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[Diagnostic Test Accuracy Review]

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ABSTRACT

Background

Early accurate detection of all skin cancer types is essential to guide appropriate management, reduce morbidity and improve survival. Basal cell carcinoma (BCC) is usually localised to the skin but has potential to infiltrate and damage surrounding tissue, while cutaneous squamous cell carcinoma (cSCC) and melanoma have a much higher potential to metastasise and ultimately lead to death. Exfoliative cytology is a non-invasive test that uses the Tzanck smear technique to identify disease by examining the structure of cells obtained from scraped samples. This simple procedure is a less invasive diagnostic test than a skin biopsy, and for BCC it has the potential to provide an immediate diagnosis that avoids an additional clinic visit to receive skin biopsy results. This may benefit patients scheduled for either Mohs micrographic surgery or non-surgical treatments such as radiotherapy. A cytology scrape can never give the same information as a skin biopsy, however, so it is important to better understand in which skin cancer situations it may be helpful.

Objectives

To determine the diagnostic accuracy of exfoliative cytology for detecting basal cell carcinoma (BCC) in adults, and to compare its accuracy with that of standard diagnostic practice (visual inspection with or without dermoscopy). Secondary objectives were: to determine the diagnostic accuracy of exfoliative cytology for detecting cSCC, invasive melanoma and atypical intraepidermal melanocytic variants, and any other skin cancer; and for each of these secondary conditions to compare the accuracy of exfoliative cytology with visual inspection with or without dermoscopy in direct test comparisons; and to determine the effect of observer experience.

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 also studied the reference lists of published systematic review articles.

Selection criteria

Studies evaluating exfoliative cytology in adults with lesions suspicious for BCC, cSCC or melanoma, compared with a reference standard of histological confirmation.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). Where possible we estimated summary sensitivities and specificities using the bivariate hierarchical model.

Main results

We synthesised the results of nine studies contributing a total of 1655 lesions to our analysis, including 1120 BCCs (14 datasets), 41 cSCCs (amongst 401 lesions in 2 datasets), and 10 melanomas (amongst 200 lesions in 1 dataset). Three of these datasets (one each for BCC, melanoma and any malignant condition) were derived from one study that also performed a direct comparison with dermoscopy. Studies were of moderate to poor quality, providing inadequate descriptions of participant selection, thresholds used to make cytological and histological diagnoses, and blinding. Reporting of participants' prior referral pathways was particularly poor, as were descriptions of the cytodiagnostic criteria used to make diagnoses. No studies evaluated the use of exfoliative cytology as a primary diagnostic test for detecting BCC or other skin cancers in lesions suspicious for skin cancer. Pooled data from seven studies using standard cytomorphological criteria (but various stain methods) to detect BCC in participants with a high clinical suspicion of BCC estimated the sensitivity and specificity of exfoliative cytology as 97.5% (95% CI 94.5% to 98.9%) and 90.1% (95% CI 81.1% to 95.1%). respectively. When applied to a hypothetical population of 1000 clinically suspected BCC lesions with a median observed BCC prevalence of 86%, exfoliative cytology would miss 21 BCCs and would lead to 14 false positive diagnoses of BCC. No false positive cases were histologically confirmed to be melanoma. Insufficient data are available to make summary statements regarding the accuracy of exfoliative cytology to detect melanoma or cSCC, or its accuracy compared to dermoscopy.

Authors' conclusions

The utility of exfoliative cytology for the primary diagnosis of skin cancer is unknown, as all included studies focused on the use of this technique for confirming strongly suspected clinical diagnoses. For the confirmation of BCC in lesions with a high clinical suspicion, there is evidence of high sensitivity and specificity. Since decisions to treat low-risk BCCs are unlikely in practice to require diagnostic confirmation given that clinical suspicion is already high, exfoliative cytology might be most useful for cases of BCC where the treatments being contemplated require a tissue diagnosis (e.g. radiotherapy). The small number of included studies, poor reporting and varying methodological quality prevent us from drawing strong conclusions to guide clinical practice. Despite insufficient data on the use of cytology for cSCC or melanoma, it is unlikely that cytology would be useful in these scenarios since preservation of the architecture of the whole lesion that would be available from a biopsy provides crucial diagnostic information. Given the paucity of good quality data, appropriately designed prospective comparative studies may be required to evaluate both the diagnostic value of exfoliative cytology by comparison to dermoscopy, and its confirmatory value in adequately reported populations with a high probability of BCC scheduled for further treatment requiring a tissue diagnosis.

PLAIN LANGUAGE SUMMARY

How accurate is exfoliative cytology ('skin scrape' cytology) for diagnosing basal cell carcinoma and other skin cancers in adults?

Why is improving the diagnosis of skin cancer important?

There are a number of different types of skin cancer. The most common is basal cell carcinoma (BCC). BCC is a localised cancer that can grow and destroy the skin around it. They rarely spread into the body like other cancers can. Very small or superficial low-risk BCCs can generally be treated with treatments such as creams rather than surgery, while it is better to surgically remove BCCs that are more likely to grow and spread. Radiotherapy (a treatment where radiation is used to kill cancer cells) can also be used if BCCs are very large or cannot be removed by surgery. Cutaneous squamous cell carcinoma (cSCC) is also usually a localised skin cancer. In a small proportion of cases it can spread to other parts of the body, so the best treatment is to remove it using surgery. Melanoma is one of the most dangerous forms of skin cancer as it has a higher potential to spread to other parts of the body, and so it is vital to recognise it and remove it early. If people with BCC do not receive the correct diagnosis (known as a false negative test result), their treatment can be delayed, making the surgical procedure more complicated. Diagnosing BCC when it is actually something else (a false positive result) may result in unnecessary treatment, surgery or other investigations and can cause the patient stress and anxiety. If BCC is incorrectly

diagnosed in an individual who actually has an cSCC or melanoma, effective treatment can be delayed and this might lead to a greater chance that the cSCC or melanoma spreads to other organs in the body, which can be very serious.

What is the aim of the review?

The aim of this Cochrane Review was to find out how accurate a technique called 'exfoliative cytology' is for diagnosing skin cancer. Researchers in Cochrane found nine studies to answer this question. Nine studies were concerned with the diagnosis of BCC, two with the diagnosis of cSCC and one with the diagnosis of melanoma.

What was studied in the review?

Exfoliative cytology means scraping the surface of a possible skin cancer with a knife and then spreading a small layer of the scrape onto a glass slide so that the cells in the scrape can be stained and looked at under a microscope. It is less invasive than skin biopsy and quick to perform, with results available immediately. This could save patients an additional clinic visit to receive skin biopsy results.

What are the main results of the review?

The review examined nine studies with a total of 1655 lesions (a mole or area of skin with an unusual appearance in comparison with the surrounding skin) that were given these final diagnoses*: 1120 BCCs, 41 cSCCs and 10 melanomas.

For identifying BCC, seven studies show the effect of using exfoliative cytology to confirm BCC in lesions that doctors already suspected were BCCs. In a group of 1000 such lesions, of which 860 (86%) actually do have BCC, then:

- an estimated 853 people will have an exfoliative cytology result confirming that a BCC is present. Of these 14 (1.6%) will not actually have a BCC (false positive result);

- of the 147 people with an exfoliative cytology result indicating that no BCC is present, 21 (14%) will in fact actually have a BCC (false negative result).

One study compared the accuracy of exfoliative cytology to using a hand-held microscope (dermoscopy) for making a diagnosis of BCC but used a different method of removing cells and included patients with a higher risk of melanoma than found in the other eight studies.

There was not enough evidence to determine the accuracy of exfoliative cytology for diagnosing cSCC or melanoma.

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

The small number of studies included in this review, poor description of how patients were selected to be included in the study, and limited information on how the test results were used to make diagnoses, reduces the reliability of our results.

The studies did not explain how patients had been referred to have the exfoliative cytology test. Most important of all, the test was only used in people in whom doctors had already diagnosed a BCC just by looking at the skin lesion. In other words, the test was being used to confirm a doctor's diagnosis. Most studies did not include enough people with skin lesions that are similar in appearance to a BCC to be sure that this test correctly identifies a BCC. This may cause exfoliative cytology to appear more accurate than it would be in actual practice.

Who do the results of this review apply to?

Studies were conducted in the UK, across Europe and in Australia. Study authors rarely described patient characteristics, such as age and location of the lesion. The percentage of people included in the studies with a final diagnosis of BCC ranged from 18% to 90% (nine studies). For cSCC it was 4% and 18% (two studies), and for melanoma it was 5% (one study). It was not possible to tell from the studies how clinicians had decided that study participants had lesions that could be a skin cancer.

What are the implications of this review?

No research has been done using exfoliative cytology to diagnose a skin cancer when a patient is first seen by a doctor. The results of this review suggest that exfoliative cytology can help to confirm BCC in patients with skin lesions that a doctor already suspects of being a BCC. This test could be useful for patients with BCCs that need non-surgical treatments, such as radiotherapy, where a tissue diagnosis is needed before the treatment can be given.

How up-to-date is this review?

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

*In these studies, biopsy was the reference standard (means of establishing the final diagnosis).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Question:	**What is the diagnostic accuracy of exfoliative cytology for detecting BCC, cSCC or cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults?**				
Population	Adults with lesions suspicious for BCC, cSCC or for melanoma				
Index test	Exfoliative cytology				
Comparator test	Dermoscopy				
Target condition	BCC				
Reference standard	Histology, any method				
Action	If accurate, positive diagnosis by exfoliative cytology would reduce the need for biopsies in suspected BCC and help to appropriately select lesions for excision				
Quantity of evidence					
Number of studies	**9**	Total lesions with test results	**1655**	Total with BCC	**1120**[a]
				Total with cSCC	**41**[b]
				Total with melanoma	**10**[c]
Limitations					
Risk of bias	High risk for patient selection due to case-control study design (2/9) or inappropriate exclusion of lesions (1/9), and unclear due to poor reporting of recruitment and exclusion criteria (3/9). Unclear risk for the index test due to lack of reporting diagnostic thresholds and blinding from the reference standard diagnosis (7/9). Unclear risk of bias due to inadequate reporting of blinding the reference standard (7/9) or the index test (7/9). High risk of bias in flow and timing domain from differential verification (2/9) and exclusion of slides from analysis (1/9); timing of tests was not mentioned in 7/9				
Applicability of evidence to question	High concern due to narrowly defined populations and multiple lesions per patient (6/9), and unclear concern due to poor reporting of patient groups (2/9), so may not be representative of populations eligible for exfoliative cytology. High concern for clinical applicability of exfoliative cytology from lack of reporting cytodiagnostic criteria in adequate detail (5/9). Little information was given concerning the expertise of the cytopathologist or histopathologist				

Detection of BCC: pooled analysis[d]				
Datasets	**Lesions**	**BCCs**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
7	1264	1045	97.5% (94.5 to 98.9)	90.1% (81.1 to 95.1)
Numbers observed in a cohort of 1000 people being tested[e]				
	True positive	**False negative**	**False positive**	**True negative**
	(Appropriately do not receive excision)	(Inappropriately receive excision or undertreated)	(Inappropriately do not receive excision, or overtreated)	(Receive appropriate management - excision or other)
At prevalence 63%	614	16	37	333
At prevalence 86%	839	21	14	126
At prevalence 88%	858	22	12	108
Detection of BCC: pooled analysis[f]				
Datasets	**Lesions**	**BCCs**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
7	1264	1045	97.3% (93.5 to 98.9)	94.2% (88.7 to 97.1)
Detection of cSCC, melanoma, any skin cancer				
Findings	Studies also evaluated cSCC (2 studies), melanoma (1 study) or any skin cancer (6 studies) • cSCC - studies could not be pooled due to different diagnostic approaches; sensitivity ranged from 89% to 100% and specificity from 75% to 99% • melanoma - only study (10 melanomas) conducted in 185 pigmented skin lesions, also providing a comparison with dermoscopy: sensitivity and specificity 100% • any skin cancer - 4 studies pooled 573 suspicious lesions, with 495 malignant lesions (476 BCCs, 13 cSCCs, 1 melanoma, 4 carcinomas of unspecified histological type, 1 apocrine carcinoma). Pooled sensitivity 97.3% (95% CI 93.5% to 98.9%) and specificity 86.0% (95% CI 73.5% to 93.1%) (uncertain diagnoses classified as test positives). When uncertain diagnoses classified as test negatives, pooled sensitivity became 96.			

	6% (95% CI 90.3% to 98.9%) and specificity 94.7% (95% CI 80.2% to 98.7%).

BCC: basal cell carcinoma; **cSCC**: cutaneous squamous cell carcinoma; **CI**: confidence interval.

[a]Total of 1122 BCC cases, of which 2 excluded due to absence of exfoliative cytology result ('test fails').

[b]Total of 55 cSCC cases, of which 14 excluded: 3 due to absence of exfoliative cytology result ('test fails') and 11 due to insufficient cSCC lesion numbers in individual studies (< 5 cSCCs per study).

[c]Total of 11 cases, of which 1 excluded due to insufficient melanoma lesion numbers in individual studies (< 5 melanomas per study).

[d]'Possible BCC' cases classified as index test positive.

[e]Numbers for a hypothetical cohort of 1000 lesions are presented for three examples representing different prevalences of BCC, estimated at 25th, 50th (median) and 75th percentiles of BCC prevalence observed across the 9 included studies.

[f]'Possible BCC' cases classified as index test negative.

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

The commonest skin cancers in white populations are keratinocyte skin cancers, namely basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) (Gordon 2013; Madan 2010). BCC is the more common of the two keratinocyte carcinomas, and approximately one third of people with a BCC will develop at least one other BCC over time (Flohill 2013). In 2003, the World Health Organization (WHO) estimated that between 2 and 3 million 'non-melanoma' skin cancers occur globally each year (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). Rather than defining BCC and cSCC by what they are not (i.e. non-melanoma skin cancer), we collectively refer to these conditions using the preferred and more accurate term of 'keratinocyte carcinoma' in this DTA review (Karimkhani 2015).

Exfoliative cytology is a simple procedure designed to detect the presence of malignancy through analysis of cell structure. Since its main benefit would be to replace histology, basal cell carcinoma has been chosen as the primary target condition for this review since this is the condition for which exfoliative cytology could potentially have the clearest role (see Role of index test(s) and Rationale below). Secondary target conditions include: cSCC,invasive melanoma and atypical intraepidermal melanocytic variants, and any other skin cancer, including keratinocyte skin cancer, invasive melanoma and atypical intraepidermal melanocytic variants.

Basal cell carcinoma

BCC can arise from multiple stem cell populations, including from the bulge and interfollicular epidermis (Grachtchouk 2011). Growth is usually localised, but it can infiltrate and damage surrounding tissue, and if left untreated it can cause 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. They typically present as slow-growing asymptomatic papules, plaques, or nodules that may bleed or form ulcers that do not heal (Firnhaber 2012). People with a BCC often present to healthcare professionals with a non-healing lesion rather than specific symptoms such as pain. Clinicians frequently make the diagnosis incidentally rather than as a result of people presenting with symptoms (Gordon 2013).

Figure 1. Sample photographs of BCC (left) and cSCC (right). Copyright © 2012 Dr Rubeta Matin: reproduced with permission.

BCCs most frequently occur on sun-exposed areas of the head and neck (McCormack 1997), and they are more common in men and in people over 40 years of age. A rising incidence of BCC in younger people has been attributed to increased recreational sun exposure (Bath-Hextall 2007a; Gordon 2013; Musah 2013). Other risk factors include Fitzpatrick skin types I and II (Fitzpatrick 1975; Lear 1997; Maia 1995); previous skin cancer history; immunosuppression; arsenic exposure; and genetic predisposition, such as in basal cell naevus (Gorlin) syndrome (Gorlin 2004; Zak-Prelich 2004). Annual incidence is increasing worldwide; Europe has experienced an average increase of 5.5% per year over the last four decades, the USA 2% per year, while estimates for the UK show incidence appears to be increasing more steeply at a rate of an additional 6/100,000 person-years (Lomas 2012). Some authors have explained the rising incidence 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 the National Institute for Health and Care Excellence (NICE) guidance (NICE 2010), low-risk BCCs that may be considered for excision include nodular lesions occurring in patients older than 24 years old who are not immunosuppressed and do not have Gorlin syndrome. Furthermore, lesions should be located below the clavicle; should be small (diameter of less than 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).

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). Advanced locally destructive BCC can arise from long-standing untreated lesions or from a recurrence of a 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.

Squamous cell carcinoma of the skin (cSCC)

Primary cSCC arises from the keratinising cells of the outermost layer of the skin. People with cSCC often present with an ulcer or firm (indurated) papule, plaque or nodule (Firnhaber 2012; Griffin 2016), sometimes 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, with an estimated annual risk of progression of anywhere from under 1% to 20% (Alam 2001), or Bowen's disease (squamous cell carcinoma in situ), with about a 5% risk of progression (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 20 mm in diameter and depth of invasion more than 4 mm and poor differentiation on pathological examination (Motley 2009).

Chronic ultraviolet light exposure through recreation or occupation is strongly linked to cSCC occurrence (Alam 2001). It is particularly common in people with fair skin and in rare 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 inhibitors; and previous skin cancer history (Baldursson 1993; Chowdri 1996; Dabski 1986; Fasching 1989; Lister 1997; Maloney 1996; O'Gorman 2014). In transplant recipients, cSCC is the most common form of skin cancer, with estimates of the risk of developing cSCC 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. Five-year survival rate following metastatic recurrence is only 25% to 40% (Rowe 1992).

Melanoma

Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. Cutaneous melanoma refers to skin lesions with malignant melanocytes present in the dermis, and includes superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma variants. Melanoma in situ describes malignant melanocytes that lay within the epidermis without invasion of the dermis, but they are at risk of progressing to melanoma if left untreated. Lentigo maligna, a subtype of melanoma-in-situ in chronically sun-damaged skin, can progress to invasive melanoma if its growth breaches the dermo-

epidermal junction during a vertical growth phase (when it becomes known as 'lentigo maligna melanoma'), however its malignant transformation is both lower and slower than for melanoma in situ (Kasprzak 2015). Melanoma in situ and lentigo maligna are both atypical intraepidermal melanocytic variants. 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 13,134 new cases of melanoma of the skin in 2014 (ACIM 2017) and in New Zealand with 2341 registered cases in 2010 (HPA and MelNet NZ 2014). For 2014 in the USA, the predicted incidence was 73,870 per annum and the predicted number of deaths was 9940 (Siegel 2015). The highest rates in Europe are seen in north-western Europe and the Scandinavian countries, with a highest incidence reported in Switzerland: 25.8 per 100,000 in 2012. Rates in England have tripled from 4.6 and 6.0 per 100,000 in men and women, respectively, in 1990, to 18.6 and 19.6 per 100,000 in 2012 (EUCAN 2012). Indeed, 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). This rising incidence is thought to be primarily related to an increase in recreational sun exposure, tanning bed use and an increasingly ageing population with higher lifetime recreational ultraviolet (UV) exposure, in conjunction with possible earlier detection (Belbasis 2016; Linos 2009). Putative risk factors are reviewed in detail elsewhere (Belbasis 2016).

A database of over 40,000 US patients from 1998 onwards, which assisted the development of the 8th American Joint Committee on Cancer (AJCC) staging system, indicated a five-year survival of 97% to 99% for stage I melanoma, dropping to between 32% and 93% in stage III disease depending on tumour thickness, the presence of ulceration and number of involved nodes (Gershenwald 2017). While these are substantial increases relative to survival in 1975 (Cho 2014), mortality rates have remained static during the same period. This observation, coupled with increasing incidence of localised disease, suggests that improvements in survival may be due to earlier detection and heightened vigilance (Cho 2014). New targeted therapies for advanced (stage IV), melanoma (e.g. BRAF inhibitors), have improved survival, and immunotherapies are evolving such that long-term survival is being documented (Pasquali 2018; Rozeman 2017). No new data regarding the survival prospects for patients with stage IV disease were analysed for the AJCC 8 staging guidelines due to lack of contemporary data (Gershenwald 2017).

Treatment

Treatment for BCC and cSCC include surgery, other destructive techniques such as cryotherapy or electrodesiccation and topical chemotherapy. A Cochrane Review of 27 randomised controlled trials (RCTs) of interventions for BCC found very little good quality evidence for any of the interventions used (Bath-Hextall 2007b). Complete surgical excision of primary BCC has a reported five-year recurrence rate of less than 2% (Griffiths 2005; Walker 2006), leading to significantly fewer recurrences than treatment with radiotherapy (Bath-Hextall 2007b). After apparent clear histopathological margins (serial vertical sections) following standard excision biopsy with 4 mm surgical peripheral margins taken, reported five-year recurrence rate is around 4% (Drucker 2017). Mohs micrographic surgery, whereby horizontal sections of the tumour undergo histological analysis, and re-excisions are made until the margins are tumour-free, can be considered for high-risk lesions such as on the centre of the face, where standard wider excision margins might lead to considerable functional impairment (Bath-Hextall 2007b; Lansbury 2010; Motley 2009; Stratigos 2015). Bath-Hextall and colleagues (Bath-Hextall 2007b) found a single trial comparing Mohs micrographic surgery with a 3mm surgical margin excision in BCC (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).

Destructive techniques other than excisional surgery include electrodesiccation and curettage (ED&C) as well as cryotherapy (Alam 2001; Bath-Hextall 2007b). Alternatively, non-surgical (or non-destructive) treatments may be options (Bath-Hextall 2007b; Kim 2014; Drew 2017), including topical chemotherapy such as imiquimod (Williams 2017), 5-fluorouracil (Arits 2013), ingenol mebutate (Nart 2015), and photodynamic therapy (Bath-Hextall 2007b; Roozeboom 2016). These non-surgical approaches are increasingly used for the superficial subtypes of BCC, for multiple lesions on low-risk sites, where there are relevant comorbidities, or where surgery would be associated with risk of poor wound healing or significant scarring (Marsden 2010). However, non-surgical techniques do not allow histological confirmation of tumour clearance, and their use is dependent on accurate characterisation of the histological subtype and depth of tumour. The 2007 systematic review of BCC interventions found limited evidence from very small RCTs for these approaches (Bath-Hextall 2007b), which have only partially been filled by subsequent studies (Bath-Hextall 2014; Kim 2014; Roozeboom 2012). Most BCC trials have compared interventions within the same treatment class, and few have compared medical versus surgical treatments (Kim 2014).

A systematic review of interventions for primary cSCC found only one RCT eligible for inclusion (Lansbury 2010). Current

practice therefore relies on evidence from observational studies, as reviewed in Lansbury 2013, for example. Surgical excision with predetermined margins is usually the first-line treatment (Motley 2009; Stratigos 2015). Observational studies suggest low recurrence rates for small, low-risk lesions treated with cryotherapy or ED&C (recurrence rates of less than 2%). Estimates of recurrence after Mohs micrographic surgery, surgical excision, or radiotherapy, which researchers are likely to have 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).

For primary melanoma, the mainstay of definitive treatment is wide local excision of the lesion, to remove both the tumour and any malignant cells that might have spread into the surrounding skin (Garbe 2016; Marsden 2010; NICE 2015a; SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness, as described in Garbe 2016, and by stage of disease at presentation, as in NICE 2015a. Following histological confirmation of diagnosis, the lesion is pathologically staged from 0 (referring to melanoma in situ) to IV (indicating the presence of distant metastasis) according to the AJCC staging system to guide treatment (Balch 2009). The main prognostic indicators can be divided into histological and clinical factors. Histologically, Breslow thickness is the single most important predictor of survival, as it is a quantitative measure of tumour invasion which correlates with the propensity for metastatic spread (Balch 2001). Independent of tumour thickness, prognosis is worse in older people, males, those with recurrent lesions, and in those with distant lymph node involvement (micro or macroscopic) and/or metastatic disease at the time of primary presentation.

Index test(s)

Exfoliative cytology is a non-invasive test that uses the Tzanck smear technique to identify disease through the examination of the structure of cells (Tzank 1949). It is also known as 'skin scrape cytology', which is perhaps a better description of the technique than 'exfoliative' which traditionally refers to the removal of superficial dead cells from the skin surface. Clinicians clean skin lesions, remove any surface crust, and then scrape the lesions with a scalpel or curette to collect cell material and subsequently smear them onto one or more glass slides (Chandra 2009). They can then fix the material using alcohol or air-drying, and then they stain it using one of several methods recommended by the British Society of Cytopathology, namely the Papanicolaou (Pap) and May-Grünwald Giemsa (MGG; also called Romanowsky) methods (Chandra 2009). A cytopathologist or a dermatologist with experience of the technique can immediately examine the slides under a microscope to determine the presence of malignant cells (Bakis 2004). Superficial shave biopsy differs from a cytological scrape in that it slices off a superficial (largely epidermal) section from a BCC that protrudes above the skin surface. The specimen retains the architecture of the part of lesion that is shaved off. Shave biopsy typically contains only tumour tissue rather than the interface between BCC and normal tissue, which provides important information on the depth and pattern of tumour invasion. Shave biopsy specimens are processed using normal paraffin block histopathology; this technique is only suitable for elevated/protruding BCCs and does not provide the immediate results that cytology can provide (Russell 1999).

Exfoliative cytology may be used for confirming the presence of clinically diagnosed BCC with a view to definitive treatment such as radiotherapy. The cellular appearance of BCC is characteristic (Figure 2), with 'palisade' arrangements of typically basal cells positioned around the margins of densely packed masses of larger and intensely stained cells (Figure 3 and Figure 4) (Ruocco 2011). Cytological features differ for the detection of cSCC, tending to show larger cells with less coherence that are more atypical in appearance with a more varied shape and size (pleomorphic) and abnormal nuclei (Bocking 1987; Fortuno-Mar 2013; Ruocco 2011). The cytological appearance of melanoma is much more varied, but it can include larger cells than those observed, which are typical of BCC, with prominent and often multiple large nuclei, large nuclear inclusions of cytoplasm, and often a presence of melanin pigment in tumour cells (Bocking 1987; Fortuno-Mar 2013).

Figure 2. Cytological image of BCC using Papanicoloau stain showing a tissue fragment of BCC on the left and anucleate squamous cells from the epidermis on the right. Copyright © 2017 Derek Roskell: reproduced with permission.

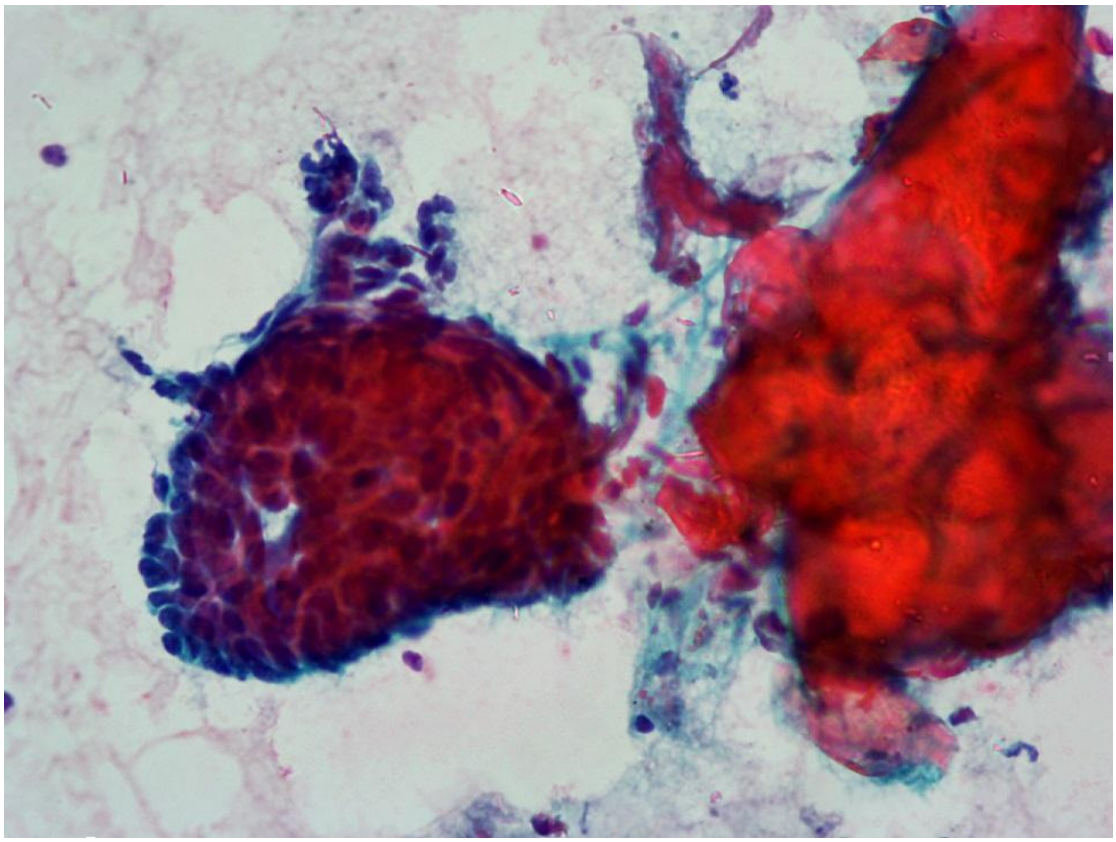


Figure 3. Cytological image of a BCC using Giemsa stain. Focally the nuclei are aligned perpendicular to the basement edge of the cluster (peripheral palisading), a feature characteristic of BCC. Copyright © 2017 Derek Roskell: reproduced with permission.

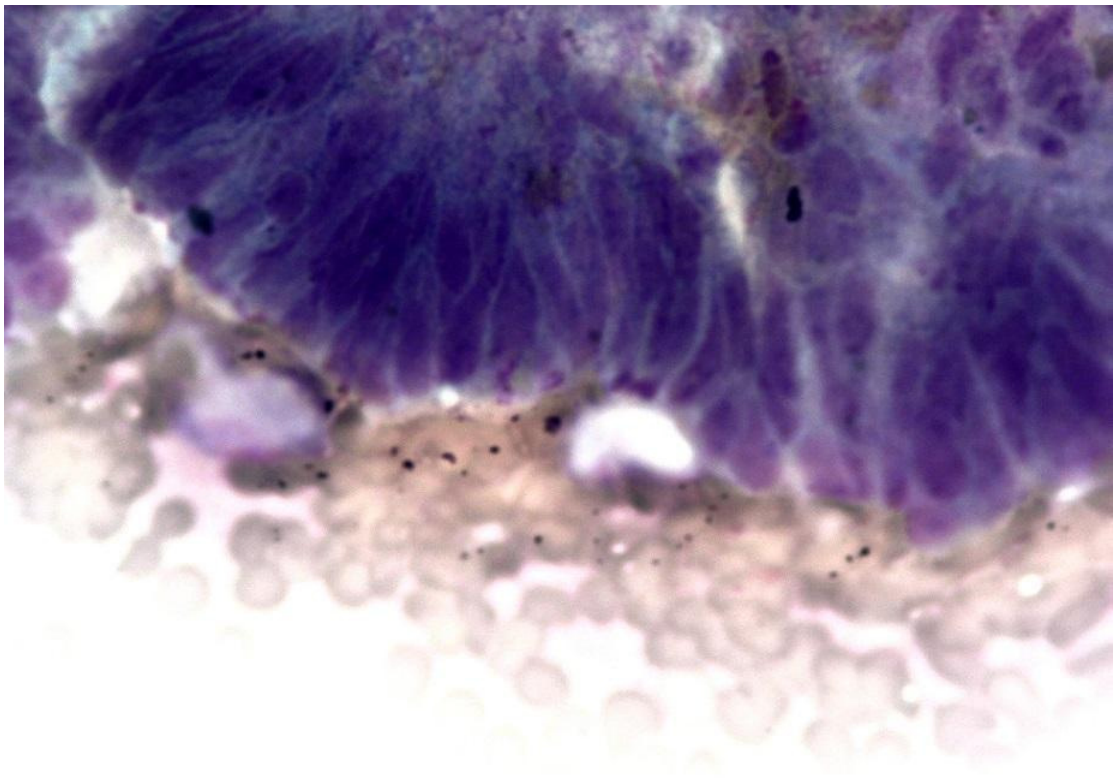
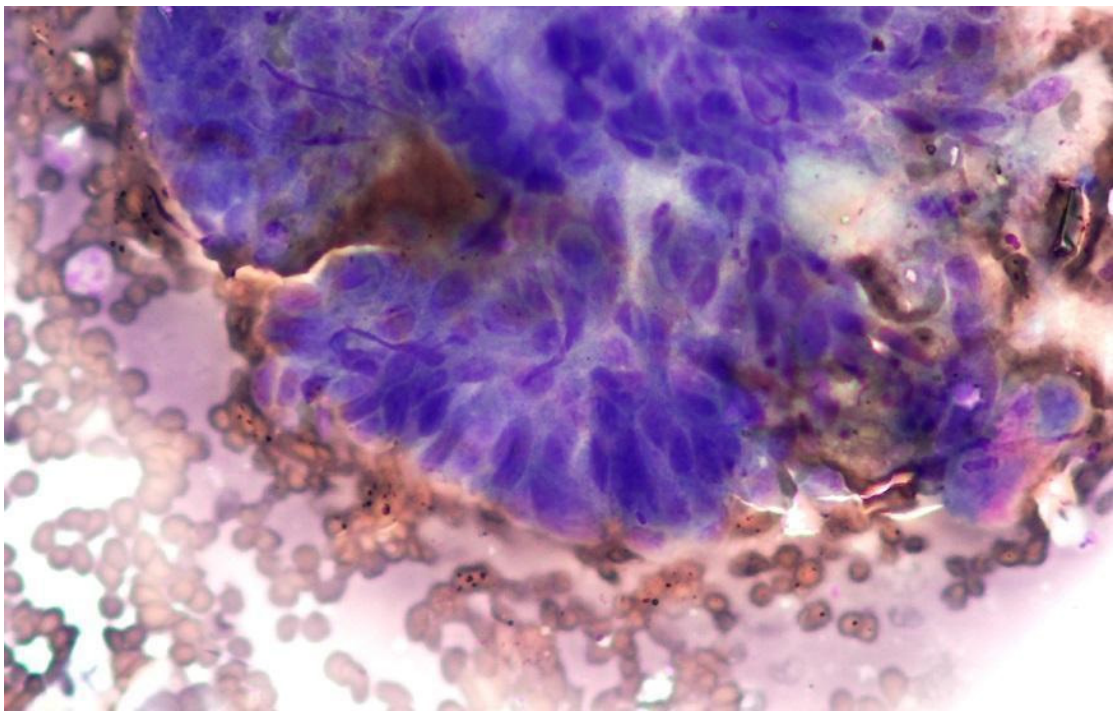


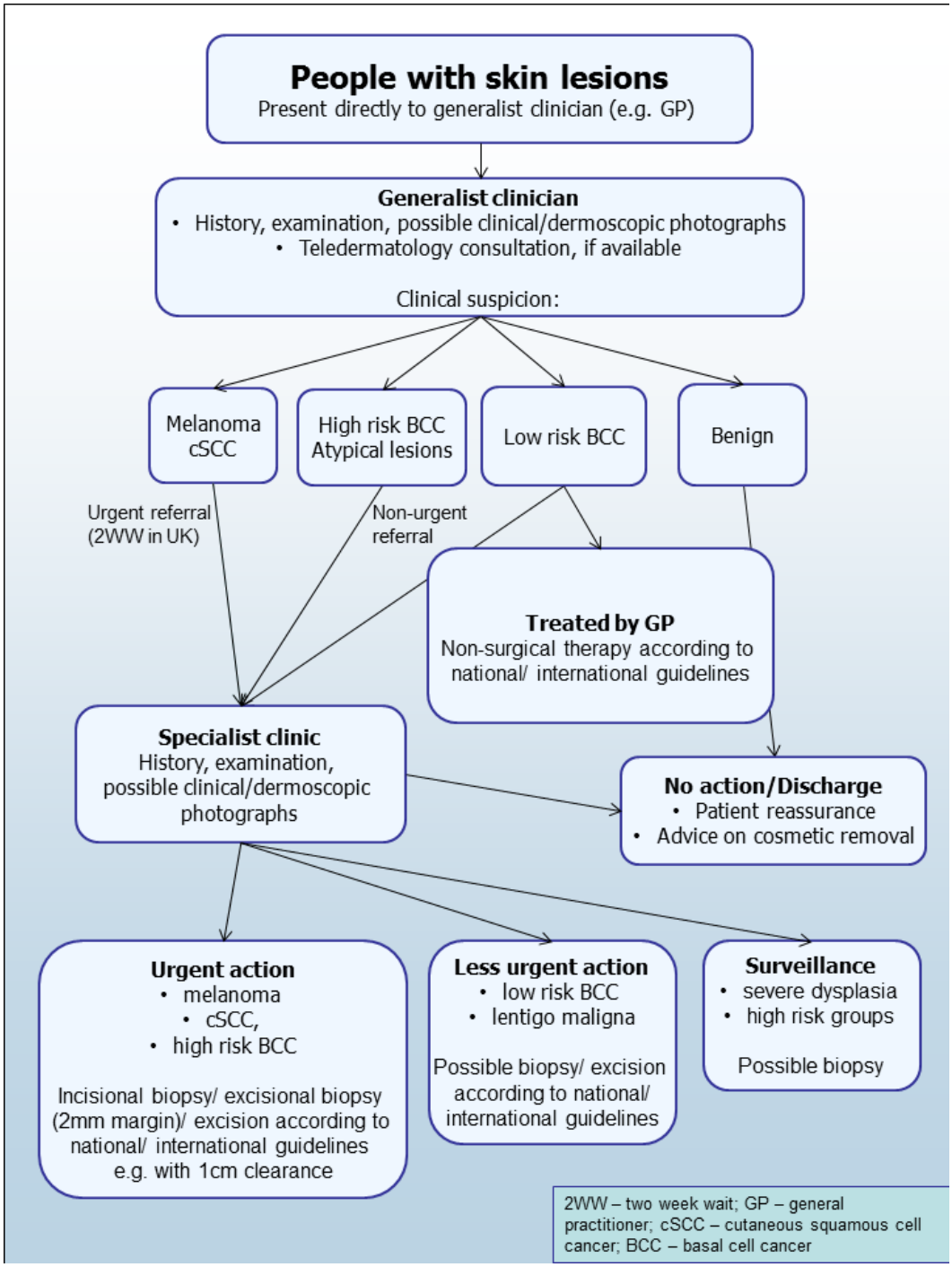
Figure 4. Cytological image of a BCC using Giemsa stain. The BCC cells are tightly cohesive in a cluster with a distinct edge to the group. Copyright © 2017 Derek Roskell: reproduced with permission.



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 (GP) or, less commonly, directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist (Figure 5). Current UK guidelines recommend that GPs should assess all suspicious pigmented lesions presenting in primary care by taking a clinical history and visually inspecting them using the revised seven-point checklist (MacKie 1990). Clinicians should refer those with suspected melanoma or cSCC for appropriate specialist assessment within two weeks (Chao 2013; London Cancer Alliance 2013; Marsden 2010; NICE 2015a). In the UK, low-risk BCCs 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 BCCs in the UK, for example by excising low-risk lesions (NICE 2010). Similar guidance is in place in Australia (CCAAC Network 2008).

Figure 5. Current clinical pathway for people with skin lesions.



For referred lesions, the specialist clinician will use history-taking, visual inspection of the lesion (in conjunction with other skin lesions), and often dermoscopy to inform a clinical decision. If melanoma or cSCC is suspected, then urgent excision is advisable. Equivocal lesions for which a definitive diagnosis cannot be reached may undergo surveillance to identify any lesion changes that would indicate biopsy or reassurance and discharge for those that remain stable over a period of time. Low-risk BCC and premalignant skin lesions potentially eligible for non-surgical treatment may undergo a diagnostic biopsy before initiating therapy.

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 where a dermatologist or other secondary care clinician makes a decision whether or not to biopsy or excise. 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 melanoma, following visual inspection (Argenziano 1998; Argenziano 2012; Haenssle 2010; Kittler 2002), although it is less well established for the diagnosis of BCC or cSCC (Dinnes 2018a). A further three reviews in this series have evaluated the diagnostic accuracy, and comparative accuracy, of visual inspection and dermoscopy (Dinnes 2018a, Dinnes 2018b, Dinnes 2018c).

Visual inspection of the skin is iterative, 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. Authors have made various attempts to formalise the mental rules involved in analytical pattern recognition, ranging from a setting out of lesion characteristics that should be considered to formal scoring systems or algorithms with explicit numerical thresholds of skin cancer (Friedman 1985; Sober 1979).

Role of index test(s)

For the diagnosis of BCC, the potential role of exfoliative cytology could be to confirm a strong clinical suspicion of malignancy. If shown to be sufficiently accurate, this simple procedure could avoid the need for an invasive diagnostic skin biopsy in patients whose lesions might be more amenable to non-surgical treatment. In ulcerated lesions (such as BCC), removing the overlying dead cells or dried exudate is straightforward, and the procedure is therefore potentially less invasive than shave or punch biopsy (though more invasive than dermatoscopic examination). Thus, exfoliative cytology could replace histology or allow treatment to be initiated prior to biopsy results in some patients. The test might also be of value to confirm a clinical suspicion of cSCC in recurrent lesions, or those that are critically located around the eyes, nose, lips, ears and neck, since these are suitable sites for Mohs micrographic surgery. The potential role for exfoliative cytology to detect melanoma is less clear, given the optimal treatment in these patients is excision (Murali 2009). Melanomas are frequently solid skin lesions for which scraping is likely to be more invasive, as removal of the dead layer alone is difficult to achieve. In these cases, histological biopsy is likely to be equally traumatic and but may provide more thorough and reliable diagnostic information.

Although skin is the largest and most accessible organ in the body, cutaneous cytology is not standard practice when diagnosing skin cancer lesions (NICE 2015a; SIGN 2014; Stratigos 2015; Telfer 2008). Although clinicians occasionally use cytology in practice to confirm a clinical diagnosis of BCC when planning radiotherapy or surgery, the nature of the sample obtained lacks the additional histological information, such as pathological subtype and interaction with surrounding skin and structures, that clinicians need to decide on best treatment and which is readily available following biopsy of suspicious lesions (Barr 1984; Ruocco 2011). Nonetheless, the simplicity, immediacy and non-invasive nature of exfoliative cytology are clearly desirable attributes, which could benefit both health services and patients, albeit in a limited number of circumstances. This is true for confirming a clinical diagnosis of BCC which can present as multiple lesions, and commonly occur on the face, head and neck, which are cosmetically critical sites (Powell 2000). Once diagnosed, superficial BCC can be treated using non-invasive treatments (listed in Target condition being diagnosed). Excisional surgery and Mohs micrographic surgery are the most successful treatments for nodular BCC, although smaller nodular BCCs in low risk areas can also be treated with topical treatments (Williams 2017); therefore, the ability to confirm a diagnosis in these patients using a fast and non-invasive approach is attractive (Ruocco 2011). The test can take place during a consultation, with negative results in the presence of clinical concerns for malignancy indicating the need to proceed to a definitive biopsy (Ozden 2013). However, such potential benefits may be outweighed by mistaking more aggressive forms of BCC for a low-risk BCC, and cytology will never be able to match the additional pathological information regarding cellular behaviour and interaction with surrounding tissues provided by routine histopathology.

In order for exfoliative cytology to realise its potential in low-risk BCC, it would need to have a high positive predictive value (from a high specificity) to be sure that patients receiving positive results could safely proceed to treatment without biopsy. Any patients with negative cytology findings would still require biopsy to be sure that cytology did not miss another malignancy. A delay in the

diagnosis of a BCC as a result of a false-negative test is usually not as serious as for melanoma because BCC is typically slow-growing and very unlikely to metastasise. However, delayed diagnosis can result in a larger and more complex excision. Very sensitive tests for BCC, however, are likely to compromise on specificity, leading to a higher false-positive rate and an enormous burden of skin surgery. Thus, a balance between sensitivity and specificity is needed. The situation for cSCC is more similar to melanoma in that the consequences of falsely reassuring a person that they do not have skin cancer can be serious and potentially fatal. 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 diagnoses without missing true cases of disease has patient and resource benefits. False-positive diagnoses not only cause unnecessary morbidity from the biopsy but could lead to initiation of inappropriate therapies and also increase patient anxiety. Notwithstanding these advantages, cytology does not allow the diagnostician to observe the tumour's histologic growth pattern, a characteristic that can influence management decisions since more aggressive growth patterns require more aggressive treatment (Oram 1997). For melanoma, high test sensitivity is a key requirement, as the cost of missing an early, thin curable lesion can make the difference between life and death.

Alternative test(s)

Standard practice for suspected skin cancer diagnosis in specialist settings involves visual and dermatoscopic examination by a dermatologist, and this review therefore considers these tests to be the comparators. In suspicious lesions these tests are followed by histopathologic analysis of biopsy or excision specimens. This review uses histopathology as the reference standard for definitive diagnosis, and does not review it as an index test. We have also omitted alternative methods of exfoliative cytology, in particular imprint or 'touch imprint' methods, which involve pressing cytology slides directly onto the surface of suspicious lesions (Christensen 2008).

Our series of Cochrane DTA reviews on the diagnosis of skin cancer also reviews a number of other tests, including visual inspection and dermoscopy, teledermatology, mobile phone applications, reflectance confocal microscopy (RCM), optical coherence tomography (OCT) and computer-assisted diagnosis techniques applied to dermoscopic and other types of image (Chuchu 2018a; Chuchu 2018b; Dinnes 2018a; Dinnes 2018b; Dinnes 2018c; Dinnes 2018d; Dinnes 2018e; Dinnes 2018f; Ferrante di Ruffano 2018a; Ferrante di Ruffano 2018b). RCM and OCT both provide depth-resolved optical reflectance imaging and are emerging as non-invasive adjuncts to dermoscopy in a specialist setting, and RCM potentially as an alternative to dermoscopy for skin cancer diagnosis (Edwards 2016). Relative to exfoliative cytology, both methods are resource intensive, and they require specialist training. High-frequency ultrasound may prove to be an additional tool to assist in the diagnosis of melanoma; however, evidence to date is scarce and generally of poor quality (Dinnes 2018a).

Computer-assisted diagnosis or artificial intelligence-based techniques use predefined algorithms to process and manipulate acquired data to identify the features that discriminate malignant from benign lesions, and they may be applied to any types of image or spectra (e.g. Wallace 2000; Wallace 2000a). They have most commonly been applied to digital dermoscopy images (Esteva 2017; Rajpara 2009), with further developments in diffuse reflectance spectroscopy such as SIAscopy (Moncrieff 2002; Walter 2012), MelaFind (Hauschild 2014; Monheit 2011; Wells 2012), and electrical impedance spectroscopy, e.g. the Nevisense system (Malvehy 2014).

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

Rationale

This review is part of a series of reviews of diagnostic tests used to assist clinical diagnosis that aims to identify the most accurate approaches to diagnosis and provide clinical and policy decision-makers with the highest possible standard of evidence on which to base diagnostic and treatment decisions. With increasing rates of skin cancer and the push towards the use of dermoscopy and other high-resolution image analysis in primary care, the anxiety around missing early cases needs to be balanced against sending too many people with benign lesions for a specialist opinion. Although its role for the diagnosis of melanoma is unconvincing because of the loss of vital additional histological information needed for optimal treatment, exfoliative cytology has the potential to improve the health of BCC patients through less invasive and more accessible diagnosis that avoids an additional visit for a skin biopsy result. These benefits must be weighed carefully against the potential limitations of exfoliative cytology to detect the additional pathological features seen on histological examination that help to identify lesions requiring immediate attention. For the subgroup of patients who will go on to receive non-invasive treatments, the technique could also enable quicker treatment with the potential for better cosmetic results - key objectives from patient groups (NICE 2010) - whilst saving health services the costs of unnecessary biopsies. Treatment of BCCs currently requires diagnostic confirmation using histopathology (NICE 2010), so it is important to assess whether these potential benefits could be attained by comparing the accuracy of exfoliative cytology against that of the reference standard, histological diagnosis.

Since assessing the appearance of a cytological smear is essentially a subjective one that depends on adequate material, the diagnostic performance of exfoliative cytology is likely to be influenced by the experience and training of the individual collecting the sample, as well as the diagnostician. Reproducibility is a known issue in other

areas of cytopathology, for example cervical cytology, where the ability to make a diagnosis is influenced by the technician's proficiency in retrieving a sufficient cell sample from scraping (Baena 2017). Evidence arising from diagnosticians' experience with other tests involving the analysis of visual images, such as histopathology, often show variation in diagnosis (Farmer 1996; Shoo 2010), as well as in the availability of clinical data used at the time of diagnosis (Ferrara 2009). This review will therefore also aim to evaluate the impact of clinician experience and training on the adequate retrieval of cell material for cytopathological analysis, as well as on the accuracy of diagnosis.

We identified a single meta-analysis published in 2004 which considered the accuracy of exfoliative cytology for differentiating between BCC and other conditions (Bakis 2004). Synthesising eight studies, it incorporated three studies not eligible for our review including those conducted on eyelid lesions and evaluating imprint techniques. It also found no studies evaluating the effect of clinician experience. Given that it only included studies published up to 2000, there is a need for an up-to-date analysis of the accuracy of exfoliative cytology for the diagnosis of BCCs as well as cSCCs and melanoma skin cancer.

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

OBJECTIVES

To determine the diagnostic accuracy of exfoliative cytology for the detection of basal cell carcinoma in adults, and to compare its accuracy with that of current standard diagnostic practice (visual inspection with or without dermoscopy).

Secondary objectives

To determine the diagnostic accuracy of exfoliative cytology for the detection of cutaneous squamous cell carcinoma, and to compare its accuracy with that of standard diagnostic practice (visual inspection with or without dermoscopy).

To determine the diagnostic accuracy of exfoliative cytology for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, and to compare its accuracy with that of standard diagnostic practice (visual inspection with or without dermoscopy).

For each of the target conditions, we aimed:

- to compare the accuracy of exfoliative cytology versus dermoscopy in direct test comparisons (where the same studies evaluated both tests);
- to determine the effect of observer experience.

Investigation of sources of heterogeneity

We set out to address a range of potential sources of heterogeneity for investigation across our series of reviews, as outlined in Dinnes 2015a and Dinnes 2015b and described in Appendix 4. Our ability to investigate these and other sources of heterogeneity was necessarily limited by the available data on each individual test reviewed.

METHODS

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that 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 and reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests, and all receive a reference standard (between-person comparative studies (BPC));
- studies that recruit series of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (see Rutjes 2005); however, we did not include studies that compared results for malignant lesions to those for healthy skin (i.e. with no lesion present); and
- both prospective and retrospective studies.

We excluded studies from which we could not extract 2 × 2 contingency data or if they included fewer than five disease-positive (for each of BCC, cSCC or melanoma) or disease-negative (i.e. benign) cases. The size threshold of five is arbitrary. However such small studies are unlikely to add precision to estimate of accuracy. Studies available only as conference abstracts were excluded; however, attempts were made to identify full papers for potentially relevant conference abstracts (Searching other resources).

Participants

We included studies in adults with lesions suspicious for BCC, cSCC or melanoma. We excluded studies that recruited only participants with malignant diagnoses. We excluded studies conducted in children or where authors clearly reported that more than 50% of participants were aged 16 years old and under.

Index tests

We included studies evaluating exfoliative cytology alone, or exfoliative cytology versus visual inspection and/or dermoscopy. All techniques involving scraping of skin lesions in vivo and subsequent cytological analysis of material were eligible. We excluded swabbed lesions, tape stripping, use of ex vivo specimens, imprint cytodiagnosis and fine needle aspiration.

We also excluded studies evaluating the accuracy of subjective assessment of the presence or absence of individual cytomorphological features (with no overall diagnosis of malignancy) as well as those using the test in intraoperative settings, such as for margin control during excision.

We made no exclusions according to the test observer.

Target conditions

The target condition was basal cell carcinoma (all types).

This decision reflected our assessment that the clearest role of exfoliative cytology would be to replace histological confirmation of disease (see Role of index test(s) and Rationale sections above). In secondary analyses, we considered three additional definitions of the target condition.

- Cutaneous squamous cell carcinoma.
- Any form of invasive cutaneous melanoma or atypical melanocytic intraepidermal variants (i.e. including melanoma in situ, or lentigo maligna, which have a risk of progression to invasive melanoma).
- Any skin cancer.

Reference standards

The ideal reference standard was histopathological diagnosis of the excised lesion or biopsy sample in all eligible lesions. All biopsy methods were eligible. A qualified pathologist or dermatopathologist should perform histopathology. Ideally, reporting should be standardised, detailing a minimum dataset to include the histopathological features of BCC, cSCC or melanoma to determine the AJCC staging system (e.g. Slater 2014a; Slater 2014b; Slater 2014c). We did not apply the reporting standard as a necessary inclusion criterion but extracted any pertinent information.

We also accepted clinical follow-up of benign-appearing lesions as an eligible reference standard, whilst recognising the risk of differential verification bias (as misclassification rates of histopathology and follow-up will differ) in our quality assessment of studies. 'Expert diagnosis' of benign lesions with no histology or clinical follow-up was also acceptable as long as at least 50% of all participants with benign lesions had a histological diagnosis. We required all study participants with a final diagnosis of malignancy to have a histological diagnosis, either subsequent to the application of the index test or after a period of clinical follow-up.

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 1 for a summary of reviews included in the programme grant). This allowed for the screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease related terms with terms related to the test names, using both text words and subject headings was formulated. The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As the majority of records were related to the searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search, to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for the staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter, was subsequently applied to all bibliographic databases as listed below (Appendix 5). The final search result was cross-checked against the list of studies included in five systematic reviews; our search identified all but one of the studies, and this study was not indexed on MEDLINE. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.

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

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

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

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 7) in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR; 2016, Issue 8) in the Cochrane Library;
- Cochrane Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2);

- CRD HTA (Health Technology Assessment) database, 2016, Issue 3;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960).

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

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

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

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

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

Searching other resources

We had not identified any potentially ongoing studies at the time of publication. We screened relevant systematic reviews identified by our searches for their included primary studies and included any missed by our searches. We checked the reference lists of all included papers, and subject experts within the author team have reviewed the final list of included studies. We did not conduct any citation searching.

Data collection and analysis

Selection of studies

At least one author (JDi or NC or both) screened titles and abstracts, discussing and resolving any queries by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. We included primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC at initial screening. Both a clinical reviewer (from one of a team of 12 clinician reviewers) and a methodologist reviewer (JDi or NC) independently applied inclusion criteria (Appendix 6) to all full-text articles, resolving disagreements by consensus or in consultation with a third party (JDe, CD, HW or RM). We contacted authors of eligible studies when studies did not present enough data to allow for the construction of 2 × 2 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 2 × 2 diagnostic contingency table for each index test using a piloted data extraction form. Diagnostic thresholds were all qualitative, with cytopathology criteria used to indicate the presence or absence of the target condition. Some studies used a third diagnostic category for 'possible disease', extracting two datasets for these studies: one grouping 'possible' cases with index test positives (used for the primary analysis), and another grouping 'possible' cases with index test negatives. Disagreements were resolved by consensus or by a third party (JDe, CD, HW or RM).

We contacted authors of conference abstracts published from 2013 to 2015 to ask whether full data were available. If we could not locate a full paper, we marked conference abstracts as 'pending' and will revisit them in a future review update. It was not necessary to contact authors of included studies due to missing information regarding the target condition or diagnostic threshold.

Dealing with multiple publications and companion papers

We did not identify multiple publications for any of our included studies.

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). We piloted the modified QUADAS-2 tool on a small number of included full-text articles. One clinical and one methodologist reviewer (JDi, NC or LFR) independently assessed quality for the remaining studies, resolving any disagreement by consensus or in consultation with a third party where necessary (JDe, CD, HW or RM).

Statistical analysis and data synthesis

Due to paucity of data and differences in patient populations and thresholds used to define test positivity, we did not undertake

meta-analysis for the diagnosis of melanoma or cSCC. However, we did perform statistical pooling for the diagnosis of BCC.

In these analyses, we considered any other skin cancers (for example melanomas or cSCCs) in the 'disease negative' group that exfoliative cytology incorrectly identified as BCCs to be false positive results. We took this decision because the clinical management of a lesion considered to be a BCC (for example, initiation of Mohs micrographic surgery, destructive techniques or non-surgical treatments) could be quite different to that for a melanoma or cSCC and could potentially lead to a negative outcome for those concerned. For the diagnosis of melanoma, however, we considered any other skin cancers (BCC, cSCC etc) that were incorrectly identified as melanomas (i.e. positive on exfoliative cytology) to be true negative test results rather than as false positives, on the basis that excision of such lesions may still have been appropriate for the participants concerned.

Our unit of analysis was the lesion rather than the person. This is because in skin cancer initial treatment is directed to the lesion rather than systemically (thus it is important to be able to correctly identify cancerous lesions for each person), and it is also the most common way in which the primary studies reported data. Although there is a theoretical possibility of correlations of test errors when the same people contribute data for multiple lesions, most studies include very few people with multiple lesions, and any potential impact on findings is likely to be very small, particularly in comparison with other concerns regarding risk of bias and applicability. For each analysis, we included only one dataset per study to avoid multiple counting of lesions. We conducted separate analyses according to the definition of the target condition, i.e. detection of BCC, melanoma or cSCC, and detection of any skin lesion requiring excision, as defined under Target condition being diagnosed. We used Review Manager 5 (RevMan 5) for preliminary analyses of the data by plotting estimates of sensitivity and specificity on coupled forest plots and in receiver operating characteristic (ROC) space (RevMan 2014). We used the bivariate model to obtain summary estimates of sensitivity and specificity (Macaskill 2013). We fitted the bivariate models using the meqrlogit command in STATA 15.

We made comparisons with standard diagnostic practice by comparing the accuracy of exfoliative cytology with visual inspection or dermoscopy. We included direct comparisons using data on the accuracy of visual inspection and/or dermoscopy only if reported in the included studies of exfoliative cytology due to the known substantial unexplained heterogeneity in all studies of the accuracy of dermoscopy (Dinnes 2018b). We did not perform comparative meta-analysis because of the limited number of studies.

We obtained 95% confidence intervals for sensitivity and specificity using the delta method and Wald tests, respectively. When the number of studies was insufficient for meta-analysis, we examined individual study results and calculated 95% CIs using the Newcombe-Wilson method without continuity correction (Newcombe 1998).

Investigations of heterogeneity

We examined heterogeneity between studies by visually inspecting forest plots and summary ROC plots. Due to the limited number of studies in each analysis, we were unable to formally assess heterogeneity using meta-regression.

Sensitivity analyses

We were unable to perform sensitivity analyses due to limited data.

Assessment of reporting bias

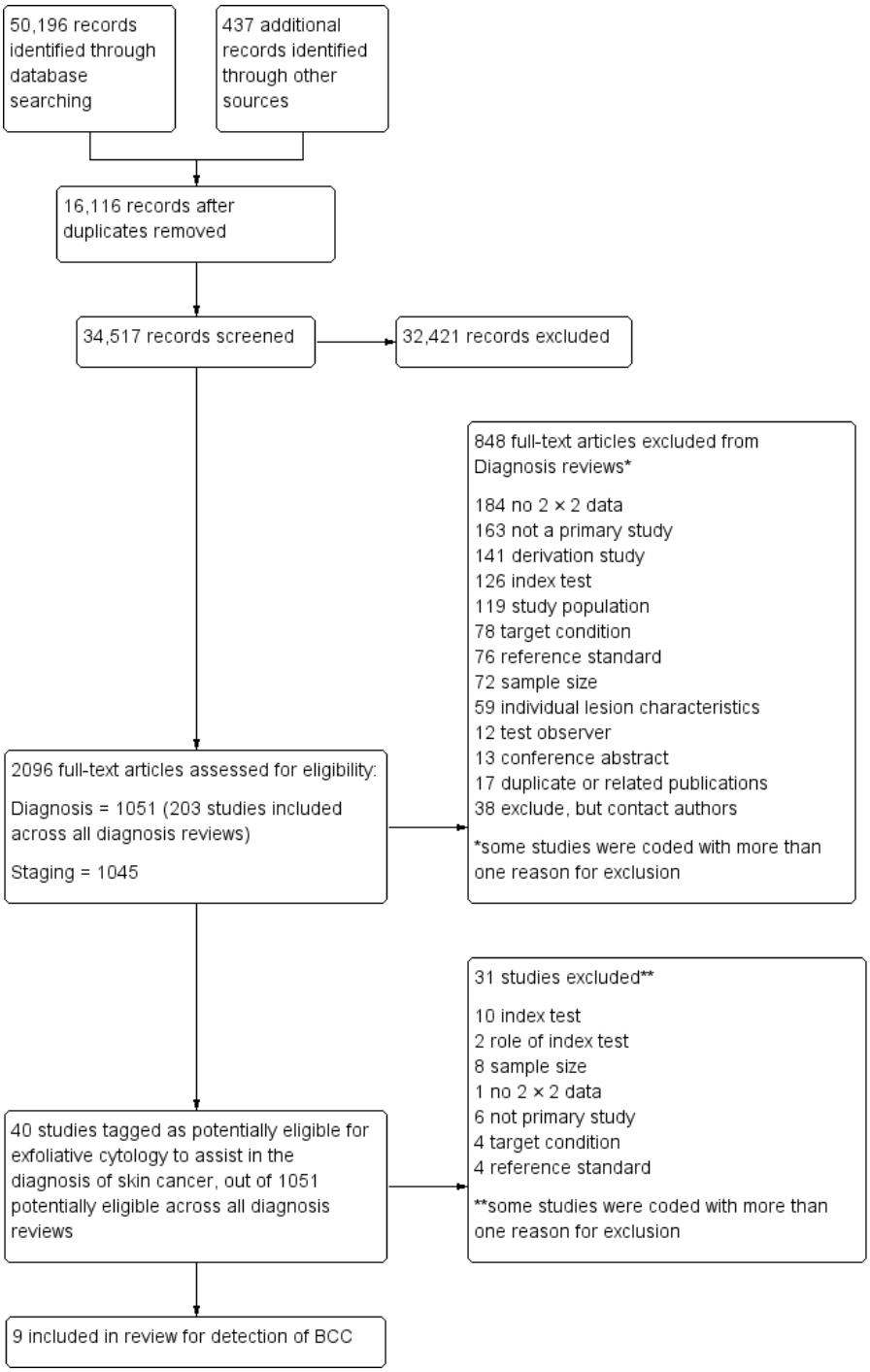
Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we did not test for publication bias.

RESULTS

Results of the search

We identified and screened a total of 34,517 unique references for inclusion. Of these, we reviewed 1051 full-text papers for eligibility for any one of the suite of DTA reviews of tests for diagnosing melanoma or keratinocyte skin cancer. Figure 6 documents a PRISMA flow diagram of search and eligibility results. We tagged 40 full-text publications as potentially eligible for this review, ultimately including 9. We excluded 9 studies that were not primary studies, 8 including fewer than five benign lesions, 1 that insufficiently reported test accuracy data, 10 that used an ineligible index test (including swabbing (Bocking 1987), tape-stripping (Berardi 1992), imprint cytology (Hering 1970; Melek 1970; Urbach 1957), and fine needle aspiration (Jakasa 1976; Korabiec 1977; Rojo 1998; von Gizycki-Nienhaus 1992; Yu 2005)), 2 using exfoliative cytology in an ineligible context (intraoperative care or margin control), 4 in an ineligible patient population, and 4 using an ineligible reference standard. We excluded three studies for multiple reasons. A list of the 31 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 (please contact skin.cochrane.org for a copy of the pdf).

Figure 6. PRISMA flow diagram.



Across all skin cancer DTA reviews, we contacted the corresponding authors of 86 studies, asking 37 to supply further information to allow study inclusion, 18 to clarify diagnostic thresholds, and 30 to define the target condition. It was not necessary to contact any authors for the current review.

Included studies

We included nine studies evaluating the use of exfoliative cytology in participants with lesions suspected of skin cancer, providing 25 datasets (14 for BCC, 2 for cSCC, 1 for melanoma, and 8 for any malignant condition). One of these also performed a direct comparison between exfoliative cytology and dermoscopy (3 datasets: one each for melanoma, BCC and any malignant condition). A total of 1697 lesions were examined by the nine studies, of which 42 were excluded from analysis due to the absence of exfoliative cytology test results (see 'Test failures' below and Table 1) leaving 1655 lesions for analysis, including 1120 BCCs, 41 cSCCs, and 10 melanomas.

Appendix 8 describes the thresholds used for diagnosis across the studies, along with summary study details.

Six studies recruited series of lesions with clinically suspected BCCs that also underwent histological evaluation by excision or biopsy. Two were prospective (Berner 1999; Gordon 1984), two retrospective (Powell 2000; Ruocco 1992), and two unclear (Brown 1979; Derrick 1994). Two case-control studies, Christensen 2008 and Nauth 1988, selectively included a mix of histologically confirmed lesions, while a single prospective case series, Durdu 2011, was conducted in participants with pigmented skin lesions considered to be difficult to diagnose on clinical grounds. No studies provided further details regarding the degree of investigation prior to receiving exfoliative cytology. Four took place in the UK (Berner 1999; Brown 1979; Derrick 1994; Powell 2000), one in Italy (Ruocco 1992), one in Norway (Christensen 2008), one in Germany (Nauth 1988), one in Australia (Gordon 1984) and one in Turkey (Durdu 2011). None reported being funded by manufacturers of diagnostic technology.

The number of participants ranged from 30 to 240 with a median of 101 (interquartile range (IQR) 73 to 188), but one study did not report this detail (Ruocco 1992). Studies included a median of 150 lesions (range 37 to 578, IQR 83 to 224). In the BCC studies, disease prevalence ranged from 52% in Gordon 1984 to 95% in Derrick 1994 in the 6 case series, and it was pre-set in the two case-control studies, at 19% in Nauth 1988 and 64% in Christensen 2008. In the series evaluating pigmented skin lesions, the prevalence of melanoma was 5% and of BCC, 17% (Durdu 2011). This was the only study to include significant numbers of melanocytic benign lesions (Durdu 2011), whilst the remaining eight studies included mainly non-melanocytic benign lesions including actinic keratoses, seborrhoeic keratoses, Bowen's disease, and keratoacanthoma. Four studies that did not contribute datasets for the analysis of cSCC included small numbers of cSCCs (Berner 1999; Brown 1979; Derrick 1994; Ruocco 1992). Two studies did not report specific benign diagnoses (Berner 1999; Nauth 1988). Appendix 8 lists a full breakdown of differential diagnoses for each study.

Studies used a variety of staining methods. Three employed Papanicolau (Christensen 2008; Gordon 1984; Nauth 1988), and three May-Grünwald Giemsa (MGG; Christensen 2008; Derrick 1994; Durdu 2011). One study used Diff-Quick (Berner 1999). Three studies used more than one technique, but two (Brown 1979; Ruocco 1992) failed to report which they had used in particular participants, and a fourth failed to report the stain method (Powell 2000). One study that performed a direct comparison of diagnoses made using Pap, MGG, and both Pap and MGG investigated the impact of varying stain methods (Christensen 2008).

All studies based their index diagnoses on cytomorphological findings, though three failed to outline the diagnostic criteria used (Brown 1979; Christensen 2008; Powell 2000). Features diagnostic for BCC were similar across the remaining studies, except for Nauth 1988, who clearly implemented a different approach by using a classification developed from vaginal cytology (the 'Munchener scheme', a modification of the original Papanicolaou classification) to decide whether a lesion was malignant. For the diagnosis of melanoma, Durdu 2011 provided a basic definition of disease, defining melanoma as the presence of 'epithelioid or spindle-type atypical nevoid cells'. Durdu 2011 also reported dermoscopic diagnoses for all patients, which followed a two-step method, differentiating melanocytic from non-melanocytic lesions before applying the ABCD algorithm. Appendix 8 lists specific diagnostic criteria for each study.

The dermatologist performed skin scrapes in one study (Durdu 2011), but the remaining studies did not describe the operating clinician. Studies described the experience of the clinician performing cytodiagnosis as the cytologist (Gordon 1984), cytopathologist (Berner 1999; Christensen 2008), pathologist (Derrick 1994), or dermatologist (Durdu 2011), but four studies did not report this (Brown 1979; Nauth 1988; Powell 2000; Ruocco 1992). No study evaluated interobserver variability.

In eight studies the reference standard diagnosis was by histology alone, while Brown 1979 used expert opinion to overrule the histological diagnosis in two lesions whose clinical and cytological appearance was 'characteristic' of BCC.

Test failures

Four studies reported instances of insufficient cellular material to make a cytological diagnosis (Christensen 2008; Durdu 2011; Gordon 1984; Nauth 1988), listed in Table 1. Comprising between 1% and 8% of slides evaluated in each study, these were con-

sidered as test failures and excluded from analysis of accuracy. One study excluded inadequate slides at study entry (Berner 1999), and the remaining four studies did not report the adequacy of cellular material, suggesting this may have been an implicit eligibility criterion (Brown 1979; Derrick 1994; Powell 2000; Ruocco 1992).

Methodological quality of included studies

Overall study quality was low or unclear, particularly in terms of the clinical applicability of results (Figure 7 and Figure 8).

Figure 7. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. One study, Durdu 2011, was assessed in the comparative domain as 'unclear' for both risk of bias and applicability concerns.

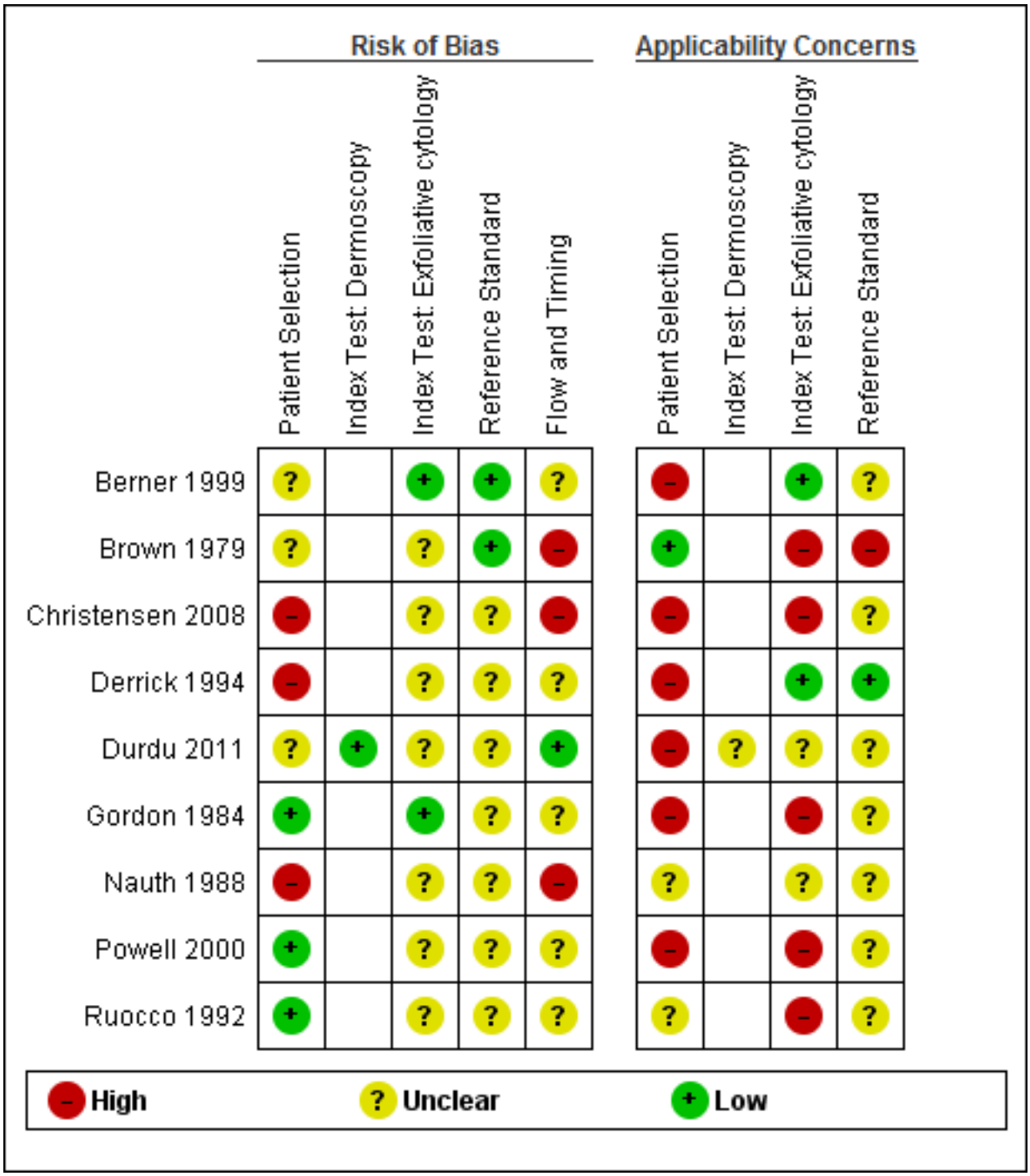
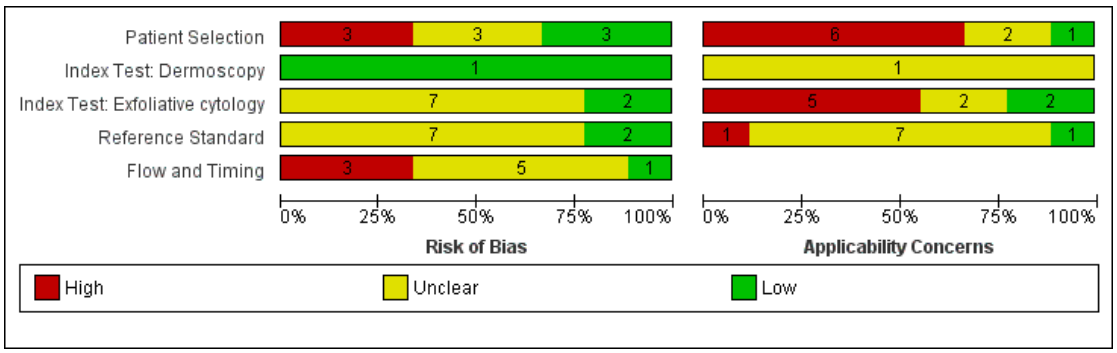


Figure 8. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies. One study, Durdu 2011, was assessed in the comparative domain as 'unclear' for both risk of bias and applicability concerns.



Three of the nine studies were at low risk of bias for participant selection (Gordon 1984; Powell 2000; Ruocco 1992); three were at high risk of bias: two because they recruited non-consecutively and selected participants according to histological diagnosis (Christensen 2008; Nauth 1988), and one because it excluded lesions inappropriately (Derrick 1994). Three did not clearly describe consecutive patient recruitment or exclusions. Concern was high for the applicability of setting and included participants in six studies: due to poor reporting regarding the composition of study populations in five (Christensen 2008; Gordon 1984; Nauth 1988; Powell 2000; Ruocco 1992), inclusion of narrowly defined study groups in two (Berner 1999; Derrick 1994), and inclusion of multiple lesions per patient in five (Berner 1999; Christensen 2008; Durdu 2011; Gordon 1984; Powell 2000). We could not determine the clinical applicability of participant populations in two studies due to insufficient reporting of study populations (Nauth 1988; Ruocco 1992).

Risk of bias for the index test was low in two studies (Berner 1999; Gordon 1984), but we could not determine this in the remaining seven studies due to poor reporting of diagnostic thresholds and whether cytology slides were interpreted without knowledge of the lesion's histology results. More than half of the studies (5/9) caused high concern regarding the applicability of the index test, since examiners did not did have access to the clinical diagnosis during review of cytology slides (Christensen 2008; Gordon 1984), and they did not report cytodiagnostic criteria in sufficient detail to allow replication (Brown 1979; Christensen 2008; Gordon 1984; Powell 2000; Ruocco 1992); we could not assess two studies due to poor reporting of the diagnostician's cytological expertise (Durdu 2011; Nauth 1988). The remaining two studies were of low concern (Berner 1999; Derrick 1994).

All studies reported the use of an acceptable reference standard with one exception: Nauth 1988 failed to state the reference standard used to confirm the absence of disease in 14 of 224 included diseased participants (Nauth 1988). Only two studies clearly blinded the reference standard diagnosis to the cytology results (Berner 1999; Brown 1979), while in the remaining seven studies a failure to clearly report this aspect meant that the risk of bias due to conduct of the reference standard was unclear. We were also unclear as to whether most studies (7/9) used the reference standard in a clinically applicable way, largely due to inadequate description of the conduct and interpretation of histology; only one study reported histopathological interpretation by an experienced dermatopathologist (Derrick 1994). We judged Brown 1979 to be of high concern due to use of expert opinion (discipline and qualifications not reported) to overrule the reference standard diagnosis in 2 of 85 cases.

We judged only one study, Durdu 2011, to be at low risk of bias for the flow and timing domain, while the rest were at high and/or unclear risk. Brown 1979 and Nauth 1988 used different reference standard tests, and Christensen 2008 excluded slides 'unavailable for examination'; these aspects conferred a high risk of bias. Seven studies were unclear in that they failed to report the time interval between exfoliative cytology and histology examinations (Berner 1999; Christensen 2008; Derrick 1994; Gordon 1984; Nauth 1988; Powell 2000; Ruocco 1992).

The single study comparing exfoliative cytology with dermoscopy, Durdu 2011, reported blinding the diagnoses of the two index tests; however, authors did not describe the time interval between

tests or give sufficient details on their conduct, thus its risk of bias and applicability in the comparative domain remain unclear.

Findings

Detection of BCC

Seven of the nine studies provided data eligible for pooling. We did not pool the remaining two studies in the meta-analysis because Nauth 1988 used a different diagnostic classification system (the Munchener scheme), and Durdu 2011 evaluated exfoliative cytology in a distinct patient group (pigmented skin lesions).

The seven pooled studies were in participants with clinically suspect BCC lesions, and they used standard cytomorphology to investigate 1264 lesions, 1045 of which were BCCs, using MGG stain (Derrick 1994), Pap stain (Gordon 1984), Diff-Quick (Berner 1999), or a mixture of stain techniques (Brown 1979; Ruocco 1992); Powell 2000 did not report the stain method. Christensen 2008 used two slides per lesion: one MGG and the other Pap stain, selecting the slide showing the greatest degree of cytological atypia for the final diagnosis. These were pooled regardless of stain method used, giving a summary sensitivity of 97.5% (95% CI 94.5% to 98.9%) with a summary specificity of 90.1% (95% CI 81.1% to 95.1%). Table 2 provides a summary of all results.

Common diagnoses mistaken for BCC were actinic keratosis in Christensen 2008 and Gordon 1984 and trichoepithelioma in Derrick 1994 and Ruocco 1992. Only 3 of the 22 false positive cases (listed in Table 3) were malignant lesions, and all 3 were confirmed carcinomas, but it was not possible to classify histological type due to insufficient biopsy material (Berner 1999). No false positive cases were melanomas. Six of the seven false positive cases in Gordon 1984 were 'possible but not diagnostic for BCC' lesions, histologically diagnosed as marked atypia (n = 4) and seborrhoeic keratosis (n = 2). Consideration of these uncertain diagnoses as test negatives did not impact on pooled sensitivity (97.3%, 95% CI 93.5% to 98.9%) but raised the specificity estimate to 94.2% (95% CI 88.7% to 97.1%; Figure 9 Figure 10). All 16 cSCCs were correctly identified as true negative cases (Berner 1999; Brown 1979; Derrick 1994; Gordon 1984; Ruocco 1992); however, two studies misdiagnosed three BCCs as cSCCs (Brown 1979; Gordon 1984).

Figure 9. Forest plot of exfoliative cytology to detect BCC in patients with suspected BCCs, showing classification of 'possible BCCs' as test positives or as test negatives.

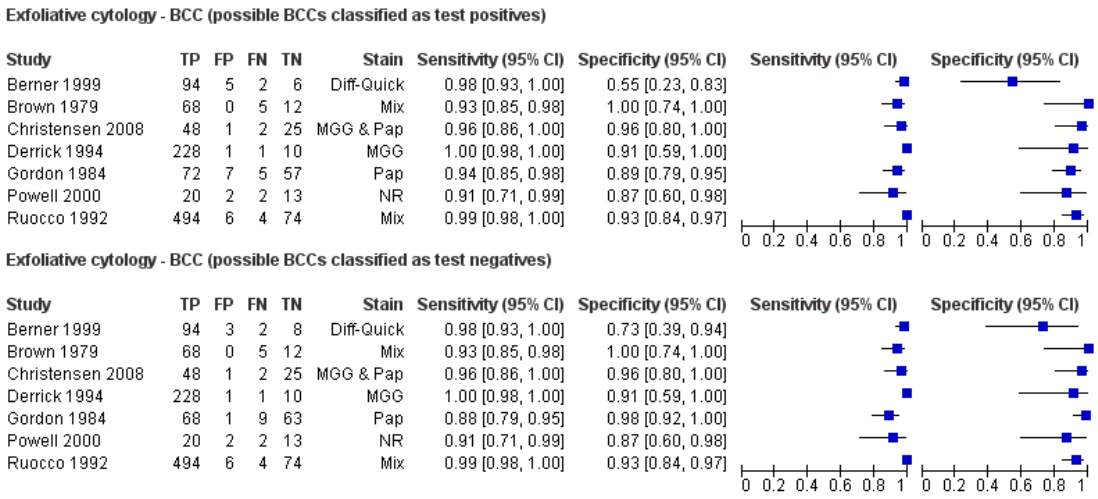
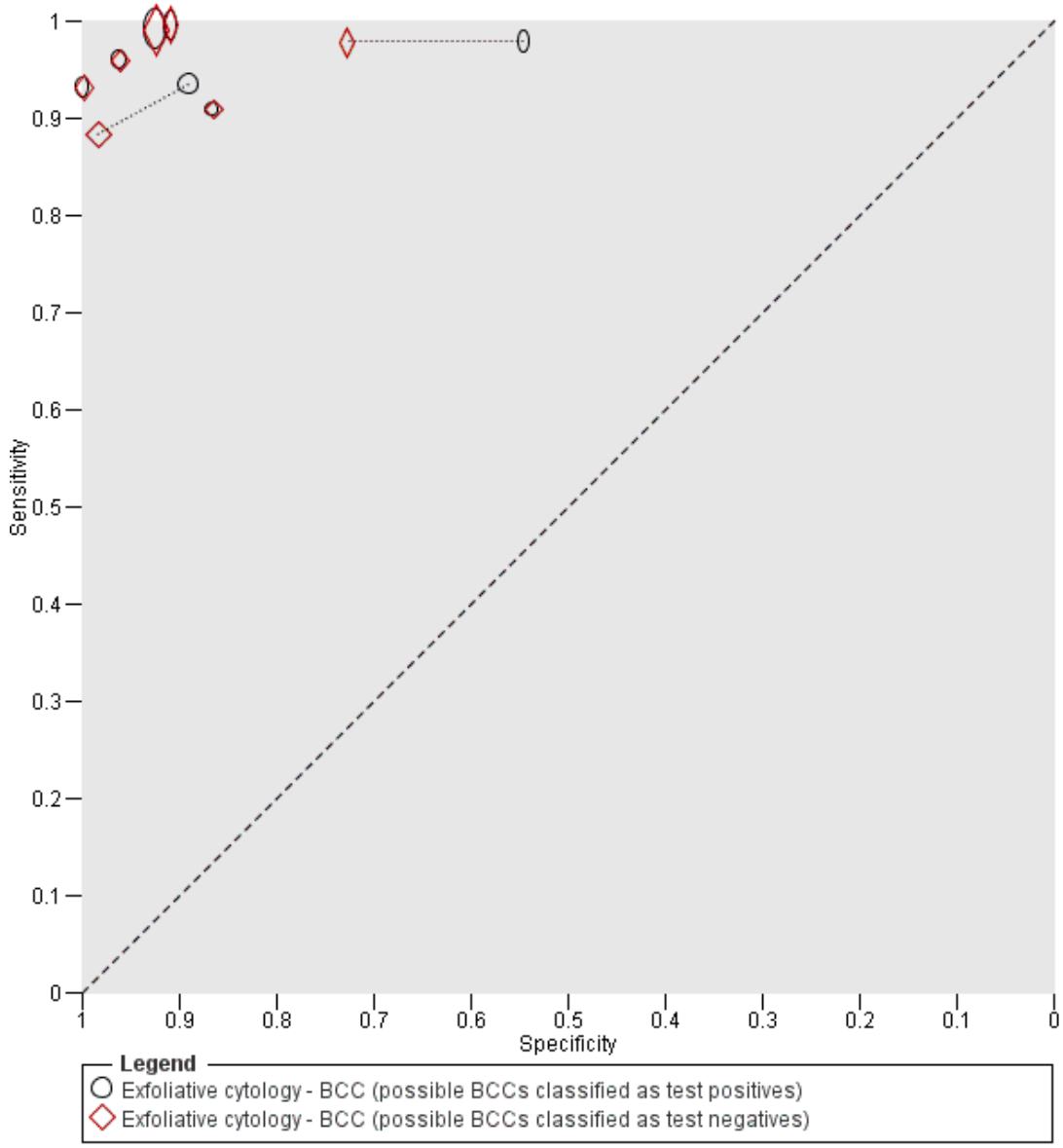


Figure 10. Summary ROC plot of exfoliative cytology to detect BCC in patients with suspected BCCs, showing classification of 'possible BCCs' as test positives or as test negatives.



The study using the Munchener scheme, Nauth 1988, identified fewer BCCs and incorrectly diagnosed 42 lesions as being BCC, giving a sensitivity of 80.5% (95% CI 66.0 to 89.8%) and specificity of 74.6% (95% CI 67.4% to 80.6%). Authors did not report misdiagnosis by lesion type.

The study in pigmented skin lesions (MGG stain) reported no false diagnoses amongst slides for 185 lesions, giving a sensitivity of 100% (95% CI 89.9% to 100%) and specificity of 100% (95% CI 97.5% to 100%) for the diagnosis of BCC (Durdu 2011); however, 15 lesions were excluded from analysis due to the retrieval of insufficient cell material. Results for dermoscopy, conducted on the full sample of 200 lesions, demonstrated a lower sensitivity of 94.1% (95% CI 80.9% to 98.4%) and higher specificity 98.2% (95% CI 94.8% to 99.4%), but the differences could be explained by chance.

Christensen 2008 found no difference in sensitivity or specificity between the three stain techniques (Pap versus MGG versus Pap + MGG), with each method identifying the same number of false positive (n = 1) and false negative (n = 2) cases to give a sensitivity of 96% and specificity of 96%.

Detection of cSCC

Six studies examined cSCC lesions, although those from four studies (totalling 11 lesions) were excluded from analysis due to each study having an inadequate number of cSCC cases (fewer than 5 per study). The two remaining studies contributed 41 analysed cSCC lesions amongst their 347 lesions, however their results were not pooled due to their use of different diagnostic criteria. Using standard cytomorphological criteria to diagnose 5 cSCC slides from 141 lesions, Gordon 1984 report a sensitivity of 100% (95% CI 56.6% to 100%) and specificity of 98.5% (95% CI 94.8% to 99.6%) with two false positive results, both showing squamous differentiation with cellular pleomorphism and a histological diagnosis of pleomorphic BCC. Nauth 1988's use of the Munchener scheme to diagnose 36 cSCC slides from 206 lesions resulted in a lower sensitivity of 88.9% (95% CI 74.7% to 95.6%) and lower specificity of 74.7% (95% CI 67.7% to 80.6%), reporting the only false negative cSCCs of any included study. Two were diagnosed as 'questionable dyskeratoses and/or questionable anaplastic tumour cells', one as mild dysplasia and the fourth as severe dysplasia.

No data were available to compare exfoliative cytology for detection of cSCC with routine diagnostic practice.

Detection of invasive melanoma and atypical intraepidermal melanocytic variants

The single study evaluating exfoliative cytology for the detection of 10 melanomas in 185 lesions, Durdu 2011, reported sensitivity of 100% (95% CI 72.3% to 100%) and specificity of 100% (95% CI 97.6% to 100%); dermoscopic diagnosis in the full sample (200 lesions, 10 melanomas) produced a sensitivity of 80.0% (95% CI 49.0% to 94.3%) and specificity of 97.4% (95% CI 94.0% to 98.9%). One other study included a single case of melanoma as a BCC-negative case (Brown 1979).

Detection of any skin cancer

Four studies in 573 clinically suspect BCC lesions provided data for detection of any skin cancer (Berner 1999; Brown 1979; Derrick 1994; Gordon 1984); 495 histologically confirmed malignant lesions were included (476 BCCs, 13 cSCCs, 1 melanoma, 4 carcinomas of unspecified histological type (Berner 1999), plus 1 apocrine carcinoma (Derrick 1994)). Pooled sensitivity was estimated to be 97.3% (95% CI 93.5% to 98.9%) with a pooled specificity of 86.0% (95% CI 73.5% to 93.1%). Consideration of uncertain diagnoses as test negatives did not impact on pooled estimates of sensitivity (96.6%, 95% CI 90.3% to 98.9%) or specificity (94.7%, 95% CI 80.2% to 98.7%; Figure 11; Figure 12; Berner 1999; Gordon 1984).

Figure 11. Forest plot of studies pooled for accuracy of exfoliative cytology to detect any skin cancer in patients with suspected BCCs, comparing: classification of 'possible BCCs' as test positives versus classification of 'possible BCCs' as test negatives.

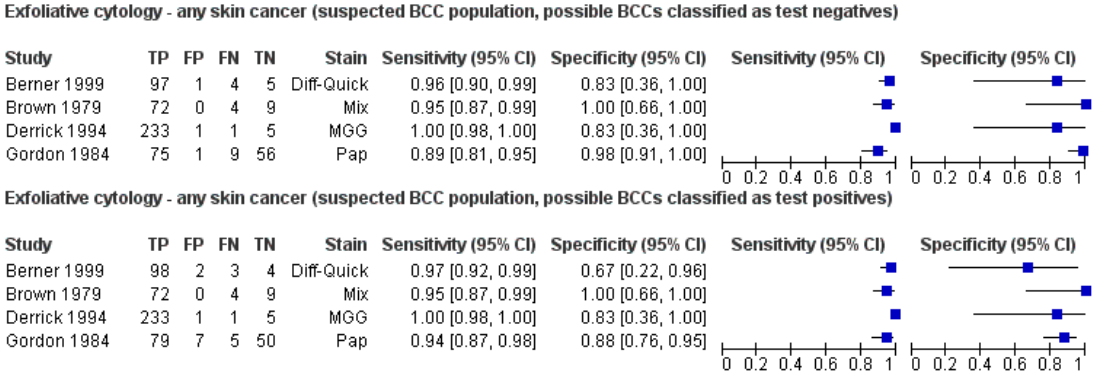
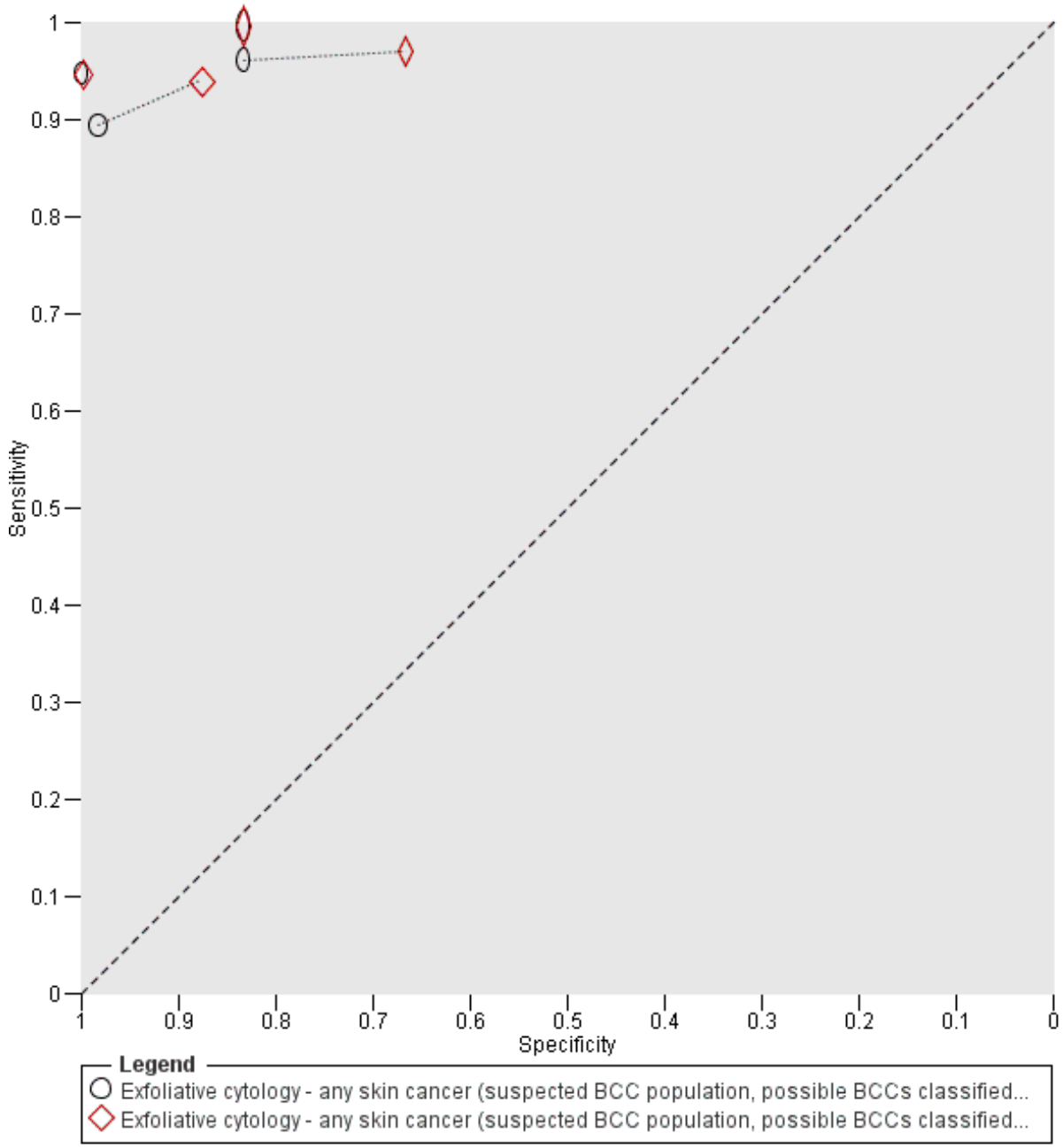


Figure 12. Summary ROC plot of pooled studies for accuracy of exfoliative cytology to detect any skin cancer in patients with suspected BCCs, comparing: classification of 'possible BCCs' as test positives versus classification of 'possible BCCs' as test negatives.



The Munchener scheme, used in Nauth 1988, was less sensitive in its detection of 36 cSCCs and 41 BCCs amongst 206 included cases, with a sensitivity of 84.4% (95% CI 74.7% to 90.9%) and specificity of 92.3% (95% CI 86.3% to 95.7%).

The study in pigmented skin lesions included 10 melanomas, 34 BCCs, 1 case of pigmented mammary Paget's disease, and 1 pigmented metastatic mammary carcinoma (Durdu 2011). In 185 lesions, exfoliative cytology was able to differentiate between these and benign conditions with a sensitivity of 100% (95% CI 92.3% to 100%) and a specificity of 100% (95% CI 97.3% to 100%). Whilst this was marginally more accurate when compared to dermoscopy alone (sensitivity 97.8%, 95% CI 88.7% to 99.6%; specificity 98.1%, 95% CI 94.4% to 99.3%), the difference could be due to chance. Also, dermoscopy was conducted on the full sample of 200 lesions (Durdu 2011).

Effect of observer experience

No included studies evaluated the effect of observer experience on the accuracy of exfoliative cytology in any skin cancer.

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 exfoliative cytology for diagnosing BCC, cSCC or melanoma in adults, yet most studies focus on its use for confirming the clinical diagnosis in lesions with a high clinical suspicion of BCC. Studies were poorly reported and of uncertain to poor methodological quality, particularly in terms of the applicability of their results to the current clinical setting in the UK, thus limiting the strength of conclusions that can be drawn. The Summary of findings presents key results for the primary target condition of BCC.

Pooled results from seven studies with 1264 clinically suspected BCC lesions that included 1045 BCCs provided a sensitivity of 97.5% (95% CI 94.5% to 98.9%) and specificity of 90.1% (95% CI 81.1% to 95.1%). The Summary of findings translates these estimates to a hypothetical cohort of 1000 lesions clinically suspected of being BCC. At the median BCC prevalence of 86%, exfoliative cytology would miss 21 BCCs and would result in 14 false positive diagnoses. As BCCs are usually relatively slow growing, delayed treatment of 21 out of 860 BCCs may not have serious consequences. However, if the test was used as a basis for initiation of non-surgical treatment, and any of the false positive results were lesions requiring excision, such as melanomas or cSCCs, the consequences could be potentially fatal. At the lower and upper quartile prevalence of BCC of 63% and 88%, 16 and 22 BCCs would be missed, respectively, with 37 and 12 false positive diagnoses. While evidence for the ability of exfoliative cytology to detect cSCC is scarce (with only one study using a clinically relevant application of exfoliative cytology), it is worth noting that all 17 cSCCs included in the primary analysis were correctly identified using standard cytomorphology, albeit with some difficulty in discriminating BCCs from cSCC correctly in the presence of pleomorphic features. This suggests that in populations with very high clinical suspicion of BCC, and therefore high prevalence of disease, exfoliative cytology could have a potential role in guiding the use of non-surgical therapy and avoiding biopsy. Decisions to start some non-surgical treatments in patients with superficial BCC, for example topical imiquimod, are in practice unlikely to require additional confirmation when clinical suspicion is already high, and thus cytodiagnosis is likely to have minimal utility in these cases. Conversely, exfoliative cytology may be most valuable to the management of patients with BCC lesions considered for radiotherapy, since a tissue diagnosis is typically required for confirmation before the therapy can proceed.

The 'perfect' results for the detection of both BCC and melanoma from the single study recruiting only pigmented lesions is likely to be explained by the unique case-mix of patients (Durdu 2011), with high proportions of benign melanocytic naevi and of benign non-melanocytic lesions such as seborrhoeic keratosis, warts and dermatofibroma (Durdu 2011). The high rate of uninterpretable benign slides in this study (8%) may also have influenced its specificity. In the absence of additional studies and greater numbers of lesions, these data did not provide sufficient evidence on the performance of exfoliative cytology to detect melanomas, its use in populations with pigmented skin lesions, or its performance using other cytological classification approaches.

Observed limitations of primary studies

Studies were limited by universally poor reporting and poor methodological quality. In addition to scarce reporting of participant selection, studies failed to outline the prior referral pathway of eligible patients, including a description of which clinical methods they had used to arrive at a clinical suspicion of BCC that was strong enough to make the patients eligible for study inclusion. For the purposes of our BCC analysis, we have assumed that all approaches resulted in similar population groups; however, in reality the spectrum of disease in included groups remains unclear and could differ considerably.

Similarly, very limited reporting of the diagnostic criteria used to define the cytomorphologic presence of disease could obscure actual differences in diagnostic thresholds. Along with missing descriptions of how histopathological diagnoses were made and the experience of clinicians performing or interpreting scrapes, these limitations of the primary studies limit the generalisability of our findings to current clinical practice, as well as our understanding of the efficacy of exfoliative cytology to distinguish between skin cancers.

There was a similar lack of clarity in description of most items necessary to determine the risk of bias, including: recruitment methods, study design, threshold selection, blinding of the reference standard to the index test result and the time interval between exfoliative cytology and definitive histology. When these details were reported, studies were often at high risk of bias, so their accuracy estimates may not adequately reflect the true sensitivity and specificity of exfoliative cytology.

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. We planned a clear analysis structure to allow estimation of test accuracy in discrete study populations using only scrape techniques to gather a cell sample for cytopathology. We undertook a detailed and replicable assessment of methodological quality. This is the only review we are aware of to have examined the accuracy of exfoliative cytology for detecting cSCC, melanoma or any skin cancer.

Published in 2004, Bakis 2004 was an earlier meta-analysis of exfoliative cytology based on eight studies including 1261 BCCs. Reviewers arrived at very similar pooled estimates (97% sensitivity and 86% specificity), despite including three studies that did not meet our inclusion criteria due to: differing target condition (Barton 1996), ineligible method of exfoliation (Bocking 1987), and insufficient numbers of individuals with benign disease (Vega-Memije 2000). By comparison, the present review provides an updated estimate of the accuracy of exfoliative cytology to detect BCC using a larger number of studies (three published after 2004), evaluating the same target conditions, and all of which have used scrape techniques to gather a cell sample for cytopathology. Ours has included a non-English language study, Nauth 1988, which was excluded from the Bakis 2004 review (because the article could not be located), so the present review constitutes a more current and comprehensive summary of the accuracy of exfoliative cytology to detect BCC.

The main concerns for this review are the small number of studies and their poor reporting of patients' prior referral pathways, criteria used to arrive at cytopathological or histopathological diagnoses, observer experience, and other aspects relating to participant selection or methods of performing exfoliative cytology. Some authors have questioned the ability of cytopathology to provide sufficient discrimination of skin cancer subtypes (Barr 1984); however, we did not address this topic in the current review. Thus, echoing the findings of Bakis 2004, the main weakness of this review is the poor reporting of primary studies, which has limited our appraisal of study quality and, critically, impedes our understanding of whether summary estimates are applicable to current clinical settings.

Applicability of findings to the review question

Not all data included in this review are likely to be generally applicable to the current clinical setting. In particular, Durdu 2011 used exfoliative cytology in a clearly different population to that in which the test is likely to be used in clinical practice, whilst Nauth 1988 used a diagnostic classification used for vaginal cytology (the Munchener scheme) to grade the degree of cell dysplasia from normal to anaplastic, an approach which is clearly different from the other seven studies that sought to determine whether a lesion was a BCC, cSCC or melanoma. We pooled the remaining seven studies, and summary accuracy estimates do appear to show that exfoliative cytology confirms clinically suspected BCC with a high sensitivity and specificity; however, poor reporting limits any more detailed statements regarding which patient populations these results would be replicated in. Furthermore, the lack of description in all studies regarding the diagnostic criteria used for both index test and reference standard may restrict applicability and transferability of results in practice.

AUTHORS' CONCLUSIONS

Implications for practice

The utility of exfoliative cytology for the primary diagnosis of skin cancer is unknown, as all included studies have focused on the use of this technique for confirming strongly suspected clinical diagnoses. Whilst our review has provided some data regarding the potential usefulness of confirming the clinical diagnosis of BCC, the small number of included studies, poor reporting and varying methodological quality of seven included studies means that we cannot draw any strong conclusions to guide practice. Bearing this in mind, for the confirmation of BCC in lesions with a high clinical suspicion, there is evidence of high sensitivity and specificity for exfoliative cytology. As such, the test might be useful for cases of BCC that can be diagnosed confidently where clinicians are contemplating treatments that require a tissue diagnosis, such as radiotherapy. However, as the main potential advantage of the test would be initiation of non-surgical treatment and avoidance of unnecessary biopsy in confirmed cases of low-risk BCC, even the

high rates of specificity observed will lead to a number of false positive diagnoses, including in populations with a high prevalence of BCC. The critical question is whether patients and clinicians are willing to accept the potential for misdiagnosis of some lesions with a worse prognosis that require excision. While none of the false positive diagnoses in these studies were melanomas or cSCCs, three carcinomas were misdiagnosed in one study, though unfortunately their precise type could not be confirmed due to the presence of inadequate sample sent for histology (Berner 1999). Even if cytology confirms a clinically suspected BCC, it can never give the same quality of histological information on parameters such as lesion architecture and infiltration or perineural invasion as does an entire skin biopsy. It is possible therefore that some of the true positives in our studies included more infiltrative forms of BCC that would have been better treated by wide excision or Mohs micrographic surgery. Exfoliative cytology poses another potential limitation in cases that require a subsequent excision, since the previous scraping process could distort measurement of total lesion depth and because a cytological scrape may induce ulceration, which would alter the prognostic classification.

Insufficient data are available to provide conclusive comments on the accuracy of exfoliative cytology to detect melanoma or cSCC. While only one study reported that exfoliative cytology missed cSCC diagnoses, not all studies included an adequate range of differential diagnoses known to present difficulties in being differentiated from cSCC using cytomorphology. It is therefore unlikely that the accuracy estimates reflect the true discriminatory power of exfoliative cytology. As for BCC, superficial scrapings of squamatous lesions cannot provide information regarding the lesion's pattern of invasion, hence the technique is potentially very limited unless it is used to confirm lesions that already have a very high clinical suspicion. For similar reasons, exfoliative cytology is very unlikely to be useful in the diagnosis of melanoma: an absence of malignant cells would require a biopsy since superficial scrapings cannot be relied upon to rule out invasion, while the presence of malignant cells would still require a further biopsy to confirm the diagnosis of melanoma and to determine depth of invasion which guides future excision margins for definitive management. Cytology is unlikely to avert the need for a biopsy of a new lesion suspected to be melanoma. Conversely, performing an adequate scrape in these lesions risks introducing inflammation and ulceration, which would alter the histopathological characteristics of the lesion that inform prognosis and treatment. On this basis we caution against the use of exfoliative cytology in non-ulcerated lesions suspected to be melanoma.

Implications for research

Whilst some (low-quality) evidence exists for evaluating the use of exfoliative cytology for confirming a BCC that has been diagnosed clinically i.e. a *confirmatory* test, the use of exfoliative cytology as a primary *diagnostic* test for suspected skin cancer at different points in the care pathway remains unknown. Given the absence of studies that evaluate the diagnostic value of exfoliative cytology in discriminating between BCC and other skin cancers and other benign lesions, studies are needed to provide a full and proper evaluation of the accuracy and ability of the test. Such studies should prospectively evaluate exfoliative cytology in comparison to an alternative diagnostic test such as dermoscopy in a standard healthcare setting, for which the most rigorous design would be a multiple test comparison study (Takwoingi 2013), in which study participants are given both diagnostic tests followed by an acceptable reference standard. Study participants should be recruited consecutively from a clearly defined population that is representative of patients who would receive the test in practice and should include sufficient numbers of participants with cSCC as well as key benign differential diagnoses.

There is also scope for further research that adequately reports its evaluation of exfoliative cytology for confirming the diagnosis of BCC in whom a clinical diagnosis has indicated a high probability of BCC in order to plan further treatment such as radiotherapy.

Whether new research examines the use of exfoliative cytology as a primary diagnostic or confirmatory treatment-planning test, such studies need to clearly define the target patient group and should include a full description of the clinical pathway (referral process), including prior testing. A multi-centred approach would allow confirmation that results are replicable across centres and that the technology can be implemented across a health service. Future studies should also explore patients' views of the test as well as costs to the health service. Prospective recruitment of a consecutive series of participants, with test interpretation blinded to the reference standard diagnosis, with pre-specified and clearly defined diagnostic thresholds for determining test positivity, is easily achieved. Clear identification of qualifications and practitioner/diagnostician training and experience is also required. Systematic follow-up of non-excised lesions avoids over-reliance on a histological reference standard and allows results to be more generalisable to routine practice. These studies would benefit from evaluating standardised techniques for performing and interpreting Tzank smears, which have yet to be developed. Developing diagnostic criteria would be useful for clinicians, facilitating ease of interpretation and ensuring that the results of future studies are fully transferable to clinical practice. Any future research study needs to be clear about the diagnostic pathway followed by study participants prior to study enrolment, and reporting should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Berner 1999

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: prospective **Period of data collection**: NR **Country**: Norway **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: lesions clinically suspected of being nodular BCCs **Setting**: secondary (unspecified) **Prior testing**: clinical suspicion of BCC (no further details) **Exclusion criteria**: lesions thinner than 2 mm, with inadequate material retrieved for cytological or histological analysis **Sample size (patients)**:**no. eligible**: 90;**no. included**: 90 **Sample size (lesions)**:**no. eligible**: 112;**no. included**: 107 **Participant characteristics**: none reported **Lesion characteristics**: all were nodular lesions, located on the head, thorax or abdomen
Index tests	**Exfoliative cytology**: initial removal of epidermal or keratin layer; scalpel or curette to obtain sample; stain method Diff-Quick **Diagnostic threshold**: qualitative - microscopic appearance of cellular scraping Diagnosis of BCC was based on a cellular smear with the presence of small dissociated hyperchromatic cells in cohesive sheets **Prior test data available**: clinical diagnosis (no further details) **Diagnosis based on single or consensus observation**: NR (3 examiners) **Observer qualifications**: NR - 'cytopathologists' **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 0
Target condition and reference standard(s)	**Type of reference standard**: histology (shave biopsy) **Details**: minute tumour fragments of sizes 1-3 mm were removed from the lesions with a curette and placed in a Shandon cytoblock cassette before fixation in 4% buffered formalin. The tumour fragments were removed without damaging neighbouring skin and without the use of anaesthesia. The histological specimens were examined by one pathologist (AB). The minute tissue fragments were fixed in 4% buffered formalin before embedding in paraffin. Sections 5 mm thick were cut at 3 levels and stained with haematoxylin and eosin. The histological diagnosis of BCC was based on the criteria defined by WHO (study reference #6) **Disease positive**: 101;**disease negative**: 6 **Final diagnoses**: • **Malignant**: 96 BCC; 1 cSCC; 4 carcinoma (type not specified) • **Benign diagnoses**: 6 (3 'benign'; 3 atypical)

Berner 1999 (*Continued*)

Flow and timing	**Index test to reference standard interval**: consecutive; quote: "tumour fragments ... were subsequently removed from the lesions" **Interval between index tests**: NA **Exclusions**: none reported
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the test applied and interpreted in a clinically applicable manner?	Yes		

Berner 1999 (*Continued*)

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Yes		
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		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		

Berner 1999 (*Continued*)

Were all patients included in the analysis?	Yes		
		Unclear	

Brown 1979

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: NR **Period of data collection**: NR **Country**: UK **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: localised lesions for which a histological diagnosis was required to confirm clinical diagnosis of BCC, or in a minority to exclude BCC **Setting**: secondary (unspecified) **Prior testing**: clinical suspicion of BCC (no further details) **Exclusion criteria**: none reported **Sample size (patients)**:**no. eligible**: NR;**no. included**: 81 **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 85 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**Exfoliative cytology**: initial removal of surface crust; scalpel or curette to obtain sample; stain method short May-Grunwald-Giemsa technique or rapid method (sample treated with 0.1% aqueous toluidine blue for 2 minutes followed by brief washing in water) **Diagnostic threshold**: NR, presumably based on qualitative appearance of scraping material Interpretation of smears includes: form of cell clusters, variation in cell size and outline, presence of squamous differentiation **Prior test data available**: clinical diagnosis (no further detail) **Diagnosis based on single or consensus observation**: NR **Observer qualifications**: NR **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 0
Target condition and reference standard(s)	**Type of reference standard**: histology (biopsy) in all, plus expert opinion in 2/85 with discordant cytological and histological findings **Details**: the biopsy tissue was fixed in 10% formalin in normal saline and processed routinely for histology. When biopsy disagreed with clinical and cytological diagnosis, expert opinion used to overrule histological diagnosis **Disease positive**: 76;**disease negative**: 9 **Final diagnoses**: • **Malignant**: 73 BCC; 2 cSCC; 1 malignant melanoma • **Benign diagnoses**: 9 (5 seborrhoeic keratosis; 4 actinic keratosis)

Brown 1979 (*Continued*)

Flow and timing	**Index test to reference standard interval**: consecutive; quote: "biopsy undertaken immediately after exfoliative cytology" **Interval between index tests**: NA **Exclusions**: none reported
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	Yes		

Brown 1979 (*Continued*)

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	No		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		

Brown 1979 (*Continued*)

Were all patients included in the analysis?	Yes		
		High	

Christensen 2008

Study characteristics	
Patient sampling	**Study design**: case-control **Data collection**: retrospective **Period of data collection**: NR **Country**: Norway **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: histologically confirmed BCC or AK lesions **Setting**: secondary (General Dermatology) **Prior testing**: NR **Exclusion criteria**: none reported **Sample size (patients)**:**no. eligible**: NR;**no. included**: 64 **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 78 **Participant characteristics**: none reported **Lesion characteristics**: 10 were recurrences; mean lesion size 9.0 mm (range 2.0-41.0 mm); Mean BCC tumour thickness (n-30) 1.6 mm (range 0.5-4.0 mm); BCC types: 16 superficial, 23 nodular, 3 micronodular, 2 infiltrating, 2 basosquamous, 4 morphoeic Lesions located on head or neck (56.72%), trunk (15.19%), extremities (7.10%)
Index tests	**Exfoliative cytology**: curette to obtain sample; 3 smears for each lesion: modified Pap technique, MGG technique, touch imprint stained with MGG **Diagnostic threshold**: qualitative appearance of cell material Cytological results grouped into 4 categories: BCC, AK, non-BCC/non-AK and non-evaluable (smears showing only keratin and/or cellular debris or inadequate cellular material). Final diagnosis for the combined diagnostic result from Pap and MGG stains determined from the slide showing the greatest degree of cytological atypia Cytological diagnosis of BCC: quote: "based on fragments of closely packed cells which tend to present in monolayers or a club-like formations, demonstrating smooth external contours and peripheral palisading of nuclei. There is little dissociation of cells. The malignant basal cells have small, oval, hyperchromatic nuclei. The nucleus to cytoplasmic ratio is extremely high. Smears from AK lesions show greater cellular dissociation and individual as well as clumps of dysplastic keratinocytes, often with ragged edges. These cells show a polyhedral or spindle-shaped configuration. The nucleus to cytoplasmic ratio is moderately high ... Each specimen was considered independently even if taken from the same patient." **Prior test data available**: none; blinded to clinical exam **Diagnosis based on single or consensus observation**: NR (2 examiners participated) **Observer qualifications**: 'Pathologists' **Experience in practice**: NR **Experience with index test**: high; extensive experience in cytology without specific training in skin scrape cytology

	Other details: within-patient comparison of stain methods conducted **Cases excluded due to insufficient cellular material on slide:** 1 (1 AK)
Target condition and reference standard(s)	**Type of reference standard**: histology alone **Details**: punch biopsies (2 or 3 mm) fixed in 10% formaldehyde, routinely processed and embedded in paraffin. Sections of 4 microns were cut at 3 levels and stained with haematoxylin-eosin-saffron. Cases of BCC were subtyped according to the WHO guidelines: superficial type; nodular/micronodular type; and infiltrating type, basosquamous type or morphoeic type **Disease positive**: 50;**disease negative**: 28 **Final diagnoses**: • **Malignant**: 50 BCC • **Benign diagnosis**: 28 actinic keratosis
Flow and timing	**Index test to reference standard interval**: not reported for 50 (67%) cases, consecutive in 28 cases; quote: "[i]n cases where no former histology report existed, a diagnostic punch biopsy was obtained approximately 3-5 minutes before cytological sampling" **Interval between index tests**: NA **Exclusions**: 3 slides 'unavailable for investigation'
Comparative	
Notes	-

Methodological quality

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

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		

Christensen 2008 (*Continued*)

		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Derrick 1994

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: NR **Period of data collection**: NR **Country**: UK **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: clinically suspected BCC on head or neck **Setting**: secondary (unspecified) **Prior testing**: clinical examination (no further details) **Exclusion criteria**: none reported **Sample size (patients)**:**no. eligible**: NR;**no. included**: 240 **Sample size (lesions)**: **no. eligible**: NR;**no. included**: 240 **Participant characteristics**: none reported **Lesion characteristics**: BCC types: ulcerative (n = 116, 48%), nodulocystic (n = 101, 42%), morphoeic (n = 19, 8%) and superficial (n = 4, 2%); located on the head or neck **Cases excluded due to insufficient cellular material on slide:** 0
Index tests	**Exfoliative cytology**: scalpel to obtain sample; MGG staining method **Diagnostic threshold**: qualitative appearance of cell material Cytological diagnosis of a BCC based on: "the presence or tight groups of uniform small cells and the presence of pink amorphous material in MGG-stained preparations. Squamous cell lesions showed less cellular adhesion, much more nuclear pleomorphism and no pink material." **Prior test data available**: clinical diagnosis **Diagnosis based on single or consensus observation**: NR **Observer qualifications**: consultant pathologists **Experience in practice**: NR **Experience with index test**: NR

Target condition and reference standard(s)	**Type of reference standard**: histology (punch biopsy) **Details**: 3-mm biopsy punch, with total surgical excision if cytology and biopsy diagnoses disagreed (n = 4). Biopsies fixed in formaldehyde, routinely processed, and embedded in paraffin. Sections of 5 microns cut and stained with haematoxylin and eosin **Disease positive**: 234;**disease negative**: 6 **Final diagnoses**: • **Malignant**: 229 BCC; 4 cSCC; 1 apocrine carcinoma • **Benign diagnoses**: 6 (1 actinic keratosis, 1 Bowen's disease, 1 trichoepithelioma, 3 no abnormality)
Flow and timing	**Index test to reference standard interval**: NR **Interval between index tests**: NA **Exclusions**: none reported
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		High	**High**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		

If a threshold was used, was it pre-specified?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	No		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Durdu 2011

Study characteristics	
Patient sampling	**Study design**: case series, within-person comparison **Data collection**: prospective **Period of data collection**: January 2006 to January 2009 **Country**: Turkey **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: pigmented skin lesions that could not be diagnosed with only dermatologic physical examination **Setting**: secondary (general dermatology) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Exclusion criteria**: none reported **Sample size (patients)**:**no. eligible**: NR;**no. included**: 176 **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 200 **Participant characteristics**: mean age 48 years (range 4-85); 64 (36.4%) males **Lesion characteristics**: 100% pigmented; 9% ulcerated; 56% papular; 17% macular; 10% nodular; 8% plaque
Index tests	**1. Exfoliative cytology: slit-skin exfoliation using scalpel**; MGG stain; evaluated with a light microscope (310 and 340 magnifications and then 3100 magnification with immersion oil) **Prior test data**: clinical examination and/or case notes. Dermoscopy was conducted by a different dermatologist **Diagnostic threshold**: qualitative - microscopic appearance of cellular scraping Cytologic diagnoses were made according to findings reported previously (several studies referenced and criteria used were tabulated) Criteria for BCC: clusters of basaloid cells containing pigment granules (Powell 2000; Vega-Memije 2000) Criteria for melanoma: epithelioid or spindle-type atypical nevoid cells (Canti 1984). **Diagnosis based on single or consensus observation**: single (1 examiner) **Observer qualifications**: dermatologist **Experience in practice**: NR **Experience with index test**: NR **2. Dermoscopy**

	Method of diagnosis: in-person diagnosis **Prior test data**: clinical examination and/or case notes **Diagnostic threshold**: NR 2-step process: 1. melanocytic and non melanocytic were differentiated (Braun 2005; Zalaudek 2008) 2. ABCD applied to melanocytic only **Diagnosis based on single or consensus observation**: single (1 examiner) **Observer qualifications**: dermatologist **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 15 (6 benign melanocytic lesions, 9 benign non-melanocytic lesions)
Target condition and reference standard(s)	**Type of reference standard**: histology (excision 166; punch biopsy 34) **Details**: biopsy specimens were stained with hematoxylin and eosin. Immunohistochemical (anti-S-100 and human melanoma black [HMB]-45) and histochemical (Fontana-Masson) stains were also applied, if necessary **Disease positive**: 46;**disease negative**: 154 **Final diagnoses**: • **Malignant**: 34 BCC; 10 melanoma (in situ and invasive, or not reported); 1 pigmented mammary Paget's disease; 1 pigmented metastatic mammary carcinoma; 1 apocrine carcinoma • **Benign diagnoses**: 154 (24 seborrhoeic keratosis, 100 benign melanocytic naevus, 30 other benign melanocytic lesions)
Flow and timing	**Index test to reference standard interval**: consecutive; exact interval not reported **Interval between index tests**: consecutive **Exclusions**: 15 slides with inadequate material for cytological diagnosis; no exclusions for dermoscopy
Comparative	
Notes	-

Methodological quality

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

Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Dermoscopy			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
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		
		Low	**Unclear**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the test applied and interpreted in a clinically applicable manner?	Yes		

Durdu 2011 (*Continued*)

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		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Durdu 2011 (*Continued*)

Were all patients included in the analysis?	Yes		
		Low	

Gordon 1984

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: prospective **Period of data collection**: NR **Country**: Australia **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: patients with cutaneous neoplasms undergoing diagnostic biopsy or definitive excision at a routine clinic **Setting**: secondary (General Dermatology) **Prior testing**: selected for excision (no further details) **Exclusion criteria**: lesions too small to retrieve adequate material for cytological or histological analysis, suspected melanomas **Sample size (patients)**:**no. eligible**: NR;**no. included**: 112 **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 150 **Participant characteristics**: none reported **Lesion characteristics**: not reported for whole sample; BCCs included 4 pleomorphic BCCs
Index tests	**Exfoliative cytology**: initial removal of ulcerated crust or keratotic surface; scalpel to obtain sample; stain method Papanicolaou **Diagnostic threshold**: qualitative appearance of cell material. Smears of BCC reported to be characterised by "many cohesive epithelial fragments composed of tightly packed small cells with uniform, oval, dark nuclei. The nuclear chromatin is dense, but granular and evenly distributed; nucleoli are small and indistinct. Cytoplasm is scanty and cyanophilic. Usually, some fragments show the marginal palisading arrangement of tumour cells familiar to the histopathologist (Figs. I and 2). Squamous differentiation may be present within BCC (keratotic BCC and metatypical epithelioma). When this is prominent and associated with nuclear enlargement and pleomorphism, the cytologic differentiation between SCC and pleomorphic BCC is difficult or impossible. Strong cohesiveness, uniformly high nuclear/cytoplasmic ratio, and evenly distributed nuclear chromatin favour a diagnosis of pleomorphic BCC (Fig. 3)." **Prior test data available**: none; blinded to clinical exam **Diagnosis based on single or consensus observation**: single **Observer qualifications**: NR, 'cytologists' **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 9 (1 BCC, 1 cSCC, 7 AK)
Target condition and reference standard(s)	**Type of reference standard**: histology (excisional or incisional biopsy) **Details**: biopsy specimens were stained with hematoxylin and eosin. Immunohistochemical (anti-S-100 and human melanoma black [HMB]-45) and histochemical (Fontana-Masson) stains were

Gordon 1984 (*Continued*)

	also applied, if necessary **Disease positive**: 84;**disease negative**: 57 **Final diagnoses**: • **Malignant**: 78 BCC; 6 cSCC; severe dysplasia: 4 marked squamous atypia • **Benign diagnoses**: 62 (9 seborrhoeic keratosis; 53 actinic keratosis)		
Flow and timing	**Index test to reference standard interval**: NR **Interval between index tests**: NA **Exclusions**: none reported 9 lesions with inadequate material for cytological diagnosis (1 BCC, 1cSCC, 7 AK)		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Exfoliative cytology			
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		

Gordon 1984 (*Continued*)

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?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Gordon 1984 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Nauth 1988

Study characteristics	
Patient sampling	**Study design**: case control **Data collection**: NR **Period of data collection**: NR **Country**: Germany **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: NR **Setting**: secondary (unspecified) **Prior testing**: NR **Exclusion criteria**: NR **Sample size (patients)**:**no. eligible**: NR;**no. included**: 224 **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 224 **Participant characteristics**: age range 11-100 years; 132 (59%) male **Lesion characteristics**: NR
Index tests	**Exfoliative cytology**: method of exfoliation not reported; Papanicolaou stain used **Prior test data**: NR **Diagnostic threshold**: qualitative threshold - assessment of the cell images was based on the findings and measures already obtained in earlier studies on vulva cytology, using the Munchener classification scheme (study reference #24) Cut-off of V (malignancy present) used **Diagnosis based on single or consensus observation**: NR **Observer qualifications**: NR **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 18 (1 BCC, 2 cSCC, 2 Severe precancerous disease, 6 Mild precancerous disease, 5 Benign tumour, 2 inflammation)
Target condition and reference standard(s)	**Type of reference standard**: histology (punch biopsy 210/224), not reported for 14/224 (inflammatory conditions) **Details**: not described **Disease positive**: 145;**disease negative**: 65 **Final diagnoses**: • **Malignant**: 42 BCC; 38 cSCC; 34 severe dysplasia; 31 moderate dysplasia • **Benign diagnoses**: 51 benign (not further specified), 28 inflammatory lesions

Nauth 1988 (*Continued*)

Flow and timing	**Index test to reference standard interval**: NR **Interval between index tests**: NA **Exclusions**: none reported		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the test applied and interpreted in a clinically applicable manner?	Unclear		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Unclear		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		

Nauth 1988 (*Continued*)

Were all patients included in the analysis?	Yes		
		High	

Powell 2000

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: retrospective **Period of data collection**: January 1999 to September 1999 **Country**: UK **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: all cytology smears taken over a 9-month period to confirm a diagnosis of BCC **Setting**: secondary (unspecified) **Prior testing**: clinical suspicion of BCC (no further details) **Exclusion criteria**: no histological specimen available **Sample size (patients)**:**no. eligible**: 72;**no. included**: 30 **Sample size (lesions)**:**no. eligible**: 82;**no. included**: 37 **Participant characteristics**: NR **Lesion characteristics**: NR
Index tests	**Exfoliative cytology**: scalpel or curette to obtain sample; stain method not reported **Diagnostic threshold**: qualitative - microscopic appearance of cellular scraping Diagnosis of BCC was based on a cellular smear with the presence of small dissociated hyperchromatic cells in cohesive sheets **Prior test data available**: clinical diagnosis (no further details) **Diagnosis based on single or consensus observation**: NR **Observer qualifications**: NR - 'histopathologist' **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 0
Target condition and reference standard(s)	**Type of reference standard**: histology (excisional or incisional biopsy) **Details**: NR - 'routine histological analysis of the lesion' **Disease positive**: 22;**disease negative**: 11 **Final diagnoses**: • **Malignant**: 22 BCC • **Benign diagnoses**: 11 (5 actinic keratosis, 1 Bowenoid actinic keratosis, 4 Bowen's disease, 1 benign lesion (type NR))
Flow and timing	**Index test to reference standard interval**: NR **Interval between index tests**: NA **Exclusions**: none reported
Comparative	

Powell 2000 (*Continued*)

Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		

Powell 2000 (*Continued*)

		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Ruocco 1992

Study characteristics	
Patient sampling	**Study design**: case series **Data collection**: retrospective **Period of data collection**: January 1971 to July 1991 **Country**: Italy **Funding**: none declared
Patient characteristics and setting	**Inclusion criteria**: nodular, papular or erythematous-infiltrative lesions for which the most likely clinical diagnosis was BCC **Setting**: secondary (General Dermatology) **Prior testing**: clinical suspicion of BCC without dermatoscopic suspicion **Exclusion criteria**: no histology slide or result, insufficient material for histology and cytology, patient undergoing treatment (diathermal coagulation, cryotherapy, radiotherapy, local chemotherapy with 5-fluorouracil or interferon a-2b), or patient treated elsewhere **Sample size (patients)**:**no. eligible**: NR;**no. included**: NR **Sample size (lesions)**:**no. eligible**: NR;**no. included**: 578 **Participant characteristics**: NR **Lesion characteristics**: solid (n = 162, 28%), cystic (n = 83, 14%), keratinous (n = 71, 12%), superficial (n = 63, 11%), pigmented (n = 57, 10%), intermediate (baso-squamous: n = 18, 3%), morfeiform (n = 12, 2%), aggressive or pleomorphic (n = 6, 1.2%), adamantinoid (n = 1, 0.2%), other (n = 25, 4%)
Index tests	**Exfoliative cytology**: initial removal of surface crust; scalpel to obtain sample; 3 slides per lesion stained using the MGG method, and either the Papanicolaou method or with pure undiluted Giemsa **Diagnostic threshold**: qualitative - microscopic appearance of cellular scraping Characteristics suggestive of BCC: basaloid cells arranged in groups, clumped in the centre and at times arranged as 'fences/palisades' around the periphery (as found in histological specimens) , slightly increased compared to normal epidermal basal keratinocytes, but in a single dimension, with an elongated shape, oval nucleus, intensely basophilic , occupying 4/5 of the entire cell with weak/thin cytoplasm, sometimes containing coarse melanin granules **Prior test data available**: clinical diagnosis without dermoscopy (no further details) **Diagnosis based on single or consensus observation**: NR **Observer qualifications**: NR **Experience in practice**: NR **Experience with index test**: NR **Cases excluded due to insufficient cellular material on slide:** 0
Target condition and reference standard(s)	**Type of reference standard**: histology (excisional or punch biopsy) **Details**: fixed at 10% formalin, initiated to the standard histological method (coloration with hematoxylin-cosine) and observed at the same microscope **Disease positive**: 507;**disease negative**: 71 **Final diagnoses**: • **Malignant**: 498 BCC; 4 cSCC; 3 cutaneous metastasis from visceral malignancy; 2 Merkel cell carcinoma • **Benign diagnoses**: 67 (19 actinic keratosis, 11 seborrhoeic keratosis, 8 senile sebaceous hyperplasia, 6 Bowen's disease, 4 keratoacanthoma, 3 molluscum contagiosum, 3 psoriasis, 3 Trichoepithelioma, 2 Syringocystadenoma papilliferum, 2 lichen planus, 2 localised scleroderma, 1 sebaceous adenoma, 1 cylindroma, 1 pilomatricoma)

	• Other: 4 'LED' (abbreviation not defined)		
Flow and timing	**Index test to reference standard interval**: NR **Interval between index tests**: NA **Exclusions**: none reported		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	Unclear		
		Low	**Unclear**
DOMAIN 2: Index Test Exfoliative cytology			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	Unclear		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results interpreted without knowledge of the referral diagnosis? (DOES NOT CONTRIBUTE TO THE REFERENCE STANDARD RISK OF BIAS JUDGEMENT)	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		

Were all patients included in the analysis?	Unclear		
		Unclear	

ABCD: asymmetry/border/colour/diameter; **AK**: actinic keratosis; **BCC**: basal cell carcinoma; **cSCC**: cutaneous squamous cell carcinoma; **H/N**: head and neck; **LED**: disease type, acronym not provided by study; **MGG**: May-Grünwald Giemsa stain technique; **NA**: not applicable; **NR**: not reported; **Pap**: Papanicolaou stain technique; **SK**: seborrhoeic keratosis; **WHO**: World Health Organization.

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

Study	Reason for exclusion
Baba 2010	Index test - margin control; study population - confirmed BCC cases only
Bakis 2004	Not primary study - systematic review and meta-analysis
Barton 1996	Target condition - periocular suspected BCCs
Berardi 1992	Index test - tape stripping cytology
Bilen 2000	sample size - < 5 benign lesions
Bocking 1987	Index test - ineligible method: use of swabbing
David 1971	Target condition - intraocular tumours
Eryilmaz 2014	Reference standard - unclear if all disease positive based on histology
Hajdu 1973	Study population - metastatic melanoma
Hatvani 1974	Study population - includes intra-ocular disease
Hering 1970	Index test - imprint cytology
Jakasa 1976	Index test - includes data for FNA; unclear whether data disaggregated by type of test
Korabiec 1977	Index test - includes FNA as well as scrape cytology; results cannot be differentiated
Melek 1970	Index test - imprint cytology
Norris 2008	Not primary study

(*Continued*)

Oram 1997	Sample size - < 5 benign cases
Ozden 2013	Sample size - < 5 benign cases
Rojo 1998	Index test - fine needle aspiration
Scanagatta 1981	Study population - only confirmed BCCs included
Schmid-Wendtner 1999	Not primary study
Sharifi 2007	Sample size - < 5 benign cases
Spinowitz 1986	Not primary study
Strokowska 1981	Reference standard - unclear if all disease positive based on histology
Tzanck 1951	Not primary study
Urbach 1957	Index test - exfoliative cytology from ex vivo biopsy samples
Vakhturova 1995	Index test - intraoperative use of cytology
Vega-Memije 2000	Sample size - < 5 benign cases
Veselovskaia 1984	Reference standard - no reference standard for index test negatives
Viglioglia 1955	Not primary study
von Gizycki-Nienhaus 1992	Index test - fine needle aspiration; Study population - includes recurrences
Yu 2005	Index test - three different cytological tests used, cannot disaggregate

BCC: basal cell carcinoma; **FNA**: fine needle aspiration.

DATA

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

Tests. Data tables by test

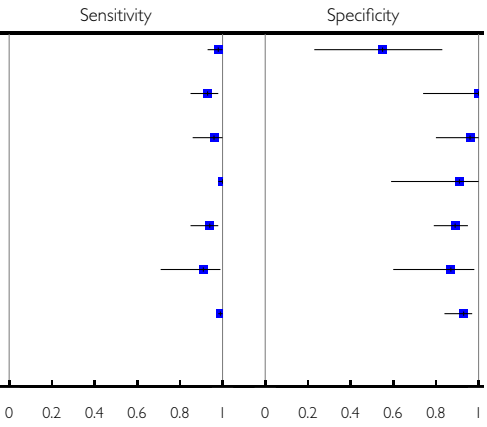
Test	No. of studies	No. of participants
1 Exfoliative cytology - BCC (possible BCCs classified as test positives)	7	1264
2 Exfoliative cytology - BCC (possible BCCs classified as test negatives)	7	1264
3 Exfoliative cytology - BCC (pigmented lesion population)	1	185
4 Dermoscopy - BCC (pigmented lesion population)	1	200
5 Exfoliative cytology - BCC (mixed population, Munchener diagnostic criteria)	1	206
6 Exfoliative cytology - cSCC (suspected BCC population)	1	141
7 Exfoliative cytology - cSCC (mixed population, Munchener diagnostic criteria)	1	206
8 Exfoliative cytology - melanoma (pigmented lesion population)	1	185
9 Dermoscopy - melanoma (pigmented lesion population)	1	200
10 Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test positives)	4	573
11 Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test negatives)	4	573
12 Exfoliative cytology - any skin cancer (pigmented lesion population)	1	185
13 Dermoscopy - any skin cancer (pigmented lesion population)	1	200
14 Exfoliative cytology - any skin cancer (mixed population, Munchener diagnostic criteria)	1	206
15 Exfoliative cytology (Papanicolaou + MGG stain) - BCC (stain comparison)	1	76

Test 1. Exfoliative cytology - BCC (possible BCCs classified as test positives).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 1 Exfoliative cytology - BCC (possible BCCs classified as test positives)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berner 1999	94	5	2	6	0.98 [0.93, 1.00]	0.55 [0.23, 0.83]
Brown 1979	68	0	5	12	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	72	7	5	57	0.94 [0.85, 0.98]	0.89 [0.79, 0.95]
Powell 2000	20	2	2	13	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]

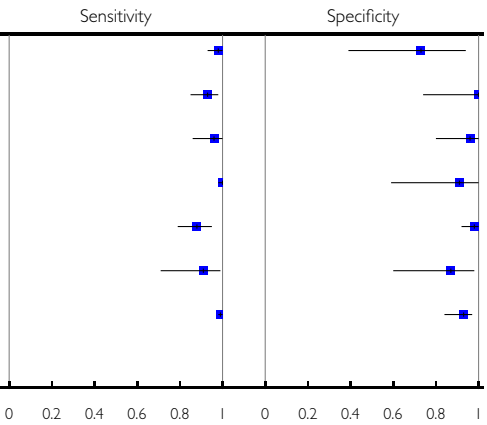


Test 2. Exfoliative cytology - BCC (possible BCCs classified as test negatives).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 2 Exfoliative cytology - BCC (possible BCCs classified as test negatives)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berner 1999	94	3	2	8	0.98 [0.93, 1.00]	0.73 [0.39, 0.94]
Brown 1979	68	0	5	12	0.93 [0.85, 0.98]	1.00 [0.74, 1.00]
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]
Derrick 1994	228	1	1	10	1.00 [0.98, 1.00]	0.91 [0.59, 1.00]
Gordon 1984	68	1	9	63	0.88 [0.79, 0.95]	0.98 [0.92, 1.00]
Powell 2000	20	2	2	13	0.91 [0.71, 0.99]	0.87 [0.60, 0.98]
Ruocco 1992	494	6	4	74	0.99 [0.98, 1.00]	0.93 [0.84, 0.97]

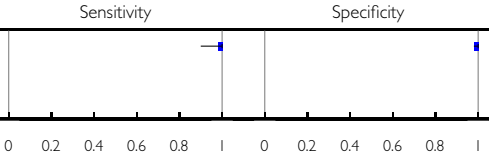


Test 3. Exfoliative cytology - BCC (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 3 Exfoliative cytology - BCC (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Durdu 2011	34	0	0	151	1.00 [0.90, 1.00]	1.00 [0.98, 1.00]

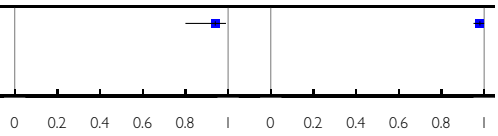


Test 4. Dermoscopy - BCC (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 4 Dermoscopy - BCC (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Durdu 2011	32	3	2	163	0.94 [0.80, 0.99]	0.98 [0.95, 1.00]		

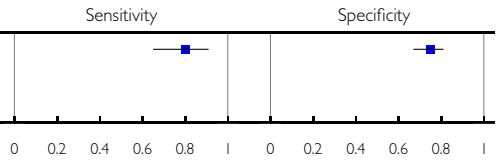


Test 5. Exfoliative cytology - BCC (mixed population, Munchener diagnostic criteria).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 5 Exfoliative cytology - BCC (mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Nauth 1988	33	42	8	123	0.80 [0.65, 0.91]	0.75 [0.67, 0.81]		

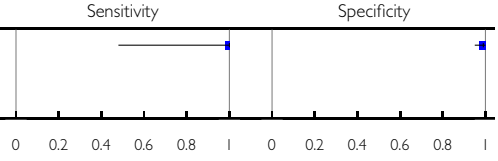


Test 6. Exfoliative cytology - cSCC (suspected BCC population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 6 Exfoliative cytology - cSCC (suspected BCC population)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Gordon 1984	5	2	0	134	1.00 [0.48, 1.00]	0.99 [0.95, 1.00]		



Test 7. Exfoliative cytology - cSCC (mixed population, Munchener diagnostic criteria).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 7 Exfoliative cytology - cSCC (mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Nauth 1988	32	43	4	127	0.89 [0.74, 0.97]	0.75 [0.67, 0.81]		

Test 8. Exfoliative cytology - melanoma (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 8 Exfoliative cytology - melanoma (pigmented lesion population)

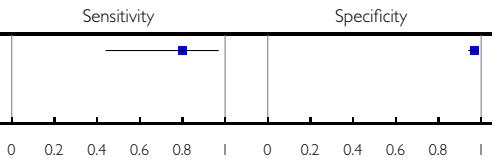
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Durdu 2011	10	0	0	175	1.00 [0.69, 1.00]	1.00 [0.98, 1.00]		

Test 9. Dermoscopy - melanoma (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 9 Dermoscopy - melanoma (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Durdu 2011	8	5	2	185	0.80 [0.44, 0.97]	0.97 [0.94, 0.99]

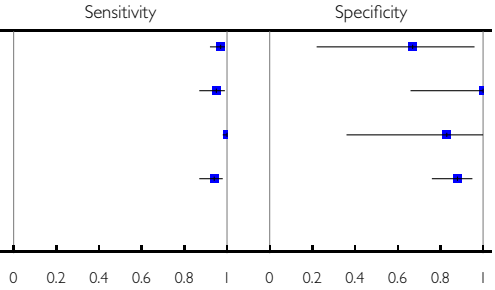


Test 10. Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test positives).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 10 Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test positives)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berner 1999	98	2	3	4	0.97 [0.92, 0.99]	0.67 [0.22, 0.96]
Brown 1979	72	0	4	9	0.95 [0.87, 0.99]	1.00 [0.66, 1.00]
Derrick 1994	233	1	1	5	1.00 [0.98, 1.00]	0.83 [0.36, 1.00]
Gordon 1984	79	7	5	50	0.94 [0.87, 0.98]	0.88 [0.76, 0.95]

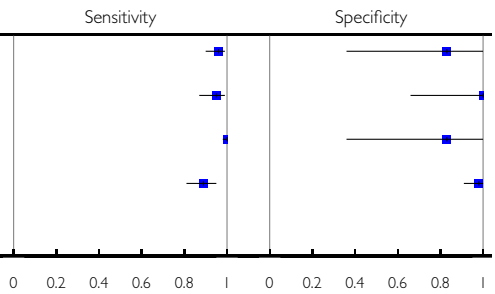


Test 11. Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test negatives).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 11 Exfoliative cytology - any skin cancer (suspected BCC population, possible BCCs classified as test negatives)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berner 1999	97	1	4	5	0.96 [0.90, 0.99]	0.83 [0.36, 1.00]
Brown 1979	72	0	4	9	0.95 [0.87, 0.99]	1.00 [0.66, 1.00]
Derrick 1994	233	1	1	5	1.00 [0.98, 1.00]	0.83 [0.36, 1.00]
Gordon 1984	75	1	9	56	0.89 [0.81, 0.95]	0.98 [0.91, 1.00]

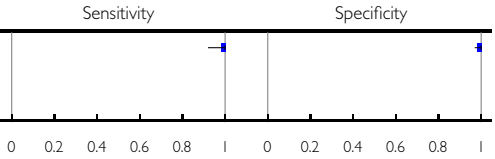


Test 12. Exfoliative cytology - any skin cancer (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 12 Exfoliative cytology - any skin cancer (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Durdu 2011	46	0	0	139	1.00 [0.92, 1.00]	1.00 [0.97, 1.00]

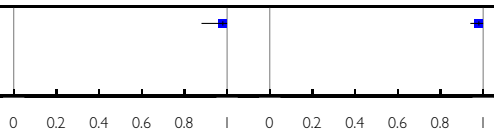


Test 13. Dermoscopy - any skin cancer (pigmented lesion population).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 13 Dermoscopy - any skin cancer (pigmented lesion population)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Durdu 2011	45	3	1	151	0.98 [0.88, 1.00]	0.98 [0.94, 1.00]		

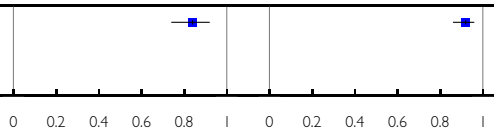


Test 14. Exfoliative cytology - any skin cancer (mixed population, Munchener diagnostic criteria).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 14 Exfoliative cytology - any skin cancer (mixed population, Munchener diagnostic criteria)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Nauth 1988	65	10	12	119	0.84 [0.74, 0.92]	0.92 [0.86, 0.96]		

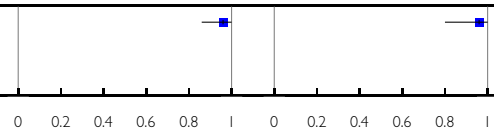


Test 15. Exfoliative cytology (Papanicolaou + MGG stain) - BCC (stain comparison).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 15 Exfoliative cytology (Papanicolaou + MGG stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Christensen 2008	48	1	2	25	0.96 [0.86, 1.00]	0.96 [0.80, 1.00]		

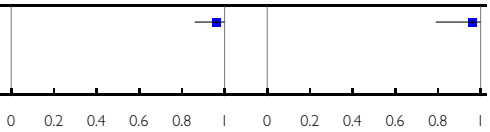


Test 16. Exfoliative cytology (MGG stain) - BCC (stain comparison).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 16 Exfoliative cytology (MGG stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Christensen 2008	47	1	2	23	0.96 [0.86, 1.00]	0.96 [0.79, 1.00]		

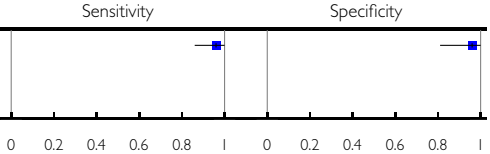


Test 17. Exfoliative cytology (Papanicolaou stain) - BCC (stain comparison).

Review: Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

Test: 17 Exfoliative cytology (Papanicolaou stain) - BCC (stain comparison)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Christensen 2008	48	1	2	26	0.96 [0.86, 1.00]	0.96 [0.81, 1.00]		



ADDITIONAL TABLES

Table 1. Test failures due to insufficient cellular material

Study	Stain technique	Slides with inadequate material n (%)	Histological diagnosis
Gordon 1984	Papanicolaou	9 (6)	BCC: 1 cSCC: 1 Actinic keratosis: 7
Christensen 2008[a]	Papanicolaou	1 (1)	Actinic keratosis: 1
	MGG	3 (4)	BCC: 1 Actinic keratosis: 2
Durdu 2011	MGG	15 (8)	Melanocytic benign: 6 Non-melanocytic benign: 9
Nauth 1988	Papanicolaou	18 (8)	BCC: 1 cSCC: 2 Severe precancerous disease: 2 Mild precancerous disease: 6 Benign tumour: 5 Inflammation: 2

BCC: basal cell carcinoma; **cSCC**: cutaneous squamous cell carcinoma; **MGG**: May-Grünwald Giemsa stain technique.
[a]When diagnosis was made using both Papanicolaou and MGG stained slides, all lesions could be diagnosed cytologically

Table 2. Summary of main results

Analysis	Target condition Test	No. studies	Lesions with cytology results (n)	Diseased lesions (n)	Sensitivity (95% CI)	Specificity (95% CI)
Detection of basal cell carcinoma (BCC)						
All studies	Studies with cases of BCC	9	1655	1120	-	-
Pooled studies	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test positive)	7	1264	1045[a]	97.5 (94.5 to 98.9)	90.1 (81.1 to 95.1)

Table 2. Summary of main results (*Continued*)

-	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test negative)	7	1264	1045[a]	97.3 (93.5 to 98.9)	94.2 (88.7 to 97.1)
Studies not pooled		2	391	75	-	-
-	Nauth 1988: different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	41[b]	80.5 (66.0 to 89.8)	74.6 (67.4 to 80.6)
-	Durdu 2011: different patient group - pigmented skin lesions (exfoliative cytology)	1	185[c]	34	100 (89.9 to 100)	100 (97.5 to 100)
-	Durdu 2011: different patient group - pigmented skin lesions (dermoscopy)	1	200	34	94.1 (80.9 to 98.4)	98.2 (94.8 to 99.4)
Detection of cutaneous squamous cell carcinoma (cSCC)						
All studies	Studies with cases of cSCC	6	1357	52	-	-
Studies not pooled		2	401	41[d]	-	-
-	Gordon 1984: standard cytological criteria used to confirm disease in participants with clinical suspicion	1	141	5[e]	100 (56.6 to 100)	98.5 (94.8 to 99.6)

Table 2. Summary of main results (*Continued*)

	of BCC					
-	Nauth 1988: different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	36[f]	88.9 (74.7 to 95.6)	74.7 (67.7 to 80.6)
Studies not included in dataset	< 5 cSCC cases	4	1010	11	-	-
Detection of invasive melanoma and atypical intraepidermal melanocytic variants (MM)						
All studies	Studies with cases of MM	2	270	11	-	-
Studies not pooled		1	185[c]	10	-	-
-	Durdu 2011: different patient group - pigmented skin lesions (exfoliative cytology)	1	185[c]	10	100 (72.3 to 100)	100 (97.6 to 100)
-	Durdu 2011: different patient group - pigmented skin lesions (dermoscopy)	1	200	10	80.0 (49.0 to 94.3)	97.4 (94.0 to 98.9)
Studies not included in dataset	< 5 MM cases	1	85	1	-	-
Detection of any potential skin cancer (BCC or other skin cancer)						
All studies	Studies with any skin cancer lesions	9	1655	1200	-	-
Pooled studies	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possi-	4	573	495	97.3 (93.5 to 98.9)	86.0 (73.5 to 93.1)

Table 2. Summary of main results (*Continued*)

	ble BCC' cases classified as BCC test positive)					
-	Standard cytological criteria used to confirm disease in participants with clinical suspicion of BCC ('possible BCC' cases classified as BCC test negative)	4	573	495	96.6 (90.3 to 98.9)	94.7 (80.2 to 98.7)
Studies not pooled		2	391	123	-	-
-	Nauth 1988: different diagnostic criteria - Munchener scheme (class V = malignant)	1	206	77[g]	84.4 (74.7 to 90.9)	92.3 (86.3 to 95.7)
-	Durdu 2011: different patient group - pigmented skin lesions (exfoliative cytology)	1	185[c]	46	100 (92.3 to 100)	100 (97.3 to 100)
-	Durdu 2011: different patient group - pigmented skin lesions (dermoscopy)	1	200	46	97.8 (88.7 to 99.6)	98.1 (94.4 to 99.3)
Studies not included in dataset	No skin cancer other than BCC (Christensen 2008; Powell 2000)	2	113	72	-	-
-	Data not reported (Ruocco 1992)	1	578	507	-	-

BCC: basal cell carcinoma; CI: confidence interval; cSCC: cutaneous squamous cell carcinoma; MM: invasive melanoma and atypical intraepidermal melanocytic variants.
[a] Two additional BCC lesions could not be analysed by exfoliative cytology, due to insufficient cell material.
[b] 1/42 BCC lesions could not be analysed by exfoliative cytology, due to insufficient cell material.
[c] From a total population of 200 lesions (15 excluded from exfoliative cytology analysis due to insufficient cell material, all 200 examined by dermoscopy).
[d] 3/44 cSCC lesions could not be analysed by exfoliative cytology, due to insufficient cell material.
[e] 1/6 cSCC lesions could not be analysed by exfoliative cytology, due to insufficient cell material.
[f] 2/38 cSCC lesions could not be analysed by exfoliative cytology, due to insufficient cell material.
[g] 3/80 lesions could not be analysed by exfoliative cytology, due to insufficient cell material.

Table 3. Exfoliative cytology for the detection of BCC: false positive diagnoses

Study	False positive n (%)	Histological diagnosis
Berner 1999	5 (4.6)	Carcinoma, type not specified: 3 atypia: 2
Brown 1979	0 (0)	-
Christensen 2008[a]	1 (1.3)	Actinic keratosis: 1
Derrick 1994	1 (0.4)	Trichoepithelioma: 2
Durdu 2011	0 (0)	-
Gordon 1984	7 (5.0)	Actinic keratosis: 1 Marked atypia: 4 Sebhorroeic keratosis: 2
Nauth 1988	18 (8)	BCC: 1 cSCC: 2 Severe precancerous disease: 2 Mild precancerous disease: 6 Benign tumour: 5 Inflammation: 2
Powell 2000	2 (5.4)	Bowenoid actinic keratosis: 1 Bowen's disease: 1
Ruocco 1992	6 (1)	Trichoepithelioma: 3 Syringocystadenoma papilliferum: 2 Pilomatricoma: 1

BCC: basal cell carcinoma; **CI**: confidence interval; **cSCC**: cutaneous squamous cell carcinoma.
[a] Diagnosis made using both Papanicolaou and May-Grünwald Giemsa stained slides

APPENDICES

Appendix 1. Current content and structure of the Programme Grant

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

(*Continued*)

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

Appendix 2. Glossary of terms

Term	Definition
Acantholytic subtypes	An uncommon squamous cell carcinoma variant characterised by acantholysis, which is the marked disruption of intercellular connections and resulting separation of epidermal cells
Arborizing blood vessels	Blood vessels in the skin that form a tree-like branching appearance. They can be a sign of basal cell carcinomas
Atypical honeycombing	This pattern arises from variation in size and shape of keratinocytic nuclei and irregular cell borders of keratinocytes in the spinous-granular epidermal layer. It is a feature of actinic keratosis and squamous cell carcinoma on optical coherence tomography and on reflective confocal microscopy examination
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma *in situ* and lentigo maligna
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin
Atypical pleomorphic keratinocytes	Abnormal skin cells of different shapes and sizes, a feature visible on histopathology
Axial resolution	Axial resolution describes the ability of an OCT system to distinguish between two points in space that lie in the direction parallel to the light beam
Basaloid cells	Cells in the skin that look like those in epidermal basal layer
BRAF V600 mutation	BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. BRAF mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs
BRAF inhibitors	Therapeutic agents which inhibit the serine-threonine protein kinase BRAF mutated metastatic melanoma
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour
Congenital naevi	A type of mole found on infants at birth

(*Continued*)

Dermoscopy	Whereby a handheld microscope is used to allow more detailed, magnified, examination of the skin compared to examination by the naked eye alone
Dermo-epidermal junction	The area where the lower part of the epidermis and top layer of the dermis meet
Dermal nests	Collections of pigment cells that are bunched together in the dermis
Dermal papilla	Small projections of the dermis into the overlying epidermis giving an undulating pattern and visible as "fingerprints" in hands and feet
Dermis	Layer of skin below the epidermis, composed of living tissue and containing blood capillaries, nerve endings, sweat glands, hair follicles and other structures
Desmoplastic subtypes of SCC	An aggressive squamous cell carcinoma variant characterised by a proliferation of fibroblasts and formation of fibrous connective tissue
Electrodessication	The use of high-frequency electric currents to cut, destroy or cauterise tissue. It is performed with the use of a fine needle-shaped instrument
Epidermis	Outer layer of the skin
False negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free
False positive	An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease
Fibrotic septa	Excess fibrous connective tissue formation separating other parts of tissue
Grey-blue ovoid nests and globules	Grey-blue coloured oval shaped areas seen under dermoscopy that may represent basal cell carcinomas
Histopathology/Histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope
Hypertrophic actinic keratosis	Precancerous scaly patches of skin that are particularly thickened
Hypoechogenic	Displaying lower echogenicity reflecting and appears darker on ultrasonography
Incidence	The number of new cases of a disease in a given time period.
Index test	A diagnostic test under evaluation in a primary study
Inflammatory dermatoses	Skin conditions where the main disease process is inflammatory, often involving immune cells, as apposed to malignant or infectious processes. The inflammatory process may be due to internal or external factors

(*Continued*)

Interferometry	The measurement of waves of light or sound after interference in order to extract information
Interfollicular epidermis	The part of the epidermis that lies in between the hair follicles
Junctional nests	Collections of pigment cells bunched up around the junction between the epidermis and dermis
Lateral resolution	Lateral resolution describes the ability of an OCT system to distinguish between two points in space that lie in a perpendicular direction to the light beam
Lentigo maligna	Unusual area of darker pigmentation contained within the epidermis which includes malignant cells but with no invasive growth. May progress to an invasive melanoma
Lymph node	Lymph nodes filter the lymphatic fluid (clear fluid containing white blood cells) that travels around the body to help fight disease; they are located throughout the body often in clusters (nodal basins)
Melanocytic naevus	An area of skin with darker pigmentation (or melanocytes) also referred to as 'moles'
Meta-analysis	A form of statistical analysis used to synthesise results from a collection of individual studies
Metastases/metastatic disease	Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system
Micrometastases	Micrometastases are metastases so small that they can only be seen under a microscope
Mitotic activity	Relates to the presence of proliferating cells and used as an index of tumour aggressiveness
Mitotic rate	Microscopic evaluation of number of cells actively dividing in a tumour
Morbidity	Detrimental effects on health
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1000, 10,000 or 100,000 people
Multidisciplinary team	A team with members from different healthcare professions and specialties (e. g. urology, oncology, pathology, radiology, and nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient

(*Continued*)

Naevus	A mole or collection of pigment cells (plural: naevi or nevi)
Nuclear dysplasia and mitoses	A histopathological term referring to abnormal nuclei with increased mitotic activity and nuclear size associated with disordered nuclear dysplasia and mitoses cell growth
Nucleated	The presence of a nuclei within a cell, which contain most of the cell's genetic material
Pagetoid cells	Abnormal pigment cells that spread upwards through the epidermis
Papillary dermis	Also called the 'upper dermis', this is the uppermost layer of the dermis that connects to the dermal-epidermal junction
Peripheral palisading	A histopathological term referring to the wall-like appearance of cells around a central focus
Pleomorphic	Variability in size or shape
Polygonal cells	Skin cells that appear to have many sides, such as taking up a pentagonal, hexagonal or octagonal appearance
Prevalence	The proportion of a population found to have a condition.
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it which might affect the patient's prognosis
Receiver operating characteristic (ROC) plot	A plot of the sensitivity and 1 minus the specificity of a test at the different possible thresholds for test positivity; represents the diagnostic capability of a test with a range of binary test results
Receiver operating characteristic (ROC) analysis	The analysis of a ROC plot of a test to select an optimal threshold for test positivity
Recurrence	Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body
Reference Standard	A test or combination of tests used to establish the final or 'true' diagnosis of a patient in an evaluation of a diagnostic test
Reflectance confocal microscopy (RCM)	A microscopic technique using infrared light (either in a handheld device or a static unit) that can create images of the deeper layers of the skin
Resolution	Resolution in an imaging system refers to its ability to distinguish two points in space as being separate points; resolution is measured in two directions: axial and lateral

(*Continued*)

Rete ridges	Also called 'epidermal ridges' or 'epidermal pegs', they represent downward projections of the epidermis into underlying connective tissue
Reticular dermis	Also called the 'lower dermis', the reticular dermis is the lower layer of the dermis, located under the papillary dermis
Sensitivity	In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test
Specificity	The proportion of individuals without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Spindle subtypes of SCC	A squamous cell carcinoma variant characterised by poorly differentiated spindle cells surrounded by collagenous stroma
Spinous-granular layer	One of several layers of the epidermis, which is the outermost layer of skin. The nuclei of keratinocytes, which contain most of the cell's genetic material are found here
Staging	Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories
Stratum corneum	The outermost layer of the epidermis. This layer is the most superficial layer of skin, which is composed of flattened skin cells organised like a brick wall. In normal conditions cells are not nucleated at this layer
Stromal reaction	Change in connective tissue microenvironment
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination
Superficial fine telangiectasia	Fine dilated blood vessels of small/varying diameter located in the superficial dermis
Targetoid hair follicles	The presence of yellow keratotic follicular plugs surrounded by a white rim on dermoscopy, more frequently known as "white circle", which can be a characteristic of squamous cell carcinoma

Appendix 3. Table of Acronyms

7PCL	seven point checklist
ABCD(E)	asymmetry, border, colour, differential structures (enlargement)
AHM	amelanotic or hypomelanotic melanoma
AK	actinic keratosis
AMN	atypical melanocytic naevi
AUC	Area under the curve
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
DF	dermatofibroma
Dx	diagnosis
ELM	epiluminescence microscopy
FN	false negative

(*Continued*)

FP	false positive
FU	follow- up
GP	general practitioner
H&E	haematoxylin and eosin stain
LPLK	lichen planus- like keratosis
LS	lentigo simplex
MiS	melanoma in situ (or lentigo maligna)
MM	malignant melanoma
MN	melanocytic naevi
N/A	not applicable
NC	non comparative
NMLs	non melanocytic lesions
NPV	negative predictive value
NR	not reported
P	prospective
PCPs	primary care providers
PLC	pigmented lesion clinic
PPV	positive predictive value
PSL	pigmented skin lesion
R	retrospective
RCM	reflectance confocal microscopy
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SD	standard deviation

(*Continued*)

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
TWR	two week rule
VI	visual inspection
WPC	within person comparison (of tests)
WPC-algs	within person comparison (of algorithms)

Appendix 4. Proposed sources of heterogeneity

i. Population characteristics

- general versus higher risk populations
- patient population: primary /secondary / specialist unit
- degree of prior clinical suspicion (highly suspicious vs. challenging/equivocal lesions)
- disease prevalence (high vs low)
- 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

iii. Reference standard characteristics

- 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
- use of an adequate reference standard
- overall risk of bias

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

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

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

Search strategy:

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

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

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

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

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

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

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

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

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

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

#18 #10 AND #17
Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

Appendix 6. Full text inclusion criteria

The table below summarises the inclusion criteria applied to each study.

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

(*Continued*)

	• High-frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other **For staging** • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology FNAC • SLNB +/high-frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	
Reference standard	**For diagnostic studies** • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) **For studies of imaging tests for staging** • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above **For studies of SLNB accuracy for staging** • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	**For diagnostic studies** • Exclude if any disease positive participants have diagnosis unconfirmed by histology • Exclude if > 50% of disease negative participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e. comparing referral decision with expert diagnosis, unless evaluations of teledermatology or mobile phone applications

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

Appendix 7. Quality assessment (based on QUADAS-2)

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

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, 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, 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. We considered studies that did not clearly describe the threshold used but required clinicians to record a diagnosis or management decision for a lesion to be unclear on this criterion. We deemed 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 to be at high risk of bias.

In terms of applicability of the index test to the review question, we required exfoliative cytology to be applied and interpreted as it would be in a clinical practice setting.

- Sample obtained by dragging scalpel/curette across lesion, possibly after removal of crust.
- Material spread directly on to a slide and wet-fixed or air-dried.
- At least one slide stained with either Pap or MGG (Romanowsky) stain

Rapid staining methods were also acceptable; however, studies were considered to be of high concern for clinical applicability if interpretation of cytology slides was made without access to the clinical referral information.

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 of skin cancer, particularly where established algorithms or checklists were not used. Studies were considered of low concern if the threshold used was established in a prior study or sufficient threshold details were presented to allow replication.

The experience of the examiner will also impact on the applicability of study results. We required studies to describe the test interpreter as 'experienced' or 'expert' in exfoliative cytology 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. 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 exfoliative cytology, this item was divided into two questions, firstly whether the reference standard was blinded to the index test result (exfoliative cytology), and secondly whether it was blinded to the clinical diagnosis. Only the response to the first part (i.e. blinding to exfoliative cytology) 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.

In assessing whether all patients were included in the analysis, we considered studies at high risk of bias if participants were excluded following recruitment for any reason other than due to inadequate collection of cellular material for cytological analysis ('test failures').

Comparative domain

A comparative domain was added to the QUADAS-2 checklist for studies comparing the accuracy of exfoliative cytology 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 exfoliative cytology 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

(*Continued*)

2) Was a case-control design avoided?	**Yes** - if consecutive or random or case-control design clearly not used **No** - if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** - if not described
3) Did the study avoid inappropriate exclusions, e.g. • 'difficult to diagnose' lesions not excluded • lesions not excluded on basis of disagreement between evaluators	**Yes** if inappropriate exclusions were avoided **No** - if lesions were excluded that might affect test accuracy, e. g. 'difficult to diagnose' lesions, or where disagreement between evaluators was observed **Unclear** - if not clearly reported but there is suspicion that difficult to diagnose lesions may have been excluded
4) For between-person comparative studies only (i.e. allocating different tests to different study participants): • **A)** were the same participant selection criteria used for those allocated to each test? • **B)** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C)** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	**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, NA - 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), NA - 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), NA - 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	

(*Continued*)

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

(*Continued*)

2) Was the diagnostic threshold at which the test was considered positive 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 NA - 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 test applied and interpreted in a clinically applicable manner?	**Yes** - sample of cells was obtained by dragging a scalpel/curette across the lesion, after removal of any crust, material was spread directly onto a slide and wet-fixed or air-dried, at least one slide was stained using either Pap or MGG technique, or a rapid staining method **No** - not all of the above were carried out OR interpretation was blinded to clinical diagnosis **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 were reported in sufficient detail to allow replication **No** - if the criteria for diagnosis 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
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

(*Continued*)

	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 NA - 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 malignancy 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 skin cancer **B) Disease-negative** - 1 or more of the following: • histological confirmation of absence of malignancy 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 malignancy underwent 1 of the listed reference standards **No** - If a final diagnosis of malignancy 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 malignancy 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

(*Continued*)

Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1) 'Yes' 2. If answer to question 1) 'No' 3. If answer to question 1) 'Unclear' **For all other tests** 1. If answers to questions 1) and 2) 'Yes' 2. If answers to questions 1) or 2) 'No' 3. If answers to questions 1) or 2) 'Unclear'	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
REFERENCE STANDARD (3) CONCERN ABOUT APPLICABILITY	
1) Expert opinion (with no histological confirmation) was not used as a reference standard 'Expert opinion' means diagnosis based on the standard clinical examination, with no histology or lesion follow-up	**Yes** - if expert opinion was not used as a reference standard for any participant **No** - if expert opinion was used as a reference standard for any participant **Unclear** - if not clearly reported
2) Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	**Yes -** if histology interpretation was reported to be carried out by an experienced histopathologist or dermatopathologist **No -** if histology interpretation was reported to be carried out by a less experienced histopathologist **Unclear** - if the experience/qualifications of the pathologist were not reported
Is there concern that the target condition as defined by the reference standard does not match the review question? 1. If answers to both questions 1), 2), 'Yes': 2. If answers to any 1 of questions 1), 2), 'No': 3. If answers to any 1 of questions 1), 2), 'Unclear':	1. Concern is low 2. Concern is high 3. Concern is unclear
FLOW AND TIMING (4): RISK OF BIAS	
1) Was there an appropriate interval between index test and reference standard? **A)** For histopathological reference standard, was the interval between index test and reference standard ≤ 1 month? **B)** If the reference standard includes clinical follow-up of borderline/benign-appearing lesions, was there at least 3 months' follow-up following application of index test(s)?	**A)** **Yes** - if study reports ≤ 1 month between index and reference standard **No** - if study reports > 1 month between index and reference standard **Unclear** - if study does not report interval between index and reference standard **B)** **Yes** - if study reports ≥ 3 months' follow-up **No** - if study reports < 3 months' follow-up **Unclear** - if study does not report the length of clinical follow-up
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

(*Continued*)

	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

Appendix 8. Summary of studies

Study, Outcomes reported	Study type	Inclusion criteria Exclusions	No. patients (lesions)	Lesion site	Stain technique	Cytopathological criteria	Uncertain cytological diagnoses	Observer qualifications (n) Test experience	Test failures	Reference standard Final diagnosis
Berner 1999 BCC Any	NC P-CS Norway	Lesions clinically suspected of being nodular BBCs, located on the head, thorax or abdomen Excluded:	90 (107)	Head, face, thorax, abdomen (%s NR)	Diff-Quick	Presence of small dissociated hyperchromatic cells in cohesive sheets. The cells have scanty cytoplasm,	2 ?BCC	Cytopathologist (n = 3) NR	Excluded at study entry	Histology alone (shave biopsy) BCC 96 cSCC 1; carcinoma - NS 4; atypia 3; benign 3

(*Continued*)

		Thickness < 2 mm, inadequate cellular material for cytological or histological evaluation				indistinct cell borders and the cohesive sheets often demonstrate palisading				
Brown 1979 BCC Any	NC NR-CS UK	Localised lesions for which a histological diagnosis was required to confirm clinical diagnosis of BCC, or in a minority to exclude BCC Exclusions not reported	81 (85)	NR	MGG or rapid stain with aqueous toluidine blue	BCC: tumour cells occur dispersed and in small clusters and large clusters with a lobulated outline; mostly of uniform size and shape, having very little cytoplasm, an oval nucleus with a smooth outline, and evenly dispersed, finely dotted chro-	0	NR (n = NR) NR	0	Histology (biopsy) plus other in selected (expert opinion, 2/81) BCC 73 cSCC 2; MM 1; SK 5; AK 4

(*Continued*)

						matin, sometimes with one or two small distinct nucleoli; The squamous tumour cells are similar in size to prickle layer cells and typically are uniform in size and occur as irregular clusters or as small nests distinct from the squamous cells of the epidermis; most tumours were uniform in size and cytological detail with only occasional				

(*Continued*)

						very large or very small forms. cSCC: cells are larger though more varied in size and outline; nuclear chromatin shows irregular clumping, nucleoli are often very conspicuous, while some heavily keratinised cells retain a densely staining, pyknotic nucleus				
Christensen 2008 BCC	NC CCS Norway	Histologically confirmed BCC or AK lesions Excluded: other diagnoses	64 (78)	H/N (56, 72%), trunk (15, 19%), extremities (7, 9%)	3 slides per lesion: Pap MGG Touch Imprint (not eval)	Fragments of closely packed cells presenting in monolayers or club-like formations, demonstrating	0	Pathologist (n=2) "Extensive experience in cytology, but no specific training in skin scrape cytology"	Pap - 1 MGG - 3	Histology (punch biopsy) BCC 50 AK 28

(*Continued*)

						smooth external contours and peripheral palisading of nuclei. Little dissociation of cells. Malignant basal cells have small, oval, hyperchromatic nuclei. Extremely high nucleus to cytoplasmic ratio. AK lesions - greater cellular dissociation, individual and clumps of dysplastic keratinocytes, often with ragged edges. Polyhedral or spindle-				

(*Continued*)

						shaped configuration. Moderately high nucleus to cytoplasmic ratio				
Derrick 1994 BCC	NC NR-CS UK	Lesion on the head or neck clinically suspected of being BCC Excluded: lesions on the trunk or extremities	240 (240)	H/N (% NR)	MGG	Presence of tight groups of uniform small cells; pink amorphous material in MGG-stained preparations. Squamous cell lesions showed less cellular adhesion, much more nuclear pleomorphism and no pink material	0	Consultant pathologist (NR) NR	0	Histology (punch biopsy + excision when cytology and histopathology discordant, n = 4) BCC 229 cSCC 4; AC 1; AK 1; BD 1; trichoepithelioma 1; No abnormality 3
Gordon 1984 BCC cSCC Any	NC P-CS Australia	Cutaneous neoplasm requiring diagnostic biopsy or definitive excision at a	112 (150)	NR	Pap	BCC characteristics: cohesive epithelial fragments composed of	10 4 BCC 4 matypia 2 SK	Cytologist (1) NR	9 1 BCC 1 cSCC 7 benign	Histology (biopsy or excision) BCC 78 cSCC 6; marked squa-

(*Continued*)

		routine clinic. Exclusions: suspected malignant melanoma or lesions that were 'too small' to allow both cytologic and histopathologic assessment				tightly packed small cells with uniform, oval, dark nuclei. The nuclear chromatin is dense, but granular and evenly distributed; nucleoli are small and indistinct. Cytoplasm is scanty and cyanophili Usually, some fragments show the marginal palisading arrangement of tumor cells familiar to the histopathologist. Squamous differen-				mous atypia 4; AK 53; SK 9

(*Continued*)

						tiation may be present within BCC (keratotic BCC and metatypical epithelioma). When this is prominent and associated with nuclear enlargement and pleomorphism, the cytologic differentiation between cSCC and pleomorphic BCC is difficult or impossible. Strong cohesiveness, uniformly high nuclear/cytoplasmic ratio, and evenly dis-				

(*Continued*)

						tributed nuclear chromatin favor a diagnosis of pleomorphic BCC				
Powell 2000 BCC	NC R-CS UK	All cytology smears taken over a 9-month period Excluded: no histological specimen available	30 (37)	NR	NR	Not described	0	NR (NR) NR	0	Histology (type NR)
Ruocco 1992	NC R-CS Italy	Patients with a suspected clinical diagnosis of BCC, for whom cytology and histology test results available. Exclusions: insufficient material for histology or cytology diagnosis, patient	NR (578)	NR	MGG and Pap or pure Giemsa	Characteristics suggestive of BCC: basaloid cells arranged in groups, clumped in the centre and at times arranged as 'fences/ palisades' around the periphery (as found in histological	0	NR (NR) NR	Excluded at study entry	Histology (excision or biospy) BCC 498 cSCC 4; 5 other malignant: 3 cutaneous metastasis from visceral malignancy, 2 Merkel cell carcinoma Benign

(*Continued*)

		undergoing treatment (diathermal coagulation, cryotherapy, radiotherapy, local chemotherapy with 5-fluorouracil or interferon a-2b) or treated elsewhere				specimens), slightly increased compared to normal epidermal basal keratinocytes, but in a single dimension, with an elongated shape, oval nucleus, intensely basophilic, occupying 4/5 of the entire cell with weak/thin cytoplasm, sometimes containing coarse melanin granules				diagnoses: 11 SK; 4 LED, 3 trichoepithelioma, 2 syringocystadenoma papilliferum, 19 AK, 8 senile sebaceous hyperplasia, 6 Bowen's disease, 4 keratoacanthoma, 3 molluscum contagiosum, 3 psoriasis, 2 lichen planus, 2 localised scleroderma, 1 sebaceous adenoma, 1 cylindroma, 1 pilomatricoma, 1 nevocytic nevus
Durdu 2011 BCC MM alone Any	WPC P-CS Turkey	Pigmented skin lesions that could not be diagnosed	176 (200)	NR	MGG	Cytologic diagnoses were made according to findings	0	Dermatologist (n = 1) single observer	15	Histology (excision-166, or punch biopsy-34)

(*Continued*)

		with only dermatologic physical examination No exclusions reported				reported previously: Pigmented BCC: clusters of basaloid cells containing pigment granules. Melanoma epithelioid or spindle-type atypical nevoid cells. Pigmented mammary Paget's disease: clusters of round to ovoid Paget cells Metastatic carcinoma: atypical (non-keratinocytic and non-nevoid) cells Melanocyt naevi:				BCC 34 Melanoma 10; 2 other malignant: 1 pigmented mammary Paget's disease; 1 pigmented metastatic mammary carcinoma; SK 24; benign melanocytic nevus 100; other benign non-melanocytic lesions 30

(*Continued*)

						epidermal and dermal-type nevoid cells. Seborrhoeic keratosis: horny cysts, pigmented keratinocytes. Warts: koilocytes Dermatofibroma: spindle-shaped fibroblasts with collagenised stroma				
Nauth 1988 BCC cSCC Any	NC CCS Germany	NR No exclusions reported	224 (224)	NR	Pap	(A) Orthokeratosis cell: small, homogeneous of polygonal shape (B) Parakeratosis cell: nuclear polygonal horn cell, about twice as large as an orthokeratosis cell (C) Slightly	13 BCC and 18 cSCC classified as anaplasia	NR (NR) NR	18	Histology (punch biospy, n-210) or other (NR-14 lesions with inflammatory conditions) BCC: 42 cSCC: 38; severe dysplasia 34; marked dysplasia 31; in-

(*Continued*)

						dyskeratotic cell: slightly polymorphic nucleated horn cell, about three times the size of an orthokeratosis cell with a cell nucleus of about twice the size of a parakeratosis cell. Slightly elevated nuclear plasma ratio (D) Massively dyskeratotic cell: polymorphic nucleated horny cell, somewhat smaller than a parakeratosis cell with a nucleus three				flammation 28; benign (not reported) 51

(*Continued*)

						times the size of a parakeratose cell. Significantly increased core-plasma ratio. (E) Severely dyskeratotic cell: highly polymorphic horny cell, approx. as large as an orthokeratose cell, with a cell nucleus approximately the same size as a moderately dyskeratotic cell. As a result, only slightly or not increased core plasma ratio (F)				

(*Continued*)

						Anaplastic tumor cells: small degraded, mostly basophilic or chromophobic cell with roundish plasma and a large round nucleus that has an atypical chromatin structure and often a prominent nucleolus				

AC: apocrine carcinoma; **AK**: actinic keratosis; **BCC**: basal cell carcinoma; **?BCC**: possible basal cell carcinoma; **BD**: Bowen's disease; **CCS**: case-control study; **cSCC**: cutnaeous squamous cell carcinoma; **H/N**: head and neck; **LED**: disease type, acronym not provided by study; **m-atypia**: marked squamous atypia; **MGG**: May-Grünwald Giemsa stain technique; **MM**: invasive melanoma and atypical intraepidermal melanocytic variants; **NC**: non-comparative study design; **NR**: not reported; **NR-CS**: case series data collection method not reported; **NS**: not specified; **Pap**: Papanicolaou stain technique; **P-CS**: prospective case series; **R-CS**: restrospective case series; **SK**: seborrhoeic keratosis; **WPC**: within-person comparison study design.

CONTRIBUTIONS OF AUTHORS

JDi was the contact person with the editorial base.

SB was the information specialist and performed the review searches.

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

All authors reviewed and contributed to the final draft.

JDi and NC screened papers against eligibility criteria.

LFR obtained data on ongoing and unpublished studies.

LFR and JDi appraised the quality of papers.

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

LFR entered data into RevMan.

YT, LFR and JDi analysed and interpreted data.

LFR, JDi and YT worked on the Methods sections.

LFR drafted the clinical sections of the background and responded to the clinical comments of the referees.

LFR responded to the methodology and statistics comments of the referees.

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

JDi is the guarantor of the update.

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DECLARATIONS OF INTEREST

Lavinia Ferrante di Ruffano: none known.

Jac Dinnes: none known.

Naomi Chuchu: none known.

Susan E Bayliss: none known.

Yemisi Takwoingi: none known.

Clare Davenport: none known.

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

We changed the primary target condition and primary objective from the detection of BCC and cSCC (as per our generic protocol for the detection of keratinocyte skin cancer (Dinnes 2015b) to the detection of BCC, since exfoliative cytology has a clearer potential role for this condition.

We added secondary target conditions, including cSCC, and cutaneous invasive melanoma and atypical intraepidermal melanocytic variants (from our generic protocol for the detection of melanoma (Dinnes 2015a)).

We have tailored secondary objectives to the individual test, with two objectives added for each primary and secondary target condition: to compare the accuracy of exfoliative cytology to dermoscopy where both tests have been evaluated in the same studies; and to determine the effect of observer experience. Sources of heterogeneity that could be investigated were restricted due to lack of data.

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

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 the volume of evidence retrieved from database searches and time restrictions, we were unable to do this.

For quality assessment, we further tailored the QUADAS-2 tool according to the review topic. In terms of analysis, we did not restrict analysis to per patient data due to lack of data. For the same reason, we did not perform the planned sensitivity analyses.