High frequency ultrasound for the diagnosis of skin cancer in adults

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Abstract

Background

Early accurate detection of all skin cancer types is essential to guide appropriate management and to improve morbidity and survival. Melanoma and 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 curable cases needs to be balanced against inappropriate referral and unnecessary excision of benign lesions. Ultrasound is a non-invasive imaging technique which relies on the measurement of sound wave reflections from the tissues of the body. At lower frequencies, the deeper structures of the body such as the internal organs can be visualised, while high frequency ultrasound (HFUS) with transducer frequencies of at least 20MHz, has a much lower depth of tissue penetration but produces a higher resolution image of tissues and structures closer to the skin surface. Used in conjunction with clinical or dermoscopic examination of suspected skin cancer, or both, HFUS may offer additional diagnostic information compared to other technologies.

Objectives

To determine the diagnostic accuracy of HFUS to assist in the diagnosis of (a) melanoma and intraepidermal melanocytic variants, (b) cutaneous squamous cell carcinoma (cSCC), and (c) basal cell carcinoma (BCC) in adults.

Search methods

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

Selection criteria

Studies evaluating HFUS (>= 20 MHz) in adults with lesions suspicious for melanoma, cSCC or BCC, compared with a reference standard of histological confirmation or clinical follow-up.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). Due to scarcity of data and poor quality of studies, no meta-analysis was undertaken for this review. For illustrative purposes, estimates of sensitivity and specificity were plotted on coupled forest plots.

Main results

Six studies were included, providing 29 datasets, 20 for diagnosis of melanoma (1125 lesions and 242 melanomas) and 9 for diagnosis of BCC (993 lesions and 119 BCCs). No data relating to the diagnosis of cSCC were identified.

Studies were generally poorly reported limiting judgements of methodological quality. Half of studies did not set out to establish test accuracy and all should be considered preliminary evaluations of the potential usefulness of HFUS. There were particularly high concerns for applicability of findings due to selective study populations and data driven thresholds for test positivity. Studies reporting qualitative assessments of HFUS images excluded up to 22% of lesions (including some melanomas) due to them not being visualised by the test.

Derived sensitivities for qualitative HFUS characteristics were at least 83% (95% CI 75% to 90%) for the detection of melanoma; the combination of three features (lesions appearing hypoechoic, homogenous and well defined) demonstrating 100% sensitivity in two studies, with variable corresponding specificities of 33% (95% CI 20% to 48%) and 73% (95% CI 57% to 85%) (lower limits of the 95% CIs for sensitivities were 94% and 82% respectively). Quantitative measurement of HFUS outputs in two studies enabled decision thresholds to be set to achieve 100% sensitivity; specificities were 93% (95% CI 77% to 99%) and 65% (95% CI 51% to 76%). It was not possible to make summary statements regarding HFUS accuracy for the diagnosis of BCC due to highly variable sensitivities and specificities.

Authors' conclusions

Insufficient data are available on the potential value of HFUS in the diagnosis of melanoma or BCC. Given the between study heterogeneity, unclear to low methodological quality and limited volume of evidence, no implications for practice can be drawn. The main value of the preliminary studies included may be in provision of guidance on the possible components of future diagnostic rules for diagnosis of melanoma or BCC using HFUS that require future evaluation. A prospective evaluation of HFUS added to visual inspection and dermoscopy alone in a standard health care setting with a clearly defined and representative population of participants would be required for a full and proper evaluation of accuracy.

Plain language summary

What is the diagnostic accuracy of high frequency ultrasound for the diagnosis of cutaneous melanoma or basal cell carcinoma in adults?

Why is improving the diagnosis of skin cancer important?

There are a number of different types of skin cancer. Melanoma is one of the most dangerous forms and it is important that it is recognised early so that it can be removed. If it is not recognised when first brought to the attention of doctors (also known as a false negative test result) treatment can be delayed resulting in the melanoma spreading to other organs in the body and possibly premature death. Cutaneous squamous cell carcinoma and basal cell carcinoma are usually localised skin cancers, although cutaneous squamous cell carcinoma can spread to other parts of the body and basal cell carcinoma can cause disfigurement if not recognised early. Diagnosing a skin cancer when it is not really a skin cancer (a false positive result) may result in unnecessary surgery and other investigations that can cause stress and anxiety to the patient. Making the correct diagnosis is important. 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 whether high frequency ultrasound can assist in the diagnosis of skin cancer. Researchers in Cochrane included six studies to try and answer this question. Five studies were concerned with the diagnosis of melanoma and three with the diagnosis of basal cell carcinoma.

What was studied in the review?

A number of tools are available to skin cancer specialists which allow a more detailed examination of the skin compared to examination by the naked eye alone. Currently a dermatoscope is used by most skin cancer specialists, which magnifies the skin lesion using a natural light. Ultrasound is another non-invasive imaging technique which measures sound wave reflections from the tissues of the body. High frequency ultrasound can produce a good quality image of structures closer to the skin surface. When used in addition to a doctor’s examination and dermoscopic examination of skin lesions, high frequency ultrasound may offer additional useful information to make a more accurate diagnosis.

What are the main results of the review?

The review included six studies: five studies with a total of 1125 skin lesions suspected of being melanoma and three studies with a total of 993 lesions suspected of being basal cell carcinoma. No studies concerned with the diagnosis of cutaneous squamous cell carcinoma were found.

The included studies were small and too different from each other to allow reliable estimates of accuracy to be made for identifying melanoma or basal cell carcinoma. Half of studies were not actually designed to establish test accuracy and all our included studies should be considered as preliminary experiments on the potential value of high frequency ultrasound. The main value of the studies included may be in helping future researchers understand the best ways of interpreting high frequency ultrasound for the diagnosis of melanoma or basal cell carcinomaCC that will require future evaluation.

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

Study results are not very reliable when considered in total. The small number and variability between studies included in this review reduces the reliability of findings. Included studies also had important limitations. In particular, those taking part in the studies and the way in which the tests were used may not reflect real life situations.

Who do the results of this review apply to?

Studies were all conducted in Europe. Average age was reported in only one study (55.3 years). The percentage of people with a final diagnosis of melanoma ranged between 14% and 58% and ranged from 8% to 49% for basal cell carcinoma. It was not possible to tell whether suspicion of skin cancer in study participants was based on clinical examination alone, or both clinical and dermoscopic examination.

What are the implications of this review?

At present, there is simply not enough good research on the use of high frequency ultrasound to help diagnose skin cancers to say very much. The results of this review suggest that high frequency ultrasound *has potential* to separate melanoma or basal cell carcinoma from particular types of benign lesions, but it is not yet clear whether it can adequately distinguish these skin cancers from the full range of the sorts of things that patients show to their doctors in everyday practice. More studies looking at the use of high frequency ultrasound alongside dermoscopy or other microscopic techniques (such as reflectance confocal microscopy) in well described groups of people with suspicious skin lesions are needed.

How up-to-date is this review?

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

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

Background

This review is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers conducted for the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. Appendix 2 provides a glossary of terms used, and a table of acronyms used is provided in Appendix 3.

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 and cutaneous squamous cell carcinoma (Gordon 2013; Madan 2010). In 2003, the World Health Organization estimated that between two and three million 'non-melanoma' skin cancers (of which BCC and cSCC are estimated to account for around 80% and 16% of cases respectively) and 132,000 melanoma skin cancers occur globally each year (WHO 2003).

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

Melanoma

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. Cutaneous melanoma refers to any skin lesion with malignant melanocytes present in the dermis, and includes superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma variants (see Figure 1). Melanoma *in situ* refers to malignant melanocytes that are contained within the epidermis and have not yet invaded the dermis, but are at risk of progression to melanoma if left untreated. Lentigo maligna, a subtype of melanoma *in situ* in chronically sun-damaged skin, denotes another form of proliferation of abnormal melanocytes. Melanoma *in situ* and lentigo maligna are both atypical intraepidermal melanocytic variants. All forms of melanoma *in situ* can progress to invasive melanoma if its growth breaches the dermo-epidermal junction during a vertical growth phase, although malignant transformation is both lower and slower for lentigo maligna than for melanoma *in situ* (Kasprzak 2015). Melanoma is one of the most dangerous forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and blood stream. It accounts for only a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths (Boring 1994; Cancer Research UK 2017).

The incidence of melanoma rose to over 200,000 newly diagnosed cases worldwide in 2012 (Erdmann 2013; Ferlay 2015), with an estimated 55,000 deaths (Ferlay 2015). The highest incidence is observed in Australia with 11,405 new cases of melanoma of the skin (ACIM 2014) and in New Zealand with 2,341 registered cases (HPA and MelNet NZ 2014) in

2010. For 2014 in the USA, the predicted incidence was 73,870 per annum and the predicted number of deaths 9,940 (Siegel 2015). The highest rates in Europe are seen in north-western Europe and the Scandinavian countries, with highest incidence reported in Switzerland of 25.8 per 100,000 in 2012. Rates in the UK have trebled from 4.6 and 6.0 per 100,000 in men and women, respectively in England in 1990, to 18.6 and 19.6 per 100,000 in 2012 (EUCAN 2012). In the UK, melanoma has one of the fastest rising incidence rates of any cancer, and has had the biggest projected increase in incidence between 2007 and 2030 (Mistry 2011). In the decade leading up to 2013, age standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2459 deaths in 2014 (Cancer Research UK 2017). Rates are higher in women than in men; however, the rate of incidence in men is increasing faster than in women (Arnold 2014).The rising incidence in melanoma is thought to be primarily related to an increase in recreational sun exposure and tanning bed use and an increasingly ageing population with higher lifetime recreational ultraviolet (UV) exposure, in conjunction with possible earlier detection (Linos 2009; Belbasis 2016). Putative risk factors, including eye and hair colour, skin type and density of freckles, history of melanoma, sunburn, and presence of particular lesion types, are reviewed in detail in Belbasis 2016.

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

Basal cell carcinoma

BCC can arise from multiple stem cell populations, including from the follicular bulge and interfollicular epidermis (Grachtchouk 2011). BCC growth is usually localised, but it can infiltrate and damage surrounding tissue, sometimes causing considerable destruction and disfigurement, particularly when located on the face (Figure 1). The four main subtypes of BCC are superficial, nodular, morphoeic or infiltrative and pigmented. BCCs typically present as slow-growing, asymptomatic papules, plaques, or nodules which may subsequently bleed or form ulcers that do not heal (Firnhaber 2012). People with a 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).

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

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

Advanced locally destructive or aggressive BCC can be found on “high risk” anatomical areas such as the eyebrow, eyelid, nose, ear and temple (these are at higher risk of invisible spread and therefore are more at risk of being incompletely excised (Baxter 2012)) (Lear 2014) and can arise from long-standing untreated lesions or from a recurrence of aggressive basal cell carcinoma after primary treatment (Lear 2012). Very rarely, BCC metastasises to regional and distant sites resulting in death, especially cases of large neglected lesions in those who are immunosuppressed or those with Gorlin syndrome (McCusker 2014). Rates of metastasis are reported at 0.0028% to 0.55% (Lo 1991), with very poor survival rates. It is recognised that basosquamous carcinoma (more like a high risk SCC 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. People with cSCC often present with an ulcer or firm (indurated) papule, plaque, or nodule (Griffin 2016) often with an adherent crust and poorly

defined margins (Madan 2010). cSCC can arise in the absence of a precursor lesion or it can develop from pre-existing actinic keratosis or Bowen's disease (considered by some to be cSCC *in situ*); the estimated annual risk of progression being <1% to 20% for newly arising lesions (Alam 2001) and 5% for pre-existing lesions (Kao 1986). It remains locally invasive for a variable length of time, but has the potential to spread to the regional lymph nodes or via the bloodstream to distant sites, especially in immunosuppressed individuals (Lansbury 2010). High risk lesions are those arising on the lip or ear, recurrent cSCC, lesions arising on non-exposed sites, scars or chronic ulcers, tumours more than 20mm in diameter, depth of invasion greater than 4mm and poor differentiation on pathological examination (Motley 2009). Perineural nerve invasion of at least > 0.1 mm in diameter is a further documented risk factor for high risk cSCC (Carter 2013).

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

Treatment

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

Treatment options for BCC and cSCC include surgery, other destructive techniques such as cryotherapy or electrodessication and topical chemotherapy. A Cochrane systematic review of 27 randomised controlled trials (RCTs) of interventions for BCC found very little good quality evidence for any of the interventions used (Bath-Hextall 2007a). Complete surgical excision of primary BCC has a reported five-year recurrence rate of < 2% (Griffiths 2005; Walker 2006), leading to significantly fewer recurrences than treatment with radiotherapy (Bath-Hextall 2007a). After apparent clear histopathological margins (serial vertical sections) after standard excision biopsy with 4mm surgical peripheral margins taken there is a 5-year reported recurrence rate of around 4% (Drucker 2017). Mohs micrographic surgery, whereby horizontal sections of the tumour are microscopically examined intraoperatively, and re-excision is undertaken until the margins are tumour-free, can be considered for high risk lesions on the face where standard wider excision margins might lead to incomplete excision or considerable functional impairment (Bath-Hextall 2007a; Motley 2009; Lansbury 2010; Stratigos 2015). Bath-Hextall and colleagues (Bath-Hextall 2007a) found a single trial comparing Mohs micrographic surgery with a 3mm 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 standard surgical excision, Mohs micrographic surgery or radiotherapy. For low risk or superficial subtypes of BCC, or for small and or multiple BCCs at low risk sites (Marsden 2010), destructive techniques other than excisional surgery may be used (e.g. electrodessication and curettage or cryotherapy (Alam 2001; Bath-Hextall 2007a)). Alternatively non-surgical (or non-destructive) treatments may be considered (Bath-Hextall 2007a; Kim 2014; Drew 2017), including topical chemotherapy imiquimod (Williams 2017), 5-fluorouracil (5-FU) (Arits 2013), ingenol mebutate (Nart 2015) and photodynamic therapy (PDT) (Roozeboom 2016). Non-surgical treatments are most frequently used for superficial forms of BCC, with one head to head trial suggesting topical imiquimod is superior to PDT and 5-FU (Jansen 2018). Although non-surgical techniques are increasingly used, they do not allow histological confirmation of tumour clearance, and their use is dependent on accurate characterisation of the histological subtype and depth of tumour. The 2007 systematic review of BCC interventions found limited evidence from very small RCTs for these approaches (Bath-Hextall 2007a), which have only partially been addressed by subsequent studies (Bath-Hextall 2014; Kim 2014; Roozeboom 2012). Most BCC trials have compared interventions within the same treatment class, and few have compared medical versus surgical treatments (Kim 2014).

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

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

Index test(s)

Ultrasound is a non-invasive imaging technique which essentially relies on the measurement of sound wave reflections from the tissues of the body. A transducer generates a focused beam of sound pulses and measures the reflections (or echoes) produced by structures within the tissue. The spatial location of a tissue structure that produced an echo is determined in the lateral direction (parallel to the skin surface) by the position of the sound beam (known) and in the axial (depth) direction by the return time of the echo (measured) and the speed of sound in the tissue (known to a good approximation) (Figure 2) (Barcaui 2016; Kleinerman 2012). An important parameter is the range of acoustic frequencies used to form the image. While low frequency ultrasound visualises the deeper structures of the body, such as the internal organs, high frequency ultrasound (HFUS), defined here as having centre (or median) frequency of at least 20MHz, has a much lower depth of tissue penetration but produces a higher resolution image of tissues and structures closer to the skin surface (Kleinerman 2012). Frequencies of 20 to 25 MHz allow visualisation of both the dermis and epidermis while higher frequencies of 50 MHz and above visualise the epidermis only (Kleinerman 2012). An example of a currently commercially available HFUS scanner is provided in Figure 3; the cost of the system can range from EUR 5,500 for a Windows tablet-based non-real-time system that works at 20 MHz (not shown), to around EUR 27,000 for a laptop-based system (Figure 3) which provides real-time images and works up to a frequency of 50 MHz (as well as 20 MHz) (Cortex Technology 2018).

In B-mode (brightness mode) ultrasound echography, the image brightness is modulated according to the amplitude of the echoes (echogenicity). This in turn is determined by a) the values of sound speed and mass-density within an echo-producing structure relative to those values in the surrounding medium, and b) the size, shape, orientation, and number-density of such structures (Barcaui 2016). Please see the following examples.

- Structural proteins, such as collagen and keratin, are dense and have high sound speed and generate strong echoes (termed hyperechoic or echogenic) when the fibres are thick, densely packed, and oriented mostly perpendicular to the ultrasound beam (e.g. reticular dermis).
- Adipose tissue; highly cellular lesions with little collagen or keratin; and regions where the collagen bundle size is small (some lesions) or oriented mostly parallel to the sound beam (e.g. papillary dermis), or both, generate weak echoes (termed hypoechoic or echo poor).
- Liquids (e.g. as in simple cysts) generate no echoes and are referred to as anechoic (Bamber 1992; Harland 1993).

The use of HFUS has been investigated for diagnosing a range of skin conditions, including skin cancer, infection, and inflammatory conditions (Kleinerman 2012), with malignant lesions reportedly appearing as hypoechogenic areas surrounded by a hyperechogenic dermis. Melanomas in particular also reportedly appear homogenous and with well-defined margins (e.g. Harland 2000). Evaluations have also been made of the ability of HFUS to quantitatively differentiate melanomas from other lesion types using entry echogenicity and attenuation (the latter being the rate of reduction in echo signal with depth). These features have been reported to be particularly useful for distinguishing melanoma from seborrhoeic keratosis, for example (Harland 2000; Rallan 2007; see Figure 4), and as being measurable even when a given lesion cannot be visualised on ultrasound.

Clinical Pathway

The diagnosis of melanoma can take place 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 usually present first to their general practitioner or, less commonly, directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, or other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist (Figure 5). 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). Those with suspected melanoma or cSCC should be referred for appropriate specialist assessment within two weeks (Chao 2013; London Cancer Alliance 2013; Marsden 2010; NICE 2015a). Evidence is emerging, however, to suggest that excision of melanoma by GPs is not associated with increased risk compared with outcomes in secondary care (Murchie 2017). In the UK, low risk BCC are usually recommended for routine referral, with urgent referral for those in whom a delay could have a significant impact on clinical outcomes, for example due to large lesion size or critical site (NICE 2015b). Appropriately qualified generalist care providers increasingly undertake management of low risk BCC in the UK such as by excision of low risk lesions (NICE 2010). Similar guidance is in place in Australia (CCAAC Network 2008).

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

Prior test(s)

The diagnosis of skin cancer is based on history-taking and clinical examination. In the UK, this is typically undertaken 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 secondary care clinician where a decision is made to biopsy or excise or

not. 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 (Friedman 1985; Grob 1998; MacKie 1985; MacKie 1990; Sober 1979; Thomas 1998) however visual inspection for keratinocyte skin cancers relies primarily on pattern recognition. Accuracy has been shown to vary according to the expertise of the clinician. Primary care physicians have been found to miss over half of BCC (Offidani 2002) and to inappropriately diagnose one third of BCC (Gerbert 2000). In contrast, an Australian study found that trained dermatologists were able to detect 98% of BCC, but with a specificity of only 45% (Green 1988).

A range of technologies have emerged to aid diagnosis to reduce the number of diagnostic biopsies or inappropriate surgical procedures. Dermoscopy using a hand-held microscope has become the most widely used tool for clinicians to improve diagnostic accuracy of pigmented lesions, in particular for melanoma (Argenziano 1998; Argenziano 2012; Haenssle 2010; Kittler 2002), although is less well established for the diagnosis of BCC or cSCC. The diagnostic accuracy, and comparative accuracy, of visual inspection and dermoscopy have been evaluated in a further three reviews in this series (Dinnes 2018a; Dinnes 2018b, Dinnes 2018c).

Role of index test(s)

Used in conjunction with clinical or dermoscopic suspicion of malignancy, or both, in pigmented lesions, HFUS may have a potential role in patient management as an additional test to identify those lesions requiring excision. The status of current medical practice and patient benefit for melanoma is particularly suited to improvement by any cost-effective diagnostic imaging method that might be developed, since early diagnosis that leads to complete excision of primary melanoma before metastatic spread has occurred, almost always results in a cure. The probability of metastases increases dramatically with increasing depth of tumour invasion of the primary melanoma (known as the Breslow thickness). This is assessed by histological examination after excision but has the potential to be assessed by imaging *in vivo*. One of the postulated advantages of HFUS is its ability to rule out melanoma as a potential differential diagnosis, by identifying pigmented seborrhoeic keratosis (a benign skin lesion) for example.

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 clear patient and resource benefits. False-positive diagnoses not only cause unnecessary scarring from a biopsy or excision procedure, but also increase patient anxiety whilst they await the definitive histological results and increase healthcare costs as the number needed to remove to yield one melanoma diagnosis increases. Pigmented lesions are common so the resource implication for even a small increase in the threshold to excise lesions in populations where melanoma rates are increasing, will avoid a considerable healthcare burden to both patient and healthcare provider, as long as lesions that are not excised turn out to be harmless.

Delay in diagnosis of a BCC as a result of a false-negative test is not as serious as for melanoma because BCCs are usually slow-growing and very unlikely to metastasise. However, delayed diagnosis can result in larger and more complex surgical procedures with consequent greater morbidity. Very sensitive diagnostic tests for BCC however may compromise on lower specificity leading to a higher false-positive rate, and an enormous burden of skin surgery, such that a balance between sensitivity and specificity is needed. As with melanoma, the consequences of falsely reassuring a person with cSCC that they do not have skin cancer can be serious and potentially fatal. Thus, a good diagnostic test for cSCC should demonstrate high sensitivity and a corresponding high negative predictive value. 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 could lead to initiation of inappropriate therapies and also increase patient anxiety.

HFUS has also been evaluated as a method for non-invasive measurement of melanoma thickness *in vivo* (Jasaitiene 2011; Machet 2009; Meyer 2014) to allow for a single surgical procedure to excise melanomas with the appropriate margin and, in addition to its optical B-mode imaging cousin, optical coherence tomography (Wang 2013), for appropriate treatment planning for BCC (Crisan 2013). For example, there is potential for refining surgical procedures, as well as the increased use and efficacy of non-surgical methods of treating BCC, if non-invasive imaging can be developed which allows confirmation of tumour clearance. None of these uses are under consideration in this review.

Alternative test(s)

Doppler ultrasound, unlike B-mode ultrasound, measures moving structures such as blood cells, as opposed to stationary tissues (Kleinerman 2012), and shows relative speed of blood flow as well as relative vessel size and density. In skin cancer, it can be used in combination with B-mode HFUS and may have value for staging or assessing the aggressiveness of malignancy due to increased vascular proliferation. Doppler ultrasound may be useful in preoperative staging due to correlation between extent of vascularisation and blood flow with Breslow thickness. As a stand-alone technique, Doppler ultrasound is not useful to differentiate skin cancers from benign lesions (Kleinerman 2012) and is therefore not included as an index test, however its use *in combination* with high frequency ultrasound has been considered as a means of improving lesion discrimination.

A number of other tests which may have a role for the diagnosis of skin cancer have been reviewed as part of our series of Cochrane DTA reviews on the diagnosis of skin cancer, for example, visual inspection and dermoscopy (Dinnes 2018a; Dinnes 2018b; Dinnes 2018c) reflectance confocal microscopy (RCM) (Dinnes 2018d; Dinnes 2018e), optical coherence tomography (OCT) (Ferrante di Ruffano 2018a), and computer-aided diagnosis (CAD) techniques

applied to various types of images including those generated by dermoscopy, diffuse reflectance spectrophotometry (DRS) and electrical impedance spectroscopy (EIS) (Ferrante di Ruffano 2018b).

RCM and OCT are two alternative ways to achieve depth-resolved optical reflectance imaging. To attain axial resolution, RCM uses a very low numerical aperture with out-of-focus data suppression while OCT uses interferometry to isolate optical reflections at a defined echo time (conceptually similar to HFUS). They are emerging as noninvasive adjuncts to dermoscopy in a specialist setting, and RCM potentially as an alternative to dermoscopy for skin cancer diagnosis (Edwards 2016).

RCM and OCT differ from each other in that RCM tends to use a shorter wavelength (830nm as opposed to 1305nm for OCT), has considerably less penetration (RCM < 300 µm; OCT < 2 mm), poorer depth of focus (RCM 3-5 µm; OCT 1 mm) and more limited basic field of view (RCM basic 500 x 500 µm in the horizontal plane; OCT basic 6 x 6 mm) than OCT, but has better lateral resolution (RCM 1 µm, cellular; OCT 7.5 µm, near cellular). They have similar axial resolution however (RCM 3-5 µm; OCT 5 µm), and both have fields of view that are extendible by mechanical scanning and image mosaicking, although for equivalent fields of view 3D imaging is much faster with OCT (RCM for mosaicked field of view and stack > 10 min; OCT 6 cross-sectional frames per second, < 2 min for 6 x 6 x 2mm volume). With RCM, the contrast for the monochrome images produced is achieved by the variation of the optical scattering properties within the skin when illuminated by a near-infrared light. At a wavelength of 830nm the greatest contrast is achieved from melanin, so that RCM is advocated as being particularly useful for assessing pigmented lesions (Dinnes 2018d). Similar to Doppler ultrasound but with higher resolution, vascular flow information can be extracted from OCT images, allowing neovascularisation to be visualised, which has potential for earlier diagnosis of melanoma (Themstrup 2015; Kokolakis 2012).

CAD or artificial intelligence-based techniques use predefined algorithms to process and manipulate acquired data to identify the features that discriminate malignant from benign lesions. The use of CAD-based techniques has potential for both reducing the subjectivity of, and de-skilling, the diagnosis of skin lesions. Although such techniques have most commonly been applied to digital dermoscopy images (Rajpara 2009; Esteva 2017) they may be applied to several types of images or spectra (e.g. Wallace 2000).

For example, SIAscopy™ and MelaFind® are based on diffuse reflectance spectrophotometry. DRS also uses optical reflectance, albeit not depth-resolved, but distinguishes between lesion types based on the lesion-average spectral shape and calibrated level of reflected light for wavelengths continuously varying from the ultraviolet (320 nm) to the near infrared (1100 nm) with a high spectral resolution (4 nm) (e.g. Marchesini 1992; Wallace 2000a). The extension to imaging spectrophotometry (DRSi) to allow spatial (dermoscopic) as well as spectral information to contribute to the diagnosis (Haddock 2003) has resulted in the development of handheld DRSi units (Bish 2014). SIAscopy™ (Moncrieff 2002; Walter 2012) and MelaFind® (Monheit 2011; Wells 2012; Hauschild 2014) are two such units with limited spectral capability which have been evaluated in both primary and secondary care settings. DRSi may also be combined with HFUS (Bamber 2007). Such approaches remain under development.

The Nevisense™ system is based on electrical impedance spectroscopy (EIS). EIS measures a combination of resistance and capacitance of the tissue as a function of frequency of an alternating applied voltage. At high frequencies, conduction occurs easily through all tissue components, including cells, but at low frequencies current tends to flow only through the extracellular space. The spectral shape is thus sensitive to cellular components and dimensions, internal structure and cellular arrangements. The Nevisense™ EIS system measures at multiple depths and at 35 frequencies logarithmically distributed from 1.0 kHz to 2.5 MHz using a 5 x 5 mm area electrode covered in tiny pins that penetrate into the stratum corneum. It has been evaluated and found to have high sensitivity but low specificity for melanoma (Malvehy 2014; Braun 2017), with concern over possible increase in needless excision of benign atypical melanocytic lesions (Ceder 2016) despite an indication of promise for reducing the need for short-term sequential digital dermoscopy (Rocha 2017).

DRS and EIS have not been the subject of individual test reviews due to an anticipated lack of data, however where available, CAD-based uses of these techniques have been included in our review of CAD for the detection of skin cancer (Ferrante di Ruffano 2018b).

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.

Rationale

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

To date, the use of tests such as RCM has been limited by expense (in terms of both equipment and staff time) and the need for specialised training. If shown to be sufficiently accurate, a test such as HFUS could prove to be a relatively low cost tool to assist in the earlier diagnosis and better management of 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 keratinocyte skin cancers (Dinnes 2015b). The Background and Methods sections of this review therefore use some text that was originally published in the protocols (Dinnes 2015a; Dinnes 2015b) and text that overlaps some of our other reviews (Dinnes 2018a; Dinnes 2018b; Dinnes 2018c).

Objectives

1. To determine the diagnostic accuracy of high frequency ultrasound to assist in the diagnosis of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults.
2. To determine the diagnostic accuracy of high frequency ultrasound to assist in the diagnosis of basal cell carcinoma in adults.
3. To determine the diagnostic accuracy of high frequency ultrasound to assist in the diagnosis of cutaneous squamous cell carcinoma in adults.

Secondary objectives

To determine the diagnostic accuracy of Doppler ultrasound in combination with high frequency ultrasound for the diagnosis of each of the three target conditions (cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, BCC or cSCC). We set out to address a range of potential sources of heterogeneity for investigation across our series of reviews, as outlined in our generic protocols (Dinnes 2015a; Dinnes 2015b) and described in Appendix 4; however our ability to investigate these was necessarily limited by the available data on each individual test reviewed. Ultimately no heterogeneity investigations were conducted for this review of HFUS.

Methods

Criteria for considering studies for this review

Types of studies

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

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

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

Participants

We included studies in adults with lesions suspicious for skin cancer. We excluded studies that recruited only participants with malignant diagnoses and studies that compared test results in participants with malignancy compared with test results based on 'normal' skin as controls, due to the bias inherent in such comparisons (Rutjes 2006). We excluded studies conducted in children, or which clearly reported inclusion of more than 50% of participants aged 16 and under.

Index tests

Studies evaluating HFUS alone or in combination with Doppler ultrasound were eligible. HFUS was considered to have been evaluated if the centre (or median) frequency of the transmitted pulse was at least 20MHz.

Studies should ideally evaluate a predefined 'rule' or algorithm describing combinations of ultrasound characteristics that determine the presence or absence of melanoma, BCC or cSCC. However, as HFUS is in a relatively early phase of development, studies were included if 2x2 contingency table data could be extracted based on the presence or absence of at least two ultrasound features related to tissue morphology or acoustic properties, for example echogenicity, homogeneity of appearance and definition of margins. Studies attempting to quantify HFUS parameters were also eligible for inclusion. There was no requirement for studies to have explicitly set out to estimate the diagnostic accuracy of the parameters assessed.

No exclusions were made according to test observer experience or qualifications.

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)

- BCC (all subtypes)
- cSCC.

Reference standards

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

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

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

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

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

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 1 for a summary of reviews included in the programme grant). This allowed for the screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease-related terms with terms related to the test names, using both text words and subject headings was formulated. The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As the majority of records were related to the searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search, to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for the staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter (Appendix 5), was subsequently applied to all bibliographic databases as listed below. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.

We searched the following bibliographic databases to 29 August 2016 for relevant published studies:

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

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

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

We searched the following databases for relevant unpublished studies:

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

We searched the following trials registers:

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

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

Searching other resources

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

Data collection and analysis

Selection of studies

Titles and abstracts were screened by at least one author (JDi or NC), with any queries discussed and resolved by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. Primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC were included at initial screening. Inclusion criteria (Appendix 6) were applied independently by both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JDi or NC) to all full text articles, disagreements were solved by discussion or by a third party, in case no consensus could be reached (JDe, CD, HW, and RM). Authors of eligible studies were contacted when insufficient data were presented to allow for the construction of 2x2 contingency tables.

Data extraction and management

One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently extracted data concerning details of the study design, participants, index test(s) or test combinations and criteria for index test positivity, reference standards, and data required to populate a 2x2 diagnostic contingency table for each index test using a piloted data extraction form. Data were extracted at all available index test thresholds. Disagreements were solved by discussion or by a third party, in case no consensus could be reached (JDe, CD, HW, and RM).

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

Dealing with multiple publications and companion papers

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

Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the QUADAS-2 checklist (Whiting 2011), tailored to the review topic (see Appendix 7). The modified QUADAS-2 tool was piloted on a small number of included full text articles. One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently assessed risk of bias and applicability for the remaining studies; any disagreements were solved by discussion or by a third party, in case no consensus could be reached (JDe, CD, HW, and RM). Authors were not contacted to clarify any methodological uncertainties. The methodological quality assessment was therefore of the study as reported and may not always fully reflect the quality of the study as conducted.

Statistical analysis and data synthesis

Due to paucity of data and between-study heterogeneity in the ultrasound characteristics and measurements that were investigated, no meta-analysis was undertaken for this review. For the diagnosis of melanoma, any BCCs or invasive cSCCs that were positively identified in the ‘disease negative’ group were considered as true negative test results rather than as false positives, on the basis that excision of such lesions would be a positive outcome for the participants concerned. For the diagnosis of BCC however, any melanomas or cSCCs that were positively identified in the ‘disease negative’ group were considered false positive results. This decision was taken on the basis that the clinical management of a lesion considered to be a BCC might be quite different to that for a melanoma or cSCC and could potentially lead to a negative outcome for the participants concerned, for example if a treatment other than excision was initiated.

Estimates of sensitivity and specificity were plotted on coupled forest plots for each characteristic or threshold under consideration. Our unit of analysis was the lesion rather than the patient as this was the most common way in which the primary studies reported data. As most participants have only one lesion to consider at a time, and as both index tests and reference standards are defined at the lesion level, the results are likely to be similar to those obtained at a participant level. Data for Doppler ultrasound was included only if reported in combination with HFUS tissue morphological or acoustic property imaging; the accuracy of Doppler ultrasound alone was not evaluated.

Investigations of heterogeneity

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

Sensitivity analyses

No sensitivity analyses were conducted due to lack of data.

Assessment of reporting bias

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

Results

Results of the search

A total of 34,347 unique references were identified and screened for inclusion. Of these, 1051 full text papers were reviewed for eligibility for any one of the suite of reviews of tests to assist in the diagnosis of melanoma or keratinocyte skin cancer. Of the 1051 full text papers assessed, 848 were excluded from all reviews in our series and 203 publications were included (see Figure 6 PRISMA flow diagram of search and eligibility results).

Of the 41 studies tagged as potentially eligible for this review of HFUS, six were included and copies of two could not be obtained from the British Library (Bens 2015; Nitsche 1992). Exclusions were due to the use of ineligible index tests (n = 16) (for example: evaluations of Doppler ultrasound (n = 9) or studies using ultrasound transducers with centre frequency less than 20 MHz (n = 7)); ineligible study populations (n = 4) (for example, recruiting only malignant lesions (n = 2) or including lesions that were not suspicious for skin cancer (n = 2)); ineligible definition of the target condition (n = 8) (including those identifying lesion thickness (n = 4), surgical margins (n = 1) or melanoma metastases (n = 2), or where lesions such as dermatofibroma or Bowen's disease were considered disease positive (n = 1)); and inadequate sample size (n = 1). A list of the 33 studies excluded from this review with reasons for exclusion is provided in Characteristics of excluded studies, with a list of all studies excluded from the full series of reviews available as a separate pdf. The authors of one publication were contacted for the purposes of this review, however they were unable to provide the additional data needed to allow the study to be included.

This review reports on a total of six cohorts of lesions published in six study publications, and providing 29 datasets, 20 for melanoma and 9 for BCC. No data relating to the diagnosis of cSCC were identified.

Studies included four case series of patients with pigmented lesions (Bessoud 2003; Clement 2001; Dummer 1995) or lesions described as suspicious for melanomas or BCC (Lassau 1997) and two case control type studies (Harland 2000; Rallan 2007) which included pigmented lesions with specific confirmed diagnoses (confirmed melanomas, seborrhoeic keratosis or benign nevi). The Bessoud 2003 paper is from the same institution and has overlapping authorship with Lassau 1997, and may have overlap in study participants. Only Rallan 2007 clearly described the basis for referral or selection for ultrasound examination, randomly selecting lesions referred from primary care due to suspicion of melanoma. Clement 2001 described the clinical diagnosis as ‘hesitant’ for more than half of included lesions, none of the other studies gave any indication as to the equivocal nature or difficulty of diagnosis of the lesions included. The number of included patients ranged from 70 to 160 (reported in four studies) and lesions from 54 to 792. Patient characteristics such as age and gender were reported in only three studies.

Data allowing the calculation of the accuracy of ultrasound for the detection of melanoma were reported in all studies apart from Clement 2001 which focused primarily on the detection of BCC; two other studies also report data for detection of BCC (Dummer 1995; Lassau 1997). The prevalence of melanoma in the study samples ranged from 14% to 58%, and appeared to be restricted to invasive melanoma only in Dummer 1995 and Lassau 1997. The prevalence of BCC was 8% (Dummer 1995), 17% (Clement 2001) and 49% (Lassau 1997). In all studies apart from Lassau 1997 and Bessoud 2003, seborrhoeic keratosis made up at least 25% of the disease negative groups, ranging as high as 66% in Harland 2000 who selected to study seborrhoeic keratosis versus melanoma.

All six studies used 20 MHz ultrasound scanners with axial resolutions of 50 to 80 µm (Dummer 1995; Lassau 1997; Clement 2001; Bessoud 2003; Harland 2000; Rallan 2007) and lateral resolutions of about 100 µm (Lassau 1997, Clement 2001; Bessoud 2003; Rallan 2007) to 300 µm (Harland 2000). Typically it was not clear how the resolution values were obtained and, from the appearances of example images in the papers, the instrumentation employed varied greatly in terms of other diagnostically important imaging performance properties such as signal dynamic range and signal to noise level, which were not reported. In some cases such performance appeared to be poor, providing little or no lesion internal detail compared with similar lesions on other systems. None of the studies described the qualifications or experience of the clinician carrying out and interpreting the ultrasound and none reported whether the clinical or dermoscopic diagnosis of the lesion was provided to aid test interpretation.

Three studies explicitly set out to establish the diagnostic accuracy of HFUS for the differentiation of melanomas from other skin lesions (Bessoud 2003; Harland 2000; Rallan 2007); the remaining three studies did not set out to evaluate test accuracy but presented data for the presence or absence of particular ultrasound characteristics that could be extracted into 2x2 contingency tables (Clement 2001; Dummer 1995; Lassau 1997). Qualitative HFUS characteristics that were considered related to echogenicity, homogeneity of appearance and definition of margins (Bessoud 2003; Clement 2001; Dummer 1995; Lassau 1997). Four studies presented data for qualitative assessment of the presence or absence of particular structural characteristics (including echogenicity, homogeneity of appearance and definition of margins) on the HFUS image either alone (Dummer 1995; Lassau 1997; Clement 2001; Bessoud 2003) or in combination with Doppler ultrasound assessment of vascularity (Lassau 1997; Clement 2001; Bessoud 2003).

The remaining two studies examined different approaches to quantitatively interpret ultrasound findings. Harland 2000

attempted to classify lesions based on objective quantifications of the extent of ultrasound shadowing and the strength of the ultrasound entry echo to differentiate between melanoma and seborrhoeic keratosis, based on the dermal echogenicity ratio (DER) and presence of a thickened entry echo line (EEL) respectively. Rallan 2007 further developed this work with a prototype 3D HFUS C-scan and "reflex transmission" imaging system to evaluate these features and make ultrasound images easier for dermatologists to interpret. Three *en face* ultrasound images are produced: a reflex transmission image (RTI), a lesional backscatter image (LBI) and an entry echo image (EEI), which relate to objectively quantified lesion attenuation properties, intralesional sound reflection and surface sound reflectance characteristics, respectively. For each image two quantitative features were estimated (contrast and heterogeneity) and compared between lesion groups (melanoma versus seborrhoeic keratosis, and melanoma versus other benign pigmented lesions). Mean RTI contrast, LBI relative heterogeneity, and EEI relative heterogeneity were each significantly different between melanoma and seborrhoeic keratosis and between melanoma and benign naevi; these three features were combined using an 'or' rule with specificity estimated at 100% sensitivity (Rallan 2007). The required values for each of the three parameters to be considered 'positive' were reported graphically but not numerically (Rallan 2007).

Three studies using qualitative HFUS interpretation reported the exclusion of lesions not visualised by ultrasound; 10% in Lassau 1997 (including 3 melanomas), 12% in Bessoud 2003 (including for 5 melanomas), and 22% in Clement 2001 (including 5 melanomas). In all studies the reference standard diagnosis was made by histology alone (i.e. all lesions either excised or biopsied). Histological diagnosis was based on excisional biopsy (Dummer 1995), surgical resection or excision (Lassau 1997; Bessoud 2003; Harland 2000; Rallan 2007) and either approach (Clement 2001).

Methodological quality of included studies

The overall methodological quality of all included studies (n = 6) is summarized in Figure 7 and Figure 8.

A third of studies (n = 2) were at high risk of bias for participant selection due to individual studies having been designed to selectively include participants with particular histological lesion types (Harland 2000; Rallan 2007). Five studies did not clearly describe participant recruitment as random or consecutive and four did not clearly report any exclusion criteria. One study was judged as low concern for applicability of participants and setting (Clement 2001). Five studies were judged as having high (n = 4) or unclear (Dummer 1995) concern for applicability of participants due to unrepresentative patient samples (n = 3), inclusion of multiple lesions per patient (n = 1), or providing insufficient information on which to make a judgement (n = 2). All studies included only lesions selected for excision.

Only one study was at low risk of bias in the index test domain. Ultrasound was considered to have been interpreted prior to the histological reference standard in all studies, but only one clearly reported prior specification of the diagnostic threshold or ultrasound characteristics used to differentiate melanomas from other lesions (Bessoud 2003). The other studies were all rated as high risk for this item either because they did not clearly set out to examine the accuracy of HFUS (Clement 2001; Dummer 1995; Lassau 1997) or because they deliberately set their thresholds to achieve 100% sensitivity (Harland 2000; Rallan 2007). A third of studies were at high concerns around the applicability of the index test, due to the use of a prototype ultrasound device on one study (Harland 2000) and a relatively experimental approach to the index test in another (Rallan 2007). All studies clearly described the criteria or diagnostic thresholds used, but no study provided information on the expertise and experience of the test operator or sonographer.

All studies reported the use of an acceptable reference standard, but only one clearly reported blinding of the reference standard to the ultrasound result (Harland 2000), and none of the studies reported blinding to the referral diagnosis (based on clinical examination or dermoscopy). 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 histopathologist or by a dermatopathologist.

The same reference standard was used in all participants in all studies and two were unclear on the interval between the application of the index test and excision for histology (Bessoud 2003; Harland 2000). Three studies reported exclusions due to lesions not being visualised on ultrasound (Bessoud 2003; Clement 2001; Lassau 1997); however, all three provided a breakdown of the final histologic diagnosis for these lesions and were therefore judged as low risk on the flow and timing domain. Three studies did not report any exclusions due to lack of visualisation of lesions (Dummer 1995; Harland 2000; Rallan 2007). Two of these allowed the ultrasound features employed to be measured regardless of whether the lesions were visualised or not and were judged as having low risk of bias on this item (Rallan 2007; Harland 2000).

Findings

Lack of data and between study variation in populations, ultrasound techniques and characteristics and measurements investigated precluded meta-analysis. Study results are summarised below according to target condition: melanoma or BCC. No data on the identification of cSCC was found. Summary details are provided in Appendix 8; forest plots of available study data are given in Figure 9 (HFUS for differentiation of melanoma), Figure 10 (for HFUS combined with Doppler US for melanoma) and Figure 11 (HFUS for differentiation of BCC).

Detection of invasive melanoma or melanoma in situ

Combinations of subjective assessments of HFUS features

HFUS data related to the qualitative assessment of the presence or absence of different combinations of lesion morphological and structural characteristics as an indicator of melanoma could be extracted from three studies (Bessoud 2003; Dummer 1995; Lassau 1997), one of which set out to assess the diagnostic accuracy of these characteristics

for the differentiation of melanoma from other lesions (Bessoud 2003) (Figure 9; Appendix 8).

Dummer 1995 reported recruitment of a series of 792 pigmented lesions with a range of final diagnoses including melanoma (14%), BCC (8%), benign naevi (39%), seborrhoeic keratosis (27%), and dermatofibroma or angioma (13%). Sensitivities and specificities estimated from the data presented ranged from 83% (95% CI 75% to 90%) and 64% (95% CI 60% to 87%) for hypoechoic and homogenous lesions to 91% (95% CI 84% to 95%) and 22% (95% CI 19% to 26%) for hypoechoic lesions with sharp lateral margins. For each of the combinations of characteristics examined in this study a number of BCCs were found to be 'test positive', i.e. displaying the characteristics under consideration. As per our protocol, these 'false positive' BCCs were reclassified as true negative test results (increasing specificity) on the basis that a positive test result leading to the excision of these BCCs would not be a negative patient outcome. The number of BCCs that we artificially reclassified as true negative despite the presence of the HFUS image features of interest ranged from 5 (for echo poor lesions with homogenous internal echoes) to 57 (for echo poor lesions with sharp basal margins).

Data for the presence of hypoechoic, homogenous, well-defined lesions were presented in Bessoud 2003 and Lassau 1997, both of which also reported results for Doppler ultrasound that could be combined with HFUS data. Bessoud 2003 included a series of 114 pigmented lesions (7 of which did not undergo Doppler ultrasound); included lesions were primarily invasive melanomas (57%) or benign naevi (29%) with smaller percentages of BCC (4%), seborrhoeic keratosis (4%) and other benign lesions. Lassau 1997 included 70 lesions clinically suspected of being melanoma (n = 38) or BCC (n = 32); seven lesions could not be visualised on ultrasound and were excluded leaving 19 (27%) invasive melanoma, 31 (44%) BCC, 1 neurosarcoma and 12 (17%) benign naevi (3 of the 7 lesions not visualised on HFUS were melanomas).

The sensitivity of the combined HFUS characteristics was 100% in both studies with specificities of 33% (95% CI 20% to 48%) in Bessoud 2003 (114 lesions; 65 melanomas) and 73% (95% CI 57% to 85%) in Lassau 1997 (63 lesions; 19 melanomas) (lower limits of the 95% CIs for sensitivities were 94% and 82% respectively). Excluding BCCs from Lassau 1997 resulted in a specificity of 8% (95% CI 0% to 36%) (32 lesions; 19 melanomas); the 12 benign naevi all being considered hypoechoic, homogenous and well defined. Both studies reported all BCCs as 'negative' on ultrasound (i.e. absence of investigated characteristics) (Bessoud 2003; Lassau 1997). Both studies also reported five melanomas amongst the lesions not visualised by ultrasound (Appendix 8).

Combinations of subjective assessments of HFUS features with Doppler US

Using data presented in Lassau 1997 for the presence of hypoechoic, homogenous, and well defined lesions on HFUS with the presence of intratumoural vessels on Doppler ultrasound (on an either or basis) makes no difference to the sensitivity and specificity achieved using HFUS alone for the discrimination of invasive melanoma (n = 19) from all other included lesions (n = 44). Only three melanomas (already picked up as test 'positive' on HFUS) displayed any evidence of vascularity on Doppler (sensitivity 100% (95% CI 82% to 100%) and specificity 73% (95% CI 57% to 85%)) (Figure 10). The HFUS and Doppler characteristics can be combined on an *and* basis for both Bessoud 2003 and Lassau 1997 (lesions that were hypoechoic, homogenous and well defined *and* exhibited intra-lesional vessels on Doppler considered test positive): sensitivities were 34% (95% CI 22% to 47%; n = 65 melanomas) and 16% (95% CI 3% to 40%; n = 19 melanomas) respectively with specificities of 100% (95% CI 92% to 100%) for both studies (n = 45 and n = 44).

Quantitative assessment of HFUS features

Two studies (Harland 2000; Rallan 2007) reported quantitative assessments of the ultrasound image using the strength and heterogeneity of ultrasound shadowing and the strength and heterogeneity of the ultrasound surface entry echo. Both studies included only melanoma, melanoma *in situ*, benign naevi or seborrhoeic keratosis (n = 19, 6, 15, 29 in Harland 2000; and n = 14, 11, 38, 24 in Rallan 2007). The main comparison in Harland 2000 was between melanoma and seborrhoeic keratosis (benign naevi excluded). Setting the DER at <3 to ensure sensitivity of 100% produced a specificity of 79% (95% CI 60% to 92%); the absence of an EEL resulted in sensitivity of 96% (95% CI 80% to 100%) and specificity 90% (95% CI 73% to 98%) for the same comparison. Combining the two characteristics on an either or basis (such that sensitivity was 100%), increased specificity to 93% (95% CI 77% to 99%) for discrimination of melanoma from seborrhoeic keratosis (Figure 9). Of the 15 benign naevi in this study, six were reported to have characteristics associated with EEL enhancement (or EEE) suggesting that nine would be considered 'test positive' (absence of an EEL); inclusion of these lesions as disease negative would reduce the observed specificity.

Rallan 2007's work on a prototype 3D HFUS C-scan with "reflex transmission" imaging, found significant differences in the mean values of RTI contrast, LBI relative heterogeneity, and EEI relative heterogeneity between melanoma and seborrhoeic keratosis and between melanoma and benign naevi. When these three features were combined using an 'or' rule with sensitivity for melanoma discrimination of 100% (95% CI 86% to 100%) resulting specificity was 65% (95% CI 51% to 76%) (Figure 9).

Detection of BCC

Combinations of subjective assessments of HFUS features

Three studies including series of pigmented lesions (Clement 2001; Dummer 1995) or including lesions suspicious for either melanoma or for BCC (Lassau 1997) reported data that could be used to derive the accuracy of ultrasound characteristics for BCC, two of which also reported data for melanoma (Dummer 1995; Lassau 1997). None of the three studies set out to establish the accuracy of the reported ultrasound characteristics. Clement 2001 included a series of 176 pigmented lesions, 38 of which were not visualised on ultrasound (including 5 melanomas); the remaining 138 lesions included one invasive melanoma, 23 (17%) BCC, 61 (44%) benign naevi, and 29 (21%) seborrhoeic keratoses, amongst others.

Using hypoechoic and homogenous appearance as a positive indicator for BCC, sensitivity and specificity were 91% (95% CI 72% to 99%) and 14% (95% CI 8% to 22%) for Clement 2001 (138 lesions; 23 BCC) and were 8% (95% CI 3% to 17%) and 54% (95% CI 50% to 57%) in Dummer 1995 (792 lesions; 65 BCC) (Figure 11).

Considering lesions that were hypoechoic and well defined as positive for BCC, resulted in sensitivity of 83% (95% CI 61% to 95%) and specificity 32% (95% CI 24% to 42%) in Clement 2001. Dummer 1995 reported numbers of lesions with sharp basal margins and with sharp lateral margins. Considering lesions that were hypoechoic with sharp basal margins as positive for BCC, resulted in sensitivity 86% (95% CI 75% to 93%) and specificity 20% (95% CI 17% to 23%); considering lesions that were hypoechoic with sharp lateral margins as positive for BCC, resulted in sensitivity 42% (95% CI 29% to 54%) and specificity 13% (95% CI 11% to 16%).

Finally, data from Lassau 1997 could be derived to consider hypoechoic, homogenous and well defined lesions as BCC (i.e. the same characteristics previously considered to be positive indicators for melanoma); this combination resulted in sensitivity of 0% (95% CI 0% to 11%) and specificity of 3% (95% CI 0% to 16%) (63 lesions; 31 BCCs; Figure 11). All BCCs were reportedly hypoechoic but with a heterogeneous echostructure and lateral extensions with irregular margins, i.e. negative on two of the characteristics considered (Lassau 1997). If one instead considers the presence of a heterogeneous echostructure and lateral extensions with irregular margins to be *positive* indicators of BCC (i.e. reversing the 2x2 contingency table), the resulting sensitivity is 100% (95% CI 89% to 100%) and specificity 97% (95% CI 84% to 100%), with no melanomas and none of the benign naevi displaying these characteristics. Bessoud 2003 also reported all four included BCCs to be heterogenous and poorly defined, however a further 12 lesions including keratosis, melanosis and neurosarcoma also demonstrated these characteristics.

Combinations of subjective assessments of HFUS features with Doppler US

Two of the studies reporting data for BCC also employed Doppler US in combination with HFUS (Lassau 1997; Clement 2001). One study allowed extraction of accuracy data only for the detection of melanoma (melanoma versus benign naevi) (Lassau 1997), while for the other, consideration of lesions that were hyperechoic on HFUS and displaying vascularity on Doppler produced a sensitivity of 0% (95% CI 0% to 15%) and specificity 89% (95% CI 81% to 94%) (Clement 2001). Considering the absence of these characteristics as indicative of BCC (i.e. hypoechoic with no vascularity on Doppler) would reverse these estimates, giving sensitivity of 100% and specificity 11%.

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 high frequency ultrasound as an aid to diagnosing melanoma, BCC and cSCC in adults. No eligible data on cSCC were identified. We included six studies evaluating high frequency ultrasound, three of which also evaluated Doppler ultrasound (Summary of findings table 1).

Studies were generally poorly reported such that methodological quality and applicability of findings could not be clearly judged; this was in part due to the fact that half of the studies did not set out to establish test accuracy. Particularly high concerns were noted in regard to the selection of study participants, with high proportions of malignant lesions and an unrepresentative spectrum of disease in the disease negative groups. The clinical pathway and referral process for ultrasound imaging was not always well described. All studies used 20MHz ultrasound devices at a range of resolutions and a number of different qualitative and quantitative thresholds, some of which were clearly data driven or not pre-specified. In half of the studies (all using qualitative or subjective assessments of HFUS images), a considerable proportion of lesions were excluded by the study authors because the lesions were not visualised by ultrasound. It is not clear from these studies whether this should be considered a failure of the test or whether the lack of visualisation of a lesion on HFUS provides further diagnostic information that may assist in the differential diagnosis. Studies applying quantitative interpretations of HFUS allowed some ultrasound features to be measured regardless of lesion ‘visibility’. No information was provided regarding the clinicians undertaking and interpreting the tests, limiting the generalisability of results particularly for those relying on qualitative interpretation of HFUS features. The final diagnoses were established by histology in all studies; blinding to the ultrasound result or referral diagnosis was reported in only one study. Sources of heterogeneity included patient selection, ultrasound techniques, test thresholds, prior testing and blinding.

For the detection of melanoma, derived sensitivities were at least 83% (95% CI 75% to 90%), with the combination of three qualitative features (lesions appearing hypoechoic, homogenous and well defined) and quantitative assessments of images demonstrating 100% sensitivity in four studies (the widest 95% CI being 80% to 100%), although in two of these the decision thresholds were deliberately set to achieve 100% sensitivity in order to discover resulting specificity. Between three and five melanomas were amongst the lesions not visualised by the HFUS in three studies, no index test ‘failures’ were reported by the two studies assessing quantitative metrics. Specificities varied from 8% (95% CI 0% to 36%) to 73% (95% CI 57% to 85%) for qualitative characteristics, all of which included BCC in the disease negative group which tends to increase specificity, and from 65% (95% CI 51% to 76%) to 90% (95% CI 73% to 98%) for quantitative measurements, none of which included BCC in the disease absent group. For the detection of BCC, sensitivities and specificities were highly variable, making summary statements difficult. One study suggested that the presence of heterogeneity and poorly defined margins might differentiate BCCs from melanomas and benign naevi, although another identified other lesions demonstrating similar characteristics that might limit their usefulness in a more widely defined population.

Strengths and weaknesses of the review

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

The main concerns for the review are a result of the poor reporting of primary studies and the fact that the studies were not all designed as test accuracy studies; in half of included studies, data to allow the estimation of sensitivity and specificity was derived from the information on image descriptions presented by the study authors. All three studies using qualitative interpretation of HFUS reported that a number of lesions (including some melanomas) had to be excluded because they could not be visualised, resulting in an over-estimation of sensitivity for the characteristics assessed. Two of the remaining studies using quantitative HFUS metrics and methodology allowed inclusion of all lesions regardless of whether the lesions were visualised, however.

When estimating accuracy for the diagnosis of melanoma, any correctly identified BCCs were classed as true negative results as opposed to false positives, on the basis that removal of a BCC in the attempt to identify melanomas would not be a negative consequence of the test. This will have the effect of increasing specificity compared to studies from which BCCs had been excluded. When estimating accuracy for the diagnosis of BCC however, any other skin cancers that were incorrectly identified as BCC (e.g. melanomas or cSCCs) were considered false positive results, as the subsequent management of a BCC can be quite different to that of a melanoma or SCC and it is important that a test can accurately differentiate between malignancies.

Applicability of findings to the review question

The data included in this review came from preliminary exploratory studies and are unlikely to be generally applicable to predicting the diagnostic accuracies that would be expected in a standard clinical practice where people present with a broad range of different lesion types. Narrow definitions of the eligible study populations, lack of clarity regarding the patient pathway and any prior testing, and wide variation in the type and performance of the HFUS equipment employed as well as in the method used for image feature scoring, restricts generalisation and applicability. It is not always clear whether the particular test methods used could be transferred to a clinical setting.

Authors' conclusions

Implications for practice

No summary estimates of test accuracy could be produced to answer the research question for this review. High frequency ultrasound may prove to be an additional tool to assist in the differentiation of melanoma from other lesions however the current evidence is based on participants with highly selected lesion types and it is unclear how their results would translate in clinical practice. The lack of visualisation of lesions on HFUS is potentially a major disadvantage unless the lack of visualisation has a clear interpretation which can be used to inform management decisions, or ultrasound metrics that do not depend on lesion visualisation can be employed, or ultrasound visualisation can be improved with equipment development. Given the between study heterogeneity, unclear to low methodological quality and applicability of findings, and limited volume of evidence, no implications for practice can be drawn. The main value of the preliminary studies included in this review may be in provision of guidance on the possible components of diagnostic rules for the diagnosis of melanoma or of BCC using HFUS that require future evaluation.

Implications for research

Prospective evaluation of high frequency ultrasound added to visual inspection and dermoscopy alone in a standard health care setting would be required for a full and proper evaluation of accuracy. A clearly defined and representative population of participants with a range of different lesion types is needed to establish the participant groups to whom study results can be applied in practice. HFUS technology continues to be developed therefore it is important that current equipment is employed, using compatible systems across centres, appropriate harmonisation in cross-centre training and, where possible, the use of objective quantitative diagnostic image features so as to minimise exclusions (due to lack of visualisation) and inter-observer variability.

Prospective recruitment of a consecutive series of participants, with double-blinding between test interpretation and the reference standard diagnosis, and with pre-specified and clearly defined diagnostic rules for determining the presence or absence of disease are necessary and easily achieved. Systematic follow-up of non-excised lesions avoids over-reliance on a histological reference standard and allows results to be more generalisable to routine practice. A standardised approach to diagnosis, and clear identification of the qualifications and level of observer training and experience required to achieve good results is also required. A multi-centred approach would allow confirmation that results are replicable across centres and that the technology can be implemented across a health service. 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).

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Contributions of authors

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

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Jac Dinnes: nothing to declare.
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Differences between protocol and review

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

This single review includes three primary objectives related to the detection of each of: melanoma, BCC and cSCC. For the detection of melanoma, the primary objectives and primary target condition have been changed from detection of invasive melanoma alone, to the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, as the latter is more clinically relevant to the practicing clinician. An additional secondary objective was added to allow the evaluation of Doppler ultrasound in combination with high frequency ultrasound for skin cancer diagnosis.

Heterogeneity investigations and sensitivity analyses were limited by the data available.

Due to the early phase nature of HFUS diagnosis for skin cancer, this text from the protocol "we will include studies developing new algorithms or methods of diagnosis (i.e. derivation studies) if they use a separate independent 'test set' of participants or images to evaluate the new approach. We will also include studies using other forms of cross validation, such as 'leave-one-out' cross-validation (Efron 1983). We will note for future reference (but not extract) any data on the accuracy of lesion characteristics individually, e.g. the presence or absence of a pigment network or detection of asymmetry" has been replaced with "Studies should ideally evaluate a predefined 'rule' or algorithm describing combinations of ultrasound characteristics that determine the presence or absence of melanoma, BCC or cSCC. However, as HFUS is in a relatively early phase of development, studies were included if 2x2 contingency table data could be extracted based on the presence or absence of at least two ultrasound features related to tissue morphology or acoustic properties, for example echogenicity, homogeneity of appearance and definition of margins. Studies attempting to quantify HFUS parameters were also eligible for inclusion. There was no requirement for studies to have explicitly set out to estimate the diagnostic accuracy of the parameters assessed."

Although we extracted any reporting of special interest or accreditation in skin cancer according to observer expertise, we were unable to analyse the effect on accuracy.

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 and to cover both melanoma and keratinocyte skin cancers. In terms of analysis, restriction to analysis of per patient data was not performed due to lack of data. Sensitivity analyses were not performed as planned due to lack of data.

Published notes

Characteristics of studies

Characteristics of included studies

Bessoud 2003

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** NR; 4 year period **Country:** France
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with pigmented skin lesions referred from the Dermatology Department to the Ultrasound Unit **Setting:** Secondary **Prior testing:** Referred from Dermatology; basis for referral not described **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 111 **Sample size (lesions):** No. eligible: 130; No. included: 114 (107 for Doppler) **Participant characteristics:** Mean age: 55.3 (SD 18; 6 to 92 yrs). Male: 47 (42%) **Lesion characteristics:** For melanomas visualised on ultrasound (n=65), thickness ranged from 0.15 to 8 mm on histology.
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	No
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Ultrasound: High frequency (20MHz) and Colour Doppler (7MHz)** Test detail: AU 4 or AU 5 Idea (Esaote-Biomedica, Genova, Italy) with a 20-MHz annular probe (axial resolution 80 µm and lateral resolution 100 µm) and 13-MHz linear electronic probe (axial resolution 200 µm and lateral resolution 400 µm); Colour Doppler adjustments included a pulse-repetition frequency (PRF) of 750 Hz to 1 kHz, with a 50-Hz filter and nine to 16 images per second **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical diagnosis provided to sonographer **Diagnostic threshold:** HFUS - Hypoechoic, homogenous and well defined margins; HFUS plus Doppler - hypoechoic, homogenous and well defined plus presence of intra-lesional vessels **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

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

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** None provided Disease positive: 70; Disease negative: 60 **Target condition (Final diagnoses)** Melanoma (invasive or in situ): 65; BCC: 4; 1 neurosarcoma 'Benign' diagnoses: 33 benign nevi, 5 seborrhoeic keratosis, 3 melanosis, 1 thrombosing capillaritis, 1 histiocytofibroma, 1 lentigo
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Not described **Exclusions:** 16 lesions 'unseen' on US were excluded (5 melanoma, 1 lentigo, and 10 benign nevi) leaving 114 lesions reported for HFUS, 107 of which underwent Doppler ultrasound
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	-

Clement 2001

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case series **Data collection:** Prospective **Period of data collection:** November 1998 to July 1999 **Country:** France
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with pigmented skin tumours including melanocytic and non melanocytic examined before resection; clinical diagnoses described as 'hesitant' (NB translation from French) for more than half of lesions **Setting:** Secondary **Prior testing:** NR; basis for referral not described **Exclusion criteria:** Difficult to reach lesions (two dermal nevus - one at the internal angle of the eye and the other between the toes) **Sample size (patients):** No. eligible: 160 **Sample size (lesions):** No. eligible: 176; No. included: 138 **Participant characteristics:** For full sample - mean age: 52.7 years (18 to 90 years). Male: 74 (46%) **Lesion characteristics:** 5 melanomas not visualised on ultrasound; all had Breslow index less than 0.35 mm
Are the included patients and chosen study setting appropriate?	Yes
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Ultrasound: High frequency (20MHz) and Colour Doppler (7 MHz)** Test detail: used an annular linear scanning probe with theoretical spatial resolution of 80 µm (axial) and 100 µm (lateral); equipped with an ultrasonic beam variable electronics management system to obtain an optimal focal area at penetration depths of 12.5 and 19 mm; for Doppler, a linear electronic probe (frequency of ultrasound: 13 MHz, axial theoretical spatial resolution: 200 µm, lateral: 400 µm) was used **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical diagnosis provided to sonographer **Diagnostic threshold:** HFUS - hypoechoic; hypoechoic and homogenous; hypoechoic and well defined; HFUS + Doppler - hypoechoic and presence of vascularity **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	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?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** None provided Disease positive: 24; Disease negative: 115 **Target condition (Final diagnoses)** Melanoma (invasive or in situ): 1; BCC: 23; 6 melanoma metastases (considered disease negative for this review) 'Benign' diagnoses: 61 benign nevi, 29 seborrhoeic keratosis, 11 histiocytofibroma, 7 angioma
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Consecutive; each lesion scanned immediately before its biopsy or surgical excision, or both **Exclusions:** 36 lesions were not visualised on US and were excluded (including 5 melanomas in the horizontal growth phase (Clark levels I and II, Breslow index less than 0.35 mm)) leaving 138 lesions reported for HFUS
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	-

Dummer 1995

Patient Selection

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

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with pigmented skin lesions referred from the outpatient clinic to the Department of Dermatology **Setting:** Secondary **Prior testing:** All patients underwent physical examination and 508 underwent dermoscopy before HFUS; basis for referral not described **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: NR **Sample size (lesions):** No. eligible: 792; No. included: **Participant characteristics:** Mean age: NR Male: NR **Lesion characteristics:** For the 108 melanomas, Breslow thickness was <0.76mm in 45; 0.76 to 1.5mm in 26; 1.5 to 4.0mm in 24; and >4.0mm in 12.
Are the included patients and chosen study setting appropriate?	Unclear
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	**Ultrasound: High frequency (20MHz)** Test detail: DUB 20 (Taberna pro Medicum, Luneburg, Germany) at axial resolution 80 µm and lateral resolution 200 µm. Several sonographic scans were carried out perpendicular to the previous ones in parallel planes for each individual tumour; B-scan section corresponds to a width of 12 .8 mm and a depth of 7.5 mm **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical or dermoscopy diagnosis provided to sonographer; no data available for overall dermoscopy diagnosis **Diagnostic threshold:** echo poor (hypoechoic); echo poor with no internal echoes; echo poor with sharp basal margins; echo poor with sharp lateral margins **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	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?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Excisional biopsy; reviewed by the dermatopathology staff at the departments of dermatology (Universities of Wurzburg and Munich [Germany]) and 78 lesions additionally reviewed by the dermatopathology staff of the department of dermatology, University Hospital, Zurich, Switzerland. Disease positive: 173; Disease negative: 619 **Target condition (Final diagnoses)** Melanoma (invasive or in situ): 108; BCC: 65; 'Benign' diagnoses: 307 benign nevi, 211 seborrhoeic keratosis, 47 angioma, and 54 dermatofibroma
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Appears consecutive; The patients were subjected to ELM and ultrasound examination. After excisional biopsy, the correlation between clinical, ELM, sonographic, and histologic diagnosis was established. **Exclusions:** No exclusions due to lack of visualisation on ultrasound.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Harland 2000

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control (only specific diagnoses included) **Data collection:** Unclear **Period of data collection:** NR **Country:** UK
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with pigmented lesions with specific presumptive clinical diagnoses (seborrhoeic keratosis, benign naevi or cutaneous malignant melanoma) recruited from a pigmented lesion clinic; the referring general practitioner had considered the diagnosis of melanoma for each lesion. **Setting:** Specialist clinic **Prior testing:** Clinical diagnosis made at PLC **Exclusion criteria:** Lesions with macroscopic ulceration **Sample size (patients):** No. eligible: NR **Sample size (lesions):** No. eligible: NR; No. included: 69 **Participant characteristics:** Mean age: NR. Male: NR. **Lesion characteristics:** None reported
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Unclear
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Ultrasound: High frequency (20MHz)** Test detail: Dermascan-CTM 20-MHz B-scanner (Cortex Technology, ApS, Hadsund, Denmark); axial resolution of 50 µm and a lateral resolution of 300 µm; in vivo slice 22´4 mm width, 13´4 mm depth (6´7 mm with zoom factor 2) and 200 µm thickness. Scanner described as "US prototype with a large unwieldy scanner head, such that certain sites, such as the inner canthus, are inaccessible to examination. However, the aim of this pilot study was not to evaluate practicality of clinical use." **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical diagnosis provided to sonographer **Diagnostic threshold:** DER - dermal echogenicity ratio < 3 set to ensure sensitivity of 100% for melanoma; EEL - absence of entry echo line (documented as either equivalent to perilesional skin (nonenhanced) or as broadened); DER <3 or absence of EEL **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

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

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Histological evaluation was performed without knowledge of the ultrasound findings. Histological sections of tumours were prepared in the same plane as the B-scans, both being centred upon the transverse reference line. **Target condition (Final diagnoses)** Melanoma (invasive): 19. Melanoma in situ: 6. BCC: 0. 'Benign' diagnoses: 15 benign nevi, 29 seborrhoeic keratosis
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Not described **Exclusions:** No exclusions due to lack of visualisation on ultrasound.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	-

Lassau 1997

Patient Selection

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

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients with skin lesions clinically suspected of being either melanoma or BCC and scheduled for resection; includes only very specific lesion groups (MM, BCC, and benign nevi) **Setting:** Secondary **Prior testing:** Clinical diagnosis; basis for referral for US not described **Exclusion criteria:** None reported **Sample size (patients):** No. eligible: 70 **Sample size (lesions):** No. included: 70 **Participant characteristics:** Mean age: NR. Male: NR. **Lesion characteristics:** Melanoma thickness on histology ranged from 0.25 to 6 mm (n=19)
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Ultrasound: High frequency (20MHz); Colour Doppler (7 MHz)** Test detail: Esaote-Biomedica AU4 Idea (Genoa, Italy). HFUS - 20-MHz annular probe with an axial resolution of 20 µm and a lateral resolution of 100 µm; Doppler - a 13-MHz linear probe with an axial resolution of 200 µm and a lateral resolution of 400 µm for performing pulsed and Colour Doppler US. Theoretical depth explored was 16 mm (HFUS) and 40 mm (linear/Doppler) **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical diagnosis provided to sonographer **Diagnostic threshold:** HFUS - Hypoechoic with a homogeneous echostructure and well-defined lower and lateral margins; HFUS plus Doppler: hypoechoic with a homogeneous echostructure and well-defined lower and lateral margins OR presence of intratumoral vessels on Doppler **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Was the test applied and interpreted in a clinically applicable manner?	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?	Unclear
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** None reported **Target condition (Final diagnoses)** Melanoma (invasive or in situ): 19; BCC: 31; plus 1 neurosarcoma 'Benign' diagnoses: 12 benign nevi, seborrhoeic keratosis
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** "After surgical resection, tumors were analyzed histologically" **Exclusions:** 6/38 clinically suspected MEL not visualised on HFUS (including 3 melanomas); plus 1/32 suspected BCC lesions were not visualised on US and were excluded leaving 63 lesions reported for HFUS
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	-

Rallan 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	**Study design:** Case control (only selected diagnoses included) **Data collection:** Unclear **Period of data collection:** NR **Country:** UK
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Inclusion criteria:** Patients referred to a skin cancer clinic with a suspicion of melanoma and with a subsequent clinical diagnosis of SK, benign nevus, or suspicion of melanoma **Setting:** Specialist clinic **Prior testing:** Clinical diagnosis by a dermatologist; basis for referral for US not described **Exclusion criteria:** Head/neck excluded; > 20 mm excluded **Sample size (patients):** No. eligible: 87 **Sample size (lesions):** No. included: 87 **Participant characteristics:** Mean age: NR (range 21 to 67y). Male: 24; 28% **Lesion characteristics:** Mean Breslow thickness for invasive melanomas: 0.97+/-0.29 mm, range 0.25 mm to 2.0 mm.
Are the included patients and chosen study setting appropriate?	No
Did the study avoid including participants with multiple lesions?	Yes
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	**Ultrasound: High frequency (20MHz) with Reflex Transmission Imaging (RTI)** Test detail: Dermascan Cv3 Cortex ApS (Denmark); three types of images generated - a reflex transmission image (RTI) predominantly influenced by ultrasonic attenuation in the focal plane, a ‘‘lesional backscatter image’’ (LBI) based on an integration zone through the lesion body and an ‘‘entry echo image’’ (EEI) based on an integration zone through the skin surface. "RTI parameters refer to lesion attenuation properties, LBI and EEI parameters depict intralesional sound reflection and surface sound reflectance characteristics, respectively". Referenced to Rallan 2006, however relatively experimental in nature. **Method of diagnosis:** In person diagnosis **Prior test data available:** Unclear whether clinical diagnosis provided to sonographer **Diagnostic threshold:** Based on presence of statistically significant characteristics related to contrast and relative heterogeneity of each type of image (these were identified from comparison of mean values between MM vs SK and MM vs BN). Three significant characteristics were identified - RTI contrast, LBI relative heterogeneity, and EEI relative heterogeneity **Diagnosis based on:** Unclear whether single or multiple observers (n=NR) **Observer qualifications:** Not reported **Experience in practice:** Not described **Experience with index test:** Not described

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

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

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	**Type of reference standard:** Histological diagnosis alone **Details:** Lesions were "removed under local anaesthetic following data acquisition. Histological diagnosis was then used to classify the lesion in one of three groups, MM, SK, or other benign-pigmented lesion. In cases of histological atypia or dyplasia, suggesting but not confirming melanoma, the lesion was classed in accordance with the clinical management protocol (usually as melanoma)." **Target condition (Final diagnoses)** Melanoma (invasive): 14; Melanoma in situ: 11; BCC: 0. 'Benign' diagnoses: 38 benign nevi, 24 seborrhoeic keratosis
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the reference standard results interpreted without knowledge of the referral diagnosis?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

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

Flow and Timing

A. Risk of Bias	
Flow and timing	**Index test to reference standard interval:** Consecutive **Exclusions:** No lesions reported that were not visualised on US
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	-

Footnotes

Characteristics of excluded studies

Akata 1998

Reason for exclusion	EXCLUDE on index test; Doppler US

Bezugly 2015

Reason for exclusion	EXCLUDE not a primary study

Bobadilla 2008

Reason for exclusion	EXCLUDE on study population; *only BCC lesions included*

Cardenas 2009

Reason for exclusion	EXCLUDE on index test; *17 MHz frequency*

Delfino 2013

Reason for exclusion	EXCLUDE on index test; 17-MHz ultrasound probe

Evans 2014

Reason for exclusion	EXCLUDE not a primary study

Fornage 1993

Reason for exclusion	EXCLUDE on reference standard; *Maximum of 41% of benign group had adequate reference standard (if assume all malignant had histology) From paper - Pathologic diagnosis obtained for 109 lesions (54%) through shave, punch, or excisional biopsy; in the absence of pathologic analysis, the diagnosis was based on the dermatologist's assessment*

Giovagnorio 2003

Reason for exclusion	EXCLUDE on target condition; *detection of metastases*

Gropper 1993

Reason for exclusion	EXCLUDE not a primary study; *Review*

Harland 1993

Reason for exclusion	EXCLUDE on sample size; *3 BCC; 1 SCC*

Hernandez 2014

Reason for exclusion	EXCLUDE not a primary study; *Comment paper*

Hughes 1987

Reason for exclusion	EXCLUDE on target condition *NO breakdown of 17 malignant lesions undergoing Doppler* EXCLUDE on index test *HFUS reported for thickness only; Doppler flow +/- also reported*

Hunger 2012

Reason for exclusion	EXCLUDE on index test; *High definition Laser Doppler*

Jambusaria-Pahlajani 2009

Reason for exclusion	EXCLUDE on study population; *Only biopsy confirmed BCC or SCC* EXCLUDE on target condition; *Detection of surgical margin*

Karaman 2001

Reason for exclusion	EXCLUDE on index test; *Power Doppler*

Krahn 1998

Reason for exclusion	EXCLUDE on target condition; *Exclude HF ultrasound data - only reports accurate detection of lesion thickness; include for VI/Dermoscopy*

Maj 2015

Reason for exclusion	EXCLUDE on 2x2 data; *Paper refers to Table I which contains 'detailed data' but there is no Table I in the paper* EXCLUDE but contact authors; *contacted Dec 2016 and May 2017*

Marques 2002

Reason for exclusion	EXCLUDE on index test; *10 Mhz ultrasound - not high frequency*

Meyer 2014

Reason for exclusion	EXCLUDE on target condition; *identification of lesion thickness only*

Ozkol 2006

Reason for exclusion	EXCLUDE on target condition; *D+ group includes 1 dermatofibroma and 1 Bowen's; cannot disaggregate* EXCLUDE on index test; *Colour Doppler*

Petik 2013

Reason for exclusion	EXCLUDE on index test; *Colour Doppler plus Power Doppler if vascularity not clearly identified*

Rallan 2006

Reason for exclusion	EXCLUDE if derivation study; *High-resolution ultrasound with reflex transmission imaging (RTI); also combined with white light clinical (WLC) photography. No separate independent test set result is given; also 'white light' data is CAD based*

Ravi 2000

Reason for exclusion	EXCLUDE on index test; *Colour Doppler*

Samimi 2010

Reason for exclusion	EXCLUDE on study population; *Blue naevus or melanoma mets* EXCLUDE on target condition; *Melanoma metastasis*

Schroder 1999

Reason for exclusion	EXCLUDE on index test; Not high frequency (10 MHz US)

Schröder 2001

Reason for exclusion	EXCLUDE on index test; Not HFUS

Scotto 2015

Reason for exclusion	EXCLUDE on index test; *US (5-17MHz) and Doppler*

Song 2014

Reason for exclusion	EXCLUDE on index test; *Not high frequency US (7-15MHz)*

Srivastava 1986

Reason for exclusion	EXCLUDE on index test; *Doppler US*

Stucker 2002

Reason for exclusion	EXCLUDE on index test; *Laser Doppler; assessment of blood flow*

Stücker 1999

Reason for exclusion	EXCLUDE on index test; *laser Doppler US* EXCLUDE on 2x2 data; *comparing mean tumour perfusion values between groups only*

Wortsman 2010

Reason for exclusion	EXCLUDE on target condition; *Can estimate sensitivity for detection of malignancy but cannot estimate specificity for benign lesions assessed to either rule in or rule out malignancy* EXCLUDE on index test; *Up to 15MHz ultrasound* EXCLUDE on 2x2 data; *could get 2x2 from Table 1 but disease negative includes huge range of diagnoses that are not relevant to our review*

Wortsman 2013

Reason for exclusion	EXCLUDE not a primary study

Footnotes

Characteristics of studies awaiting classification

Bens 2015

Patient Sampling	-
Patient characteristics and setting	-
Index tests	-
Target condition and reference standard(s)	-
Flow and timing	-
Comparative	-
Notes	British Library unable to supply copy of the paper; author contacted

Nitsche 1992

Patient Sampling	-
Patient characteristics and setting	-
Index tests	-
Target condition and reference standard(s)	-
Flow and timing	-
Comparative	-
Notes	British Library unable to supply copy of the paper

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of results tables

1 Summary of findings

Question	What is the diagnostic accuracy of high frequency ultrasound (HFUS) for the diagnosis of cutaneous melanoma or BCC in adults?				
Participants	Adults with suspicious skin lesions.				
Prior testing and prevalence	Studies varied in, or did not report, the basis for participant referral for ultrasound. One implied that half of included lesions were difficult to diagnose and two included only three lesion types. Prevalence of melanoma ranged from 14% to 58% (median 30%) and BCC from 8% to 49% (median 17%).				
Settings	Secondary care and specialist lesion clinics.				
Target condition(s)	Invasive melanoma and melanocytic intraepidermal variants; basal cell carcinoma				
Index test	High frequency ultrasound (> 20 MHz) alone and in combination with Doppler ultrasound. Lesions not visualised on ultrasound were excluded by some studies.				
Reference standard	Histology				
Action:	If accurate, positive results of HFUS will help to appropriately select lesions for excision				
Limitations					
Risk of bias:	Patient selection methods unclear or at high risk of bias due to selective inclusion of lesion types. Test interpretation was blinded to reference standard, but test thresholds were clearly prespecified in only one study and were data driven (2/6) or not pre-specified (3/6) in the remainder. Reference standard blinding was not described. Timing of index and reference standards was not reported. Exclusions due to test failures were not reported (3/6).				
Applicability of evidence to question:	High (4) or unclear (1) concerns about applicability due to unrepresentative participant samples with high disease prevalence. Test observers were not described (6/6) and prototype or relatively novel devices used (2/6). Reference standard interpretation by experienced histopathologists was not described (5/6). Half of studies were not designed to investigate test accuracy.				
Total number of studies:	**6**	Total participants with test results	**1263**	Total number melanoma or BCC	**349**
Detection of melanoma					
Number of studies	**5**	Total participants with test results	**1125**	Total with melanoma	**242**
Findings	No pooled analysis was conducted due to between study heterogeneity and small study numbers. Derived sensitivities for investigated HFUS characteristics were at least 83% (95% CI 75% to 90%); the combination of three qualitative features (lesions appearing hypoechoic, homogenous and well defined) demonstrating 100% sensitivity in two studies, with variable specificities of 33% (95% CI 20% to 48%) and 73% (95% CI 57% to 85%). Quantitative measurement of HFUS outputs in two studies enabled decision thresholds to be set to achieve 100% sensitivity; resulting specificities were 93% (95% CI 77% to 99%) and 65% (95% CI 51% to 76%). Between 7 and 38 lesions were not visualised on HFUS (reported in 3 studies); including between 3 and 5 melanomas not visualised (in each of the 3 studies).				
Detection of BCC					
Number of studies	**3**	Total participants with test results	**993**	Total with BCC	**119**
Findings	Only qualitative thresholds were assessed; sensitivities and specificities were highly variable, making summary statements difficult.				

Footnotes

HFUS - high frequency ultrasound; BCC - basal cell carcinoma; CI - confidence interval.

Additional tables

References to studies

Included studies

Bessoud 2003

* Bessoud B, Lassau N, Koscielny S, Longvert C, Avril MF, Duvillard P, et al. High-frequency sonography and color Doppler in the management of pigmented skin lesions. Ultrasound in Medicine & Biology 2003;29(6):875-9. [Other: ER4:20569435; PubMed: 12837502]

Clement 2001

Clement A, Hoeffel C, Fayet P, Benkanoun S, Sahut D'izarn J, Oudjit A, et al. [Value of high frequency (20mhZ) and doppler ultrasound in the diagnosis of pigmented cutaneous tumors]. Journal de Radiologie 2001;82(5):563-71. [PubMed: 11416794]

Dummer 1995

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Rallan 2007

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Akata D, Ozmen MN, Madani S, Akhan O, Atakan N. Doppler spectral analysis of skin lesions: Differential diagnosis between benign and malignant tumors. Ultrasound International 1998;4(2):86-92. [EMBASE: 28429607]

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Classification pending references

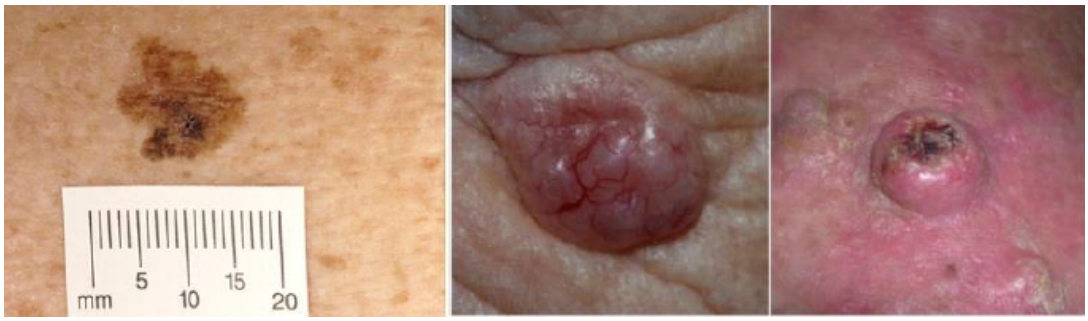
Data and analyses

Data tables by test

Test	Studies	Participants
1 Melanoma - hypoechoic	1	792
2 Melanoma - hypoechoic and homogenous	1	792
3 Melanoma - hypoechoic and sharp basal margins	1	792
4 Melanoma - hypoechoic and sharp lateral margins	1	792
5 Melanoma - hypoechoic, homogenous and well defined	2	177
6 Melanoma (MM vs BN) - hypoechoic, homogenous and well defined	1	32
7 Melanoma (MM vs SK) - DER<3	1	54
8 Melanoma (MM vs SK) - absence of EEL	1	54
9 Melanoma (MM vs SK) - DER<3 OR absence of EEL	1	54
10 Melanoma (MM vs SK/BN) - absence of EEL	1	69
11 Melanoma - RTI contrast/LBI rel. heterogeneity/EEI rel. heterogeneity	1	87
12 Melanoma - HFUS+ve OR Doppler +ve	1	63
13 Melanoma (MM vs BN) - HFUS+ve OR Doppler +ve	1	32
14 Melanoma - HFUS+ve AND Doppler +ve	2	170
15 BCC - hypoechoic	2	930
16 BCC - hypoechoic and homogenous	2	930
17 BCC - hypoechoic and well defined	1	138
18 BCC - hypoechoic and sharp basal margins	1	792
19 BCC - hypoechoic and sharp lateral margins	1	792
20 BCC - hypoechoic, homogenous and well defined	1	63
21 BCC - hypoechoic, heterogenous with irregular margins	1	63
22 BCC - HFUS+ve AND Doppler +ve	1	138

Figures

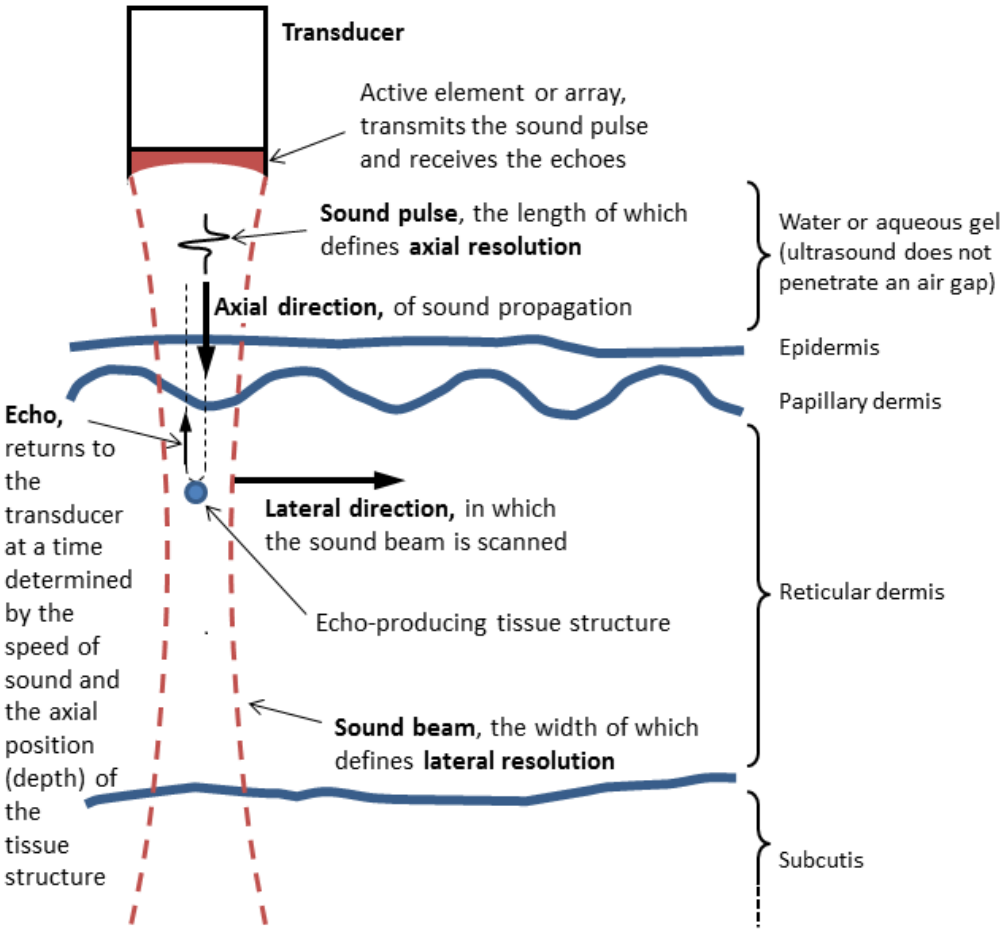
Figure 1



Caption

Sample photographs of superficial spreading melanoma (left), BCC (centre), and cSCC (right)

Figure 2



Caption

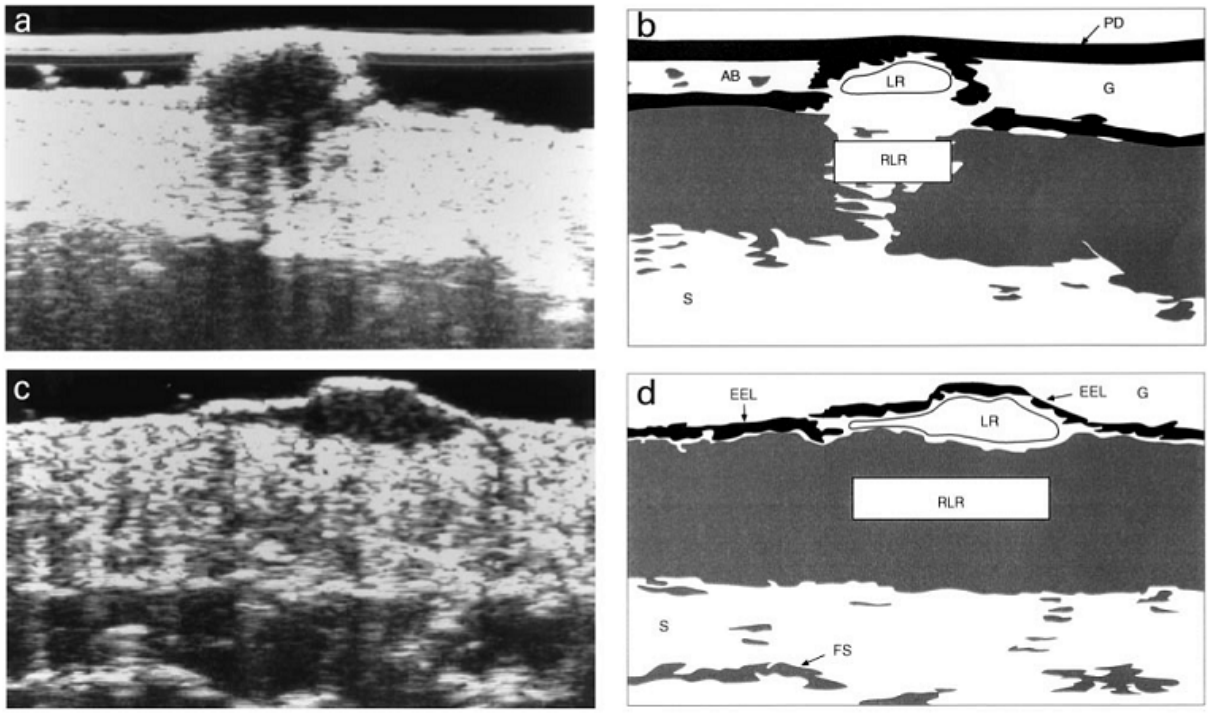
The principles of B-mode ultrasound echographic imaging of the skin

Figure 3

Caption

Modern laptop based DermaScan C® (2D) (Copyright © 2018 Cortex Technology ApS: reproduced with permission)

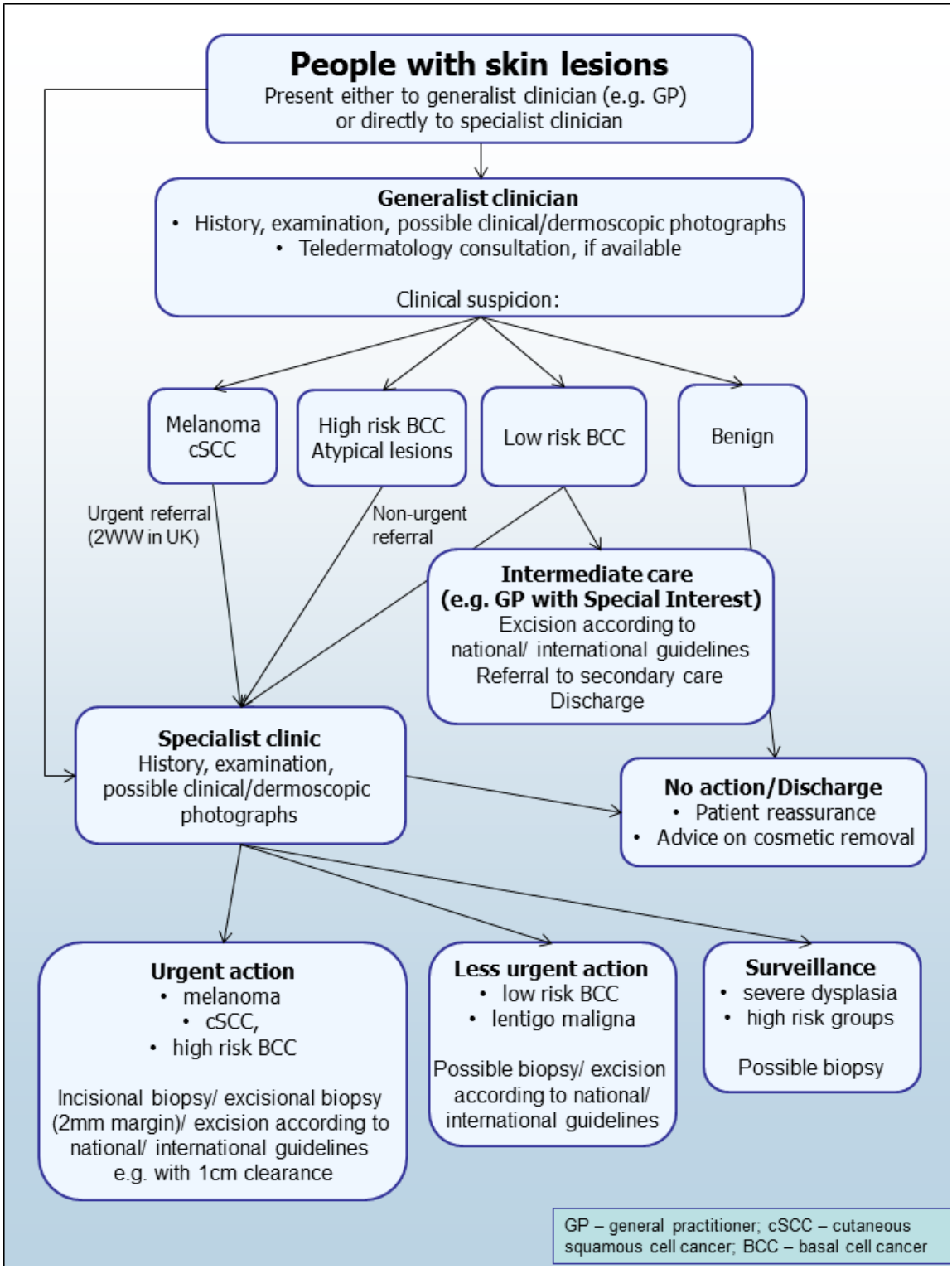
Figure 4



Caption

Illustrates the well defined margins, low level and homogenous internal echoes, lack of strong entry echo and lack of acoustic shadowing for melanoma (c. and d.) and contrasting image for BCC (a. and b.) (from Harland 2001, Copyright © 2018 John Wiley and Sons, reproduced with permission)

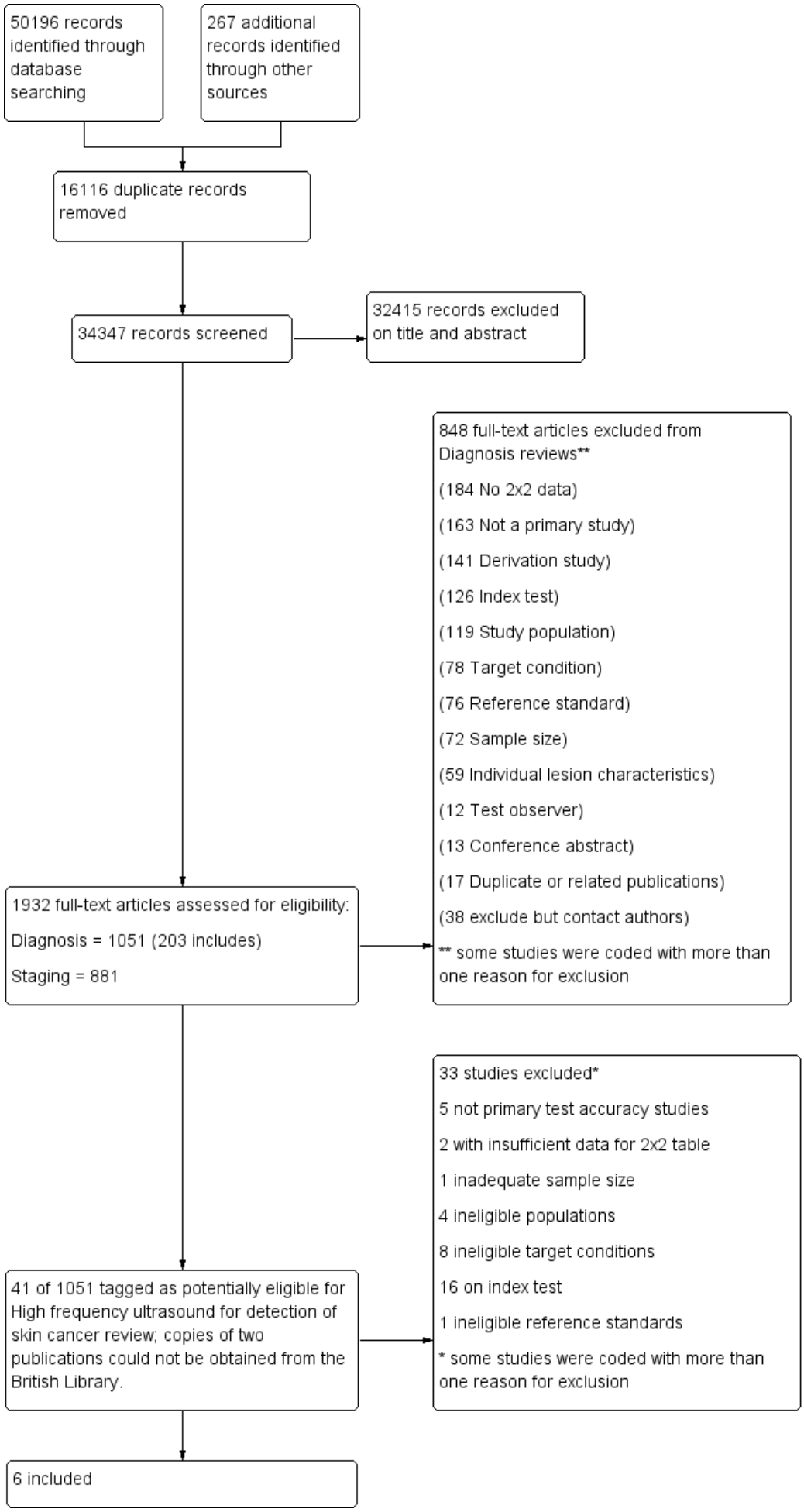
Figure 5



Caption

Current clinical pathway for people with skin lesions

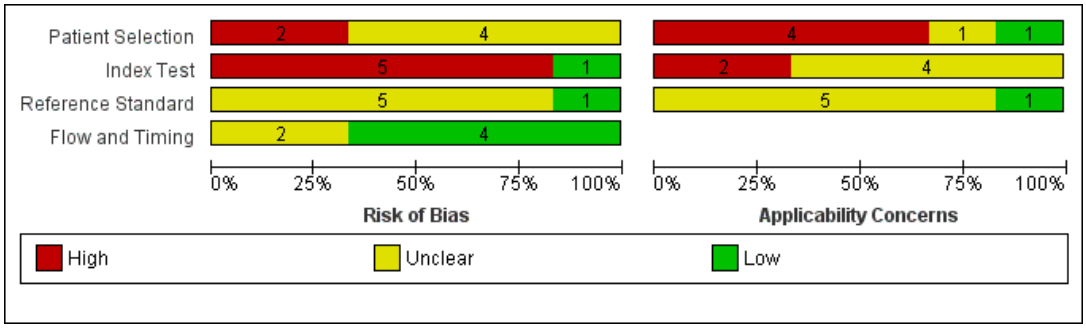
Figure 6


50196 records identified through database searching
267 additional records identified through other sources
16116 duplicate records removed
34347 records screened
32415 records excluded on title and abstract
848 full-text articles excluded from Diagnosis reviews**
(184 No 2x2 data)
(163 Not a primary study)
(141 Derivation study)
(126 Index test)
(119 Study population)
(78 Target condition)
(76 Reference standard)
(72 Sample size)
(59 Individual lesion characteristics)
(12 Test observer)
(13 Conference abstract)
(17 Duplicate or related publications)
(38 exclude but contact authors)
** some studies were coded with more than one reason for exclusion
1932 full-text articles assessed for eligibility:
Diagnosis = 1051 (203 includes)
Staging = 881
33 studies excluded*
5 not primary test accuracy studies
2 with insufficient data for 2x2 table
1 inadequate sample size
4 ineligible populations
8 ineligible target conditions
16 on index test
1 ineligible reference standards
* some studies were coded with more than one reason for exclusion
41 of 1051 tagged as potentially eligible for High frequency ultrasound for detection of skin cancer review; copies of two publications could not be obtained from the British Library.
6 included

Caption

PRISMA flow diagram.

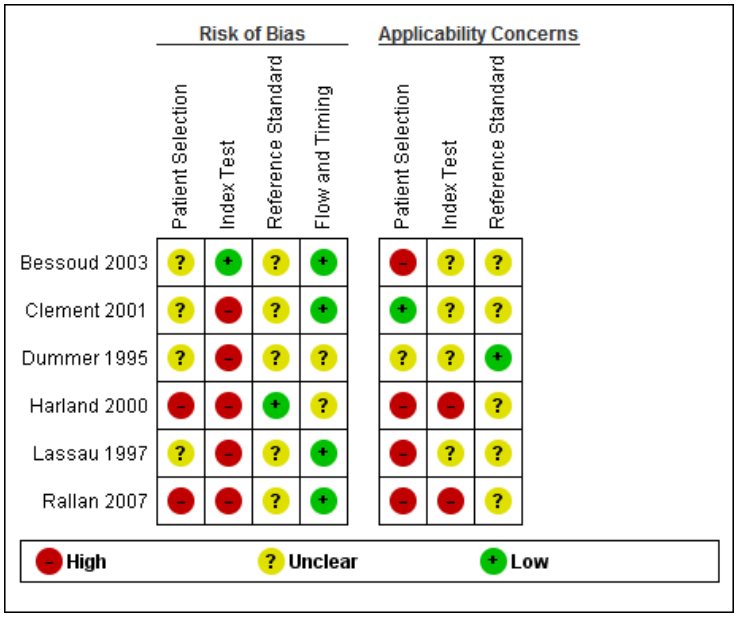
Figure 7



Caption

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

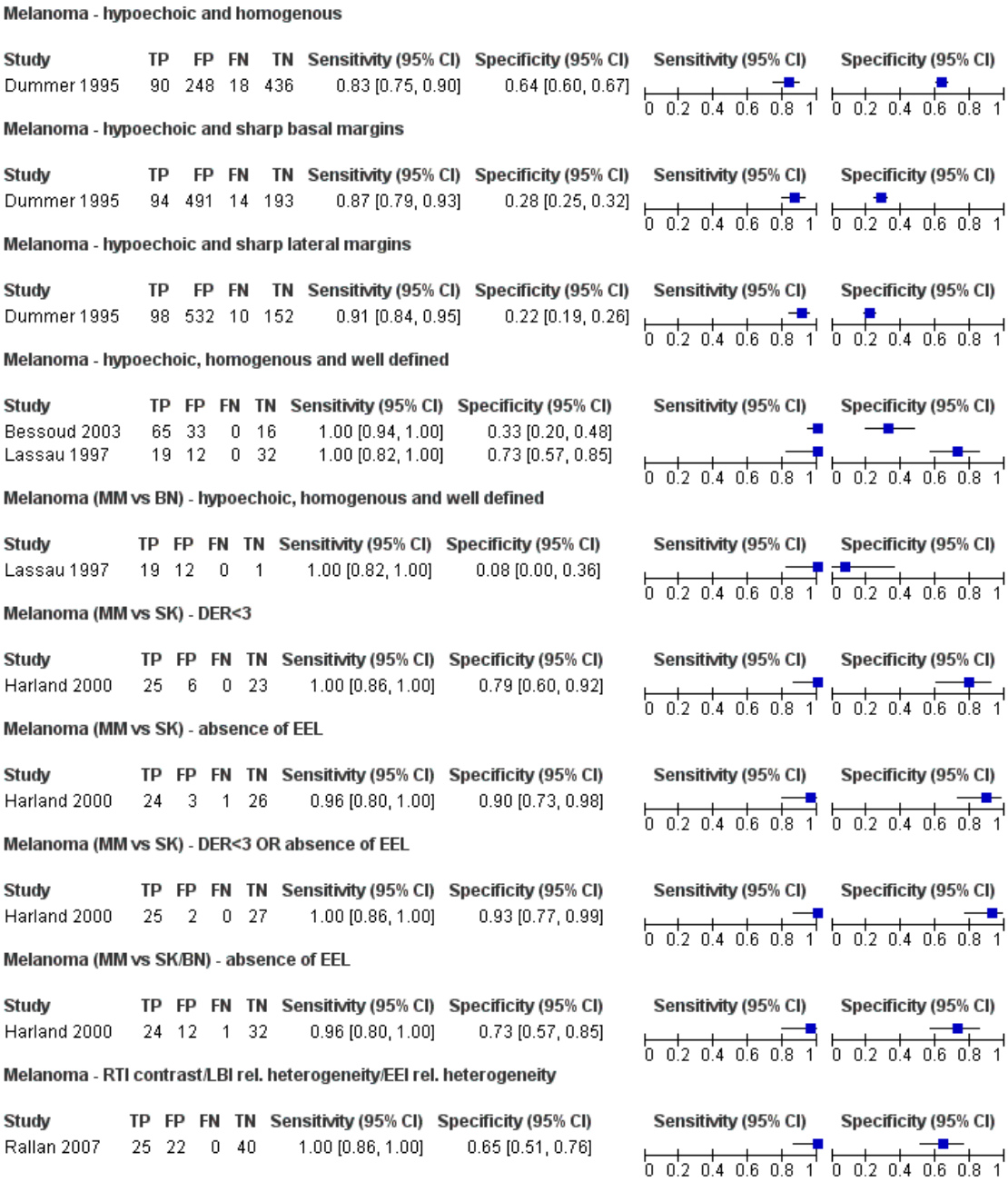
Figure 8



Caption

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

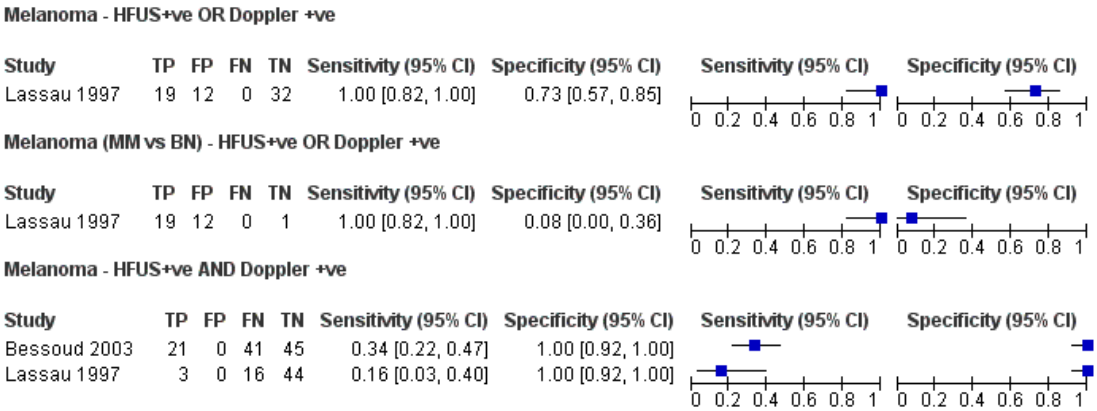
Figure 9 (Analysis 1)



Caption

Forest plot of tests for differentiation of melanoma from other lesions using combinations of HFUS characteristics and quantitative measurements of HFUS outputs

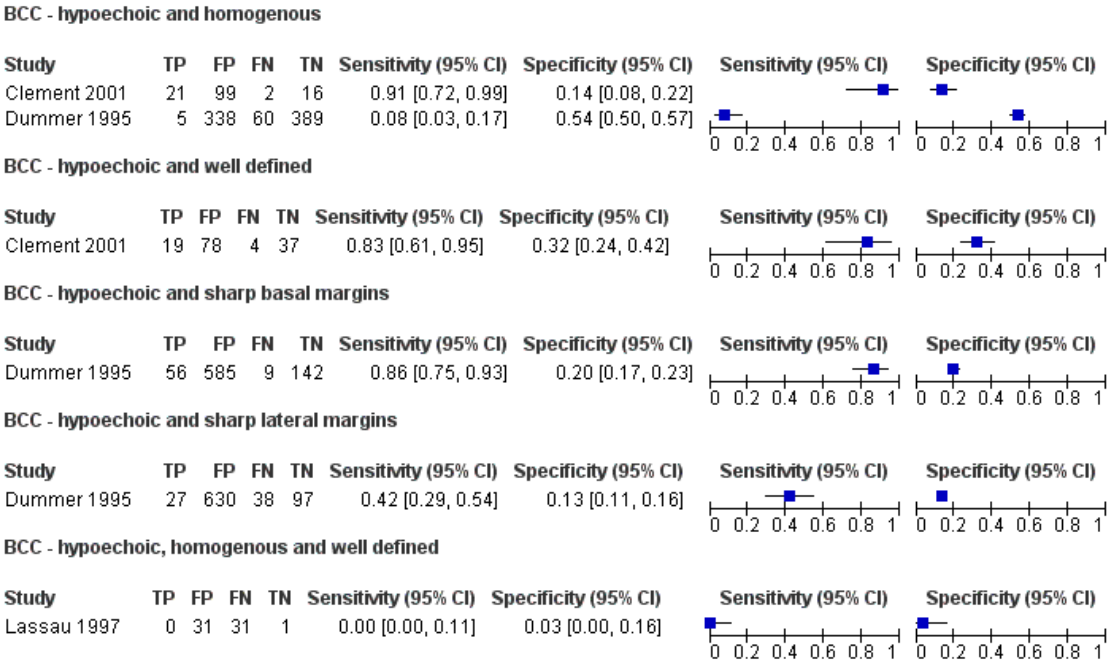
Figure 10 (Analysis 2)



Caption

Forest plot of tests for the differentiation of melanoma from other lesions using HFUS and Doppler US

Figure 11 (Analysis 3)



Caption

Forest plot of tests for the differentiation of BCC from other lesion types using HFUS

Sources of support

Internal sources

- No sources of support provided

External sources

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

Feedback

Appendices

1 Current content and structure of the Programme Grant

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

2 Glossary of terms

Term	Definition
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma *in situ* and lentigo maligna
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin
BRAF V600 mutation	BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. BRAF mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs.
BRAF inhibitors	Therapeutic agents which inhibit the serine-threonine protein kinase BRAF mutated metastatic melanoma.
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour.
Congenital naevi	A type of mole found on infants at birth

Term	Definition
Dermoscopy	Whereby a handheld microscope is used to allow more detailed, magnified, examination of the skin compared to examination by the naked eye alone
False negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.
False positive	An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease.
Histopathology/Histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope.
Incidence	The number of new cases of a disease in a given time period.
Index test	A diagnostic test under evaluation in a primary study
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 rate	Microscopic evaluation of number of cells actively dividing in a tumour.
Morbidity	Detrimental effects on health.
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1000, 10,000 or 100,000 people.
Multidisciplinary team	A team with members from different healthcare professions and specialties (e.g. urology, oncology, pathology, radiology, and nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.
Prevalence	The proportion of a population found to have a condition.
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it which might affect the patient’s prognosis.
Receiver operating characteristic (ROC) plot	A plot of the sensitivity and 1 minus the specificity of a test at the different possible thresholds for test positivity; represents the diagnostic capability of a test with a range of binary test results
Receiver operating characteristic (ROC) analysis	The analysis of a ROC plot of a test to select an optimal threshold for test positivity
Recurrence	Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.
Reference Standard	A test or combination of tests used to establish the final or ‘true’ diagnosis of a patient in an evaluation of a diagnostic test
Reflectance confocal microscopy (RCM)	A microscopic technique using infrared light (either in a handheld device or a static unit) that can create images of the deeper layers of the skin
Sensitivity	In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test
Specificity	The proportion of individuals without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Staging	Clinical description of the size and spread of a patient’s tumour, fitting into internationally agreed categories.

Term	Definition
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination.
Systemic treatment	Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area.

3 Table of acronyms and abbreviations used

Acronym	Definition
µm	micrometre
AHM	amelanotic or hypomelanotic melanoma
AK	actinic keratosis
AMN	atypical melanocytic naevi
AUC	area under the curve
B-mode	brightness mode
BCC	basal cell carcinoma
BD	Bowen's disease
BN	benign naevi
BNM	benign non-melanocytic
BPC	between person comparison (of tests)
CAD	computer assisted diagnosis
CCS	case control study
CD	compact disc
CM	cutaneous melanoma
CMM	cutaneous malignant melanoma
CS	case series
CSCC	cutaneous squamous cell carcinoma
D-	disease negative
D+	disease positive
DER	dermal echogenicity ratio
DF	dermatofibroma
Dx	diagnosis
EEI	entry echo image
EEL	entry echo line
ELM	epiluminescence microscopy
FN	false negative
FP	false positive
FU	Follow- up
GP	general practitioner
H&E	haematoxylin and eosin stain
HFUS	high frequency ultrasound
Hz	hertz
KHz	kilohertz
LBI	lesional backscatter image
LPLK	lichen planus- like keratosis

Acronym	Definition
LS	lentigo simplex
MEL	melanoma (invasive or in situ)
MHz	megahertz
MiS	melanoma in situ (or lentigo maligna)
MM	malignant melanoma
mm	millimetre
MN	melanocytic naevi
MSDSLA	multispectral digital skin lesion analysis device
n	number
N/A	not applicable
NC	non comparative
NMLs	non melanocytic lesions
No.	number
NPV	negative predictive value
NR	not reported
P	prospective
PCPs	primary care providers
PLC	pigmented lesion clinic
PPV	positive predictive value
PRF	pulse-repetition frequency
PSL	pigmented skin lesion
R	retrospective
RCM	reflectance confocal microscopy
RCT	randomised controlled trial
RTI	reflex transmission image
SCC	squamous cell carcinoma
SD	standard deviation
SDDI	Short-term sequential digital dermoscopy imaging
se	sensitivity
sp	specificity
SK	seborrhoeic keratosis
SN	Spitz nevi
SSM	superficial spreading melanoma
TD	teledermatology
TN	true negative
US	ultrasound
VI	visual inspection
WPC	within person comparison (of tests)
WPC-algs	within person comparison (of algorithms)

4 Proposed sources of heterogeneity

i. Population characteristics

- general versus higher risk populations
- patient population: Primary /secondary / specialist unit

- lesion suspicion: general suspicion/atypical/equivocal/NR
- lesion type: any pigmented; melanocytic
- inclusion of multiple lesions per participant
- ethnicity

ii. Index test characteristics

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

iii. Reference standard characteristics

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

iv. Study quality

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

5 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)

6 Full text inclusion criteria

Criterion	Inclusion	Exclusion

Study design	**For diagnostic and staging reviews**
	• Any study for which a 2×2 contingency table can be extracted, e.g.
	  ◦ diagnostic case control studies
	  ◦ 'cross-sectional' test accuracy study with retrospective or prospective data collection
	  ◦ studies where estimation of test accuracy was not the primary objective but test results for both index and reference standard were available
	  ◦ RCTs of tests or testing strategies where participants were randomised between index tests and all undergo a reference standard (i.e. accuracy RCTs)
		• < 5 melanoma cases (diagnosis reviews)
		• < 10 participants (staging reviews)
		• Studies developing new criteria for diagnosis unless a separate 'test set' of images were used to evaluate the criteria (mainly digital dermoscopy)
		• Studies using 'normal' skin as controls
		• Letters, editorials, comment papers, narrative reviews
		• Insufficient data to construct a 2×2 table

Target condition	• Melanoma
	• Keratinocyte skin cancer (or non-melanoma skin cancer)
	  ◦ BCC or epithelioma
	  ◦ cSCC
		• Studies exclusively conducted in children
		• Studies of non-cutaneous melanoma or SCC

Criterion	Inclusion	Exclusion
Population	<u>For diagnostic reviews</u> • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms include pigmented skin lesion/nevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC <u>For staging reviews</u> • 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	<u>For diagnosis</u> • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscpoy • Smartphone/mobile phone applications • Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other <u>For staging</u> • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology FNAC • SLNB +/high frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders • Tests to improve histopathology diagnose • LND
Reference standard	<u>For diagnostic studies</u> • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) <u>For studies of imaging tests for staging</u> • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above <u>For studies of SLNB accuracy for staging</u> • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	<u>For diagnostic studies</u> • Exclude if any disease positive participants have diagnosis unconfirmed by histology • Exclude if > 50% of disease negative participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e. comparing referral decision with expert diagnosis, unless evaluations of teledermatology or mobile phone applications

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; CT: computed tomography; FNAC: fine needle aspiration cytology; LND: lymph node dissection; MRI: magnetic resonance imaging; PET: positron emission tomography; PET-CT: positron emission tomography computed tomography; RCT: randomised controlled trial; SCC: squamous cell carcinoma; SLN+: positive sentinel lymph node; SLn: negative sentinel lymph node; SLNB: sentinel lymph node biopsy.

7 Quality assessment (based on QUADAS-2)

The QUADAS-2 checklist (Whiting 2011) was tailored to the review topic as follows below.

Patient selection domain (1)

Selective recruitment of study participants can be a key influence on test accuracy. In general terms, all participants eligible to undergo a test should be included in a study, allowing for the intended use of that test within the context of the study. We considered studies that separately sampled malignant and benign lesions to have used a case-control design; and those that supplemented a series of suspicious lesions with additional malignant or benign lesions to be at unclear risk of bias

In terms of exclusions, we considered studies that excluded particular lesion types (e.g. lentigo maligna), particular lesion sites, or that excluded lesions on the basis of image quality or lack of observer agreement (e.g. on histopathology) to be at high risk of bias.

In judging the applicability of patient populations to the review question, we considered restriction to particular lesion populations, such as melanocytic, nodular, high risk or restrictions by size to be of high concern for applicability.

Given that diagnosis of skin cancer is primarily lesion-based, there is the potential for study participants with multiple lesions to contribute disproportionately to estimates of test accuracy, especially if they are at particular risk of having skin cancer. We considered studies that include a high number of lesions in relation to the number of study to be less representative than studies conducted in a more general population participants (i.e. if the difference between the number of included lesions and number of included participants is greater than 5%).

Index test domain (2)

Given the potential for subjective differences in test interpretation for melanoma, the interpretation of the index test blinded to the result of the reference standard is a key means of reducing bias. For prospective studies and retrospective studies that used the original index test interpretation, the diagnosis will by nature be interpreted and recorded before the result of the reference standard is known; however, studies using previously acquired images could be particularly susceptible to information bias. For these studies to be at low risk of bias, we required a clear indication that observers were unaware of the reference standard diagnosis at time of test interpretation. An item was also added to assess the presence of blinding between interpretations of different algorithms, however this item was not included in the overall assessment of risk of bias.

Pre-specification of the index test threshold was considered present if the study clearly reported that the threshold used was not data driven, i.e. was not based on study results. Studies that did not clearly describe the threshold used but that required clinicians to record a diagnosis or management decision for a lesion were considered to be unclear on this criterion. Studies reporting accuracy for multiple numeric thresholds, where ROC analysis was used to select the threshold, or that reported accuracy for the presence of independently significant lesion characteristics with no separate test set of lesions were considered at high risk of bias.

In terms of applicability of the index test to the review question, we required the test to be applied and interpreted as it would be in a clinical practice setting, i.e. in-person or face-to-face with the patient, and by a single observer as opposed to a consensus decision or average across multiple observers. Image-based studies were considered to be high concern, although for some tests (e.g. RCM) image interpretations where the observer was also supplied with a clinical or dermoscopic image of the lesion along with some patient characteristics were considered ‘unclear’.

Despite the often subjective nature of test interpretation, it is also important for study authors to outline the particular lesion characteristics that were considered to be indicative for melanoma, particularly where established algorithms or checklists were not used. Studies were considered of low concern if the threshold used was established in a prior study or sufficient threshold details were presented to allow replication.

The experience of the examiner will also impact on the applicability of study results. We required studies to describe the test interpreter as ‘experienced’ or ‘expert’ to have low concern about applicability.

Reference standard domain (3)

In an ideal study, consecutively recruited participants should all undergo incisional or excisional biopsy of the skin lesion regardless of level of clinical suspicion of melanoma. In reality, both partial and differential verification bias are likely. Partial verification bias may occur where histology is the only reference standard used, and only those participants with a certain degree of suspicion of malignancy based on the result of the index test undergo verification, the others either being excluded from the study or defined as being disease-negative without further assessment or follow-up, as discussed above.

Differential verification bias will be present where other reference standards are used in addition to histological verification of suspicious lesions. A typical example of verification bias in skin cancer occurs when investigators do not biopsy people with benign-appearing lesions but instead follow them up for a period of time to determine whether any malignancy subsequently develops (these would be false-negatives on the index test). We defined an 'adequate' reference standard as: all disease-positive individuals having a histological reference standard either at the time of application of the index test or after a period of clinical follow-up; and at least 80% of disease-negative participants have received a histological diagnosis, with up to 20% undergoing at least three months' follow-up of benign-appearing lesions.

A further challenge is the potential for incorporation bias, i.e. where the result of the index test is used to help determine the reference standard diagnosis. It is normal practice for the clinical diagnosis (usually by visual inspection or dermoscopy) to be included on pathology request forms and for the histopathologist to use this diagnosis to help with the pathology interpretation. Although inclusion of such clinical information on the histopathology request form is theoretically a form of incorporation bias, blinded interpretation of the histopathology reference standard is not normal practice, and enforcement of

such conditions would significantly limit the generalisability of the study results. For studies evaluating tests other than visual inspection or dermoscopy, this item was divided into two questions, firstly whether the reference standard was blinded to the index test result, and secondly whether it was blinded to the clinical diagnosis. Only the response to the first part (i.e. blinding to index test) was included in our overall assessment of risk of bias for the reference standard domain.

In judging the applicability of the reference standard to our review question, scored studies as high concern around applicability if they used expert diagnosis (with no follow-up) as a reference standard in any patient, or did not report histology interpretation by a dermatopathologist.

Flow and timing domain (4)

In the ideal study, the diagnosis based on the index test and reference standard should be made consecutively or as near to each other in time as possible to avoid changes in lesion over time. For lesions with a histological reference standard, we have defined a one-month period as an appropriate interval between application of the index test and the reference standard. For studies using clinical follow-up, a minimum three-month follow-up period has been defined as at low risk of bias for detecting false-negatives. This interval was chosen based on a study showing that most false-negative melanomas will be diagnosed within three months of the initial negative index test although a small number will be diagnosed up to 12 months subsequently (Altamura 2008).

In assessing whether all patients were included in the analysis, we considered studies at high risk of bias if participants were excluded following recruitment.

Comparative domain

A comparative domain was added to the QUADAS-2 checklist for studies comparing the accuracy of RCM and dermoscopy. Items were included to assess the presence blinding of interpretation between tests, and to specify a maximum of one month interval between application of index tests, as intervals greater than these may be accompanied by changes in tumour characteristics. As it would not be normal practice for RCM to be interpreted blinded to the clinical or dermoscopic diagnosis, the scoring of this item did not contribute to our overall assessment of risk of bias. We also considered whether both tests were applied and interpreted in a clinically applicable manner.

The following tables use text that was originally published in the QUADAS-2 tool by Whiting and colleagues (Whiting 2011 *).*

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
1) Was a consecutive or random sample of participants or images enrolled?	**Yes** – if paper states consecutive or random **No** – if paper describes other method of sampling **Unclear** – if participant sampling not described
2) Was a case-control design avoided?	**Yes** – if consecutive or random or case-control design clearly not used **No** – if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** – if not described
3) Did the study avoid inappropriate exclusions, e.g. • 'difficult to diagnose' lesions not excluded • lesions not excluded on basis of disagreement between evaluators	**Yes** - if inappropriate exclusions were avoided **No** – if lesions were excluded that might affect test accuracy, e.g. 'difficult to diagnose' lesions, or where disagreement between evaluators was observed **Unclear** – if not clearly reported but there is suspicion that difficult to diagnose lesions may have been excluded

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
4) For between-person comparative studies only (i.e. allocating different tests to different study participants): • **A)** were the same participant selection criteria used for those allocated to each test? • **B)** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C)** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	**For A)** • **Yes** – if same selection criteria were used for each index test, **No** – if different selection criteria were used for each index test, **Unclear** – if selection criteria per test were not described, **N/A** – if only 1 index test was evaluated or all participants received all tests **For B)** • **Yes** – if adequate randomisation procedures are described, **No** – if inadequate randomisation procedures are described, **Unclear** – if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient), **N/A** – if only 1 index test was evaluated or all participants received all tests **For C)** • **Yes** – if appropriate methods of allocation concealment are described, **No** – if appropriate methods of allocation concealment are not described, **Unclear** – if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required), **N/A** – if only 1 index test was evaluated
Could the selection of participants have introduced bias? **For non-comparative and within person-comparative studies** 1. If answers to all of questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': **For between-person comparative studies** 1. If answers to all of questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	**For non-comparative and within person-comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear **For between-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear
PARTICIPANT SELECTION (1) - CONCERNS REGARDING APPLICABILITY	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
1) Are the included participants and chosen study setting appropriate to answer the review question, i.e. are the study results generalisable? • This item is not asking whether exclusion of certain participant groups might bias the study's results (as in Risk of Bias above), but is asking whether the chosen study participants and setting are appropriate to answer our review question. Because we are looking to establish test accuracy in both primary presentation and referred participants, a study could be appropriate for 1 setting and not for the other, or it could be unclear as to whether the study can appropriately answer either question • For each study assessed, please consider whether it is more relevant for A) participants with a primary presentation of a skin lesion or B) referred participants, and respond to the questions in either A) or B) accordingly. If the study gives insufficient details, please respond **Unclear** to both parts of the question	**A) For studies that will contribute to the analysis of participants with a primary presentation of a skin lesion (i.e. test naive)** **Yes** – if participants included in the study appear to be generally representative of those who might present in a usual practice setting **No** – if study participants appear to be unrepresentative of usual practice, e.g. in terms of severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants **B) For studies that will contribute to the analysis of referred participants (i.e. who have already undergone some form of testing)** **Yes** – if study participants appear to be representative of those who might be referred for further investigation. If the study focuses only on those with equivocal lesions, for example, we would suggest that this is not representative of the wider referred population **No** – if study participants appear to be unrepresentative of usual practice, e.g. if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols **Unclear –** if insufficient details are provided to determine the generalisability of study participants
2) Did the study **avoid including** participants with multiple lesions?	**Yes** – if the difference between the number of included lesions and number of included participants is less than 5% **No** – if the difference between the number of included lesions and number of included participants is greater than 5% **Unclear –** if it is not possible to assess
Is there concern that the included participants do not match the review question? 1. If the answer to question 1) or 2) 'Yes': 2. If the answer to question 1) or 2) 'No': 3. If the answer to question 1) or 2) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
INDEX TEST (2) - RISK OF BIAS (to be completed per test evaluated)	
1) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	**Yes** – if index test described as interpreted without knowledge of reference standard result or, for prospective studies, if index test is always conducted and interpreted prior to the reference standard **No** – if index test described as interpreted in knowledge of reference standard result **Unclear** – if index test blinding is not described

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
2) Was the diagnostic threshold at which the test was considered positive (i.e. melanoma present) prespecified?	**Yes** – if threshold was prespecified (i.e. prior to analysing study results) **No** – if threshold was not prespecified **Unclear** – if not possible to tell whether or not diagnostic threshold was prespecified
3) For within-person comparisons of index tests or testing strategies (i.e. > 1 index test applied per participant): was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	**Yes** – if all index tests were described as interpreted without knowledge of the results of the others **No** – if the index tests were described as interpreted in the knowledge of the results of the others **Unclear** – if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation **N/A** – if only 1 index test was evaluated
Could the conduct or interpretation of the index test have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to either questions 1) or 2) 'No': 3. If answers to either questions 1) or 2) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), for any index test and 3) 'Yes': 2. If answers to any 1 of questions 1) or 2) for any index test or 3) 'No': 3. If answers to any 1 of questions 1) or 2) for any index test or 3) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
INDEX TEST (2) - CONCERN ABOUT APPLICABILITY	
1) Was the diagnostic threshold to determine presence or absence of disease established in a previously published study? E.g. previously evaluated/established • algorithm/checklist used • lesion characteristics indicative of melanoma used • objective (usually numerical) threshold used	**Yes** – if a previously evaluated/established tool to aid diagnosis of melanoma was used or if the diagnostic threshold used was established in a previously published study **No** – if an unfamiliar/new tool to aid diagnosis of melanoma was used, if no particular algorithm was used, or if the objective threshold reported was chosen based on results in the current study **Unclear** – if insufficient information was reported
2) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? Study results can only be reproduced if the diagnostic threshold is described in sufficient detail. This item applies equally to studies using pattern recognition and those using checklists or algorithms to aid test interpretation	**Yes** – If the criteria for diagnosis of melanoma were reported in sufficient detail to allow replication **No** – if the criteria for diagnosis of melanoma were not reported in sufficient detail to allow replication **Unclear** – If some but not sufficient information on criteria for diagnosis to allow replication were provided

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
3) Was the test interpretation carried out by an experienced examiner?	**Yes** – if the test was interpreted by 1 or more speciality-accredited dermatologists, or by examiners of any clinical background with special interest in dermatology and with any formal training in the use of the test **No** – if the test was not interpreted by an experienced examiner (see above) **Unclear** – if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners were described as 'Expert' with no further detail given **N/A** – if system-based diagnosis, i.e. no observer interpretation
Is there concern that the index test, its conduct, or interpretation differ from the review question? 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to questions 1), 2), or 3) 'No': 3. If answers to questions 1), 2), or 3) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
REFERENCE STANDARD (3) - RISK OF BIAS	
1) Is the reference standard likely to correctly classify the target condition? A) Disease-positive – 1 or more of the following: • histological confirmation of melanoma following biopsy or lesion excision • clinical follow-up of benign-appearing lesions for at least 3 months following the application of the index test, leading to a histological diagnosis of melanoma B) Disease-negative – 1 or more of the following: • histological confirmation of absence of melanoma following biopsy or lesion excision in at least 80% of disease-negative participants • clinical follow-up of benign-appearing lesions for a minimum of 3 months following the index test in up to 20% of disease-negative participants	A) Disease-positive **Yes** – if all participants with a final diagnosis of melanoma underwent 1 of the listed reference standards **No** – If a final diagnosis of melanoma for any participant was reached without histopathology **Unclear** – if the method of final diagnosis was not reported for any participant with a final diagnosis of melanoma or if the length of clinical follow-up used was not clear or if a clinical follow-up reference standard was reported in combination with a participant-based analysis and it was not possible to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test B) Disease-negative **Yes** – If at least 80% of benign diagnoses were reached by histology and up to 20% were reached by clinical follow-up for a minimum of 3 months following the index test **No** – if more than 20% of benign diagnoses were reached by clinical follow-up for a minimum of 3 months following the index test or if clinical follow-up period was less than 3 months **Unclear** – if the method of final diagnosis was not reported for any participant with benign or non-melanoma diagnosis
2) Were the reference standard results interpreted without knowledge of the results of the index test? Please score this item for all studies even though histopathology interpretation is usually conducted with knowledge of the clinical diagnosis (from visual inspection or dermoscopy or both). We will deal with this by not including the response to this item in the 'Risk of bias' assessment for these tests. For reviews of all other tests, this item will be retained	**Yes** – if the reference standard diagnosis was reached blinded to the index test result **No** – if the reference standard diagnosis was reached with knowledge of the index test result **Unclear** – if blinded reference test interpretation was not clearly reported

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1) 'Yes': 2. If answer to question 1) 'No': 3. If answer to question 1) 'Unclear': **For all other tests** 1. If answers to questions 1) and 2) 'Yes': 2. If answers to questions 1) or 2) 'No': 3. If answers to questions 1) or 2) 'Unclear':	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
REFERENCE STANDARD (3) - CONCERN ABOUT APPLICABILITY	
1) Are index test results presented separately for each component of the target condition (i.e. separate results presented for those with invasive melanoma, melanoma in situ, lentigo maligna, severe dysplasia, BCC, and cSCC)?	**Yes –** if index test results for each component of the target condition can be disaggregated **No –** if index test results for the different components of the target condition cannot be disaggregated **Unclear** – if not clearly reported
2) Expert opinion (with no histological confirmation) was not used as a reference standard 'Expert opinion' means diagnosis based on the standard clinical examination, with no histology or lesion follow-up ***do not complete this item for teledermatology studies	**Yes** – if expert opinion was not used as a reference standard for any participant **No** – if expert opinion was used as a reference standard for any participant **Unclear** – if not clearly reported
3) Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	**Yes –** if histology interpretation was reported to be carried out by an experienced histopathologist or dermatopathologist **No –** if histology interpretation was reported to be carried out by a less experienced histopathologist **Unclear** – if the experience/qualifications of the pathologist were not reported
Is there concern that the target condition as defined by the reference standard does not match the review question? 1. If answers to all questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': *****For teledermatology studies only** 1. If answers to all questions 1) and 3) 'Yes': 2. If answers to questions 1) or 3) 'No': 3. If answers to questions 1) or 3) 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear *****For teledermatology studies only** 1. Concern is low 2. Concern is high 3. Concern is unclear
FLOW AND TIMING (4): RISK OF BIAS	

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
1) Was there an appropriate interval between index test and reference standard? **A)** For histopathological reference standard, was the interval between index test and reference standard ≤ 1 month? **B)** If the reference standard includes clinical follow-up of borderline/benign-appearing lesions, was there at least 3 months' follow-up following application of index test(s)?	**A)** **Yes** – if study reports ≤ 1 month between index and reference standard **No** – if study reports > 1 month between index and reference standard **Unclear** – if study does not report interval between index and reference standard **B)** **Yes** – if study reports ≥ 3 months' follow-up **No** – if study reports < 3 months' follow-up **Unclear** – if study does not report the length of clinical follow-up
2) Did all participants receive the same reference standard?	**Yes** – if all participants underwent the same reference standard **No** – if more than 1 reference standard was used **Unclear** – if not clearly reported
3) Were all participants included in the analysis?	**Yes** – if all participants were included in the analysis **No** – if some participants were excluded from the analysis **Unclear**– if not clearly reported
4) **For within-person comparisons of index tests** Was the interval between application of index tests ≤ 1 month?	**Yes** – if study reports ≤ 1 month between index tests **No** – if study reports > 1 month between index tests **Unclear** – if study does not report the interval between index tests
Could the participant flow have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1), 2), and 3) 'Yes': 2. If answers to any 1 of questions 1), 2), or 3) 'No': 3. If answers to any 1 of questions 1), 2), or 3) 'Unclear': **For within-person comparative studies** 1. If answers to all questions 1), 2), 3), and 4) 'Yes': 2. If answers to any 1 of questions 1), 2), 3), or 4) 'No': 3. If answers to any 1 of questions 1), 2), 3), or 4) 'Unclear':	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.	

8 Summary study details

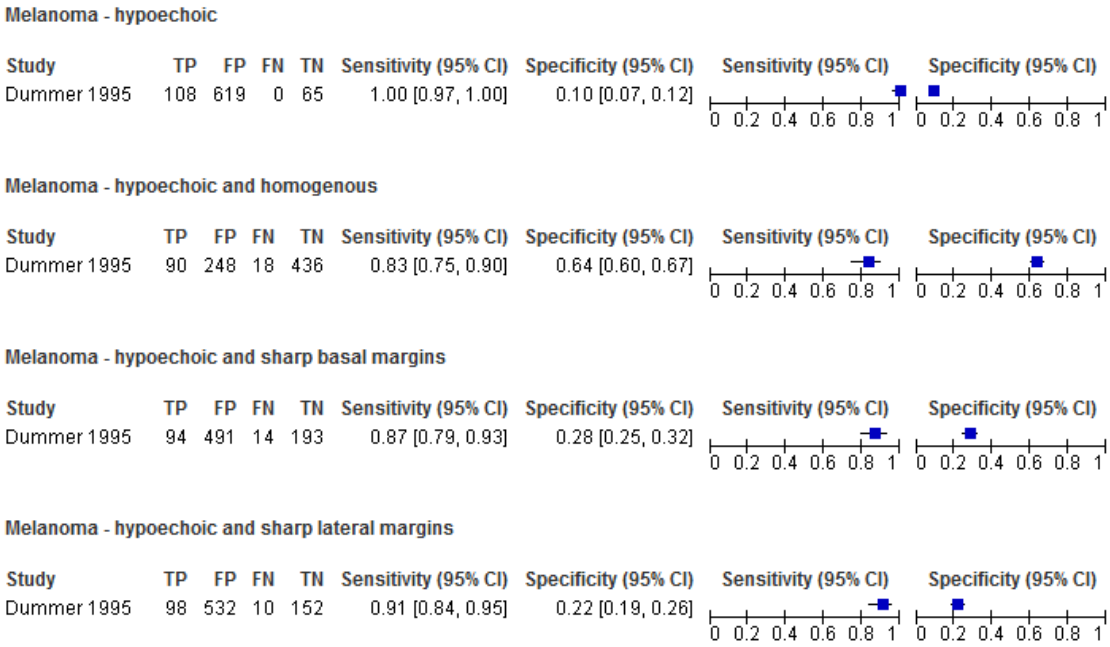
Study author Outcomes reported	Study type	Inclusion criteria	Number of patients / lesions	US machine	Frequency Resolution	Threshold	Observer qual. (n) and experience	Reference standard Final diagnoses	Exclusions
Bessoud 2003 MEL	WPC P-CS France Secondary	Patients with PSLs referred from the Dermatology Department to the Ultrasound Unit	111 / 130	AU 4 or AU 5 Idea (Esaote-Biomedica, Genoa, Italy) Doppler	20-MHz axial 80 µm; lateral 100 µm 7 MHz	1. Hypoechoic, homogenous and well defined HFUS+Doppler As above AND intra-lesional vessels present	Not described	Histology MM 65; 4 BCC; 1 neurosarcoma BN 33; SK 5; Other 6 (3 melanosis, 1 thrombosing capillaritis, 1 histiocytofibroma, 1 lentigo)	16 'unseen ultrasound (16/130=12 5 melanom 11 benign r (including 1 lentigo) Further 8 lesions not imaged with Doppler (ba for selectio NR)
Clement 2001 BCC	WPC P-CS France Secondary	Patients with PSLs including melanocytic and non melanocytic examined before resection (recruited 1998-1999)	160 / 176	AU4 then AU5 Idea, (Esaote Biomedica, Genoa, Italy) Doppler	20 MHz 80 µm axial; 100 µm lateral 7 MHz	1. Hypoechoic 2. Hypoechoic and homogenous 3. Hypoechoic and well defined HFUS+Doppler Hypoechoic AND vascularity present	Not described	Histology MM 1; BCC 23; Mel metastases 6; BN 6; SK 29; histiocytofibroma 11; angioma 7	38 not visualised, including tv that were difficult to reach (38/1 = 21.6%); 5 melanom (all in the horizontal growth pha 33 benign nevus)
Dummer 1995 MEL BCC	NC NR-CS Germany Secondary	Patients with PSLs referred from the outpatient clinic to the Department of Dermatology	NR / 792	DUB 20 , Taberna pro Medicum, Luneburg, Germany	20 MHz axial 80 µm; lateral 200 µm	1. Hypoechoic 2. Hypoechoic and homogenous 3. Hypoechoic and well defined (1) Sharp basal margins; 2) Sharp lateral margins)	Not described	Histology MM 108; BCC 65 BN 307; SK 211; DF 54; angioma 47	None repor
Harland 2000	NC CCS UK Specialist	Patients with PSLs with specific presumptive clinical diagnoses (SK, BN, MM) from a PSL clinic; the referring GP had considered the diagnosis of melanoma for each lesion.	NR / 54	Dermascan-CTM B-scanner (Cortex Technology, ApS, Hadsund, Denmark)	20 MHz axial 50 µm; lateral 300 µm	1. Dermal echogenicity ratio (DER) <3 (to ensure sensitivity of 100%) 2. Absence of Entry Echo line (EEL) - (either equivalent to perilesional skin (nonenhanced) or as broadened); 3. Either 1. Or 2.	Not described	Histology MM 19; MiS 6 BN 15; SK 29	BN exclude from sensitivity a specificity estimates

Study author Outcomes reported	Study type	Inclusion criteria	Number of patients / lesions	US machine	Frequency Resolution	Threshold	Observer qual. (n) and experience	Reference standard Final diagnoses	Exclusions
Lassau 1997 MEL BCC	WPC P-CS France Secondary	Patients with skin lesions clinically suspected of being either melanoma or BCC and scheduled for resection	70 / 70	Esaote-Biomedica AU4 Idea (Genoa, Italy) Doppler	20 MHz axial 20 µm; lateral 100 µm 7 MHz	1. Hypoechoic, homogenous and well defined HFUS+Doppler As above OR intratumoral vessels present	Not described	Histology MM 19; BCC 31; neurosarcoma 1 BN 12	6/38 clinica suspected MEL not visualised HFUS (including 3 melanomas plus 1/32 suspected BCCs (whi proved to b an actinic keratosis); (7/70 = 10%
Rallan 2007	NC CCS UK Specialist	Patients referred to a skin cancer clinic with a suspicion of melanoma and with a subsequent clinical diagnosis of SK, BN, or suspicion of melanoma	87 / 87	Dermascan Cv3 Cortex ApS, Denmark); 20 MHz, modified for RTI using a transducer with an f-number of 0.95		1. presence of either RTI contrast, LBI relative heterogeneity, OR EEI relative heterogeneity; mechanism/values indicative of presence of each feature NR	Not described	Histology MM 14; MiS 11 BN 38; SK 24	None repor

NC – non comparative study; WPC – within person comparison study; P – prospective; NR – not reported; CS – case series; C – case control study; HFUS – high frequency ultrasound; PSL – pigmented skin lesion; MEL – melanoma (invasive and *in situ*); MM – invasive melanoma; MiS – melanoma *in situ*; BCC – basal cell carcinoma; BN – benign naevi; SK – seborrhoeic keratosis DF – dermatofibroma; RTI – reflex transmission imaging; LBI - lesional backscatter image; EEL - entry echo line; EEI - entry ec image; DER - dermal echogenicity ratio; GP - general practitioner.

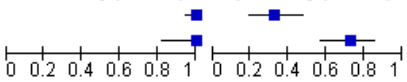
*Also reports in person diagnosis for VI and for Dermoscopy

Graphs



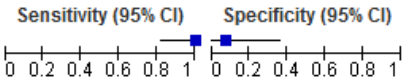
Melanoma - hypoechoic, homogenous and well defined

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bessoud 2003	65	33	0	16	1.00 [0.94, 1.00]	0.33 [0.20, 0.48]
Lassau 1997	19	12	0	32	1.00 [0.82, 1.00]	0.73 [0.57, 0.85]



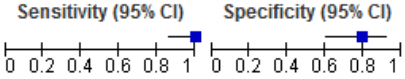
Melanoma (MM vs BN) - hypoechoic, homogenous and well defined

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lassau 1997	19	12	0	1	1.00 [0.82, 1.00]	0.08 [0.00, 0.36]



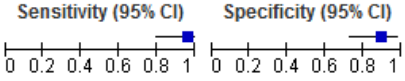
Melanoma (MM vs SK) - DER<3

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harland 2000	25	6	0	23	1.00 [0.86, 1.00]	0.79 [0.60, 0.92]



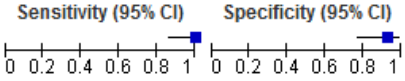
Melanoma (MM vs SK) - absence of EEL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harland 2000	24	3	1	26	0.96 [0.80, 1.00]	0.90 [0.73, 0.98]



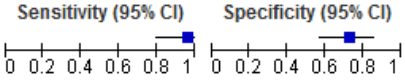
Melanoma (MM vs SK) - DER<3 OR absence of EEL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harland 2000	25	2	0	27	1.00 [0.86, 1.00]	0.93 [0.77, 0.99]



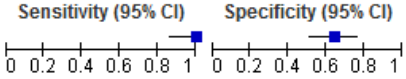
Melanoma (MM vs SK/BN) - absence of EEL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harland 2000	24	12	1	32	0.96 [0.80, 1.00]	0.73 [0.57, 0.85]



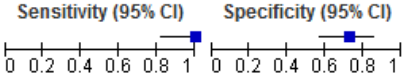
Melanoma - RTI contrast/LBI rel. heterogeneity/EEI rel. heterogeneity

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Rallan 2007	25	22	0	40	1.00 [0.86, 1.00]	0.65 [0.51, 0.76]



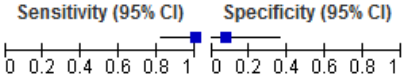
Melanoma - HFUS+ve OR Doppler +ve

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lassau 1997	19	12	0	32	1.00 [0.82, 1.00]	0.73 [0.57, 0.85]



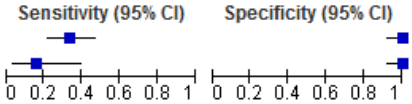
Melanoma (MM vs BN) - HFUS+ve OR Doppler +ve

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lassau 1997	19	12	0	1	1.00 [0.82, 1.00]	0.08 [0.00, 0.36]



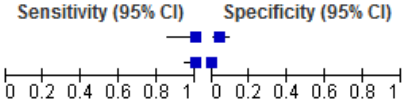
Melanoma - HFUS+ve AND Doppler +ve

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bessoud 2003	21	0	41	45	0.34 [0.22, 0.47]	1.00 [0.92, 1.00]
Lassau 1997	3	0	16	44	0.16 [0.03, 0.40]	1.00 [0.92, 1.00]



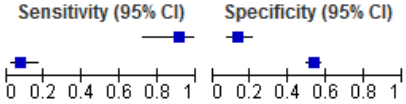
BCC - hypoechoic

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Clement 2001	23	110	0	5	1.00 [0.85, 1.00]	0.04 [0.01, 0.10]
Dummer 1995	65	727	0	0	1.00 [0.94, 1.00]	0.00 [0.00, 0.01]



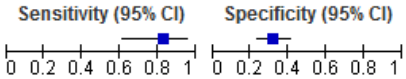
BCC - hypoechoic and homogenous

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Clement 2001	21	99	2	16	0.91 [0.72, 0.99]	0.14 [0.08, 0.22]		
Dummer 1995	5	338	60	389	0.08 [0.03, 0.17]	0.54 [0.50, 0.57]		



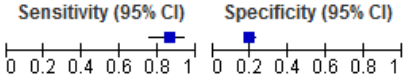
BCC - hypoechoic and well defined

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Clement 2001	19	78	4	37	0.83 [0.61, 0.95]	0.32 [0.24, 0.42]		



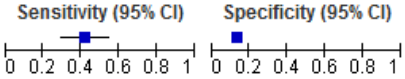
BCC - hypoechoic and sharp basal margins

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dummer 1995	56	585	9	142	0.86 [0.75, 0.93]	0.20 [0.17, 0.23]		



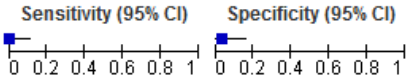
BCC - hypoechoic and sharp lateral margins

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dummer 1995	27	630	38	97	0.42 [0.29, 0.54]	0.13 [0.11, 0.16]		



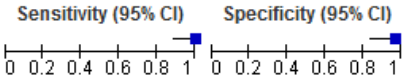
BCC - hypoechoic, homogenous and well defined

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Lassau 1997	0	31	31	1	0.00 [0.00, 0.11]	0.03 [0.00, 0.16]		



BCC - hypoechoic, heterogenous with irregular margins

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Lassau 1997	31	1	0	31	1.00 [0.89, 1.00]	0.97 [0.84, 1.00]		



BCC - HFUS+ve AND Doppler +ve

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Clement 2001	0	13	23	102	0.00 [0.00, 0.15]	0.89 [0.81, 0.94]