Optical coherence tomography for the diagnosis of skin cancer in adults

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DOI:
10.1002/14651858.CD013189

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Ferrante di Ruffano, L, Dinnes, J, Deeks, J, Chuchu, N, Bayliss, S, Davenport, C, Takwoingi, Y, Godfrey, K, O'Sullivan, C, Matin, RN, Tehrani, H & Williams, HC 2018, 'Optical coherence tomography for the diagnosis of skin cancer in adults', *Cochrane Database of Systematic Reviews*, no. 12, CD013189. https://doi.org/10.1002/14651858.CD013189

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Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD013189.

DOI: 10.1002/14651858.CD013189.

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[Diagnostic Test Accuracy Review]

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Editorial group: Cochrane Skin Group.
Publication status and date: New, published in Issue 12, 2018.

Citation: 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 diagnosing skin cancer in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No.: CD013189. DOI: 10.1002/14651858.CD013189.

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

We included studies of any design 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 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

We included five studies with 529 cutaneous lesions (282 malignant lesions) providing nine datasets for OCT, two for visual inspection alone, and two for visual inspection plus dermoscopy. Studies were of moderate to unclear quality, using data-driven thresholds for test positivity and giving poor accounts of reference standard interpretation and blinding. Studies may not have been representative of populations eligible for OCT in practice, for example due to high disease prevalence in study populations, and may not have reflected how OCT is used in practice, for example by using previously acquired OCT images.

It was 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 of OCT as 95% (95% confidence interval (CI) 91% to 97%) and specificity of 77% (95% CI 69% to 83%).

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 plus 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 plus dermoscopy).

Authors' conclusions

Insufficient data are available on the use of OCT for the detection of melanoma or cSCC. Initial data suggest conventional OCT may have a role for the diagnosis of BCC in clinically challenging lesions, with our meta-analysis showing a higher sensitivity and higher specificity when compared to visual inspection plus 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 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 several 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 dermoscope is used by most skin cancer specialists, which magnifies the skin lesion (a mole or area of skin with an unusual appearance in comparison with the surrounding skin) 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. Review authors examined how useful OCT is to help diagnose skin cancers when used after visual inspection or visual inspection plus dermoscopy.

What are the main results of the review?

The review included five studies: two studies with 97 participants with 133 skin lesions suspected of being melanoma, and three studies with 305 participants with 396 lesions suspected of being BCC of which one (50 lesions) also analysed cSCCs (nine 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 showed the effects of skin specialists using OCT after visual inspection alone, or visual inspection with dermoscopic examination. These two studies indicated that in theory, if OCT were to be used in a group of 1000 people with skin lesions that were particularly difficult to diagnose, of whom 600 (60%) actually had BCC, then:

- an estimated 662 people would have an OCT result confirming that a BCC was present and of these 93 (14%) would not actually have had a BCC (false-positive result);

- of the 338 people with an OCT result indicating that no BCC was present, 31 (9%) would actually have a BCC (false-negative result).

Compared to making a diagnosis of BCC using visual inspection plus 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 people really had skin cancer. However, the small number of studies included in this review, and variability between them, reduced 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 (e.g. 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. Average 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 on using 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 standard comparisons.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Question	**What is the diagnostic accuracy of OCT 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); BCC (3)
Index test:	Conventional and high density 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:	Participant 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	237				
Total cSCC lesions	9				

Detection of invasive melanoma or atypical intraepidermal melanocytic variants

Number of studies	Total lesions with test results	Total lesions with melanoma
2	133	36 (32 invasive, 4 melanoma in situ)

Findings

2 studies evaluated invasive melanoma or atypical intraepidermal melanocytic variants:

- conventional OCT at an attenuation coefficient of 5.4 mm^{-1}: sensitivity 89% (95% CI 52% to 100%) and specificity 61% (95% CI 42% to 78%) (1/2);
- HD-OCT sensitivity 74% (95% CI 54% to 89%) and specificity 92% (95% CI 83% to 97%) using scoring system based on OCT characteristics (1/2); both melanoma in situ 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]	237 [208]

Pooled analyses			**Numbers observed in a cohort of 1000 lesions being tested (at mean prevalence 60%)[c]**			
2 studies of observer diagnosis with VI alone, VI p and with OCT (tc n = 208)	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True positive (received necessary excision)**	**False positive (received unnecessary excision)**	**False negative (did not receive required excision)**	**True negative (appropriately not excised)**
VI alone:	80% (55% to 93%)	37% (24% to 52%)	478	252	122	148

VI plus dermoscopy:	86% (76% to 92%)	55% (46% to 63%)	516 (38)	180 (72)	84 (38)	220 (72)
OCT:	95% (91% to 97%)	77% (69% to 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 $\geq$ 8 (sensitivity 97%, 95% CI 82% to 100%) and specificity 76%, 95% CI 53% to 92%) with lower sensitivity (66%, 95% CI 46% to 82%) and higher specificity (86%, 95% CI 64% to 97%) at the higher score of $\geq$ 12. Unclear whether this would be replicated in usual practice setting					
Detection of cSCC						
Findings	1 case-control study with 9 cSCCs, total number of lesions = 50: • poor sensitivity for OCT obtained using Berlin score at $\geq$ 8 (sensitivity 56%. 95% CI 21% to 86%) and specificity 100%, 95% CI 91% to 100%) with lower sensitivity (33%, 95% CI 7% to 70%) and the same specificity (100%) at the higher score of $\geq$ 12. Unclear whether this would be replicated in usual practice setting.					

[a] All results use lesions as the unit of analysis.
[b] Squared brackets indicate numbers used in pooled analysis.
[c] Numbers estimated at 25th, 50th (median), and 75th percentiles of BCC prevalence observed across 2 datasets reporting evaluations of OCT added to dermoscopy and VI.
BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; CI: confidence interval; HD-OCT: high-definition optical coherence tomography; n: number; OCT: optical coherence tomography; VI: visual inspection.

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

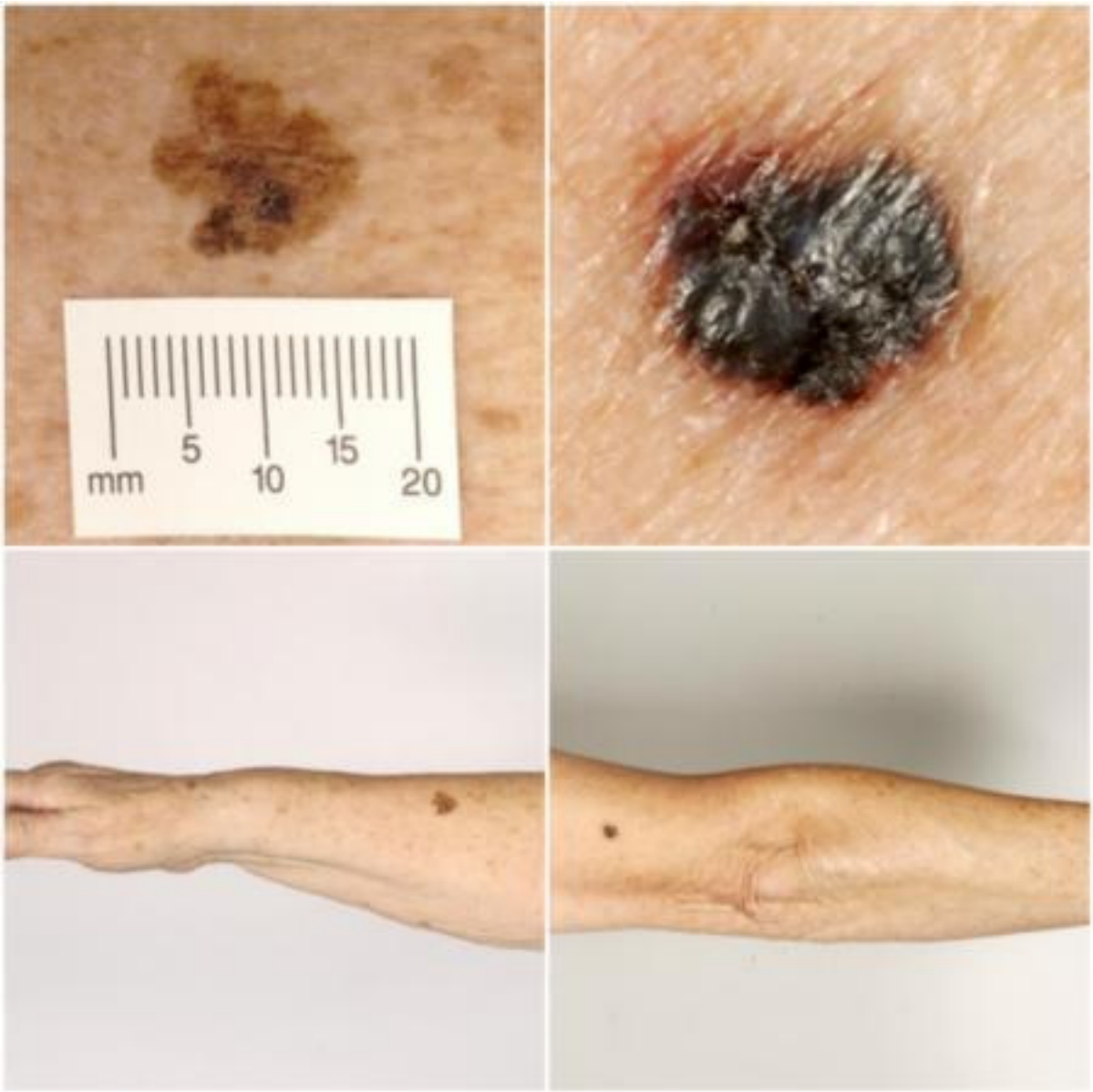
There are three main forms of skin cancer. Melanoma has the highest skin cancer mortality (Cancer Research UK 2017); however, the most common skin cancers in Caucasian populations are those arising from keratinocyte cells: basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) (Gordon 2013; Madan 2010). In 2003, the World Health Organization estimated that between two and three million 'non-melanoma' skin cancers (of which BCC is estimated to account for around 80% and cSCC for around 16% of cases) and 132,000 melanoma skin cancers occur globally each year (WHO 2003).

In this DTA review, the target conditions of interest were: melanoma, BCC, and cSCC. We also examined accuracy for the target condition of 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 dermoepidermal junction (DEJ) during a vertical growth phase, although malignant transformation is both lower and slower for lentigo maligna than for melanoma in situ (Kasprzak 2015). 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 bloodstream. 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 13,134 new cases of melanoma of the skin in 2014 (ACIM 2017) and in New Zealand with 2341 registered cases in 2010 (HPA and MelNet NZ 2014). For 2014 in the USA, the predicted incidence was 73,870 per annum and the predicted number of deaths was 9940 (Siegel 2015). The highest rates in Europe are seen in north-western Europe and the Scandinavian countries, with a highest incidence reported in Switzerland: 25.8 per 100,000 in 2012. Rates in England have tripled from 4.6 and 6.0 per 100,000 in men and women, respectively, 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 (Belbasis 2016; Linos 2009). 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).

Figure 1. Sample photographs of superficial spreading melanoma (left) and nodular melanoma (right). Copyright © 2010 Dr Rubeta Matin: reproduced with permission.

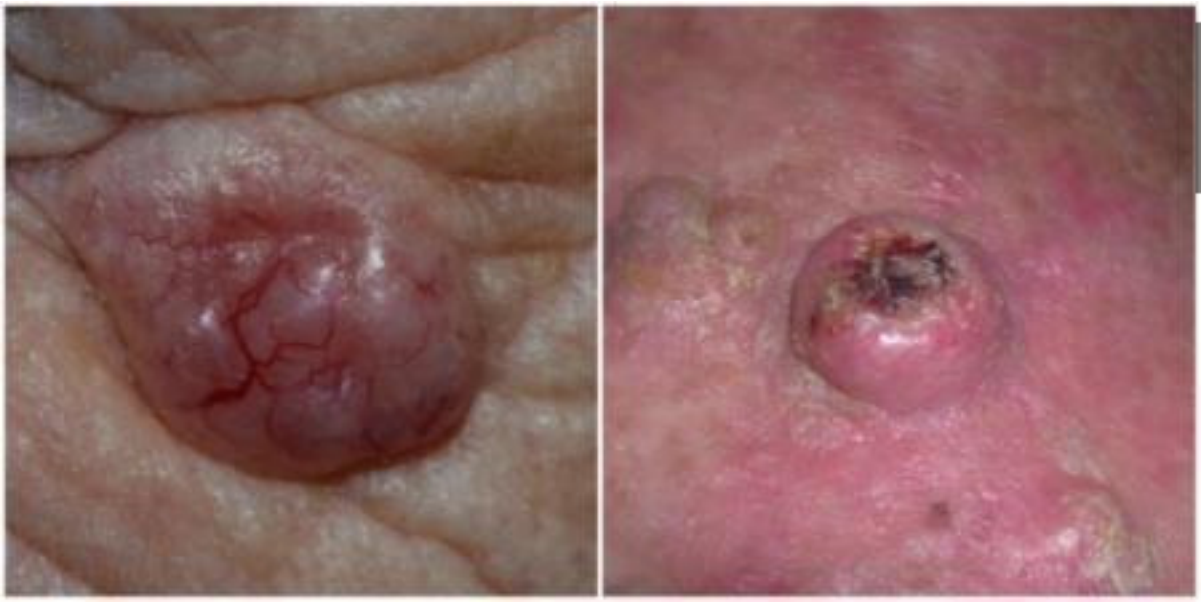


A database of over 40,000 US patients from 1998 onwards which assisted the development of the 8th American Joint Committee on Cancer (AJCC) Staging System indicated a five-year survival of 97% to 99% for stage I melanoma, dropping to between 32% and 93% for stage III disease depending on tumour thickness, 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 BCC often present themselves to healthcare professionals with a non-healing lesion rather than specific symptoms such as pain. Many lesions are diagnosed incidentally (Gordon 2013).

Figure 2. Sample photographs of basal cell carcinoma (left) and cutaneous squamous cell carcinoma (right). Copyright © 2012 Dr Rubeta Matin: reproduced with permission.



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 years. 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's) syndrome (Gorlin 2004; Zak-Prelich 2004). Annual incidence is increasing worldwide; Europe has experienced a mean increase of 5.5% per year since the late 1970s, 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 per 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 UV radiation, and improved detection due to the increased awareness among 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 who are not immunosuppressed and do not have Gorlin's syndrome. Furthermore, lesions should be located below the clavicle; should be small (less than 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 (PDT), 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 BCC 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 people who are immunosuppressed, or people with Gorlin's 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 clinicians to be cSCC in situ); the estimated annual risk of progression being less than 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 people (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 20 mm in diameter and tumours with a histological depth of invasion exceeding 4 mm, and poor differentiation status on pathological examination (Motley 2009). Perineural nerve invasion (PNI) of at least 0.1 mm in diameter is a further documented risk factor for high-risk cSCC (Carter 2013).

Chronic UV 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 recurrence of cSCC at five years is estimated at 8% and metastatic recurrence at 5%. 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 (Garbe 2016; Marsden 2010; NICE 2015a; SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness (Garbe 2016), and stage of disease at presentation (NICE 2015a). Following histological confirmation of diagnosis, the lesion is staged according to the 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 are also associated with worse prognosis (Moreau 2013; Shaikh 2012). Independent of tumour thickness, prognosis is worse in: older people, males, people with recurrent lesions, and in people with distant lymph node involvement (micro or macroscopic) or metastatic disease (or both) 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 is a range of primary treatment options that include surgery, other destructive techniques such as cryotherapy or electrodesiccation, and topical chemotherapy. One 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 less than 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 4 mm surgical peripheral margins taken there is a five-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 or cosmetic impairment, or both (Bath-Hextall 2007b; Lansbury 2010; Motley 2009; Stratigos 2015). Bath-Hextall 2007b found a single trial comparing Mohs micrographic surgery with a 3 mm surgical margin excision in BCC (Smeets 2004); the update of this study showed 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).

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 or multiple (or both) 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 was 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).

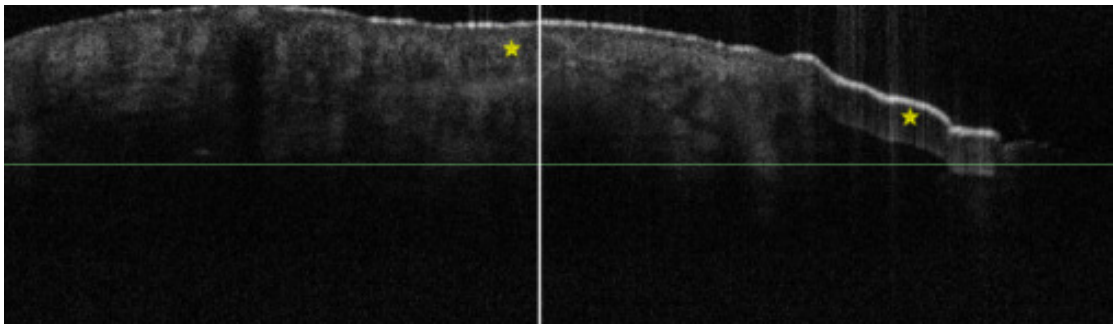
One systematic review of interventions for primary cSCC found only one RCT eligible for inclusion (Lansbury 2010). Therefore, current practice relies on evidence from observational studies, as reviewed in Lansbury 2013, for example. Surgical excision with predetermined margins is usually the first-line 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 less than 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 hand-held 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; Figure 4). Both two-dimensional (2D) and three-dimensional (3D) images can be created. There are several 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)).

Figure 3. Swept-source optical coherence tomography scanner (Michelson Diagnostics VivoSight Rx). Copyright © 2017 Guy's & St Thomas' Hospital Trust: reproduced with permission.

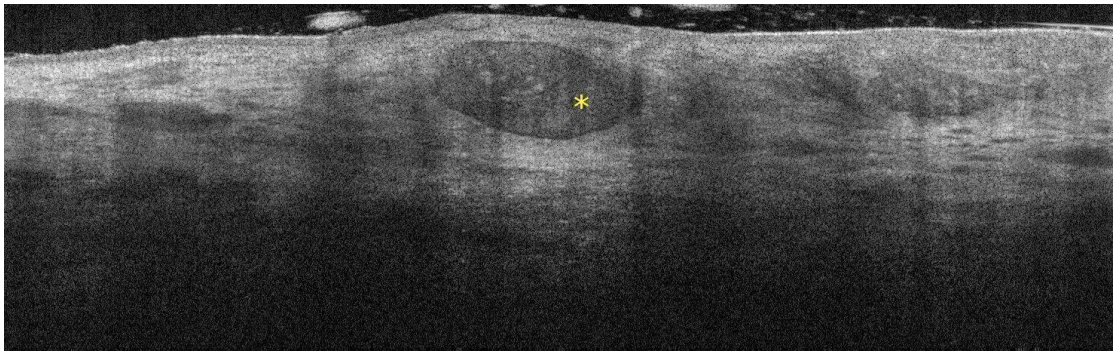
Figure 4. Optical coherence tomography (OCT) image of a 7 mm basal cell carcinoma (BCC) on the cheek showing several BCC cell nests (left hand star is above and to the left of a BCC nest) and the position of the 2 mm margin as drawn with a reflective ink pen (right hand star). The ink pen gives the appearance 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 Guy's & St Thomas' Hospital Trust: reproduced with permission.



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 axial resolutions of up to 7.5 µm and lateral resolutions of 5 µm (Hussain 2015; Olsen 2015). Skin features that can be visualised include the epidermis (for which many cancers display an alteration in histology); the 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 3 µm (thereby allowing single cells to be visualised) at a depth of up to 0.57 mm (Boone 2015a; Hussain 2015; Olsen 2015).

OCT is not routinely used in current practice (NICE 2015a). It is considered 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 2015a; Olsen 2015). Preliminary work using high-definition (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 2015b). One review suggested that eight characteristics associated with BCC have been variously reported for conventional OCT including: disruption of layering, hyporeflective 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, and 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 2015a), and very bright irregularly broadened cell outlines masking the nucleus, which are thought to represent atypical keratinocytes (Reggiani 2015).

Figure 5. Optical coherence tomography (OCT) image of a nodular basal cell carcinoma (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 © 2013 Michelson Diagnostics Ltd: reproduced with permission.

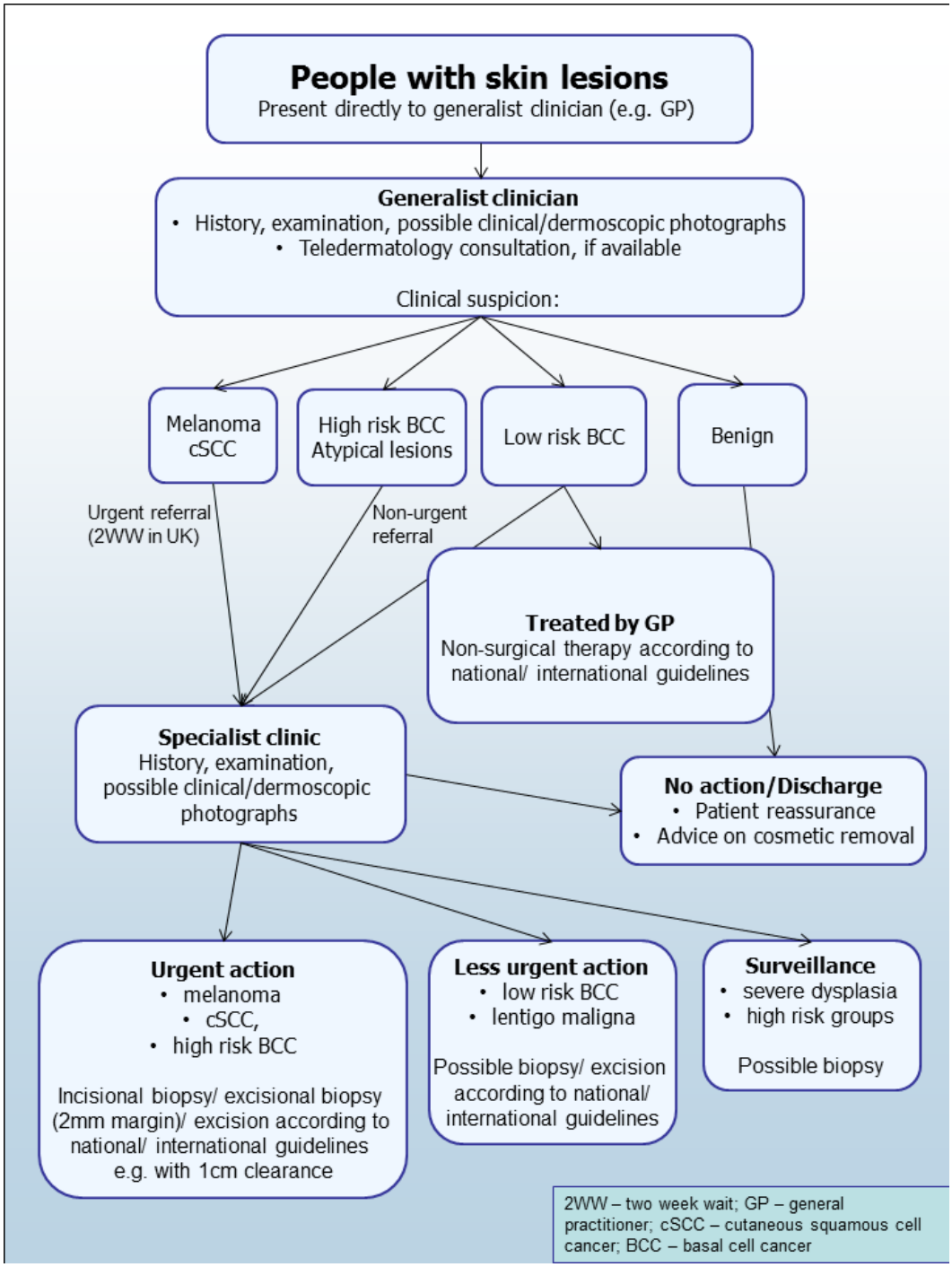


Internationally, there are numerous companies producing different commercially available OCT devices, across a range of medical specialities; Gambichler 2015a lists nine different devices applied in dermatology. Imaging can reportedly be undertaken by clinicians or technicians, taking around 30 seconds 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 (GP) or directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, general surgeon, 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).

Figure 6. Current clinical pathway for people with skin lesions.



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 or greater (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, one 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 handheld microscope and incident light (with or without oil immersion) to reveal subsurface images of the skin at increased magnification of ×10 to ×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 2015a; Hussain 2015; Reggiani 2015). OCT is considered to lie within the 'imaging gap' between HR 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 (830 nm as opposed to 1305 nm for OCT), has considerably deeper penetration (RCM less than 300 µm; OCT less than 2 mm) meaning it can visualise deeper into the dermis, has a greater depth of focus (RCM 3 μm to 5 µm; OCT 1 mm), and wider basic field of view (RCM basic 500 × 500 µm in the horizontal plane; OCT basic 6 × 6 mm). However, OCT has lower lateral resolution in comparison to RCM (RCM 1 µm, cellular; OCT 7.5 µm, near cellular), although newer HD 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 greater than 10 minutes; OCT six cross-sectional frames per second, less than 2 minutes for 6 × 6 × 2 mm volume). Therefore, OCT may 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 people 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 non-surgical treatments (listed in Target condition being diagnosed), which could be advantageous for multiple lesions or lesions 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 people 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 2015a; 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), RCM (Dinnes 2018d; Dinnes 2018e), high-frequency ultrasound (HFUS) (Dinnes 2018f), and computer-assisted 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 about 1 μm, 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).

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 (Esteva 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 (Malvehy 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 HFUS with transducer frequencies of at least 20 MHz has a much lower depth of tissue penetration but produces a higher resolution image of tissues and structures closer to the skin surface. Therefore, HFUS may 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 people with large numbers of typical or atypical naevi, and histopathological confirmation following lesion excision. Histopathological confirmation 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 HR image analysis in primary care, the anxiety around missing early cases needs to be balanced 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, while 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' among 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 sufficiently accurate 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 DTA. In addition, none reported undertaking any assessment of quality assessment or attempted meta-analysis (Calin 2013; Gambichler 2015a; Hussain 2015; Olsen 2015), and all were 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 atypical 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 atypical intraepidermal melanocytic variants, BCC, or cSCC 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 was necessarily limited by the data available for each reviewed test.

1. Population characteristics

- General versus higher-risk populations.
- Participant population: primary/secondary/specialist unit.
- Lesion type: any pigmented; melanocytic.
- Inclusion of multiple lesions per participant.
- Ethnicity.

2. Index test characteristics

- In-person versus remote image-based test interpretations.
- Nature and definition of criteria for test positivity.
- Observer experience with the index test.

3. Reference standard characteristics

- Reference standard used.
- Whether histology-reporting met pathology-reporting guidelines.
- Use of excisional versus diagnostic biopsy.
- Whether two independent dermatopathologists reviewed histological diagnosis.

4. 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 were 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 received a single index test and a reference standard;
- studies where all participants received more than one index test(s) and reference standard;
- studies where participants were allocated (by any method) to receive different index tests or combinations of index tests and all received a reference standard (between-person comparative (BPC) studies);
- studies that recruited series of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruited diseased and non-diseased groups (see Rutjes 2005); however, we did not include studies that compared results for malignant lesions to those for healthy skin (i.e. with no lesion present);
- both prospective and retrospective studies; and
- studies that retrieved and prospectively interpreted previously acquired clinical or dermoscopic images for study purposes.

We excluded studies from which we could not extract 2×2 contingency data or if they included fewer than five disease-positive or five disease-negative cases. The size threshold of five was arbitrary. However, such small studies are unlikely to add precision to estimate of accuracy.

Studies available only as conference abstracts were excluded; however, attempts were made to identify full papers for potentially relevant conference abstracts (Searching other resources).

Participants

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

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

Index tests

We included studies evaluating OCT alone, or OCT in comparison to visual inspection or dermoscopy, or both. We included all established algorithms or checklists to assist diagnosis. We included studies developing new algorithms or methods of diagnosis (i.e. derivation studies), if they:

- used a separate independent 'test set' of participants or images to evaluate the new approach; or
- investigated lesion characteristics that had previously been suggested as associated with melanoma, BCC, or cSCC and the study reported accuracy based on the presence or absence of specific combinations of characteristics.

We excluded studies if they:

- used a statistical model to produce a data-driven equation, or algorithm based on multiple diagnostic features, with no separate test set;
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983);
- evaluated the accuracy of the presence or absence of individual OCT characteristics or morphological features, with no overall diagnosis of malignancy.

There were no exclusions made according to test observer.

Target conditions

The target conditions were defined as the detection of:

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

- BCC (all types);
- Invasive cSCC (we did not consider cutaneous SCC in situ, such as Bowen's disease, as disease-positive); and
- 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 have perform histopathology. Ideally, reporting should be standardised detailing a minimum dataset to include the histopathological features of melanoma to determine the 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, while 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.

We considered all of the above eligible reference standards with the following caveats:

- all study participants with a final diagnosis of the target disorder must have had 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 had 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. 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 (Appendix 2). 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 was 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) 2016, Issue 7, in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR) 2016, Issue 8, in the Cochrane Library;
- Cochrane Database of Abstracts of Reviews of Effects (DARE) 2015, Issue 2;
- CRD HTA (Health Technology Assessment) database 2016, Issue 3; and
- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960).

We searched the following databases for relevant unpublished studies using a strategy based on the MEDLINE search:

- CPCI (Conference Proceedings Citation Index), via Web of Science™ (from 1990; searched 28 August 2016); and
- SCI Science Citation Index Expanded™ via Web of Science™ (from 1900, using the 'Proceedings and Meetings Abstracts' Limit function; searched 29 August 2016).

We searched the following trials registers using the search terms 'melanoma', 'squamous cell', 'basal cell' and 'skin cancer' combined

with 'diagnosis':

- Zetoc (from 1993; searched 28 August 2016).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov); searched 29 August 2016.
- NIHR Clinical Research Network Portfolio Database (www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/); searched 29 August 2016.
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/); searched 29 August 2016.

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress). We applied no date limits.

Searching other resources

We screened relevant systematic reviews identified by the searches for their included primary studies, and included any missed by our searches. We checked the reference lists of all included papers, and subject experts within the author team reviewed the final list of included studies. We conducted no electronic citation searching.

Data collection and analysis

Selection of studies

At least one review author (JD or NC) screened titles and abstracts, 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. We included primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC at initial screening. Both a clinical reviewer (from one of a team of 12 clinician reviewers) and a methodologist reviewer (JD or NC) independently applied the inclusion criteria independently to all full-text articles (Appendix 3); we resolved disagreements by consensus or by a third party (JJD, CD, HW, and RM). We contacted authors of eligible studies when studies presented insufficient data to allow for the construction of 2×2 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 complete a 2×2 diagnostic contingency table for each index test using a piloted data extraction form. We extracted data at all available index test thresholds. We resolved disagreements by consensus or by a third party (JJD, CD, HW, and RM). We entered data into Review Manager 5 (Review Manager 2014).
We contacted authors of included studies 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. We contacted authors of conference abstracts published from 2013 to 2015 to ask whether full data were available. If we identified no full paper, we marked conference abstracts as 'pending' and will revisit them in a future review update.

Dealing with multiple publications and companion papers

Where we identified multiple reports of a primary study, 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). We piloted the modified QUADAS-2 tool 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; we resolved any disagreement 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, we undertook no meta-analysis for the diagnosis of melanoma or cSCC. We undertook statistical pooling 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. However, for the diagnosis of BCC, any other skin cancers (e.g. 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 (e.g. 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.
We plotted estimates of sensitivity and specificity on coupled forest plots for each threshold under consideration. Our unit of analysis

was the lesion rather than the person. This is because 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 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 included very few people with multiple lesions and any potential impact on findings was likely to be very small, particularly in comparison with other concerns regarding risk of bias and applicability. For each analysis, we included only one dataset 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 intervals (CI) and prediction regions using the bivariate hierarchical model (Chu 2006; Reitsma 2005). Where inadequate data were available for the model to converge, we simplified the model by assuming no correlation between estimates of sensitivity and specificity (Takwoingi 2017).

We included data on the accuracy of visual inspection or dermoscopy (or both) 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). We extended the bivariate model by addition of covariates to allow for differences in sensitivity and specificity between OCT and visual inspection or dermoscopy (or both), 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. There were insufficient numbers of studies to allow meta-regression to investigate potential sources of heterogeneity.

Sensitivity analyses

We performed no sensitivity analyses.

Assessment of reporting bias

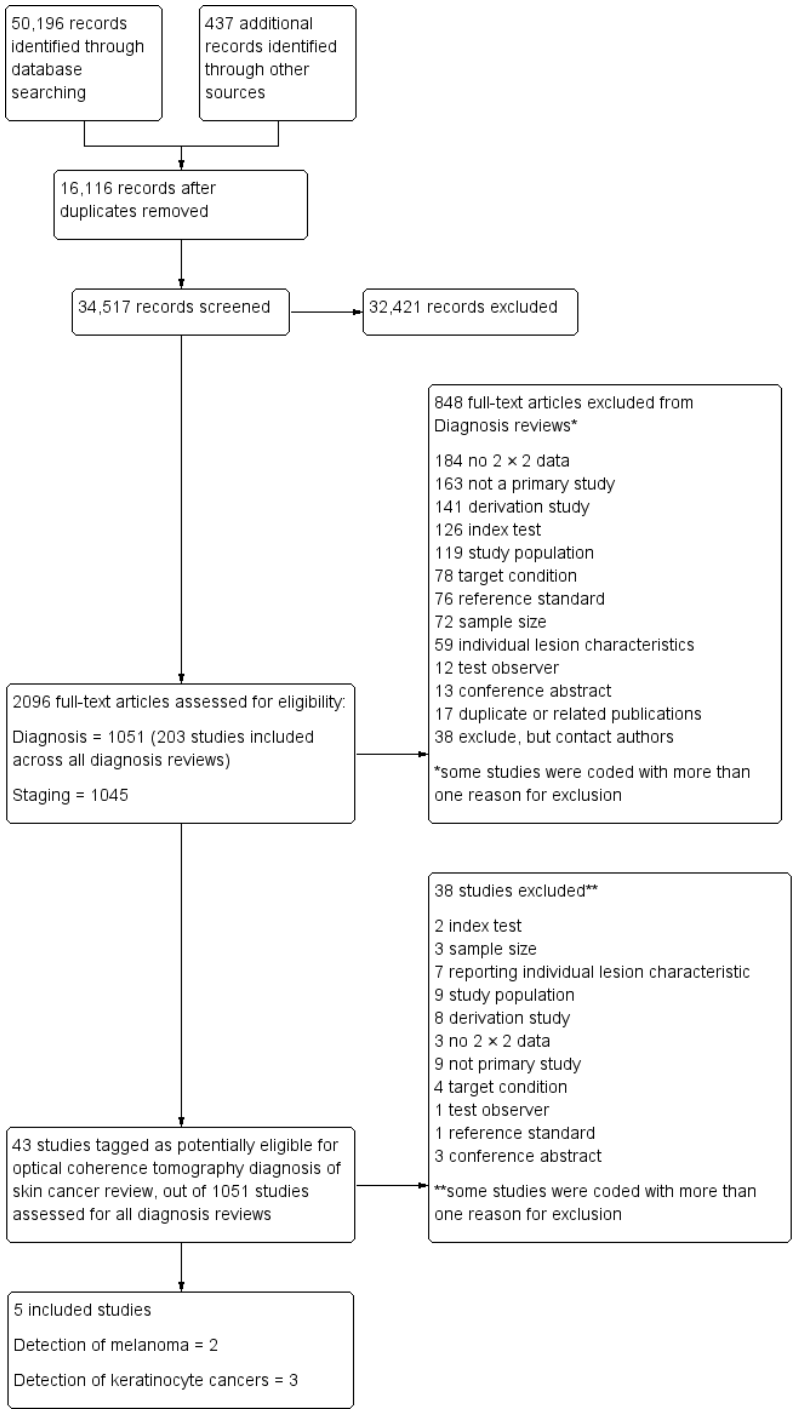
Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we performed no tests to detect publication bias.

RESULTS

Results of the search

The search identified and we screened 34,517 unique references for inclusion. Of these, we reviewed 1051 full-text papers 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 the 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 five 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 potentially eligible for this review; ultimately five publications (reporting five studies) were included. A list of the 38 studies excluded from this review with reasons for exclusion is provided in the Characteristics of excluded studies table, with a list of all studies excluded from the full series of reviews available as a separate pdf (please contact skin.cochrane.org for a copy of the pdf).

Figure 7. PRISMA flow diagram.



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

Characteristics of included studies

This review reported on five cohorts of participants with lesions suspected of skin cancer, published in five study publications, and providing nine 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 2015c; Ulrich 2015; Wahrlich 2015), one in the Netherlands (Wessels 2015), and one in the US (Markowitz 2015). OCT manufacturers funded three studies (Gambichler 2015c; Markowitz 2015; Ulrich 2015); in Wahrlich 2015, the manufacturer provided the OCT device, and Wessels 2015 did not report company funding.

Two studies were in participants with pigmented (Wessels 2015) or melanocytic lesions (Gambichler 2015c) and focused on identification of melanomas. The remaining three studies examined a 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 non-pigmented 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 2015c), 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).

The five studies included 402 participants with 529 lesions, with 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 2015c) 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 among others (there were no cSCC lesions included). 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 HD OCT for diagnosis of melanoma (Gambichler 2015c). The studies assessed several different thresholds for test positivity (Table 2). For the detection of melanoma, Gambichler 2015c 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 participant concerned); with only Ulrich 2015 describing OCT scans interpreted in real-time following clinical examination and then dermoscopy of the lesions. One study described observer qualifications (with interpretation by a dermatopathologist) (Wahrlich 2015), and three studies described observers as experienced or regular users of an OCT device (Gambichler 2015c; Ulrich 2015; Wahrlich 2015). Only Wahrlich 2015 described any test failures (see Methodological quality of included studies). All studies made the reference standard diagnosis by histology alone.

Methodological quality of included studies

Overall, study quality was moderate to unclear, with considerable concerns regarding the clinical applicability of results (Figure 8; Figure 9).

Figure 8. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

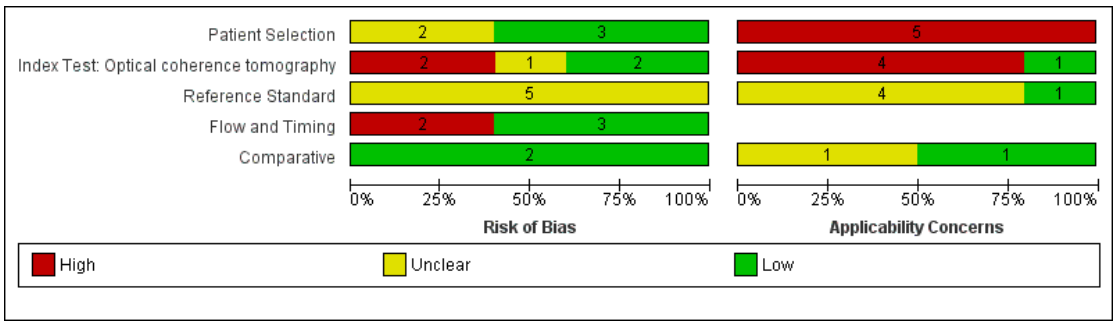
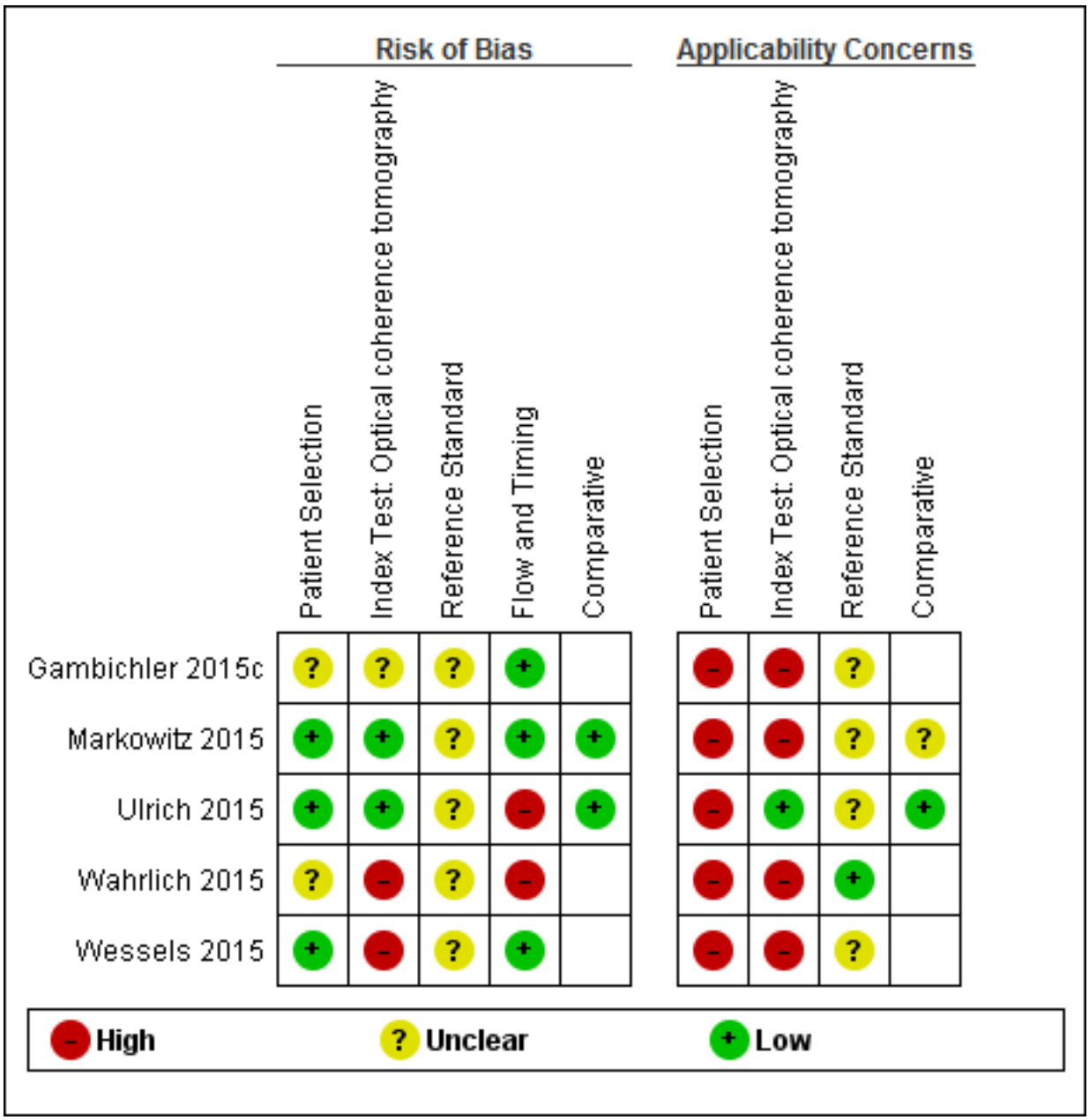


Figure 9. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



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

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 (high risk, Wahrlich 2015)), one used a data-driven threshold (high risk, Wessels 2015), and one did not describe the approach to selection of the numeric threshold used (unclear risk, Gambichler 2015c). Four studies had 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 not clinically applicable due to the use of image-based diagnosis remote from the study participants. Two studies did not report the expertise of the clinician interpreting the OCT scan (Markowitz 2015; Wessels 2015). Furthermore, one reported blinding to all other clinical information (Gambichler 2015c), and two did not clearly describe what information was provided to test observers (Markowitz 2015; Wessels 2015).

All studies reported the use of an acceptable reference standard, but none 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 (Wahrlich 2015); 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; of the two studies at high risk of bias, 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. Markowitz 2015 scored the same item as unclear 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 or whether clinical or dermoscopic images were provided to assist OCT diagnosis.

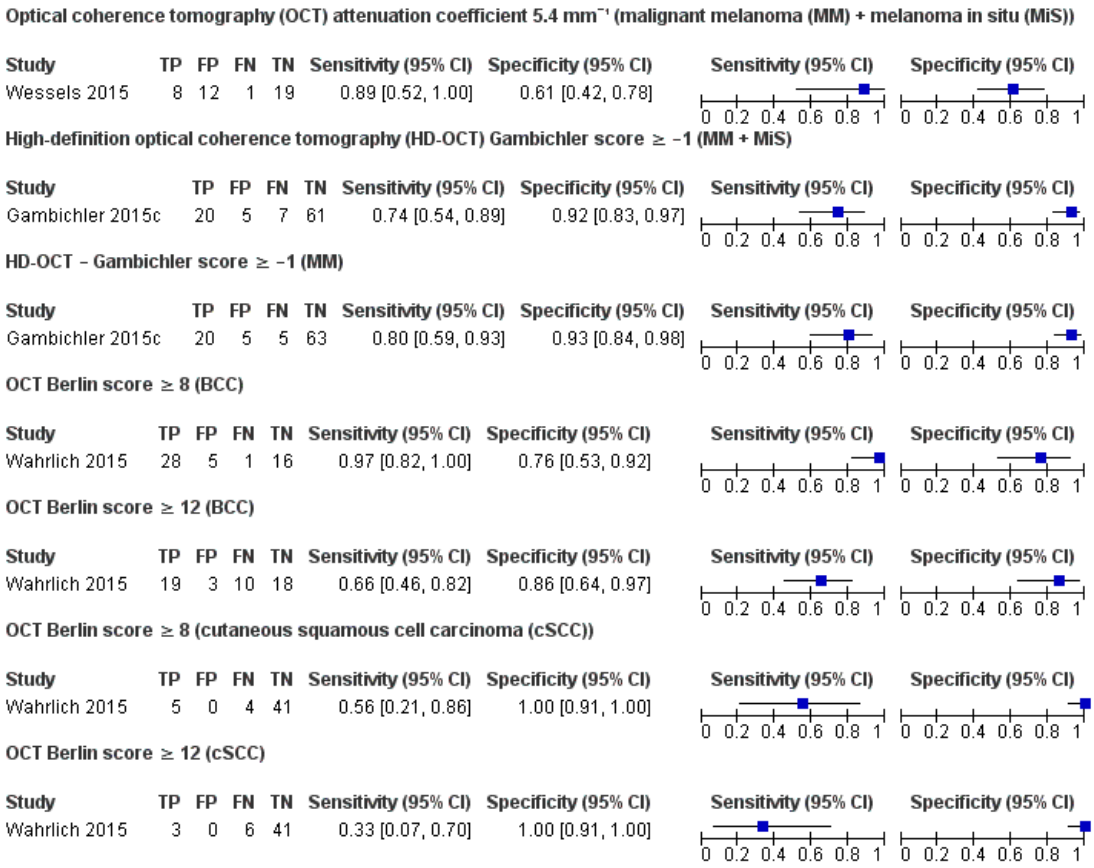
Findings

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 atypical intraepidermal melanocytic variants

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 atypical intraepidermal melanocytic variants in 40 lesions selected for excision reported sensitivity of 89% (95% CI 52% to 100%) and specificity of 61% (95% CI 42% to 78%) at an attenuation coefficient of 5.4 mm^{-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 in making a melanoma diagnosis, due to the insufficient resolution provided by the conventional OCT system.

Figure 10. 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). CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive.



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

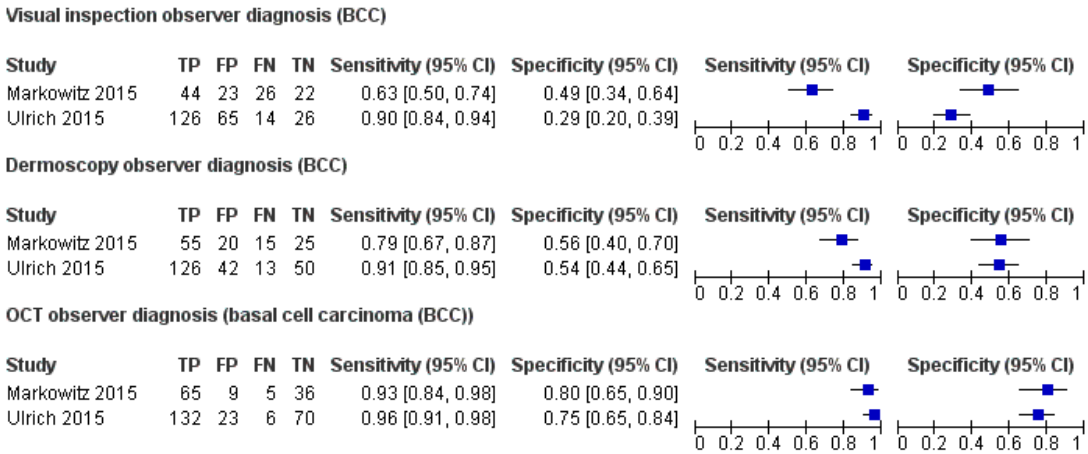
Detection of basal cell carcinoma

All three studies used conventional swept-source OCT for the detection of 237 BCCs in 396 analysed lesions. Wahrlich 2015 used quantitative scoring of OCT characteristics that resulted in a sensitivity of 97% (95% CI 82% to 100%) and specificity of 76% (95% CI 53% to 92%) at a Berlin score of 8 or greater, with lower sensitivity (66%, 95% CI 46% to 82%) and higher specificity (86%, 95% CI 64% to 97%) at the higher score of 12 or greater (Figure 10). Four of the five false-positive results at 8 or greater and all three at 12 or greater 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 208 BCCs) pro-

duced a pooled sensitivity for OCT of 95% (95% CI 91% to 97%) and pooled specificity of 77% (95% CI 69% to 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.

Figure 11. Forest plot of tests: pooled data for the detection of basal cell carcinoma (BCC) using visual inspection, dermoscopy, and optical coherence tomography (OCT). CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive.



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

Figure 12. Summary ROC plot of studies comparing optical coherence tomography (OCT) and visual inspection for the detection of basal cell carcinoma (BCC).

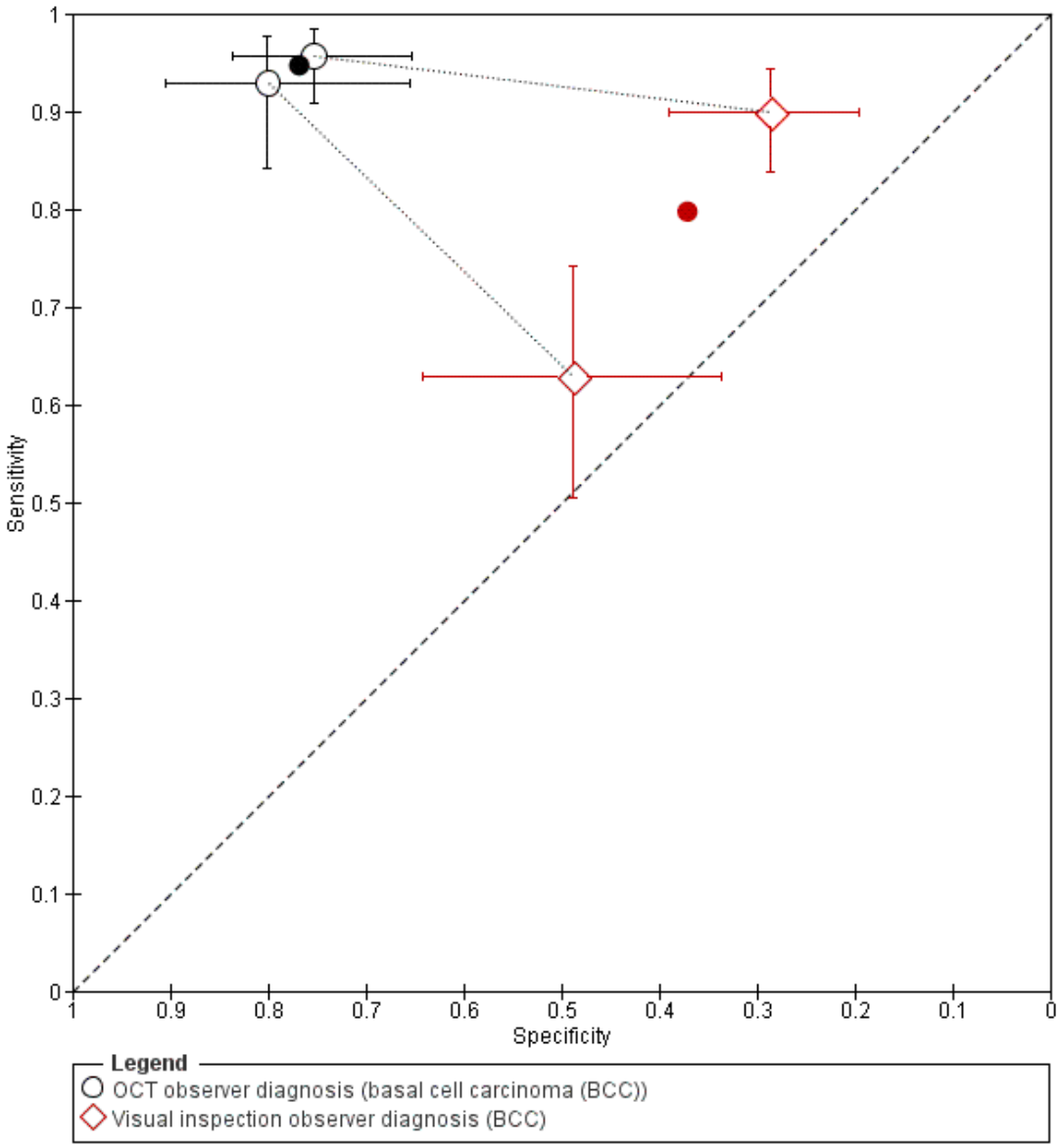
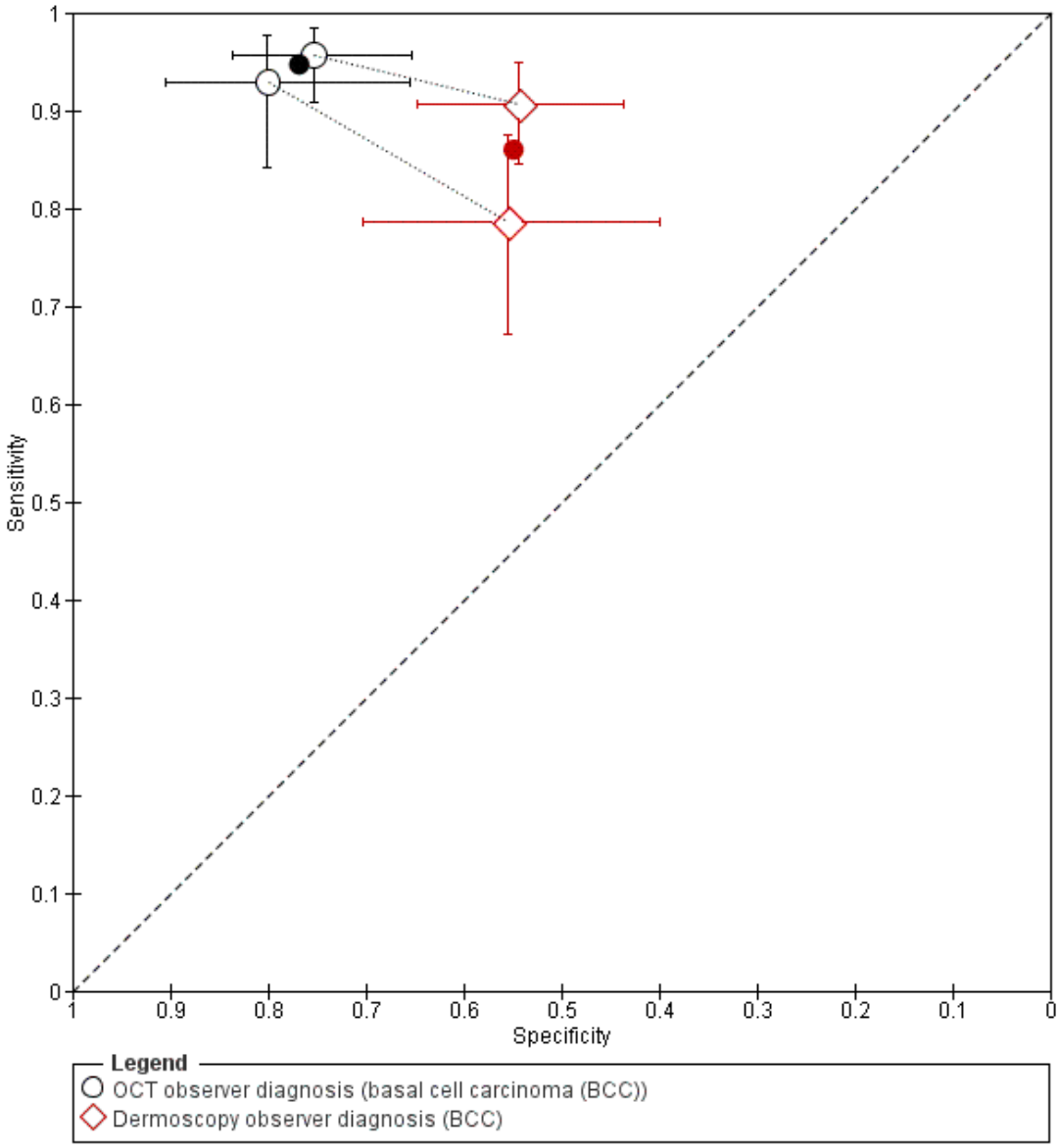


Figure 13. Summary ROC plot of studies comparing optical coherence tomography (OCT) and dermoscopy for the detection of basal cell carcinoma (BCC).



Detection of cutaneous squamous cell carcinoma

One study reported OCT results for the diagnosis of nine cSCCs among a group of 50 lesions consisting of BCCs (29 lesions),

actinic keratoses (five lesions), and Bowen's disease (seven lesions) (Wahrlich 2015). Using the quantitative scoring of conventional swept-source OCT characteristics reported above, sensitivity was 56% (95% CI 21% to 86%) and specificity was 100% (91% to 100%) at a score of 8 or greater, with a lower sensitivity using a score of 12 or greater (33%, 95% CI 7% to 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.

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 OCT as an aid to diagnosing melanoma, BCC, or cSCC in adults. We included five studies evaluating OCT, two of which also evaluated visual inspection and visual inspection plus dermoscopy (Summary of findings).

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 several 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. There was limited information provided regarding the qualifications of the clinicians undertaking and interpreting the tests. All studies established the final diagnoses by histology; however, reference standard interpretation was poorly described.

For the detection of melanoma, the paucity of studies, small sample sizes, and differences in the tests made 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% to 100%) and specificity of 61% (95% CI 42% to 78%); however, low resolution was problematic. HD 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% to 89%) and specificity of 92% (95% CI 83% to 97%) for the detection of melanoma or atypical intraepidermal melanocytic variants. We found no data 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 a pooled sensitivity of 95% (95% CI 91% to 97%) and specificity of 77% (95% CI 69% to 83%). In both studies, OCT was statistically significantly more sensitive and more specific compared to visual inspection alone (sensitivity 15% higher and specificity 40% higher) and compared to visual inspection plus dermoscopy (sensitivity 9% higher and specificity 22% higher). Summary of findings translated 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 plus 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 plus 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 was unclear whether these results would be reproducible. Producing the only evidence for the detection of cSCC, this study suggested that OCT was poor in its ability to discriminate between BCC and cSCC when the 'Berlin score' was used. However, the study included few cSCC cases that were retrospectively selected as 'controls' against the detection of BCC cases, and so was at high risk of having produced biased results. No studies evaluated HD OCT technology for the detection and discrimination of keratinocyte skin cancers.

Strengths and weaknesses of the review

The strengths of this review included 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 methodological quality was undertaken.

The main concerns for the review regarding 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 prespecification 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 raised 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 optical coherence tomography (OCT) for the detection of melanoma or cutaneous squamous cell carcinoma (cSCC). For the detection of basal cell carcinoma (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 OCT 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 high-definition (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 reflectance confocal microscopy (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 prespecified 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 participants 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 Ann 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;

• our expert advisor and co-author on the review, Hamid Tehrani, and on the protocol for keratinocyte skin cancer, Fiona Bath-Hextall; and

• all members of our Advisory Group (Jonathan Bowling, Seau Tak Cheung, 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, Angela Webster).

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, as well as Anne Lawson, who copy-edited this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gambichler 2015c

Study characteristics	
Patient sampling	**Study design:** case series **Data collection:** prospective **Period of data collection:** NR **Country:** Germany **Funding:** Agfa Healthcare
Patient characteristics and setting	**Inclusion criteria:** people 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, histopathological confirmation of non-melanocytic skin lesion **Sample size (participants):** number eligible: NR; number included: 64 **Sample size (lesions):** number eligible: NR; number included: 93 **Participant characteristics:** none reported **Lesion characteristics:** mean Breslow thickness of correctly identified melanoma (all invasive) 1.2 (SD 1.1) mm; 20 lesions. Mean Breslow thickness of missed melanoma (false negatives) 0.29 (SD 0.23) mm for 5 invasive MM, plus melanoma in situ
Index tests	**HD-OCT** (Skintell; Agfa, Belgium); resolution 3 μm lateral by 5 μm axial; tissue penetration 570 μm; centre wavelength 1300 nm; the 3D images of the scans showing the best quality (i.e. no artefacts) were chosen **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 $\geq$ -1 indicated melanoma, a score $\geq$ -1.5 indicated benign melanocytic skin lesion, i.e. melanoma present if score $\geq$ -1 and < -1.5 **Method of diagnosis:** image-based **Prior test data available:** none; blinded to clinical examination and dermoscopy **Diagnosis based on:** single (1) **Observer qualifications:** NR; presumed dermatologist **Experience in practice:** NR **Experience with index test:** high; described as "OCT-experienced investigator" **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."

Gambichler 2015c (*Continued*)

Target condition and reference standard(s)	**Type of reference standard:** histology alone **Details:** lesions completely excised and processed for routine haematoxylin and eosin staining, plus immunohistochemistry for S100 and MART/Melan-A **Disease positive:** 27; **disease negative:** 66 **Target condition (final diagnoses):** invasive melanoma: 25; melanoma in situ: 2. Benign nevi: 66 (23 compound naevi, 20 junctional naevi, 10 dermal naevi, 9 dysplastic naevi, 2 nevoid lentigo and 2 blue naevi)
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
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included participants and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Optical coherence tomography			
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		
		Unclear	**High**
DOMAIN 2: Index Test Dermoscopy			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
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		
DOMAIN 3: Reference Standard			
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		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		

Gambichler 2015c (*Continued*)

Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
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 1 algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

Markowitz 2015

Study characteristics	
Patient sampling	**Study design:** case series **Data collection:** prospective **Period of data collection:** NR **Country:** USA **Funding:** study was sponsored by Michelson Diagnostics
Patient characteristics and setting	**Inclusion criteria:** consecutive participants with clinically challenging pink lesions on the head or neck and that were suspicious for BCC and therefore to be biopsied to rule BCC in or out; also

	required to be eligible for Mohs surgery; maximum of 3 lesions per participant **Setting:** secondary (general dermatology) **Prior testing:** clinical or dermoscopic suspicion of malignancy; decision to perform diagnostic biopsy was made following clinical, dermoscopic, and OCT evaluation **Setting for prior testing:** secondary (general dermatology) **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 **Sample size (participants):** number included: 100 **Sample size (lesions):** number included: 115 **Participant characteristics:** none reported **Lesion characteristics:** all head and neck
Index tests	**Visual inspection:** 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 non-healing area of concern or the clinician's inability to rule out BCC **Diagnosis based on:** unclear; likely in clinic diagnoses (number 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 Malvehy 2002 **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Diagnostic threshold:** dermoscopic features consistent with BCC: arborised 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 **OCT:** no algorithm; multi-beam swept-source frequency domain (VivoSight; Michelson Diagnostics, UK); resolution axial 10 μm, lateral 7.5 μm; tissue penetration 2000 μm; centre wavelength 1305 nm; "multi-1" setting automatically provided 60 lateral scans of 6 mm length every 100 μm **Method of diagnosis:** image-based; OCT scans obtained at time of visual inspection and dermoscopic diagnoses and read within 1 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 (Maier 2013; Ulrich 2015; Wahrlich 2015): "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
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)

Flow and timing	**Excluded participants:** none reported **Time interval to reference test:** appeared consecutive; Figure 2 described the OCT scans undertaken at the time of clinical examination and dermoscopy; diagnostic biopsy was then performed and the "OCT scan is read within a week, prior to obtaining the results of the diagnostic biopsy."
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 1 week
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included participants and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Optical coherence tomography			
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		
		Low	**High**

DOMAIN 2: Index Test Visual inspection			
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		
		Low	**Unclear**
DOMAIN 2: Index Test Test group E			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
DOMAIN 2: Index Test Test group F			
Was the test applied and interpreted in a clinically applicable manner?	Unclear		
DOMAIN 2: Index Test Test group G			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
DOMAIN 2: Index Test Test group H			
Was the test interpretation carried out by an experienced examiner?	Unclear		
DOMAIN 2: Index Test Dermoscopy			
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?			
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		
		Low	**Unclear**
DOMAIN 2: Index Test Test group J			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
DOMAIN 2: Index Test Test group K			
Was the test applied and interpreted in a clinically applicable manner?	Unclear		
DOMAIN 2: Index Test Test group L			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
DOMAIN 2: Index Test Test group M			
Was the test interpretation carried out by an experienced examiner?	Unclear		
DOMAIN 3: Reference Standard			

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		
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		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
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 1 algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	
DOMAIN 5: Comparative			
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 1 month?	Yes		
Were all tests applied and interpreted in a clinically applicable manner?	Unclear		
		Low	**Unclear**

Ulrich 2015

Study characteristics	
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)
Patient characteristics and setting	**Inclusion criteria:** people 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) **Setting:** multi-centre study; authors' institutions included 4 Dermatology departments and 3 private dermatology clinics **Prior testing:** inclusion was based on clinical assessment alone, without the assistance of dermoscopy **Setting for prior testing:** unspecified **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. People with unstable or uncontrolled clinically significant medical conditions were excluded. 21 Lesions with missing histology also excluded

	Sample size (participants): number eligible: 164; number included: 155 **Sample size (lesions):** number eligible: 256; number included: 235 (different sets of 231 lesions were available for each test) **Participant characteristics:** median age: 70 years (range 33-90 years) **Lesion characteristics:** head/neck: 41%; upper body 48.8%
Index tests	**Visual inspection:** 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 macules, patches, or small papules with or without scale **Diagnosis based on:** single observer; (number NR; 6 centres participated) **Observer qualifications:** 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 or case notes (or both) **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, USA), attached to a Sony Cybershot DSC-W710 camera (Sony, Tokyo, Japan) (supplied by MDL). As polarised 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 10 μm, lateral 7.5 μm; tissue penetration 2000 μm; centre wavelength 1305 nm; the function 'multi-1' setting automatically provided 60 lateral scans of 6 mm length every 100 μm **Method of diagnosis:** in-person; OCT images were assessed following dermoscopy by naked eye for features affecting the epidermis, DEJ, and dermis **Prior test data available:** clinical examination 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 cited Boone 2012 as having been published since the study was designed. **Observers:** as above. All centres described as regular users of OCT, with $\geq$ 3 months of practical experience with the device. Nonetheless, all centres received training before participating in the study
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 AK, 17 BD, 6 SK, 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 2×2 varied		
Flow and timing	**Excluded participants:** histology was missing for 21 lesions, and 1 case had a combination of both BCC and SK or AK, leaving 235 lesions for analysis in the ITT group **Time interval to reference test:** consecutively done after index test, "All diagnostic steps had to be completed before histological confirmation was made."		
Comparative	Time interval between index test(s): consecutive		
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included participants and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Optical coherence tomography			
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		
		Low	**Low**

DOMAIN 2: Index Test Visual inspection			
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		
		Low	**Low**
DOMAIN 2: Index Test Test group E			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
DOMAIN 2: Index Test Test group F			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
DOMAIN 2: Index Test Test group G			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
DOMAIN 2: Index Test Test group H			
Was the test interpretation carried out by an experienced examiner?	Yes		
DOMAIN 2: Index Test Dermoscopy			
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?			
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		
		Low	**Low**
DOMAIN 2: Index Test Test group J			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
DOMAIN 2: Index Test Test group K			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
DOMAIN 2: Index Test Test group L			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
DOMAIN 2: Index Test Test group M			
Was the test interpretation carried out by an experienced examiner?	Yes		
DOMAIN 3: Reference Standard			

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		
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		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
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?			

Ulrich 2015 (*Continued*)

If more than 1 algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	
DOMAIN 5: Comparative			
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 1 month?	Yes		
Were all tests applied and interpreted in a clinically applicable manner?	Yes		
		Low	**Low**

Wahrlich 2015

Study characteristics	
Patient sampling	**Study design:** unclear **Data collection:** retrospective **Period of data collection:** September 2011 to June 2012 **Country:** Germany **Funding:** none; OCT device provided by Michelson Diagnostics
Patient characteristics and setting	**Inclusion criteria:** participants with non-melanoma skin cancer including BCC or other skin lesions; phase 1 of study excluded as student observers **Setting:** secondary (Dermatology) **Prior testing:** unclear **Exclusion criteria:** preoperated or ulcerated lesions **Sample size (participants):** number eligible: NR; number included: 50 **Sample size (lesions):** number eligible: 50; number included: 50 **Participant characteristics:** mean age 62.8 years; 46% men **Lesion characteristics:** none reported
Index tests	**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 10 μm, lateral 7.5 μm; tissue penetration 2000 μm; centre wavelength 1305 nm; performed using

	free-run and multi-slice functions on an area of 6 × 6 × 2 mm. Affected areas were shaved (hairy areas) or pretreated with Sellotape (scaly lesions) as required **Diagnostic threshold:** 2 thresholds assessed, Berlin score ≥ 8 (T1 limit) and of ≥ 12 (T2 limit) **Method of diagnosis:** unclear **Prior test data available:** unclear; appeared that following histological diagnosis the histologist then retrospectively examined the OCT images **Diagnosis based on:** single (1) **Observer qualifications:** dermatopathologist; described as "dermatological specialist/dermatopathologist and expert familiar with OCT" **Experience in practice:** high **Experience with index test:** high **Other detail:** BCC features subdivided into major (dark borders underneath the tumour, hyporeflective nests and ovoid structures) and minor criteria (disruption of DEJ and cysts). Presence of feature classed between 0 (absent) and 3 (clearly recognisable 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 2009a; Sabban 2004; Vogt 2003; Zhao 2008).
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; BD 7; AK 5
Flow and timing	**Index test to reference standard interval:** consecutive; OCT described as followed by excision or biopsy **Exclusions:** discussion reported exclusion of 3 participants due to anatomical position, different scan 'heights' and shadow artefacts
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		

Are the included participants and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Optical coherence tomography			
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		
		High	**High**
DOMAIN 2: Index Test Dermoscopy			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
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		
DOMAIN 3: Reference Standard			
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		
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		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
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 1 algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

		High	

Wessels 2015

Study characteristics	
Patient sampling	**Study design:** case series **Data collection:** prospective **Period of data collection:** November 2011 to April 2012 **Country:** Netherlands **Funding:** none declared
Patient characteristics and setting	**Inclusion criteria:** consecutive participants 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 (participants):** number eligible: NR; number included: 33 **Sample size (lesions):** number eligible: NR; number included: 40 **Participant characteristics:** mean age 46 (SD 16) years; 42% men; 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 of melanomas was 4.28 mm^{-1}
Index tests	**OCT:** no algorithm; swept-source OCT (Santec Inner Vision 2000); resolution axial 10 μm, lateral 20 μm; tissue penetration 2000 μm; centre wavelength 1300 nm; for each lesion 5 2D and 1 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 **Diagnostic threshold:** investigated accuracy of 2 morphological features on 3D scans (absence of clear DEJ and no lower boundary of lesion visible) and attenuation coefficient based on 2D scans 5.4 mm^{-1} (optimal threshold estimated via Youden index) **Method of diagnosis:** image-based **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." **Diagnosis based on:** single (1) **Observer qualifications:** unclear; investigator institution Department of Surgery **Experience in practice:** not described **Experience with index test:** not described **Other detail:** epidermal layer thickness and the attenuation coefficient (μoct 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)."

Target condition and reference standard(s)	**Type of reference standard:** histology alone **Details:** excision; all stained sections were reviewed by 1 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)		
Flow and timing	**Index test to reference standard interval:** consecutive; "After OCT-imaging, excision was performed." **Exclusions:** none reported		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included participants and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Optical coherence tomography			
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		

		High	**High**
DOMAIN 2: Index Test Dermoscopy			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	No		
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		
DOMAIN 3: Reference Standard			
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		
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		

		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
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 1 algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

2D: two dimensional; 3D: three dimensional; AK: actinic keratosis; BCC: basal cell carcinoma; BD: Bowen's 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; OCT: optical coherence tomography; RCM: reflectance confocal microscopy; SD: standard deviation; SK: seborrhoeic keratosis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alawi 2013	Exclude on index test OCT used to determine surgical margins

(*Continued*)

Bechara 2004	Exclude on sample size only 3 BCCs Exclude if individual lesion characteristics
Boone 2014	Exclude if individual lesion characteristics
Boone 2015a	Exclude on study population included healthy volunteers; also preselected AK and SCC Exclude if derivation study Study developed a diagnostic algorithm for HD-OCT (no independent test population)
Boone 2015b	Exclude if derivation study Exclude on 2×2 data
Boone 2016	Exclude if derivation study Appeared to be first study assessing optical properties of HD-OCT rather than diagnosis by morphological characteristics
Brudermanns 2008	Exclude not a primary study Comment on Gambichler 2007
Calin 2013	Exclude not a primary study Systematic review
Coleman 2013	Exclude on study population No results for benign lesions
Cunha 2011	Exclude on study population All BCC cases (no benign lesions)
de Boer 2016	Exclude not a primary study Systematic review (not addressing OCT)
de Giorgi 2005	Exclude if individual lesion characteristics Exclude if derivation study
Evans 2014	Exclude not a primary study Editorial review
Forsea 2010	Exclude on sample size Exclude if derivation study
Gambichler 2007	Exclude if derivation study. First study of OCT in skin cancer; looking at features of OCT and comparing with histology Exclude on 2×2 data - not enough data to complete 2x2 table
Gambichler 2014	Exclude on study population BCCs only included

(*Continued*)

Gambichler 2015b	Exclude if individual lesion characteristics Exclude if derivation study
Hinz 2011	Exclude on target condition Assessed tumour thickness only
Hussain 2015	Exclude not a primary study Systematic review
Hussain 2016	Exclude on study population People undergoing follow-up for recurrent BCC Exclude on target condition Recurrent BCC
Jorgensen 2008	Exclude on index test Machine learning OCT
Maier 2013	Exclude on study population - BCCs only included (no disease-negative included)
Marneffe 2016	Exclude on study population AK, SCC, normal skin
Meyer 2014	Exclude on target condition Detection of lesion thickness only
Mogensen 2009a	Exclude on study population Differentiating NMSC from normal skin Exclude on reference standard Not clearly reported; described as 'clinically diagnosed'
Mogensen 2009b	Exclude not a primary study Review/opinion paper
Mogensen 2009c	Exclude on target condition Precision of tumour size measurements
Moraes 2015	Exclude if individual lesion characteristics
Olmedo 2006	Exclude on study population - BCCs only included (no disease-negative included)
Olsen 2015	Exclude not a primary study Systematic review
Picard 2013	Exclude not a primary study Case report
Reggiani 2015	Exclude not a primary study Systematic review

(*Continued*)

Strasswimmer 2004	Exclude on sample size 2 cases presented Exclude if derivation study
Ulrich 2014	Exclude conference abstract Included full paper (Ulrich 2015)
Welzel 1998	Exclude on 2×2 data Not test accuracy; preliminary study of OCT
Wessels 2013	Exclude conference abstract Included full paper (Wessels 2015)
Zakharov 2014	Exclude conference abstract
Zakharov 2015	Exclude on index test Ex-vivo diagnosis not relevant to the review

AK: actinic keratosis; BCC: basal cell carcinoma; HD-OCT: high-definition optical coherence tomography; NMSC: non-melanoma skin cancer; OCT: optical coherence tomography; SCC: squamous cell carcinoma.

Characteristics of studies awaiting classification *[ordered by study ID]*

Cheng 2016

Study characteristics	
Patient sampling	Consecutive group of people at moderate to very high risk of melanoma presenting to Melanoma Institute Australia from April 2014 to March 2015 with possible sBCC based on clinical and dermoscopic findings
Patient characteristics and setting	168 lesions; 52% sBCC, 26% other BCC variants and remaining lesions were AK, squamous cell carcinoma in situ, other benign inflammatory processes, and 2 other malignant tumours
Index tests	Visual examination, dermoscopy, OCT
Target condition and reference standard(s)	BCC, histology (punch biopsy)
Flow and timing	Biopsy performed immediately after OCT scanning
Comparative	No

Cheng 2016 (*Continued*)

Notes	Comparison of 3 observers with varying levels of OCT experience. Confidence in the diagnosis also recorded

Olsen 2016

Study characteristics	
Patient sampling	Retrospective study of image bank from scans performed 2010 to 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 identified in update search; awaiting author communication to allow inclusion (contacted 7 July 2017)

AK: actinic keratosis; BCC: basal cell carcinoma; OCT: optical coherence tomography; sBCC: superficial basal cell carcinoma.

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

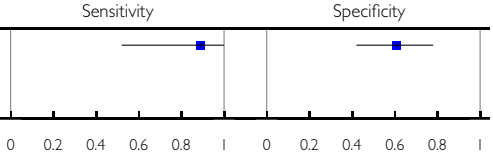
Test	No. of studies	No. of participants
1 Optical coherence tomography (OCT) attenuation coefficient 5.4 mm^{-1} (malignant melanoma (MM) + melanoma in situ (MiS))	1	40
2 High-definition optical coherence tomography (HD-OCT) Gambichler score ≥ -1 (MM + MiS)	1	93
3 HD-OCT - Gambichler score ≥ -1 (MM)	1	93
4 OCT observer diagnosis (basal cell carcinoma (BCC))	2	346
5 Visual inspection 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 (cutaneous squamous cell carcinoma (cSCC))	1	50
10 OCT Berlin score ≥ 12 (cSCC)	1	50

Test 1. Optical coherence tomography (OCT) attenuation coefficient 5.4 mm^{-1} (malignant melanoma (MM) + melanoma in situ (MiS)).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 1 Optical coherence tomography (OCT) attenuation coefficient 5.4 mm^{-1} (malignant melanoma (MM) + melanoma in situ (MiS))

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



Test 2. High-definition optical coherence tomography (HD-OCT) Gambichler score ≥ -1 (MM + MiS).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 2 High-definition optical coherence tomography (HD-OCT) Gambichler score ≥ - 1 (MM + MiS)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Gambichler 2015c	20	5	7	61	0.74 [0.54, 0.89]	0.92 [0.83, 0.97]		

Test 3. HD-OCT - Gambichler score ≥ -1 (MM).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 3 HD-OCT – Gambichler score ≥ - 1 (MM)

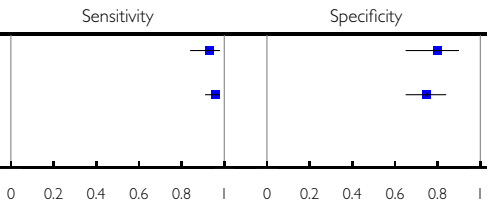
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Gambichler 2015c	20	5	5	63	0.80 [0.59, 0.93]	0.93 [0.84, 0.98]		

Test 4. OCT observer diagnosis (basal cell carcinoma (BCC)).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 4 OCT observer diagnosis (basal cell carcinoma (BCC))

Study	TP	FP	FN	TN	Sensitivity	Specificity
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]

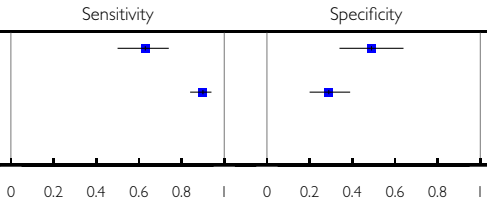


Test 5. Visual inspection observer diagnosis (BCC).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 5 Visual inspection observer diagnosis (BCC)

Study	TP	FP	FN	TN	Sensitivity	Specificity
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]

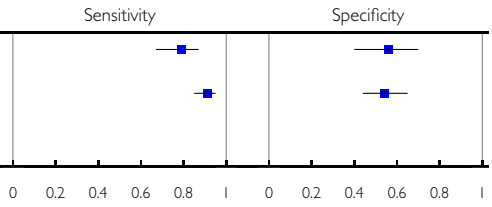


Test 6. Dermoscopy observer diagnosis (BCC).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 6 Dermoscopy observer diagnosis (BCC)

Study	TP	FP	FN	TN	Sensitivity	Specificity
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]

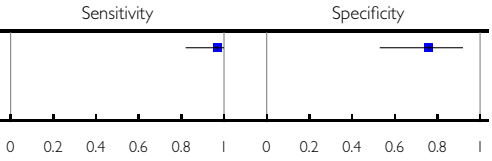


Test 7. OCT Berlin score ≥ 8 (BCC).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 7 OCT Berlin score ≥ 8 (BCC)

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

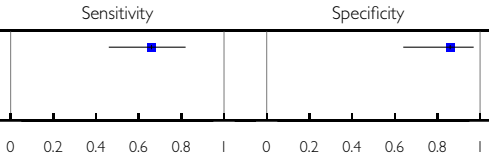


Test 8. OCT Berlin score ≥ 12 (BCC).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 8 OCT Berlin score ≥ 12 (BCC)

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

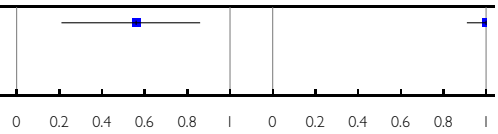


Test 9. OCT Berlin score ≥ 8 (cutaneous squamous cell carcinoma (cSCC)).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 9 OCT Berlin score ≥ 8 (cutaneous squamous cell carcinoma (cSCC))

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

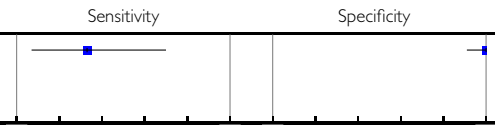


Test 10. OCT Berlin score ≥ 12 (cSCC).

Review: Optical coherence tomography for diagnosing skin cancer in adults

Test: 10 OCT Berlin score ≥ 12 (cSCC)

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



ADDITIONAL TABLES

Table 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
Arborising 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 in situ and lentigo maligna
Atypical naevi	Unusual looking but non-cancerous mole or area of darker pigmentation of the skin
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 optical coherence tomography system to distinguish between 2 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 inhibitors	Therapeutic agents which inhibit the serine-threonine protein kinase BRAF-mutated metastatic melanoma
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
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in millimetres from the top layer of skin to the bottom of the tumour
Congenital naevi	A type of mole found on infants at birth
Dermal nests	Collections of pigment cells that are bunched together in the dermis

Table 1. Glossary of terms (*Continued*)

Dermal papilla	Small projections of the dermis into the overlying epidermis giving an undulating pattern and visible as 'fingerprints' in hands and feet
Dermoepidermal junction	The area where the lower part of the epidermis and top layer of the dermis meet
Dermoscopy	Whereby a hand-held microscope is used to allow more detailed, magnified examination of the skin compared to examination by the naked eye alone
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 squamous cell carcinoma	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 using a fine needle-shaped instrument
Epidermis	Outer layer of the skin
False negative	A person who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free
False positive	A person 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
Horizontal signal intense cords	Thick hyperechogenic lines that form a mesh like network, orientated horizontally, with hypoechogenic areas within it
Hyperechogenic	An area of brightness on an OCT scan representing an increased response of tissue during imaging
Hypertrophic actinic keratosis	Precancerous scaly patches of skin that are particularly thickened
Hypoechogenic	Displaying lower echogenicity reflecting and appears darker on ultrasonography
Incidence	The number of new cases of a disease in a given time period

Table 1. Glossary of terms (*Continued*)

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 opposed 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	Describes the ability of an optical coherence tomography system to distinguish between 2 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
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

Table 1. Glossary of terms (*Continued*)

	expressed as deaths per 100, 1000, 10,000, or 100,000 people
Multi-disciplinary team	A team with members from different healthcare professions and specialities (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	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	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
ROC analysis	The analysis of an 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

Table 1. Glossary of terms (*Continued*)

Reflectance confocal microscopy (RCM)	A microscopic technique using infrared light (either in a hand-held 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 2 points in space as being separate points; resolution is measured in 2 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
Sensitivity	In this context the term is used to mean the proportion of people with a disease who have that disease correctly identified by the study test
Specificity	The proportion of people without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Spectroscopy	Study of the interaction between matter and electromagnetic radiation
Spindle subtypes of SCC	A squamous cell carcinoma variant characterised by poorly differentiated spindle cells surrounded by collagenous stroma
Spinous-granular layer	1 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 person'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

Table 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 subscores 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 (+) or protective (-) (or both) 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 subscores for the various particular criteria."
Wessels 2015 SS-OCT	Attenuation coefficient 5.4 mm^{-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 5.4 mm^{-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 (μoct)' plots OCT signal decay by its penetration depth. The authors hypothesised that this tracks morphological and physiological changes in tissue.) Study also investigated accuracy of 2 morphological features on 3D scans (absence of clear DEJ 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 analysed for protrusions into the dermis with shadowing;

Table 2. Description of diagnostic thresholds used by optical coherence tomography for the detection of all target conditions (*Continued*)

		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')."
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 cited Boone 2012's identification of features for BCC as having been published since the study was designed
Wahrlich 2015 SS-OCT	1. Berlin score $\geq$ 8 2. Berlin score $\geq$ 12	BCC features subdivided into major (dark borders underneath the tumour, hyporeflective nests, and ovoid structures) and minor criteria (disruption of DEJ and cysts). The presence of each feature was classed between 0 (absent) and 3 (clearly recognisable 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 $\geq$ 8 and T2 $\geq$ 12. Main diagnostic features were based on already existing data from other study groups (Khandwala 2010; Mogensen 2009a; Sabban 2004; Vogt 2003; Zhao 2008).

2D: two dimensional; 3D: three-dimensional; BCC: basal cell carcinoma; DEJ: dermoepidermal junction; HD-OCT: high-definition optical coherence tomography; MM: malignant melanoma; MSL: melanocytic skin lesion; OCT: optical coherence tomography; RCM: reflectance confocal microscopy; SS-OCT: swept-source optical coherence tomography.

APPENDICES

Appendix 1. Current content and structure of the Programme Grant

	LIST OF REVIEWS	Number of studies
	Diagnosis of melanoma	
1	Visual inspection	49
2	Dermoscopy +/- visual inspection	104
3	Teledermatology	22
4	Smartphone applications	2
5a	Computer-assisted diagnosis - dermoscopy-based techniques	42
5b	Computer-assisted diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
6	Reflectance confocal microscopy	18
7	High-frequency ultrasound	5
	Diagnosis of keratinocyte skin cancer (BCC and cSCC)	
8	Visual inspection +/- Dermoscopy	24
5c	Computer-assisted diagnosis - dermoscopy-based techniques	Review amalgamated into 5a
5d	Computer-assisted diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
9	Optical coherence tomography	5
10	Reflectance confocal microscopy	10
11	Exfoliative cytology	9
	Staging of melanoma	
12	Imaging tests (ultrasound, CT, MRI, PET-CT)	38
13	Sentinel lymph node biopsy	160
	Staging of cSCC	
	Imaging tests review	Review dropped; only one study identified

(*Continued*)

13	Sentinel lymph node biopsy	Review amalgamated into 13 above (n = 15 studies)

Appendix 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 nmsc.ti,ab.
6 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
7 (BCC or CSCC or NMSC).ti,ab.
8 keratinocy$.ti,ab.
9 or/1-8
10 dermoscop$.ti,ab.
11 dermatoscop$.ti,ab.
12 photomicrograph$.ti,ab.
13 (epiluminescence adj2 microscop$).ti,ab.
14 (confocal adj2 microscop$).ti,ab.
15 (incident light adj2 microscop$).ti,ab.
16 (surface adj2 microscop$).ti,ab.
17 (visual adj (inspect$ or examin$)).ti,ab.
18 ((clinical or physical) adj examin$).ti,ab.
19 3 point.ti,ab.
20 three point.ti,ab.
21 pattern analys$.ti,ab.
22 ABCD$.ti,ab.
23 menzies.ti,ab.
24 7 point.ti,ab.
25 seven point.ti,ab.
26 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.

27 artificial intelligence.ti,ab.
28 AI.ti,ab.
29 computer assisted.ti,ab.
30 computer aided.ti,ab.
31 neural network$.ti,ab.
32 MoleMax.ti,ab.
33 image process$.ti,ab.
34 automatic classif$.ti,ab.
35 image analysis.ti,ab.
36 SIAscop$.ti,ab.
37 Aura.ti,ab.
38 (optical adj2 scan$).ti,ab.
39 MelaFind.ti,ab.
40 SIMSYS.ti,ab.
41 MoleMate.ti,ab.
42 SolarScan.ti,ab.
43 VivaScope.ti,ab.
44 (high adj3 ultraso$).ti,ab.
45 (canine adj2 detect$).ti,ab.
46 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
47 smartphone$.ti,ab.
48 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
49 Mole Detective.ti,ab.
50 Spot Check.ti,ab.
51 (mole$1 adj2 map$).ti,ab.
52 (total adj2 body).ti,ab.
53 exfoliative cytolog$.ti,ab.
54 digital analys$.ti,ab.
55 (image$1 adj3 software).ti,ab.
56 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.
57 (optical coherence adj (technolog$ or tomog$)).ti,ab.
58 (computer adj2 diagnos$).ti,ab.
59 (sentinel adj2 node).ti,ab.
60 nevisense.mp. or HFUS.ti,ab.
61 electrical impedance spectroscopy.ti,ab.
62 history taking.ti,ab.
63 patient history.ti,ab.
64 (naked eye adj (exam$ or assess$)).ti,ab.
65 (skin adj exam$).ti,ab.
66 ugly duckling.mp. or UD.ti,ab.
67 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.
68 ABCDE.mp. or VOC.ti,ab.
69 clinical accuracy.ti,ab.
70 (Family adj (Practice or Physicians)).ti,ab.
71 (confocal adj2 microscop$).ti,ab.
72 clinical competence.ti,ab.
73 diagnostic algorithm$1.ti,ab.
74 checklist$.ti,ab.
75 virtual imag$1.ti,ab.
76 volatile organic compound$1.ti,ab.
77 dog$1.ti,ab.
78 gene expression analy$.ti,ab.

79 reflex transmission imag$.ti,ab.
80 thermal imaging.ti,ab.
81 elastography.ti,ab.
82 or/10-81
83 (CT or PET).ti,ab.
84 PET-CT.ti,ab.
85 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
86 deoxy-glucose.ti,ab.
87 deoxyglucose.ti,ab.
88 CATSCAN.ti,ab.
89 positron emission tomograph$.ti,ab.
90 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
91 Doppler echography.ti,ab.
92 sonograph$.ti,ab.
93 ultraso$.ti,ab.
94 doppler.ti,ab.
95 magnetic resonance imag$.ti,ab.
96 or/83-95
97 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
98 96 and 97
99 82 or 98
100 9 and 99

Database: Embase 1974 to 29 August 2016

Search strategy:
1 *melanoma/
2 *skin cancer/
3 *basal cell carcinoma/
4 basalioma$.ti,ab.
5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$ or adenoma$ or epithelioma$ or lesion$ or malignan$ or nodule$)).ti,ab.
6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.
7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
8 nmsc.ti,ab.
9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
10 (BCC or cscc).mp. or NMSC.ti,ab.
11 keratinocyte.ti,ab.
12 keratinocy$.ti,ab.
13 or/1-12
14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.
17 *epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.

28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 MoleMax.ti,ab.
38 exp diagnosis, computer-assisted/
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 (optical adj2 scan$).ti,ab.
44 Aura.ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 confocal microscop$.ti,ab.
51 (high adj3 ultraso$).ti,ab.
52 (canine adj2 detect$).ti,ab.
53 ((mobile or cell$ or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
54 smartphone$.ti,ab.
55 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
56 Spot Check.ti,ab.
57 Mole Detective.ti,ab.
58 (mole$1 adj2 map$).ti,ab.
59 (total adj2 body).ti,ab.
60 exfoliative cytolog$.ti,ab.
61 digital analys$.ti,ab.
62 (image$1 adj3 software).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.
64 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$).mp. or tele-dermatoscop$.ti,ab.
65 (computer adj2 diagnos$).ti,ab.
66 *sentinel lymph node biopsy/
67 (sentinel adj2 node).ti,ab.
68 nevisense.ti,ab.
69 HFUS.ti,ab.
70 electrical impedance spectroscopy.ti,ab.
71 history taking.ti,ab.
72 patient history.ti,ab.
73 (naked eye adj (exam$ or assess$)).ti,ab.
74 (skin adj exam$).ti,ab.
75 *physical examination/
76 ugly duckling.ti,ab.
77 UD sign$.ti,ab.
78 ((physician$ or clinical or physical) adj (exam$ or recog$ or triage)).ti,ab.
79 ABCDE.ti,ab.

80 clinical accuracy.ti,ab.
81 *general practice/
82 (confocal adj2 microscop$).ti,ab.
83 clinical competence/
84 diagnostic algorithm$.ti,ab.
85 checklist$1.ti,ab.
86 virtual image$1.ti,ab.
87 volatile organic compound$1.ti,ab.
88 VOC.ti,ab.
89 dog$1.ti,ab.
90 gene expression analys$.ti,ab.
91 reflex transmission imaging.ti,ab.
92 thermal imaging.ti,ab.
93 elastography.ti,ab.
94 dog$1.ti,ab.
95 gene expression analys$.ti,ab.
96 reflex transmission imaging.ti,ab.
97 thermal imaging.ti,ab.
98 elastography.ti,ab.
99 or/14-93
100 PET-CT.ti,ab.
101 (CT or PET).ti,ab.
102 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
103 exp Deoxyglucose/
104 CATSCAN.ti,ab.
105 deoxyglucose.ti,ab.
106 deoxy-glucose.ti,ab.
107 *positron emission tomography/
108 *computer assisted tomography/
109 positron emission tomograph$.ti,ab.
110 *nuclear magnetic resonance imaging/
111 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
112 *echography/
113 Doppler.ti,ab.
114 sonograph$.ti,ab.
115 ultraso$.ti,ab.
116 magnetic resonance imag$.ti,ab.
117 or/100-116
118 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
119 "Sensitivity and Specificity"/
120 *cancer staging/
121 or/118-120
122 117 and 121
123 99 or 122
124 13 and 123

Database: Cochrane Library (Wiley) 2016 searched 30 August 2016 CDSR Issue 8 of 12 2016 CENTRAL Issue 7 of 12 2016 HTA Issue 3 of 4 July 2016 DARE Issue 3 of 4 2015

Search strategy:

#1 melanoma* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyte*
#2 MeSH descriptor: [Melanoma] explode all trees
#3 "skin cancer*"
#4 MeSH descriptor: [Skin Neoplasms] explode all trees

#5 skin near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#6 nmsc
#7 "squamous cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*) near/2 (skin or epiderm* or cutaneous)
#8 "basal cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#9 pigmented near/2 (lesion* or nevus or mole* or naevi or naevus or nevi or skin)
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 dermoscop*
#12 dermatoscop*
#13 Photomicrograph*
#14 MeSH descriptor: [Dermoscopy] explode all trees
#15 confocal near/2 microscop*
#16 epiluminescence near/2 microscop*
#17 incident next light near/2 microscop*
#18 surface near/2 microscop*
#19 "visual inspect*"
#20 "visual exam*"
#21 (clinical or physical) next (exam*)
#22 "3 point"
#23 "three point"
#24 "pattern analys*"
#25 ABDC
#26 menzies
#27 "7 point"
#28 "seven point"
#29 digital near/2 (dermoscop* or dermatoscop*)
#30 "artificial intelligence"
#31 "AI"
#32 "computer assisted"
#33 "computer aided"
#34 AI
#35 "neural network*"
#36 MoleMax
#37 "computer diagnosis"
#38 "image process*"
#39 "automatic classif*"
#40 SIAscope
#41 "image analysis"
#42 "optical near/2 scan*"
#43 Aura
#44 MelaFind
#45 SIMSYS
#46 MoleMate
#47 SolarScan
#48 Vivascope
#49 "confocal microscopy"
#50 high near/3 ultraso*
#51 canine near/2 detect*
#52 Mole* near/2 map*
#53 total near/2 body
#54 mobile* or smart near/2 phone*

#55 cell next phone*
#56 smartphone*
#57 "mitotic index"
#58 DermoScan or SkinVision or DermLink or SpotCheck
#59 "Mole Detective"
#60 "Spot Check"
#61 mole* near/2 map*
#62 total near/2 body
#63 "exfoliative cytolog*"
#64 "digital analys*"
#65 image near/3 software
#66 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatolog*
#67 "optical coherence" next (technolog* or tomog*)
#68 computer near/2 diagnos*
#69 sentinel near/2 node*
#70 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
#71 ultraso*
#72 sonograph*
#73 MeSH descriptor: [Ultrasonography] explode all trees
#74 Doppler
#75 CT or PET or PET-CT
#76 "CAT SCAN" or "CATSCAN"
#77 MeSH descriptor: [Positron-Emission Tomography] explode all trees
#78 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#79 MRI
#80 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#81 MRI or fMRI or NMRI or scintigraph*
#82 "magnetic resonance imag*"
#83 MeSH descriptor: [Deoxyglucose] explode all trees
#84 deoxyglucose or deoxy-glucose
#85 "positron emission tomograph*"
#86 #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85
#87 stage* or staging or metasta* or recurrence or sensitivity or specificity or "false negative*" or thickness*
#88 MeSH descriptor: [Neoplasm Staging] explode all trees
#89 #87 or #88
#90 #89 and #86
#91 #70 or #90
#92 #10 and #91
#93 BCC or CSCC or NMCS
#94 keratinocy*
#95 #93 or #94
#96 #10 or #95
#97 nevisense
#98 HFUS
#99 "electrical impedance spectroscopy"
#100 "history taking"
#101 "patient history"
#102 naked next eye near/1 (exam* or assess*)
#103 skin next exam*

#104 “ugly duckling” or (UD sign*)
#105 MeSH descriptor: [Physical Examination] explode all trees
#106 (physician* or clinical or physical) near/1 (exam* or recog* or triage*)
#107 ABCDE
#108 “clinical accuracy”
#109 MeSH descriptor: [General Practice] explode all trees
#110 confocal near microscop*
#111 “diagnostic algorithm*”
#112 MeSH descriptor: [Clinical Competence] explode all trees
#113 checklist*
#114 “virtual image*”
#115 “volatile organic compound*”
#116 dog or dogs
#117 VOC
#118 “gene expression analys*”
#119 “reflex transmission imaging”
#120 “thermal imaging”
#121 elastography
#122 #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or # 112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121
#123 #70 or #122
#124 #96 and #123
#125 #96 and #90
#126 #125 or #124
#127 #10 and #126

Database : CINAHL Plus (EBSCO) 1937 to 30 August 2016

Search strategy:
S1 (MH “Melanoma”) OR (MH “Nevi and Melanomas+”)
S2 (MH “Skin Neoplasms+”)
S3 (MH “Carcinoma, Basal Cell+”)
S4 basalioma*
S5 (basal cell) N2 (cancer* or carcinoma* or mass or masses or tumor* or tumour* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
S6 (pigmented) N2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin)
S7 melanom* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt*
S8 nmsc
S9 TX BCC or cscc or NMSC
S10 (MH “Keratinocytes”)
S11 keratinocyt*
S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S13 dermoscop* or dermatoscop* or photomicrograph* or (3 point) or (three point) or ABCD* or menzies or (7 point) or (seven point) or AI or Molemax or SIASCOP* or Aura or MelaFind or SIMSYS or MoleMate or SolarScan or smartphone* or DermoScan or SkinVision or DermLink or SpotCheck
S14 (epiluminescence or confocal or incident or surface) N2 (microscop*)
S15 visual N1 (inspect* or examin*)
S16 (clinical or physical) N1 (examin*)
S17 pattern analys*
S18 (digital) N2 (dermoscop* or dermatoscop*)
S19 (artificial intelligence)
S20 (computer) N2 (assisted or aided)
S21 (neural network*)
S22 (MH “Diagnosis, Computer Assisted+”)
S23 (image process*)

S24 (automatic classif*)
S25 (image analysis)
S26 SIAScop*
S27 (optical) N2 (scan*)
S28 (high) N3 (ultraso*)
S29 elastography
S30 (mobile or cell or cellular or smart) N2 (phone*) N2 (app or application*)
S31 (mole*) N2 (map*)
S32 total N2 body
S33 exfoliative cytolog*
S34 digital analys*
S35 image N3 software
S36 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatoscop* teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop*
S37 (optical coherence) N1 (technolog* or tomog*)
S38 computer N2 diagnos*
S39 sentinel N2 node
S40 (MH "Sentinel Lymph Node Biopsy")
S41 nevisense or HFUS or checklist* or VOC or dog*
S42 electrical impedance spectroscopy
S43 history taking
S44 "Patient history"
S45 naked eye
S46 skin exam*
S47 physical exam*
S48 ugly duckling
S49 UD sign*
S50 (physician* or clinical or physical) N1 (exam*)
S51 clinical accuracy
S52 general practice
S53 (physician* or clinical or physical) N1 (recog* or triage)
S54 confocal microscop*
S55 clinical competence
S56 diagnostic algorithm*
S57 checklist*
S58 virtual image*
S59 volatile organic compound*
S60 gene expression analys*
S61 reflex transmission imag*
S62 thermal imaging
S63 S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62
S64 CT or PET
S65 PET-CT
S66 FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical*
S67 (MH "Deoxyglucose+")
S68 deoxy-glucose or deoxyglucose
S69 CATSCAN
S70 CAT-SCAN
S71 (MH "Deoxyglucose+")
S72 (MH "Tomography, Emission-Computed+")

S73 (MH "Tomography, X-Ray Computed")
S74 positron emission tomograph*
S75 (MH "Magnetic Resonance Imaging+")
S76 MRI or fMRI or NMRI or scintigraph*
S77 echography
S78 doppler
S79 sonograph*
S80 ultraso*
S81 magnetic resonance imag*
S82 S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81
S83 stage* or staging or metasta* or recurrence or sensitivity or specificity or (false negative*) or thickness
S84 (MH "Neoplasm Staging")
S85 S83 OR S84
S86 S82 AND S85
S87 S63 OR S86
S88 S12 AND S87

Database: Science Citation Index SCI Expanded (Web of Science) 1900 to 30 August 2016
Conference Proceedings Citation Index (Web of Science) 1900 to 1 September 2016

Search strategy:
#1 (melanom* or nonmelanom* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyt*)
#2 (basalioma*)
#3 ((skin) near/2 (cancer* or carcinoma or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#4 ((basal) near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#5 ((pigmented) near/2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin))
#6 (nmsc or BCC or NMSC or keratinocy*)
#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#8 (skin or epiderm* or cutaneous)
#9 #8 AND #7
#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))
#12 ((nevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))
#13 #11 or #12
#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))
#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))
#16 #14 AND #15
#17 #16 OR #13
#18 #10 AND #17

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

Appendix 3. Full-text inclusion criteria

The title and abstract screening led to the retrieval of a large number of full-text journal papers and conference abstracts from which to complete the four sets of test accuracy reviews and the intervention review. The systematic reviews were largely be carried out sequentially, beginning with the reviews of tests for melanoma diagnosis; however, the full-text papers needed 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 were transferred to an Excel spreadsheet or Google Forms so that pertinent information could be recorded about each eligible study and reasons for exclusion recorded about each ineligible study.

Criterion	Inclusion	Exclusion
Study design	**For diagnostic and staging reviews** • Any study for which a 2×2 contingency table can be extracted, e.g. ○ diagnostic case-control studies ○ 'cross-sectional' test accuracy study with retrospective or prospective data collection ○ studies where estimation of test accuracy was not the primary objective but test results for both index and reference standard were available ○ RCTs of tests or testing strategies where participants were randomised between index tests and all undergo a reference standard (i.e. accuracy RCTs)	• < 5 melanoma cases (diagnosis reviews) • < 10 participants (staging reviews) • Studies developing new criteria for diagnosis unless a separate 'test set' of images were used to evaluate the criteria (mainly digital dermoscopy) • Studies using 'normal' skin as controls • Letters, editorials, comment papers, narrative reviews • Insufficient data to construct a 2×2 table
Target condition	• Melanoma • Keratinocyte skin cancer (or non-melanoma skin cancer) ○ BCC or epithelioma ○ cSCC	• Studies exclusively conducted in children • Studies of non-cutaneous melanoma or SCC
Population	**For diagnostic reviews** • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms included pigmented skin lesion/nevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC **For staging reviews** • Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both	• People suspected of other forms of skin cancer • Studies conducted exclusively in children
Index tests	**For diagnosis** • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscopy • Smartphone/mobile phone applications	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders

(*Continued*)

	• Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High-frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other **For staging** • CT • PET • PET-CT • MRI • Ultrasound +/FNAC • SLNB +/high-frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	• Tests to improve histopathology diagnose • LND
Reference standard	**For diagnostic studies** • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign-appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) **For studies of imaging tests for staging** • Histopathology (via LND or SLNB) • Clinical/radiological follow-up • A combination of the above **For studies of SLNB accuracy for staging** • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	**For diagnostic studies** • 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

Appendix 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?	**Yes** - if paper states consecutive or random **No** - if paper describes other method of sampling **Unclear** - if participant sampling not described
2) Was a case-control design avoided?	**Yes** - if consecutive or random or case-control design clearly not used **No** - if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** - if not described
3) Did the study avoid inappropriate exclusions? • Lesions not excluded on basis of disagreement between evaluators	**Yes** - if inappropriate exclusions were avoided **No** - if lesions were excluded that might affect test accuracy, e.g. where disagreement between evaluators was observed **Unclear** - if not clearly reported
4) For between-person comparative studies only (i.e. allocating different tests to different study participants): • **A)** were the same participant selection criteria used for those allocated to each test? • **B)** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C)** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	**For A)** • **Yes** - if same selection criteria were used for each index test, **No** - if different selection criteria were used for each index test, **Unclear** - if selection criteria per test were not described, **N/A** - if only 1 index test was evaluated or all participants received all tests. **For B)** • **Yes** - if adequate randomisation procedures are described, **No** - if inadequate randomisation procedures are described, **Unclear** - if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient), **N/A** - if only 1 index test was evaluated or all participants received all tests. **For C)** • **Yes** - if appropriate methods of allocation concealment are described, **No** - if appropriate methods of allocation concealment are not described, **Unclear** - if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required), **N/A** - if only 1 index test was evaluated.
Could the selection of participants have introduced bias? **For non-comparative and within-person comparative studies** 1. If answers to all of questions 1), 2), and 3) 'Yes' 2. If answers to any 1 of questions 1), 2), or 3) 'No' 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear' **For between-person comparative studies** 1. If answers to all of questions 1), 2), 3), and 4) 'Yes' 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No'	**For non-comparative and within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For between-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear

(*Continued*)

3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear'	
Participant selection (1) -concerns regarding applicability	
1) Are the included participants and chosen study setting appropriate to answer the review question, i.e. are the study results generalisable? This item is not asking whether exclusion of certain participant groups might bias the study's results (as in 'Risk of bias' above) , but is asking whether the chosen study participants and setting are appropriate to answer our review question	**A) For studies that will contribute to the analysis of participants with suspected melanoma** **Yes** - if study participants appear to be representative of those who might be referred for further investigation. Studies focusing on participant populations with equivocal findings on clinical or dermoscopic (or both) investigation are considered representative of those who could receive OCT in practice **No** - if study participants appear to be unrepresentative of usual practice, e.g. if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear -** if insufficient details are provided to determine the generalisability of study participants **B) For studies that will contribute to the analysis of participants with suspected keratinocyte cancers** **Yes** - if study participants appear to be representative of those who might be referred for further investigation. Studies focusing on participant populations with equivocal findings on clinical or dermoscopic (or both) investigation are considered representative of those who could receive OCT in practice **No** - if study participants appear to be unrepresentative of usual practice, e.g. if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear -** if insufficient details are provided to determine the generalisability of study participants
2) Did the study **avoid including** participants with multiple lesions?	**Yes** - if the difference between the number of included lesions and number of included participants is less than 5% **No** - if the difference between the number of included lesions and number of included participants is greater than 5% **Unclear -** if it is not possible to assess
Is there concern that the included participants do not match the review question? 1. If the answer to question 1) or 2) 'Yes' 2. If the answer to question 1) or 2) 'No' 3. If the answer to question 1) or 2) 'Unclear'	1. Concern is low 2. Concern is high 3. Concern is unclear
Index test (2) -risk of bias (to be completed per test evaluated)	

(*Continued*)

1) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	**Yes** - if index test described as interpreted without knowledge of reference standard result or, for prospective studies, if index test is always conducted and interpreted prior to the reference standard **No** - if index test described as interpreted in knowledge of reference standard result **Unclear** - if index test blinding is not described
2) Was the diagnostic threshold at which the test was considered positive (i.e. melanoma, BCC or cSCC present) prespecified?	**Yes** - if threshold was prespecified (i.e. prior to analysing study results) **No** - if threshold was not prespecified **Unclear** - if not possible to tell whether or not diagnostic threshold was prespecified
3) For within-person comparisons of index tests or testing strategies (i.e. > 1 index test applied per participant): was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	**Yes** - if all index tests were described as interpreted without knowledge of the results of the others **No** - if the index tests were described as interpreted in the knowledge of the results of the others **Unclear** - if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation **N/A** - if only 1 index test was evaluated.
Could the conduct or interpretation of the index test have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1) and 2) 'Yes' 2. If answers to either questions 1) or 2) 'No' 3. If answers to either questions 1) or 2) 'Unclear' **For within-person comparative studies** • If answers to all questions 1), 2), and 3) for any index test 'Yes' • If answers to any 1 of questions 1), 2), or 3) for any index test 'No' • If answers to any 1 of questions 1), 2), or 3) for any index test 'Unclear'	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
Index test (2) -concern about applicability	
1) Was the test applied and interpreted in a clinically applicable manner?	**Yes** - if a single clinician interpreted the scan with the participant present, and made the diagnosis alone **No** - If the accuracy 2×2 data are based on a mean of multiple observers, or consensus across observers; OR if the scan was interpreted using the image alone, as opposed to with the participant present **Unclear** - if insufficient information was reported.
2) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? Study results can only be reproduced if the diagnostic threshold is described in sufficient detail. This item applies equally to studies	**Yes** - if the criteria for diagnosis of melanoma, BCC, or cSCC were reported in sufficient detail to allow replication **No** - if the criteria for diagnosis of melanoma, BCC, or cSCC were not reported in sufficient detail to allow replication

(*Continued*)

using pattern recognition and those using checklists or algorithms to aid test interpretation	**Unclear** - if some but not sufficient information on criteria for diagnosis to allow replication were provided
3) Was the test interpretation carried out by an experienced examiner?	**Yes** - if the test was interpreted by 1 or more speciality-accredited dermatologists, or by examiners of any clinical background with special interest in dermatology and with any formal training in the use of the test, **No** - if the test was not interpreted by an experienced examiner (see above), **Unclear** - if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners described as 'Expert' with no further detail given, **N/A** - if system-based diagnosis, i.e. no observer interpretation
Is there concern that the index test, its conduct, or interpretation differ from the review question? 1. If answers to questions 1), 2), and 3) 'Yes' 2. If answers to questions 1), 2), or 3) 'No' 3. If answers to questions 1), 2), or 3) 'Unclear'	1. Concern is low 2. Concern is high 3. Concern is unclear
Reference standard (3) -risk of bias	
1) Is the reference standard likely to correctly classify the target condition? **A) Disease-positive** - 1 or more of the following: • histological confirmation of melanoma, 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. **B) Disease-negative** - 1 or more of the following: • 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.	**A) Disease-positive** **Yes** - if all participants with a final diagnosis of melanoma, BCC, or cSCC underwent 1 of the listed reference standards **No** - if a final diagnosis of melanoma, BCC, or cSCC for any participant was reached without histopathology **Unclear** - if the method of final diagnosis was not reported for any participant with a final diagnosis of 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 **B) Disease-negative** **Yes** - if at least 80% of benign diagnoses were reached by histology and up to 20% were reached by clinical follow-up for a minimum of 6 (or 3) months following the index test **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 **Unclear** - if the method of final diagnosis was not reported for any participant with benign diagnosis
2) Were the reference standard results interpreted without knowledge of the results of the index test? Please score this item for all studies even though histopathology interpretation is usually conducted with knowledge of the clinical diagnosis (from visual inspection or dermoscopy or both). We will	**Yes** - if the reference standard diagnosis was reached blinded to the index test result **No** - if the reference standard diagnosis was reached with knowledge of the index test result **Unclear** - if blinded reference test interpretation was not clearly

(*Continued*)

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	reported
Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1) 'Yes' 2. If answer to question 1) 'No' 3. If answer to question 1) 'Unclear' **For all other tests** 1. If answers to questions 1) and 2) 'Yes' 2. If answers to questions 1) or 2) 'No' 3. If answers to questions 1) or 2) 'Unclear'	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
Reference standard (3) -concern about applicability	
1) 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 $\leq$ 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 $\leq$ 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 $\geq$ 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

(*Continued*)

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
Could the participant flow have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1), 2), and 3) 'Yes' 2. If answers to any 1 of questions 1), 2), or 3) 'No' 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear' **For within-person comparative studies** 1. If answers to all questions 1), 2), 3), and 4) 'Yes' 2. :If answers to any 1 of questions 1), 2), 3), or 4) 'No' 3. :If answers to any 1 of questions 1), 2), 3), or 4) is 'Unclear'	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma	

Appendix 5. Summary of included study details

Study author Outcomes reported	Study type	Inclusion criteria	Number of participants	Lesion site	Test machine	Resolution tissue penetration centre wavelength	Threshold	Diagnostic method	Observer qualifications (n) Test experience	Test failures	Reference standard	Final diagnoses	Prevalence
Melanoma													
Gambichler 2014 MM alone MM+Mi	NC P-CS Ger	MSL for excision Excluded: frank ulcer-	64/93	Any (not described)	HD-OCT Skintell HD-OCT (Agfa,	Axial 5 μm, lateral 3 μm 570 μm	Score ≥ -1 MM; score of ≥ -1.5 be-	Image-based Blinded to VI/ der-	NR (n = 1) "experienced"	NR	Histology	MM 25; MiS 2; BN 64	27%

(*Continued*)

		ation, marked hyperkeratosis			Belgium)	1300 nm	nign MSL based on sum of subscores for various OCT characteristics	matosco					
Wessels 2015 MM+Mi	NC P-CS Netherlands	PSL scheduled for excision, identified during routine skin cancer screening (all clinically suspicious for melanon 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 10 μm, lateral 20 μm 2000 μm 1300 nm	Attenuation coefficient 5.4 mm^{-1} (data on morphological characteristics excluded)	Image-based Blinding NR	NR (n = 1) NR	NR	Histology	MM 7; MiS 2; BN 31	23%
BCC													

(*Continued*)

Markow 2015 BCC	WPC P-CS USA	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 mets, topical actinic therapy within 8 weeks prior to evaluation, other skin	100/115	Head/neck (not further described)	OCT (swept source) VivoSigh OCT Also reported in-person diagnosis for VI and for dermoscopy	Axial 10 μm, lateral 7.5 μm 2000 μm 1300 nm	Diagnostic judgement (BCC present/absent)	Image-based (unclear if VI/dermoscopy images provided)	NR (n = NR) NR	NR	Histology (biopsy)	BCC 70; other 45 (not described)	61%

(*Continued*)

		conditions within lesion											
Ulrich 2015 BCC	WPCP-CS Germany	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 reported in-person diagnosis for VI and for dermoscopy	Axial 10 μm, lateral 7.5 μm 2000 μm 1300 nm	Diagnostic judgement (BCC present/absent)	In-person (following VI/dermoscopy	NR (n = NR) "regular users;" $\geq$ 3 months' experience	NR	Histology (biopsy or excision)	BCC 141; SK 6; AK 32; BD 17; other 40	60%
Wahrlich 2015 BCC	NCCCS Germany	Selected participants with	50/50	NR	OCT (swept source)	axial 10 μm, lat-	1. Berlin score $\geq$ 8	Image-based (reviewed	Dermatopathologist (n = 1)	NR	Histology	BCC 29; cSCC 9; AK	58%

(*Continued*)

		BCC, cSCC, BD, AK based on prior clinical examination and dermatosco Excluded: ulcerated			VivoSigh OCT	eral 7.5 μm 2000 μm 1300 nm	2. Berlin score $\geq$12	following histopat ogy)	"familiar with OCT"			5; BD 7	
cSCC													
Wahrlich 2015 cSCC	NC CCS Germany	Selected participants with BCC, cSCC, BD, AK based on prior clinical examination and dermatosco Excluded: ulcerated	50/50	NR	OCT (swept source) VivoSigh OCT	Axial 10 μm, lateral 7.5 μm 2000 μm 1300 nm	1. Berlin score $\geq$ 8 2. Berlin score $\geq$12	Image-based (reviewed following histopath ogy)	Dermatopath ogist (n = 1) "familiar with OCT"	NR	Histology	BCC 29; cSCC 9; AK 5; BD 7	18%

AK: actinic keratosis; BCC: basal cell carcinoma; BD: Bowen's disease; BN: benign naevus; CCS: case-control study; cSCC: cutaneous squamous cell carcinoma; HD-OCT: high-definition optical coherence tomography; MiS: melanoma in situ; MM: malignant melanoma; MSL: melanocytic skin lesion; NC: non-comparative study design; NR: not reported; OCT: optical coherence tomography; P-CS: prospective case series; PSL: pigmented skin lesion; SK: seborrhoeic keratosis; VI: visual inspection; WPC: within-person comparison study design.

CONTRIBUTIONS OF AUTHORS

LFR was the contact person with the editorial base.

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

SB conducted the literature searches.

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 Review Manager 5.

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 coauthor 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 (NIHR), via Cochrane Infrastructure funding to the Cochrane Skin Group and Cochrane Programme Grant funding. The views and opinions expressed therein are those of the reviews authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

DECLARATIONS OF INTEREST

LFR: nothing to declare.

JD: nothing to declare.

JJD: nothing to declare.

NC: nothing to declare.

SEB: nothing to declare.

CD: nothing to declare.

YT: nothing to declare.

KG: nothing to declare.

CO: nothing to declare.

RNM: "my institution received a grant for a Barco NV commercially sponsored study to evaluate digital dermoscopy in the skin cancer clinic. My institution also received Oxfordshire Health Services Research Charitable Funds for carrying out a study of feasibility of using the Skin Cancer Quality of Life Impact Tool (SCQOLIT) in non melanoma skin cancer. I have received royalties for the Oxford Handbook of Medical Dermatology (Oxford University Press) and payment from the UK Photopheresis Society for a lecture on cutaneous graft versus host disease (October 2017). I have no conflicts of interest to declare that directly relate to the publication of this work."

HT: nothing to declare.

HCW: "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).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

For the detection of melanomas, we changed primary objectives and primary target condition from detection of cutaneous invasive melanoma alone to the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, as the latter is more clinically relevant to the practicing clinician. These were 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 was instead included as a secondary objective. Due to the fact that a single review covering both melanoma and keratinocyte skin cancers was conducted, the third definition of the target condition as defined in the melanoma protocol was adopted and the following definition from the keratinocyte protocol was dropped "the target condition will include any skin lesion requiring excision. Studies reporting data for keratinocyte skin cancer combined, and not differentiated according to BCC or cSCC, will be included in this analysis, along with any melanoma, or rare skin cancer (e.g. Merkel or amelanotic melanoma) that may be detected. In situ cancers or actinic keratosis will not be considered disease positive."

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.

We amended the text to clarify that studies available only as conference abstracts would be excluded from the review unless full papers could be identified; studies available only as conference abstracts do not allow a comprehensive assessment of study methods or methodological quality.

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 the following: "We 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; or
- investigated lesion characteristics that had previously been suggested as associated with melanoma, BCC or cSCC and the study reported accuracy based on the presence or absence of particular combinations of characteristics.

We excluded studies if they:

- used a statistical model to produce a data driven equation, or algorithm based on multiple diagnostic features, with no separate test set;
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983);
- evaluated the accuracy of the presence or absence of individual OCT characteristics or morphological features, with no overall diagnosis of malignancy."

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 (participant 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.