelescu G. Clinical application of optical coherence tomography for the imaging of non-melanocytic cutaneous tumors: a pilot multi-modal study.[Erratum appears in *J Med Life*. 2011 Jan-Mar; 4(1):7 p following 123]. *Journal of Medicine and Life* 2010;3(4):381-9. [[PubMed: 21254735](#)]

Gambichler 2007

Gambichler T, Regeniter P, Bechara FG, Orlikov A, Vasa R, Moussa G, et al. Characterization of benign and malignant melanocytic skin lesions using optical coherence tomography in vivo. *Journal of the American Academy of Dermatology* 2007;57(4):629-37. [[PubMed: 17610989](#)]

Gambichler 2014

Gambichler T, Plura I, Kampilafkos P, Valavanis K, Sand M, Bechara FG, et al. Histopathological correlates of basal cell carcinoma in the slice and en face imaging modes of high-definition optical coherence tomography. *British Journal of Dermatology* 2014, 2014;170(6):1358-61. [[PubMed: 24359160](#)]

Gambichler 2015a

Gambichler T, Plura I, Schmid-Wendtner M, Valavanis K, Kulichova D, Stucker M, et al. High-definition optical coherence tomography of melanocytic skin lesions. *Journal of Biophotonics* 2015;8(8):681-6. [[PubMed: 25237005](#)]

Hinz 2011

Hinz T, Ehler LK, Voth H, Fortmeier I, Hoeller T, Hornung T, et al. Assessment of tumor thickness in melanocytic skin lesions: comparison of optical coherence tomography, 20-MHz ultrasound and histopathology. *Dermatology* 2011; 223(2):161-8. [[PubMed: 22024981](#)]

Hussain 2015

Hussain AA, Themstrup L, Jemec GB. Optical coherence tomography in the diagnosis of basal cell carcinoma. *Archives of Dermatological Research* 2015;307(1):1-10. [[PubMed: 25223745](#)]

Hussain 2016

Hussain AA, Themstrup L, Nurnberg BM, Jemec G. Adjunct use of optical coherence tomography increases the detection of recurrent basal cell carcinoma over clinical and dermoscopic examination alone. *Photodiagnosis and Photodynamic Therapy* 2016;14:178-84. [[PubMed: 27109055](#)]

Jorgensen 2008

Jorgensen TM, Tycho A, Mogensen M, Bjerring P, Jemec GB. Machine-learning classification of non-melanoma skin cancers from image features obtained by optical coherence tomography. *Skin Research and Technology* 2008;14(3):364-9. [[PubMed: 19159385](#)]

Maier 2013

Maier T, Braun-Falco M, Hinz T, Schmid-Wendtner MH, Ruzicka T, Berking C. Morphology of basal cell carcinoma in high definition optical coherence tomography: en-face and slice imaging mode, and comparison with histology. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2013;27(1):e97-104. [[PubMed: 22540280](#)]

Marneffe 2016

Marneffe A, Suppa M, Miyamoto M, Del Marmol V, Boone M. Validation of a diagnostic algorithm for the discrimination of actinic keratosis from normal skin and squamous cell carcinoma by means of high-definition optical coherence tomography. *Experimental Dermatology* 2016;25(9):684-7. [[PubMed: 27095632](#)]

Meyer 2014

Meyer N, Lauwers-Cances V, Lourari S, Laurent J, Konstantinou MP, Lagarde JM, et al. High-frequency ultrasonography but not 930-nm optical coherence tomography reliably evaluates melanoma thickness in vivo: a prospective validation study. *British Journal of Dermatology* 2014;171(4):799-805. [[PubMed: 24863700](#)]

Mogensen 2009

Mogensen M, Joergensen TM, Nurnberg BM, Morsy HA, Thomsen JB, Thrane L, et al. Assessment of optical coherence tomography imaging in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: observer-blinded evaluation by dermatologists and pathologists. *Dermatologic Surgery* 2009;35(6):965-72. [[PubMed: 19397661](#)]

Mogensen 2009a

Mogensen M, Thrane L, Joergensen TM, Andersen PE, Jemec GB. Optical coherence tomography for imaging of skin and skin diseases. *Seminars in Cutaneous Medicine and Surgery* 2009;28(3):196-202. [[PubMed: 19782944](#)]

Mogensen 2009b

Mogensen M, Nurnberg BM, Forman JL, Thomsen JB, Thrane L, Jemec GB. In vivo thickness measurement of basal cell carcinoma and actinic keratosis with optical coherence tomography and 20-MHz ultrasound. *British Journal of Dermatology* 2009;160(5):1026-33. [[PubMed: 19183171](#)]

Moraes 2015

Moraes Pinto Blumetti TC, Cohen MP, Gomes EE, Petaccia de Macedo M, Ferreira de Souza Begnami MD, Tavares Guerreiro Fregnani JH, et al. Optical coherence tomography (OCT) features of nevi and melanomas and their association with intraepidermal or dermal involvement: A pilot study. *Journal of the American Academy of Dermatology* 2015; 73(2):315-7. [[PubMed: 26183975](#)]

Olmedo 2006

Olmedo JM, Warschaw KE, Schmitt JM, Swanson DL. Optical coherence tomography for the characterization of basal cell carcinoma in vivo: a pilot study. *Journal of the American Academy of Dermatology* 2006;55(3):408-12. [[PubMed: 16908344](#)]

Olsen 2015

Olsen J, Themstrup L, Jemec GB. Optical coherence tomography in dermatology. *Giornale Italiano di Dermatologia e Venereologia* 2015;150(5):603-15. [[PubMed: 26129683](#)]

Picard 2013

Picard A, Tsilika K, Long-Mira E, Hofman P, Passeron T, Lacour JP, et al. Use of high-definition optical coherent tomography (HD-OCT) for imaging of melanoma. *British Journal of Dermatology* 2013, 2013;169(4):950-2. [[PubMed: 23663029](#)]

Reggiani 2015

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

Strasswimmer 2004

Strasswimmer J, Pierce MC, Park BH, Neel V, de Boer JF. Polarization-sensitive optical coherence tomography of invasive basal cell carcinoma. *Journal of Biomedical Optics* 2004;9(2):292-8. [[PubMed: 15065894](#)]

Ulrich 2014

Ulrich M, Maier T, Kurzen H, Dirschka T, Kellner C, Sattler E, et al. Multicentre study evaluating the sensitivity and specificity of optical coherence tomography for the diagnosis of basal cell carcinoma. *British Journal of Dermatology* 2014;171(Suppl 4):8. [EMBASE: 71619972]

Welzel 1998

Welzel J, Lankenau E, Birngruber R, Engelhardt R. Optical coherence tomography of the skin. *Current Problems in Dermatology* 1998;26:27-37. [[PubMed: 9597313](#)]

Wessels 2013

Wessels R, De Bruin DM, Relyveld GN, Faber DJ, Vincent AD, Sanders J, et al. Optical coherence tomography (OCT) in pigmented lesions. *European Journal of Cancer* 2013;49(Suppl 2):S249. [EMBASE: 71217661]

Zakharov 2014

Zakharov VP, Bratchenko IA, Kozlov SV, Moryatov AA, Kornilin DV, Myakinin OO, et al. Advances in tumor diagnosis using OCT and Raman spectroscopy. In: Popp J, Tuchin VV, Matthews DL, Pavone FS, Garside P, editors(s). *Proceedings of SPIE. Biophotonics: Photonic Solutions for Better Health Care IV* edition. Vol. 9129. May 08, 2014. [DOI: 10.1117/12.2052145]

Zakharov 2015

Zakharov VP, Bratchenko IA, Artemyev DN, Myakinin OO, Kornilin DV, Kozlov SV, et al. Comparative analysis of combined spectral and optical tomography methods for detection of skin and lung cancers. *Journal of Biomedical Optics* 2015; 20(2):25003. [[PubMed: 25652702](#)]

Studies awaiting classification

Cheng 2016

Cheng HM, Lo S, Scolyer R, Meekings A, Carlos G, Guitera P. Accuracy of optical coherence tomography for the diagnosis of superficial basal cell carcinoma: a prospective, consecutive, cohort study of 168 cases. *British Journal of Dermatology* 2016;175(6):1290-1300. [[PubMed: 27146027](#)]

Olsen 2016

Olsen J, Themstrup L, De Carvalho N, Mogensen M, Pellacani G, Jemec GB. Diagnostic accuracy of optical coherence tomography in actinic keratosis and basal cell carcinoma. *Photodiagnosis and Photodynamic Therapy* 2016;16:44-9. [[PubMed: 27519350](#)]

Ongoing studies

Other references

Additional references

Abaffy 2010

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

ACIM 2014

Australian Cancer Database. Melanoma of the skin for Australia (ICD10 C43).. In: Australian Cancer Incidence and Mortality (ACIM) Books (<http://www.aihw.gov.au/acim-books/>). Australian Institute of Health and Welfare, 2011.

Alam 2001

Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *New England Journal of Medicine* 2001;344(13):975-83. [[PubMed: 11274625](#)]

Annessi 2007

Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions: the importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. *Journal of the American Academy of Dermatology* 2007;56(5):759-67. [[PubMed: 17316894](#)]

Argenziano 1998

Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Archives of Dermatology* 1998;134(12):1563-70. [[PubMed: 9875194](#)]

Argenziano 2001

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

Argenziano 2012

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

Arits 2013

Arits AH, Mosterd K, Essers BA, Spoorenberg E, Sommer A, De Rooij MJ, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncology* 2013;14(7):647-54. [DOI: 10.1016/S1470-2045(13)70143-8; [PubMed: 23683751](#)]

Arnold 2014

Arnold M, Holterhues C, Hollestein LM, Coebergh JW, Nijsten T, Pukkala E, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *Journal of the European Academy of Dermatology & Venereology* 2014; 28(9):1170-8. [[PubMed: 23962170](#)]

Balch 2001

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

Balch 2009

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

Baldursson 1993

Baldursson B, Sigurgeirsson B, Lindelof B. Leg ulcers and squamous cell carcinoma. An epidemiological study and a review of the literature. *Acta Dermato-Venereologica* 1993;73(3):171-4. [[PubMed: 8105611](#)]

Bath-Hextall 2007a

Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. *International Journal of Cancer* 2007;121(9):2105-8. [[PubMed: 17640064](#)]

Bath-Hextall 2007b

Bath-Hextall Fiona J, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD003412 DOI: 10.1002/14651858.CD003412.pub2.

Bath-Hextall 2014

Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, Miller PS, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncology* 2014;15(1):96-105. [[PubMed: 24332516](#)]

Batra 2002

Batra RS, Kelley LC. A risk scale for predicting extensive subclinical spread of nonmelanoma skin cancer. *Dermatologic Surgery* 2002;28(2):107-12; discussion 112. [[PubMed: 11860418](#)]

Belbasis 2016

Belbasis L, Stefanaki I, Stratigos AJ, Evangelou E.. Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: An umbrella review of meta-analyses. *Journal of Dermatological Science* 2016;84(3):330-339. [[PubMed: 27663092](#)]

Binder 1997

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

Boone 2012

Boone MA, Norrenberg S, Jemec GB, Del Marmol V. Imaging of basal cell carcinoma by high-definition optical coherence tomography: histomorphological correlation. A pilot study. *British Journal of Dermatology* 2012;167(4):856-64. [DOI: 10.1111/j.1365-2133.2012.11194.x; [PubMed: 22862425](#)]

Boring 1994

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

Bossuyt 2015

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *British Medical Journal* 2015;351:h5527. [[PubMed: 26511519](#)]

Cancer Research UK 2017

Cancer Research UK. Statistics by cancer type - skin cancer. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/incidence> (accessed 19 May 2017).

Carter 2013

Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. *JAMA Dermatology* 2013;149(1):35-41. [DOI: 10.1001/jamadermatol.2013.746; [PubMed: 23324754](#)]

CCAAC Network 2008

Cancer Council Australia & Australian Cancer Network. Basal Cell Carcinoma, Squamous Cell Carcinoma (and related lesions) - a guide to clinical management in Australia. www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/Basal_cell_carcinoma_Squamous_cell_carcinoma_Guid_Final_with_Corrigendums.pdf 2008 (accessed 19 May 2015).

Chao 2013

Chao D, London Cancer North and East. London Cancer, Guidelines for Cutaneous Malignant Melanoma Management August 2014. www.londoncancer.org/media/76373/london-cancer-melanoma-guidelines-2013-v1.0.pdf (accessed 25 February 2015).

Chapman 2011

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in

melanoma with BRAF V600E mutation. New England Journal of Medicine 2011;364(26):2507-16. [[PubMed: 21639808](#)]

Chapman 2012

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

Cho 2014

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

Chowdri 1996

Chowdri NA, Darzi MA. Postburn scar carcinomas in Kashmiris. Burns 1996;22(6):477-82. [[PubMed: 8884010](#)]

Chu 2006

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

Church 2001

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

D'Amico 2008

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

Dabski 1986

Dabski K, Stoll HL Jr, Milgrom H. Squamous cell carcinoma complicating late chronic discoid lupus erythematosus. Journal of Surgical Oncology 1986;32(4):233-7. [[PubMed: 3736067](#)]

De Carvalho 2018

De Carvalho N, Schuh S, Kindermann N, Kastle R, Holmes J, Welzel J. Optical coherence tomography for margin definition of basal cell carcinoma before micrographic surgery—recommendations regarding the marking and scanning technique. Skin Res Technol. 2018;24(1):145-51. [DOI: <https://doi.org/10.1111/srt.12407>; [PubMed: 29057513](#)]

Deeks 2005

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

DermNet New Zealand 2013

Clark C, Markowitz O. Optical coherence tomography. <https://www.dermnetnz.org/topics/optical-coherence-tomography> 2013;accessed 07-06-2017.

Dinnes 2018a

Dinnes J, Deeks JJ, Chuchu N, Matin RN, Wong KY, Aldridge RB, et al. Visual examination and dermoscopy, alone or in combination, for the diagnosis of keratinocyte skin cancers in adults. Cochrane Database of Systematic Reviews (in press).

Dinnes 2018b

Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, et al. Dermoscopy, with and without visual inspection, for the diagnosis of melanoma in adults. Cochrane Database of Systematic Reviews (in press).

Dinnes 2018c

Dinnes J, Deeks JJ, Grainge MJ, Chuchu N, Ferrante di Ruffano L, Matin RN, et al. Visual inspection for the diagnosis of cutaneous melanoma in adults. Cochrane Database of Systematic Reviews (in press).

Dinnes 2018d

Dinnes J, Deeks JJ, Chuchu N, Saleh D, Bayliss SE, Takwoingi Y, et al. Reflectance confocal microscopy for the diagnosis of keratinocyte skin cancers in adults. Cochrane Database of Systematic Reviews (in press).

Dinnes 2018e

Dinnes J, Deeks JJ, Saleh D, Chuchu N, Bayliss SE, Patel L, et al. Reflectance confocal microscopy for the diagnosis of cutaneous melanoma in adults. Cochrane Database of Systematic Reviews (in press).

Dinnes 2018f

Dinnes J, Bamber J, Chuchu N, Bayliss SE, Takwoingi Y, Davenport C, et al. High frequency ultrasound for the diagnosis of skin cancer in adults. Cochrane Database of Systematic Reviews (in press).

Drew 2017

Drew BA, Karia PS, Mora AN, Liang CA, Schmults CD. Treatment patterns, outcomes, and patient satisfaction of primary epidermally limited nonmelanoma skin cancer. *Dermatologic Surgery* 2017;43(12):1423-30. [DOI: 10.1097/DSS.0000000000001225; [PubMed: 28661992](#)]

Drucker 2017

Drucker A, Adam GP, Langberg V, Gazula A, Smith B, Moustafa F, Weinstock MA, Trikalinos TA. Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin. *Comparative Effectiveness Reviews*, No. 199.. Rockville (MD): Agency for Healthcare Research and Quality (US), 2017.

Dummer 2014

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

Edwards 2016

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

Efron 1983

Efron B. Estimating the error rate of a prediction rule: improvement on cross-validation. *Journal of the American Statistical Association* 1983;78(382):316-331. [DOI: 10.1080/01621459.1983.10477973]

Eggermont 2007

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

Erdmann 2013

Erdmann F, Lortet-Tieulent J, Schuz J, Zeeb H, Greinert R, Breitbart EW, et al. International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? *International Journal of Cancer* 2013; 132(2):385-400. [[PubMed: 22532371](#)]

Esteva 2017

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

EUCAN 2012

EUCAN, International Agency for Research on Cancer. Malignant melanoma of skin: Estimated incidence, mortality & prevalence for both sexes, 2012. eco.iarc.fr/eucan/Cancer.aspx?Cancer=20 (accessed 29 July 2015).

Faber 2004

Faber D, van der Meer F, Aalders M, van Leeuwen T. Quantitative measurement of attenuation coefficients of weakly scattering media using optical coherence tomography. *Optics Express* 2004;12(19):4353-65. [[PubMed: 19483984](#)]

Fasching 1989

Fasching MC, Meland NB, Woods JE, Wolff BG. Recurrent squamous-cell carcinoma arising in pilonidal sinus tract--multiple flap reconstructions. Report of a case.. *Diseases of the Colon and Rectum* 1989;32(2):153-8. [[PubMed: 2914529](#)]

Ferlay 2015

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

Ferrante di Ruffano 2018a

Ferrante di Ruffano L, Takwoingi Y, Dinnes J, Chuchu N, Bayliss SE, Davenport C, et al. Computer assisted diagnosis techniques (dermoscopy and spectroscopy-based) for the diagnosis of skin cancer in adults. *Cochrane Database of Systematic Reviews* (in press).

Ferrante di Ruffano 2018b

Ferrante di Ruffano L, Dinnes J, Chuchu N, Bayliss SE, Takwoingi Y, Davenport C, et al. Exfoliative cytology for the diagnosis of basal cell carcinoma and other skin cancers in adults. *Cochrane Database of Systematic Reviews* (in press).

Ferris 2012

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

Firnhaber 2012

Firnhaber JM. Diagnosis and treatment of basal cell and squamous cell carcinoma. American Family Physician 2012; 86(2):161-168. [[PubMed: 22962928](#)]

Fitzpatrick 1975

Fitzpatrick TB. Soleil et peau. Journal de Médecine Esthétique 1975;2:33-4.

Friedman 1985

Friedman HI, Cooper PH, Wanebo HJ. Prognostic and therapeutic use of microstaging of cutaneous squamous cell carcinoma of the trunk and extremities. Cancer 1985;56(5):1099-105. [[PubMed: 4016700](#)]

Gallagher 2008

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

Gambichler 2015b

Gambichler T, Pljakic A, Schmitz L. Recent advances in clinical application of optical coherence tomography of human skin. Clinical, Cosmetic and Investigational Dermatology 2015;8:345-354. [[PubMed: 26185462](#)]

Garbe 2016

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

Garcia 2009

Garcia C, Poletti E, Crowson AN. Basosquamous carcinoma. Journal of the American Academy of Dermatology 2009; 60(1):137-43. [[PubMed: 19103364](#)]

Gerbert 2000

Gerbert B, Bronstone A, Maurer T, Hofmann R, Berger T. Decision support software to help primary care physicians triage skin cancer: a pilot study. Archives of Dermatology 2000;136(2):187-92. [[PubMed: 10677094](#)]

Gereli 2010

Gereli MC, Onsun N, Atilganoglu U, Demirkesen C. Comparison of two dermoscopic techniques in the diagnosis of clinically atypical pigmented skin lesions and melanoma: seven-point and three-point checklists. International Journal of Dermatology 2010;49(1):33-8. [[PubMed: 20465608](#)]

Gershenwald 2017

Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: A Cancer Journal for Clinicians 2017; 67(6):472-492. [DOI: 10.3322/caac.21409]

Gordon 2013

Gordon R. Skin cancer: an overview of epidemiology and risk factors. Seminars in Oncology Nursing 2013;29(3):160-9. [[PubMed: 23958214](#)]

Gorlin 2004

Gorlin RJ. Nevroid basal cell carcinoma (Gorlin) syndrome. Genetics in Medicine 2004;6(6):530-9. [[PubMed: 15545751](#)]

Grachtchouk 2011

Grachtchouk M, Pero J, Yang SH, Ermilov AN, Michael LE, Wang A, et al. Basal cell carcinomas in mice arise from hair follicle stem cells and multiple epithelial progenitor populations. Journal of Clinical Investigation 2011;121(5):1768-81. [[PubMed: 21519145](#)]

Green 1988

Green A, Leslie D, Weedon D. Diagnosis of skin cancer in the general population: clinical accuracy in the Nambour survey. Medical Journal of Australia 1988;148(9):447-50. [[PubMed: 3283506](#)]

Griffin 2016

Griffin LL, Ali FR, Lear JT. Non-melanoma skin cancer. Clinical Medicine 2016;16(1):62-65. [[PubMed: 26833519](#)]

Griffiths 2005

Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? British Journal of Plastic Surgery 2005;58(6):795-805. [[PubMed: 16086990](#)]

Grob 1998

Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis

for melanoma screening. Archives of Dermatology 1998;134(1):103-4. [[PubMed: 9449921](#)]

Haenssle 2010

Haenssle HA, Korpas B, Hansen-Hagge C, Buhl T, Kaune KM, Rosenberger A, et al. Seven-point checklist for dermoscopy: performance during 10 years of prospective surveillance of patients at increased melanoma risk. Journal of the American Academy of Dermatology 2010;62(5):785-93. [[PubMed: 20226567](#)]

Hamid 2013

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

Hartevelt 1990

Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990;49(3):506-9. [[PubMed: 2316011](#)]

Hauschild 2014

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

Hodi 2010

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

Hodi 2016

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

Hoorens 2016

Hoorens I, Vossaert K, Pil L, Boone B, De Schepper S, Ongenaes K, et al. Total-body examination vs lesion-directed skin cancer screening. JAMA Dermatology 2016;152(1):27-34. [[PubMed: 26466155](#)]

HPA and MelNet NZ 2014

Health Promotion Agency and the Melanoma Network of New Zealand (MelNet). New Zealand Skin Cancer Primary Prevention and Early Detection Strategy 2014 to 2017. www.sunsmart.org.nz/sites/default/files/documents/NZ%20Skin%20Cancer%20PrimaryPrevention%20and%20EarlyDetection (accessed 29 May 2018).

Jansen 2018

Jansen MHE, Mosterd K, Arits AHMM, Roozeboom MH, Sommer A, Essers BAB, et al. Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod, and topical 5-fluorouracil in patients with superficial basal cell carcinoma. Journal of Investigative Dermatology 2018;138(3):527-33. [DOI: 10.1016/j.jid.2017.09.033; [PubMed: 29045820](#)]

Jensen 1999

Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. Journal of the American Academy of Dermatology 1999;40(2 Pt 1):177-86. [[PubMed: 10025742](#)]

Kao 1986

Kao GF. Carcinoma arising in Bowen's disease. Archives of Dermatology 1986;122(10):1124-6. [[PubMed: 3767398](#)]

Kasprzak 2015

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

Kelleners-Smeets 2017

Kelleners-Smeets NW, Mosterd K, Nelemans PJ. Treatment of low-risk basal cell carcinoma. Journal of Investigative Dermatology 2017;137(3):539-40. [[PubMed: 28235442](#)]

Khandwala 2010

Khandwala M, Penmetsa BR, Dey S, Schofield JB, Jones CA, Podoleanu A. Imaging of periocular basal cell carcinoma using en face optical coherence tomography: a pilot study. British Journal of Ophthalmology 2010;94(10):1332-6. [[PubMed: 20516143](#)]

Kim 2014

Kim DD, Tang JY, Ioannidis JP. Network geometry shows evidence sequestration for medical vs. surgical practices: treatments for basal cell carcinoma. *Journal of Clinical Epidemiology* 2014;67(4):391-400. [[PubMed: 24491794](#)]

Kittler 2002

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

Kittler 2011

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

Kwak 2013

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

Kyrgidis 2015

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

Lansbury 2010

Lansbury L, Leonardi-Bee J, Perkins W, Goodacre T, Tweed JA, Bath-Hextall FJ. Interventions for non-metastatic squamous cell carcinoma of the skin. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: CD007869 DOI: 10.1002/14651858.CD007869.pub2.

Lansbury 2013

Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ* 2013;347:f6153. [[PubMed: 24191270](#)]

Larkin 2014

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

Larkin 2015

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

Lear 1997

Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, et al. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *Journal of the Royal Society of Medicine* 1997;90(7):371-4. [[PubMed: 9290417](#)]

Lear 2012

Lear JT. Oral hedgehog-pathway inhibitors for basal-cell carcinoma. *New England Journal of Medicine* 2012;366(23):2225-6. [[PubMed: 22670909](#)]

Lear 2014

Lear JT, Corner C, Dziewulski P, Fife K, Ross GL, Varma S, et al. Challenges and new horizons in the management of advanced basal cell carcinoma: a UK perspective. *British Journal of Cancer* 2014;111(8):1476-81. [DOI: 10.1038/bjc.2014.270; [PubMed: 25211660](#)]

Leff 2008

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

Linos 2009

Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. *Journal of Investigative Dermatology* 2009;129(7):1666-74. [[PubMed: 19131946](#)]

Lister 1997

Lister RK, Black MM, Calonje E, Burnand KG. Squamous cell carcinoma arising in chronic lymphoedema. *British Journal of Dermatology* 1997;136(3):384-7. [[PubMed: 9115922](#)]

Lo 1991

Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a

review of the literature. Journal of the American Academy of Dermatology 1991;24(5 Pt 1):715-9. [[PubMed: 1869642](#)]

Lomas 2012

Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. British Journal of Dermatology 2012;166(5):1069-80. [[PubMed: 22251204](#)]

London Cancer Alliance 2013

London Cancer Alliance. Guidelines for the Treatment and Referral of Squamous Cell Carcinoma (SCC) of the Skin. Vol. 1.0. www.londoncancer.org/media/76391/london-cancer-scc-guidelines-2013-v1.0.pdf (accessed prior to 2 October 2017).

Mackie 1990

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

Madan 2010

Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375(9715):673-85. [[PubMed: 20171403](#)]

Maia 1995

Maia M, Proenca NG, de Moraes JC. Risk factors for basal cell carcinoma: a case-control study. Revista de Saude Publica 1995;29(1):27-37. [[PubMed: 8525311](#)]

Maio 2015

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

Maley 2014

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

Maloney 1996

Maloney ME. Arsenic in Dermatology. Dermatologic Surgery 1996;22(3):301-4. [[PubMed: 8599743](#)]

Malveyh 2002

Malveyh J, Puig S. Follow-up of melanocytic skin lesions with digital total-body photography and digital dermoscopy: a two step method. Clinics in Dermatology 2002;20(3):297-304. [[PubMed: 12074871](#)]

Malveyh 2014

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

Marghoob 2010

Marghoob AA, Braun R. Proposal for a revised 2-step algorithm for the classification of lesions of the skin using dermoscopy. Archives of Dermatology 2010;146(4):426-428. [[PubMed: 20404234](#)]

Marghoob 2012

Marghoob AA, Malveyh J, Braun R, eds. An Atlas of Dermoscopy.. London: Informa Healthcare, 2012.

Marsden 2010

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

McCormack 1997

McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Archives of Dermatology 1997;133(5):593-6. [[PubMed: 9158412](#)]

McCusker 2014

McCusker M, Basset-Seguín N, Dummer R, Lewis K, Schadendorf D, Sekulic A, et al. Metastatic basal cell carcinoma: Prognosis dependent on anatomic site and spread of disease. European Journal of Cancer 2014;50(4):774-83. [[PubMed: 24412051](#)]

Menzies 1996

Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Archives of Dermatology 1996;132(10):1178-82. [[PubMed: 8859028](#)]

Menzies 2000

Menzies SW, Westerhoff K, Rabinovitz H, Kopf AW, McCarthy WH, Katz B. Surface microscopy of pigmented basal cell carcinoma. Archives of Dermatology 2000;136(8):1012-1016. [[PubMed: 10926737](#)]

Mistry 2011

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

Mocellin 2013

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

Moeckelmann 2018

Moeckelmann N, Ebrahimi A, Dirven R, Liu J, Low TH, Gupta R, et al. Analysis and comparison of the 8th Edition American Joint Committee on Cancer (AJCC) nodal staging system in cutaneous and oral squamous cell cancer of the head and neck. *Annals of Surgical Oncology* 2018;25(6):1730-6. [DOI: 10.1245/s10434-018-6340-x; [PubMed: 29352431](#)]

Moncrieff 2002

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

Monheit 2011

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

Moreau 2013

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

Morton 2014

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

Motley 2009

Motley RJ, Preston PW, Lawrence CM. Multi-professional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. www.bad.org.uk/shared/get-file.ashx?id=59&itemtype=document (accessed 24 August 2017).

Musah 2013

Musah A, Gibson JE, Leonardi-Bee J, Cave MR, Ander EL, Bath-Hextall F. Regional variations of basal cell carcinoma incidence in the U.K. using The Health Improvement Network database (2004-10). *British Journal of Dermatology* 2013; 169(5):1093-9. [[PubMed: 23701520](#)]

Nachbar 1994

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

Nart 2015

Nart IF, Armayones SG, Medina FV, Orti MB, Orpinell XB. Basal cell carcinoma treated with ingenol mebutate. *Journal of the American Academy of Dermatology* 2015;5(Suppl 1):AB180.

Navarrete-Dechent 2016

Navarrete-Dechent C, Bajaj S, Marchetti MA, Rabinovitz H, Dusza SW, Marghoob AA. Association of shiny white blotches and strands with nonpigmented basal cell carcinoma: evaluation of an additional dermoscopic diagnostic criterion. *JAMA Dermatology* 2016;152(5):546-552. [[PubMed: 26792406](#)]

NICE 2010

National Institute of Clinical Excellence. NICE Guidance on Cancer Services. Improving outcomes for people with skin tumours including melanoma (update). www.nice.org.uk/guidance/csgstim (accessed 19 May 2015).

NICE 2012a

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

NICE 2012b

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

NICE 2014a

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

NICE 2014b

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

NICE 2015a

National Collaborating Centre for Cancer. Melanoma: assessment and management. www.nice.org.uk/guidance/ng14 (accessed prior to 2 October 2017).

NICE 2015b

National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral. www.nice.org.uk/guidance/ng12 (accessed prior to 2 October 2017).

NICE 2015c

National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral. www.nice.org.uk/guidance/ng12 (accessed prior to 2 October 2017).

NICE 2015d

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

NICE 2016a

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

NICE 2016b

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

NICE 2017

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

Norman 2009

Norman G, Barraclough K, Dolovich L, Price D. Iterative diagnosis. *BMJ* 2009;339:b3490. [[PubMed: 19773326](https://pubmed.ncbi.nlm.nih.gov/19773326/)]

O'Gorman 2014

O'Gorman SM, Murphy GM. Photosensitizing medications and photocarcinogenesis. *Photodermatology, Photoimmunology & Photomedicine* 2014;30(1):8-14. [[PubMed: 24393207](https://pubmed.ncbi.nlm.nih.gov/24393207/)]

Offidani 2002

Offidani A, Simonetti O, Bernardini M L, Alpagut A, Cellini A, Bossi G. General practitioners' accuracy in diagnosing skin cancers. *Dermatology* 2002;205(2):127-30. [[PubMed: 12218226](https://pubmed.ncbi.nlm.nih.gov/12218226/)]

Pasquali 2014

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

Pasquali 2018

Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD011123 DOI: 10.1002/14651858.CD011123.pub2.

Pehamberger 1987

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

Powell 2000

Powell CR, Menon G, Harris AJ. Cytological examination or basal cell carcinoma - a useful tool for diagnosis? *British Journal of Dermatology* 2000;143(Suppl. 57):71.

Rajpara 2009

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

Randle 1996

Randle HW. Basal cell carcinoma. Identification and treatment of the high-risk patient. *Dermatologic Surgery* 1996; 22(3):255-61. [[PubMed: 8599737](#)]

Reitsma 2005

Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology* 2005;58(10):982-90. [[PubMed: 16168343](#)]

Roozeboom 2012

Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and nonrandomized trials. *British Journal of Dermatology* 2012;167(4):733-56. [[PubMed: 22612571](#)]

Roozeboom 2016

Roozeboom MH, Arits AH, Mosterd K, Sommer A, Essers BA, de Rooij MJ, et al. Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. *Journal of Investigative Dermatology* 2016;136(8):1568-74. [[PubMed: 27113429](#)]

Rutjes 2005

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

Sabban 2004

Sabban F, Collinet P, Cosson M, Mordon S. Fluorescence imaging technique: diagnostic and therapeutic interest in gynecology. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 2004;33(8):734-8. [[PubMed: 15687945](#)]

Segura 2009

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

Sekulic 2012

Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *New England Journal of Medicine* 2012;366(23):2171-9. [[PubMed: 22670903](#)]

Shaikh 2012

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

Siegel 2015

Siegel R, Miller K, Jemal A. Cancer statistics, 2015. *CA: a Cancer Journal for Clinicians* 2014;65(1):5-29. [[PubMed: 25559415](#)]

SIGN 2017

Scottish Intercollegiate Guidelines Network. Cutaneous Melanoma. www.sign.ac.uk/assets/sign146.pdf (accessed prior to 2 October 2017).

Sladden 2009

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

Slater 2014

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

Sober 1979

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

Steiner 1987

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

Stolz 1994

Stolz W, Riemann A, Cognetta AB, Pillet L, Abmayer W, Holzel D, et al. ABCD rule of dermatoscopy: A new practical method for early recognition of malignant melanoma. *European Journal of Dermatology* 1994;4(7):521-7. [EMBASE: 24349113]

Stratigos 2015

Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *European Journal of Cancer* 2015;51(14):1989-2007. [[PubMed: 26219687](#)]

Sznol 2013

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

Takwoingi 2017

Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. *Statistical Methods in Medical Research* 2017;26(4):1896-1911. [[PubMed: 26116616](#)]

Tang 2012

Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *New England Journal of Medicine* 2012;366(23):2180-8. [[PubMed: 22670904](#)]

Themstrup 2015

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

Thomas 1998

Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology* 1998;197(1):11-7. [[PubMed: 9693179](#)]

van Loo 2014

van Loo E, Mosterd K, Krekels GA, Roozeboom MH, Ostertag JU, Dirksen CD, et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up. *European Journal of Cancer* 2014;50(17):3011-20. [[PubMed: 25262378](#)]

Verkouteren 2017

Verkouteren JAC, Ramdas KHR, Wakkee M, Nijsten T. Epidemiology of basal cell carcinoma: scholarly review. *British Journal of Dermatology* 2017;177(2):359-72. [DOI: 10.1111/bjd.15321.; [PubMed: 28220485](#)]

Villanueva 2010

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

Vogt 2003

Vogt M, Knüttel A, Hoffmann K, Altmeyer P, Ermer H. Comparison of high frequency ultrasound and optical coherence tomography as modalities for high resolution and non invasive skin imaging. *Biomedizinische Technik. Biomedical Engineering* 2003;48(5):116-21. [[PubMed: 12838793](#)]

Von Hoff 2009

Von Hoff DD, LoRusso PM, Rudin CM, Reddy JC, Yauch RL, Tibes R, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *New England Journal of Medicine* 2009;361(12):1164-72. [DOI: 10.1056/NEJMoa0905360; [PubMed: 19726763](#)]

Wachsman 2011

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

Walker 2006

Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. *Australasian Journal of Dermatology* 2006;47(1):1-12. [[PubMed: 16405477](#)]

Walter 2012

Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: randomised controlled trial. *BMJ* 2012;345:e4110. [[PubMed: 22763392](#)]

Wells 2012

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

Welzel 1997

Welzel J, Lankenau E, Birngruber R, Engelhardt R. Optical coherence tomography of the human skin. *Journal of the American Academy of Dermatology* 1997;37(6):958-63. [[PubMed: 9418764](#)]

Whiting 2011

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

WHO 2003

World Health Organization. INTERSUN: The Global UV Project. A guide and compendium. www.who.int/uv/publications/en/Intersunguide.pdf (accessed 20 May 2015).

Williams 1989

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

Williams 2017

Williams HC, Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, et al. Surgery Versus Imiquimod for Nodular and Superficial Basal Cell Carcinoma (SINS) Study Group. Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial. *Journal of Investigative Dermatology* 2017; 137(3):614-9. [[PubMed: 27932240](#)]

Zak-Prelich 2004

Zak-Prelich M, Narbutt J, Sysa-Jedrzejowska A. Environmental risk factors predisposing to the development of basal cell carcinoma. *Dermatologic Surgery* 2004;30(2 Pt 2):248–252. [[PubMed: 14871217](#)]

Zemelman 2014

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

Zhao 2008

Zhao J, Lui H, McLean DI, Zeng H. Real-time Raman spectroscopy for non-invasive skin cancer detection - preliminary results. In: 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2008:3107-9. [DOI: 10.1109/IEMBS.2008.4649861]

Other published versions of this review

Dinnes 2015a

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

Dinnes 2015b

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

Classification pending references

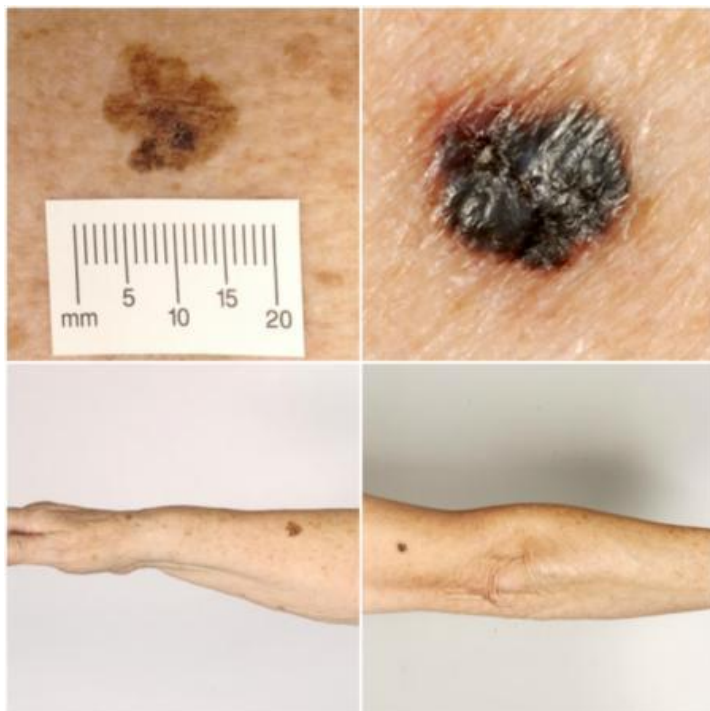
Data and analyses

Data tables by test

Test	Studies	Participants
1 OCT Attenuation coefficient 5.4mm^{-1} (MM+Mis)	1	40
2 HD-OCT Gambichler score ≥ -1 (MM+Mis)	1	93
3 HD-OCT - Gambichler score ≥ -1 (MM)	1	93
4 OCT observer diagnosis (BCC)	2	346
5 VI observer diagnosis (BCC)	2	346
6 Dermoscopy observer diagnosis (BCC)	2	346
7 OCT Berlin score ≥ 8 (BCC)	1	50
8 OCT Berlin score ≥ 12 (BCC)	1	50
9 OCT Berlin score ≥ 8 (cSCC)	1	50
10 OCT Berlin score ≥ 12 (cSCC)	1	50

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)

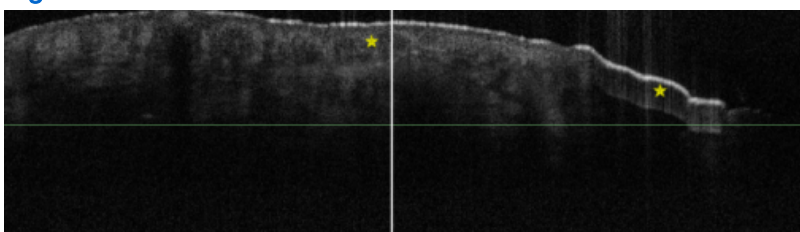
Figure 3



Caption

Swept-source Optical Coherence Tomography scanner (Michelson Diagnostics VivoSight Rx). **Copyright © 2017 Rakesh Patalay; reproduced with permission.**

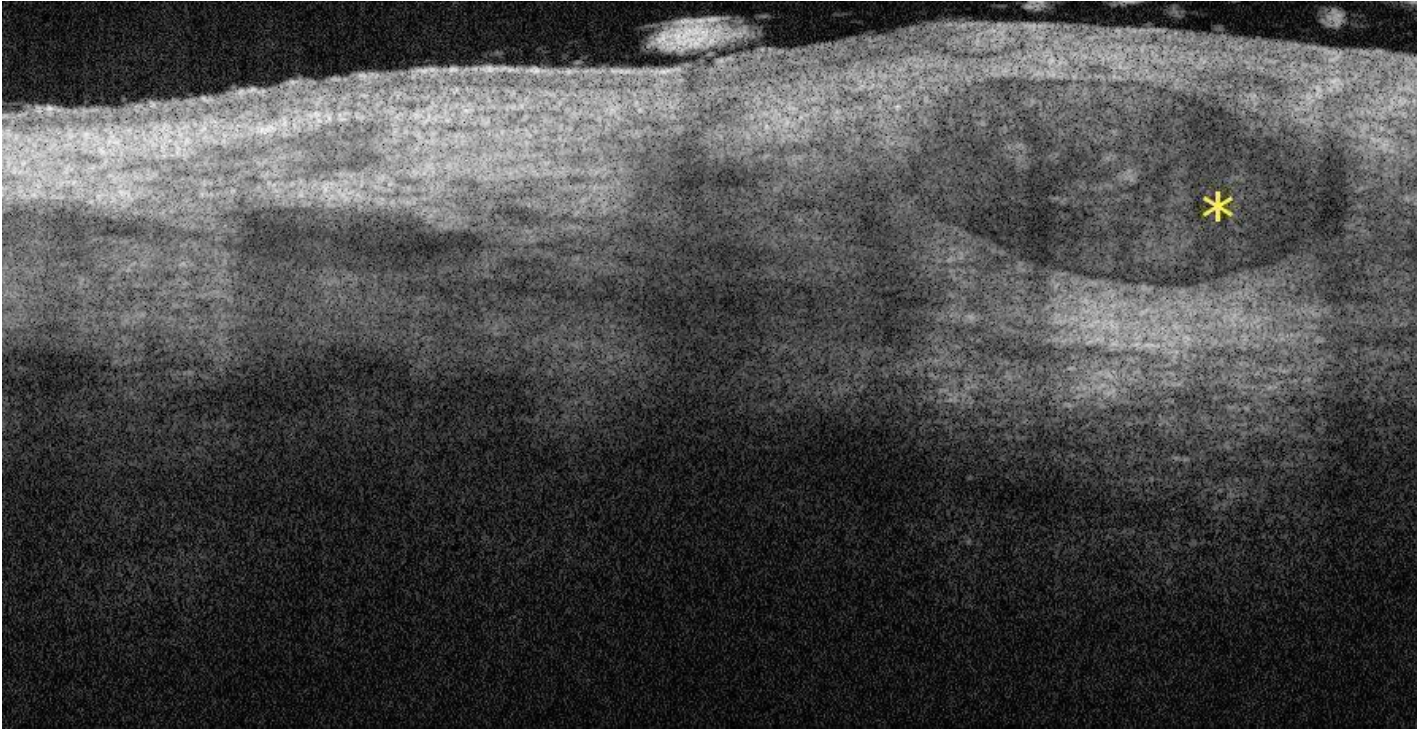
Figure 4



Caption

OCT image of a 7mm BCC on the cheek showing several BCC cell nests (left hand star is above and to the left of a BCC nest) and the position of the 2mm margin as drawn with a reflective ink pen (right hand star). The ink pen gives the appearance of increased reflectivity in the epidermis, and causes a fine vertical linear interference of the OCT signal of the skin, giving a unique OCT signature. In this case, the interference is also seen to mask the OCT signal from the dermis under the pen mark. **Copyright © 2017 Rakesh Patalay; reproduced with permission.**

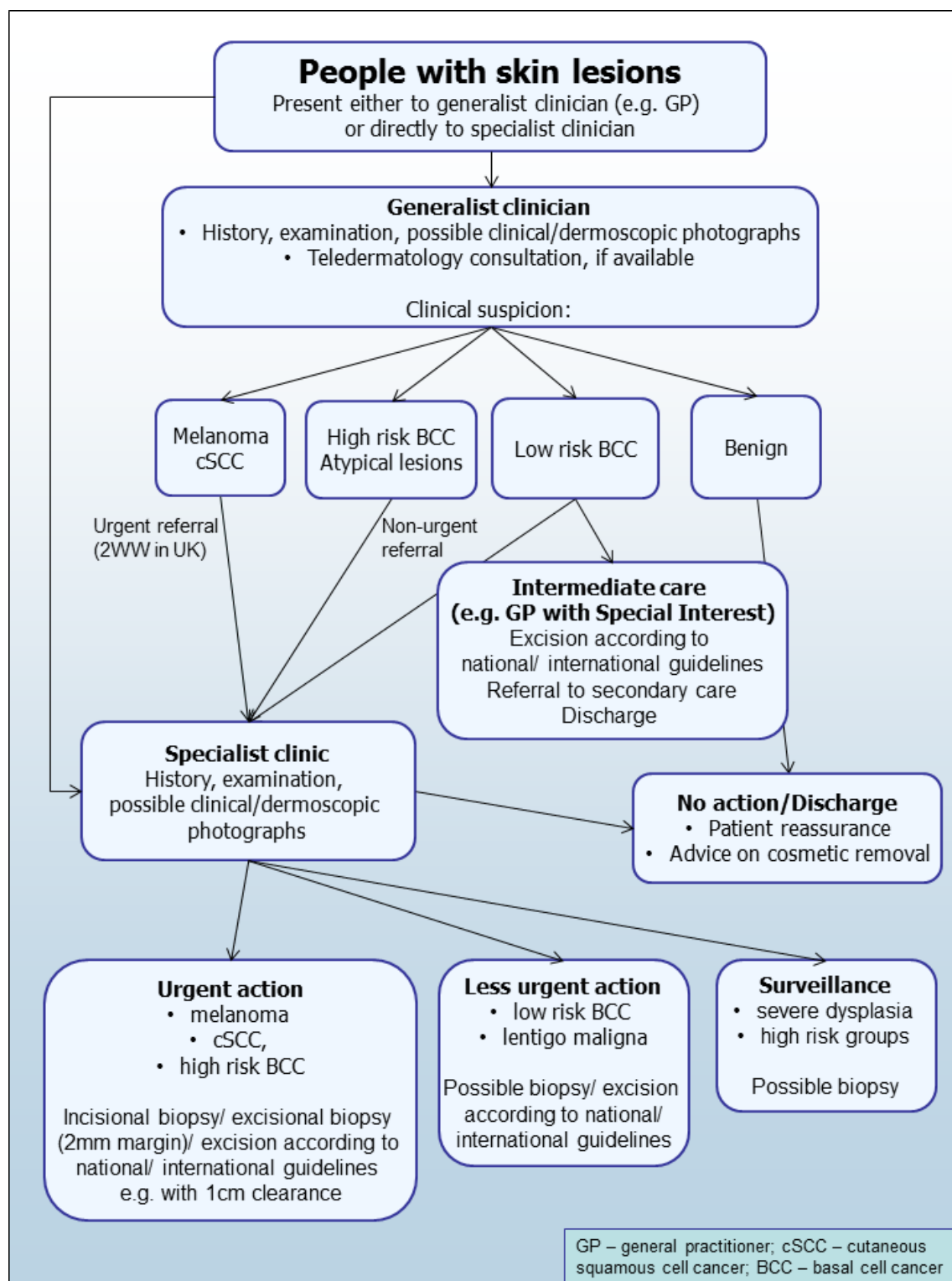
Figure 5



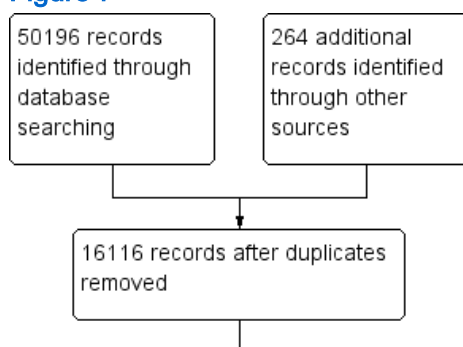
Caption

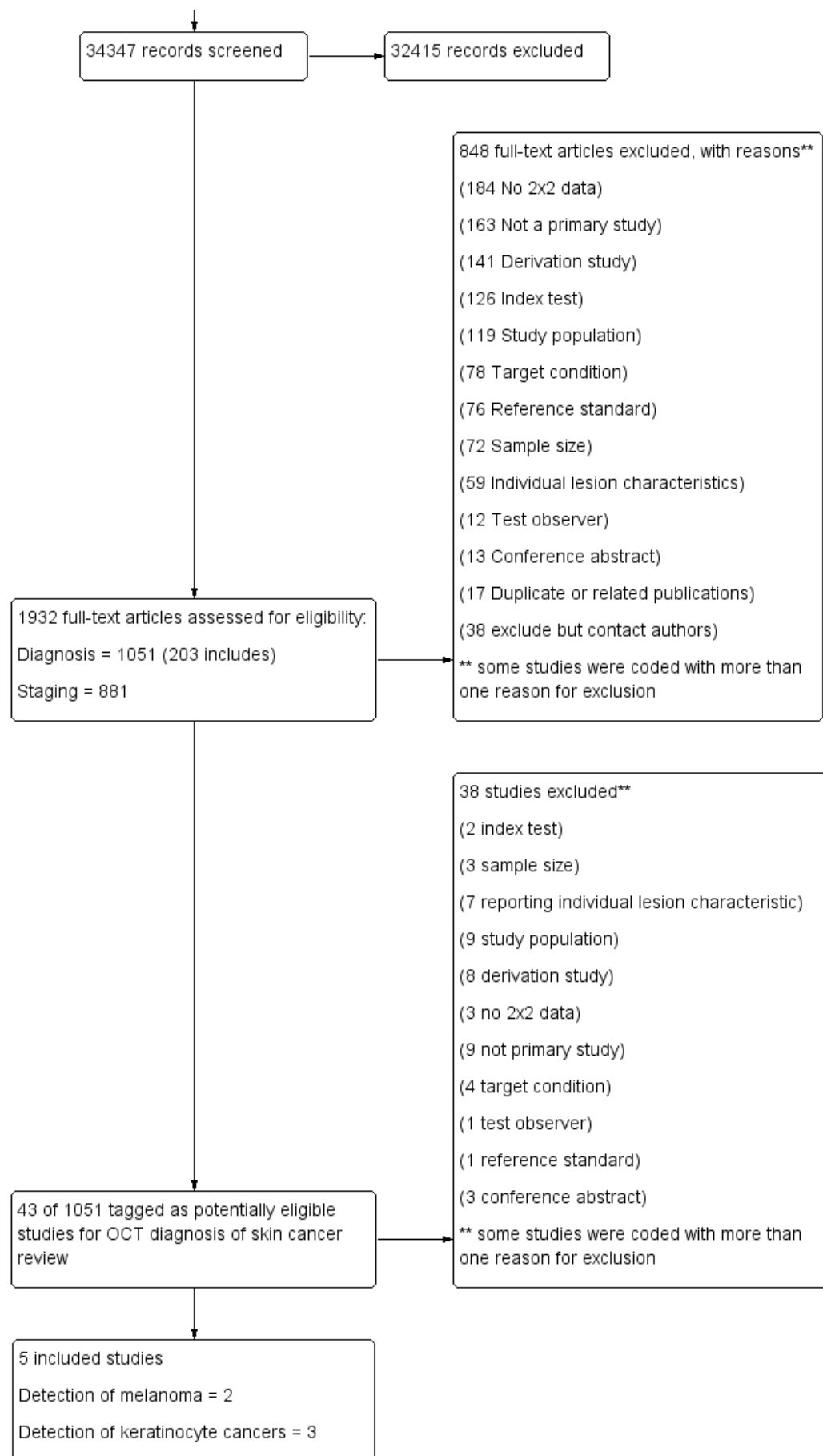
OCT image of a nodular BCC showing a basal nest centrally (star). The Dark halo appearance is due to a cleft region fully encompassing the nest and the presence of peripheral palisading. **Copyright © 2018 Michelson Diagnostics / Vivosight**

Figure 6

**Caption**

Current clinical pathway for people with skin lesions

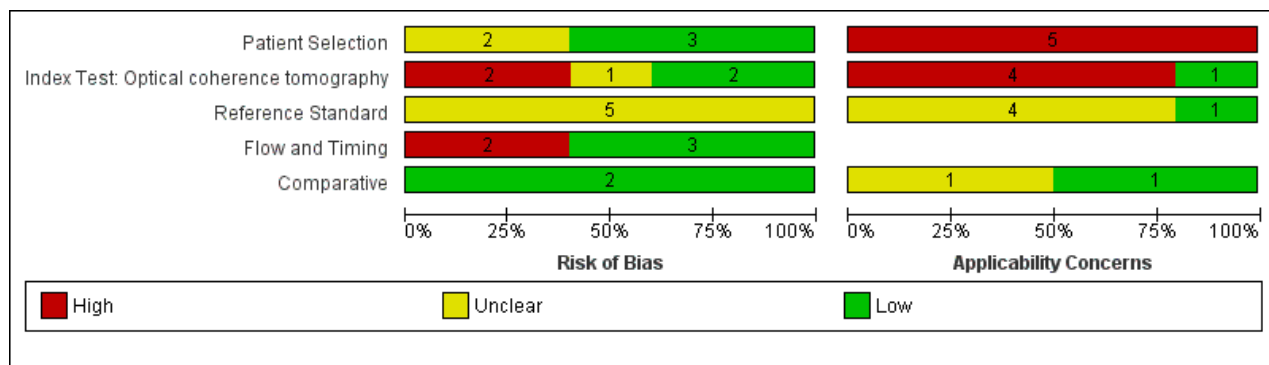
Figure 7



Caption

PRISMA flow diagram.

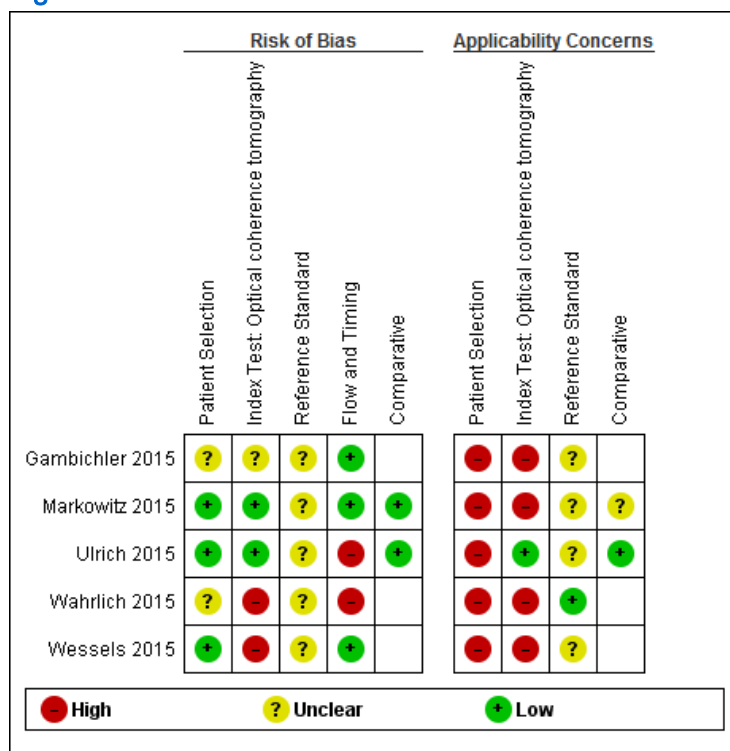
Figure 8



Caption

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

Figure 9



Caption

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

Figure 10 (Analysis 1)

OCT Attenuation coefficient 5.4mm-1 (MM+Mis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wessels 2015	8	12	1	19	0.89 [0.52, 1.00]	0.61 [0.42, 0.78]		

HD-OCT Gambichler score ≥ -1 (MM+Mis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gambichler 2015	20	5	7	61	0.74 [0.54, 0.89]	0.92 [0.83, 0.97]		

HD-OCT - Gambichler score ≥ -1 (MM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gambichler 2015	20	5	5	63	0.80 [0.59, 0.93]	0.93 [0.84, 0.98]		

OCT Berlin score ≥ 8 (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	28	5	1	16	0.97 [0.82, 1.00]	0.76 [0.53, 0.92]		

OCT Berlin score ≥ 12 (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	19	3	10	18	0.66 [0.46, 0.82]	0.86 [0.64, 0.97]		

OCT Berlin score ≥ 8 (cSCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	5	0	4	41	0.56 [0.21, 0.86]	1.00 [0.91, 1.00]		

OCT Berlin score ≥ 12 (cSCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	3	0	6	41	0.33 [0.07, 0.70]	1.00 [0.91, 1.00]		

Caption

Forest plot of threshold data that could not be pooled for the diagnosis of melanoma and atypical intraepidermal melanocytic variants (MM + Mis), invasive melanoma alone (MM), basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

Figure 11 (Analysis 2)**VI observer diagnosis (BCC)**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Markowitz 2015	44	23	26	22	0.63 [0.50, 0.74]	0.49 [0.34, 0.64]		
Ulrich 2015	126	65	14	26	0.90 [0.84, 0.94]	0.29 [0.20, 0.39]		

Dermoscopy observer diagnosis (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Markowitz 2015	55	20	15	25	0.79 [0.67, 0.87]	0.56 [0.40, 0.70]		
Ulrich 2015	126	42	13	50	0.91 [0.85, 0.95]	0.54 [0.44, 0.65]		

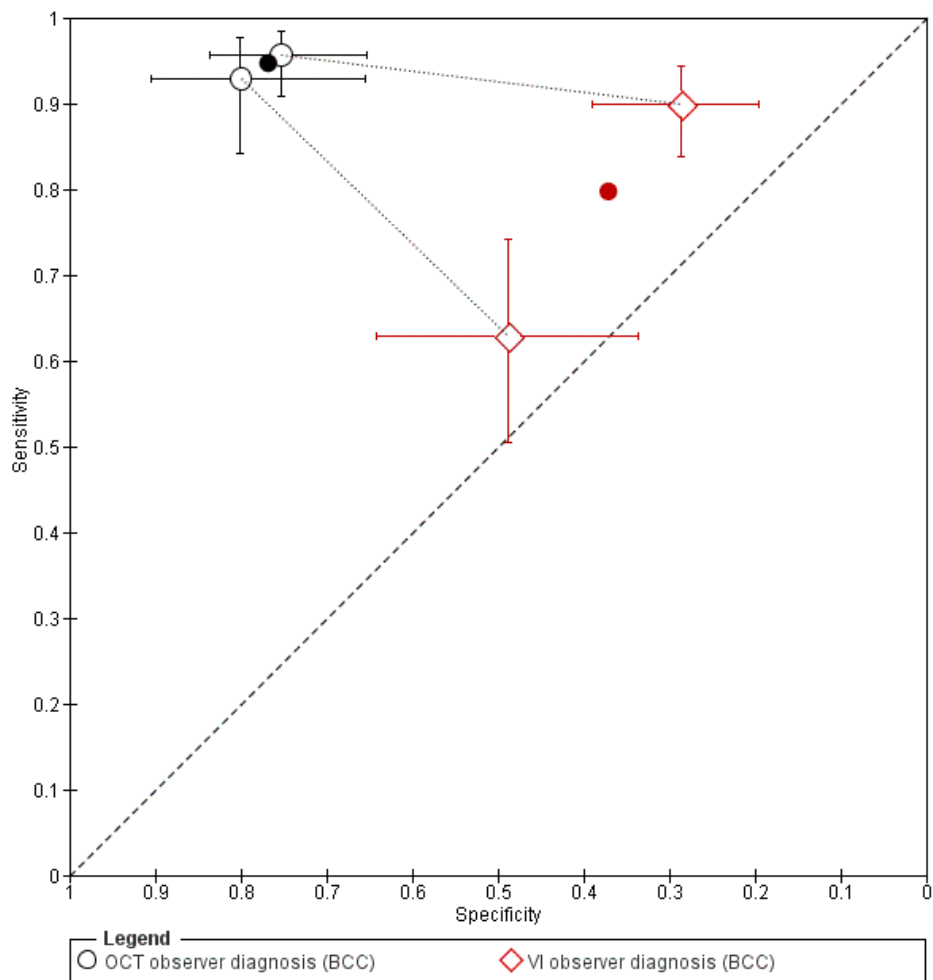
OCT observer diagnosis (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Markowitz 2015	65	9	5	36	0.93 [0.84, 0.98]	0.80 [0.65, 0.90]		
Ulrich 2015	132	23	6	70	0.96 [0.91, 0.98]	0.75 [0.65, 0.84]		

Caption

Forest plot of tests: Pooled data for the detection of basal cell carcinoma (BCC) using Visual inspection (VI), Dermoscopy, and optical coherence tomography (OCT).

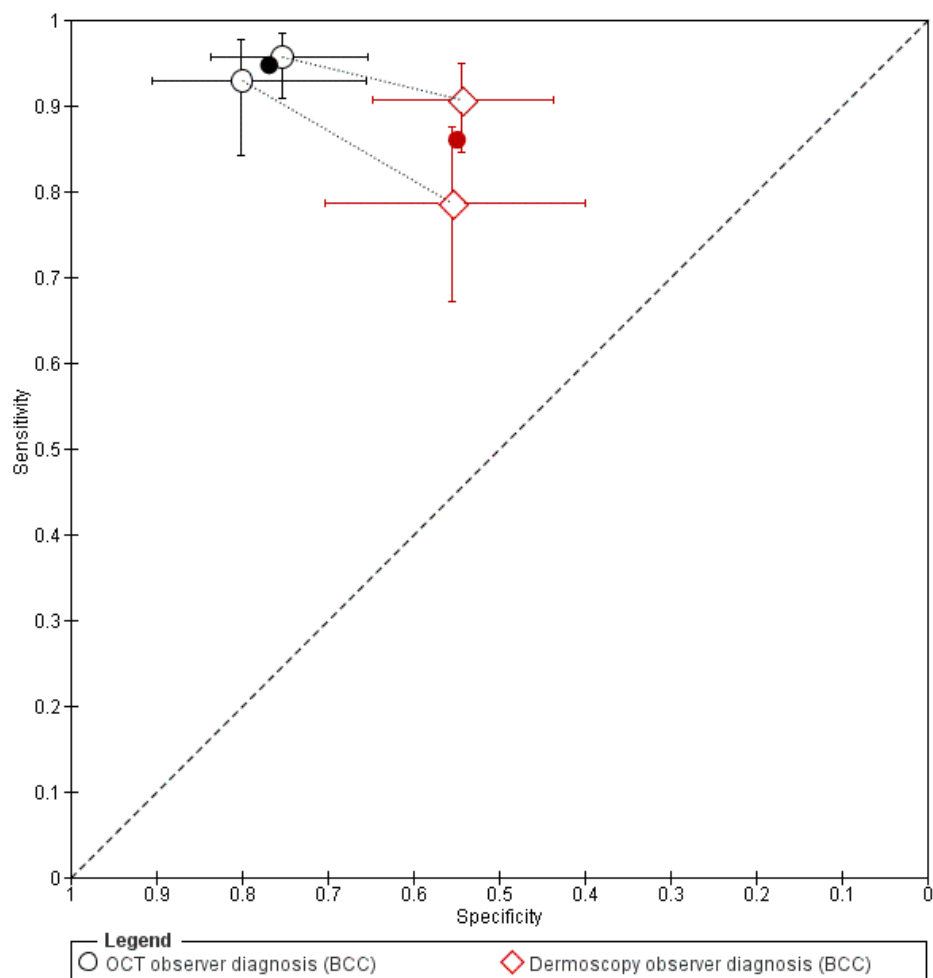
Figure 12 (Analysis 3)



Caption

Summary ROC Plot of studies comparing optical coherence tomography (OCT) and visual inspection (VI) for the detection of basal cell carcinoma (BCC).

Figure 13 (Analysis 4)



Caption

Summary ROC Plot of studies comparing optical coherence tomography (OCT) and dermoscopy for the detection of basal cell carcinoma (BCC)

Sources of support

Internal sources

- No sources of support provided

External sources

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

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. <i>Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination</i>	–
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. <i>Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination</i>	–
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. <i>Overview: comparing the accuracy of tests for which sufficient evidence was identified either alone or in combination</i>	–
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 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 nmisc.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 keratinocyt\$.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\$.ti,ab.
- 76 volatile organic compound\$.ti,ab.
- 77 dog\$.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 csc).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 nmisc

S9 TX BCC or cscs 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 (nmisc or BCC or NMISC or keratinocyt*)

#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#8 (skin or epiderm* or cutaneous)

#9 #8 AND #7

#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))

#12 ((nevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))

#13 #11 or #12

#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))

#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))

#16 #14 AND #15

#17 #16 OR #13

#18 #10 AND #17

Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

3 Full text inclusion criteria

The title and abstract screening will lead to the retrieval of a large number of full text journal papers and conference abstracts from which to populate the four sets of test accuracy reviews and the intervention review. The systematic reviews will largely

be carried out sequentially, beginning with the reviews of tests for melanoma diagnosis; however, the full text papers need to be screened at the beginning of the Programme Grant and papers meeting the inclusion criteria tagged accordingly per review.

The table below summarises the inclusion criteria to be applied; these will be transferred to an Excel spreadsheet or Google Forms so that pertinent information can be recorded about each eligible study and reasons for exclusion recorded about each ineligible study.

Criterion	Inclusion	Exclusion
Study design	<p><u>For diagnostic and staging reviews</u></p> <ul style="list-style-type: none"> Any study for which a 2×2 contingency table can be extracted, e.g. <ul style="list-style-type: none"> 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) 	<ul style="list-style-type: none"> < 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	<ul style="list-style-type: none"> Melanoma Keratinocyte skin cancer (or non-melanoma skin cancer) <ul style="list-style-type: none"> BCC or epithelioma cSCC 	<ul style="list-style-type: none"> Studies exclusively conducted in children Studies of non-cutaneous melanoma or SCC
Population	<p><u>For diagnostic reviews</u></p> <ul style="list-style-type: none"> 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 <p><u>For staging reviews</u></p> <ul style="list-style-type: none"> Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both 	<ul style="list-style-type: none"> People suspected of other forms of skin cancer Studies conducted exclusively in children

Criterion	Inclusion	Exclusion
Index tests	<p><u>For diagnosis</u></p> <ul style="list-style-type: none"> • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscropy • 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 <p><u>For staging</u></p> <ul style="list-style-type: none"> • CT • PET • PET-CT • MRI • Ultrasound +/-fine needle aspiration cytology FNAC • SLNB +/-high frequency ultrasound • Other <p>Any test combination and in any order</p> <p>Any test positivity threshold</p> <p>Any variation in testing procedure (e.g. radioisotope used)</p>	<ul style="list-style-type: none"> • 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
Reference standard	<p><u>For diagnostic studies</u></p> <ul style="list-style-type: none"> • 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) <p><u>For studies of imaging tests for staging</u></p> <ul style="list-style-type: none"> • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above <p><u>For studies of SLNB accuracy for staging</u></p> <ul style="list-style-type: none"> • 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 <i>previously investigated</i> nodal basin 	<p><u>For diagnostic studies</u></p> <ul style="list-style-type: none"> • 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.

4 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?	<p>Yes – if paper states consecutive or random</p> <p>No – if paper describes other method of sampling</p> <p>Unclear – if participant sampling not described</p>

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
2) Was a case-control design avoided?	<p>Yes – if consecutive or random or case-control design clearly not used</p> <p>No – if study described as case-control or describes sampling specific numbers of participants with particular diagnoses</p> <p>Unclear – if not described</p>
3) Did the study avoid inappropriate exclusions?	<p>Yes – if inappropriate exclusions were avoided</p> <p>No – if lesions were excluded that might affect test accuracy, e.g. where disagreement between evaluators was observed</p> <p>Unclear – if not clearly reported</p>
4) For between-person comparative studies only (i.e. allocating different tests to different study participants):	<p>For A)</p> <ul style="list-style-type: none"> 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 <p>For B)</p> <ul style="list-style-type: none"> 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 <p>For C)</p> <ul style="list-style-type: none"> 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
<p>Could the selection of participants have introduced bias?</p> <p>For non-comparative and within-person comparative studies</p> <ol style="list-style-type: none"> If answers to all of questions 1), 2), and 3) 'Yes': If answers to any 1 of questions 1), 2), or 3) 'No': If answers to any 1 of questions 1), 2), or 3) 'Unclear': <p>For between-person comparative studies</p> <ol style="list-style-type: none"> If answers to all of questions 1), 2), 3), and 4) 'Yes': If answers to any 1 of questions 1), 2), 3), or 4) 'No': If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear': 	<p>For non-comparative and within-person comparative studies</p> <ol style="list-style-type: none"> Risk is low Risk is high Risk unclear <p>For between-person comparative studies</p> <ol style="list-style-type: none"> Risk is low Risk is high Risk unclear
PARTICIPANT SELECTION (1) - CONCERNS REGARDING APPLICABILITY	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
<p>1) Are the included participants and chosen study setting appropriate to answer the review question, i.e. are the study results generalisable?</p> <p>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.</p>	<p>A) For studies that will contribute to the analysis of participants with suspected melanoma</p> <p>Yes – if study participants appear to be representative of those who might be referred for further investigation. Studies focussing on participant populations with equivocal findings on clinical and/or dermoscopic investigation are considered representative of those who could receive OCT in practice.</p> <p>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 co-morbidity, setting of the study, and previous testing protocols</p> <p>Unclear – if insufficient details are provided to determine the generalisability of study participants</p> <p>B) For studies that will contribute to the analysis of participants with suspected keratinocyte cancers</p> <p>Yes – if study participants appear to be representative of those who might be referred for further investigation. Studies focussing on participant populations with equivocal findings on clinical and/or dermoscopic investigation are considered representative of those who could receive OCT in practice.</p> <p>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 co-morbidity, setting of the study, and previous testing protocols</p> <p>Unclear – if insufficient details are provided to determine the generalisability of study participants</p>
2) Did the study avoid including participants with multiple lesions?	<p>Yes – if the difference between the number of included lesions and number of included participants is less than 5%</p> <p>No – if the difference between the number of included lesions and number of included participants is greater than 5%</p> <p>Unclear – if it is not possible to assess</p>
<p>Is there concern that the included participants do not match the review question?</p> <p>1. If the answer to question 1) or 2) 'Yes':</p> <p>2. If the answer to question 1) or 2) 'No':</p> <p>3. If the answer to question 1) or 2) 'Unclear':</p>	<p>1. Concern is low</p> <p>2. Concern is high</p> <p>3. Concern is unclear</p>
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?	<p>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</p> <p>No – if index test described as interpreted in knowledge of reference standard result</p> <p>Unclear – if index test blinding is not described</p>
2) Was the diagnostic threshold at which the test was considered positive (i.e. Melanoma, BCC or cSCC present) prespecified?	<p>Yes – if threshold was prespecified (i.e. prior to analysing study results)</p> <p>No – if threshold was not prespecified</p> <p>Unclear – if not possible to tell whether or not diagnostic threshold was prespecified</p>

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
3) For within-person comparisons of index tests or testing strategies (i.e. > 1 index test applied per participant): was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	<p>Yes – if all index tests were described as interpreted without knowledge of the results of the others</p> <p>No – if the index tests were described as interpreted in the knowledge of the results of the others</p> <p>Unclear – if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation</p> <p>N/A – if only 1 index test was evaluated</p>
<p>Could the conduct or interpretation of the index test have introduced bias?</p> <p>For non-comparative and between-person comparison studies</p> <p>1. If answers to questions 1) and 2) 'Yes': 2. If answers to either questions 1) or 2) 'No': 3. If answers to either questions 1) or 2) 'Unclear':</p> <p>For within-person comparative studies</p> <p>1. If answers to all questions 1), 2), and 3) for any index test 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) for any index test 'No': 3. If answers to any 1 of questions 1), 2), or 3) for any index test 'Unclear':</p>	<p>For non-comparative and between-person comparison studies</p> <p>1. Risk is low 2. Risk is high 3. Risk is unclear</p> <p>For within-person comparative studies</p> <p>1. Risk is low 2. Risk is high 3. Risk is unclear</p>
INDEX TEST (2) - CONCERN ABOUT APPLICABILITY	
1) Was the test applied and interpreted in a clinically applicable manner?	<p>Yes – if a single clinician interpreted the scan with the participant present, and made the diagnosis alone</p> <p>No – If the accuracy 2x2 data are based on an average of multiple observers, or consensus across observers; OR if the scan was interpreted using the image alone, as opposed to with the participant present.</p> <p>Unclear – if insufficient information was reported</p>
<p>2) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?</p> <p>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</p>	<p>Yes – if the criteria for diagnosis of Melanoma, BCC or cSCC were reported in sufficient detail to allow replication</p> <p>No – if the criteria for diagnosis of Melanoma, BCC or cSCC were not reported in sufficient detail to allow replication</p> <p>Unclear – if some but not sufficient information on criteria for diagnosis to allow replication were provided</p>
3) Was the test interpretation carried out by an experienced examiner?	<p>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</p> <p>No – if the test was not interpreted by an experienced examiner (see above)</p> <p>Unclear – if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners described as 'Expert' with no further detail given</p> <p>N/A – if system-based diagnosis, i.e. no observer interpretation</p>

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
<p>Is there concern that the index test, its conduct, or interpretation differ from the review question?</p> <p>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':</p>	<p>1. Concern is low 2. Concern is high 3. Concern is unclear</p>
REFERENCE STANDARD (3) - RISK OF BIAS	
<p>1) Is the reference standard likely to correctly classify the target condition?</p> <p>A) Disease-positive - 1 or more of the following:</p> <ul style="list-style-type: none"> histological confirmation of Melanoma, BCC or cSCC following biopsy or lesion excision clinical follow-up of benign-appearing lesions for at least 6 (or 3 for cSCC) months following the application of the index test, leading to a histological diagnosis of BCC or cSCC <p>B) Disease-negative - 1 or more of the following:</p> <ul style="list-style-type: none"> histological confirmation of absence of Melanoma, BCC or cSCC following biopsy or lesion excision in at least 80% of disease-negative participants clinical follow-up of benign-appearing lesions for a minimum of 6 months (or 3 for cSCC) following the index test in up to 20% of disease-negative participants 	<p>A) Disease-positive</p> <p>Yes – if all participants with a final diagnosis of Melanoma, BCC or cSCC underwent 1 of the listed reference standards</p> <p>No – if a final diagnosis of Melanoma, BCC or cSCC for any participant was reached without histopathology</p> <p>Unclear – if the method of final diagnosis was not reported for any participant with a final diagnosis of BCC or cSCC 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</p> <p>B) Disease-negative</p> <p>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 6 (or 3) months following the index test</p> <p>No – if more than 20% of benign diagnoses were reached by clinical follow-up for a minimum of 6 (or 3) months following the index test or if clinical follow-up period was less than 6 (or 3) months</p> <p>Unclear – if the method of final diagnosis was not reported for any participant with benign diagnosis</p>
<p>2) Were the reference standard results interpreted without knowledge of the results of the index test?</p> <p>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</p>	<p>Yes – if the reference standard diagnosis was reached blinded to the index test result</p> <p>No – if the reference standard diagnosis was reached with knowledge of the index test result</p> <p>Unclear – if blinded reference test interpretation was not clearly reported</p>
<p>Could the reference standard, its conduct, or its interpretation have introduced bias?</p> <p>For visual inspection/dermoscopy evaluations</p> <p>1. If answer to question 1) 'Yes': 2. If answer to question 1) 'No': 3. If answer to question 1) 'Unclear':</p> <p>For all other tests</p> <p>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':</p>	<p>For visual inspection/dermoscopy evaluations</p> <p>1. Risk is low 2. Risk is high 3. Risk is unclear</p> <p>For all other tests</p> <p>1. Risk is low 2. Risk is high 3. Risk is unclear</p>
REFERENCE STANDARD (3) - CONCERN ABOUT APPLICABILITY	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
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 either question 1) or 2) 'No': 3. If answers to either question 1) or 2)	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 6 (or 3) months' follow-up following application of index test(s) for studies of Melanoma, BCC (or cSCC)?	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 ≥ 6 (or 3 for cSCC) months' follow-up No – if study reports < 6 (or 3 for cSCC) months' follow-up Unclear – if study does not report length of clinical follow-up
2) Did all participants receive the same reference standard?	Yes – if all participants underwent the same reference standard No – if more than 1 reference standard was used Unclear – if not clearly reported
3) Were all participants included in the analysis?	Yes – if all participants were included in the analysis No – if some participants were excluded from the analysis Unclear – if not clearly reported
4) For within-person comparisons of index tests Was the interval between application of index tests ≤ 1 month?	Yes – if study reports ≤ 1 month between index tests No – if study reports > 1 month between index tests Unclear – if study does not report interval between index tests

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
<p>Could the participant flow have introduced bias?</p> <p>For non-comparative and between-person comparison studies</p> <p>1. If answers to questions 1), 2), and 3) 'Yes':</p> <p>2. If answers to any 1 of questions 1), 2), or 3) 'No':</p> <p>3. If answers to any 1 of questions 1), 2), or 3) 'Unclear':</p> <p>For within-person comparative studies</p> <p>1. If answers to all questions 1), 2), 3), and 4) 'Yes':</p> <p>2. If answers to any 1 of questions 1), 2), 3), or 4) 'No':</p> <p>3. If answers to any 1 of questions 1), 2), 3), or 4) is 'Unclear':</p>	<p>For non-comparative and between-person comparison studies</p> <p>1. Risk is low</p> <p>2. Risk is high</p> <p>3. Risk is unclear</p> <p>For within-person comparative studies</p> <p>1. Risk is low</p> <p>2. Risk is high</p> <p>3. Risk is unclear</p>
BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.	

5 Summary of included study details

Study author	Study type	Incl criteria	No. patients	Lesion site	Test Machine	Resolution Tissue penetration Centre wavelength	Threshold	Diagnostic method	Observer qualifications Test experience
Melanoma									
Gambichler 2014 MM alone MM+MiS	NC P-CS Ger	MSL for excision Excluded: Frank ulceration, marked hyperkeratosis	64 / 93	Any (not described)	HD-OCT Skintell HD-OCT (Agfa, Belgium)	axial 5µm, lateral 3µm 570µm 1300nm	Score ≥ -1 MM; score of ≥ -1.5 benign MSL based on sum of sub-scores for various OCT characteristics	Image-based Blinded to VI/Derm	NR (n = 1) "experienced"
Wessels 2015 MM+MiS	NC P-CS NL	PSL scheduled for excision, identified during routine skin cancer screening (all clinically suspicious for melanoma; 14 with dermoscopic suspicion) Excluded: none reported	33 / 40	Trunk and Neck (28, 70%), arms and legs (12, 30%)	OCT (Swept source) Santec Inner Vision 2000	axial 10µm, lateral 20µm 2000µm 1300nm	Attenuation coefficient 5.4mm ⁻¹ (Data on morphological characteristics excluded)	Image-based Blinding NR	NR (n = 1) NR
BCC									

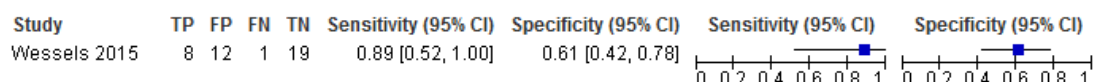
Study author Outcomes reported	Study type	Incl criteria	No_patients	Lesion_site	Test Machine	Resolution Tissue penetration Centre wavelength	Threshold	Diagnostic method	Observer qualifications Test experience
Markowitz 2015 BCC	WPC P-CS US	Pink lesions suspicious for BCC and clinically challenging (head/neck only); requiring biopsy for confirmation of diagnosis, and eligible for Mohs surgery Excluded: History or evidence of metastasis, topical actinic therapy within 8wks prior to eval, other skin conditions within lesion	100 / 115	Head/Neck (not further described)	OCT (Swept source) VivoSight OCT Also reports in person diagnosis for VI and for Dermoscopy	axial 10µm, lateral 7.5µm 2000µm 1300nm	Diagnostic judgement (BCC present/absent)	Image-based (unclear if VI/dermoscopy images provided)	NR (n = NR) NR
Ulrich 2015 BCC	WPC P-CS Ger	Non-pigmented pink lesions with clinical suspicion of BCC; requiring biopsy for diagnostic confirmation Excluded: Typical clinical appearance BCC, PSL, unstable or uncontrolled clinically significant medical conditions	164 / 256	Head (41%), Upper body (48.8%), Other (0.2%)	OCT (Swept source) VivoSight OCT Also reports in person diagnosis for VI and for Dermoscopy	axial 10µm, lateral 7.5µm 2000µm 1300nm	Diagnostic judgement (BCC present/absent)	In person (following VI/Derm)	NR (n = NR) "regular user 3mos experience"
Wahrlich 2015 BCC	NC CCS Ger	Selected participants with BCC, cSCC, BD, AK based on prior clinical examination and dermoscopy Excluded: ulcerated	50 / 50	NR	OCT (Swept source) VivoSight OCT	axial 10µm, lateral 7.5µm 2000µm 1300nm	1. Berlin score ≥ 8 2. Berlin score ≥ 12	Image-based (reviewed following histopathology)	Dermatopathologist (n = 1) "familiar with"
cSCC									

Study author	Study type	Incl criteria	No. patients	Lesion site	Test Machine	Resolution Tissue penetration Centre wavelength	Threshold	Diagnostic method	Observer qualifications Test experience
Wahrlich 2015 cSCC	NC CCS Ger	Selected participants with BCC, cSCC, BD, AK based on prior clinical examination and dermatoscopy Excluded: ulcerated	50 / 50	NR	OCT (Swept source) VivoSight OCT	axial 10µm, lateral 7.5µm 2000µm 1300nm	1. Berlin score ≥ 8 2. Berlin score ≥ 12	Image-based (reviewed following histopathology)	Dermatopath (n = 1) "familiar with

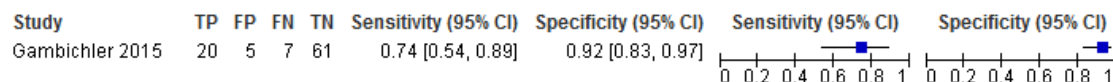
Footnotes: AK - actinic keratosis; BCC - basal cell carcinoma; ?BCC - possible basal cell carcinoma; BD - Bowens disease; BN - benign naevus; CCS - case-control study; cSCC - cutaneous squamous cell carcinoma; Derm - dermatoscopy; Ger - Germany; HD - high definition; H/N - Head and neck; LED - disease type, acronym not provided by study; Mis - melanoma *in situ*; MM - malignant melanoma; MSL - melanocytic skin lesion; NC - non-comparative study design; NR - not reported; NR-CS - case series data collection method not reported; NS - not specified; OCT - optical coherence tomography; P-CS - prospective case series; PSL - pigmented skin lesion; R-CS - retrospective case series; SK - seborrhoeic keratosis; US - United States of America; VI - visual inspection; WPC - within-person comparison study design.

Graphs

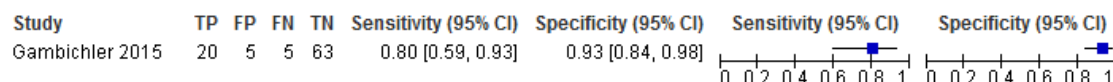
OCT Attenuation coefficient 5.4mm-1 (MM+Mis)



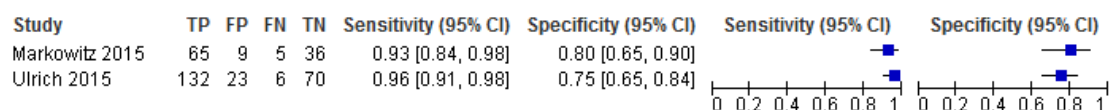
HD-OCT Gambichler score ≥ -1 (MM+Mis)



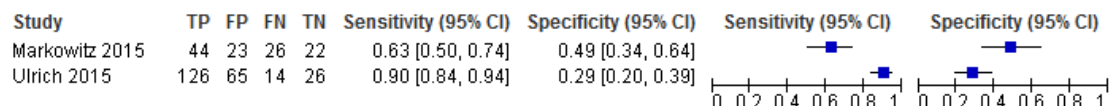
HD-OCT - Gambichler score ≥ -1 (MM)



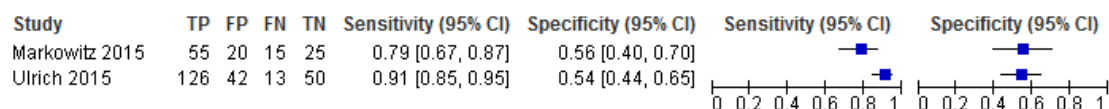
OCT observer diagnosis (BCC)



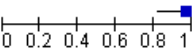
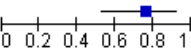
VI observer diagnosis (BCC)



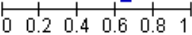
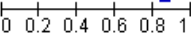
Dermoscopy observer diagnosis (BCC)




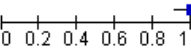
OCT Berlin score ≥ 8 (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	28	5	1	16	0.97 [0.82, 1.00]	0.76 [0.53, 0.92]		

OCT Berlin score ≥ 12 (BCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	19	3	10	18	0.66 [0.46, 0.82]	0.86 [0.64, 0.97]		

OCT Berlin score ≥ 8 (cSCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	5	0	4	41	0.56 [0.21, 0.86]	1.00 [0.91, 1.00]		

OCT Berlin score ≥ 12 (cSCC)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wahrlich 2015	3	0	6	41	0.33 [0.07, 0.70]	1.00 [0.91, 1.00]	