NICE National Institute for Health and Care Excellence

Diagnostics Assessment Programme

Diagnostics Consultation Document: VivaScope 1500 and 3000 imaging systems for detecting and monitoring skin cancer lesions

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

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National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Skin cancer: the VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions

This overview summarises the key issues for consideration by the Diagnostics Advisory Committee. This document is intended to be read together with the final scope and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical effectiveness and cost effectiveness of using the VivaScope 1500 and 3000 imaging systems to rule out biopsy of skin lesions and to define the margins of skin lesions that require excision surgery.

The VivaScope 1500 and 3000 imaging systems are non-invasive, high resolution reflectance confocal microscope systems that are designed to help diagnose potentially malignant skin lesions. They are intended to provide a highly magnified image of skin cells that is reportedly comparable to microscopic examination of a skin specimen (biopsy).

Provisional recommendations on the use of these technologies will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 29 April 2015.

1.2 Scope of the evaluation

Decision question	1. What is the clinical effectiveness and cost effectiveness of using the VivaScope 1500 and 3000 imaging systems to rule out biopsy of skin lesions relative to current practice? 2. What is the clinical effectiveness and cost effectiveness of the VivaScope 3000 imaging systems in defining the margins of skin lesions relative to current practice?
Population	1. People with equivocal skin lesions and people with lentigo maligna If evidence permits, the following sub-populations will be included: • People with suspected melanoma • People with suspected basal cell carcinoma • People with suspected squamous cell carcinoma 2. People with skin lesions that require excision surgery. If evidence permits, the following sub-populations will be included: • People with melanoma • People with basal cell carcinoma • People with squamous cell carcinoma • People with lentigo maligna
Interventions	VivaScope 1500 and VivaScope 3000 imaging systems
Comparator	1 Examination of skin using dermoscopy and clinical judgement to detect potentially cancerous lesions 2 Examination of skin using dermoscopy and clinical judgement to determine tumour margins
Healthcare setting	Secondary Care

Outcomes	Decision question 1: Diagnosis Outcomes may include: • Diagnostic accuracy • Time to test result • Test failure rate e.g. imaging failure • Number of scans deemed impractical because of the site of the lesion • Number of biopsies performed and repeat biopsies • Morbidity associated with biopsy such as pain and swelling • Extent of scarring and associated psychological impact • Adverse events from biopsy including infections • Adverse events from false test results including patient distress and sequalae • Health related quality of life Decision question 2: Defining tumour margins Outcomes may include • Diagnostic accuracy • Time to test result • Test failure rate e.g. imaging failure • Number of surgical procedures/surgical stages • Morbidity associated with excision surgery such as pain and swelling • Extent of scarring and associated psychological impact • Adverse events from surgery including infections • Adverse events from false test results including patient distress and sequalae • Recurrence rates • Health related quality of life

	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of equipment • Costs of staff and training of staff • Maintenance costs • Costs of procedures including biopsy, histological examination and surgery and associated time • Medical costs arising from ongoing care following test results including those associated with surgery, time spent in hospital, and treatment of cancer. • Medical costs arising from adverse events including those associated with biopsies, surgery, and false test results.
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparators, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

2.1 Clinical Effectiveness

The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of the VivaScope 1500 and 3000 imaging systems. The aim of the review was to address the following questions:

- What is the clinical and cost effectiveness of the VivaScope 1500 and 3000 imaging systems, to avoid unnecessary biopsy of equivocal skin lesions suspected to be malignant melanoma, lentigo maligna (LM), basal cell carcinoma (BCC), or squamous cell carcinoma (SCC) compared to current practice;

- What is the clinical and cost effectiveness of the VivaScope 3000 imaging system in defining the margins of melanoma, BCC, SCC, and LM skin lesions compared to current practice.

Evidence on earlier versions of the VivaScope 1500 and 3000 imaging systems, 1000 and 2500, respectively, were also considered because it may provide additional information on the current versions.

Full details of the systematic review can be found starting on page 37 of the diagnostics assessment report.

Overview of studies

The External Assessment Group identified 16 studies that met the inclusion criteria for the review. Out of the 16 included studies, 13 indicated the use of VivaScope or reflectance confocal microscopy (RCM) in diagnosing suspected or equivocal lesions, and 3 studies indicated its use in lesion margin delineation. Of the 13 studies indicated for lesion diagnosis, two used VivaScope 1500 with dermoscopy, four used Vivascope 1500 without dermoscopy as a comparator, and one study used VivaScope 1500 or 3000 with dermoscopy as comparator. Due to lack of data, the EAG included additional studies without dermoscopy as comparator.

For earlier versions of VivaScope, one study used VivaScope 1000 with dermoscopy as comparator, two used VivaScope 1000 without a comparator, two studies used both VivaScope 1000 and VivaScope 1500, with one using dermoscopy as comparator while the other had no comparator. Only one study used VivaScope 2500.

Two of the studies indicated for lesion margin diagnosis used VivaScope 1500 with or without dermoscopy as comparator and the remaining study used VivaScope 2500.

In 10 out of the 13 studies indicated for lesion diagnosis, consecutive patients were enrolled prospectively from settings including melanoma or dermatology clinics in

tertiary or university hospitals, while 1 study retrospectively selected images of previously imaged set of lesions, or excised lesions.

Of the 3 studies indicated for delineating lesion margins, 1 study retrospectively assessed and interpreted lesion images in patients previously enrolled in 2 university-based clinics/hospitals and 2 studies prospectively recruited patients with lesions randomly from a dermatology department or Mohs surgery unit.

None of the included studies was conducted in the UK. The majority of the 15 included studies are from countries whose skin cancer rates and treatment pathways may be different from the UK settings (eight studies from Australia and Italy, two from Brazil and USA, two each from Spain and Australia, and one each from China and Canada). Two studies, Alarcon *et al.* (2014) and Pellacani *et al.* (2014), which used VivaScope in diagnosis, were conducted in Spain and Italy, respectively. Guitera et al. (2013) which used Vivascope in margin delineation was conducted in Australia and Italy. Expert opinion considered these three studies to be the most representative of clinical practice in the UK.

The majority of the included studies had low risk of bias and low applicability concerns in patient selection (11 studies), conduct of the index test (13 studies) and reference standard (13 studies). However concerning flow and timing, the risk of bias in the majority of the studies (13 studies) was unclear due to poor reporting and insufficient data. Further details on the quality assessment can be found on page 39 of the diagnostics assessment report.

Included studies were considered too heterogeneous to have their results combined by meta-analysis. This was due to study design (e.g. not post-dermoscopy), patient population (e.g. different prior history of melanoma) or insufficient reporting of results (e.g. patient based or lesion based). Details of results on test accuracy, clinical effectiveness and quality assessment for each included study are presented in structured tables and as a narrative summary.

Evidence on lesion diagnosis – diagnostic accuracy

Diagnostic accuracy was the most commonly reported outcome in studies, reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Other diagnostic accuracy data such as false positive (FP), false negative (FN), and true negative (TN) were rarely reported and had to be estimated and calculated using other reported diagnostic data where possible.

Dermoscopy plus VivaScope 1500 compared with dermoscopy

Three studies compared dermoscopy with VivaScope 1500 following dermoscopy.

Alarcon et al. (2014)

Alarcon et al. (2014) assessed the impact of reflectance confocal microscopy (RCM) analysis on dermoscopically equivocal pigmented lesions. Of the 343 lesions that underwent RCM examination, only 264 were excised (79 lesions were followed up for one year without any melanoma diagnosed). Of 92 melanomas diagnosed using dermoscopy alone, histopathology proved that there were 6 false negatives, and two false negatives with dermoscopy plus VivaScope 1500.

Based on the 264 excised lesions, there were statistically significant differences in sensitivity in the diagnosis of melanoma (97.8% vs 94.6%, p=0.043) and specificity in non-melanoma (92.4% vs 26.74%, p<0.000001) respectively, in the use of dermoscopy plus VivaScope 1500 and dermoscopy alone. Using a 2x2 contingency table and assuming the 79 lesions followed up were true negatives, the sensitivity (RCM 97.8% vs dermoscopy 93.5%) and specificity (RCM 94.8% vs dermoscopy 49.0%) were calculated. Thus, while the sensitivities of reflectance confocal microscopy and dermoscopy were similar when the 79 lesions were included in the analysis, the specificity for dermoscopy was higher (26.7% vs 49.0%) compared with analysis based on 264 excised lesions.

Table 1. Diagnostic accuracy of melanoma in Alarcon et al. 2014 (both patient and lesion level data)

Intervention/ comparator	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV % (95% CI)	NPV (95% CI)
Based on excised lesions (n=264)				
VivaScope 1500 following dermoscopy	97.8[§] (91.6–99.6)	92.4[§] (87.2–95.7)	87.4 (79.0–92.8)	98.8 (95.1–99.8)
Dermoscopy alone	94.6 (87.2–98.0)	26.74[‡] (87.2–98.0)	40.8 (34.2–47.8)	90.2[†] (77.8–96.3)
Based on all lesions that underwent RCM (n=343)				
VivaScope 1500 following dermoscopy	97.83 (92.35–99.67)	94.82 (91.3–97.21)	87 (79–93)	99 (97–100)
Dermoscopy alone	93.48 (86.34–97.55)	49.0 (42.66–55.37)	40 (34–47)	95 (90–98)

Abbreviations used in table: CI, confidence interval; n, number of patients or lesions; NPV, negative predictive value; PPV, positive predictive value.

Footnotes used in table: [§]significant difference between two groups ($p<0.05$); [‡]data based on difficult and doubtful lesions and not for the whole 264 patients

Pellacani et al. (2014)

Pellacani et al. (2014) assessed prospectively the potential impact of reflectance confocal microscopy when implemented in a routine melanoma workflow. At dermoscopy, patients were referred to one of the following pathways:

- no further examination;
- referral to RCM:
    - reflectance confocal microscopy documentation (lesions with consistent suspicious clinical/dermoscopic criteria, already qualified and scheduled for surgical excision);
    - reflectance confocal microscopy consultation for equivocal lesions (or moderately suspicious), where reflectance confocal microscopy diagnosis would determine lesion definite outcome, that is, either excision or digital follow-up.

Of a total of 493 lesions referred for reflectance confocal microscopy examination, two patients refused reflectance confocal microscopy imaging so lesions were excised, and histopathology reported one BCC and one benign lesion. Of the remaining 491 lesions, 183 underwent reflectance confocal microscopy documentation and 308 reflectance confocal microscopy consultations. In the reflectance confocal microscopy documentation group, histopathology confirmed 110 positives using reflectance confocal microscopy (23 melanomas, 19 BCCs and 68 benign lesions) and 73 negatives using reflectance confocal microscopy (73 benign lesions). In all melanomas and BCCs identified at histology, reflectance confocal microscopy had recommended excision.

In the reflectance confocal microscopy consultation group, reflectance confocal microscopy identified 81 positives and 227 negatives. Of the 81 reflectance confocal microscopy positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 reflectance confocal microscopy negatives followed-up for 3-12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision).

Using a 2x2 contingency table, sensitivity and specificity were calculated. Based on the assumption that all the 21 reflectance confocal microscopy negatives lost to follow-up in the reflectance confocal microscopy consultation group were true negatives, the sensitivity (RCM documentation 100% vs RCM consultation 100%) and specificity (RCM documentation 51.77% vs RCM consultation 78.6%) were calculated. However when the 21 reflectance confocal microscopy negatives lost to follow-up were excluded, the sensitivity was 100% and specificity 80.2% for reflectance confocal microscopy consultation.

Table 2. Diagnostic accuracy of lesions recommended for excision in Pellacani et al. 2014 (lesion level data)

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
RCM documentation	100 (91.51–100)	51.77 (43.21-60.26)	38 (29–48)	100 (95–100)
RCM consultation (based on 227 TNs)	100 (86.16 – 100)	80.21 (75.09–84.69)	31 (21–42)	100 (98–100)
RCM consultation (based on 206 TNs, i.e. excluding the 21 lesions lost to follow up)	100 (86.16–100)	78.63 (73.16–83.43)	31 (21–42)	100 (98–100)
Abbreviations used in the table: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; RCM, reflectance confocal microscopy				

Ferrari et al (2014)

Ferrari et al. (2014), evaluated the most relevant reflectance confocal microscopy features for the detection of difficult melanomas by dermoscopy: score 0–2 (featureless lesions), score 3–4 (positive-borderline lesions), and score 5–10 (positive- clear cut' lesions). In the population with a score of 0–2, the presence of at least one of the two independent parameters accounted for the detection of all six melanomas (100% sensitivity and 82.3% specificity). Similarly in the population with a dermoscopic score of 3–4, the presence of at least one of the two independent parameters accounted for the detection of 16/17 melanomas (94.1% sensitivity and 62.4% specificity).

Dermoscopy plus VivaScope 1500

Four studies reported the diagnostic accuracy of VivaScope 1500 following dermoscopy without a comparator.

Curchin et al. (2011)

Curchin et al. (2011) reported sensitivity and specificity data on 50 equivocal lesions on 42 patients. On VivaScope 1500 following dermoscopy, 12/13 melanomas (92.3% sensitivity, 75% specificity), 19/22 benign naevi (86% sensitivity, 95% specificity), 6/9 BCC (66.7% sensitivity, 100% specificity) and 6/6 squamous cell carcinoma (SCC) and its precursors (100% sensitivity, 75% specificity) were diagnosed correctly.

Table 3. Diagnostic accuracy in Curchin et al. 2011 (lesion level data)

Lesion type	Histopathology proven cases, n	Sensitivity, %	Specificity, %
Melanoma	12/13	92.3	75
Benign naevi	19/22	86	95
BCC	6/9	66.7	100
SCC and its precursors	6/6	100	75
Abbreviations used in table: BCC, basal cell carcinoma; n, number of lesions; SCC, squamous cell carcinoma.			

Guitera et al. (2010)

Guitera et al. (2010) assessed which reflectance confocal microscopy features could distinguish LM from benign macules (BMs) of the face such as solar lentigo, actinic keratosis, and seborrheic keratosis, and to test different algorithms for diagnosing LM. A LM score of ≥2 resulted in a sensitivity of 85% and specificity of 76% for the diagnosis of LM (odds ratio [OR] for LM 18.6; 95%CI: 9.3 to 37.1).

Rao et al. (2013)

Rao et al. (2013) assessed the diagnostic accuracy of VivaScope 1500 compared with histopathology in the diagnosis of cutaneous lesions by two readers of varying degrees of experience; a bedside trained physician compared with a distant expert. Lesions diagnosed by reader 1 as malignant with VivaScope 1500 represented 66.7% of histologically diagnosed melanoma, 74.1% of BCC, and 37.2% of SCC. For reader 2, lesions diagnosed as malignant represented 88.9% of melanoma, 51.9% of BCC, and 72.1% of SCC. Out of 284 lesions evaluated by both readers, 212 were benign and 72 malignant based on histopathology.

Table 4. Diagnostic accuracy in Rao et al. 2013 (lesion level data)

Reader/reviewer	Agreement between VivaScope 1500 and histopathology, %	Sensitivity, %	Specificity, %
Reader 1 (bedside trained physician): evaluated 317 of 334 cases (94.9%)	Melanoma = 66.7; BCC = 74.1 SCC = 37.2	93.1	64.1
Reader 2 (distant expert): evaluated 323 of 334 cases (96.7%)	Melanoma = 88.9; BCC = 51.9 SCC = 72.1	97.4	80.5
Overall (reader 1 and 2)	NR	98.6	44
Abbreviations used in table: BCC, basal cell carcinoma; n, number of lesions; NR, not reported; SCC, squamous cell carcinoma.			

Stanganelli et al. (2014)

Stanganelli et al. 2014 assessed whether combining sequential dermoscopy imaging with VivaScope 1500 can improve melanoma detection and reduce unnecessary excisions. Of 30 out of 70 lesions (43%) classified as melanoma by dermoscopy plus VivaScope 1500, 11/12 were histologically confirmed (11 true positives and 1 false negative), and 19 as false positives.

Table 5. Diagnostic accuracy in Stanganelli et al. 2014 (lesion level data)

Note threshold(s) where appropriate:		Reference standard	
		Disease	No disease
VivaScope 1500	Disease	TP = 11	FP = 19
	No disease	FN = 1	TN = 39
Abbreviations used in the table: FN, false negative; FP, false positive; TN, true negative; TP, true positive			

Dermoscopy plus VivaScope 1000 vs dermoscopy

Langley et al. (2007)

Langley et al. (2007) evaluated the diagnostic accuracy of VivaScope 1000 compared with dermoscopy in patients with benign and malignant melanocytic lesions. The sensitivity of VivaScope 1000 following dermoscopy compared with dermoscopy alone was 97.3% vs 89.2% and specificity was 83.0% vs 84.1%. Using a 2x2 contingency table to estimate histologically proven positive and negative

diagnostic test, the numbers of patients/lesions correctly (TP + TN) and incorrectly (FP + FN) diagnosed were similar using VivaScope 1000 following dermoscopy compared with dermoscopy alone.

Table 6.Diagnostic accuracy Langley et al. (2007) (patient and lesion level data)

Intervention/ comparator	Sensitivity, %	Specificity, %	PPV, %	NPV, %	TP, n	TN, n	FP, n	FN, n
VivaScope 1000	97.3	83.0	70.6	98.6	37	72	15	1
Dermoscopy	89.2	84.1	70.2	94.9	33	74	14	4
Abbreviations used in table: FN, false negative; FP, false positive; n, number of patients or lesions; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.								

VivaScope 1000

Two publications from the same trial reported the diagnostic accuracy of VivaScope 1000 without a comparator.

Gerger et al. (2006)

In the trial by Gerger et al. (2006), 117 melanocytic skin lesions and 45 non-melanocytic skin lesions were consecutively sampled and examined by four independent observers using VivaScope 1000. The overall (total of the 4 observers) diagnostic differentiation of benign from malignant lesions (melanoma and BCC) reached sensitivity of 94.65%, specificity of 96.67%, PPV of 97.50%, and NPV of 92.99% based on histopathology.

Table 7. Diagnostic accuracy in Gerger et al. 2006 (lesion level data)

Diagnostic differentiation of benign from malignant lesions based on biopsy documented lesions	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Observer 1	90.48	96.6	NR	NR
Observer 2	95.24	100	NR	NR
Observer 3	95.24	96.6	NR	NR
Observer 4	97.62	100	NR	NR
Overall (observers 1-4)	94.65	96.67	97.50	92.99
Abbreviations used in table: NPV, negative predictive value; PPV, positive predictive value.				

Gerger et al. (2008)

In a supplementary publication of Gerger et al. (2006), Gerger et al. (2008) retrospectively evaluated 3,709 selected images of 70 lesions (20 malignant melanomas and 50 benign naevi) obtained by VivaScope 1000. Overall performance of the four observers who reviewed the images showed a sensitivity of 97.5%, specificity of 99.0%, PPV of 97.5%, and a NPV of 99.0%.

Table 8. Diagnostic accuracy in Gerger et al. 2008 (lesion level data)

Reader/observer	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Observers 1–3	100	100	NR	NR
Observer 4	90	96	NR	NR
Overall (observers 1–4)	97.5	99	97.5	99
Abbreviations used in table: NPV, negative predictive value; NR, not reported; PPV, positive predictive value.				

VivaScope 1000 or 1500 vs dermoscopy

Guitera et al. (2009)

In a trial by Guitera et al. (2009), possible additive value of VivaScope 1000 and 1500 in the management of melanocytic lesions were evaluated at two centres. In terms of diagnosis of melanoma, there was no significant difference in sensitivities between VivaScope 1000/1500 (91%, 95% CI: 84.6 to 95.5) and dermoscopy (88%, 95% CI: 80.7 to 92.6) but specificities differed significantly: VivaScope 1000/1500 had a specificity of 68% (95% CI: 61.1 to 74.3) and dermoscopy 32% (95% CI: 25.9 to 38.7).

VivaScope 1000 or 1500

Pellacani et al. (2007)

Pellacani et al. (2007) evaluated the sensitivity and specificity of confocal features for the diagnosis of melanoma and benign naevi using RCM score thresholds compared with models obtained from statistical analysis. The VivaScope 1000/1500 demonstrated optimal sensitivity for a score of ≥2 (96.3%), with 52.1% specificity.

Dermoscopy plus VivaScope 1500 compared with dermoscopy plus VivaScope 3000

Castro et al. (2014)

Castro et al. (2014) compared the accuracy of VivaScope 3000 with VivaScope 1500 in the identification of BCC. Among 54 lesions imaged with both RCM devices, 45 were biopsy-proven BCCs. Comparison between VivaScope 1500 following dermoscopy and VivaScope 3000 following dermoscopy was as follows: sensitivity (100% vs 93%), specificity (78% for both RCMs), positive predictive value (96% vs 95%), and negative predictive value (100% vs 70%) respectively.

Table 9. Diagnostic accuracy of BCC in Castro et al. (2014) (lesion level data)

	VivaScope 1500 following dermoscopy	**VivaScope 3000 following dermoscopy**
Sensitivity, %	100	93
Specificity, %	78	78
PPV, %	96	95
NPV, %	100	70
Abbreviations used in the table: BCC, basal cell carcinoma; NPV, negative predictive value; PPV, positive predictive value		

Evidence on lesion diagnosis - lesion recurrence

None of the included studies indicated for lesion diagnosis reported lesion recurrence data.

Evidence on lesion diagnosis - misdiagnosis

VivaScope 1000/1500 compared with dermoscopy

Guitera et al. (2009),

In the trial by Guitera et al. (2009), 15 melanomas (12%) were misclassified by dermoscopy, 11 melanomas (9%) were misclassified by the VivaScope 1000/1500, and only 2.4% by both techniques.

Dermoscopy plus VivaScope 1000 compared with dermoscopy

Langley et al. (2007),

In the trial by Langley et al. (2007), there were 5/37 melanomas for which VivaScope 1000 following dermoscopy and dermoscopy alone produced differing diagnoses. VivaScope 1000 following dermoscopy correctly classified 4/5 melanomas, whereas dermoscopy alone correctly classified 1/5 melanoma. Additionally, there were seven benign naevi for which both diagnoses were incorrect. Two of the melanomas were misdiagnosed by the investigator using dermoscopy alone, but correctly diagnosed by dermoscopy plus VivaScope 1000 as amelanotic or hypomelanotic melanomas.

Dermoscopy plus VivaScope 1500

In the trial conducted by Pellacani et al. (2014), overall VivaScope 1500 proposed diagnosis was concordant with histopathological diagnosis in 216/283 (76.3%) evaluated cases. BCC was the most accurate diagnosis (37/38 [97.4%]), followed by melanoma (24/28 [85.7%]). Spitz nevus was the most frequently misclassified diagnosis (accurate diagnosis: 4/13 [30.8%]); six were misclassified as Clark's naevi and three as melanoma.

Table 10. Misdiagnosis/misclassification of lesions

Study	Comparison group	n (%) of lesions misdiagnosed/ misclassified
Guitera et al. 2009[37]	Dermoscopy	Melanomas: 15 (12%)
	VivaScope 1000/1500 following	Melanoma: 11 (9%)
	Dermoscopy plus VivaScope 1000/15000	Melanoma: (2.4%)
Langley et al. 2007[39]	Dermoscopy	Melanoma: 4
	VivaScope 1000	Melanoma: 1
	Dermoscopy plus VivaScope 1000	NR
Pellacani et al. 2014[45]	Overall VivaScope 1500	Overall lesions: 67 (naevi, 42; BCC, 1; melanoma, 4; Spitz naevi, 9)
Abbreviations used in the table: BCC, basal cell carcinoma; n, number of lesions; NR, not reported; RCM, reflectance confocal microscopy		

Evidence on lesion diagnosis - change in management

No included study indicated for lesion diagnosis reported change in management of lesions after diagnosis.

Evidence on lesion diagnosis – adverse events

None of the included studies indicated for lesion diagnosis or lesion margin delineation reported data on adverse events and side effects of excision including pain, swelling, infections, distress, and scarring.

Evidence on margin delineation – diagnostic accuracy

Dermoscopy plus VivaScope 1500 vs dermoscopy

Guitera et al. (2013

Guitera et al. (2013) analysed LM and lentigo maligna melanoma (LMM) cases to determine whether VivaScope 1500 mapping might alter patient care, and management. Out of 60 positive sites for LM confirmed by histopathology, 55 (FN=5) had been confirmed by VivaScope 1500 and 21 (FN=39) by dermoscopy, and out of 125 LM sites confirmed as negative by histopathology, 121 (FP=4) had been confirmed by VivaScope 1500 and 122 (FP=3) by dermoscopy. Histopathology also showed 17/29 patients with visible lesions had evidence of subclinical disease more than 5 mm beyond the edge of the dermoscopically identified margin. In addition both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500. Thus, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.

Table 11. Diagnostic accuracy in Guitera et al. (2013)

Finding	**Methods of diagnosis**		
	Histopathology, n	**Dermoscopy, n**	**VivaScope 1500, n**
Number of sites positive for LM	60	21 (39 FN)	55 (5 FN)
Number of sites negative for LM	125	122 (3 FP)	121 (4 FP)
Abbreviations used in table: LM, lentigo maligna; LMM, lentigo maligna melanoma; n, number of sites; FN, false negative; FP, false positive			

VivaScope 1500

Pan et al. (2012)

Pan et al. (2012) investigated the feasibility of VivaScope 1500 in defining the margins of lesions clinically suggestive of BCC before surgery. The margins of 10 lesions were evaluated using VivaScope 1500, and biopsies of the margins were used to confirm the results. In seven of 10 (70%) cases, the margins of the cancer were identified using VivaScope 1500 and confirmed by histopathological analysis. In three of 10 (30%) cases, the margin of the lesions could not be detected because of the unevenness of the surface.

Table 12. Histological confirmation of margins in Pan et al. (2012)

	N (%) of cases/margins confirmed by histology
VivaScope 1500	7 (70%)

VivaScope 2500

Bennassar et al. (2014)

Bennassar et al. (2014) evaluated the sensitivity and specificity of ex vivo imaging with fluorescence confocal microscopy (FCM) for the detection of residual BCC in Mohs tissue excisions, and to calculate the time invested up to the diagnosis for both FCM and frozen sections. The overall sensitivity and specificity of detecting residual BCC in surgical margins were 88% and 99%, respectively. The number of images/mosaic correctly diagnosed as TP was 79 (89%) and TN was 390 (99.7%). There was only one (0.3%) false positive. In addition average VivaScope 2500 reduced the evaluation time by 18 minutes ($p<0.001$) when compared with the processing of a frozen section.

Evidence on margin delineation - lesion recurrence

Guitera et al. (2013),

In the trial conducted by Guitera et al. (2013), none of the 17/37 patients treated surgically after histopathology confirmed LM/LMM had developed recurrence during a median follow-up of 37 months. Recurrence was suspected in one imiquimod-

treated patient after one year follow-up, and three patients treated with radiotherapy after 12, 24 and 36 months follow-up respectively.

Table 13. Lesion recurrence in Guitera et al. 2013

Method of treatment of confirmed LM/LMM	Number of patients with recurrence	Follow-up period
Surgical (n=17)	0	12 months
Non-surgical (n=20):		
Imiquimod	1	12 months
Radiotherapy	1	12 months
	1	24 months
	1	36 months

Evidence on margin delineation - misdiagnosis

No studies on lesion margin delineation reported misdiagnosis or misclassification of lesions.

Evidence on margin delineation - change in management

Guitera et al. (2013)

In the trial conducted by Guitera et al. (2013), VivaScope 1500 mapping changed the management of lesions in 27 patients (73%): 11 patients had a major change in their surgical procedure, and 16 were offered radiotherapy or imiquimod treatment. Treatment was surgical in 17/37 patients.

Evidence on margin delineation - adverse events

None of the included studies indicated for lesion margin delineation reported data on adverse events and side effects of excision including pain, swelling, infections, distress, and scarring.

2.2 Costs and cost effectiveness

The External Assessment Group conducted a search to identify existing economic studies investigating the cost effectiveness of VivaScope 1500 and 3000 in the diagnosis of skin lesions suspected for skin cancer and in the margin delineation of malignant skin lesions, including lentigo maligna, prior to surgical treatment. The External Assessment Group also constructed a de novo economic model.

Systematic review of cost effectiveness evidence

Full details of the review can be found starting on page 66 the diagnostics assessment report. No studies were considered eligible for inclusion in the systematic review.

During the development of this report, the company made available to the EAG an unpublished study of the cost effectiveness of reflectance confocal microscopy in the diagnosis of skin lesions suspicious for skin cancer [redacted]
The study had a retrospective design, and therefore did not meet the inclusion criteria for economic evaluations. Nevertheless, due to lack of any relevant economic evidence on the cost effectiveness of VivaScope, it was decided to relax the respective inclusion criterion and thus include this study in the systematic literature review.

[redacted]

Economic analysis

The External Assessment Group developed a de novo economic model designed to assess the cost effectiveness of VivaScope 1500 and 3000 in the diagnosis of skin lesions suspected for skin cancer and in the margin delineation of malignant skin lesions, including lentigo maligna, prior to surgical treatment.

According to the study populations that were identified as relevant for the economic evaluation of VivaScope, three separate 'part' economic models were developed:

- Use of VivaScope in the diagnosis of equivocal lesions suspected for melanoma. This model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of equivocal lesions but each will be used as appropriate according to the location of the equivocal lesion to be examined.

- Use of VivaScope in the diagnosis of suspected BCC lesions following a positive or equivocal finding in dermoscopy. As with the previous model, this model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of suspected BCC lesions but each will be used as appropriate according to the location of the skin lesion to be examined.

- Use of VivaScope for the margin delineation of lentigo maligna prior to surgical therapy. This model assessed the cost effectiveness of VivaScope 3000 as a stand-alone device, since only this device is appropriate for margin delineation.

Five economic analyses were undertaken, examining the cost effectiveness of VivaScope in:

a. The diagnostic assessment of equivocal lesions suspected for melanoma (integrated use of VivaScope 1500 & 3000);

b. The diagnostic assessment of lesions suspected for BCC following a positive or equivocal result in dermoscopy (integrated use of VivaScope 1500 & 3000);

c. The diagnostic assessment of skin lesions suspected for skin cancer, either melanoma (following an equivocal finding in dermoscopy) or BCC (following a positive or equivocal finding in dermoscopy) – this analysis combined the results of the two respective ‘part’ models;

d. The margin delineation of lentigo maligna prior to surgical treatment (use of VivaScope 3000 as a stand-alone device);

e. The diagnostic assessment of skin lesions suspected for either melanoma or BCC, and the margin delineation of lentigo malignas (integrated use of VivaScope 1500 & 3000) – this analysis combined the results of all three 'part' models.

The final economic analysis synthesised all cost and effectiveness data from each of the 'part' economic models to obtain an estimate of the overall cost effectiveness of the VivaScope imaging system used for all indicated purposes assessed in economic modelling in a skin cancer multi-disciplinary team service.

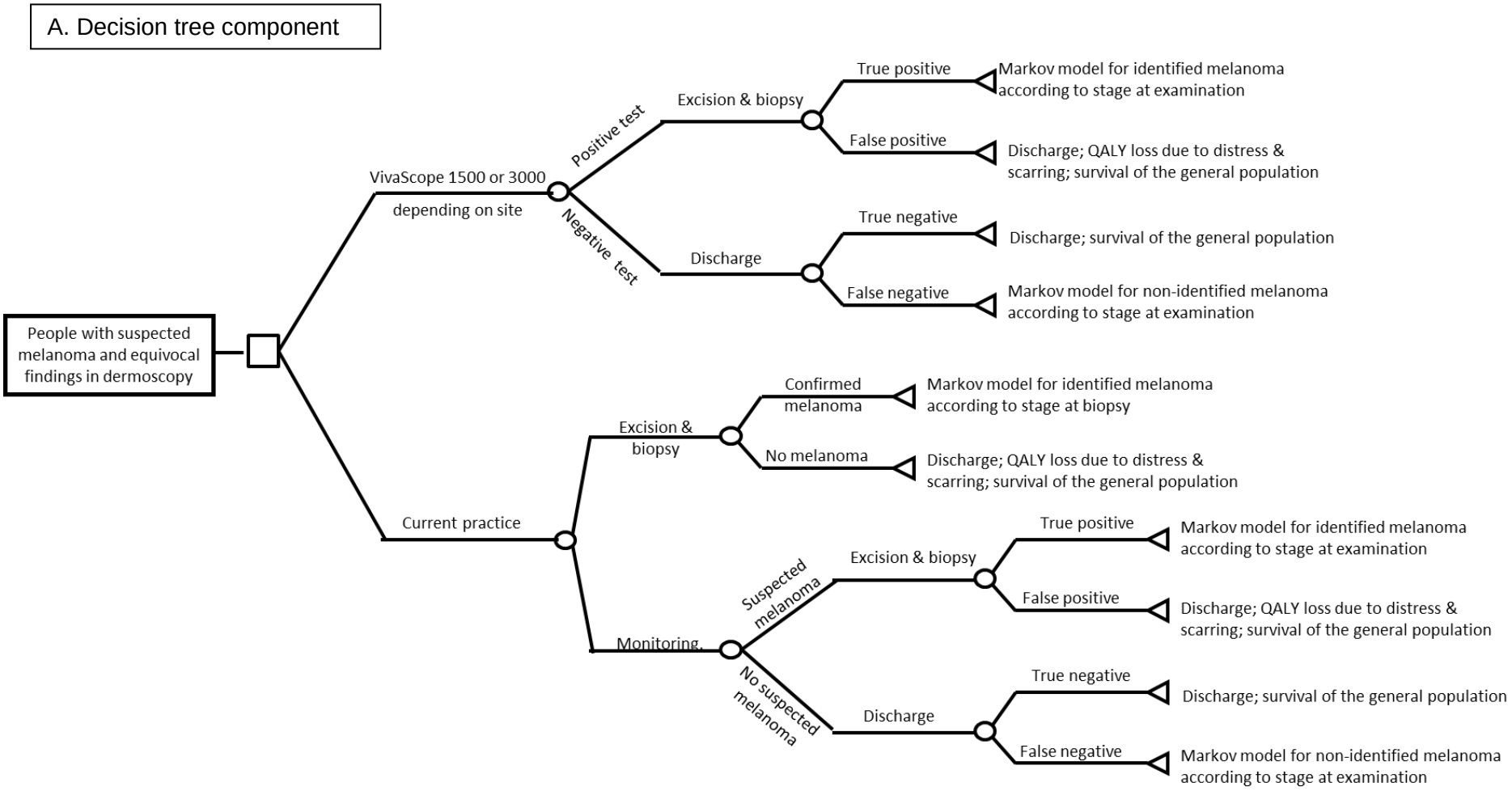
Diagnostic economic model on suspected melanoma lesions following an equivocal finding in dermoscopy

Model structure

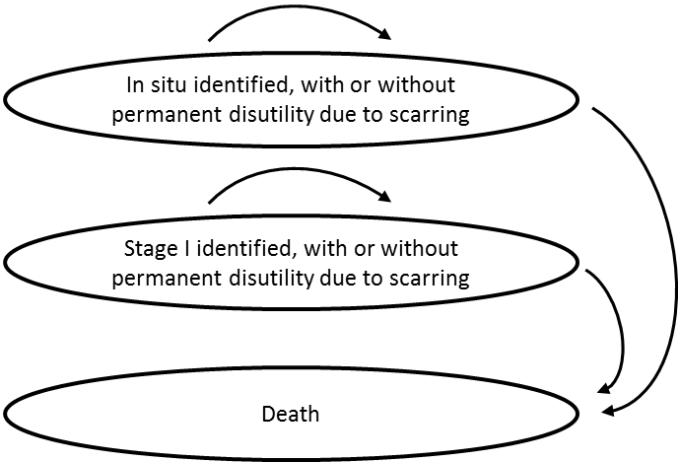
A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the diagnosis of people with lesions suspected for melanoma following an equivocal finding in dermoscopy. The model structure was determined by clinical expert advice and availability of relevant data. People aged 55 years, with dermoscopically equivocal lesions suspected for melanoma, were either examined with VivaScope 1500 or 3000 as appropriate (according to the location of the lesion), or received routine management, comprising excision and biopsy of the majority of the suspicious lesions and monitoring of a smaller proportion of less suspicious ones.

Figure 1 shows a schematic diagram of the VivaScope diagnostics model on suspected melanoma following an equivocal finding in dermoscopy.

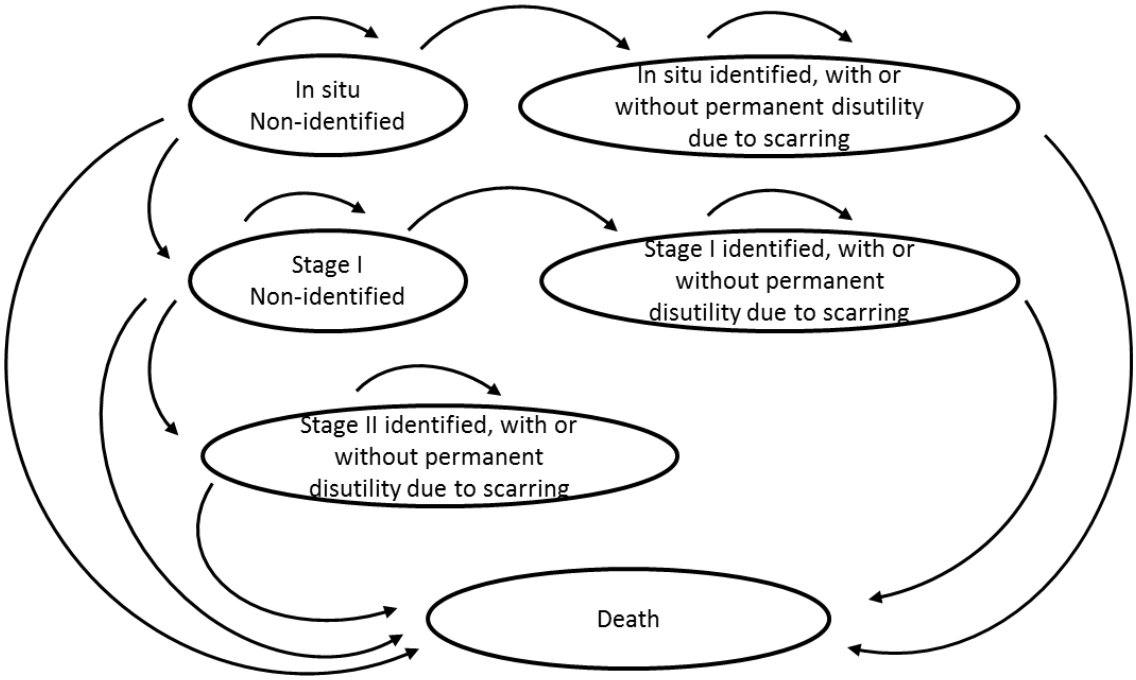
Figure 1. Schematic diagram of the VivaScope diagnostics model on suspected melanoma following an equivocal finding in dermoscopy



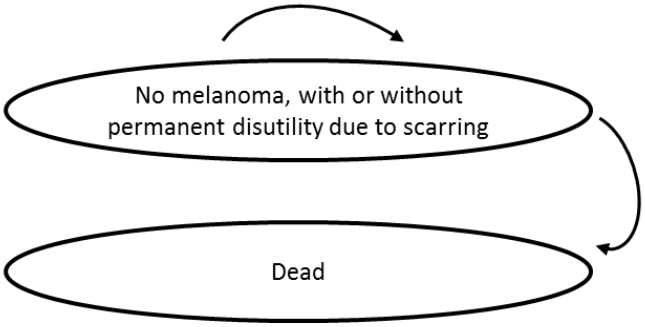
Progression of people with melanomas following identification (VivaScope True Positive or identified at biopsy or during monitoring)



Progression of people with melanomas following initial non-identification (VivaScope False Negative or not identified during monitoring)



Progression of people without melanoma (VivaScope False Positive or True Negative, or identified as negative following biopsy or monitoring)



Model inputs

The model was populated with data derived from the clinical effectiveness review, published literature and routine sources of cost and prevalence data. Where published data were unavailable, the External Assessment Group used expert opinion to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects. Further details on the model input parameters can be found starting on page 112 of the diagnostics assessment report. As diagnostic accuracy data were not synthesised, the base-case economic analysis used data on the diagnostic accuracy of VivaScope 1500 in people with equivocal lesions suspected from melanoma from Alarcon et al. (2014), and Pellacani et al. (2014) in 2 separate analyses, because these two studies were considered to be the most representative of the UK setting. The input parameters used in the model are listed in table 36 on page 151 of the diagnostics assessment report.

Costs

Costs considered in this economic model included the cost of diagnostic assessment of a suspected melanoma with VivaScope following an equivocal finding in dermoscopy, the cost of routine management (cost of excision or monitoring of suspected melanomas), the management cost of confirmed melanomas (true positives) following diagnostic assessment, the cost of missed melanomas (false negatives) that were identified at a later time, and costs associated with metastatic melanoma and terminal illness. The costs in the model are discussed in pages 124-127 of the diagnostics assessment report.

Health related quality of life and QALY decrements

The sources of the utility values for the model are described in pages 118-124 of the DAR.

People in the model experienced utility (or disutility) associated with one or more of the following:

- disutility due to excision and biopsy of a lesion suspected of melanoma, that caused distress as well as anxiety while waiting for the results;

- disutility due to permanent scarring following surgical excision of a lesion on head or neck;
- health-state related utility, which was associated with the stage of melanoma (in people with melanoma) or with the average utility of the general population (in people without a melanoma).

Values used in the model are listed in table 29 on page 123 of the diagnostics assessment report.

Base-case results

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. The following assumptions were applied in the base case analysis:

- The model assumed that confirmed cases of skin cancer are of the same type of cancer as initially suspected (in the case of this model, melanoma), although occasionally skin cancers identified may be of different type of that initially estimated by the clinician at dermoscopy.
- Those who were false positive (i.e. biopsy showed that their lesion was not a melanoma) were assumed to have a benign tumour that did not require treatment and were discharged after the (unnecessary) excision and biopsy.
- The diagnostic accuracy of VivaScope 3000 in equivocal lesions suspected for melanoma was assumed to be equal to that of VivaScope 1500 in the economic model, due to lack of relevant data specific to VivaScope 3000.
- Excision and biopsy was considered in the economic model to be the 'gold standard' for the diagnosis of melanoma, that is, it was assumed to have 100% sensitivity and specificity.

Results of the diagnostic model of suspected melanomas are presented in Table 38 and Table 39 (results derived when diagnostic data from Alarcon et al. were used) and in Table 40 and Table 41 (results derived when diagnostic data from Pellacani et al. were utilised) starting on page 162 of the diagnostics assessment report. The cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas with an equivocal finding in dermoscopy was affected by the diagnostic accuracy data utilised in the model, when VivaScope was assumed to be exclusively

used for this purpose. Using the more 'optimistic' diagnostic data from Alarcon et al. resulted in a deterministic incremental cost effectiveness ratio (ICER) of £8,877/QALY (£9,362/QALY in probabilistic analysis), while the 'less favourable' diagnostic data from Pellacani et al. resulted in a deterministic ICER of £19,095/QALY (£25,453/QALY in probabilistic analysis). When use of VivaScope was expanded to include other indications assessed in the economic analysis, the use of VivaScope became the dominant strategy over routine management of equivocal lesions suspected for melanoma.

Sensitivity analyses

One-way sensitivity analyses were performed on all input parameters that were given a probability distribution in the economic model.

The following inputs had the greatest impact on model for the diagnostic assessment of suspected melanomas:

- the percentage of people experiencing permanent disutility due to scarring;
- the disutility due to anxiety while waiting for the biopsy results;
- the percentage of equivocal lesions excised under routine management the permanent disutility due to scarring from 1st excision;
- the annual volume of suspected melanomas eligible for examination for VivaScope (if VivaScope was used exclusively for examination of suspected melanomas);
- the VivaScope sensitivity and specificity;
- the prevalence of melanomas in equivocal lesions;
- the cost of first excision;
- the disutility due to first excision.

It should be noted that when VivaScope was assumed to be used exclusively for the diagnosis of suspected melanomas and when diagnostic data from Alarcon et al. were used in the model, the only parameter that potentially resulted in negative incremental net benefit was the disutility due to anxiety (page 288 of the DAR). When VivaScope was assumed to be used exclusively for the diagnosis of suspected melanomas and when diagnostic data from Pellacani et al. were used in

the model, then several parameters resulted in negative incremental net benefits (page 290 of the DAR). However, when the assumption on the use of VivaScope was changed to include all indications, none of the influential parameters resulted in a negative incremental net benefit.

Results of the additional sensitivity analyses are shown in Table 48 page 170 in the diagnostics assessment report. When diagnostic accuracy data from Pellacani et al. are used and VivaScope is assumed to be exclusively used for the diagnostic assessment of suspected melanomas, the use of Vivascope becomes less cost effective in the different scenarios. However, when wider use of VivaScope is assumed for all indications, the results are unaffected by the scenarios tested.

Two-way sensitivity analyses were performed to test the impact of different combinations of sensitivity and specificity of VivaScope on its cost effectiveness in the diagnostic assessment of equivocal lesions suspected for melanoma. The results on the diagnosis of suspected melanomas are shown in Table 49 and Table 50 on page 171 of the diagnostics assessment report. The results indicate that VivaScope needs to have a relatively high diagnostic accuracy in order to be cost-effective, in particular when it is used exclusively for the diagnostic assessment of suspected melanomas.

Figure 13 in the diagnostics assessment report (page 172) shows the ICERs obtained in each model plotted against different values of the annual volume of each type of lesion examined with VivaScope. These graphs help identify the minimum number of each type of lesion that needs to be examined with VivaScope per year, for examination with VivaScope to be a cost-effective strategy. Only exclusive use of VivaScope for the examination of suspected melanomas is shown in the graphs, because consideration of wider use of VivaScope resulted in VivaScope being dominant in the diagnosis of suspected melanomas, even when a negligible number of lesions examined (close to zero) was assumed.

Figure 16 page 173 of the diagnostics assessment report shows the impact of a change in the percentage of equivocal lesions suspected for melanoma that are excised under routine management. The shape of the line is determined by the fact

that the percentage of equivocal lesions sent for excision affects both the cost and disutility of routine management, but also the diagnostic accuracy of VivaScope, which differs between highly suspicious and low-moderately suspicious lesions in Pellacani et al. The ICER is less than £20,000/QALY when the percentage of equivocal lesions excised is approximately 10% and below, or 60% and above.

Diagnostic economic model on lesions suspected for basal cell carcinoma following a positive or equivocal dermoscopic finding

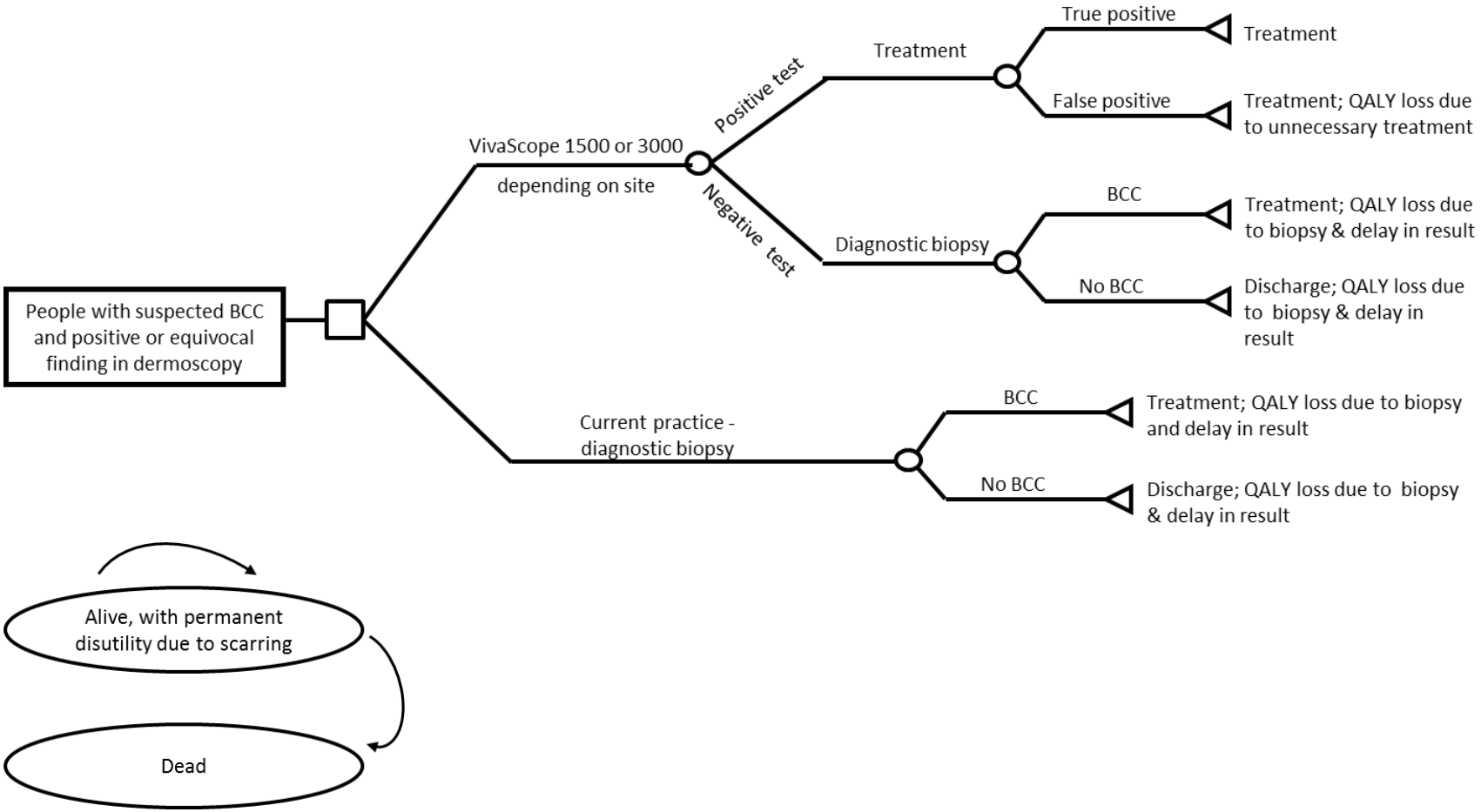
Model structure

The study population for this model comprised people with suspected BCC lesions with a positive or equivocal result in dermoscopy. The aim of examination of the suspected BCC lesions with VivaScope was to make or confirm diagnosis, respectively, as an alternative to diagnostic biopsy.

A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the diagnosis of people with lesions suspected for BCC that had a positive or equivocal finding in dermoscopy. The model structure was determined by clinical expert advice and availability of relevant data. People aged 63 years, with lesions suspected for BCC following a positive or equivocal finding in dermoscopy, were either examined with VivaScope 1500 or 3000 as appropriate (according to the location of the lesion), or had a diagnostic biopsy for confirmation of BCC. The model assumed that confirmed cases of skin cancer are of the same type of cancer as initially suspected (in the case of this model, BCC), although occasionally skin cancers identified may be a different type to that initially identified by the clinician at dermoscopy.

A schematic diagram of the VivaScope diagnostics model on suspected BCC following a positive or equivocal finding in dermoscopy is shown in Figure 2.

Figure 2. Schematic diagram of the VivaScope diagnostics model on suspected BCC following a positive or equivocal finding in dermoscopy



Model inputs

The model was populated with data derived from the clinical effectiveness review, published literature and routine sources of cost and prevalence data. Where published data was unavailable, the External Assessment Group used expert opinion to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects. Further details on the model input parameters can be found starting on page 133 of the diagnostics assessment report. Diagnostic accuracy data for VivaScope were taken from the results of the systematic review of clinical evidence. Castro et al. (2014) reported the sensitivity and specificity of both VivaScope 1500 and VivaScope 3000 in the diagnosis of suspected BCC in patients presenting with at least suspicious lesion for BCC (clinically and dermoscopically) that were recruited from 2 dermatology skin cancer clinics. According to this study, the sensitivity of VivaScope 1500 and VivaScope 3000 was 100% and 93.3%, respectively. The specificity of both devices was 77.8%. The input parameters used in the model are listed in table 36 on page 151 of the diagnostics assessment report.

Costs

Costs considered in this economic model included the cost of diagnostic assessment with VivaScope following a positive result in dermoscopy, the cost of diagnostic biopsy, and cost of treatment (including cost of unnecessary treatment for skin lesions with a false positive result in VivaScope examination). These are discussed starting on page 136 of the diagnostics assessment report.

Health related quality of life and QALY decrements

The sources of the utility values for the model are described in pages 133-135 of the diagnostics assessment report.

Patients in this model experienced a reduction in their HRQoL for one of the following reasons:

- due to diagnostic biopsy that caused distress as well as anxiety while waiting for the results;

- due to surgical treatment (all people undergoing surgical excision or Mohs surgery in the model) and unnecessary non-surgical treatment (people with false positive lesions);
- due to permanent scarring following surgical treatment of a lesion on head or neck.

Utility values used in the model are listed in table 32 on page 135 of the diagnostics assessment report.

Base-case results

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. The following assumptions were applied in the base case analysis:

- The model assumed that confirmed cases of skin cancer are of the same type of cancer as initially suspected (in the case of this model, BCC), although occasionally skin cancers identified may be of different type of that initially estimated by the clinician at dermoscopy.
- Diagnostic biopsy was considered in the model to be the 'gold standard' for the diagnosis of BCC, that is, it was assumed to have 100% sensitivity and specificity.

VivaScope was shown to be the dominant strategy when used for the assessment of suspected BCCs, regardless of whether it was used exclusively for assessing BCC's or all indications (suspected melanomas and lentigo malignas) (Further details are shown in Table 42 and Table 43 page 164).

Sensitivity analyses

The following inputs had the most impact in the model for the diagnostic assessment of suspected BCCs:

- The percentage of people experiencing permanent disutility due to scarring from biopsy;
- the disutility due to anxiety while waiting for the results;
- the diagnostic biopsy cost;
- the prevalence of BCC in examined lesions;

- the permanent disutility due to scarring from biopsy;
- the annual volume of suspected BCCs that would be examined with VivaScope;
- the disutility due to biopsy;
- the percentage of patients treated with surgical therapy;
- the sensitivity of VivaScope 3000;
- the number of lesions per person;
- the percentage of people experiencing permanent disutility due to scarring from surgery.

However, none of the parameters had such an impact so as to turn the incremental net benefit to negative values, even when VivaScope was used exclusively in the diagnostic assessment of suspected BCCs (page 169 of the DAR).

A two-way sensitivity analysis for the diagnosis of suspected BCCs (Table 49 and Table 50 on page 171 of the DAR) showed that any combination of sensitivity and specificity from values as low as 0.40 resulted in VivaScope being a cost-effective strategy (the maximum ICER, when sensitivity and specificity were 0.40, was £7,083/QALY).

Figure 14 in the DAR (page 172) shows the ICERs obtained in each model plotted against different values of the annual volume of each type of lesion examined with VivaScope. These graphs help identify the minimum number of each type of lesion that needs to be examined with VivaScope per year, for examination with VivaScope to be a cost-effective strategy.

Pre-surgical margin delineation economic model

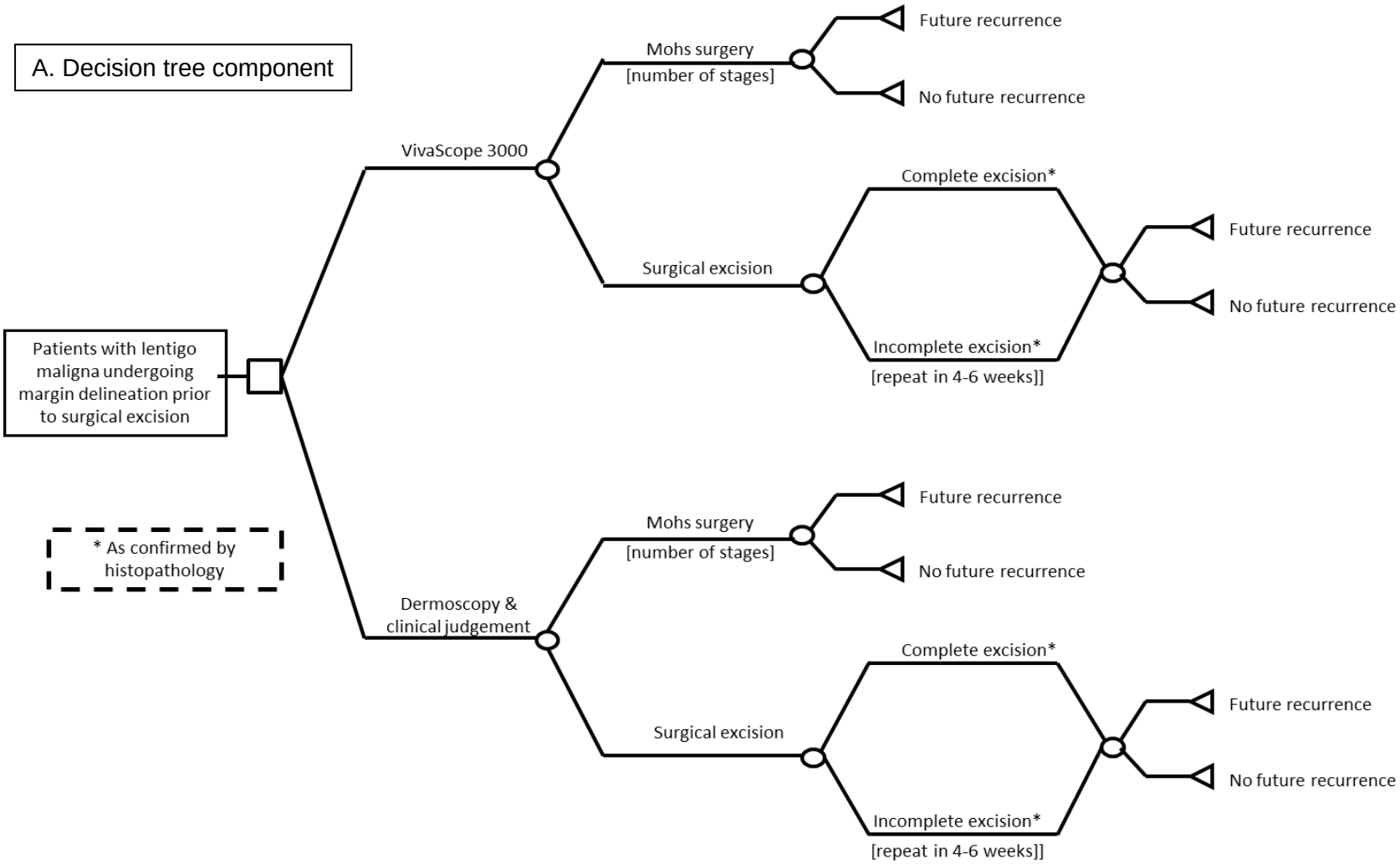
Model structure

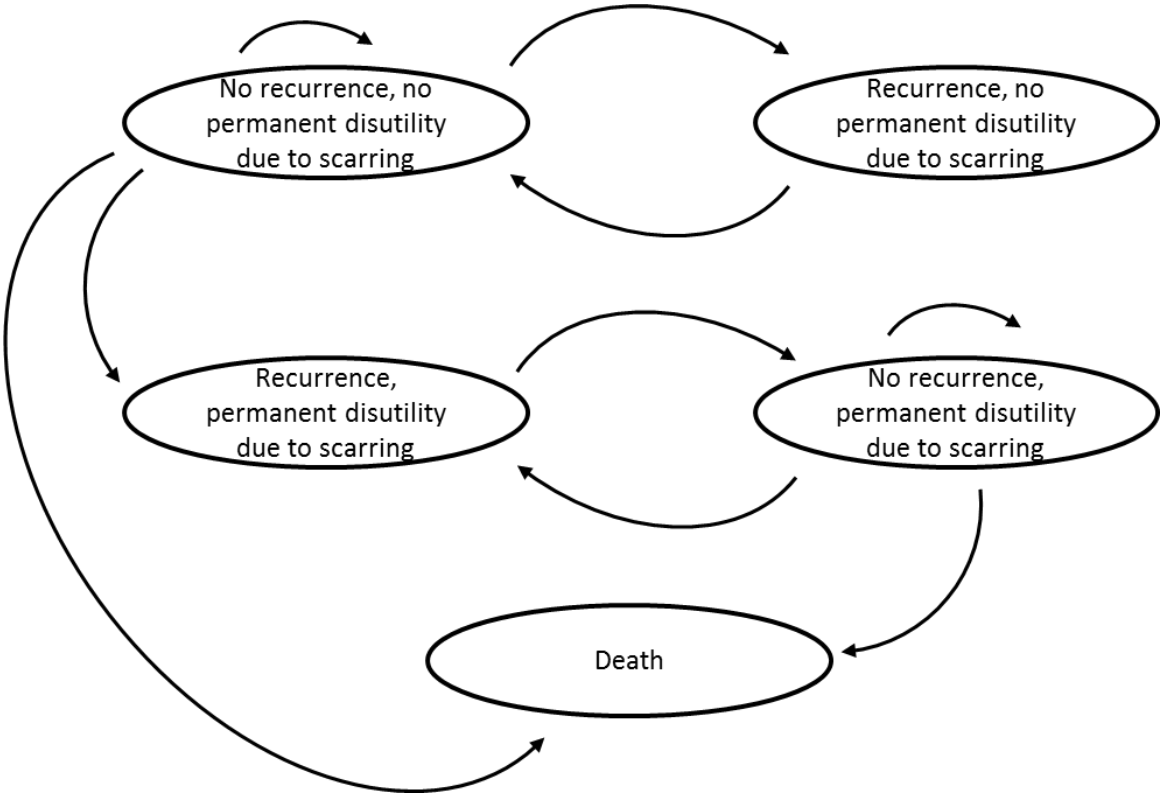
The study population for this model comprised patients with lentigo maligna, aged 70 years, undergoing margin delineation prior to receiving surgical treatment. The aim of examination of lentigo malignas with VivaScope prior to surgical removal was accurate definition of tumour margins. A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the margin delineation of lentigo malignas prior to surgical treatment. The model structure was

determined by clinical expert advice and availability of relevant data. Patients of 70 years of age with a lentigo maligna planned for surgical treatment either had their tumour examined with VivaScope 3000 for margin delineation prior to surgery, or underwent routine management, comprising pre-surgical assessment of lentigo maligna margins with dermoscopy and/or clinical judgement.

A schematic diagram of the VivaScope margin delineation model is shown in Figure 3.

Figure 3. Structure of the margin delineation model





Model inputs

The model was populated with data derived from the clinical effectiveness review, published literature and routine sources of cost and prevalence data. Where published data was unavailable, the External Assessment Group used expert opinion to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects. Further details on the model input parameters can be found starting on page 143 of the diagnostics assessment report.

The impact of VivaScope on surgical outcomes following pre-surgical margin delineation of lentigo malignas was taken from the results of systematic review. The risk of incomplete surgical excisions following margin delineation with VivaScope 3000 was taken from Guitera et al. (2013), which reported that out of 17 patients with lentigo maligna that was surgically excised, 2 had re excisions and margins were confirmed by histopathology (12%). Regarding future recurrence, the study reported that no recurrence of lentigo malignas treated surgically was observed in any of the patients by last follow up

(median follow-up 37 months, range 7-66 months). However, this observation was based on a small number of lentigo malignas excised.

The input parameters used in the model are listed in table 36 on page 151 of the diagnostics assessment report.

Costs

Costs included the cost of pre-surgical mapping of lentigo malignas with either VivaScope 3000 or dermoscopy/clinical judgement, the cost of treatment with either surgical excision or Mohs surgery and the cost of potential future treatment due to recurrence (page 147 of the diagnostics assessment report)

Health related quality of life and QALY decrements

The sources of the utility values used in the model are described in pages 145-147 of the diagnostics assessment report.

Patients in this model experienced a reduction in their HRQoL for one of the following reasons:

- due to surgical treatment (either surgical excision or Mohs surgery) ;
- due to permanent scarring following surgical treatment of a lentigo maligna on head or neck.

Utility values used in the model are listed in table 34 on page 147 of the diagnostics assessment report.

2.1.1 Base-case results

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. The following assumptions were applied in the base case analysis:

- Lentigo malignas in the economic model were assumed not to progress to lentigo maligna melanomas, as the relevant risk was low, given that all lentigo malignas in the model were treated.

- In order to populate the economic model it was assumed that the risk of recurrence of lentigo malignas after margin delineation with the use of VivaScope 3000 was equal to the risk of recurrence of lentigo malignas following Mohs surgery, regardless of the type of surgical treatment (i.e. surgical excision or Mohs surgery) following mapping with VivaScope 3000. This was considered by clinical experts to be a conservative assumption.
- After 10 years, it was assumed that the risk of recurrence fell at zero.

Regarding margin delineation of lentigo malignas, mapping with VivaScope was shown to be cost-effective, even if it used exclusively for this purpose, as indicated by an ICER of £10,241/QALY obtained in deterministic analysis (Table 44 page 164 of the diagnostics assessment report) and £11,651/QALY in probabilistic analysis (Table 45 page 165 of the diagnostics assessment report). When use of VivaScope was expanded to other indications covered in this economic analysis, VivaScope became the dominant option.

Sensitivity analyses

The following inputs had the most impact on the cost effectiveness of pre-surgical mapping of lentigo malignas using Vivascope:

- the probability of incomplete surgical excision following routine mapping;
- the probability of annual recurrence after surgical excision;
- the probability of incomplete surgical excision following mapping with VivaScope;
- the permanent disutility due to scarring from surgical treatment;
- the percentage of people with permanent disutility from scarring;
- the probability annual recurrence following VivaScope mapping and surgical excision;
- the VivaScope mapping (staff) time;
- the cost of surgical excision;
- the number of Mohs stages under routine mapping;
- the disutility due to surgery.

When it is assumed that VivaScope is used only for the mapping of lentigo malignas prior to surgical treatment, negative incremental net benefits are possible when a number of parameters are varied (page 293 of the diagnostic assessment report).However, when a wider use of VivaScope was assumed, the incremental net benefit remained positive under any values of the influential parameters examined.

Figure 15 in the diagnostics assessment report (page 173) shows the ICERs obtained in each model plotted against different values of the annual volume of each type of lesion examined with VivaScope. This graph helps identify the minimum number of each type of lesion that needs to be examined with VivaScope per year, for examination with VivaScope to be a cost-effective strategy. Only exclusive use of VivaScope for the examination of lentigo maligna is shown in the graphs, because consideration of wider use of VivaScope resulted in VivaScope being dominant in the mapping of lentigo maligna, even when a negligible number of lesions examined (close to zero) was assumed.

3 Summary of key findings

A summary of the key results can be found starting page 175 of the diagnostics assessment report.

4 Issues for consideration

Clinical effectiveness

None of the included studies were conducted in the UK. The majority of the 15 included studies are from countries (8 studies from Australia and Italy, 2 from Brazil and USA, 2 each from Spain and Australia, and 1 each from China and Canada) whose skin cancer rates and treatment pathways may be different from the UK setting. Two studies, Alarcon *et al.* (2014) and Pellacani *et al.*

(2014), which used Vivascope in diagnosis, were conducted in Spain and Italy, respectively. Guitera et al. (2013) which used Vivascope in margin delineation was conducted in Australia and Italy. Expert opinion considered these 3 studies to be the most representative of clinical practice in the UK.

The majority of the included studies had low risk of bias and low applicability concerns in patient selection, conduct of the index test and reference standard. However concerning flow and timing, the risk of bias in the majority of the studies was unclear due to poor reporting and/or insufficient data.

Expert opinion indicated that highly suspicious equivocal lesions can be defined in a number of ways:

- lesions with at least 2 positive dermoscopic features including one major criterion,
- lesions with 3 minor positive features suggestive of melanoma
- and/or lesions clearly changed after digital follow-up
- and/or new or growing lesions in an adult with at least one dermoscopic positive criterion
- or papular/nodular or pink or spitzoid lesions.

There may be considerable variation in the interpretation of equivocal lesions and also the treatment of them: some may be removed or they may just be monitored.

Many of the studies used earlier versions of the Vivascope imaging system and therefore the comparability of these systems with the current version will need to be considered.

Apart from diagnostic accuracy and lesion recurrence rate (only reported by 1 study), none of the outcomes specified in the protocol were reported in the included studies.

It was not possible to calculate sensitivity and specificity from all studies because the quantity and quality of data on the number of patients with

positive and negative results was variable. There was substantial heterogeneity between studies and therefore it was not possible to perform a meta-analysis of the clinical effectiveness data. Heterogeneity was due to study design (for example, not post-dermoscopy), patient population (for example, different prior history of melanoma) or regarding reporting of results (for example, patient based or lesion based).

None of the included studies reported diagnostic accuracy results of SCC with VivaScope.

Cost effectiveness

National guidance and expert opinion was used to ensure that the care pathways considered in this model reflect, as close as possible, clinical practice in the NHS, although there appears to be wide variation in the management of suspected and/or confirmed skin cancer across services.

The diagnostic and mapping accuracy data that were utilised in the model were taken from studies included in the systematic literature review of clinical evidence conducted for this guideline. However, data were limited and it was not possible to synthesise the results in a meta-analysis due to heterogeneous nature of the studies identified. Moreover, none of the studies were conducted in the UK, which may have implications for the generalisability of not only the clinical, but also the economic findings, since the prevalence of the skin cancer and the population phenotype distribution may affect the diagnostic accuracy of VivaScope.

Sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility due to scarring following surgical intervention of skin lesions on head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy. However, utility data relating to these events were very limited and of poor quality or non-existent, and a number of assumptions were needed in order to inform the model.

Other complications of excision and biopsy, which was the main comparator of VivaScope in the diagnostic assessment of suspected cancerous lesions, such as bleeding, bruising, infection or allergic reaction to the topical antibiotic were not considered in the model. Clinical experts acknowledged that these are not common complications, but their omission may have potentially underestimated, to some extent, the cost-effectiveness of VivaScope.

The annual volume of lesions eligible for examination with VivaScope is important in determining the cost of VivaScope per lesion examined and, ultimately, in determining its cost-effectiveness. There appears to be wide variation across dermatology in the UK in terms of the number and type of lesions examined annually. Although this parameter has been tested in sensitivity analysis in the economic model, the cost-effectiveness of VivaScope may potentially vary across different dermatology centres in the UK, depending on the volume and type of lesions assessed and managed at each service.

The primary economic analysis considered the costs and benefits associated with use of VivaScope in the diagnostic assessment of skin lesions suspected for melanoma or BCC and in the margin delineation of lentigo maligna prior to surgical treatment. However, there may be additional benefits resulting from use of VivaScope that could not be factored in the economic analysis, including:

- Monitoring and selection of suspicious lesions for biopsy in very high-risk patients
- Monitoring of less suspicious lesions by digital dermoscopy, given that a high definition digital dermoscopy has been integrated into all VivaScope in vivo devices
- Post-therapy monitoring of skin lesions
- Margin delineation of lentigo maligna planned for non-surgical treatment
- Contribution to the monitoring and management of benign skin tumours

The tariff used for Vivascope examination was based on a consultant lead ultrasound tariff which may not be truly representative.

Training in the use of VivaScope and the clinical interpretation of the findings is an important factor that is likely to impact the diagnostic accuracy of VivaScope in the diagnostic assessment of suspected skin cancers and the mapping of skin lesions prior to surgical treatment. The economic analysis did consider formal training costs when estimating the cost associated with the use of VivaScope. However, expert opinion indicated that there is a substantial learning curve following formal training, and the overall training required for a clinician to reach a good level of expertise takes between 4 and 6 months in time. Specifically, clinical experts estimated that approximately 1000 to 2000 cases (including more than 200 cases of melanoma) would need to be evaluated with confocal microscopy for a clinician to gain the level of experience necessary.. This means that the benefits and cost-savings associated with using VivaScope are likely to take some time to realise, particularly as the diagnostic accuracy of VivaScope was determined from studies conducted in dermatology centres with expertise in using the VivaScope imaging system. The imaging failure rate was not considered in the economic analyses because it was not a reported outcome in the included studies.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

As these cancers have a link to UV light exposure they are more prevalent in white skinned individuals.

The risk of the majority of skin cancers increases with age. Older people may also be more likely to be in receipt of other treatments, such as anticoagulation and poor wound healing, which limit the desirability of biopsy approaches.

People with cancer are protected by the Equality Act 2010 from the point of diagnosis.

People who are HIV positive and immunocompromised are at higher risk of squamous cell carcinoma, as well as certain of the rarer skin cancers, such as Kaposi's sarcoma.

6 Implementation

A substantial amount of time and resources may be required to train staff in the use of the technology and in interpreting the electronic images. For example, dermatologists may require training in the interpretation of quasi-histopathological images to correctly interpret the VivaScope images.

The initial setup time to attach the VivaScope 1500 device over a lesion and obtain an image is estimated to be 10 minutes although this may vary depending on the experience of the user. In a clinical setting, this may mean that an "operator" is required to setup the device, leaving the clinician free to see other patients until the images are available.

7 Authors

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Technical Adviser

April 2015

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by BMJ Technology Assessment Group (BMJ-TAG)

Edwards SJ, Mavranezouli I, Osei-Assibey G, Marceniuk G, Wakefield V, Karner C. VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. A Diagnostic Assessment Report. BMJ-TAG, London. 2015.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- MAVIG GmbH

Other commercial organisations:

- Michaelson Diagnostics
- XY Consulting

Professional groups and patient/carer groups:

- Royal College of Pathologists
- Royal College of Physicians
- British Association of Dermatologists

Research groups:

- Cancer Research UK
- Skin Cancer Research Fund

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government
- University of Birmingham

Appendix B: Glossary of terms

Actinic keratosis, also known as solar keratosis: a pre-cancerous skin condition caused by too much exposure to the sun. In some cases, actinic keratoses may turn into squamous cell cancers. Most actinic keratoses do not become cancers, but it can sometimes be hard for doctors to tell these apart from true skin cancers, so doctors often recommend treating them.

Basal cell carcinoma (BCC): a slow developing cancer of the epidermis that usually occurs on the face and is associated with intensive ultraviolet radiation (UV) exposure in childhood and adolescence, particularly in those who burn easily.

Dermatoscope: a handheld magnifying glass with a polarised light source, also called a dermascope or epiluminescent microscope.

Melanoma skin cancer: types of cancer developing from the pigmented cells (melanocytes) of the epidermis. This classification includes melanomas, which can become malignant and spread and lentigo maligna, which also has the capacity to spread.

Mohs Surgery: a complex form of surgery where tissue is removed, examined histologically and mapped to the boundaries of the lesion to guide the further removal of tissue. It can be time-consuming and expensive but has a high cure rate.

Near infra-red (**NIR) light**: this is light at the infra-red end of the spectrum which is not visible to the human eye but can be used extensively in medicine. Human tissues transmit and absorb NIR depending on important factors, such as their haemoglobin content.

Non-melanoma skin cancer: types of cancer developing from the epidermal cells involved in the production of the skin protein keratin. These keratinocytes can develop into either basal cell carcinomas – if the cells lie deep in the epidermis – or squamous cell carcinomas – if keratinocytes elsewhere in the skin are involved.

Reflectance confocal microscope (Confocal imaging/microscopy): confocal microscopy uses a small point (laser) light source and lenses focussed on the same point, combined with a confocal pinhole filter which means only the light from the plane of focus reaches the detector. This means all the out of focus light is not detected giving a very high resolution clear

image. However, this requires much enhanced optical systems because most of the light is filtered out at the pinhole detector.

Squamous cell carcinoma (**SCC):** a cancer of the outermost layer of skin cells and is associated with chronic UV radiation exposure in the earlier decades of life

VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation
DAR ASSESSMENT REPORT

STRICTLY CONFIDENTIAL

This report was commissioned by the NIHR HTA Programme as project number 14/69/02

BMJ Technology Assessment Group

Title: VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation.

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Date completed: 30/03/2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/69.

Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Acknowledgements:
The Assessment Group thanks Dr Andrew Coleman (Head of non-ionising radiation physics), Dr Emma Craythorne (Consultant Dermatologist and Dermatological Surgeon), Dr Louise Fearfield (Consultant Dermatologist), Dr Jennifer Garioch (Consultant Dermatologist), James Hawkins (Health Economist), Dr Rakesh Patalay (Consultant Dermatologist and Dermatological Surgeon), Professor Giovanni Pellacani (Department of Dermatology, University of Modena and Reggio Emilia), Matthew Prettyjohns (Senior Health Economist) and Dr Julia Schoffield (Consultant Dermatologist) for their input throughout the project. Thanks also to Mr Marc Moncrieff (Consultant Plastic & Reconstructive Surgeon) for reviewing the report. The Assessment Group would also like to thank Dr Fay Crawford for her contributions to the background section and to the appraisal and data abstraction of the literature retrieved by the clinical searches, and Mariana Bacelar for her contribution to the design of the economic model and the acquisition of input data.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Edwards SJ, Mavranezouli I, Osei-Assibey G, Marceniuk G, Wakefield V, Karner C. VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. A Diagnostic Assessment Report. BMJ-TAG, London. 2015.

Contributions of authors:
Please refer to the International Committee of Medical Journal Editors (ICMJE) **Uniform Requirements for Manuscripts Submitted to Biomedical Journals see** http://www.icmje.org/

Steve Edwards	Project lead: supervised the production of the final report; report writing; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence
Ifigeneia Mavranezouli	Devised and carried out the economic literature searches; study selection; data extraction; critical appraisal of the economic evidence; development of the economic model; carried out the economic analysis and report writing.
George Osei-Assibey	Devised and carried out the clinical literature searches; study selection; data extraction; critical appraisal of the clinical evidence and report writing.
Gemma Marceniuk	Devised and carried out the economic literature searches; study selection; data extraction; critical appraisal of the economic evidence; development of the economic model and report writing.
Victoria Wakefield	Study selection; data extraction; critical appraisal of the clinical evidence and report writing.
Charlotta Karner	Devised and carried out the clinical literature searches; study selection; data extraction and critical appraisal of the clinical evidence.

All authors read and commented on draft versions of the DAR

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Abbreviation	Description
AFC	Agenda for change
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
BAD	British Association of Dermatology
BCC	Basal cell carcinoma
CA	California
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
Cm	Centimetre
CRD	Centre for Reviews and Dissemination
CT	computerised tomography
DARE	Database of Abstracts of Reviews and Effects
EAG	Evidence Assessment Group
EED	Economic Evaluation Database
FN	False negative
FP	False positive
GP	General practitioner
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
Inc	Incorporated
INMB	Incremental net monetary benefit
IQR	Interquartile range
LLC	Limited liability company
LM	Lentigo maligna
LMM	Lentigo maligna melanoma
LSMDT	Local hospital skin cancer multidisciplinary team
MDT	Multidisciplinary team
Mm	Millimetre
mW	Milli watts
NA	Not applicable
NC	No comparator
NPV	Negative predictive value
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
Nm	nano metre
NNE	Number needed to excise
NR	Not reported
NY	New York
PBR	Payment by results

PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life yeas
QUADAS	Quality assessment of diagnostic accuracy studies
RCM	Reflectance confocal microscopy
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SK	Seborrheic keratosis
SL	Solar lentigo
SLNB	Sentinel lymph node biopsy
SROC	Summary receiver operating characteristics
SSMDT	Specialist skin cancer multidisciplinary team
TP	True positive
TN	True negative
TTO	Time trade-off
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Background

Skin cancer is one of the most common cancers in the United Kingdom (UK). It is commonly classified into melanoma skin cancer (or malignant melanoma) which develops from pigmented cells in the epidermis, and non-melanoma skin cancer, which develops from cells that produce keratin. Non-melanoma skin cancer can be further divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Malignant melanoma, SCC and BCC make up more than 95% of all skin cancers.

Malignant melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cases, with incidence rates higher in younger people, and almost twice as common in young women (up to age 34) as in young men. In 2011, 13,300 cases of malignant melanoma were diagnosed in the UK, out of which 2,200 people died from the disease.

In 2010 around 100,000 people were diagnosed with non-melanoma skin cancer in the UK and 638 deaths were reported from it in 2012. BCC makes up about 75% of non-melanoma cases, and is more common in older people (people aged over 75 years are about five times more likely to have a BCC than those people aged between 50–55 years) and in males than females. SCC makes up around 20% of diagnosed non-melanoma skin cancers.

The main risk factors for developing skin cancer include exposure to ultraviolet (UV) radiation in the form of sunlight or use of sun beds. Other factors include age, sex, ethnicity, occupation, personal and family history of skin cancer, socioeconomic status and certain physical characteristics (such as light eyes or hair, fair skin which sunburns easily; having a lot of moles, unusually shaped or large moles, or a lot of freckles).

According to clinical experts, patients with suspicious skin lesions first come to secondary care via a general practitioner (GP) referral. After a dermoscope examination, patients with benign lesions are discharged and those with any concerning dermoscope or clinical features present go for surgical excision. Thus the importance of identifying truly positive lesions while curtailing the number of unnecessary biopsies cannot be over-emphasised. Reflectance confocal microscopy (RCM) is a non-invasive technique that allows examination of the epidermis and papillary dermis at cellular resolution.

The VivaScope© imaging system is a non-invasive RCM technology designed to diagnose potentially malignant skin lesions. It captures highly magnified images of the upper layer of the skin. It is designed to be used in conjunction with dermoscopy to investigate potentially malignant skin lesions, thus providing a more accurate diagnosis leading to fewer biopsies of benign lesions and earlier

detection of skin cancers. It may also be used as a guide to surgery to provide more accurate pre-surgical margins, preventing unnecessarily large scars for skin cancers in anatomic areas where tissue preservation is (e.g. face, hands, feet, genitals), and reducing the risk of recurrence.

VivaScope 1500 and VivaScope 3000 are the current versions of the VivaScope technology. VivaScope 1500 is a stationary device designed for lesion diagnosis on extremities such as the back of the hand or the back, chest, leg, arm, cheek, forehead. The handheld VivaScope 3000 is designed to access difficult to reach skin regions such as around the nose, ears, and eyes, or between fingers. From the technical specification, VivaScope 3000 can be used for diagnosis, as well as a guide to surgery to provide pre-surgical margins of tumours.

1.2 Objectives

The following questions are addressed in the clinical effectiveness section of the technology assessment report:

- What is the clinical and cost effectiveness of the non-invasive RCM VivaScope 1500 and 3000 imaging systems, to avoid unnecessary biopsy of equivocal skin lesions suspected to be malignant melanoma, LM, BCC, or SCC relative to current practice;
- What is the clinical and cost effectiveness of the non-invasive RCM VivaScope 3000 imaging system in defining the margins of melanoma, BCC, SCC, and LM skin lesions relative to current practice.

Although this report is mainly aimed at the current versions of VivaScope (1500 and 3000), VivaScope 1000 and 2500 which are earlier models of VivaScope 1500 and 3000, respectively were also considered as they may provide additional information on the current versions.

The comparator eligible for inclusion for the assessment of both diagnostic accuracy and delineation of lesion margins was visual assessment of the lesion followed by dermoscopy and clinical judgement by an experienced dermatology specialist. The eligible reference standard for the assessment of diagnostic accuracy and margin delineation was histopathology of biopsy of the excised skin lesion.

1.3 Methods

This assessment comprises of a systematic review of clinical and cost-effectiveness studies, and the development of three *de novo* economic models.

1.3.1 Clinical effectiveness systematic review

Evidence for the clinical effectiveness of the interventions outlined in the protocol was assessed by conducting a systematic review of published research evidence. The systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and in the NICE Diagnostic Assessment Programme manual.

RCTs and observational studies were considered the most appropriate study designs for inclusion in the systematic review. Reviews, pre-clinical and animal studies, as well as case reports were excluded.

Electronic databases (MEDLINE, EMBASE, Cochrane Library) were searched from database inception on 14th October 2014 and updated on 11th February 2015. No limits relating to language of publication were applied to the searches. Two reviewers independently screened all titles and abstracts according to the inclusion criteria. Full paper manuscripts of any abstracts of potential relevance were obtained and assessed for inclusion. Authors were also contacted for clarification where needed. Discrepancies between the two reviewers were resolved by consensus, with involvement of a third reviewer when necessary.

Reference lists of included papers were assessed for additional relevant studies, and clinical experts were also contacted for additional information on published and unpublished studies. In addition, abstracts from key conference proceedings were searched for relevant studies from 2012.

Data from included studies were extracted using a standardised data extraction form by two reviewers, and the two extractions were validated. The quality of diagnostic studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool, according to recommendations by the Cochrane Handbook for Diagnostic Test Accuracy Reviews.

Evidence on the following outcome measures was considered: diagnostic accuracy; time to test result; test failure rate, e.g. imaging failure; number of biopsies performed and repeat biopsies; morbidity associated with biopsy such as pain and swelling; recurrence rate (lesion margin delineation only); morbidity associated with excision surgery such as pain and swelling (lesion margin delineation only); adverse events from biopsy including infections; adverse events from false test results including patient distress and sequelae; health related quality of life (HRQoL).

Extracted data and quality assessment for each study were presented in structured tables and as a narrative summary.

1.3.2 Assessment of cost-effectiveness

A systematic literature review was undertaken to identify studies assessing the cost effectiveness of VivaScope in the diagnostic assessment of skin lesions suspected for cancer and the margin delineation of cancerous lesions prior to surgical treatment. In addition to the electronic sources searched for the clinical effectiveness review, the Health Technology Assessment (HTA) and the NHS Health Economic Evaluation database were searched for economic evaluations addressing the review question. The search strategy combined terms capturing the interventions and comparators of

interest, the target condition, and, for searches undertaken in MEDLINE and EMBASE, terms to capture economic evaluations.

In addition, the Evidence Assessment Group (EAG) constructed a *de novo* economic model in Microsoft Excel to estimate the cost-effectiveness of VivaScope 1500 and 3000 imaging system in the diagnosis of potentially malignant skin lesions and the margin delineation of diagnosed malignant lesions prior to surgical treatment. The economic analysis focused on the following populations, based on availability of relevant data and clinical expert advice:

- people with suspected melanoma, who have equivocal lesions following dermoscopy;
- people with suspected BCC, whose lesions have an equivocal or positive result in dermoscopy, to make the diagnosis or to confirm diagnosis, respectively, as an alternative to diagnostic biopsy;
- Patients with lentigo maligna prior to surgical management.

According to the study populations that were identified as most relevant for the economic evaluation of VivaScope, three separate 'part' economic models were developed:

- Use of VivaScope in the diagnosis of equivocal lesions suspected for melanoma. This model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of equivocal lesions but each will be used as appropriate according to the location of the equivocal lesion to be examined.
- Use of VivaScope in the diagnosis of suspected BCC lesions following a positive or equivocal finding in dermoscopy. As with the previous model, this model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of suspected BCC lesions but each will be used as appropriate according to the location of the skin lesion to be examined.
- Use of VivaScope for the margin delineation of lentigo maligna prior to surgical therapy. This model assessed the cost effectiveness of VivaScope 3000 as a stand-alone device, since only this device is appropriate for margin delineation.

The results of the three 'part' models were assessed independently, but were also synthesised to give an overall estimate of the cost-effectiveness of VivaScope in the diagnostic assessment of skin lesions suspected for cancer (diagnostic model on suspected melanomas and diagnostic model on suspected BCCs) and also in the diagnostic assessment of skin lesions suspected for cancer as well as the margin delineation of skin lesions prior to surgical treatment (all three 'part' models).

The analysis adopted the perspective of the NHS and Personal Social Services (PSS). Costs consisted of intervention costs of VivaScope (including purchase and maintenance costs, costs of parts and consumables required for the examination, staff training and staff time required for the examination),

costs associated with the comparators of the analysis (such as costs of biopsy, histological examination and monitoring including any required consultations with clinicians), costs of management of skin lesions following correct (i.e. true negative and true positive cases) or incorrect (false negative and false positive cases) diagnosis, as well as costs incurred following the pre-surgical mapping of malignant skin lesions. Costs of management of future events such as progression and recurrence of skin cancer, where relevant, were also considered. All costs were expressed in 2014 prices. The outcome measure of the economic analysis was the QALY. The impact of the intervention and its comparators on people's HRQoL was associated with the potential distress from excision and/or diagnostic biopsy of a lesion, the anxiety while waiting for the diagnostic results, the unnecessary treatment of people with false positive lesions, the progression of the disease in people with false negative lesions, and the permanent disutility due to scarring following surgical intervention of skin lesions on head or neck. Costs and outcomes were discounted at an annual rate of 3.5%.

The clinical effectiveness parameters required for the economic models (diagnostic accuracy of VivaScope 1500 and 3000 and clinical outcomes on margin delineation) were predominately informed by the systematic review of the clinical evidence. Other clinical input parameters were taken from published literature. Utility data were taken from a systematic review of the literature. An assumption of the annual volume of lesions eligible for examination with VivaScope that are likely to be assessed by one dermatology multi-disciplinary team (MDT) per year, which was required in order to determine the intervention cost per lesion examined with VivaScope, was estimated based on clinical expert advice, and published epidemiological and service data. Costs associated with the intervention (VivaScope 1500 and 3000 imaging system), including purchase price of the equipment, part and maintenance costs, were provided by the company. Other resource use data were based on national guidelines and additional published evidence supplemented with clinical expert opinion. Unit costs were taken from national sources.

At all steps of designing the economic models, clinical expert opinion was sought to confirm that diagnostic and assessment pathways were consistent with current clinical practice in the UK, as well as with anticipated changes in practice following a potential introduction of VivaScope within the NHS context. Clinical expert opinion was also employed to supplement the economic models with parameter estimates, in areas that relevant published evidence was lacking.

Each of the 'part' models consisted of a decision-tree (which reflected initial diagnostic or mapping assessment of the skin lesions and immediate outcomes), followed by a Markov model which followed patient and measured future consequences (costs and outcomes) over lifetime.

Deterministic and probabilistic analyses of all three part models were undertaken. All input parameters were tested in one-way sensitivity analysis; Tornado diagrams were produced for different analyses to show the impact of the most influential parameters on the results. Additional one-way sensitivity analyses were undertaken to estimate the impact of alternative scenarios and model assumptions on the results. Finally, two-way sensitivity analyses were carried out to test the impact of concurrently varying sensitivity and specificity of VivaScope in the diagnostic assessment of eligible skin lesions suspected for melanoma or BCC on the cost effectiveness results.

1.4 Results

1.4.1 Clinical effectiveness systematic review

Eleven studies met the inclusion criteria from the initial electronic database searches in 14th October 2014. When the searches were updated from October 2014 to February 2015, a further two studies that met the inclusion criteria were identified. Three additional studies were obtained by contacting clinical experts in the field. Thus in total 16 studies were identified that met the inclusion criteria for the review. No study was identified from conference proceedings that met the inclusion criteria.

Out of the 16 included studies, 13 indicated the use of VivaScope in diagnosing suspected or equivocal lesions, and three studies indicated VivaScope in lesion margin delineation. Of the 13 studies indicated for lesion diagnosis, two used VivaScope 1500 with dermoscopy, four without dermoscopy as comparator, and one study used VivaScope 1500 or 3000 with dermoscopy as comparator. Due to lack of data, we included additional studies without dermoscopy as comparator.

For earlier versions of VivaScope, one study used VivaScope 1000 with dermoscopy as comparator, two used VivaScope 1000 without a comparator, two studies used both VivaScope 1000 and VivaScope 1500, with one using dermoscopy as comparator while the other had no comparator. Only one study used VivaScope 2500.

Two of the studies indicated for lesion margin diagnosis used VivaScope 1500 with or without dermoscope as comparator and one used VivaScope 2500.

For the 13 studies indicated for lesion diagnosis, the number of participants enrolled ranged from 42 to 423 while the number of participants indicated for studies in lesion margin delineation ranged from 10 to 74. The reported median age ranged from 47 to 62 years, and mean age from 44.2 to 71 years.

In 10/13 studies indicated for lesion diagnosis, consecutive patients were enrolled prospectively from settings including melanoma or dermatology clinics in tertiary or university hospitals, while the rest retrospectively selected images of previously imaged set of lesions or excised lesions. Of the three studies indicated for lesion margin diagnosis, one retrospectively assessed and interpreted lesion

images in patients previously enrolled in two university-based clinics/hospitals and two prospectively recruited patients/lesions randomly from a dermatology department or Mohs surgery unit.

The majority of the 16 included studies had low risk of bias and low applicability concerns in patient selection, conduct of the index test and reference standard. However concerning flow and timing, the risk of bias in majority of the studies was unclear due to poor reporting and/or insufficient data.

Included studies were considered too heterogeneous to have their results combined by meta-analysis. This was due to study design (e.g. not post-dermoscopy), patient population (e.g. different prior history of melanoma) or regarding reporting of results (e.g. patient based or lesion based).

Diagnostic accuracy

Diagnostic accuracy was the most commonly reported outcome, reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Other diagnostic accuracy data such as false positive (FP), false negative (FN), and true negative (TN) were rarely reported and had to be estimated/calculated using other reported diagnostic data where possible.

Two studies (Alarcon *et al.* 2014 from Spain, and Pellacani *et al.* 2014 from Italy) investigated lesion diagnosis and were deemed to be the most representative of clinical practice in the UK setting from the studies identified. However Alarcon was the preferred choice since it is the most representative of patients diagnosed with melanoma in the UK. This was validated by our clinical experts and therefore formed the basis of the health economic analysis for diagnosis of malignant melanoma.

Alarcon *et al.* 2014 assessed the impact of RCM analysis on dermoscopically equivocal pigmented lesions. Of the 343 lesions that underwent RCM examination, only 264 were excised (79 lesions were followed up for one year without any melanoma diagnosed). Of 92 melanomas diagnosed using dermoscopy alone, histopathology proved that there were six FNs, and two FNs with dermoscopy plus VivaScope 1500. Based on the 264 excised lesions, there was statistically significant differences in sensitivity in the diagnosis of melanoma (97.8% vs 94.6%, $p=0.043$) and specificity in non-melanoma (92.4% vs 26.74%, $p<0.000001$) respectively in the use of dermoscopy plus VivaScope 1500 and dermoscopy alone.

Using a 2x2 contingency table and assuming the 79 lesions followed up were TNs, the sensitivity (RCM 97.8% vs dermoscope 93.5%) and specificity (RCM 94.8% vs dermoscope 49.0%) were calculated. Thus, while the sensitivities of RCM and dermoscopy were similar when the 79 lesions were included in the analysis, the specificity for dermoscopy was higher (26.7% vs 49.0%) compared with analysis based on 264 excised lesions.

Pellacani *et al*. 2014 prospectively assessed the potential impact of RCM when implemented in a routine melanoma workflow. At dermoscopy, patients were referred to one of the following pathways:

- No further examination;
- Referral to RCM:
    - RCM documentation (lesions with consistent suspicious clinical/dermoscopic criteria, already qualified and scheduled for surgical excision);
    - RCM consultation for equivocal lesions (or moderately suspicious), where RCM diagnosis would determine lesion definite outcome, i.e. either excision or digital follow-up.

Of a total of 493 lesions referred for RCM examination, two patients refused RCM imaging so lesions were excised, and histopathology reported one BCC and one benign lesion. Of the remaining 491 lesions, 183 underwent RCM documentation and 308 RCM consultations. In the RCM documentation group, histopathology confirmed 110 RCM positives (23 melanomas, 19 BCCs and 68 benign lesions) and 73 RCM negatives (73 benign lesions). In all melanomas and BCCs identified at histology, RCM had recommended excision.

In the RCM consultation group, RCM identified 81 positives and 227 negatives. Of the 81 RCM positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 RCM negatives followed-up for 3-12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision).

Using a 2x2 contingency table, sensitivity and specificity were calculated. Based on the assumption that all the 21 RCM negatives lost to follow-up in the RCM consultation group were TNs, the sensitivity (RCM documentation 100% vs RCM consultation 100%) and specificity (RCM documentation 51.77% vs RCM consultation 78.6%) were calculated. However when the 21 RCM negatives lost to follow-up were excluded, the sensitivity was 100% and specificity 80.2% for RCM consultation.

One study (Guitera *et al*. 2013) investigated lesion margin delineation and was also deemed to be the most representative of clinical practice in the UK setting. This was validated by our clinical experts and this trial formed the basis for the health economic analysis of VivaScope assisted margin delineation.

Guitera *et al*. 2013 analysed LM and LMM cases to determine whether VivaScope 1500 mapping might alter patient care, and management. Out of 60 positive sites for LM confirmed by histopathology, 55 (FN=5) had been confirmed by VivaScope 1500 and 21 (FN=39) by dermoscopy,

and out of 125 LM sites confirmed as negative by histopathology, 121 (FP=4) had been confirmed by VivaScope 1500 and 122 (FP=3) by dermoscopy.

Histopathology also showed 17/29 patients with visible lesions had evidence of subclinical disease more than 5 mm beyond the edge of the dermoscopically identified margin. In addition both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500. Thus, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.

1.4.2 Cost-effectiveness results

Existing evidence on the cost-effectiveness of VivaScope is particularly limited. One unpublished economic evaluation

The results of primary economic modelling indicate that VivaScope is likely a cost-effective strategy in the diagnostic assessment of skin lesions suspected for cancer (suspected melanomas with an equivocal finding in dermoscopy and suspected BCCs with an equivocal or positive finding in dermoscopy) and in the margin delineation of lentigo maligna prior to surgical treatment, even when VivaScope is used exclusively for one of the three indications assessed in the economic analysis. Results were affected by the intended use of VivaScope (i.e. exclusive use on diagnostic assessment of suspected melanomas, or diagnostic assessment of suspected BCCs, or pre-surgical mapping of lentigo maligna, or combined use for the diagnosis of suspected melanomas and BCCs, or use in all of the above indications). This is because the capital, maintenance and training costs of VivaScope are spread across a different number of lesions eligible for examination, which affects the intervention cost per lesion examined, and, ultimately, the total cost associated with the use of VivaScope.

The cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas with an equivocal finding in dermoscopy was affected by the diagnostic accuracy data utilised in the model, when VivaScope was assumed to be exclusively used for this purpose. Using the more 'optimistic' diagnostic data from Alarcon *et al*. resulted in a deterministic incremental cost effectiveness ratio (ICER) of £8,877/QALY (£9,362/QALY in probabilistic analysis), while the 'less favourable' diagnostic data from Pellacani *et al*. resulted in a deterministic ICER of £19,095/QALY (£25,453/QALY in probabilistic analysis). When use of VivaScope was expanded to include other indications assessed in the economic analysis, the use of VivaScope became the dominant strategy over routine management of equivocal lesions suspected for melanoma.

VivaScope was shown to be a dominant strategy when used for the diagnostic assessment of suspected BCCs with a positive or equivocal finding in dermoscopy, and this was independent of the intended use of the device (i.e. it was a dominant strategy when it was exclusively used for this purpose or when it was used for other indications covered by the economic analysis as well).

Regarding margin delineation of lentigo maligna, mapping with VivaScope was shown to be cost-effective, even if it was used exclusively for this purpose, as indicated by a deterministic ICER of £10,241/QALY (£11,651/QALY in probabilistic analysis). When VivaScope was used for diagnosis as well as mapping of lentigo maligna, then the intervention cost was reduced and it became a dominant strategy.

Overall, in the analyses that combined the different 'part' models designed for this report, VivaScope was shown to be a dominant strategy over routine management in the diagnostic assessment of suspected melanomas and BCCs alone or combined with margin delineation of lentigo maligna prior to surgical treatment.

One-way sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility due to scarring following surgical intervention of skin lesions on head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy.

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. All scenario analyses that were performed exclusively for the diagnostic assessment of suspected melanomas raised the ICER above the base case. However, when wider use of VivaScope was assumed, the results (VivaScope dominance) remained unaffected by the scenarios tested. Overall, the dominance of VivaScope was robust and unaffected by use of alternative data and assumptions when the system was assumed to be used for a combination of indications assessed in the economic analysis.

1.5 Discussion

The clinical effectiveness systematic review provides the most up-to-date evidence of the clinical effectiveness of VivaScope 1500 and 3000 for detecting and monitoring skin cancer, and with a low likelihood of missing any key or pivotal trial.

However there are some limitations of the review. First, there was absence of UK data in the included studies, hence the generalisability of the results in the UK setting. This has implications for the National Health Service (NHS).

Second, apart from diagnostic accuracy and lesion recurrence rate (only reported by one study), none of the outcomes specified in the protocol were reported in the included studies. Third, none of the included studies reported diagnostic accuracy results of SCC with VivaScope. This confirms evidence in the literature which suggest SCCs can be difficult to view using imaging techniques because their upper surface is often scaly, which can make it difficult to obtain sufficient resolution detail. Use of VivaScope in the evaluation of SCCs was not considered in the health economic evaluation.

Lastly in some of the included studies, there was paucity and/or quality of reported data on positive and negative test results, making it impossible to construct a 2x2 contingency table to calculate sensitivity and specificity.

On generalisability of the findings, although none of the included studies was conducted in the UK, two studies (Alarcon *et al.* 2014 from Spain, and Pellacani *et al.* 2014 from Italy) were deemed to be the most representative of clinical practice in the UK setting. This was validated by our clinical experts and these trials were taken forward for the health economic analysis.

The primary economic analysis undertaken for this assessment suggests that VivaScope is likely to be a cost-effective strategy in the diagnosis of suspected melanomas with an equivocal finding in dermoscopy, suspected BCCs with a positive or equivocal finding in dermoscopy, and in the mapping of lentigo maligna prior to surgical treatment in the UK. The economic analysis was based on the development of three 'part' models, each designed to simulate the care pathways of people with skin lesions eligible for examination with VivaScope that undergo assessment of their skin lesions in a dermatology MDT service. The care pathways were designed based on national guidelines and following advice from clinical experts, and were specific to each type of lesion considered in the economic analysis. Use of national guidance and consultation with clinical experts ensured that the care pathways considered in this model reflect, as close as possible, clinical practice in the NHS, although there appears to be wide variation in the management of suspected and/or confirmed skin cancer across services.

Model input parameters were based on national guidelines and other published evidence, clinical expert opinion and national unit costs. The diagnostic and mapping accuracy data were taken from studies included in the systematic literature review of clinical evidence conducted for this guideline. However, data were limited and it was not possible to synthesise the results in a meta-analysis due to heterogeneous nature of the studies identified. Moreover, none of the studies were conducted in the UK, which may have implications for the generalisability of the clinical, as well as the economic findings, since the prevalence of the skin cancer and the population phenotype distribution may affect the diagnostic accuracy of VivaScope.

Training in the use of VivaScope and the clinical interpretation of the findings is an important factor that is likely to drive the accuracy of VivaScope in the diagnostic assessment of suspected skin cancers and the mapping of skin lesions prior to surgical treatment. Although training costs were taken into account in the economic model, clinical expert advice indicated that, as expected, there is a learning curve following formal training, and the overall training required for a clinician to reach a good level of expertise comprises between 4 and 6 months' time, and approximately 1000 to 2000 cases evaluated with confocal microscopy in a setting including a sufficient number of melanomas (more than 200). This means that the benefits and cost-savings associated with VivaScope use that were suggested by the results of the economic analysis are likely to take some time to realise, as the diagnostic accuracy of VivaScope utilised in the economic analyses was taken from studies conducted in dermatology centres with expertise in the use of VivaScope, so optimal diagnostic outcomes were obtained.

The annual volume of lesions eligible for examination with VivaScope is important in determining the cost of VivaScope per lesion examined. There appears to be wide variation across dermatology in the UK in terms of the number and type of lesions examined annually. Nevertheless, this parameter was tested in sensitivity analysis.

Sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility due to scarring following surgical intervention of skin lesions on head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy. However, utility data relating to these events were very limited and of poor quality or non-existent, and a number of assumptions were needed in order to inform the model. Other complications of excision and biopsy, which was the main comparator of VivaScope in the diagnostic assessment of suspected cancerous lesions, such as bleeding, bruising, infection or allergic reaction to the topical antibiotic were not considered. Clinical experts acknowledged that these are not common complications, but their omission may have potentially underestimated, to some extent, the cost-effectiveness of VivaScope.

1.6 Conclusions

There is a paucity of randomised controlled trial (RCT) evidence for both diagnostic accuracy and margin delineation with VivaScope 1500 and 3000. However, VivaScope subsequent to dermoscopy may improve diagnostic accuracy of equivocal skin lesions compared to dermoscopy alone, particularly for malignant melanomas. In terms of margin delineation, VivaScope 1500 mapping for LM and LMM may improve the accuracy in terms of complete excision of lesions compared with dermoscopically determined margins.

In addition, use of VivaScope appears to be a cost-effective strategy in the diagnostic assessment of suspected skin cancer (more specifically, of suspected melanomas with an equivocal finding in dermoscopy and suspected BCCs with a positive or equivocal finding in dermoscopy) and the margin delineation of lentigo maligna prior to surgical treatment, in particular when VivaScope is used for all three indications considered in the economic analysis.

The use of VivaScope following dermoscopy may improve patient care and management, although there is an absence of UK data in the included studies and therefore generalisability of the results to the UK population is unclear. The results of the economic analysis indicate that use of VivaScope in dermatology MDT services is likely to reduce the patient distress and anxiety associated with diagnostic biopsy and excision of lesions suspected for skin cancer, reduce the future recurrence of lentigo maligna and the distress to the patients associated with surgical treatment, and lead to cost-savings to the NHS.

However, high quality RCTs are required in a UK population to assess diagnostic accuracy of dermoscopy plus VivaScope compared with dermoscopy alone in people with equivocal skin lesions and margin delineation accuracy of VivaScope compared with dermoscopy alone. Further research is also needed on the impact of tools and procedures associated with the diagnostic assessment and management of potentially cancerous skin lesions on people's health-related quality of life (HRQoL) in order to determine the cost effectiveness of alternative diagnostic strategies in this area with higher certainty.

2 BACKGROUND

2.1 Condition(s) and aetiology(ies)

Skin cancer is one of the most common cancers in the United Kingdom (UK). In 2011, 13,300 cases of malignant melanoma were diagnosed, and around 2,200 people died from the disease in the UK.[1] In 2010, around 100,000 people were diagnosed with non-melanoma skin cancer and there were 638 deaths from non-melanoma skin cancer in 2012.[2]

Skin cancer is commonly classified into melanoma skin cancer (also known as malignant melanoma) which develops from pigmented cells (melanocytes) in the epidermis, and non-melanoma skin cancer, which develops from cells that produce keratin (keratinocytes).[1]

Non-melanoma skin cancer can be further divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Malignant melanoma, SCC and BCC make up more than 95% of all skin cancers. In addition there are other rare types of non-melanoma skin cancer including Merkel cell carcinoma, Kaposi's sarcoma and T-cell lymphoma of the skin.[3]

The main risk factor for developing most types of skin cancer is exposure to ultraviolet (UV) radiation in the form of sunlight or use of sun beds. Other factors that may influence the risk of developing skin cancer include: age and sex, ethnicity, occupation, personal and family history of skin cancer, socioeconomic status and certain physical characteristics (light eyes or hair, fair skin which sunburns easily; having a lot of moles, unusually shaped or large moles, or a lot of freckles).[1,4-6]

2.1.1 Melanoma

Malignant melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cases[2] Like most cancers, skin cancer is more common with increasing age, but malignant melanoma rates are disproportionately high in younger people.[2] Malignant melanoma is almost twice as common in young women (up to age 34) as in young men, but more men die from it.[2] Malignant melanoma incidence rates have increased more than fivefold since the mid-1970s. People from more affluent areas are more likely to be diagnosed with malignant melanoma at an earlier stage than those from more deprived areas. The most common sites of melanoma in men are the trunk, head and neck, and arms, whereas in women they are trunk, legs and arms.[4] Survival of malignant melanoma has been improving for the last 25 years and is now amongst the highest for any cancer. Five-year survival ranges from 100% in cases diagnosed at the earliest stage, to 8% (men) and 25% (women) in cases diagnosed once the disease has spread. Around two-thirds of malignant melanoma cases are diagnosed at the earliest stage.[7]

There are several different types of melanoma:

Superficial spreading melanoma makes up around 70% of malignant melanomas. Initially this type usually grows outwards with low risk of metastasis, but when it eventually starts to grow down into the dermis it can acquire the capacity for invasion.[4]

Nodular melanoma is the most aggressive form of malignant melanoma. Fourteen percent of all melanomas are nodular and these comprise 37% of ultimately fatal lesions. They grow quickly downwards into the skin, and usually very dark with a raised area of skin, but may not necessarily develop from an existing mole.[8]

Lentigo maligna melanoma (LMM) arises from lentigo maligna (LM) or Hutchinson's freckle which present as macular pigmented lesions. It most commonly appears on the face or other areas of the skin which has high sun exposure. LM grows outwards very slowly, and it becomes malignant when it starts to grow down into the deeper layers of the skin. Around 10% of malignant melanomas are LMM.[4]

Acral lentiginous melanoma is a rare form of melanoma most commonly found on the palms of the hand, the soles of the feet or under or around the nails. It is the most common type of melanoma in people with dark skin.[4]

Amelanotic melanoma lacks the dark colour of usual melanomas. They are usually non-pigmented and may appear pink or red with light brown or grey edges. They make up around 5% of melanomas and are difficult to diagnose as they can easily be mistaken for other skin conditions.[4]

2.1.2 Non-melanoma skin cancers

There is known under-recording of non-melanoma skin cancer incidence with an estimated 30–50% of BCC and around 30% of SCC going unrecorded. This is partly because many cases are treated in primary care or privately and are not notified to the cancer registries, and partly because most cancer registries record only the first diagnosis of BCC or SCC.[7] Since non-melanoma skin cancer registrations are known to be incomplete, they are usually excluded from incidence totals for all cancers combined. Although non-melanoma skin cancer is extremely common, in the vast majority of cases it is detected early and is not usually life-threatening. However, around 590 people died from non-melanoma skin cancer in 2011 in the UK.[7]

2.1.3 Basal cell carcinoma (BCC)

BCC is the most common type of non-melanoma skin cancer, making up about 75% of non-melanoma cases.[6] It develops on areas of the skin with a high sun exposure like the nose, forehead and cheeks. BCC is slow growing and rarely spreads or becomes fatal, however it can invade other types of tissue such as cartilage and bone in the nose or ears. BCCs can be divided into several

subtypes based on morphology and development including nodular, superficial, morphoeic and pigmented BCCs.

BCC is more common in older people; people aged over 75 years are about five times more likely to have a BCC than those people aged between 50–55 years.[6] BCC is also more common in males than females. In the UK, the recorded incidence between 2000–2010 was around 36% in males and 32% in females.[9]

2.1.4 Squamous cell carcinoma (SCC)

SCC is a more serious, but less common, type of non-melanoma skin cancer than BCC, which has the potential to metastasize to other organs of the body.[10] Around 20% of diagnosed non-melanoma skin cancers are SCCs.[6] Between 2000–2010, the recorded incidence of SCC was 34% in males and 39% in females.[9]

SCC lesions often develop on sun exposed skin such as the head and neck, but they can also develop in areas of the skin that have been ulcerated for a long time, in scars, burns or in pre-existing lesions such as Bowen's disease. SCCs are usually crusty or scaly, but can also present as an ulcer without keratinisation.

2.2 Description of technology(ies) under assessment

The aim of skin cancer diagnosis is to identify truly positive lesions while curtailing the number of unnecessary biopsies. Reflectance confocal microscopy (RCM) is a non-invasive technique that allows examination of the epidermis and papillary dermis at cellular resolution.[11]

The VivaScope© imaging systems are non-invasive technologies designed to diagnose potentially malignant skin lesions. They capture highly magnified images of the upper layer of the skin. They are designed to be used in conjunction with dermoscopy to investigate potentially malignant skin lesions, thus providing a more accurate diagnosis leading to fewer biopsies of benign lesions and earlier detection of skin cancers. They may also be used as a guide to surgery to provide more accurate pre-surgical margins, preventing unnecessarily large scars for skin cancers in anatomic areas where tissue preservation is (e.g. face, hands, feet, genitals), and reducing the risk of recurrence.

A near infrared light source is used to visualize skin structures at different horizontal levels within the upper layer of the skin.[12] The images produced are based on the reflection and scattering of light from the examined tissue section. Different cell structures lead to different reflection patterns, which are seen as shades of grey in the captured image. Melanin, haemoglobin, cellular microstructures, and collagen serve as "endogenous" contrast agents. Melanocytic lesions could therefore be potentially well imaged using VivaScope.

2.2.1 VivaScope 1500

The stationary device of the VivaScope 1500 is designed for use on extremities such as the back of the hand or the back, chest, leg, arm, cheek, forehead. The horizontal resolution is reported to be 1.25 μm and the vertical resolution (layer thickness) is 3–5 μm, which corresponds to the layer thickness of normal histological examinations.[13] With the VivaScope 1500 individual images are 500 x 500 μm in size, however in total images of an area of between 1 x 1 mm to 8 x 8 mm may be captured. The imaging depth includes the upper layers of the reticular dermis.

VivaScope 1500 is a console-based unit. Examination using the VivaScope 1500 involves applying an adhesive window on the stainless steel ring of the device, which is fixed on the skin over the lesion. The VivaScope 1500 is positioned on the tissue ring and images can be recorded. The VivaScope 1500 also includes an integrated dermoscope.

2.2.2 VivaScope 3000

The handheld VivaScope 3000 is designed to access difficult to reach skin regions such as around the nose, ears, and eyes, or between fingers. From the technical specification, VivaScope 3000 can be used for diagnosis, as well as a guide to surgery to provide pre-surgical margins of tumours. The resolution for the VivaScope 3000 is the same as for the 1500, but the individual images are 1000 x 1000 μm for VivaScope 3000 and the image depth is reported as up to 200 μm depending on the tissue type.[13] The VivaScope 1500 and 3000 can be used as stand-alone units or together.

Earlier versions of VivaScope include VivaScope 1000 and VivaScope 2500. VivaScope 1000 is a stationary laser microscope device capable of imaging living tissue at the cellular level.[14] The VivaScope 2500 surgical cellular confocal imager allows the capture cellular resolution images of the skin and supporting stroma. These images are captured from bulk, excised tissue without the need for lengthy staining and sectioning protocols.[15]

2.2.3 Costs of VivaScope 1500/3000 and training needs

The costs associated with examination of skin lesions with VivaScope comprise the purchase (capital) cost of the VivaScope imaging system, maintenance costs, costs of equipment parts and other consumables required for the examination, and costs of training staff in operating the system and in the assessment and interpretation of the images obtained. They also include costs of staff time required for the examination with VivaScope and subsequent assessment of skin lesions.

According to the company, the purchase price and annual maintenance costs of VivaScope 3000 as an add-on device to VivaScope 1500 is lower than the respective costs of VivaScope 3000 as a stand-alone device.

Table 1. Summary of cost of VivaScope provided in the briefing note by company

Item	Cost
Indicative price of technology	£90,224 for VivaScope System (dermoscopy + RCM integrated)*
Consumables	£1.50/ adhesive window per patient lesion
Service/maintenance cost and frequency	£4,380
Anticipated life span of technology	10 years
Average length of use per treatment	10–15 minutes per treatment
Average frequency of use	15–20 per day
Average cost per treatment**	£120
Additional costs:	
• Adhesive windows*	100x/ 1 box = £147 (*for VivaScope® only)
• Tissue ring*	£55 (very durable steel ring, usually no replacement required unless loss)*
• Crodamol oil	£7.80
• Mediware Alco tip*	£3.30 (usually already available in the hospital, or other disinfectant)*
• Ultrasound gel*	£3.20 (usually already available in the hospital)*
• Cap for VivaScope 3000	£192 (2 caps are provided with the device, only in case of loss)*
* This price is for the VivaScope 1500 system. Price for a VivaScope 3000 as an add-on scan head to a VS1500 system is an additional £41,600; Price for a VivaScope 3000 stand-alone system (no VS1500) is £62,300; all prices +VAT, price variable depending on EUR:GBP exchange rate, based at 1 EUR = 84 GBP. ** The average costs per treatment are estimated on the basis of the 2014 NHS reference costs for dermatology outpatient attendance, non-admitted, face-to-face consultant-led examination. This is £109 and is taken to include dermoscopy. The additional time required for the VivaScope examination and the small additional consumable cost is factored in to arrive at an estimate of the average cost per treatment for the dermoscopy + VivaScope examination.	

Training on the use of VivaScope consists of the following (information provided by the company, supplemented by one of the clinical experts providing the training):

- Introductory training: this is provided on-site for free with the purchase of VivaScope, lasts approximately 1–2 days and involves mainly technical training but some basic clinical information is also offered. The purpose of training is to give technicians and clinicians (i.e. consultant dermatologist, consultant dermatological surgeon, technical assistant, pathologist, researcher) the ability to properly use the machine and the software, provide them with an understanding of the anatomical location of the image on the monitor and detect the most common and evident structures. Participants are given information image acquisition, data management, operational precautions, etc. The training course consists of presentations, the revision of manuals, the discussion of imaging guidelines and the consideration of appropriate studies of interest.

- Independent study with textbooks: this is complementary to the introductory training; VivaScope users are expected to revise two sophisticated imaging textbooks.

- Intensive expert training: this is also provided for free with the purchase of VivaScope and follows the introductory training and independent study; it is a 3-day course currently offered

4 times a year at the University of Modena and Reggio Emilia in Italy, but there are plans to expand it to referral centres in Europe, including the UK. The training in Italy is provided by four confocal experts that have been working with the VivaScope for more than 10 years, who guide the participants through the diagnosis of melanocytic lesions, non-melanocytic lesions, inflammatory skin diseases, cosmetic applications and others. It is considered essential part of the training.

- Online training course: provided for free with the purchase of VivaScope, this course consists of 100 cases with expert evaluation made available after student evaluation. It is considered part of the intensive expert training and is available with the purchase of VivaScope. The aim of this course is to establish the learning and test the trainee's skills.

2.2.4 Diagnosis using VivaScope

VivaScope can be used for diagnosis of different kinds of skin cancer by providing detailed images that show the morphology of potentially cancerous cells.

According to the company, the main criteria for a diagnosis of malignant melanoma with VivaScope include: the absence of the normal epidermis architecture, lack of delineation of the papillae (non-edged papillae), irregular nests of atypical melanocytes, and the presence of large and highly refractile cells with prominent nucleus in higher epidermal layers.[12]

VivaScope can also be used to diagnose BCC. Five main criteria have been described by the company as characteristic BCC changes that can be identified using the VivaScope: elongated, monomorphic nuclei; polarization of these cells along an axis; pronounced inflammatory infiltrate; increased as well as dilated blood vessels; and loss of epidermal honeycomb structure.[12] In addition, tumour cell islands with peripheral palisading, distinguishable from the dermis by a dark gap, are often identified in the dermis. This optical gap formation corresponds histologically to the accumulation of mucin.

SCCs can be difficult to view using imaging techniques because their upper surface is often scaly, which can make it difficult to obtain sufficient resolution detail.[12]

2.2.5 Relevant comparators

In clinical practice, lesions suspected of malignancy are assessed by visual examination of the lesion followed by dermoscopy by an experienced diagnostic clinician (dermatologist, plastic surgeon, nurse specialist, GPs). Decisions on tumour margin delineation prior to surgery are based on guidelines by the British Association of Dermatology (BAD).[16] For e.g. all suspected melanomas are excised with a 2.0 mm margin and then re-excision is based on the Breslow thickness. BCCs are generally excised with a 3.0 – 4.0 mm margin unless they are being excised by Mohs and if they are recurrent a 6.0 mm margin is sometimes used.[16]

2.3 Care pathways/current practice

According to clinical experts, patients with suspicious skin lesions are referred to secondary care by their general practitioner (GP). After a dermoscope examination, patients with benign lesions are discharged and those with suspicious clinical and dermoscopic features go straight diagnostic excision biopsy.

2.3.1 Melanoma

Melanoma remains relatively uncommon in primary care settings and therefore the opportunities to develop specific diagnostic skills are limited and all suspected melanoma lesions should therefore be referred within two weeks to an appropriate-core member of the local specialist multidisciplinary skin cancer team, Local Hospital Skin Cancer Multidisciplinary Team (LSMDT).[17]

The National Institute for Health and Care Excellence (NICE)[18] has produced the following draft guideline on the assessment and management of melanoma:

Box 1. NICE[18] draft guidelines on the diagnosis and management of melanoma

1. Dermoscopy and other visualisation techniques
    - Assess all pigmented skin lesions that are referred for further assessment, and during follow-up, using dermoscopy carried out by healthcare professionals trained in this technique;
    - Do not routinely use confocal microscopy or computer-assisted diagnostic tools to assess pigmented lesions.

2. Photography
    - For a clinically atypical melanocytic lesion that does not need excision at first presentation:

(a) Use baseline photography (preferably dermoscopic) and

(b) Review the clinical appearance of the lesion, using the baseline photographic images, three months after first presentation to identify early signs of melanoma.

3. Borderline and spitzoid melanocytic lesions
    - Discuss all suspected atypical spitzoid lesions at the specialist skin cancer multidisciplinary team meeting;
    - Make the diagnosis of a spitzoid tumour of unknown malignant potential on the basis of the histology, clinical features and behaviour;
    - Manage spitzoid tumours of unknown malignant potential as melanoma.

4. Managing American Joint Committee on Cancer (AJCC) stages 0–II melanoma
    - *Excision*

(a) Consider excision with a clinical margin of at least 0.5 cm for people with in situ (stage 0) melanoma;

(b) If an adequate histological margin is not achieved after excision for in situ melanoma, discuss further management with the multidisciplinary team;
(c) Offer excision with a clinical margin of at least 1.0 cm to people with AJCC stage I (Breslow thickness less than 2.0 mm) melanoma;
(d) Offer excision with a clinical margin of at least 2.0 cm to people with AJCC stage II (Breslow thickness 2.0 mm or more) melanoma.

In secondary care, assessment of suspected malignant lesions can be improved using dermoscopy. According to the Revised UK Melanoma Guidelines, [17] if malignancy cannot be excluded the lesion should be photographed and then completely excised. The excision biopsy should include the whole tumour with a clinical peripheral margin of 2.0 mm with a cuff of underlying sub-dermal fat. Definitive diagnosis is then made by histopathological review of the biopsy. If malignancy is confirmed subsequent treatment options are then based on the Breslow thickness of the tumour.

In cases where it is not possible to diagnose a lesion as a melanoma or a benign melanocytic naevi (the so-called 'melanocytic lesion of uncertain malignant potential' (MUMP)) ,[19] the patient should be referred to a Specialist Skin Cancer Multidisciplinary Team (SSMDT) for clinical and pathological review.[17] A decision to treat as a melanoma should be made by the SSMDT in discussion with the patient.

Incision or punch biopsy may be used for diagnosis of LM or acral melanoma. However, with LM there is a risk of subclinical microinvasion i.e. progression into an LMM, which may be missed because of sampling errors when using incisional biopsies.

Surgery is the only curative treatment for melanoma. Following excision biopsy for diagnosis, a wider and deeper margin, based on Breslow thickness, may be needed to ensure complete removal of the primary lesion and any micro-metastases.[17] Recommended surgical excision margins are summarized in Table 1. Though, the final decision about the size of the margin should be made after discussion with the patient, taking into consideration functional and cosmetic implications of the margin chosen.

Table 2. Recommended surgical excision margins

Breslow thickness	Excision margins
In situ	5.0 mm
< 1.0 mm	1.0 cm
1.01–2 mm	1–2 cm
2.1–4 mm	2.0 cm
> 4 mm	2–3 cm[20,21]

For LM the aim is to excise the lesion completely with a clear histological margin after which no

further treatment is then required. For large in situ LMM, surgical margins greater than 0.5 cm may be necessary to achieve histologically negative margins.[22] There may also be clinical situations where treatment by other methods such as radiotherapy, or observation only may be appropriate.

2.3.2 Basal cell carcinoma (BCC)

Lower-risk nodular BCC may be removed in primary care by suitably qualified GPs (only in low risk sites, below the head and neck and less than 2cm in diameter). However, if there is uncertainty around the diagnosis or if the BCC is of any other, high-risk subtype it should be referred to a LSMDT.[23] In most cases dermatologists can make a confident diagnosis of BCC by visual examination of the lesion, which may be helped by dermoscopy. If there is uncertainty around the BCC diagnosis or around the subtype of BCC, which may influence prognosis or treatment selection, diagnosis should be confirmed by biopsy and histology. The aim of treatment of BCC is to remove the tumour while resulting in a cosmetic outcome that is acceptable to the patient.[23]

The treatment options for BCC depend on if the lesion is classified as low- or high-risk of recurrence following treatment, which depends on a range of prognostic factors including:

- Tumour size (increasing size indicate a higher risk of recurrence);
- Tumour site (lesions on the central face, especially around the eyes, nose, lips and ears, are at higher risk of recurrence);
- Definition of clinical margins (poorly defined lesions are at higher risk of recurrence);
- Histological subtype (certain subtypes leads to a higher risk of recurrence);
- Failure of previous treatment (recurrent lesions are at higher risk of further recurrence).

Techniques that do not allow histological confirmation of tumour clearance are generally only used for low-risk BCC lesions. These include cryosurgery, curettage, radiotherapy, topical treatments such as imiquimod, and photodynamic therapy. The exception is radiotherapy and Mohs surgery which are also used for high-risk BCC. Surgical excision is widely used to treat both low- and high-risk BCC.[23]

2.3.3 Squamous cell carcinoma (SCC)

In common with all suspected melanoma, every SCC presenting in primary care should be referred, under the two week rule, to the Local Skin Multidisciplinary Team (LSMDT), which will establish the diagnosis histologically.[17]

The majority of SCC tumours are at low risk of metastases, but it is essential to identify the estimated 5% of SCC tumours that are high risk.[10] SCC tumours are deemed low or high risk based on several

prognostic factors that may influence their metastatic potential, including: tumour site, size, thickness and level of invasion, rate of growth, aetiology, presence of perineural or lymphovascular invasion, degree of histological differentiation (subtype), and host immunosuppression.[10] However, the malignant behaviour of SCC tumours varies greatly.

The aim of treatment is complete removal of the primary tumour and any metastases. The success of treatment is highly dependent on definition of tumour margin. The gold standard for tumour margin identification is histological assessment. However, determining tumour extent may be challenging, particularly when the margins of the tumour are ill-defined or any metastases are discontinuous from the primary tumour. Locally recurrent tumours may arise either due to failure to treat the primary tumour, or from local metastases.[10]

Surgical excision (including Mohs micrographic surgery (MMS), a highly specialised surgical method for removing high risk skin tumours) is the primary treatment option for the majority of SCCs. The advantage of surgical excision is that it provides tissue for histological examination, which allows assessment of the adequacy of treatment and for further surgery if necessary. Other treatment options include curettage and cautery, and cryosurgery for small, well-defined, low-risk tumours, and radiotherapy for non-resectable tumours with ill-defined margins.[10]

2.3.4 Place of intervention in diagnosis and treatment pathway

VivaScope 1500 is intended as an add-on test to dermoscopy used in hospital settings to avoid biopsy for potential malignant melanoma, LM, BCC, or SCC skin lesions. It may also be used to diagnose skin cancer in patients with equivocal melanocytic skin lesions who would otherwise have been biopsied. VivaScope 3000 can be used both for lesion diagnosis and to define the margins of melanoma, BCC, SCC, and LM skin lesions to guide surgical excision.

The NICE[18] guideline on the assessment and management of melanoma, is currently out for consultation with stakeholders until 13 March 2015. The final publication is expected in July 2015.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

Population

The VivaScope 1500 and 3000 imagine system was assessed in the diagnosis of skin cancer in the following populations:

- People with suspected melanoma, who have equivocal lesions following dermoscopy;
- People with suspected BCC, whose lesions have a positive result in dermoscopy, to confirm diagnosis as an alternative to diagnostic biopsy.

The above populations were considered to be the most relevant to undergo diagnostic assessment with VivaScope, according to clinical experts to the Evidence Assessment Group (EAG). NICE scope defines the study population as 'people with equivocal lesions following dermoscopy'; however, clinical experts advised the EAG that suspected BCC lesions are rarely equivocal in dermoscopy and that the use of VivaScope in suspected BCC would be mainly to confirm diagnosis in lesions that were found positive in dermoscopy, as an alternative to diagnostic biopsy.

Equivocal lesions include any lesions that are suspected for melanoma based on a number of characteristics in dermoscopy, with the exception of clear positive (cancerous) lesions that have all the dermoscopic characteristics of melanoma and clear negative (benign) lesions that show no features for melanoma (no changes) in dermoscopy.

The risk of equivocal lesions being malignant is overall low. There are different degrees of 'equivocalness', depending on the dermoscopic characteristics of the lesion and subjective experience and interpretation.

Clinical expert advice indicated that highly suspicious equivocal lesions are:

- Lesions with at least two positive dermoscopic features including one major criterion, or three minor positive features suggestive of melanoma, and/or
- Lesions clearly changed after digital follow-up, and/or
- New or growing lesions in an adult with at least one dermoscopic positive criterion, or papular/nodular or pink or spitzoid lesions.

In all those cases excision is prompted and examination with VivaScope does not represent a real advantage since the risk to miss a melanoma remains too high.

Moderately or low suspicious equivocal lesions are:

- Lesions with only one major dermoscopic positive feature or two minor features, and/or
- No clear history or minor changes.

In such cases, excision is possible but other options could be taken into account, such as digital follow-up, especially in the case of flat lesions in patients with multiple moles; however, digital follow-up has the risk to delay a melanoma diagnosis. The majority of moderately or low suspicious equivocal lesions that are excised are benign and examination with VivaScope can play a major role in reducing this burden of unnecessary excisions.

Clinical experts advised that VivaScope is less suitable for the detection and assessment of skin lesions suspected for SCC, as this type of skin cancer is usually scaly because of severe hyperkeratosis. This often limits the evaluation of SCC lesions as it is more difficult to capture images of structures deeper in the tissue. Moreover, no evidence on the diagnostic accuracy of VivaScope in this type of skin cancer was identified in the systematic review of clinical evidence. Therefore, it was decided not to include people with skin lesions suspected for SCC in the diagnostic economic model.

Regarding margin delineation, VivaScope 3000 was assessed in the following population:

- Patients with lentigo maligna prior to surgical management.

According to clinical expert advice, margin delineation of melanomas with VivaScope is not useful in clinical practice, as the margins of melanomas are clearly defined and can be completely excised following BAD guidance;[(5)] consequently, VivaScope mapping of melanomas does not offer any clinical utility and therefore was not considered further for economic modelling.

Clinical experts advised that margin delineation of BCCs using VivaScope may be difficult, as BCCs may be too deep so their margins may not be accurately mapped with VivaScope.

VivaScope is not appropriate for the assessment of SCC lesion margins, due to the reasons discussed above.

Setting: Secondary care.

Intervention and comparator

Interventions:

- Diagnosis – Assessment of the lesion by dermoscopy plus VivaScope or VivaScope alone by an experienced skin cancer specialist.
- Delineation of lesion margins – Assessment of the lesion by dermoscopy plus VivaScope or VivaScope alone by an experienced skin cancer specialist.

Although this report is mainly aimed at the current versions of VivaScope (1500 and 3000), earlier versions such VivaScope 1000 and 2500 were also considered as they may provide additional potential information on the current versions.

Comparators:

- The comparator eligible for inclusion for the assessment of both diagnostic accuracy and delineation of lesion margins was visual assessment of the lesion followed by dermoscopy and clinical judgement by experienced skin cancer specialist.

Reference standard:

- The eligible reference standard for the assessment of diagnostic accuracy and margin delineation was histopathology or biopsy of the excised skin lesion.

Outcomes

The following outcomes were considered subject to available evidence from included studies;

Diagnosis:

- Diagnostic accuracy;
- Time to test result;
- Test failure rate, e.g. imaging failure;
- Number of biopsies performed and repeat biopsies;
- Morbidity associated with biopsy such as pain and swelling;
- Extent of scarring and associated psychological impact;
- Adverse events from biopsy including infections;
- Adverse events from false test results including patient distress and sequelae;
- Health related quality of life (HRQOL);
- Cost-effectiveness.

Delineation of lesion margins:

- Diagnostic accuracy;
- Time to result;
- Imaging failure rate;
- Number of surgical procedures/surgical stages;
- Morbidity associated with excision surgery such as pain and swelling;

- Recurrence rates;
- Extent of scarring and associated psychological impact;
- Adverse events from false test results including patient distress and sequelae;
- Adverse events from surgery including infections;
- Health related quality of life;
- Cost-effectiveness.

3.2 Overall aims and objectives of assessment

To evaluate the clinical and cost effectiveness of the non-invasive reflectance confocal microscopy (RCM) VivaScope 1500 and 3000 imaging systems, to avoid unnecessary biopsy of equivocal skin lesions suspected to be malignant melanoma, LM, BCC, or SCC relative to current practice.

To evaluate the clinical and cost effectiveness of the non-invasive RCM VivaScope 3000 imaging system in defining the margins of melanoma, BCC, SCC, and LM skin lesions relative to current practice.

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

4.1 Methods for reviewing clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of VivaScope 1500 for lesion diagnosis and VivaScope 3000 for margin delineation. However, the scope was broadened to include previous or earlier versions such as VivaScope 1000 and 2500 in order to capture data that may be missing with the current versions.

The systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[24] and in the NICE Diagnostic Assessment Programme manual.[25]

4.1.1 Inclusion and exclusion criteria

Inclusion and exclusion criteria in terms of population, interventions and comparators, reference standard test and outcome measures have been described in Section 2.

Study design

The following types of studies were eligible for inclusion:

- Randomised controlled trials or observational studies, where participants are assigned to dermoscopy plus VivaScope or VivaScope alone for diagnosis or skin lesion delineation, and where outcomes are compared at follow-up.
- Test accuracy studies assessing the test accuracy of dermoscopy plus VivaScope or VivaScope alone with histology of biopsy as the reference standard.

The following study/publication types were excluded:

- Pre-clinical and animal studies;
- Reviews, editorials, and opinion pieces;
- Case reports.

4.1.2 Search strategy

The searches combined terms for the condition and terms for the technology being assessed. For the technology we used both generic terms (e.g. reflectance confocal microscope) and terms for the specific product (e.g. VivaScope). The search strategy was refined by scanning key papers identified during the review, through discussion with the review team, clinical experts and information specialists.

Electronic sources included: MEDLINE, EMBASE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, and CENTRAL).

Electronic databases were searched from database inception on 14th October 2014 and results uploaded into Endnote Version 7.2 and de-duplicated. Full details of the terms used in the searches are presented in Appendix 9.1. The searches were updated on 11th February 2015.

Two reviewers independently screened all titles and abstracts according to the inclusion criteria. Full paper manuscripts of any titles/abstracts of potential relevance were obtained and assessed independently by two reviewers. Authors of papers for which insufficient details were available to allow data extraction and/or critical appraisal of study quality were contacted. Discrepancies between the two reviewers were resolved by consensus, with involvement of a third reviewer when necessary.

Potentially important ongoing and unpublished UK-based studies were also searched using: clinicaltrials.gov, controlled-trials.com, clinicaltrialsregister.eu. Reference lists of included papers were assessed for additional relevant studies, and clinical experts were also contacted for additional information on published and unpublished studies.

Relevant reviews and guidelines were identified through searching additional resources, including Clinical Evidence, National Institute for Health and Care Excellence (NICE) website, National Institute for Health Research (NIHR) Health Technology Assessment Programme, National Health Service (NHS) Evidence – National Library of Guidelines, Scottish Intercollegiate Guidelines Network (SIGN) Guidelines, and Guidelines International Network (GIN) website.

In addition, abstracts from the following key conference proceedings were searched for relevant studies from 2012:

- Annual meeting of the British Association of Dermatologists (BAD);
- Annual meeting of the British Society of Dermapathology (BSD);
- Congress of European Association of Dermato-Oncology (EADO);
- Annual meeting of the American Academy of Dermatology (AAD);
- Annual meeting of the American Society of Dermapathology (ASDP).

No limits relating to language of publication were applied to the searches.

4.1.3 Inclusion screening and data extraction

Data were extracted using a standardised data extraction form by one reviewer, and validated by a second reviewer after the pilot of 6 studies that was done in duplicate. Information extracted included details of the study's design and methodology, intervention and comparator tests, reference standard,

baseline characteristics of participants, and outcome measures, including clinical outcome efficacy and any adverse events. Discrepancies between the two data extractors were resolved by discussion, with involvement of a third reviewer if necessary or contact with study authors for clarification.

4.1.4 Quality assessment

The quality of included studies was assessed by two reviewers and the two extractions were validated. Any disagreements were resolved by consensus and if necessary a third reviewer was consulted. The quality of diagnostic studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool,[26] according to recommendations by the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[27] Where clinical effectiveness studies were identified that met the eligibility criteria we assessed their quality according to the study design; randomised controlled trials according to recommendations by the CRD and the Cochrane Handbook for Systematic Reviews of Interventions[28,29] and recorded using the Cochrane Risk of Bias Tool. When suitable for inclusion, cohort studies were assessed using the Newcastle–Ottawa Scale.[30]

4.1.5 Methods of analysis/synthesis

Details of results on test accuracy, clinical effectiveness and quality assessment for each included study was presented in structured tables and as a narrative summary.

For test accuracy data, results of sensitivity, specificity, PPV, and NPV are presented in this report. Where these were not reported, absolute numbers of true positive, false negative, false positive and true negative test results were used to calculate sensitivity and specificity values.

Where results could be combined, we intended to use absolute numbers of effect or aggregate data (means) with standard deviations in standard frequentist meta-analyses to produce forest plots of pooled data. Heterogeneity was to be assessed by doing a sensitivity analysis regardless of the I^2 statistic.

We also planned to analyse accuracy data using patient-level data and not lesion-level data because of the difficulty in estimating within-study variance.[31] Estimates of sensitivity and specificity and their respective confidence intervals were to be plotted in forest plots to explore heterogeneity in the first instance. A random effects meta-analysis was planned to fit the bivariate summary receiver operating characteristics (SROC) curve model with the with-in study variance fitted as binomial.[32]

4.2 Results of the assessment of clinical effectiveness

4.2.1 Quantity and quality of research available

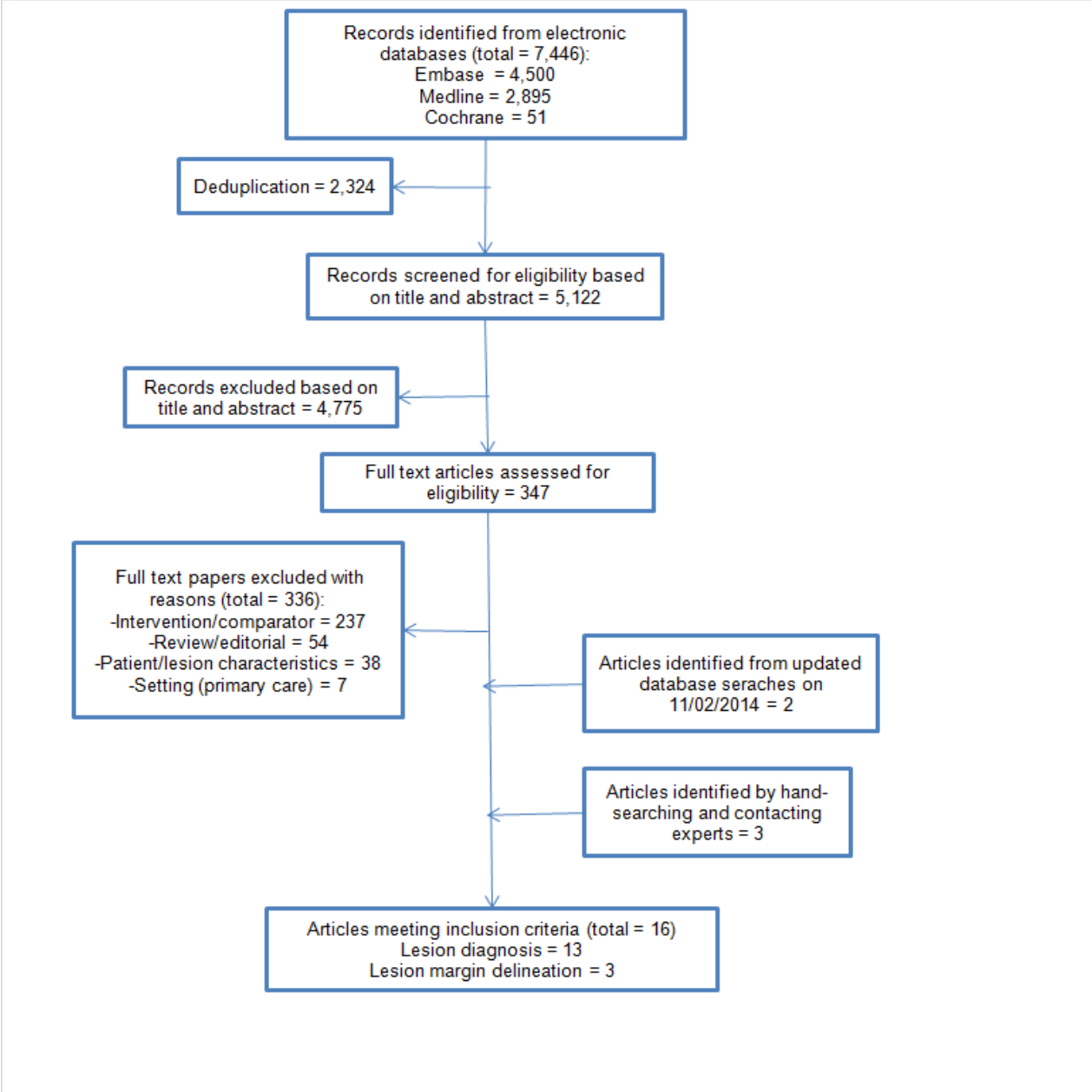
4.2.1.1 Included studies

A total of 7,446 records were identified from clinical effectiveness searches in electronic databases. After de-duplication, 5122 records were screened for eligibility based on title and abstract (Figure 1).

Full publications of 347 references were ordered and after screening for eligibility, 11 studies[33-43] met the inclusion criteria. The database searches were updated from October 2014 to February 2015, and a further two studies[44,45] that met the inclusion criteria were identified. Three additional studies[46-48] were obtained by contacting clinical experts in the field. Thus in total 16 studies were identified that met the inclusion criteria for the review. No study was identified from conference proceedings that met the inclusion criteria.

Figure 1 shows the flow diagram for included and excluded studies of clinical effectiveness. A list of excluded references (with reason for exclusion) is presented in Appendix 9.4, and Appendix 9.5 shows a list of ongoing trials identified from searching trial registers.

Figure 1. PRISMA flow diagram for studies included and excluded from the clinical effectiveness review



4.2.1.2 Study characteristics

Study indication

Out of the 16 included studies, thirteen[33-37,39,41-43,46-49] indicated the use of VivaScope or reflectance confocal microscopy (RCM) in diagnosing suspected or equivocal lesions, and three studies indicated in lesion margin delineation.[38,40,44]

Population

There were different inclusion criteria for all the included studies. Patients in the 13 studies indicated for lesion diagnosis had suspicious lesions[39,42,43,49] or dermoscopically equivocal lesions (melanoma, basal cell carcinoma [BCC]).[33-37,41,46,48] The three studies indicated for lesion margin diagnosis enrolled patients with LM lesion larger than 5 cm that would require complex reconstructive surgery or recurrent lentigo maligna (LM)[38] or patients with clinically suggestive BCC[40] or surgically removed BCCs.[44]

Only three studies specified exclusion criteria. Reasons for exclusion included LM and lesions of the soles and palms;[37] or lesions not amenable to RCM (i.e. physically inaccessible site), or if they had a previous diagnostic biopsy done on the lesion;[39] or clinical and/or dermoscopic clear-cut epithelial tumours.[45]

For the 13 studies indicated for lesion diagnosis, the number of participants enrolled ranged from 42[34] to 423[45] while the number of participants indicated for studies in lesion margin delineation ranged from 10[40] to 74[44]. However the unit of analysis in the included studies was patient level data[33,37,39,48] or lesion level data[33-36,41,42,45,46] or the number of positive or negative sites[38,40,44]. The reported median age ranged from 47[37] to 62 years,[43] and mean age from 44.2[39] to 71 years.[38]

Study design

In 10 out of the 13 studies indicated for lesion diagnosis, consecutive patients were enrolled prospectively from settings including melanoma or dermatology clinics in tertiary or university hospitals,[33-35,37,39,41-43,45,46] while one study each retrospectively selected images of previously imaged set of lesions[36] or excised lesions[43,48]. Of the three studies indicated for lesion margin diagnosis, one retrospectively assessed and interpreted lesion images in patients previously enrolled in two university-based clinics/hospitals[38] and two prospectively recruited patients/lesions randomly from a dermatology department[40] or Mohs surgery unit.[44]

Intervention and comparator

Of the 13 studies indicated for lesion diagnosis, two used VivaScope 1500 with dermoscopy,[33,45] four and without dermoscopy[34,42,43,48] as comparator, and one study used VivaScope 1500 or 3000 with dermoscopy as comparator.[46] Due to lack of data, we included additional studies without dermoscopy as comparator.

For earlier versions of VivaScope, one study used VivaScope 1000 with dermoscopy as comparator,[39] two used VivaScope 1000 without a comparator,[35,36] two studies used both VivaScope 1000 and VivaScope 1500, with one[37] using dermoscopy as comparator while the other had no comparator.[41] Only one study[44] used VivaScope 2500.

Two of the studies indicated for lesion margin diagnosis used VivaScope 1500 with[38] or without dermoscope as comparator[40] and one used VivaScope 2500.[44]

The VivaScope used in the included studies were from two companies: VivaScope 1500, 2500 and 3000 (Caliber Imaging and Diagnostics, Rochester, NY, USA) and VivaScope 1000 and VivaScope 1500 (Lucid Inc, Rochester, NY, USA or Lucid Inc., MAVIG GmbH, Munich, Germany). The source of light in the VivaScope was 830 nm near infra red laser beam with a power of either ≥35 mW or <35 mW.

Assessors who reviewed and interpreted images obtained from VivaScope were trained in the RCM technology. All the studies except four[40,42,45,48] reported qualitative and/or quantitative diagnostic thresholds using morphological features or algorithms validated in previous published studies.

Dermoscopy used as a comparator test in some studies was either dermoscope© (DermLite Photo; 3Gen LLC, Dana Point, CA, USA)[33,37,39,42,45] or a dermoscopic camera attached to a VivaScope 1500.[34]

Histopathological assessment of excised lesions (biopsy) was used as reference standard in all the included studies before[35-37,44] or after use of VivaScope.[33,34,38-42,45,46,48] Where histopathology was done before the use of VivaScope, assessors of the results of the histopathology were blinded to the results of the VivaScope. Details regarding histopathological analysis were described in only one study.[40]

Characteristics of the studies included in the review are given in Table 3.

Table 3. Summary of studies included in the review of clinical effectiveness

Study and Location	Study design	Participant and lesion characteristics	Prevalence of skin cancer/lesions in the study population	Index test characteristics	Comparator characteristics	Reference standard
Lesion diagnosis						
Alarcon *et al.* 2014[33] Spain	Prospective observational	Patients (n=343) with equivocal pigmented lesions 343 lesions (92 melanomas, 12 BCCs, benign naevi and others, 239) Age: median 54.7 years (range 8-89)	Melanoma = 26.8% BCC = 3.5% Benign lesions = 69.7%	VivaScope 1500 Caliber Imaging and Diagnostics, Rochester, NY, U.S.A.). Light source: 830 nm near-infrared laser at maximum power of 35 mW	Dermoscope (DermLite Photo; 3Gen LLC, Dana Point, CA, U.S.A.)	Histopathology
Castro *et al.* 2014[46] Brazil and USA	Prospective observational	Patients (n=73) with skin lesions suspicious for BCC based on clinical and dermoscopic examination. 92 lesions	BCC = 83%	Vivascope3000; (CaliberID) Vivascope1500; (CaliberID)	NC	Histopathology
Curchin *et al.* 2011[34] Australia	Prospective observational	Patients (n=42) with equivocal lesions 50 lesions (13 melanomas, 22 benign naevi, 9 BCC, and 6 SCC) Age: NR	Melanoma = 26% BCC = 18% SCC = 12%	VivaScope 1500 (Lucid Inc, Rochester, NY, USA) with a dermoscopic camera attached	NC	Histopathology
Ferrari *et al.* 2014[47] Italy	Retrospective observational	322 melanocytic lesions excised on the basis of equivocal clinical and/or dermoscopic features		VivaScope1500; MAVIG GmbH, Munich	Dermoscope (Dermlite Photo (3GEN, S Juan Capistrano, CA, USA)	Histopathology
Gerger *et al*. 2006[35] Austria	Prospective observational	Patients (n=119) with skin tumours 27 melanomas, 15 BCC, 90 benign naevi, 30 seborrheic keratosis [SK]) Age: NR	Melanoma = 16.7% BCC = 9.3%	VivaScope 1000. Light source:830 nm near infra red diode laser Power: <35 mW	NC	Histopathology
Gerger *et*	Retrospective	Patients (n=60) with melanocytic	Melanoma = 28.6%	VivaScope 1000; Lucid	NC	Histopathology

Study and Location	Study design	Participant and lesion characteristics	Prevalence of skin cancer/lesions in the study population	Index test characteristics	Comparator characteristics	Reference standard
al. 2008[36]‡ Austria	observational	skin tumours 20 melanomas, and 50 benign naevi) Age: NR		Inc., Rochester, NY). Light source: 830 nm diode laser at power of <35 mW		
Guitera *et al.* 2009[37] Australia and Italy	Prospective observational	Patients (n=326) with equivocal lesions selected for excision after clinical examination 326 lesions (123 melanomas and 203 naevi) Age: median 47 years (range 6-90)	Melanoma = 37.7%	VivaScope 1000 or VivaScope 1500, Lucid Inc., Henrietta, NY). Light source: 830 nm laser	Dermoscope	Histopathology
Guitera *et al.* 2010[43] Australia and Italy	Retrospective observational	Patients (n=219) with clinically equivocal, macules of the face 284 lesions (81 LM and 203 benign macules) Age: mean 62 years (range 51-72)	LM = 28.5% Benign macules = 71.5%	VivaScope 1500, Lucid, Henrietta, NY, Light source: 830 nm laser beam with a maximum power of 35mW	NC	Histopathology
Langley *et al.* 2007[39] Canada	Prospective observational	Patients (n=125) scheduled for biopsy of suspected lesions 125 lesions (37 melanomas, and 88 melanocytic naevi) Age: mean 44.2 years (range 16-84)	Melanoma = 29.6%	VivaScope 1000, Lucid Inc., Henrietta, N.Y., USA	Dermoscope, specifications not reported	Histopathology
Pellacani *et al.* 2007[41] Italy	Prospective observational	Patients (n=332) with melanoma and equivocal lesions 136 melanomas, and 215 naevi Age: median 47.7 years (IQR 36 - 60)	Melanoma = 38.7%	VivaScope 1000/1500, Lucid Inc., Henrietta, New York. Light source: 830 nm near infrared laser beam at maximum power of 35mW	NC	Histopathology
Pellacani *et al.* 2014[45]	Prospective observational	Patients (n=423) with suspicious requiring a mole check and/or with a suspect of melanoma	Melanoma = 5.9% BCC = 7.9% Benign lesions =	VivaScope 1500, MAVIG GmbH, Munich, Germany.	Dermoscopy (Dermlite HR (3Gen® LLC, San Juan	Histopathology

Study and Location	Study design	Participant and lesion characteristics	Prevalence of skin cancer/lesions in the study population	Index test characteristics	Comparator characteristics	Reference standard
Italy		493 lesions (29 melanomas, 39 BCC, 425 benign lesions) Age: mean 40.7 years (range 28.5 - 52.5)	86.2%	Light source: 830 nm near-infrared laser beam at power of 20 mW	Capistrano, CA, U.S.A)	
Rao *et al.* 2013[42] USA	Prospective observational	Patients (n=334) with lesions selected for removal 9 melanomas, 27 BCC, 43 SCC, 255 naevi, 26 AK, 24 other benign lesions Age: NR	Melanoma = 2.3% BCC = 7% SCC = 11.2%	VivaScope 1500, CaliberID, Rochester, NY.	NC	Histopathology
Stanganelli *et al.* 2014[48] Italy	Retrospective observational	Patients (n=70) with equivocal lesions that lacked clear dermoscopy criteria for melanoma 70 lesions (12 melanomas, 58 benign lesions) Age: NR	Melanoma = 17.14% Benign lesions = 82.9%	VivaScope 1500 (Lucid Inc., MAVIG GmbH, Munich, Germany). Light source: 830-nm laser at a maximum power of 20 mW.	NC	Histopathology
Lesion margin delineation						
Bennassar *et al.* 2014[44] Spain	Prospective observational	Patents (n=74) with surgically removed BCCs from Mohs surgery. 80 BCC with 480 images	BCC = 100%	VivaScope 2500; Caliber Imaging and Diagnostics, Rochester, NY, USA	NC	Histopathology
Guitera *et al.* 2013[38] Australia and Italy	Retrospective observational	Patients (n=37) with large facial lesions requiring surgery 32 LM, and 5 LMM Age: mean 71 years (range 47-88)	LM/LMM = 100%	VivaScope 1500; Lucid Inc. Light source: 830-nm laser beam at maximum power of 35 mW	Dermoscope	Histopathology
Pan *et al.* 2012[40] China	Prospective observational	Patients (n=10) with lesions clinically suggestive of BCC 10 lesions	BCC = 70%	VivaScope 1500; Lucid Technologies, Henrietta, NY). Light source: 830 nm	NC	Histopathology

Study and Location	Study design	Participant and lesion characteristics	Prevalence of skin cancer/lesions in the study population	Index test characteristics	Comparator characteristics	Reference standard
		Age: NR		laser with a power of <15 mW		
Abbreviations used in table: AK, actinic keratosis; BCC, basal cell carcinoma; IQR, interquartile range; LM, lentigo maligna; LMM, lentigo maligna melanoma; NC, no comparator; SCC, squamous cell carcinoma; SK, seborrheic keratosis; SL, solar lentigo. Footnote used in the table: ‡supplementary publication of Gerger 2006.						

Outcomes

The outcomes of interest to this review, which were reported in the included studies are listed in Table 3. The most commonly reported outcome specified in the methods section is diagnostic accuracy, which was reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Other diagnostic accuracy data such as false positive (FP), false negative (FN), and true negative (TN) were rarely reported and had to be estimated/calculated using other reported diagnostic data where possible.

Therefore due to the absence of more clinical data as specified in the protocol, additional clinical outcomes not specified in the methods section but deemed clinically relevant are reported in Table 3. These included misdiagnosis or misclassification of lesions, and change in management of lesions after confirmation or final diagnosis with histopathology.

Table 4 shows outcomes of interest reported in included studies.

Table 4. Outcomes of interest reported in included studies of clinical effectiveness

Studies	Diagnostic accuracy	Time to test failure (e.g. imaging failure rate)	Number of biopsies performed and repeat biopsies	Morbidity associated with excision such as pain and swelling	Extent of scarring and associated psychological impact	Lesion recurrence rates	Adverse events from biopsy or false test results	Health-related quality of life	Misdiagnosis/ misclassification of lesions	Change in management of lesions
Alarcon 2014[33]	✓					NA				
Bennassar 2014[44]	✓	NA	NA							
Castro 2014[46]	✓					NA				
Curchin 2011[34]	✓					NA				
Ferrari 2014[47]	✓					NA				
Gerger 2006[35]	✓					NA				
Gerger 2008[36]	✓					NA				
Guitera 2009[37]	✓					NA			✓	
Guitera *et al.* 2010[43]	✓					NA				
Guitera 2013[38]	✓	NA	NA			✓				✓

Studies	Diagnostic accuracy	Time to test failure (e.g. imaging failure rate)	Number of biopsies performed and repeat biopsies	Morbidity associated with excision such as pain and swelling	Extent of scarring and associated psychological impact	Lesion recurrence rates	Adverse events from biopsy or false test results	Health-related quality of life	Misdiagnosis/ misclassification of lesions	Change in management of lesions
Langley 2007[39]	✓					NA			✓	
Pan 2012[40]	✓	NA	NA							
Pellacani 2007[41]	✓					NA				
Pellacani 2014[45]	✓					NA			✓	
Rao 2013[42]	✓					NA				
Stanganelli 2014[48]	✓					NA				
Abbreviations used in this table: NA, not applicable										

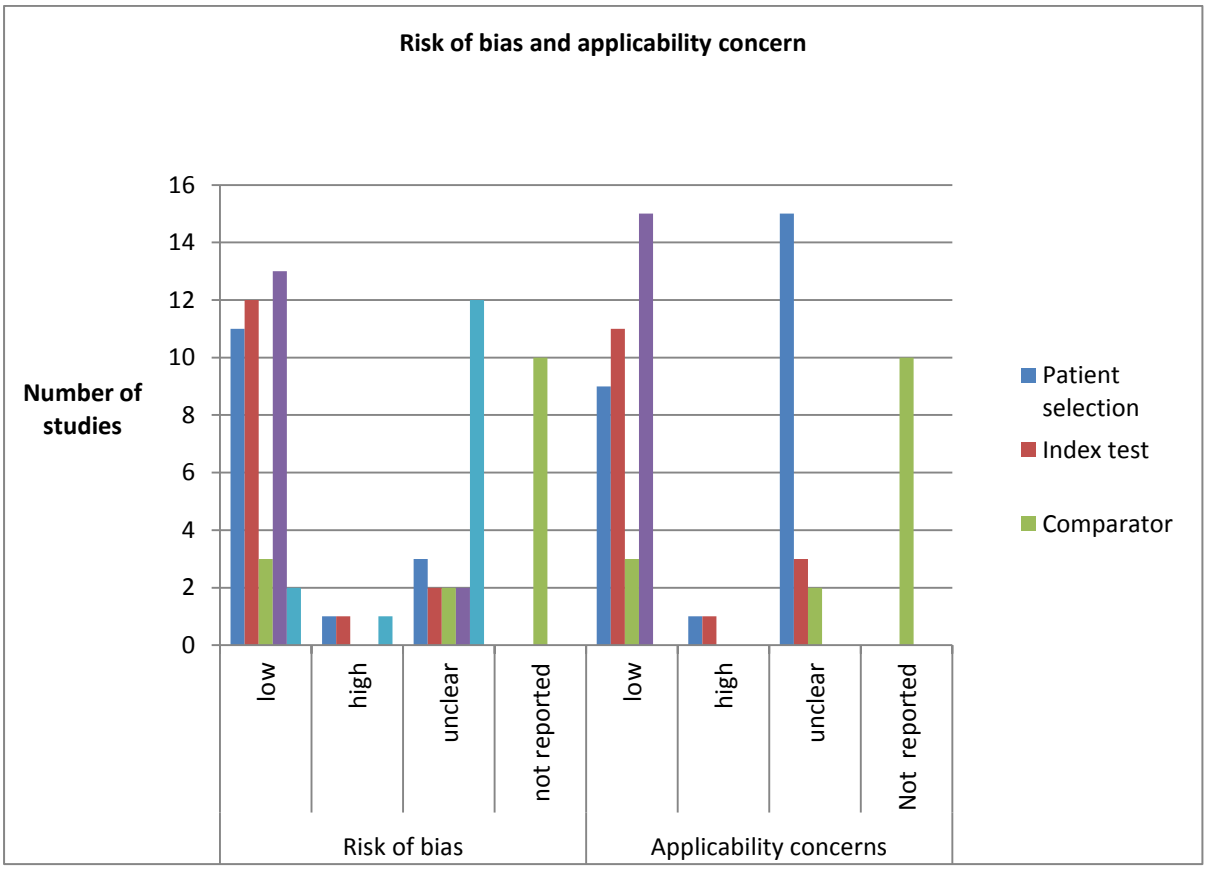
4.2.1.3 Quality assessment of studies included in clinical effectiveness review

The QUADAS-2 which separates the evaluation of study quality into two main areas: risk of bias and concerns regarding applicability of patient selection, index test, reference standard, and flow of timing was used to assess quality of included studies.

A summary of the results of the quality assessment of the included studies is shown in Appendix 9.2. The majority of the included studies had low risk of bias and low applicability concerns in patient selection,[33,35-37,39,41,43-48] conduct of the index test [33-37,39-41,43,44,46-48] and reference standard.[34-39,41,43-48] However concerning flow and timing, the risk of bias in majority of the studies was unclear[35,36,38-48] due to poor reporting and/or insufficient data.

Figure 2 shows a summary of risk of bias and applicability concerns of included studies.

Figure 2. Summary of risk of bias and applicability concerns of included studies



4.3 Clinical effectiveness results

4.3.1 Diagnostic accuracy

4.3.1.1 Lesion diagnosis

Dermoscopy plus VivaScope 1500 vs dermoscopy

Three studies[33,45,47] compared dermoscopy with VivaScope 1500 following dermoscopy.

Alarcon *et al.* 2014[33] assessed the impact of RCM analysis on dermoscopically equivocal pigmented lesions. Of the 343 lesions that underwent RCM examination, only 264 were excised (79 lesions were followed up for one year without any melanoma diagnosed). Of 92 melanomas diagnosed using dermoscopy alone, histopathology proved that there were six FNs, and two FNs with dermoscopy plus VivaScope 1500.

Based on the 264 excised lesions, combined use of dermoscopy and VivaScope was more likely to diagnose melanoma compared with dermoscopy alone (sensitivity, 97.8% *vs* 94.6%, p=0.043), and more likely to diagnose those without melanoma (non-melanoma) (specificity, 92.4% *vs* 26.74%, p<0.000001). Similar results were obtained when the analysis was based on all 343 patients who underwent RCM, assuming all the 79 patients/lesions who were followed up were TNs.

Table 5. Diagnostic accuracy of melanoma in Alarcon et al. 2014[33] (both patient and lesion level data)

Intervention/ comparator	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV % (95% CI)	NPV (95% CI)
Based on excised lesions (n=264)				
VivaScope 1500 following dermoscopy	97.8§ (91.6–99.6)	92.4§ (87.2–95.7)	87.4 (79.0–92.8)	98.8 (95.1–99.8)
Dermoscopy alone	94.6 (87.2–98.0)	26.74‡ (87.2–98.0)	40.8 (34.2–47.8)	90.2† (77.8–96.3)
Based on all lesions that underwent RCM (n=343)				
VivaScope 1500 following dermoscopy	97.83 (92.35–99.67)	94.82 (91.3–97.21)	87 (79–93)	99 (97–100)
Dermoscopy alone	93.48 (86.34–97.55)	49.0 (42.66–55.37)	40 (34–47)	95 (90–98)
Abbreviations used in table: CI, confidence interval; n, number of patients or lesions; NPV, negative predictive value; PPV, positive predictive value. Footnotes used in table: §significant difference between two groups (p<0.05); ‡data based on difficult and doubtful lesions and not for the whole 264 patients				

Pellacani *et al*. 2014[45] prospectively assessed the potential impact of RCM when implemented in a routine melanoma workflow. At dermoscopy, patients were referred to one of the following pathways:

- No further examination;
- Referral to RCM:

- RCM documentation (lesions with consistent suspicious clinical/dermoscopic criteria, already qualified and scheduled for surgical excision);

- RCM consultation for equivocal lesions (or moderately suspicious), where RCM diagnosis would determine lesion definite outcome, i.e. either excision or digital follow-up.

Of a total of 493 lesions referred for RCM examination, two patients refused RCM imaging so lesions were excised, and histopathology reported one BCC and one benign lesion. Of the remaining 491 lesions, 183 underwent RCM documentation and 308 RCM consultations. In the RCM documentation group, histopathology confirmed 110 RCM positives (23 melanomas, 19 BCCs and 68 benign lesions) and 73 RCM negatives (73 benign lesions). In all melanomas and BCCs identified at histology, RCM had recommended excision.

In the RCM consultation group, RCM identified 81 positives and 227 negatives. Of the 81 RCM positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 RCM negatives followed-up for 3-12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision).

Table 6 shows the sensitivity and specificity (based on a 2x2 contingency table) based on two alternative assumptions: one where all the 21 RCM negatives lost to follow-up were TNs or the 21 RCM negatives lost to follow-up are excluded from the sensitivity and specificity analysis.

Table 6. Diagnostic accuracy of lesions recommended for excision in Pellacani *et al.* 2014[45] (lesion level data)

	Sensitivity, % (95% CI)	**Specificity, % (95% CI)**	**PPV, % (95% CI)**	**NPV, % (95% CI)**
RCM documentation	100 (91.51–100)	51.77 (43.21-60.26)	38 (29–48)	100 (95–100)
RCM consultation (based on 227 TNs)	100 (86.16 –100)	80.21 (75.09–84.69)	31 (21–42)	100 (98–100)
RCM consultation (based on 206 TNs, i.e. excluding the 21 lesions lost to follow up)	100 (86.16–100)	78.63 (73.16–83.43)	31 (21–42)	100 (98–100)
Abbreviations used in the table: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; RCM, reflectance confocal microscopy				

Ferrari *et al.* 2014,[47] evaluated the most relevant RCM features for the detection of difficult melanomas by dermoscopy: score 0–2 (featureless lesions), score 3–4 (positive-borderline lesions), and score 5–10 (positive- clear cut' lesions). For RCM, previously published confocal parameters for melanoma detection were used. In the population with dermoscopic score of 0–2, the presence of at

least one of the two independent parameters accounted for the detection of all six melanomas (100% sensitivity and 82.3% specificity). Similarly in the population with dermoscopic score of 3–4, the presence of at least one of the two independent parameters accounted for the detection of 16/17 melanomas (94.1% sensitivity and 62.4% specificity).

Dermoscopy plus VivaScope 1500

Four studies[34,42,43,48] reported the diagnostic accuracy of VivaScope 1500 following dermoscopy without a comparator.

Curchin *et al.* 2011[34] reported sensitivity and specificity data on 50 equivocal lesions on 42 patients. On VivaScope 1500 following dermoscopy, 12/13 melanomas (92.3% sensitivity, 75% specificity), 19/22 benign naevi (86% sensitivity, 95% specificity), 6/9 BCC (66.7% sensitivity, 100% specificity) and 6/6 squamous cell carcinoma (SCC) and its precursors (100% sensitivity, 75% specificity) were diagnosed correctly.

Table 7. Diagnostic accuracy in Curchin *et al.* 2011[34] (lesion level data)

Lesion type	Histopathology proven cases, n	Sensitivity, %	Specificity, %
Melanoma	12/13	92.3	75
Benign naevi	19/22	86	95
BCC	6/9	66.7	100
SCC and its precursors	6/6	100	75
Abbreviations used in table: BCC, basal cell carcinoma; n, number of lesions; SCC, squamous cell carcinoma.			

Guitera *et al.* 2010[43] assessed which RCM features could distinguish LM from benign macules (BMs) of the face such as solar lentigo, actinic keratosis, and seborrheic keratosis, and to test different algorithms for diagnosing LM.

In addition to describing RCM diagnostic features for LM, an algorithm was developed (LM score) to distinguish LM from BM (two major features each scoring +2 points [non-edged papillae and round large pagetoid cells >20 μm], and four minor features; three scored +1 point each [three or more atypical cells at the dermoepidermal junction, follicular localization of atypical cells, and nucleated cells within the dermal papillae], and one [negative] feature scored -1 point [a broadened honeycomb pattern]). A LM score of ≥2 resulted in a sensitivity of 85% and specificity of 76% for the diagnosis of LM (odds ratio [OR] for LM 18.6; 95%CI: 9.3 to 37.1).

Rao *et al*. 2013[42] assessed the diagnostic accuracy of VivaScope 1500 compared with histopathology in the diagnosis of cutaneous lesions by two readers of varying degrees of experience; a bedside trained physician compared with a distant expert. Lesions diagnosed by reader 1 as malignant with VivaScope 1500 represented 66.7% of histologically diagnosed melanoma, 74.1% of BCC, and 37.2%

of SCC. For reader 2, lesions diagnosed as malignant represented 88.9% of melanoma, 51.9% of BCC, and 72.1% of SCC. Out of 284 lesions evaluated by both readers, 212 were benign and 72 malignant based on histopathology.

Table 8. Diagnostic accuracy in Rao *et al.* 2013[42] (lesion level data)

Reader/reviewer	Agreement between VivaScope 1500 and histopathology, %	Sensitivity, %	Specificity, %
Reader 1 (bedside trained physician): evaluated 317 of 334 cases (94.9%)	Melanoma = 66.7 BCC = 74.1 SCC = 37.2	93.1	64.1
Reader 2 (distant expert): evaluated 323 of 334 cases (96.7%)	Melanoma = 88.9; BCC = 51.9 SCC = 72.1	97.4	80.5
Overall (reader 1 and 2)	NR	98.6	44
Abbreviations used in table: BCC, basal cell carcinoma; n, number of lesions; NR, not reported; SCC, squamous cell carcinoma.			

Stanganelli *et al.* 2014[48] assessed whether combining sequential dermoscopy imaging with VivaScope 1500 can improve melanoma detection and reduce unnecessary excisions. Of 30 out of 70 lesions (43%) classified as melanoma by dermoscopy plus VivaScope 1500, 11/12 were histologically confirmed (11 TP and 1 FN), and 19 as false positives.

Table 9. Diagnostic accuracy in Stanganelli *et al.* 2014[48] (lesion level data)

Note threshold(s) where appropriate:		Reference standard	
		Disease	No disease
VivaScope 1500	Disease	TP = 11	FP = 19
	No disease	FN = 1	TN = 39
Abbreviations used in the table: FN, false negative; FP, false positive; TN, true negative; TP, true positive			

Dermoscopy plus VivaScope 1000 vs dermoscopy

Langley et al. 2007[39] evaluated the diagnostic accuracy of VivaScope 1000 compared with dermoscopy in patients with benign and malignant melanocytic lesions. The sensitivity of VivaScope 1000 following dermoscopy compared with dermoscopy alone was 97.3% vs 89.2% and specificity was 83.0% vs 84.1%.

Using a 2x2 contingency table to estimate histologically proven positive and negative diagnostic test, the numbers of patients/lesions correctly (TP + TN) and incorrectly (FP + FN) diagnosed were similar using VivaScope 1000 following dermoscopy compared with dermoscopy alone.

Table 10. Diagnostic accuracy in Langley *et al.* 2007[39] (both patient and lesion level data)

Intervention/ comparator	Sensitivity, %	Specificity, %	PPV, %	NPV, %	TP, n	TN, n	FP, n	FN, n
VivaScope 1000	97.3	83.0	70.6	98.6	37	72	15	1
Dermoscope	89.2	84.1	70.2	94.9	33	74	14	4

Abbreviations used in table: FN, false negative; FP, false positive; n, number of patients or lesions; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

VivaScope 1000

Two publications[35,36] from the same trial reported the diagnostic accuracy of VivaScope 1000 without a comparator.

In the trial by Gerger *et al.* 2006,[35] 117 melanocytic skin lesions and 45 non-melanocytic skin lesions were consecutively sampled and examined by four independent observers using VivaScope 1000. The overall (total of the 4 observers) diagnostic differentiation of benign from malignant lesions (melanoma and BCC) reached sensitivity of 94.65%, specificity of 96.67%, PPV of 97.50%, and NPV of 92.99% based on histopathology.

Table 11. Diagnostic accuracy in Gerger *et al.* 2006[35] (lesion level data)

Diagnostic differentiation of benign from malignant lesions based on biopsy documented lesions	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Observer 1	90.48	96.6	NR	NR
Observer 2	95.24	100	NR	NR
Observer 3	95.24	96.6	NR	NR
Observer 4	97.62	100	NR	NR
Overall (observers 1-4)	94.65	96.67	97.50	92.99

Abbreviations used in table: NPV, negative predictive value; PPV, positive predictive value.

In a supplementary publication of Gerger *et al.* 2006,[35] Gerger *et al.* 2008[36] retrospectively evaluated 3,709 selected images of 70 lesions (20 malignant melanomas and 50 benign naevi) obtained by VivaScope 1000. Overall performance of the four observers who reviewed the images showed a sensitivity of 97.5%, specificity of 99.0%, PPV of 97.5%, and a NPV of 99.0%.

Table 12. Diagnostic accuracy in Gerger *et al.* 2008[36] (lesion level data)

Reader/observer	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Observers 1–3	100	100	NR	NR
Observer 4	90	96	NR	NR
Overall (observers 1–4)	97.5	99	97.5	99
Abbreviations used in table: NPV, negative predictive value; NR, not reported; PPV, positive predictive value.				

VivaScope 1000 or 1500 vs dermoscopy

In a trial by Guitera et al. 2009,[37] possible additive value of VivaScope 1000 and 1500 in the management of melanocytic lesions were evaluated at two centres. In terms of diagnosis of melanoma, there was no significant difference in sensitivities between VivaScope 1000/1500 (91%, 95% CI: 84.6 to 95.5) and dermoscope (88%, 95% CI: 80.7 to 92.6) but specificities differed significantly: VivaScope 1000/1500 (68%, 95% CI: 61.1 to 74.3) and dermoscope (32%, 95% CI: 25.9 to 38.7).

When VivaScope 1000/1500 is used in addition to dermoscopy, the number of patients correctly diagnosed (histologically proven) with melanoma (TP, n=100 [81.3%]) or without melanoma (TN, n=3 [2.4%]) was higher than the number incorrectly diagnosed with melanoma (FP+FN, n=20 [16.3%]).

Table 13. Diagnostic accuracy in Guitera *et al.* 2009[37] (lesion level data)

Lesion	Diagnostic test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Double positive (TP), n (%)	Double negative (TN), n (%)	Single positive (FP+FN), n (%)
Melanoma (n=123)	VivaScope 1000/1500	91 (84.6-95.5)	68 (61.1-74.3)	100 (81.3%)	3 (2.4%)	20 (16.3%)
	Dermoscope	88 (80.7-92.6)	32 (25.9-38.7)			
Benign naevi (n=203)	VivaScope 1000/1500	68	15	46 (22.7%)	46 (22.7%)	111 (54.7%)
	Dermoscope	32	11			
Abbreviations used in table: CI, confidence interval; n, number of lesions; FN, false negative; FP, false positive; TN, true negative; TP, true positive						

VivaScope 1000 or 1500

Pellacani *et al.* 2007[41] evaluated the sensitivity and specificity of confocal features for the diagnosis of melanoma and benign naevi using RCM score thresholds compared with models obtained from

statistical analysis. The VivaScope 1000/1500 demonstrated optimal sensitivity for a score of ≥2 (96.3%), with 52.1% specificity.

Dermoscopy plus VivaScope 1500 vs dermoscopy plus VivaScope 3000

Castro *et al.* 2014[46] compared the accuracy of VivaScope 3000 with VivaScope 1500 in the identification of BCC. Among 54 lesions imaged with both RCM devices, 45 were biopsy-proven BCCs. Comparison between VivaScope 1500 following dermoscopy and VivaScope 3000 following dermoscopy was as follows: sensitivity (100% *vs* 93%), specificity (78% for both RCMs), positive predictive value (96% *vs* 95%), and negative predictive value (100% *vs* 70%) respectively.

Table 14. Diagnostic accuracy of BCC in Castro *et al.* 2014[46] (lesion level data)

	VivaScope 1500 following dermoscopy	**VivaScope 3000 following dermoscopy**
Sensitivity, %	100	93
Specificity, %	78	78
PPV, %	96	95
NPV, %	100	70
Abbreviations used in the table: BCC, basal cell carcinoma; NPV, negative predictive value; PPV, positive predictive value		

4.3.1.2 Lesion margin delineation

Dermoscopy plus VivaScope 1500 vs dermoscopy

Guitera *et al*. 2013[38] analysed LM and LMM cases to determine whether VivaScope 1500 mapping might alter patient care, and management. Out of 60 positive sites for LM confirmed by histopathology, 55 (FN=5) had been confirmed by VivaScope 1500 and 21 (FN=39) by dermoscopy, and out of 125 LM sites confirmed as negative by histopathology, 121 (FP=4) had been confirmed by VivaScope 1500 and 122 (FP=3) by dermoscopy. Histopathology also showed 17/29 patients with visible lesions had evidence of subclinical disease more than 5 mm beyond the edge of the dermoscopically identified margin. In addition both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500. Thus, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.

Table 15. Diagnostic accuracy in Guitera *et al.* 2013[38]

Finding	Methods of diagnosis		
	Histopathology, n	Dermoscope, n	VivaScope 1500, n
Number of sites positive for LM	60	21 (39 FN)	55 (5 FN)
Number of sites negative for LM	125	122 (3 FP)	121 (4 FP)
Abbreviations used in table: LM, lentigo maligna; LMM, lentigo maligna melanoma; n, number of sites; FN, false negative; FP, false positive			

VivaScope 1500

Pan *et al.* 2012[40] investigated the feasibility of VivaScope 1500 in defining the margins of lesions clinically suggestive of BCC before surgery. The margins of 10 lesions were evaluated using VivaScope 1500, and biopsies of the margins were used to confirm the results. In seven of 10 (70%) cases, the margins of the cancer were identified using VivaScope 1500 and confirmed by histopathological analysis. In three of 10 (30%) cases, the margin of the lesions could not be detected because of the unevenness of the surface.

Table 16. Histological confirmation of margins in Pan *et al.* 2012[40]

	N (%) of cases/margins confirmed by histology
VivaScope 1500	7 (70%)

VivaScope 2500

Bennassar *et al.* 2014[44] evaluated the sensitivity and specificity of *ex vivo* imaging with fluorescence confocal microscopy (FCM) for the detection of residual BCC in Mohs tissue excisions, and to calculate the time invested up to the diagnosis for both FCM and frozen sections. The overall sensitivity and specificity of detecting residual BCC in surgical margins were 88% and 99%, respectively. The number of images/mosaic correctly diagnosed as TP was 79 (89%) and TN was 390 (99.7%). There was only one (0.3%) false positive. In addition average VivaScope 2500 reduced the evaluation time by 18 minutes ($p<0.001$) when compared with the processing of a frozen section.

4.3.2 Lesion recurrence

4.3.2.1 Lesion diagnosis

None of the included studies indicated for lesion diagnosis reported lesion recurrence data.

4.3.2.2 Lesion margin delineation

In the trial conducted by Guitera *et al.* 2013,[38] none of the 17/37 patients treated surgically after histopathology confirmed LM/LMM had developed recurrence during a median follow-up of 37

months. Recurrence was suspected in one imiquimod-treated patient after one year follow-up, and three patients treated with radiotherapy after 12, 24 and 36 months follow-up respectively.

Table 17. Lesion recurrence in Guitera *et al.* 2013[38]

Method of treatment of confirmed LM/LMM	Number of patients with recurrence	Follow-up period
Surgical (n=17)	0	12 months
Non-surgical (n=20):		
Imiquimod	1	12 months
Radiotherapy	1	12 months
	1	24 months
	1	36 months

4.3.3 Misdiagnosis/misclassification of lesions

4.3.3.1 Lesion diagnosis

VivaScope 1000/1500 vs dermoscope

In the trial by Guitera *et al*. 2009,[37] 15 melanomas (12%) were misclassified by dermoscopy, 11 melanomas (9%) were misclassified by the VivaScope 1000/1500, and only 2.4% by both techniques.

Dermoscopy plus VivaScope 1000 vs dermoscopy

In the trial by Langley *et al.* 2007,[39] there were 5/37 melanomas for which VivaScope 1000 following dermoscopy and dermoscopy alone produced differing diagnoses. VivaScope 1000 following dermoscopy correctly classified 4/5 melanomas, whereas dermoscopy alone correctly classified 1/5 melanoma. Additionally, there were seven benign naevi for which both diagnoses were incorrect. Two of the melanomas were misdiagnosed by the investigator using dermoscopy alone, but correctly diagnosed by dermoscopy plus VivaScope 1000 as amelanotic or hypomelanotic melanomas.

Dermoscopy plus VivaScope 1500

In the trial conducted by Pellacani *et al.* 2014,[45] overall VivaScope 1500 proposed diagnosis was concordant with histopathological diagnosis in 216/283 (76.3%) evaluated cases. BCC was the most accurate diagnosis (37/38 [97.4%]), followed by melanoma (24/28 [85.7%]). Spitz nevus was the most frequently misclassified diagnosis (accurate diagnosis: 4/13 [30.8%]); six were misclassified as Clark's naevi and three as melanoma.

Table 18. Misdiagnosis/misclassification of lesions

Study	Comparison group	n (%) of lesions misdiagnosed/ misclassified
Guitera *et al.* 2009[37]	Dermoscope	Melanomas: 15 (12%)
	VivaScope 1000/1500 following	Melanoma: 11 (9%)
	Dermoscope plus VivaScope 1000/15000	Melanoma: (2.4%)
Langley *et al.* 2007[39]	Dermoscope	Melanoma: 4
	VivaScope 1000	Melanoma: 1
	Dermoscope plus VivaScope 1000	NR
Pellacani *et al.* 2014[45]	Overall VivaScope 1500	Overall lesions: 67 (naevi, 42; BCC, 1; melanoma, 4; Spitz naevi, 9)
Abbreviations used in the table: BCC, basal cell carcinoma; n, number of lesions; NR, not reported; RCM, reflectance confocal microscopy		

4.3.3.2 Lesion margin delineation

The only included study indicated for lesion margin delineation[2] did not report on misdiagnosis or misclassification of lesions.

4.3.4 Change in management of lesions

4.3.4.1 Lesion diagnosis

No included study indicated for lesion diagnosis reported change in management of lesions after diagnosis.

4.3.4.2 Lesion margin delineation

In the trial conducted by Guitera *et al.* 2103,[38] VivaScope 1500 mapping changed the management of lesions in 27 patients (73%): 11 patients had a major change in their surgical procedure, and 16 were offered radiotherapy or imiquimod treatment. Treatment was surgical in 17/37 patients.

4.3.5 Adverse events

None of the included studies indicated for lesion diagnosis or lesion margin delineation reported data on adverse events and side effects of excision including pain, swelling, infections, distress, and scarring.

4.4 Summary of clinical effectiveness results

The systematic review of clinical effectiveness identified 16 studies, 13 of which are indicated for lesion diagnosis and three for lesion margin delineation. For the index test, included studies used VivaScope 1500 or 1000 or 2500 or 3000 with or without dermoscopy as adjunctive technology or as comparator.

Two studies (Alarcon *et al.* 2014 from Spain, and Pellacani *et al.* 2014 from Italy) investigated lesion diagnosis and were deemed to be the most representative of clinical practice in the UK setting from the studies identified.

Alarcon *et al.* 2014 assessed the impact of RCM analysis on dermoscopically equivocal pigmented lesions. Based on the 264 excised lesions, there was statistically significant differences in sensitivity in the diagnosis of melanoma (97.8% vs 94.6%, p=0.043) and specificity in non-melanoma (92.4% vs 26.74%, p<0.000001) respectively in the use of dermoscopy plus VivaScope 1500 and dermoscopy alone.

Pellacani *et al*. 2014 prospectively assessed the potential impact of RCM when implemented in a routine melanoma workflow. Following dermoscopy, patients who were referred to RCM underwent either:

- RCM documentation (lesions with consistent suspicious clinical/dermoscopic criteria, already qualified and scheduled for surgical excision); or
- RCM consultation for equivocal lesions (or moderately suspicious), where RCM diagnosis would determine lesion definite outcome, i.e. either excision or digital follow-up.

Of a total of 491 lesions, 183 underwent RCM documentation and 308 RCM consultations. Using a 2x2 contingency table, sensitivity and specificity were calculated. Based on the assumption that all the 21 RCM negatives lost to follow-up in the RCM consultation group were TNs, the sensitivity (RCM documentation 100% vs RCM consultation 100%) and specificity (RCM documentation 51.77% vs RCM consultation 78.6%) were calculated. However when the 21 RCM negatives lost to follow-up were excluded, the sensitivity was 100% and specificity 80.2% for the RCM consultation.

One study (Guitera *et al*. 2013) investigated lesion margin delineation and was also deemed to be the most representative of clinical practice in the UK setting. Guitera *et al*. 2013 analysed LM and LMM cases to determine whether VivaScope 1500 mapping might alter patient care, and management. Histopathology showed 17/29 patients with visible lesions had evidence of subclinical disease more than 5 mm beyond the edge of the dermoscopically identified margin. In addition both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500. Thus, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.

4.5 Generalisability of results

Although none of the included studies in the review of clinical effectiveness were conducted in the UK, two studies (Alarcon *et al.* 2014[33] from Spain, and Pellacani *et al.* 2014[45] from Italy) on diagnosis and one study on margin delineation (Guitera et al. 2013[38]) were deemed to be the most

representative of clinical practice in the UK setting. This was validated by our clinical experts and these trials were taken forward for the health economic analysis.

5 ASSESSMENT OF COST EFFECTIVENESS

5.1 Systematic literature review of existing economic evidence

5.1.1 Methods

A systematic review of the literature was undertaken in October 2014 in order to identify published economic evaluations that assessed the cost effectiveness of VivaScope 1500 and 3000 in the diagnosis of skin lesions suspected for skin cancer and in the margin delineation of malignant skin lesions, including lentigo maligna, prior to surgical treatment. In addition, two further systematic reviews were conducted, in December 2014 and October 2014 respectively, aiming to identify:

- studies reporting resource use and cost data associated with the care pathways of skin cancer, including the initial assessment and diagnosis of skin lesions suspected for malignancy, that could be utilised in primary economic modelling;
- studies providing utility (preference-based) data on the health-related quality of life (HRQoL) of people with suspected or confirmed skin cancer, that could be used for the estimation of quality-adjusted life years (QALYs) in the economic models developed as part of this report.

The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- HTA database (HTA);
- NHS Economic Evaluations Database (NHS EED).

Further to the database searches, experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies. Finally, the NICE website was searched for any recently published guidance relating to skin cancer that had not been already identified via the database searches.

The search strategy for existing economic evaluations combined terms capturing the interventions (RCM, i.e. VivaScope) and comparators of interest (dermoscopy, surgical excision and biopsy), the target condition (types of skin cancer) and, for searches undertaken in MEDLINE and EMBASE, terms to capture economic evaluations. The search strategies for resource use and cost data as well as for utility data were not restricted by intervention, and used terms capturing the target condition; in searches undertaken in MEDLINE and EMBASE, these terms were combined with cost of illness terms (resource use and cost data searches) and HRQoL terms (searches for utility data).

No restrictions on language or setting were applied to any of the searches. The search for resource use and cost data was limited to the UK/NHS setting, as the aim of this search was to identify data

directly relevant to the NHS context that could inform the economic model; however, no country restrictions were applied to searches for existing economic evaluations or studies reporting utility data relating to skin cancer. Searches for HRQoL data were restricted by date, starting from 1997, due to the high volume of search hits if this restriction was not imposed; the year 1997 was selected as this was the year the utility index for the EQ-5D was published. Limits were applied to remove animal studies and case studies. Conference abstracts were considered for inclusion from 1st January 2013, as high-quality studies reported in abstract form before 2013 were expected to have been published in a peer-reviewed journal. Full details of the search strategies are presented in Appendix 9.6.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists using pre-defined eligibility criteria. Due to the high volume of studies retrieved by the HRQoL search, one health economist reviewed all identified citations and a second health economist reviewed a random sample of 1,000 citations, to confirm that the same studies were included for second pass.

The inclusion and exclusion criteria for each of the three systematic reviews described above are outlined in Table 19.

Table 19: Inclusion and exclusion criteria for the systematic reviews of economic and preference-based health-related quality of life evidence

Inclusion criteria – existing economic evaluations
• intervention or comparators according to the scope of the assessment; • study population according to the scope of the assessment; • full economic evaluations (cost-utility, cost-effectiveness, cost-benefit or cost-consequence analyses) that assess both costs and outcomes associated with the interventions of interest; • economic evaluations that utilise clinical effectiveness data from randomised or non-randomised clinical trials, prospective cohort studies or systematic reviews and meta-analyses of clinical studies; economic analyses that utilise clinical data from studies with a mirror-image or other retrospective design will not be considered.
Inclusion criteria – resource use and costing studies
• study population according to the scope of the assessment; • UK resource use or costing studies; • any setting (to be as inclusive as possible).
Inclusion criteria – studies reporting utility data relating to skin cancer
• studies reporting utility data elicited using a generic or a condition-specific preference-based measure, vignettes or self-report and a validated, choice-based technique for valuation (i.e. time trade-off or standard gamble); • utility data referring to specific health states associated with skin cancer through the care pathway.
Exclusion criteria – all
• abstracts with insufficient methodological details; • conference papers pre January 2013.

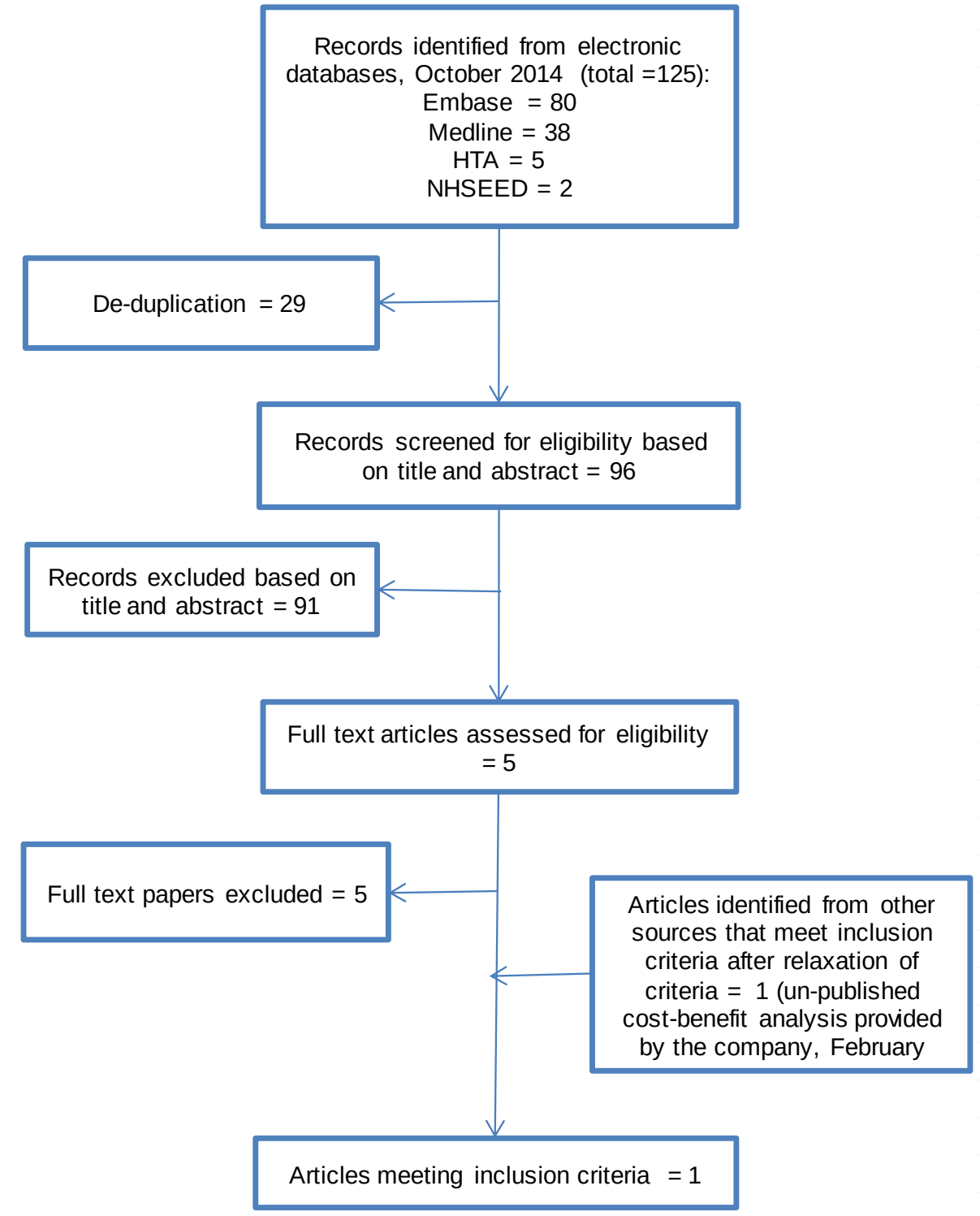
5.1.2 Results

5.1.2.1 Economic evaluations

The systematic literature search identified a total of 125 papers. Of those, 91 were excluded on the basis of title and abstract and 29 were duplicates. Therefore, a total of 5 papers were identified as potentially relevant and were ordered for full review based on the criteria listed in Table 19. Of the 5 papers ordered, none were considered to meet the predefined inclusion criteria listed in Table 19. Reasons for exclusion of the ordered papers are provided in Appendix 9.6.

During the development of this report, the company made available to the EAG an unpublished study of the cost effectiveness of RCM in the diagnosis of skin lesions suspicious for skin cancer ([redacted] The study had a retrospective design, and therefore did not meet the inclusion criteria for economic evaluations described in Table 19. Nevertheless, due to paucity of any relevant economic evidence on the cost effectiveness of VivaScope, it was decided to relax the respective inclusion criterion and thus include this study in the systematic literature review. None of the 5 potentially relevant papers that had been excluded according to the predefined inclusion criteria met the relaxed inclusion criteria. Figure 3 provides the flowchart of the process of the systematic search for economic evaluations.

Figure 3. Flowchart of the process of the systematic search for economic evaluations



[redacted]

The methodological quality of the unpublished study by [redacted], assessed against the NICE reference checklist for economic evaluations, is presented in Table 20. The evidence table with the summary of methods and results of the study is provided in Table 21.

Table 20 NICE reference case checklist for base case analysis: [redacted]

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	[redacted]
Comparator(s)	Alternative therapies routinely used in the NHS	[redacted]
Perspective costs	NHS and Personal Social Services	[redacted]
Perspective benefits	All health effects on individuals	[redacted]
Form of economic evaluation	Cost-utility analysis	[redacted]
Time horizon	Sufficient to capture differences in	[redacted]

	costs and outcomes	
Synthesis of evidence on outcomes	Systematic review	[redacted]
Outcome measure	QALYs	[redacted]
Health states for QALY	Described using a standardised and validated instrument	[redacted]
Benefit valuation	TTO or standard gamble	[redacted]
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	[redacted]
Discount	An annu	[redacted]

rate	al rate of 3.5% on both costs and health effects	
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	[redacted]
Sensitivity analysis	PSA	[redacted]
Abbreviations used in the table: HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; NA, not applicable; NNE, number needed to excise; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life yeas; RCM, reflectance confocal microscopy; TTO, time trade-off.		

Table 21. Evidence table of the identified economic evaluation

Study ID Country Study type	Intervention & comparator	Study population Study design Data sources	Costs: perspective, description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

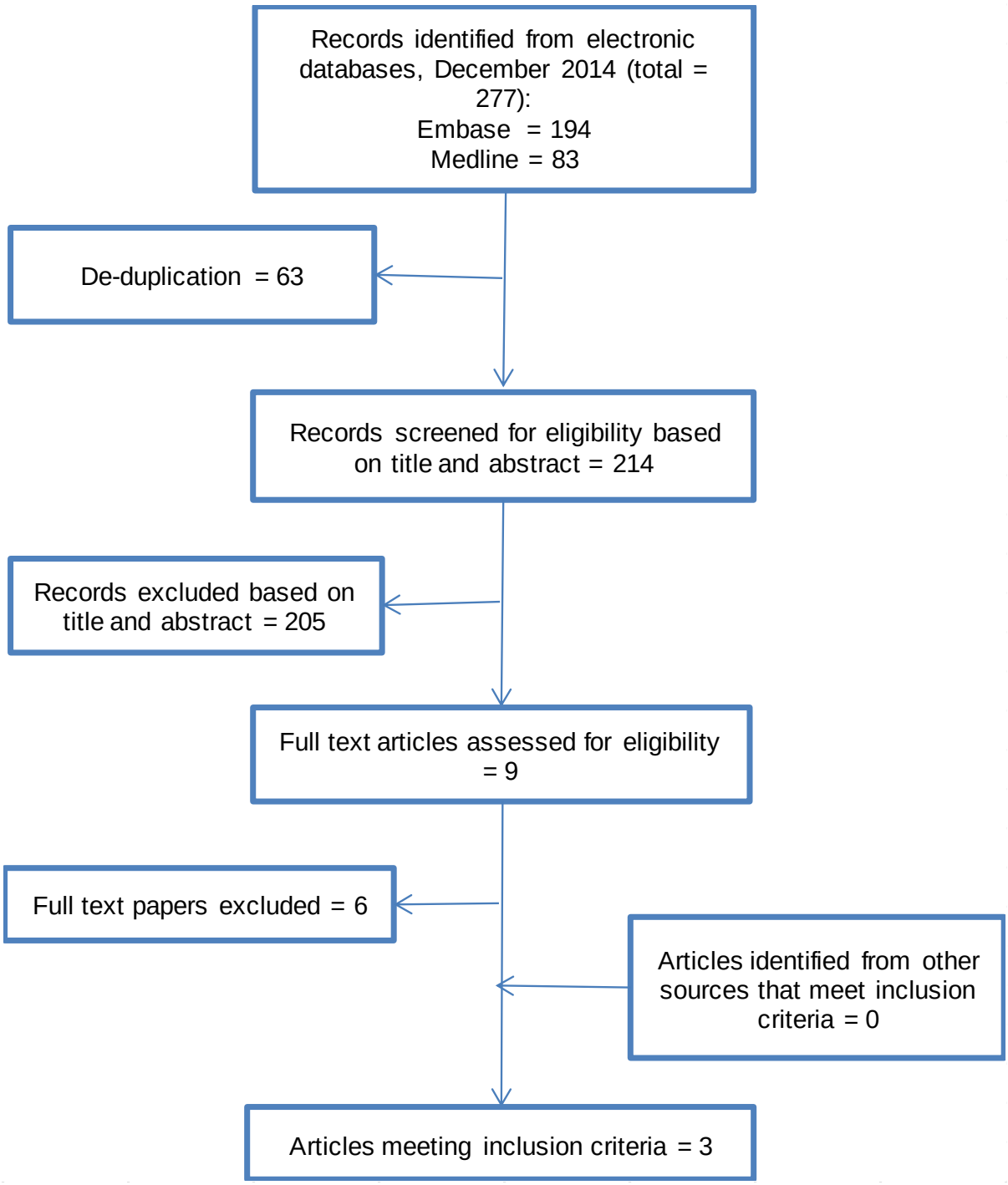
Abbreviations used in table: NNE, number needed to excise; RCM, reflectance confocal microscopy

5.1.2.2 Resource use and costing studies

A total of 277 papers were identified from the systematic search of the literature. Of those, 205 were excluded on the basis of title and abstract and 63 were duplicates. Therefore, a total of 9 papers were identified as potentially relevant and were ordered for full review based on the criteria listed in Table 19. On the basis of the full text, 6 studies were excluded. Reasons for exclusion of the ordered papers are provided in Appendix 9.6. The remaining 3 studies identified from the search included relevant UK cost data on skin cancer.

Figure 4 provides the flowchart of the process of the systematic search for resource use and costing studies.

Figure 4. Flowchart of the process of the systematic search for resource use and costing studies



Of the 3 studies included in this review, one (Wilson *et al*. 2013) was an economic evaluation of a diagnostic aid (the MoleMate system) versus best practice in people with pigmented skin lesions in primary care.[50] The other two studies (Morris *et al*. 2009[51] and Vallejo-Torres *et al*. 2014[52]) estimated the cost of skin cancer in England.

Wilson *et al*. (2013) conducted a model-based economic evaluation that assessed the life time costs and QALYs associated with diagnostic assessment of people with at least one suspicious pigmented skin lesion presenting to UK primary care.[50] The economic model consisted of a decision-tree and a Markov model that followed true positive, true negative, false positive and false negative cases (based on diagnostic assessment) over life time. The analysis, which adopted the NHS perspective, considered explicitly only costs and outcomes of melanoma, as it did not differentiate between melanoma and non-melanoma skin cancer. Costs included diagnostic assessment costs and costs of true positive, true negative, false positive and false negative cases over life time. Costs were calculated using a bottom-up approach. Treatment costs were estimated according to stage of melanoma, including initial treatment (biopsy excision and definitive surgery), investigations, follow-up surgery for positive lymph nodes, treatment of metastatic disease, follow-up, and terminal care. Resource use and costs associated with management of each melanoma stage were reported separately. Resource use estimates for the treatment of distinct melanoma stages were based on the 2010 UK guidelines for the management of cutaneous melanoma,[16] supplemented by expert opinion. Unit costs were based on the NHS reference costs 2009.[53] The cost year was 2009.

The study appears to report cost data that are potentially useful for economic modelling. However, clinical experts advised that costs associated with treatment of more advanced melanoma stages (stages III and IV) are likely to have changed recently, with the introduction of new chemotherapeutic agents, such as ipilimumab and vemurafenib, in the treatment of advanced melanoma in the NHS.

Morris *et al*. (2009) reported the costs associated with malignant melanoma and other malignant neoplasms of the skin in England from a societal perspective.[51] Healthcare costs included GP assessment, inpatient stays, outpatient attendances and day-cases; in addition, travel costs, incapacity benefits and productivity losses were estimated. The cost year was 2002. Costs were estimated using a top-down approach; total costs were divided by the number of registrations to estimate the mean cost per registration. Resource use data and unit costs were taken from national sources. The study reported the mean NHS and societal cost per registration of melanoma to be £2,179 and £20,020, respectively. The mean NHS and societal cost per registration of other malignant skin neoplasms was £1,149 and £1,413, respectively.

The resource use data utilised by this study in order to estimate costs are out-of-date, as some estimates are more than 20 years old; moreover the top-down approach allows only a rough estimation

of relevant costs. Finally, it is noted that the study provides an overall cost per case with skin cancer (either melanoma or non-melanoma) but, in the case of melanoma, does not report costs by stage of skin cancer.

Vallejo-Torres *et al*. (2014) also reported the costs associated with melanoma and non-melanoma skin cancer in England, but from a NHS perspective.[52] The study used both a top-down and a bottom-up approach in order to produce cost estimates. The cost year was 2008. The top-down approach was adapted from Morris *et al*. (2009) using more up-to-date costs, and was not used to estimate a cost per case.[51] The bottom-up approach used a simplified model of skin cancer care in the NHS, which utilised probabilities of people with suspected skin cancer using different treatment pathways; costs for each pathway were estimated separately. Data to populate the model were taken from UK guidelines for the management of skin cancer, other published reports and clinical expert opinion. Treatment pathways included initial examination, treatment in primary care or referral to a specialist, diagnostic biopsy of suspicious lesions and treatment according to the biopsy results.

Even though the study by Vallejo-Torres *et al*. (2014)[52] uses more up-to-date resource use figures and unit costs, the probabilities of treatment received by patients may no longer represent clinical practice as they were based on an out-dated study (Orr *et al*., 1993)[54]. Moreover, the study provides separately costs per treatment pathway, but, in the case of melanoma, does not report costs by stage of skin cancer.

The overall methods of the resource use and costing studies, the resource use elements that are potentially relevant for the economic model developed for this report, and the estimated costs associated with management of skin cancer are presented in Table 22.

Table 22: UK resource use and cost estimates associated with management of skin cancer identified in the systematic review

Patient population **Perspective** **Costs considered** **Cost year**	**Methods** **Sources of resource use estimates and unit costs**	**Available resource use estimates that are potentially relevant to the economic models constructed for this report**
Wilson *et al*. 2013[50]		
Adults with at least one suspicious pigmented lesion undergoing diagnostic assessment. Following assessment, true positive, true negative, false positive and false negative cases are followed over life time. The analysis considered explicitly only costs melanoma, as it did not differentiate between melanoma and non-melanoma skin cancer NHS perspective Costs included diagnostic assessment costs and costs of true positive, true negative, false positive and false negative cases over life time. Treatment costs according to stage of melanoma were estimated. Cost year 2009	Combination of resource use with respective unit costs using a bottom-up approach Resource use estimates for treatment of melanoma based on UK guidelines for the management of cutaneous melanoma supplemented by expert opinion Unit costs taken from published national sources	Diagnostic assessment costs not relevant (MoleMate system, GP examination) <u>Initial treatment</u> All melanomas have a biopsy excision (£132), staging, and definitive surgery (£150). <u>Further treatment</u> Stages 0, Ia, and Ib undergo no further treatment; Stages IIa and above undergo sentinel lymph node biopsy at the same time with definitive surgery (£34); Stages IIb and above undergo chest X-ray (£27), CT scan (£151), liver function test (£3), and full blood cell count (£3); Patients with a positive sentinel lymph node biopsy (stages IIIa, IIIb, IIIc) undergo follow-up surgery comprising preoperative CT scan (£143) and radical lymph node dissection (£891); Stage IV melanomas undergo surgery for removal of localized metastases (£738), a course of 10 fractions of radiotherapy (£1,962), and six cycles of dacarbazine- based chemotherapy (£1,605). <u>Follow-up</u> Stage 0 disease have only 1 follow-up appointment in dermatology (£82); Stage I disease are followed up every 3 months for 3 years before discharge (12 visits, £919); Stage II and above followed up 3 monthly for 3 years, then 2 yearly for 2 years (16 visits, £1,200). <u>Terminal care costs</u> Costs in the final year of life are assumed to be the same as for the treatment of metastatic disease (surgical removal of localised metastases, radiotherapy and chemotherapy) totalling £4,305. <u>False negatives</u> Patients with undiagnosed melanoma are assumed to not incur any costs unless their disease is opportunistically detected (in which case treatment costs are dependent on stage at diagnosis), or they die of their disease, in which case terminal care costs are incurred. <u>Total treatment and terminal care costs</u> Stage 0: £361; Stage Ia & IIb: £1,198; Stage IIa: £1,505; Stage IIb & IIc: £1,680; Stage IIIa to IIIc: £2,714 Stage IV: £5,985; Terminal year: £4,305
Morris *et al*. 2009[51]		
Patients with skin cancer in England Costs estimated separately for malignant melanoma and other malignant skin neoplasms	Combination of resource use with respective unit costs using a top-down approach; mean cost per registration	Mean NHS cost per registration of malignant melanoma: £2,179 (mean total societal cost £20,020). Mean NHS cost per registration of other malignant skin neoplasms: £1,149 (mean total societal cost £1,413) (Travel costs, incapacity benefits and productivity losses not relevant)

Societal perspective Costs included: GP assessment, inpatient stays, outpatient attendances and day-cases; travel costs, incapacity benefits and productivity losses Cost year 2002	estimating by dividing total healthcare and societal costs by the number of registrations Healthcare resource use data and taken from national sources	
Vallejo-Torres *et al*. 2014[52]		
Patients with skin cancer in England. Costs estimated separately for malignant melanoma and non-melanoma skin cancer NHS perspective Costs included: GP assessment and treatment of non-melanoma skin cancers, diagnostic biopsy, treatment of non-melanoma skin cancer (surgical excision, Mohs surgery, cryotherapy, radiotherapy, curettage and cautery, topical treatment with imiquimod, phototherapy), treatment of melanoma (surgical excision, radiotherapy, radical lymph node dissection), follow up Cost year 2008	Combination of resource use with respective unit costs using a bottom-up and a top-down approach Top-down approach not used in estimation of cost per case Bottom-up approach based on a model simulating skin cancer care in the NHS; resource use based on UK guidelines, other health guides and clinical expert input. Data on probabilities of patients following each treatment pathway and unit costs taken from published papers and reports, administrative data and national sources.	<u>Probability and cost of therapy – non-melanoma skin cancer</u> Mohs surgery: 0.004; £114 Cryotherapy: 0.031; £204 Radiotherapy: 0.017; £2,260 Curettage and cautery: 0.075; £137 Topical treatment (Imiquimod): 0.005; £200 Phototherapy: 0.008; £3,910 Surgical excision of BCC in primary care: 0.860; £85 <u>Probability and cost of therapy – melanoma</u> Surgical excision: 0.879; £885 Radiotherapy: 0.011; £2,260 Excision and radiotherapy: 0.022; £3,145 Radical lymph node dissection: 0.088; £16,808 Follow-up in secondary care: £68 <u>NHS expected cost per case</u> (using the bottom-up costing approach and including initial management in primary care) malignant melanoma: £2607 Non-melanoma skin cancer: £889 Benign lesion: £181
Abbreviations used in the table: CT, computerised tomography; GP, general practitioner.		

5.1.2.3 Studies reporting utility data

A total of 11,497 citations were identified from the systematic literature search. Of those, 3,547 were duplicates and 7,909 studies were excluded on the basis of title and abstract. A total of 43 full texts were assessed against inclusion criteria listed in Table 19; these included 41 studies identified from the database search and the 2 studies identified from the reference list search.

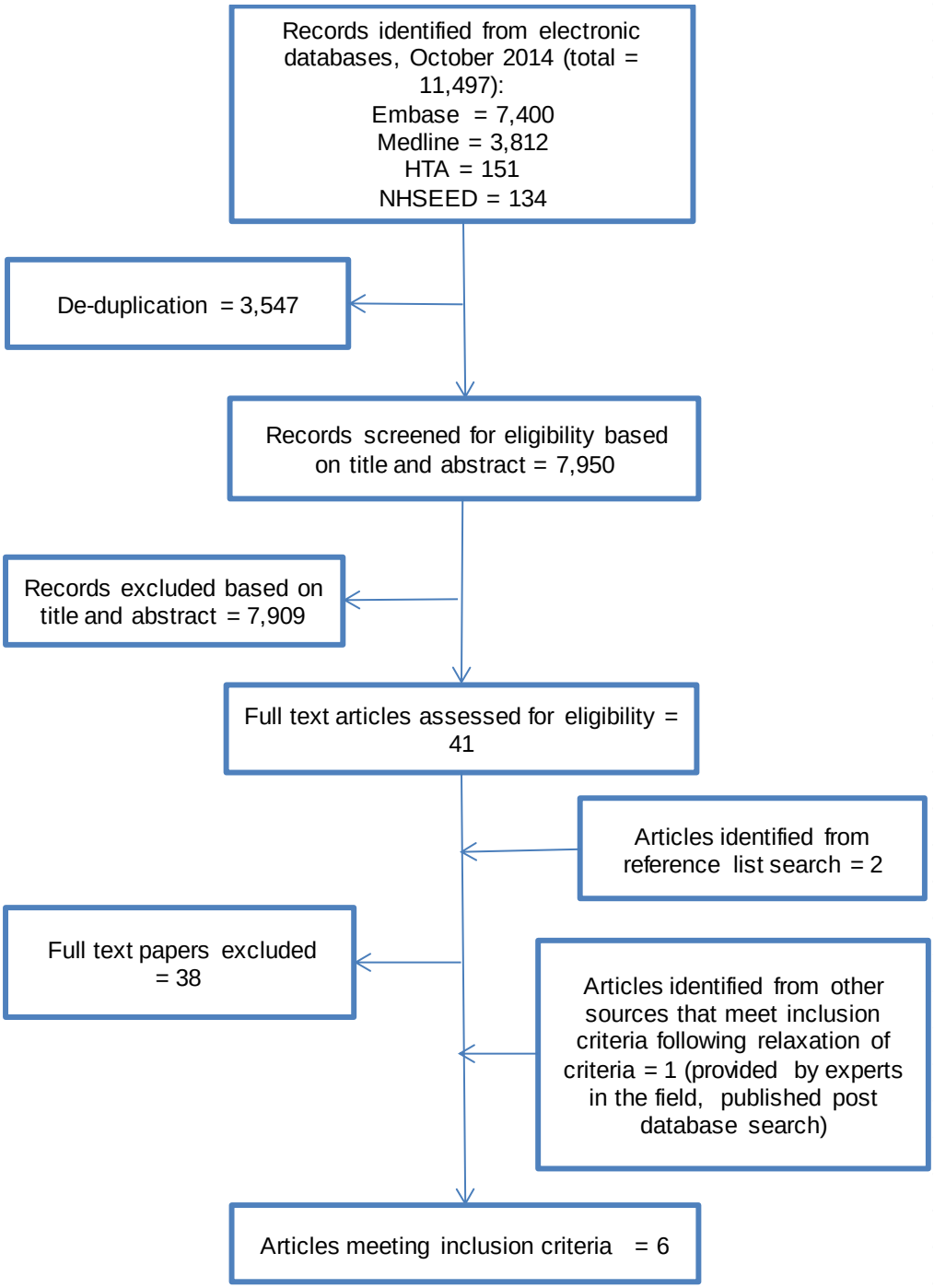
Of the 41 ordered studies identified from the database search, 17 were cost-effectiveness studies that obtained utility values from the literature to estimate QALYs. Consequently, the sources used to inform the utility values in these studies were identified and reviewed for inclusion. Two further studies were identified from the references lists of those 17 cost-effectiveness studies retrieved from the database search. A full list of the sources used to inform the cost-effectiveness studies is provided in Appendix 9.6. After full-text review, 38 studies were excluded. Reasons for exclusion of the ordered papers are also presented in Appendix 9.6. Out of the 43 full-texts assessed for inclusion, a total of 5 studies met the inclusion criteria defined in Table 19.

After the systematic search was completed, the EAG was informed by experts in the field of an additional recently published paper that provided relevant utility data (Tromme *et al*. 2014).[55] Subsequently, the EAG included this paper in the systematic review, after assessing the full-text against the set inclusion criteria. It needs to be noted that one of the inclusion criteria specifies a requirement for a choice-based technique for valuation (i.e. time trade-off or standard gamble); Tromme *et al*. (2014) does not meet this criterion, as valuation of health states was based on Visual Analogue Scale (VAS).[55] However, since this study reported utility values that were generated using EQ-5D, which is the preferred measure by NICE, and EQ-5D has been valued by the Flemish population in Belgium using VAS, it was decided to relax the inclusion criteria in order to include this study in this review. None of the 38 potentially relevant studies that had been excluded according to the predefined inclusion criteria met the relaxed inclusion criteria.

In total, 6 studies were included in the review of studies reporting preference-based HRQoL data (utility data) for skin cancer.

Figure 5 provides the flowchart of the process of the systematic search for studies reporting utility data.

Figure 5. Flowchart of the process of the systematic search for studies reporting utility data



Four of the 6 studies included in the review reported utility values for melanoma-related health states (Askew *et al*. 2011[56]; Beusterien *et al*. 2009[57]; King *et al*. 2011[58]; Tromme *et al*. 2014[55]). One study reported utility values for health states of advanced BCC (Shingler *et al*. 2013[59]), and the other study reported utility values associated with scarring following facial and auricular non-melanoma skin cancer surgery and reconstruction (Seidler *et al*. 2009[60]).

Askew *et al*. (2011) reported EQ-5D utility values for different melanoma stages derived from 273 patients with melanoma, 75 of which were undergoing treatment and 198 were follow-up surveillance at the time of the study, all of which attended a tertiary cancer care centre in the US.[56] The median age of the study sample was 52 years; 98% of them were white and 58% male. The numbers of patients at each melanoma stage were 102 at stage I/II, 100 at stage III and 71 at stage IV. The utility values were generated using patient responses on the EQ-5D. The US EQ-5D tariff was used, which has been developed following a valuation survey of 4,048 representative members of the US population using time-trade off (TTO) (Shaw *et al*. 2005).[61]

Beusterien *et al*. (2009) reported utility values for various hypothetical advanced melanoma-related health states, elicited from 140 members of the general population (77 from Australia and 63 from the UK), using standard gamble (SG).[57] The hypothetic health states (vignettes) included 4 advanced melanoma treatment-related response states, one symptomatic melanoma state, and nine toxicity-related health states, and were constructed based on published literature and refined following an iterative review by five clinical experts, two oncology nurses, three quality-of-life researchers, and a pilot test with individuals from the general public. The 4 treatment-related response states were defined as follows: partial response was defined by >50% decrease in lesion mass; stable disease was defined by a >25% decrease or increase in lesion mass; progressive disease was defined by the appearance of new lesions or increase by >25% in lesion mass; for best supportive care there was no indicated or desired cancer treatment. A symptomatic melanoma health state represented symptoms experienced in advanced melanoma. The health states were described as being treated for cancer (melanoma was not specified), whether or not treatment is working, and changes in tumour size, pain levels, appetite, effort required to perform daily activities, and fatigue. Each of the toxicity descriptions was described in association with partial response so that the respective utility decrements for toxicities could be calculated by subtracting the utility for partial response from the utility of the toxicity state.

King *et al*. (2011) developed vignettes describing health states associated with each of the melanoma stages (I, II, III, and IV) based on published literature and relevant websites; the hypothetical health states were valued by 163 adult patients with melanoma attending a cancer clinic in the US using TTO.[58] Patients were divided into new cases (if they had 1 year or less from diagnosis), and established cases (if they had more than year after diagnosis, or more than 6 months if stage IV). Patients were asked to value stages other that their own: patients with stage I disease imagined having a new diagnosis of stage II, III, or IV, while patients with higher-stage disease imagined the impact of a new stage I diagnosis. Utilities derived from new cases, established cases, and all patients participating in the study were reported separately.

Tromme *et al*. (2014) reported EQ-5D utility values for different melanoma stages derived from 356 patients with melanoma.[55] Patients completed the 5-level version of EQ-5D (EQ-5D-5L); 39 patients completed the EQ-5D-5L questionnaire twice, as they were seen in two different phases (treatment and follow-up) and/or stages during the study. Patients were classified into eight groups using 4 melanoma stages (I, II, III, IV), with each stage subdivided into treatment and remission phases.

Patients with stage 0 and Ia melanoma were pooled with the justification that they had marginal differences regarding their surgical treatment and follow-up. Patients with stage Ib and II melanoma were also pooled because, according to the authors, these patients had undergone sentinel lymph node biopsy (SLNB) that had not been followed by elective node dissection and also because of evidence that surgical resection margins did not appear to influence HRQoL.

Based on expert opinion, treatment duration was estimated to be 1, 2 and 3 months for stages 0–Ia, Ib–II and III, respectively; and more than 10 months for stage IV. The remission period for stages 0/Ia and Ib/II was estimated at 2 years of follow-up, as it has been shown that after 2 years the HRQoL of these patients is similar to that of the general population (Schlesinger-Raab *et al*. 2010).[62] Patients with stage IV melanoma in remission but still under treatment were classified as patients under treatment in order for the impact of side effects on HRQoL to be captured. The mean age of the patients was 52.6 years, and 74% were male. EQ-5D-5L profiles were first mapped onto EQ-5D-3L profiles, which were subsequently converted into utility values using the Belgian EQ-5D tariff, which has been developed following a valuation survey of 2,754 Flemish adults from the general public in Belgium using VAS (Cleemput, 2010).[63]

Shingler *et al*. (2013) reported utility values for a number of hypothetical advanced BCC-related health states, elicited from a representative sample of 100 members of the UK general public, using TTO.[59] The health state vignettes associated with advanced BCC were constructed based on a literature review, consultation with two clinical experts, and validation / piloting with 3 members of the general public. At the end of this process 9 health state vignettes were developed, reflecting level of treatment response. The 9 vignettes describing advanced BCC health states were as follows: complete response; post-surgical state; partial response with small (2 cm) or large (6 cm) growth; stable disease with small (2 cm) or large (6 cm) growth or multiple growths (2 cm); progressed disease with small (2 cm) or large (6 cm) growth.

Seidler *et al*. (2009) developed simple health state vignettes describing the type of repair and subsequent scar after facial and auricular non-melanoma skin cancer surgery and reconstruction.[60] One state comprised surgery for facial non-melanoma skin cancer, a second state described simple repairs or scars (granulation and primary closure) due to surgery and a third state described complex

repairs or scars (local flap and graft) due to surgery of non-melanoma skin cancer. The 3 health states were valued by 5 healthy adults from the general public in the US using TTO.

Table 23 summarises the methods used to derive and value health states associated with skin cancer and the resulting utility scores, as reported in the 6 studies included in this systematic review.

Table 23. Summary of studies reporting utility data for health states experienced by people with skin cancer

Study	Definition of health states	Valuation method	Population providing valuations	Health states and corresponding utility scores
Melanoma skin cancer				
Askew *et al*. 2011[56]	EQ-5D data from 273 patients with melanoma, 75 undergoing treatment and 198 in follow-up surveillance at a tertiary cancer care centre in the US. Median age 52 (range 20 to 79); white 98%, male 58% Melanoma stage I/II: n=102; III: n=100; IV: n=71	TTO	4,048 representative members of the US population	Stage I/II: 0.91(SD 0.14) Stage III: 0.85 (SD 0.13) Stage IV: 0.86 (SD 0.11)
Beusterien *et al*. 2009[57]	Vignettes constructed for 4 advanced melanoma treatment-related response states, one symptomatic melanoma state, and nine toxicity-related health states based on published literature and refined following an iterative review by 5 clinical experts,2 oncology nurses, 3 quality-of-life researchers, and a pilot test with individuals from the general public. The health states were described as being treated for cancer (melanoma not mentioned), whether or not treatment is working, and changes in tumour size, pain levels, appetite, effort required to perform daily activities, and fatigue. Toxicity scenarios added on description of partial response. The 4 response states were defined as follows: Partial response: >50% decrease in lesion mass Stable disease: >25% decrease or increase in lesion mass Progressive disease: appearance of new lesions or increase by >25% in lesion mass Best supportive care: no indicated or desired cancer treatment	SG	140 members of the general population (77 from Australia and 63 from the UK)	<u>UK sample values</u> <u>Clinical response states</u> Partial response 0.85 (SE 0.02) Stable disease 0.77 (SE 0.02) Progressive disease 0.59 (SE 0.02) Best supportive care 0.59 (SE 0.02) <u>Utility decrement for toxicity states</u> Hair loss -0.03 (SE 0.01) Skin reaction -0.03 (SE 0.01) Diarrhoea -0.06 (SE 0.01) Nausea/vomiting -0.07 (SE 0.01) Flu-like syndrome -0.09 (SE 0.01) Stomatitis -0.10 (SE 0.02) 1-day in/outpatient stay for severe toxicity -0.11 (SE 0.02) Symptomatic melanoma -0.11 (SE 0.02) 2/5-day hospitalisation for severe toxicity -0.13 (SE 0.02)
King *et al*. 2011[58]	Vignettes describing different stages of melanomas (I, II, III and IV) constructed based on published literature and relevant websites.	TTO	163 adult patients with melanoma in the US; mean age 51 years, 99% white, 45% male New cases (1 year or less from diagnosis); established cases (more than year after diagnosis, or more than 6 months if stage IV) Stage I: n= 15; 80 Stage II: n = 4; 11 Stage III: n = 8; 10 Stage IV: n = 11; 24 Patients asked to value stages other that their own	Stage I 0.926 (SD 0.119) New cases' values: 0.904 (SD 0.129) Established cases' values: 0.931 (SD 0.118) Stage II 0.915 (SD 0.127) New cases' values: 0.956 (SD 0.052) Established cases' values: 0.900 (SD 0.145) Stage III 0.720 (SD 0.282) New cases' values: 0.534 (SD 0.291) Established cases' values: 0.908 (SD 0.123) Stage IV 0.580 (SD 0.340) New cases' values: 0.693 (SD 0.329) Established cases' values: 0.527 (SD 0.339)

Tromme *et al*. 2014[55]	395 EQ-5D-5L questionnaires from 356 patients with melanoma (mean age 52.6, male 74%); 39 patients completed questionnaires twice, as they were seen in two different phases (treatment and follow-up) and/or stages. Patients grouped according to melanoma stage (I, II, III, IV), and phase of stage (treatment or remission). Based on expert advice, treatment duration was assumed to be 1, 2 and 3 months for stages 0-Ia, Ib-II and III, respectively; and more than 10 months for stage IV. Remission period for stages 0/Ia and Ib/II was 2 years. Patients with stage IV melanoma in remission but still under treatment were classified as patients under treatment. <u>Patient sample size (mean age) by health state</u> Stage 0/Ia treatment: n= 68, (51.7); remission: n= 98, (46.5) Stage Ib/II treatment: n=33, (54.5); remission: n= 76, (53.2) Stage III treatment: n=15, (55.9); remission: n = 50, (53.3) Stage IV treatment: n=41, (61.4); remission: n=14, (64.8) EQ-5D-5L profiles were mapped onto EQ-5D-3L profiles	VAS	2,754 Flemish adults from the general public in Belgium	Stage 0/Ia Month 1, treatment 0.687 (SD 0.192) Months 2–24, remission 0.809 (SD 0.179) Stage Ib/II Months 1–2, treatment 0.579 (SD 0.272) Months 3–24,remission 0.802 (SD 0.166) Stage III Months 1–3, treatment 0.535 (SD 0.278) From Month 4, remission 0.703 (SD 0.156) Stage IV From start of treatment 0.583 (SD 0.192) From start of remission 0.796 (SD 0.167)
Non-melanoma skin cancer				
Shingler *et al*. 2013[59]	Health state vignettes associated with advanced BCC constructed based on a literature review, consultation with two clinical experts, and validation/piloting with 3 members of the general public. Final health state vignettes: Complete response; Post-surgical state Partial response with small (2 cm) or large (6 cm) growth Stable disease with small (2 cm) or large (6 cm) growth or multiple growths (2 cm) Progressed disease with small (2 cm) or large (6 cm) growth	TTO	Representative sample of 100 members of the UK general public (mean age 39.1 years, 96% white, 57% female)	Complete response 0.94 (SD 0.08) Post-surgical state 0.72 (SD 0.24) Partial response with small growth (2 cm) 0.88 (SD 0.12) with large growth (6 cm) 0.82 (SD 0.16) Stable disease with small growth (2 cm) 0.82 (SD 0.16) with multiple growths (2 cm) 0.80 (SD 0.20) with large growth (6 cm) 0.76 (SD 0.20) Progressed disease with small growth (2 cm) 0.74 (SD 0.21) with large growth (6 cm) 0.67 (SD 0.25)
Surgical excision				
Seidler *et al*. 2009[60]	Health state vignettes describing the type of repair and subsequent scar after facial and auricular non-melanoma skin cancer surgery and reconstruction. The health states were: surgery for facial non-melanoma skin cancer simple repairs/scars (granulation and primary closure) complex repairs/scars (local flap and graft)	TTO	5 healthy people from the general public in the US (mean age 40 year)	Excision procedure: 0.996 (range 0.984-1) Simple repairs/scars 0.984 (range 0.974-1) Complex repairs/scars 0.974 (range 0.953-1)
Abbreviations used in table: BCC, basal cell carcinoma; SD, standard deviation; SE, standard error; SG, standard gamble; TTO, time trade-off.				

According to NICE guidance on the selection of utility values for use in cost-utility analysis, the measurement of changes in HRQoL should be reported directly by people with the condition examined, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as the TTO or SG, in a representative sample of the UK population. When changes in HRQoL cannot be obtained directly from the people with the condition examined, then data should be obtained from their carers. NICE recommends EQ-5D for use in cost-utility analyses of interventions for adults. When EQ-5D scores are not available or are inappropriate for the condition or effects of treatment, the Institute recommends that the valuation methods be fully described and comparable to those used for the EQ-5D (NICE, 2013).[64]

None of the studies included in the review meets the above criteria set by NICE. Two of the studies (Askew *et al*. 2011[56]; Tromme *et al*. 2014[55]) used EQ-5D for the description of HRQoL experienced by patients with melanoma. However, none of them used the UK EQ-5D tariff[65] for the valuation of health states: Askew *et al*. (2011)[56] used the US EQ-5D tariff, which was developed using TTO, whereas Tromme *et al*. (2014)[55] used the Belgian EQ-5D tariff, which was developed using VAS – a valuation method that is not choice-based and thus is not among NICE preferred valuation methods.

All the remaining studies generated utility values for health states described in vignettes. Of those, Beusterien *et al*. (2009) elicited utility values for melanoma-related health states from members of the general population in Australia but also in the UK, so in this aspect, the study meets the NICE criterion for valuation of states by the UK general population.[57] The same applies to Shingler *et al*. (2013), who reported utility values for advanced BCC-related health states obtained from members of the UK general public.[59] In contrast, King *et al*. (2011)[58] reported melanoma-related utility values elicited from patients with melanoma in the US, while Seidler *et al*. (2009)[60] reported utility values associated with facial non-melanoma skin cancer surgery and reconstruction that were elicited from only 5 healthy adults in the US.

A comparison of the utility values available for melanoma-related health states according to stage revealed that the utility values reported by Askew *et al.* (2011)[56] for melanoma stages III and IV are considerably higher than those reported by King *et al.* (2011)[58] and Tromme *et al.* (2014).[55] Moreover, the utility values reported by Tromme *et al.* (2014)[55] for melanoma early stages I and II are substantially lower than the utility values reported for respective stages in Askew *et al.* (2011)[56] and King *et al.* (2011).[58] These discrepancies are potentially attributable to differences in measurement and valuation across the 3 studies. Measurement of HRQoL in two studies (Askew *et al*. 2011[56]; Tromme *et al*. 2014[55]) was taken from patients with melanoma using EQ-5D, whereas King *et al.* (2011)[58] used vignettes to describe the HRQoL associated with melanoma stages. In the two studies reporting EQ-5D-based utility values (Askew *et al*. 2011[56]; Tromme *et al*. 2014[55]) values had been elicited from members the general population in two different countries (US versus

Belgium) using two different valuation techniques (TTO versus VAS). King *et al.* (2011) elicited values from patients with melanoma.[58] These differences in valuation may also be responsible for the differences in resulting utility values.

In addition, it is noted that utility values for stage III appear to be lower than utility values for stage IV in Tromme *et al.* (2014), however this may be attributable to the variation in values due to the small number of patients providing EQ-5D ratings for stage III in treatment (n=15) and stage IV in remission (n=14).[55]

Consideration of the available utility values for skin cancer, the methods used in their development and underlying limitations as well as their eligibility for use in economic modelling according to NICE criteria is discussed in respective sub-sections of economic modelling later in Section 1.2.

5.2 Economic modelling

5.2.1 Introduction – overview of methods

This section gives an overview of the economic modelling approach, the overall objectives and methods employed. The economic analysis consists of three 'part' models that were eventually combined into one analysis. The specific methods employed for each 'part' model are described separately for each model in respective sections below.

5.2.1.1 Overall objective

The overall objective of the economic analysis as defined by the scope of this diagnostic assessment was to assess the cost effectiveness of VivaScope 1500 and 3000 imaging system in the diagnosis of potentially malignant skin lesions, including lentigo maligna, and the margin delineation of diagnosed malignant lesions, including lentigo maligna, prior to surgical treatment. Not all potentially malignant or diagnosed skin lesions are suitable for diagnosis or pre-surgical margin delineation, respectively, with the use of the VivaScope imaging system. The selection of population groups with suspected (or diagnosed) skin cancer for consideration in economic modelling was determined by the availability of relevant clinical data and clinical expert opinion.

5.2.1.2 Study population

The VivaScope 1500 and 3000 imagine system was assessed in the diagnosis of skin cancer in the following populations:

- people with suspected melanoma, who have equivocal lesions following dermoscopy;
- people with suspected BCC, whose lesions have an equivocal or positive result in dermoscopy, to make the diagnosis or to confirm diagnosis, respectively, as an alternative to diagnostic biopsy.

The above populations were considered to be the most relevant to undergo diagnostic assessment with VivaScope, according to clinical experts to the EAG. Clinical experts also advised that the type of skin cancer is suspected prior to examination with VivaScope, hence the type of suspected skin cancer was pre-specified at early stages of designing the economic model. The NICE scope defines the study population as 'people with equivocal lesions following dermoscopy'; however, clinical experts advised the EAG that the use of VivaScope in suspected BCC lesions has two purposes: to make a diagnosis when results of dermoscopy are not certain; and to confirm diagnosis in lesions that are found positive in dermoscopy; in both cases the VivaScope is used as an alternative to diagnostic biopsy. Thus the economic model considered all people with suspected BCC lesions eligible for dermoscopy, and not only those with equivocal lesions suspected for BCC, as the latter are rather a minority of the cases eligible for examination with VivaScope.

Equivocal lesions among those suspected for melanoma include any lesions that are suspected for melanoma based on a number of characteristics in dermoscopy, with the exception of clear positive (malignant) lesions that have all the dermoscopic characteristics of melanoma and clear negative (benign) lesions that show no features for melanoma (no changes) in dermoscopy. The risk of equivocal lesions being malignant is overall low. There are different degrees of 'equivocalness', depending on the dermoscopic characteristics of the lesion and subjective experience and interpretation. Clinical expert advice indicated that highly suspicious equivocal lesions are lesions with at least 2 positive dermoscopic features including one major criterion, or 3 minor positive features suggestive of melanoma, and/or lesions clearly changed after digital follow-up, and/or new or growing lesions in an adult with at least one dermoscopic positive criterion, or papular/nodular or pink or spitzoid lesions. In all those cases excision is prompted and examination with VivaScope does not represent a real advantage since the risk to miss a melanoma remains too high. Moderately or low suspicious equivocal lesions are lesions with only one major dermoscopic positive feature or two minor features, and/or not clear history or minor changes. In such cases, excision is possible but other options could be taken into account, such as digital follow-up, especially in the case of flat lesions in patients with multiple moles; however, digital follow-up has the risk to delay a melanoma diagnosis. The majority of moderately or low suspicious equivocal lesions that are excised are benign and examination with VivaScope can play a major role in reducing this burden of unnecessary excisions.

Clinical experts advised that VivaScope is less suitable for the detection and assessment of skin lesions suspected for SCC, as this type of skin cancer is usually scaly because of severe hyperkeratosis. This often limits the evaluation of SCC lesions as it is more difficult to capture images of structures deeper in the tissue. Moreover, no evidence on the diagnostic accuracy of VivaScope in this type of skin cancer was identified in the systematic review of clinical evidence. Therefore, it was decided not to include people with skin lesions suspected for SCC in the diagnostic economic model.

Regarding margin delineation, VivaScope 3000 was assessed in the following population:

- Patients with lentigo maligna prior to surgical management.

According to clinical expert advice, margin delineation of melanomas with VivaScope is not useful in clinical practice, as the margins of melanomas are clearly defined and can be completely excised following BAD guidance;[16] consequently, VivaScope mapping of melanomas does not offer any clinical utility and therefore was not considered further for economic modelling.

Clinical experts advised that margin delineation of BCCs using VivaScope may be difficult, as BCCs may be too deep so their margins may not be accurately mapped with VivaScope. Therefore, it was decided not to consider margin delineation of BCC lesions with the use of VivaScope in the economic model, considering also the lack of evidence in this area. Nevertheless, it is acknowledged that although margin delineation of BCCs using VivaScope prior to surgical excision was not considered in the economic analysis, this may be used as an alternative to Mohs surgery, as advised by clinical experts.

VivaScope is not appropriate for the assessment of SCC lesion margins, due to the reasons discussed above.

5.2.1.3 Economic models developed – Decision problems addressed

According to the study populations that were identified as relevant for the economic evaluation of VivaScope, three separate 'part' economic models were developed:

- Use of VivaScope in the diagnosis of equivocal lesions suspected for melanoma. This model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of equivocal lesions but each will be used as appropriate according to the location of the equivocal lesion to be examined.
- Use of VivaScope in the diagnosis of suspected BCC lesions following a positive or equivocal finding in dermoscopy. As with the previous model, this model assessed the cost effectiveness of VivaScope 1500 and 3000, as one integrated system, assuming that both devices will be available for the diagnosis of suspected BCC lesions but each will be used as appropriate according to the location of the skin lesion to be examined.
- Use of VivaScope for the margin delineation of lentigo maligna prior to surgical therapy. This model assessed the cost effectiveness of VivaScope 3000 as a stand-alone device, since only this device is appropriate for margin delineation.

Development of two separate models for the diagnosis of equivocal lesions suspected for melanoma and of suspected BCC lesions with a positive or equivocal dermoscopy finding, respectively, was necessary, because both the diagnostic accuracy of VivaScope and the treatment pathways and

associated costs and outcomes following diagnosis vary greatly between these two types of skin cancer.

Using the results of the above 3 'part' models, 5 economic analyses were undertaken, examining the cost effectiveness of VivaScope in:

a. The diagnostic assessment of equivocal lesions suspected for melanoma (integrated use of VivaScope 1500 & 3000);

b. The diagnostic assessment of lesions suspected for BCC following a positive or equivocal result in dermoscopy (integrated use of VivaScope 1500 & 3000);

c. The diagnostic assessment of skin lesions suspected for skin cancer, either melanoma (following an equivocal finding in dermoscopy) or BCC (following a positive or equivocal finding in dermoscopy) – this analysis combined the results of the two respective 'part' models;

d. The margin delineation of lentigo maligna prior to surgical treatment (use of VivaScope 3000 as a stand-alone device);

e. The diagnostic assessment of skin lesions suspected for either melanoma or BCC, and the margin delineation of lentigo malignas (integrated use of VivaScope 1500 & 3000) – this analysis combined the results of all three 'part' models.

The final economic analysis synthesised all cost and effectiveness data from each of the 'part' economic models to obtain an estimate of the overall cost effectiveness of the VivaScope imaging system used for all indicated purposes assessed in economic modelling in a skin cancer MDT service.

The analyses that combined results of 'part' models used weighed total costs and benefits according to the expected relative volume of each type of lesion diagnosed and/or mapped with VivaScope in one dermatology multi-disciplinary team (MDT) service.

5.2.1.4 Costs and outcomes considered in the analysis

The perspective of the analysis was that of the NHS and Personal Social Services (PSS). Costs consisted of intervention costs of VivaScope (including equipment and maintenance costs, costs of consumables, staff training and staff time required for the examination), costs associated with the comparators of the analysis (such as costs of biopsy, histological examination and monitoring including any required consultations with clinicians), costs of management of skin lesions following correct (i.e. true negative and true positive cases) or incorrect (false negative and false positive cases) diagnosis, as well as costs incurred following the pre-surgical mapping of malignant skin lesions.

Costs of management of future events such as progression and recurrence of skin cancer, where relevant, were also considered. All costs were expressed in 2014 prices.

The outcome measure of the economic analysis was the QALY. Discounting of costs and outcomes was applied at an annual rate of 3.5%, in accordance with NICE methodology guidance.[64]

5.2.1.5 Sources of model input parameters

The clinical effectiveness parameters required for the economic models (diagnostic accuracy of VivaScope 1500 and 3000 and clinical outcomes on margin delineation) were informed, where possible, by the systematic review of the clinical evidence reported in Section 4. A non-systematic review of model-based economic studies assessing strategies and interventions for the prevention, assessment or management of skin cancer was also undertaken, aiming to provide an insight into the modelling methods in the area of skin cancer and also identify relevant input parameters that could be potentially utilised in the economic models assessing VivaScope. These studies were predominantly identified by re-running the search for existing economic evaluations of VivaScope (described in Section 5.1.1) after omitting the terms capturing the interventions and comparators of interest from the search strategy. The search resulted in a very high number of hits (approximately 9K) that did not permit a review of the findings in a systematic way due to time and resource constraints. Nevertheless, this review helped identify a range of useful clinical (as well as resource use) data and model structural components that contributed to the construction of the model structures for the economic assessment of VivaScope. In addition, relevant NICE guidance (including clinical and public health guidelines, technology appraisals and interventional procedure guidance) was reviewed for clinical and cost data that could be potentially useful in economic modelling.

Preference-based data on the HRQoL of people experiencing health states or events associated with suspected or confirmed skin cancer were derived from the relevant published literature identified in the respective systematic review, the results of which are provided in Section 5.1.2.

Following clinical expert advice, the EAG undertook a review of conference abstracts presented at the British Association of Dermatologists' Annual Meetings since 2010, which are available from the *British Journal of Dermatology*. This review aimed at identifying audits reporting data on health service use from patients with skin cancer in the UK, as well as recent trends in epidemiological data directly relevant to the UK population, that could inform the economic models. Clinical experts also provided references to studies reporting data that were potentially useful in populating the economic models.

Finally, at all steps of designing the economic models, clinical expert opinion was sought to confirm that diagnostic and assessment pathways were consistent with current clinical practice in the UK, as

well as with anticipated changes in practice following a potential introduction of VivaScope within the NHS context. Clinical expert opinion was also employed to supplement the economic models with parameter estimates, in areas that relevant published evidence was lacking.

Costs associated with the intervention (VivaScope 1500 and 3000 imaging system), including purchase price of the equipment, part and maintenance costs, were provided by the company. Other healthcare unit costs were obtained from national sources such as the NHS Drug Tariff for February 2015[66], the national Unit Costs of Health and Social Care for 2014[67], and the NHS reference costs for 2014[68]. The latter were preferred over the Payment by Results (PbR) tariffs because they represent actual national average costs incurred as a result of healthcare services provided by the NHS, hence they reflect opportunity costs, whereas the PbR tariffs represent payments rather than the actual cost of services to the NHS.

5.2.1.6 Annual volume of cases eligible for examination with VivaScope in a dermatology multi-disciplinary team (MDT) clinic in the UK

The annual volume of cases eligible for examination with VivaScope in a dermatology MDT clinic was needed in order to determine the total cost per case associated with VivaScope examination, as the overall cost of VivaScope (including purchase and maintenance cost, training costs and any other ancillary costs) is spread across the number of lesions examined. Given the high cost of purchasing VivaScope and the considerable training required for obtaining and interpreting VivaScope images, an adequate number of VivaScope examinations needs to be performed every year, so that the benefit from VivaScope use offsets the intervention cost.

In order to estimate the total number of people that are assessed with VivaScope in one year three approaches were followed:

The first approach was to ask clinical experts working in the dermatology department of Guy's and St Thomas' Hospital, London, where VivaScope is currently in use, about the annual volume of cases examined with VivaScope in their practice.

This approach yielded the following information:

- Approximately one suspected melanoma is assessed with VivaScope per week; however, it was suggested that this number is probably lower than the typical number of lesions suspected for melanoma that would normally be examined by a tertiary service and that would be eligible for examination with VivaScope.
- Approximately 15 suspected BCC lesions are assessed with VivaScope per week; however, it was suggested that this number may be higher than the typical number of suspected BCC lesions that would normally be examined by a tertiary dermatology service.

- Approximately 1-2 lentigo malignas are mapped with VivaScope per week, but this includes lentigo malignas planned for surgical therapy as well as radiotherapy and topical immunotherapy.

Based on the above information, the annual volume of lesions examined with VivaScope was estimated to comprise 75-100 equivocal lesions suspected for melanoma (estimated as 1.5-2 expected to be seen per week x 50 weeks); 500 suspected BCC lesions (estimated as 10 expected to be seen per week x 50 weeks); and 75 lentigo malignas prior to treatment (estimated as 1.5 expected to be seen per week x 50 weeks, and considering that the vast majority of lentigo malignas are treated surgically, as advised by clinical experts).

The second approach was to seek information from clinical experts working in other dermatology services, who were approached for expert opinion and advice on the preparation of this report, on the annual volume of suspected melanomas, suspected BCCs and lentigo malignas eligible for examination with VivaScope that were assessed in their practice.

This approach yielded the following information:

- The dermatology clinic at the Norfolk and Norwich University Hospital examines approximately 600-800 lesions suspected for melanoma per year. No information was available on the number of lesions suspected for BCC or lentigo malignas examined per year.
- The dermatology service at the Lincoln hospitals serves a population of about 0.75 million. Using population incidence data, it was estimated that every year the service diagnoses about 160 melanomas, 1000 BCCs and roughly 60-80 lentigo malignas. The vast majority of BCCs are easy to diagnose clinically or with dermoscopy; sometimes they are so typical that no dermoscopy is needed.
- The department of dermatology at the Chelsea & Westminster Hospital examines around 300 suspected BCCs and manages at maximum 20 lentigo malignas annually. No information was available on the number of suspected melanomas examined per year.

Clinical experts advised that in every 5-6 lesions that are excised due to suspicion for melanoma, one melanoma is confirmed. Using the estimate of 160 diagnosed melanomas, the number of suspected melanomas examined by the service in Lincoln (i.e. lesions giving a positive or equivocal result in dermoscopy) should be approximately 800-960 per year.

Of the suspected melanomas examined in each service, only those giving an equivocal finding in dermoscopy would be eligible for examination with VivaScope. Therefore, to estimate the number of suspected melanomas eligible for examination with VivaScope in each service, the proportion of equivocal lesions among the number of suspected melanomas examined in each service is needed. For this reason, a review of the studies included in the systematic review of clinical evidence reported in Section 4 was undertaken, attempting to identify the proportion of suspected melanomas examined by a dermatology MDT clinic that give an equivocal finding in dermoscopy. The review considered

studies reporting prospective or retrospective recruitment of consecutive people attending a dermatology clinic for skin lesions suspected for melanoma, who were assessed with a dermoscope, as there were likely to be more representative of the population of people with suspected melanomas likely to be seen at a dermatology clinic. Studies that had selectively recruited people with suspicious skin lesions and those that assessed retrospectively lesions that had already been excised on the basis of their dermoscopic features were not considered, as their study samples were not necessarily representative of the study population. In addition, studies that had excluded 'clear-cut positive lesions in dermoscopy' from recruitment were not considered useful, as they provided an overestimate of the proportion of equivocal lesions among the total number of lesions examined with dermoscopy.

The only suitable study included in the systematic review of clinical evidence reported in Section 4 was Alarcon *et al*. (2014), who assessed the impact of VivaScope examination of equivocal lesions suspected for melanoma following diagnostic assessment with dermoscopy.[33] From 5,520 patients attending a hospital dermatology unit in Barcelona, the study identified 1,534 people with lesions suspicious for melanoma that underwent dermoscopy. Of those, 1,191 had lesions with a clear finding according to the authors, which were subsequently either immediately planned for excision or scheduled for digital follow-up. The remaining 343 lesions had an equivocal finding and were thus suitable for examination with VivaScope 1500. Thus the percentage of equivocal lesions among all lesions suspected for melanoma and assessed with dermoscopy was 22.4% (343/1,534).

A Belgian observational study assessed the extent of cost reduction resulting from use of sequential digital dermoscopy in people presenting to dermatologists because of their own concern for melanoma and having 1-3 equivocal melanocytic lesions.[69] The study reported that, of the 9,360 consecutive people with 1-3 lesions suspected for cancer that were assessed with a dermoscope over one year (2009-2010), 822 had equivocal lesions, according to dermatologists, making the percentage of equivocal lesions among lesions suspected for melanoma 8.78%. However, the study population was people presenting to dermatology services rather than being referred, and therefore the prevalence of melanoma, and subsequently the prevalence of equivocal lesions was most likely lower than the prevalence of melanoma and prevalence of equivocal lesions in populations referred to dermatology MDTs from primary care in the UK.

It needs to be noted that the proportion of equivocal lesions among lesions suspected for melanoma that are examined with a dermoscope is affected by a number of other factors, such as the experience of the dermatologist performing the examination and the underlying prevalence of melanomas.

Expert opinion indicated that the proportion of equivocal lesions out of lesions suspected for melanoma undergoing dermoscopic evaluation in England must be between the figures observed in the two studies described above.[33,69] Therefore, estimations of the volume of lesions suspected for

melanoma that are suitable for VivaScope examination (i.e. they have an equivocal finding in dermoscopy) were based on the assumption that approximately 15% of lesions examined by skin cancer MTD services are equivocal.

Using the estimates of suspected melanomas seen annually in each of the two services (600-800 cases at the dermatology clinic at the Norfolk and Norwich University Hospital and 800-960 cases at the dermatology clinic in Lincoln) and a proportion of equivocal lesions following dermoscopy of 15% among all cases examined, the estimated number of equivocal lesions suspected for melanoma that would be eligible for examination with VivaScope seen by each service per year was 90-120 in Norfolk and Norwich University Hospital and 120-144 in Lincoln.

Regarding BCCs diagnosed at the dermatology clinic at Lincoln Hospitals, it was stated that the vast majority was easy to diagnose and sometimes did not require use of dermoscope. Expert opinion suggested that of the 1000 confirmed BCCs, 600-700 would be expected to have a clear-cut picture in clinical examination (and a positive finding in dermoscopy). For the remaining 300-400 confirmed BCC lesions, clinical expert advice indicated that these would have been identified after roughly 500-600 lesions suspected for BCC would have been examined with VivaScope (following an equivocal finding in dermoscopy). In total, at least 500-600 lesions would be eligible for examination with VivaScope to make a diagnosis, and 600-700 clear-cut positive BCC lesions would be eligible for examination with VivaScope for confirmation of diagnosis, leading to a total estimate of 1200-1400 lesions suspected for BCC that would be eligible for examination with VivaScope in the dermatology service of Lincoln hospitals annually.

The number of suspected BCCs examined at the dermatology department of the Chelsea & Westminster Hospital annually was approximately 300. Similarly to the above estimations, about 180-200 would be expected to have given a positive dermoscopy finding, and 100-120 would have likely given an equivocal dermoscopy finding; the latter, would have been identified after roughly 150-200 lesions suspected for BCC would have been examined with VivaScope following an equivocal finding in dermoscopy, resulting in a total estimate of around 330-400 lesions suspected for BCC that would be eligible for examination with VivaScope in the dermatology department of the Chelsea & Westminster Hospital.

The number of lentigo malignas examined annually at the dermatology department of Chelsea & Westminster Hospital was 20 at maximum, whereas at Lincoln hospitals every year roughly 60-80 lentigo malignas are diagnosed. It was assumed that practically all of them were treated surgically.

The third approach was to estimate the numbers of lesions/cases eligible for VivaScope examination indirectly, by estimating the numbers of people being referred to dermatology services per year in the UK and, from that, estimate the volume of people in a large dermatology MDT service.

This approach considered dermatology MDT clinics serving a large population of people, which are likely to see a high volume of skin lesions suspected for skin cancer. Specialist Skin Cancer multidisciplinary team (SSMDT) clinics were selected for this purpose, which are expected to be referred a higher number of suspected skin cancers compared with Local Skin Cancer MDTs (LSMDTs). These serve a catchment population for referral (their own local catchment plus the catchment of referring LSMDTs) of at least 750,000, and serve as the Local Skin MDT for their local (secondary) catchment population (National peer review programme 2014).[70]

In 2009-10, 882,000 patients were referred to dermatologists in England (approximately 16 per 1,000 population).[71] Up to 50% of referrals relate to skin cancer (including both diagnosis and management). Dermatologists screen over 90% of skin cancer referrals and treat approximately 75%.[71] In the period between 2000 and 2007, there was an increase of about 5.6% in new patients visiting dermatology specialists.[72] This is an increase of approximately 0.8% per year. Applying this annual rate of increase to the data from 2010, in 2015 the expected number of people referred to dermatologists in England is 16.63 per 1,000 population. With 50% of referrals relating to skin cancer and 90% of them being screened, this results in an estimate of approximately 7.49 examinations for skin cancer per 1,000 population per year.

Assuming a catchment area of 750,000, one SSMDT would examine around 5,614 people for skin cancer per year. Assuming the ratio of referred lesions suspected for BCC, SCC and melanoma is approximately the same with the ratio of confirmed skin cancers, and taking into account that in 2011 there were 102,628 cases of non-melanoma skin cancer in the UK (of which BCC comprised 74%) and 13,348 cases of melanoma in the UK,[2] then, of the 5,614 people examined for skin cancer annually, 11.5% (646) would be examined for suspected melanoma and 65.5% (3,676) would be examined for suspected BCC.

Using an estimated proportion of equivocal lesions among lesions suspected for melanoma of 15%, a SSMDT serving a population of 750,000 would see 97 equivocal lesions suspected for melanoma per year.

Clinical expert advice was that the number of 3,676 lesions suspected for BCC appears to be unrealistically high. Therefore it was assumed that only 50% of them were actually suspected to be BCCs. Using estimates described earlier, it was calculated that roughly 2,000-2,300 lesions suspected for BCC would be potentially eligible for VivaScope examination.

Epidemiological data specific to lentigo maligna are rather sparse and not routinely available in UK cancer statistics. Incidence data on lentigo maligna were reported in a US study, which identified all adult residents with a first lifetime diagnosis of lentigo maligna between 1970 and 2007 in Olmsted County, Minnesota.[73] The study reported that the overall age- and sex-adjusted incidence of lentigo maligna among adults was 6.3 per 100,000 person-years, increasing from 2.2 between 1970 and 1989 to 13.7 between 2004 and 2007.[73] Although the incidence of lentigo maligna in the UK population, as well as the mixture of the UK population may be different from those in Minnesota, using the incidence of 13.7 per 100,000 person-years in a population of 750,000 people would result in 103 cases identified and treated in a dermatology service annually.

The estimates derived from the 3 approaches are summarised in Table 24.

Table 24. Estimates of the annual volume of skin lesions eligible for examination with VivaScope, including equivocal lesions suspected for melanoma, suspected BCC lesions and lentigo malignas prior to treatment

Approach	Estimates on annual volume of skin lesions eligible for examination with VivaScope (including equivocal lesions suspected for melanoma, suspected BCC lesions and lentigo maligna prior to treatment)
Clinical advice from experts working in UK services where VivaScope is available	• 75-100 equivocal lesions suspected for melanoma • 500 suspected BCC lesions • 75 diagnosed lentigo malignas undergoing treatment
Clinical advice from experts working in UK services & further assumptions on proportion of lesions eligible for examination with VivaScope	• 90-144 equivocal lesions suspected for melanoma • 330-400 (low estimate) to 1200-1400 (high estimate) suspected BCC lesions • 20 (low estimate) to 60-80 (high estimate) diagnosed lentigo malignas
Synthesis of epidemiological data and national statistics	• 97 equivocal lesions suspected for melanoma • 2,000-2,300 suspected BCC lesions • 103 diagnosed lentigo malignas
Abbreviations used in table: BCC, basal cell carcinoma	

As it can be seen, with the exception of BCC lesions, where there is a wide range in estimates, the estimated number of equivocal lesions suspected for melanoma and the estimated number of lentigo malignas that are eligible for examination with VivaScope using each of the 3 approaches are very close. In order to estimate the cost of VivaScope per skin lesion assessed, the following estimates in the number of lesions examined annually with VivaScope in a dermatology service were utilised:

- 100 equivocal lesions suspected for melanoma;
- 500 suspected lesions for BCC (use of a low, relatively conservative estimate, which was based on information derived from the only setting in the UK that currently uses VivaScope for the diagnostic or pre-surgical assessment of skin lesions);
- 75 lentigo malignas prior to treatment.

Lesions suitable for examination with VivaScope 3000

Lesions suspected for melanoma or BCC that are suitable for examination with VivaScope 3000 are predominately those on head or neck. Due to lack of relevant data on lesions suspected for skin cancer, it was assumed that the proportion of equivocal lesions suspected for melanoma on head or neck was equal to the proportion of diagnosed melanomas on head or neck; similarly, the proportion of lesions suspected for BCC with a positive finding in dermoscopy that present on head or neck was assumed to equal the proportion of diagnosed BCCs on head or neck.

The proportion of confirmed melanomas on head or neck is approximately 14% in females and 22% in males.[74] In 2011 there were 13,348 new cases of melanoma in the UK, 6,495 of which were in male,[75] so that the proportion of men in the population of people with newly diagnosed melanoma was 48.7%. Using these data, the proportion of melanomas on head or neck out of all melanomas was estimated to reach 17.9%. This figure was used as a proxy to represent the proportion of lesions suspected for melanoma with an equivocal finding presenting on head or neck, due to lack of more specific data.

Regarding BCC, a review on facial BCC has reported that up to 85% of BCCs are on head or neck.[76] A study that analysed data on all cases of BCC diagnosed at a single centre of dermatopathology during 1967–96 in Strasbourg, France, reported that the BCCs of the head and neck were more frequent in women (85.2%) than in men (81%), independent of their histological subtype.[77]Another study analysing trends in the demographic, clinical and socioeconomic profile of more than 50.000 cases of non-melanoma skin cancer registered between 1994 and 2011 by the Irish National Cancer Registry, reported that 69% of diagnosed BCCs over that period were on the face.[78] In the UK, an audit of all BCC excisions performed in a single centre in 2008 showed that 68.1% of those (631/926) were removed from the face.[79] Similarly, a regional audit of BCC histopathology reports using the Cancer Registry Cancer-Base Enquiry System to extract data on the first 100 BCC 'de novo' cases per trust for the year 2007 showed that, of the 1318 BCC excised lesions for which the anatomical site of the tumour was available, 915 (69.4%) were found on head or neck.[80] The figure of 69.4% was used as a proxy to represent the proportion of suspected BCC lesions with a positive dermoscopic finding presenting on head or neck.

Estimation of the proportion of lentigo malignas presenting on head or neck was not relevant in the context of examination with VivaScope 1500 or 3000, as all lentigo malignas are mapped with VivaScope 3000 prior to surgical excision.

5.2.1.7 Cost of VivaScope 1500 and 3000

This section reports the costs associated with examination of skin lesions with the VivaScope imaging system, either for the diagnostic assessment of lesions suspected for melanoma or BCC, or for the margin delineation of lentigo maligna prior to surgical treatment.

The costs associated with examination of skin lesions with VivaScope comprise the purchase (capital) cost of the VivaScope imaging system, maintenance costs, costs of equipment parts and other consumables required for the examination, and costs of training staff in operating the system and in the assessment and interpretation of the images obtained. They also include costs of staff time required for the examination with VivaScope and subsequent assessment of skin lesions.

The purchase price of VivaScope 1500 and 3000, as well as the annual maintenance costs, were provided by the company. The purchase price and annual maintenance costs of VivaScope 3000 as an add-on device to VivaScope 1500 were stated to be lower than the respective costs of VivaScope 3000 as a stand-alone device. For the use of VivaScope in the diagnostic assessment of lesions suspected for skin cancer, VivaScope 1500 and 3000 have been considered to be used according to indications and suitability (i.e. the economic models assumed that VivaScope 1500 is used for the diagnostic assessment of body skin lesions, while VivaScope 3000 is used for the diagnosis of skin lesions on the head or neck). Thus, the lower purchase price and annual maintenance costs for VivaScope 3000 as an add-on device to VivaScope 1500 were utilised in the estimation of costs in all economic analyses that included any of the diagnostic 'part' economic models. In contrast, mapping of lentigo malignas prior to surgical treatment can be achieved only with the use of VivaScope 3000. Therefore, in the analysis that assessed the cost effectiveness of VivaScope used exclusively for pre-surgical margin delineation of lentigo malignas, the purchase and annual maintenance costs of VivaScope 3000 as a stand-alone device were used.

The purchase price of VivaScope 1500 and 3000 was annuitised over the expected lifetime of the technology, which was reported by the company to be 10 years. The equivalent annual cost was calculated from the purchase price of the technology and the useful life of the equipment, as advised by the company, using an inflation rate of costs of 3.5%.

The costs of parts refer to the cost of the tissue ring and the cost of a cap for VivaScope 3000. At the purchase of VivaScope 2 tissue rings and 2 caps are provided with the device at no extra cost. The costs of parts are incurred only for the purchase of extra parts following loss or damage, and therefore were not considered in the estimation of the total cost of VivaScope.

The consumables required for an examination of a skin lesion with VivaScope include, according to the company, an adhesive window that is attached on the lesion only for examination with VivaScope

1500; crodamol oil used as a lubricant; alcotip sachets, which are used for the preparation (disinfection) of the skin; and ultrasound gel. The cost of adhesive windows was provided by the company. For the other consumables, a small cost per lesion examined was assumed, estimated after considering the market prices of the consumables and the fact that only a small portion of each is required per lesion examination.

Training on the use of VivaScope consists of the following (information provided by the company, supplemented by one of the experts providing the training):

- Introductory training: this is provided on-site for free with the purchase of VivaScope, lasts approximately 1-2 days and involves mainly technical training but some basic clinical information is also offered. The purpose of training is to give technicians and clinicians (consultant dermatologist, consultant dermatological surgeon, technical assistant, pathologist, researcher) the ability to properly use the machine and the software, provide them with an understanding of the anatomical location of the image on the monitor and detect the most common and evident structures. Participants are given information image acquisition, data management, operational precautions, etc. The training course consists of presentations, the revision of manuals, the discussion of imaging guidelines and the consideration of appropriate studies of interest.

- Independent study with textbooks: this is complementary to the introductory training; VivaScope users are expected to revise two sophisticated imaging textbooks.

- Intensive expert training: this is also provided for free with the purchase of VivaScope and follows the introductory training and independent study; it is a 3-day course currently offered 4 times a year at the University of Modena and Reggio Emilia in Italy, but there are plans to expand it to referral centres in Europe, including the UK. The training in Italy is provided by four confocal experts that have been working with the VivaScope for more than 10 years, who guide the participants through the diagnosis of melanocytic lesions, non-melanocytic lesions, inflammatory skin diseases, cosmetic applications and others. It is considered essential part of the training.

- Online training course: provided for free with the purchase of VivaScope, this course consists of 100 cases with expert evaluation made available after student evaluation. It is considered part of the intensive expert training and is available with the purchase of VivaScope. The aim of this course is to establish the learning and test the trainee's skills.

According to clinical expert opinion, after this 'first degree' level of training, which usually lasts 3-5 weeks, trainees are able to recognise features, describe cases and identify diagnoses following algorithms, but they cannot be considered fully trained for routine activity, that is, they cannot fully achieve the clinical advantages offered by optimal use of VivaScope. Clinicians trained in the use of VivaScope will need to develop their skills further and gain experience and a good level of confidence in interpreting VivaScope images before they achieve the outcomes described in the literature following examination of skin lesions with VivaScope.

At the University of Modena and Reggio Emilia in Italy, this 'first degree' of training is followed by 'second degree' training, consisting of an intense teaching program with a duration ranging from 3 to 5 months. This includes a total of approximately 30 hours of frontal teaching (including a short basic course on histopathology), 50 hours of 'tutored cases' (case review with an expert and group discussion of the cases), and 100 hours of activities in the skin cancer unit (systematically using confocal microscopy). After this program the trainees should achieve a consistent increase in confidence (translated in clinical benefits from VivaScope use that is comparable with literature data), and also a reduction in some initial mistakes in the management of difficult situations (such as pink lesions, undefined papule/nodules, etc.).

According to clinical experts with experience in the use of VivaScope, the overall training required for a clinician to reach a good level of confidence and expertise, comprises between 4 and 6 months' time, and approximately 1000 to 2000 cases evaluated with confocal microscopy in a setting including a sufficient number of melanomas (more than 200). This is broadly consistent with the view expressed by [redacted], according to which "[redacted]

Further to the above training, the company indicated the availability of the following services:

- Online expert tutorial: clinicians may send very difficult confocal cases that may arise during the daily clinical routine, to a confocal expert for a 'second opinion'. This way, clinicians may expand their knowledge and increase their ability to diagnose difficult-to-assess lesions with a high degree of reliability and accuracy. This service is intended as an educational tool and requires a revised VivaNet telemedicine service.
- Independent International Circle of Experts: this is a group of expert VivaScope users, which offers interdisciplinary discussions in order to establish the confocal laser scanning microscopy as the standard in the dermatological diagnosis.

Estimation of training costs and staff time required for examination of skin lesions with VivaScope has been based on the information described above regarding the training courses available, and expert advice according to which a VivaScope facility run by a skin cancer MDT service requires staffing with a well-trained Band 7 radiographer, who is sufficiently qualified to interpret images, and a well-trained consultant dermatologist or specialist registrar.

The estimation of training costs for the purpose of this evaluation has been based on the information provided by the company regarding the "first-level" training (introductory training and intensive expert training course). No course fees have been considered, since both courses are provided for free with the purchase of VivaScope. In terms of staff time, 1.5 days of two radiographers and two

dermatologists (for the introductory training) and 4 further days of two dermatologists (for the 3-day intensive expert training plus travel time to/from Italy) were included in the cost. Moreover, £2,000 travel, hotel and subsistence costs for each dermatologist attending the intensive expert training were included in the estimation of training costs.

It needs to be noted, though, that the estimation of training costs above has not taken into account the substantial further time of on-going training during routine clinical practice (about 3-5 months) that is required so that dermatologists obtain a good level of confidence and expertise before the full clinical benefits resulting from the use of VivaScope can be enjoyed. This means that the conclusions of the economic analysis undertaken to support this report, which has utilised optimal diagnostic accuracy data for VivaScope as reported in relevant applications, are applicable after dermatologists using VivaScope obtain a good level of expertise, i.e. at about 3-5 months of routine clinical practice following training, in order to achieve the outcomes reported for VivaScope in the literature.

No further training costs for new radiographers and dermatologists using VivaScope in the future were considered, as it has been assumed that the radiographers and dermatologists that were originally trained can subsequently train and pass their experience onto new colleagues expected to use the device, on-site and during routine clinical practice.

The total estimated training costs were annuitised over 10 years (equal to the expected lifetime of the device). The equivalent annual cost was calculated using an inflation rate of costs of 3.5%.

In terms of staff time, clinical experts with experience in using VivaScope indicated that examination of skin lesions suspected for cancer with VivaScope 1500 requires 10 minutes of radiographer's time (from the time patient enters the consultation room until end of visit, including radiographer's time for attaching the adhesive window and obtaining the image) plus 5 minutes of a dermatologist's time for evaluation of images. Examination of skin lesions suspected for cancer with VivaScope 3000 requires 10 minutes of dermatologist's time (from the time patient enters the consultation room until end of visit, including dermatologist's time for obtaining and interpreting the image). Where more than one suspected lesions per person were assumed, 50% of radiographer's and dermatologist's time from patient entering the consultation room until end of visit was assumed to be fixed, and the remaining 50% was attributed to each lesion examined. Mapping of lentigo malignas with VivaScope 3000 prior to surgical treatment requires 30 minutes of dermatologist's time.

The unit costs of radiographers and dermatologists were taken from national sources.[67] The unit cost of a hospital Band 5 radiographer was £38 per hour in 2014, based on the mean full-time equivalent basic salary for Agenda for Change (AfC) band 5 for qualified allied health professionals of the July 2013 – June 2014 NHS staff earnings estimates. This unit cost included salary (considering also

overtime, shift work and geographic allowances) and salary oncosts, capital and other overheads, and qualification costs. The mean annual basic pay of AfC Band 7 qualified allied health professionals was approximately 63% higher compared with the respective pay at AfC Band 5,[67] and therefore the unit cost for a Band 7 radiographer was estimated to equal £62 per hour (this was estimated by the EAG, as no relevant figures were available in the literature).

The unit cost of a medical consultant was £140 per contract hour in 2014, including, as above, salary and salary oncosts, capital and other overheads, and qualification costs.[67] The unit cost of a specialist registrar was not available (a mean unit cost was available for the registrar group, which comprise a heterogeneous group of registrars, senior registrars, specialist and specialty registrars). The unit cost of an associate specialist was reported to be £124 per hour (under a 40 hour week). For costing purposes, the economic analysis assumed that the clinical examination with VivaScope is performed by a consultant dermatologist.

The equivalent annual purchase and training and annual maintenance costs of VivaScope were each divided by the annual number of cases (skin lesions) expected to be examined with VivaScope 1500 or 3000 for either diagnosis or margin delineation in a skin cancer MDT service in order to distribute these costs across the lesions examined and estimate an annual fixed and training cost per examined lesion. The cost of adhesive windows was omitted from the cost of suspicious skin lesions on the head or neck, as these are examined with VivaScope 3000. As reported in Section 5.2.1, it was estimated that approximately 100 suspected melanomas with equivocal dermoscopy finding, 500 lesions suspected for BCC and 75 diagnosed lentigo malignas prior to surgical treatment are eligible for examination with VivaScope by a skin cancer MDT service over a year. The percentage of equivocal lesions suspected for melanoma and of suspected BCC lesions that are on head or neck was estimated to be 17.9% and 69.4%, respectively.

The economic analysis that assessed the integrated use of VivaScope 1500 & 3000 for the diagnostic assessment of equivocal lesions suspected for melanoma considered exclusively a volume of 100 lesions per year. The analysis that assessed use of VivaScope for diagnostic assessment of lesions suspected of BCC used a volume of 500 lesions per year. The economic analysis considering diagnostic assessment of both types of lesions suspected for skin cancer with VivaScope assumed an annual volume of 600 lesions. The analysis that evaluated the use of VivaScope 3000 in the margin delineation of lentigo malignas prior to surgical treatment assumed an annual volume of 75 lesions. Finally, the overall analysis of all three uses of VivaScope imaging system that were considered in the economic modelling undertaken for this report utilised an annual volume of 675 lesions eligible for examination with VivaScope.

The cost of VivaScope examination per skin lesion examined, by type of skin lesion and analysis considered is shown in Table 25.

Table 25. Costs associated with examination of skin lesions with VivaScope

Characteristics and cost elements of VivaScope 1500 & 3000	Value
Purchase price of VivaScope (no VAT)*	VivaScope 1500 (dermoscopy and RCM integrated): £90,224 VivaScope 3000 as an add on to VivaScope 1500: £41,600 VivaScope 3000 as stand-alone device: £62,300 Combined purchase of VivaScope 1500 and VivaScope 3000: £131,824
Equivalent annual capital cost (assuming 3.5% interest rate and using a 10-year lifetime of equipment, as advised by company)	**VivaScope 1500 and VivaScope 3000 as an add on: £15,315** **VivaScope 3000 as stand-alone device: £7,238**
Annual maintenance cost	**£4,100 for VivaScope 1500 or VivaScope 3000 as stand-alone device;** **£1400 for VivaScope 3000 as an add on to VivaScope 1500**
Costs of parts (incurred only in case of loss of parts) Tissue ring: £55 (2 tissue rings provided with the device) Cap for VivaScope 3000: £192 (2 caps provided with the device)	**Not included in the estimation of cost per lesion**
Costs of consumables: Adhesive windows £147/box (containing 100; only needed for VivaScope 1500) Crodamol oil (lubricant): £7.8 per bottle Alcotip (disinfectant): £1.85 per 100 sachets Ultrasound gel: £3.2 per tube	**£2.97 per lesion examined with VivaScope 1500** **£1.50 per lesion examined with VivaScope 3000** (rough estimates)
Training cost (includes 1.5 day of introductory training [x 8 hours] for two radiographers Band 7, 1.5 of introductory training +3 days of intensive expert training [x 8 hours] for two consultant dermatologists, 1 day travel time for two consultant dermatologists to attend the expert training course, and £2,000 for travel, hotel and subsistence per consultant dermatologist attending the expert training in Italy)	£17,816
Equivalent annual training cost (assuming 10 years of training 'lifetime' and 3.5% interest rate)	**£2,070**
Mean staff cost per lesion examined Diagnostic assessment: VivaScope 1500: 10 minutes of radiographer Band 7 + 5 minutes of consultant dermatologist VivaScope 300: 10 minutes of consultant dermatologist Margin delineation of lentigo maligna: 30 minutes of consultant dermatologist Unit cost of radiographer Band 7: £62 per hour, using the unit cost of radiographer Band 5 and the ratio of salary of Band 7 : Band 5 AfC for qualified allied health professionals Unit cost of consultant dermatologist: £140 per hour of contract	Diagnostic assessment with VivaScope 1500: £22 Diagnostic assessment with VivaScope 3000: £22 for BCC; £23 for melanoma Mapping with VivaScope 3000: £70
Volume of lesions examined per year	**Suspected melanomas with an equivocal finding in dermoscopy: 100** **Suspected BCC with a positive dermoscopic result: 500** **Lentigo malignas assessed for margin delineation: 75**
Proportion of lesions suspected for cancer on head or neck, that would be suitable for examination with VivaScope 3000	**Suspected melanomas with an equivocal finding in dermoscopy: 17.9%** **Suspected BCC with a positive dermoscopic result: 69.4%**
Total cost of VivaScope examination per lesion examined	**Per suspected melanoma:** • **Exclusive use of device for suspected melanomas: £254**

	• **Exclusive use of device for diagnostic assessment: £63** • **Use of device across all 3 types of lesions: £59** **Per suspected BCC:** • **Exclusive use of device for suspected BCCs: £70** • **Exclusive use of device for diagnostic assessment: £62** • **Use of device across all 3 types of lesions: £58** **Per mapped lentigo maligna:** • **Exclusive use of device for mapping of lentigo malignas: £250** • **Use of device across all 3 types of lesions: £105**
Abbreviations used in table: AfC: agenda for change; BCC, basal cell carcinoma; RCM: reflectance confocal microscopy; VAT: value-added tax * based on an exchange rate of 1 euro = 0.84 pounds Information on purchase cost, annual maintenance cost, costs of parts and consumables obtained from the company; unit costs of staff time based on Curtis (2014)[67]	

5.2.2 Diagnostic economic model on suspected melanoma lesions following an equivocal finding in dermoscopy - methods

5.2.2.1 Study population

The study population for this model comprised people with lesions suspected for melanoma and an equivocal finding in dermoscopy.

The BAD guidelines on management of cutaneous melanoma define populations at greatly increased risk of melanoma (more than 10 times that of the general population).[16] These include people with a giant congenital pigmented hairy naevus (such as 20 cm or more in diameter or 5% of body surface area), people with a strong family history of melanoma or pancreatic cancer (3 or more family members), people with 2 family members affected with melanoma who also have the atypical mole syndrome, or a history of multiple primary melanomas in an individual, or pancreatic cancer. This greatly high-risk subgroup of patients requires regular monitoring (approximately every 6 months), often over lifetime, as the risk of some of their skin lesions being malignant or their risk to develop a new melanoma over time is high. In greatly high-risk patient sub-groups with multiple lesions, current practice is selection and excision of a number of lesions based on dermoscopy and clinical judgement, and monitoring of the remaining lesions, as it is not possible to excise all suspicious lesions. If a melanoma is not identified, it will likely be picked up during routine monitoring within 6 months to 1 year. Examination with VivaScope would be beneficial in this sub-group of patients, as it would help identify melanomas among the suspicious lesions so that they are excised earlier rather than later and also would help avoid unnecessary diagnostic biopsies of non-malignant lesions. These greatly high-risk sub-populations were not considered in the economic model as their management (routine monitoring) differs from that of the 'average' population with suspected melanoma; populations at greatly increased risk of melanoma comprise a very small proportion of people at risk of melanoma, whose management, nevertheless, can be very resource-intensive.

Other categories of moderately increased risk patients (approximately 8–10 times that of the general population), including organ transplant recipients, those with either a previous primary melanoma or large numbers of moles, some of which may be clinically atypical changing naevi, as well as people with other risk factors for melanoma (e.g., age ≥50 years, prior history of cancer), for whom long-term follow up is not routinely recommended, were included in the study population of the analysis.

The mean age of the study population, that is, people with suspected melanoma with an equivocal finding in dermoscopy, was assumed to be the same with the age of people at diagnosis of melanoma. Clinical expert advice was that the mean age of people with equivocal lesions suspected for melanoma does not differ from the mean age of people with lesions suspicious for melanoma in general. Malignant melanoma incidence is related to age, but it has an unusual pattern compared with other types of cancer: in the UK between 2008 and 2010, an average of 27% of cases were diagnosed in

those aged under 50 years, and an average of 45% of cases were diagnosed in those aged 65 years and over.[75] Age-specific incidence rates increase steadily from around age 20-24 years, reaching a peak at age 85+ years for both sexes (with the increase being sharper for males from age 55-59 years onwards).[75] The mean age of patients at presentation of melanoma has been reported to be 55 years, although different types of melanoma typically present at different ages.[81] A retrospective study of 1,769 people with melanoma that had been referred to a tertiary centre in London from 1999 to 2012 showed that the mean age of patients was 58 years.[82] Using the available information, the age of the study population in the economic model was assumed to be 55 years.

In 2011 there were 13,348 new cases of melanoma in the UK, 6,495 of which were in male,[75] so that the proportion of men in the population of people with newly diagnosed melanoma was 48.7%. This figure was used in the economic model to reflect the percentage of men in the population with suspected melanoma following an equivocal finding in dermoscopy as well as the population of men with (identified or non-identified) melanoma.

The proportion of confirmed melanomas on head or neck is approximately 14% in females and 22% in males.[74] These figures were also used to reflect the proportion of suspected and confirmed melanomas with an equivocal finding that are on head or neck in women and men, respectively.

Each person with suspected melanoma may present with more than one equivocal lesion in dermoscopy, although clinical experts advised that the majority of people present with only one lesion suspected for melanoma. In studies included in the systematic review of clinical evidence that assessed the diagnostic accuracy of VivaScope in identification of melanomas among equivocal lesions and reported both number of study participants and number of equivocal lesions, the number of suspected melanomas with an equivocal finding per person ranged from 1.00[33] to 1.17[45]. However, the number of confirmed melanomas per person reported in the studies was 1, and this was in agreement with clinical expert opinion. For simplicity purposes, the economic model assumed that every person presents with one suspected melanoma with equivocal finding in dermoscopy.

The annual volume of equivocal lesions suspected for melanoma examined at a dermatology MDT service in the UK was estimated to be approximately 100, as reported in Section 5.2.1 under 'annual volume of cases eligible for examination with VivaScope in a dermatology multi-disciplinary team clinic in the UK'.

5.2.2.2 Intervention and comparator

The intervention assessed in this model was VivaScope 1500 (for body lesions) and VivaScope 3000 (for lesions on head or neck) for the diagnostic assessment of skin lesions suspected for melanoma, following an equivocal finding in dermoscopy. The comparator was routine management of equivocal

lesions suspected for melanoma, comprising excision and biopsy for the majority of the equivocal lesions (highly suspicious lesions), and monitoring for the rest of them (moderately/low suspicious lesions). Monitoring consisted of one outpatient dermatology visit at 3 months, followed by discharge if there was no indication of melanoma.

5.2.2.3 Model structure

A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the diagnosis of people with lesions suspected for melanoma following an equivocal finding in dermoscopy. According to the model structure, which was determined by clinical expert advice and availability of relevant data, people aged 55 years, with dermoscopically equivocal lesions suspected for melanoma, were either examined with VivaScope 1500 or 3000 as appropriate (according to the location of the lesion), or received routine management, comprising excision and biopsy of the majority of the suspicious lesions and monitoring of a smaller proportion of less suspicious ones.

The model assumed that confirmed cases of skin cancer are of the same type of cancer as initially suspected (in the case of this model, melanoma), although occasionally skin cancers identified may be of different type of that initially estimated by the clinician at dermoscopy.

People whose lesions were examined with VivaScope received the results of the examination immediately. People whose lesions were found positive under VivaScope examination had an excision and biopsy. The results of biopsy were received 2 weeks after the excision. Those who were true positive (i.e. their lesion was confirmed in biopsy to be a melanoma) were further treated for their melanoma according to its stage, as recommended by national guidelines. Those who were false positive (i.e. biopsy showed that their lesion was not a melanoma) were assumed to have a benign tumour that did not require treatment and were discharged after the (unnecessary) excision and biopsy. People whose lesions were found negative under VivaScope examination were discharged and advised to visit their GP if they noticed changes in their skin lesion. If they were true negative (i.e. their lesion was not a melanoma) they were assumed to have a benign tumour that did not require treatment. If they were false negative (i.e. their lesion was an unidentified melanoma), they were assumed to return to the service at a later time, with their melanoma having potentially progressed to a more advanced stage.

People who received routine management, whose lesions were excised and biopsied, received the results of biopsy 2 weeks after the excision. Those who had a positive result (i.e. their lesion was confirmed in biopsy to be a melanoma) were treated for their melanoma according to its stage, as recommended by national guidelines. Those who had a negative result (i.e. biopsy showed that their lesion was not a melanoma) were assumed to have a benign tumour that did not require treatment and

were discharged after the (unnecessary) excision and biopsy. People under routine management who were selected for monitoring attended an outpatient dermatology follow-up appointment at 3 months for re-evaluation of their lesion. If their lesion was found suspicious for melanoma they had an excision and biopsy, which was followed by further appropriate treatment if biopsy confirmed the presence of malignancy, or by discharge, if the result of biopsy was negative. If at the follow-up appointment their lesion was found not suspicious, they were discharged and advised to visit their GP if they noticed changes in their skin lesion. If their lesion was not malignant, they were assumed not to require further treatment. If their lesion was malignant but was not identified at the follow-up meeting, they were assumed to return to the service at a later time, with their melanoma having potentially progressed to a more advanced stage. However, if a malignant lesion was identified at the 3-month follow-up meeting, it was assumed not to have progressed to a more advanced stage.

All people undergoing excision and biopsy of their lesion experienced distress due to the procedure; they also experienced anxiety while waiting for the results of biopsy, whether they had been examined with VivaScope prior to excision or not. People with a false positive result due to VivaScope experienced anxiety thinking that they have melanoma, until results of biopsy were available.

Following the outcome of the diagnostic assessment, people entered a Markov model and followed one of the following pathways:

- Patients with a confirmed melanoma (i.e. those with a true positive result after VivaScope examination and subsequent excision and biopsy, as well as those who, under routine management, had a positive result after excision and biopsy, either immediately or following monitoring) entered a Markov chain of 'identified melanomas'. All melanomas were assumed to be in situ or stage I (Ia or Ib) at identification, as clinical experts advised that an equivocal finding in dermoscopy suggests early stages of melanoma. All identified melanomas were treated according to national guidelines, and were assumed not to progress to a more advanced stage. Patients with an identified melanoma had a reduction in their HRQoL. A proportion of those who had a melanoma on head or neck experienced an additional permanent reduction in their HRQoL due to the scarring following excision and biopsy. Patients with an identified melanoma stage Ib were at increased risk of mortality, due to their melanoma, for the first 10 years following identification of their melanoma. After the period of 10 years, the risk of mortality of people with identified melanomas returned to that of the general population of the same age. People dying because of their melanoma were assumed to become terminally ill in the year in which they died.
- Patients with a missed melanoma (i.e. those with a false negative result after VivaScope examination, as well as those who, under routine management, were selected for monitoring and were not identified) entered a Markov chain of 'non-identified melanomas'. All melanomas were assumed to be in situ or stage I (Ia or Ib) at the point of examination, however, they could progress to more advanced stages over time. Every year patients could remain in their undiagnosed status with their melanoma remaining at the same stage or progressing to the next stage (without incurring any costs for its management), or could return to the dermatology service due to changes in their lesion and be diagnosed and treated, or die due to their cancer. Clinical experts advised that any unidentified melanomas would be recognised by the time they reached stage II (IIa, IIb or IIc), and within 5 years at maximum after the initial examination that resulted in the equivocal dermoscopic finding. People with

an unidentified melanoma had a HRQoL equal to that of the general population of the same age, until their melanoma was identified, in which case they experienced a reduction in their HRQoL. A proportion of those who had an identified melanoma on head or neck experienced an additional permanent reduction in their HRQoL due to the scarring following excision and biopsy. Unidentified melanomas did not incur any costs; identified melanomas were treated according to national guidelines, and were assumed not to progress to a more advanced stage. People with an unidentified or identified melanoma at stage Ib or II were at increased risk of mortality, due to their melanoma, from the start of the model and for the first 10 years after identification of their melanoma. After that period, their risk of mortality became equal to that of the general population of the same age. People dying because of their melanoma were assumed to become terminally ill in the year in which they died. People with newly identified melanomas entered tunnel states over a period of 10 years, so that the time-dependent risk of mortality over that period could be applied.

- People without a melanoma (i.e. those with a false positive or true negative result after VivaScope examination, as well as those who, under routine management, had a negative result after excision and biopsy, either immediately or following monitoring) entered a Markov chain of 'no melanomas'. A proportion of people with a benign lesion on head or neck, who had undergone unnecessary excision and biopsy, experienced a permanent reduction in their HRQoL due to the resulting scarring. Otherwise, the HRQoL in this Markov chain and the mortality risk were equal to that of the general population of the same age.

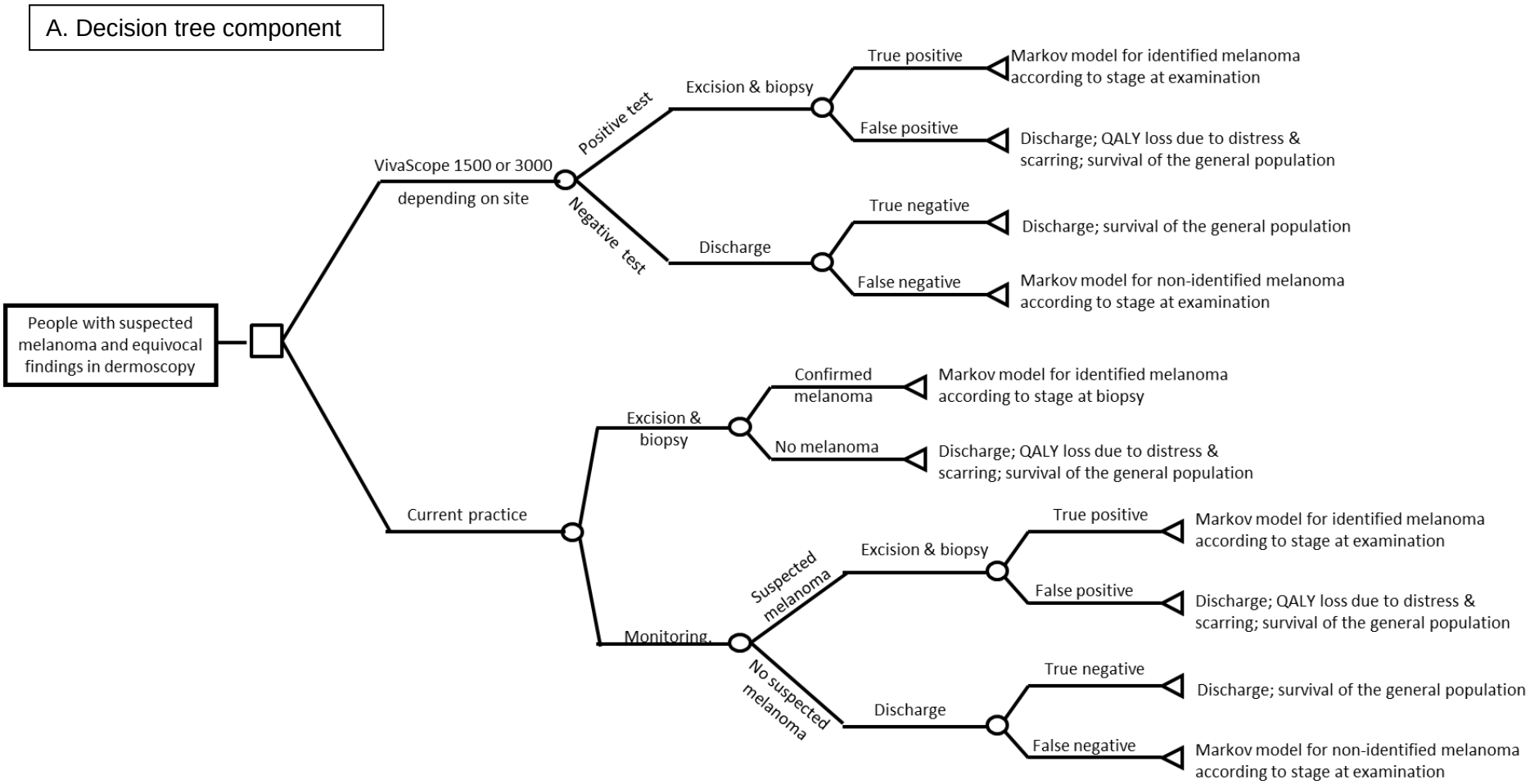
The care pathways described above were adapted from Wilson *et al*. (2013), who developed an economic model to assess the cost effectiveness of a device aiming at the diagnostic assessment of pigmented skin lesions in primary care in the UK.[50] The pathways designed for the model developed for this report were finalised following clinical expert advice.

Management of identified melanomas comprised surgical excision with a wider and deeper margin for all melanomas, SLNB for 50% of melanomas of stage Ib and all stage II melanomas, and follow-up visits. Patients dying due to their cancer incurred terminal disease costs in the year in which they died. These included costs of radiological examination, costs of metastatic disease (costs of chemotherapy including costs of adverse events), inpatient care and outpatient attendances, as well as costs of terminal and palliative care.

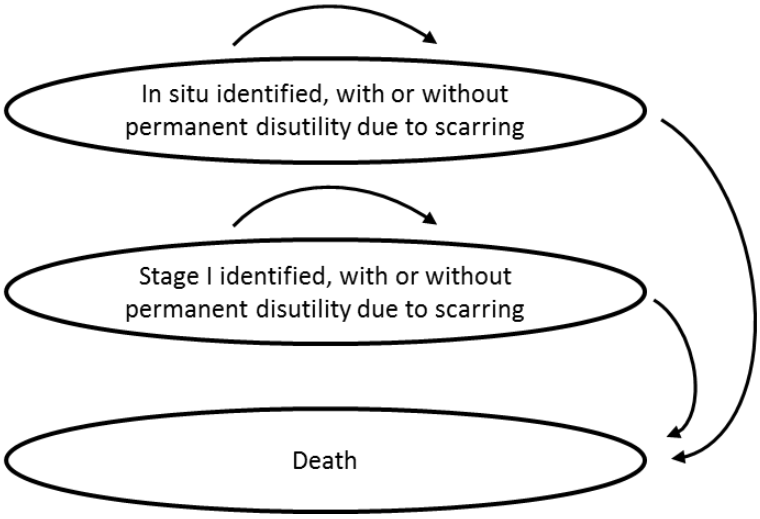
The time horizon of the economic model was over lifetime (up to 100 years of age). The cycle-length of the Markov model was 1 year and half-cycle correction was applied.

Figure 6 shows a schematic diagram of the VivaScope diagnostics model on suspected melanoma following an equivocal finding in dermoscopy.

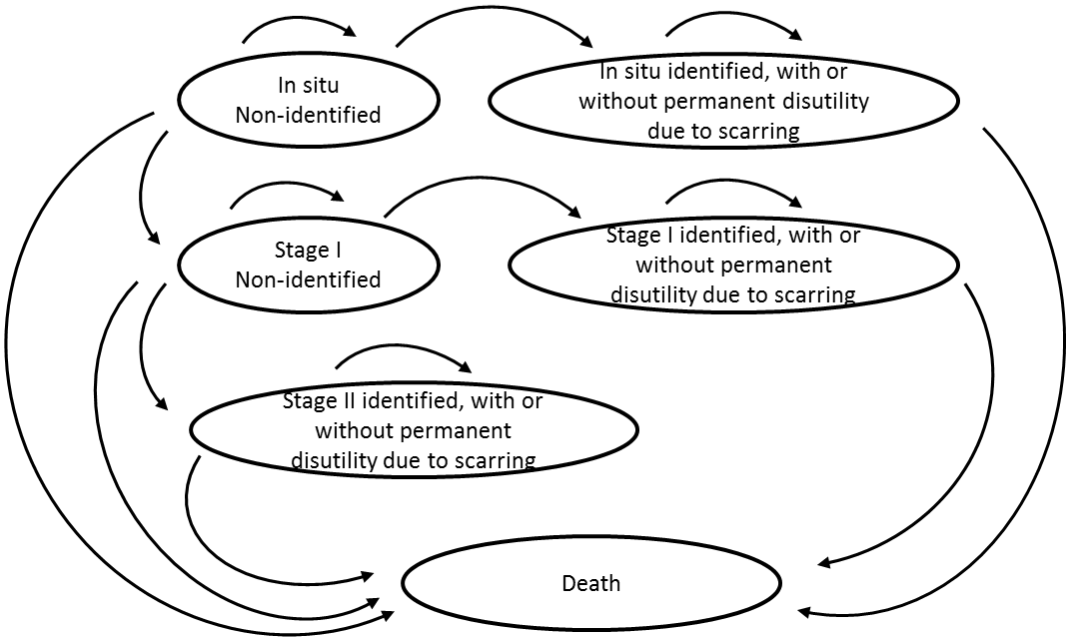
Figure 6. Schematic diagram of the VivaScope diagnostics model on suspected melanoma following an equivocal finding in dermoscopy

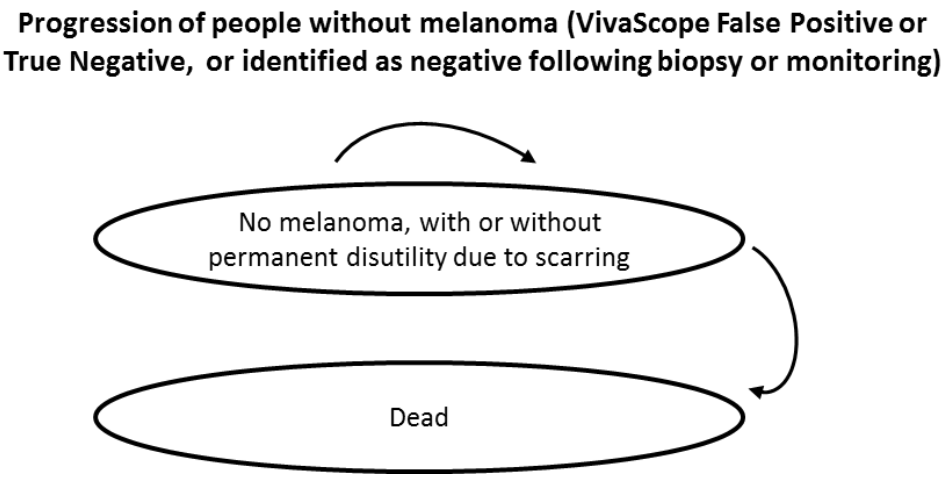


Progression of people with melanomas following identification
(VivaScope True Positive or identified at biopsy or during monitoring)



Progression of people with melanomas following initial non-identification
(VivaScope False Negative or not identified during monitoring)





5.2.2.4 Clinical input parameters

Diagnostic accuracy data

Diagnostic accuracy data for VivaScope were based on the findings of the systematic review of clinical evidence reported in Section 4.3. As diagnostic accuracy data were not synthesised, the base-case economic analysis utilised data on the diagnostic accuracy of VivaScope 1500 in people with equivocal lesions suspected from melanoma from Alarcon *et al*. (2014)[33], and Pellacani *et al*. (2014)[45] in two separate analyses, as these two studies were considered to be the most representative of the UK setting, as discussed in Section 4.2. The diagnostic accuracy of VivaScope 3000 in equivocal lesions suspected for melanoma was assumed to be equal to that of VivaScope 1500 in the economic model, due to lack of relevant data specific to VivaScope 3000. However, it is acknowledged that this assumption, which was applied to 17.9% of the study population who had equivocal lesions on head or neck, may have overestimated the diagnostic accuracy of VivaScope 3000.

In Alarcon *et al*. (2014), the sensitivity and specificity of VivaScope 1500 in people with equivocal lesions suspected from melanoma were 97.8% and 94.8%, respectively.[33] These figures were used for people with equivocal lesions that would have been excised under routine care, as well as for those with equivocal lesions that would have been selected for monitoring under routine care. However, it is acknowledged that diagnostic accuracy may differ across different sub-populations as it may be affected by the prevalence of the disease.[83]

In Pellacani *et al*. (2014) the sensitivity and specificity of VivaScope 1500 in identifying malignant lesions in people with highly suspicious equivocal lesions (i.e. lesions with consistent suspicious

clinical/dermoscopic criteria, already qualified and scheduled for surgical excision) were 100% and 51.8%, respectively, whereas in people with moderately/low suspicious equivocal lesions (i.e. lesions where VivaScope examination would determine whether to excise or monitor digitally) the respective figures were 100.0% and 80.2%, respectively.[45] These two sets of diagnostic accuracy values were applied to patients with suspected melanomas that would be routinely excised and monitored, respectively. The overall sensitivity and specificity of VivaScope 1500 in people with equivocal lesions suspected for melanoma were 100.0% and 70.8%, respectively.

Excision and biopsy was considered in the economic model to be the 'gold standard' for the diagnosis of melanoma, that is, it was assumed to have 100% sensitivity and specificity.

The outcomes of monitoring, in terms of identified and missed melanomas at 3 months, were taken from Altamura *et al*. (2008), who conducted a study to assess the optimal interval for, and sensitivity of, short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma.[84] The study included 1850 consecutive people with 2602 atypical skin lesions examined at a tertiary referral centre for melanomas, whose lesions were monitored using short-term sequential digital dermoscopy imaging. Half of the patients underwent 6-week monitoring followed by 3-month monitoring if changes were not seen. The remainder underwent 3-month monitoring only. Any change during this time led to excision. Lesions unchanged at 3 months were followed up over a period of time that ranged from 6 to more than 12 months from baseline. According to the study findings, over 3 months 487 lesions showed changes in digital dermoscopy and were subsequently excised, of which 81 were melanomas (true positive) and 406 were benign lesions (false positive). Of the 2,115 lesions that were negative at 3 months, 9 proved to be melanomas at follow-up (false negatives), 1,118 showed no changes or showed changes but proved to be benign following excision (true negatives), and 988 were lost to follow-up. Based on these data, the sensitivity and specificity of monitoring were estimated to be 90.0% and 73.4%, respectively.

Proportion of lesions excised versus monitored under routine management

Clinical experts advised that in UK routine clinical practice, about 2/3 of equivocal lesions suspected for melanoma are excised and the remaining 1/3 are monitored, as they are less suspicious for malignancy.

Prevalence of melanoma in lesions with an equivocal dermoscopic finding

A review of the prevalence of melanoma in equivocal lesions suspected for melanoma in relevant studies considered in the systematic review of clinical evidence reported in Section 4 gave the following results:

In Alarcon *et al*. (2014), the prevalence of melanoma in 343 equivocal lesions that were planned for excision was 26.8%.[33] Curchin *et al*. (2011) reported a very similar prevalence of melanoma in 50 equivocal lesions that were excised (26.0%).[34] In Guitera *et al*. (2009), the prevalence of melanoma in 326 skin lesions that were excised on the basis of clinical suspicion was 37.7%.[37] In Stanganelli *et al*. (2014), the prevalence of melanoma in equivocal pigmented lesions that lacked clear dermoscopy criteria for melanoma at baseline (all scoring 0-2 points at the seven-point checklist score) but were excised subsequently because of changes during digital monitoring was 17.1%.[48]

In Pellacani *et al*. (2014), the prevalence of melanoma in 183 equivocal lesions with consistent suspicious clinical/dermoscopic criteria already qualified and scheduled for surgical excision was 12.6%; the prevalence of melanoma in 287 equivocal lesions (308 minus 21 that were lost to follow-up) where VivaScope examination would determine whether to excise or to monitor digitally was 2.1%. The ratio of the prevalence of melanoma in highly versus moderately suspicious lesions was 6:1.[45]

In Ferrari *et al*. (2014), the prevalence of melanoma in 130 featureless lesions with a 0-2 score on the 7-point checklist score in dermoscopy was 4.6%; in 102 positive-borderline lesions with a score of 3-4, the prevalence of melanoma was 16.7%. The ratio of the prevalence of melanoma in positive borderline versus featureless lesions was 4:1.[47]

Regarding the remaining studies included in the review, Gerger *et al*. (2006)[35], reported a 16.7% prevalence of melanoma in 117 melanocytic skin lesions and 45 nonmelanocytic skin tumours examined with VivaScope, whereas in Gerger *et al*. (2008)[36], the prevalence of melanoma in 70 melanocytic skin tumours included in the study was 28.5%. In Langley *et al*. (2007), the prevalence of melanoma in 125 patients with 125 suspicious pigmented lesions was 29.6%.[39] Rao *et al*. (2013) reported a prevalence of 2.3% for melanoma in 334 lesions selected for removal for either cosmetic or medical reasons.[42]

In Altamura *et al*. (2008), the prevalence of melanomas in 2,602 atypical lesions selected for digital monitoring was 5.58%.[84]

In Tromme *et al*. (2014), an observational study of people presenting to dermatologists because of their own concern for melanoma and having 1-3 equivocal melanocytic lesions, the prevalence of melanoma in 892 equivocal lesions observed in 822 people was 12.41%.[69]

It needs to be noted that none of the above studies was conducted in the UK and therefore the overall prevalence of melanoma in the study populations may differ from that in the UK population, thus potentially affecting the prevalence of melanoma in equivocal lesions. Moreover, the categorisation of a skin lesion as ‘equivocal’ depends to a significant degree on the experience of the dermatologist

undertaking the dermoscopic examination, and the definition of 'equivocal' across the studies. Clinical experts advised that in the UK, out of 5-6 equivocal lesions that get excised because of dermoscopically equivocal findings, one is histopathologically confirmed to be a melanoma, translating into a prevalence of 16.7-20%.

The economic model utilised an overall prevalence of melanoma in equivocal lesions of 15.0%, and assumed that the prevalence of melanoma in suspicious lesions excised is 5 times the prevalence of melanoma in suspicious lesions selected for monitoring. In a sample of lesions where 2/3 are excised and 1/3 are monitored, as advised by clinical experts for routine UK practice and utilised in the model, these figures and assumptions translate into a prevalence of melanoma of 20.6% in suspicious lesions excised and 4.1% in suspicious lesions selected for monitoring.

Stages of identified and missed melanomas

According to clinical expert opinion, melanomas that give an equivocal finding in dermoscopy are at early stages of development, most likely in situ or stage I, and this was also suggested by the available information in the studies included in the systematic literature review of clinical evidence. Following clinical expert advice, melanomas undergoing diagnostic assessment in the economic model were assumed to be 60% in situ and 40% at stage I. This estimate was applied to both men and women with melanomas that give an equivocal finding in dermoscopy. Melanomas that were not identified by VivaScope examination or after monitoring (i.e. false negatives) were expected to be even less advanced; however, the exact staging of false negative melanomas would be determined by the diagnostic characteristics of VivaScope and monitoring and would require further assumptions for its estimation. For this reason, the staging of all melanomas giving an equivocal finding in dermoscopy was assumed to be the same for all melanomas (i.e. 60% in situ and 40% in stage I), regardless of the result (true positive or false negative) of VivaScope examination or monitoring.

Melanomas in stage I were further classified into stage Ia and stage Ib. Unidentified melanomas that progressed to stage II were further classified into sub-stages IIa, IIb and IIc. Classification of melanomas into sub-stages was essential, as management costs and mortality may differ between sub-stages within the same stage. Initial proportions of melanomas in each sub-stage (i.e. at the stage of identification or progression to the next stage) were estimated using data from Balch *et al*. (2009), who conducted a multivariate analysis of 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma to revise and clarify TNM (tumour, lymph nodes, metastasis) classifications and stage grouping criteria.[85] The number and proportion of people in each melanoma sub-stage are presented in Table 26. After that point in time, proportions of people in each sub-stage changed, due to different mortality characterising each sub-stage.

Progression

In the economic model unidentified melanomas could only progress by one stage and never regressed. The annual rate of progression of unidentified melanomas is unknown, as no naturalistic data that would suggest the rate of progression in identified melanomas are available, since lack of provision of therapy would be unethical. However, according to a report on the impact of earlier diagnosis of cancer to the NHS published by the Department of Health,[86] the mean duration of stage I melanoma is 50 months. Assuming that at 50 months 50% of melanomas of stage I progress to the next stage and that progression to the next stage is characterised by exponential function, the annual probability of progression of melanomas stage I to stage II was estimated to be 15.3%. This annual probability was also applied to unidentified in situ melanomas progressing to stage I.

Clinical experts expressed the opinion that all unidentified melanomas should be identified when they reach stage II at the latest, and should have been detected by 5 years after the initial diagnostic assessment. These two hypotheses were broadly satisfied by using an annual probability of identification of 35% in the economic model, which appeared to be a reasonable estimate according to clinical experts. Any unidentified melanomas by year 5 were imposed to be identified at this point.

Mortality

The risk of mortality of people in the model depended on the status of their skin lesions following diagnostic assessment.

People with true negative or false positive lesions (i.e. people without melanoma) were assumed to have normal lifespan and therefore their mortality rates were assumed to equal those of the UK general population in both arms of the model. Mortality in this group of patients was considered in order to allow estimation of the lifetime permanent disutility experienced due to scarring. Gender-and age-specific mortality rates were taken from recent UK national mortality statistics[87] and were applied separately to men and women in every arm of the model. It is acknowledged that the mortality of people in the general population incorporates mortality due to melanoma, but given that the incidence and mortality from melanoma is rather low in the general population (incidence and mortality per 100,000 population in the UK is 17.4 and 2.5, respectively),[2] general population mortality rates were not adjusted to exclude deaths due to melanoma. Moreover, it is possible that people who had not developed melanoma at the start of the model could develop melanoma later in life, and therefore applying the overall mortality of the UK general population, which incorporated the future risk of dying from a melanoma, appeared to be valid.

People with true positive or false negative lesions (i.e. people with identified or unidentified melanoma after the initial diagnostic assessment) were assumed to be at increased risk of mortality due to their melanoma. Balch *et al*. (2009)[85] reported the 5-year and 10-year overall survival of

patients with melanoma in each stage. These data were used to determine a mean annual mortality rate for years 1-5 and for years 6-10 for each sub-stage assuming an exponential survivor function (Table 26). The overall annual mortality risk for stage Ia that was reported in Balch *et al*. (2009)[85] was very similar to the mean mortality of the UK general population of age 55-60 (i.e. of the model study population over the first 5 years of the Markov model). Clinical experts confirmed that the mortality risk of people with stage Ia melanoma, as well as of people with in situ melanoma, is very close to that of the general population. Therefore, the economic model assumed that people with identified or unidentified melanoma in situ or stage Ia had the same mortality risk with the UK general population of the same gender and age, taken from UK national mortality statistics.[87]

Patients with unidentified melanoma were assumed to be at increased mortality risk corresponding to the stage of their melanoma for the whole period over which their melanoma remained unidentified (i.e. maximum 5 years). Patients with identified melanoma were assumed to be at increased mortality risk due to their melanoma over 10 years (5 years at a higher mortality risk, and another 5 years at a lower mortality risk, which was, nevertheless, higher than the mortality risk of the general population of same gender and age). The excess risk of mortality estimated by subtracting the gender- and age-specific UK general population mortality[87] from the annual mortality risk derived from analysis of data in Balch *et al*. (2009)[85] was attributed to melanoma metastatic disease and was assumed to be associated with metastatic disease and terminal illness costs.

Beyond the 10 years from identification of melanoma, patients with melanoma were assumed to have survived their cancer and to return to the mortality risk of the general population, according to their gender and age, although there is evidence that a small proportion of patients may present with metastatic melanoma more than 10 years after they are diagnosed with melanoma.[88] However, the proportion of patients presenting with late recurrence of melanoma (beyond 10 years) was deemed to be small, and therefore the assumption of complete cure from melanoma 10 years after identification was considered to be reasonable.

Table 26. 5-year and 10-year survival rates by melanoma stage (as reported in Balch *et al*.)[85] and estimated annual mortality of people with melanoma in the economic model

Stage	N (% within stage)[85]	Survival rate[85]		Annual probability of death in the model	
		5-year	10-year	Unidentified & first 5 years from identification	Next 5 years from identification
Ia	9,452 (51.5)	0.97	0.930	Gender- and age-adjusted mortality of general population	
Ib	8,918 (48.5)	0.92	0.860	0.017	0.012
IIa	4,644 (50.1)	0.81	0.670	0.041	0.030
IIb	3,228 (34.8)	0.70	0.570	0.069	0.027
IIc	1,397 (15.1)	0.53	0.390	0.119	0.030

5.2.2.5 Utility values

People in the model experienced utility (or disutility) associated with one or more of the following:

- disutility due to excision and biopsy of a lesion suspected of melanoma, that caused distress as well as anxiety while waiting for the results;
- disutility due to permanent scarring following surgical excision of a lesion on head or neck;
- health-state related utility, which was associated with the stage of melanoma (in people with melanoma) or with the average utility of the general population (in people without a melanoma).

As reported in Section 5.1.2.3, the systematic literature review identified 4 studies reporting utility data relating to melanoma health states.[55-58] Beusterien *et al*. (2009)[57] reported utility data associated with partial response to treatment, stable or progressive disease, best supportive care and toxicity from chemotherapy. The health state descriptions were vignette-based. Utility values were elicited from members of the general population in Australia and the UK using SG. The utility values reported by Beusterien *et al*. (2009) referred to health states that did not directly correspond to melanoma stages, and therefore were unsuitable for use in the economic model.

The remaining three studies reported utility values associated with melanoma stages. None of the studies was conducted in the UK. Two of the studies (Askew *et al*. 2011[56]; Tromme *et al*. 2014[55]) used EQ-5D for the description of HRQoL experienced by patients with melanoma. However, none of them used the UK EQ-5D tariff[65] for the valuation of health states, as recommended by NICE. Askew *et al*. (2011)[56] used the US EQ-5D tariff, which was developed using TTO, whereas Tromme *et al*. (2014)[55] used the Belgian EQ-5D tariff, which was developed using VAS – a valuation method that is not choice-based and thus is not among NICE preferred valuation methods. King *et al*. (2011)[58] reported melanoma-related utility values elicited from patients with melanoma in the US; health state descriptions were based on vignettes. A comparison of the utility values reported in these three studies revealed inconsistencies in the available data. For example, the utility values reported by Askew *et al*. (2011)[56] for melanoma stages III and IV were considerably higher than those reported by King *et al*. (2011)[58] and Tromme et al. (2014)[55]; the utility values reported by Tromme *et al*. (2014)[55] for melanoma early stages I and II were substantially lower than the utility values reported for respective stages in Askew *et al*. (2011)[56] and King *et al*. (2011).[58] These discrepancies are potentially attributable to differences in measurement and valuation across the 3 studies. Quite importantly, the utility values reported for all melanoma stages (I to IV) in Askew *et al*. (2011)[56] and for stages I and II in King *et al*. (2011)[58] were considerably higher than reported mean utility values for the UK general population aged 55 years (which was the age of the study population at the start of the model): in Askew *et al*. (2011)[56], the utility values of melanoma stages I to IV ranged from 0.91 to 0.86. King *et al*. (2011)[58] reported utility values of 0.93 and 0.92 for melanoma stages I and II,

respectively. In contrast, Kind *et al*. (1999)[58,89], who analysed EQ-5D data obtained from 3,395 participants in the Measurement and Valuation of Health survey conducted in the UK in 1993, reported a mean EQ-5D utility value for people in the UK aged 55-64 years of 0.78 for men and 0.81 for women. More recently, Sullivan *et al*. (2011)[90] produced a catalogue of EQ-5D utilities for the UK population by applying the UK EQ-5D tariff[65] to EQ-5D descriptive questionnaire responses obtained from participants in the US-based Medical Expenditure Panel Survey. The mean utility value for people aged 50-59 years was 0.798. Consequently, the utility data reported in Askew *et al*. (2011)[56] and King *et al*. (2011)[58] appeared to lack face validity compared with UK population norms, and could not be used in the economic model in their 'raw' form, as this would result in patients with melanoma having a higher utility than people without melanoma (who are expected to have the utility of the general population of same gender and age).

The other utility study under consideration was the one conducted by Tromme *et al*. (2014).[55] The study reported utility values associated with melanoma stages 0 (in situ)/Ia, Ib/II, III and IV, subdivided into treatment and remission phases. The reported utility values appeared to be sound when compared with mean utility values of the UK general population, as the utility values of treatment phase were always lower than the utility of the UK general population aged 55 years (mean age of patients at presentation of melanoma) and utility values of remission phase were lower than (stages III and IV) or comparable to (stages 0-II) the utility of the UK general population aged 55 years. Utility values reported in Tromme *et al*. (2014) were estimated from EQ-5D responses using the Belgian EQ-5D tariff, which has been developed following a valuation survey of 2,754 Flemish adults from the general public in Belgium using VAS.[63] The Flemish EQ-5D tariff has shown good correlation with the UK EQ-5D tariff that was derived using VAS[91], with a correlation coefficient of 0.979.[63] In the lack of melanoma utility data more directly relevant to the UK population, melanoma-related utility values from Tromme *et al*. (2014) were selected for use in the economic model.[55]

The utility values obtained from Tromme *et al*. (2014)[55] were adjusted for age in the economic analysis, using a coefficient of -0.00029 per year that was reported by Sullivan *et al*. (2011);[90] this study involved multiple regression analyses using ordinary least squares, Tobit, and censored least absolute deviations regression methods and reported regression coefficients for a number of clinical conditions and demographic characteristics of the study population, including age.

Table 27 shows the patient characteristics and mean utility values by melanoma stage reported in Tromme *et al*. (2014)[55] as well as the resulting utility values for patients with melanoma aged 55 years, after adjusting for age, that were used in the economic model.

Table 27. Population characteristics and utility values reported in Tromme *et al*.[55] and utility values adjusted for the age of 55 years as used in the economic model

Stage	Time period	Number of respondents	Mean age	Mean utility value (SD)	Mean utility values adjusted for age (55 years)
0/Ia-treatment	Month 1	68	51.7	0.687 (0.192)	0.6860
0/Ia-remission	Months 2-24	98	46.5	0.809 (0.179)	0.8065
Ib/II-treatment	Months 1-2	33	54.5	0.579 (0.272)	0.5789
Ib/II-remission	Months 3-24	76	53.2	0.802 (0.166)	0.8015
III-treatment	Months 1-3	15	55.9	0.535 (0.278)	0.5849
III-remission	From month 4	50	53.3	0.703 (0.156)	0.6860
IV-treatment	From start of treatment	41	61.4	0.583 (0.192)	0.8065
IV-remission	From start of treatment	14	64.8	0.796 (0.167)	0.5789
Abbreviations used in table: SD, standard deviation Note: utility values adjusted for age using a coefficient of age of -0.00029 reported by Sullivan et al.[90]					

The utility values of stages 0/Ia and Ib/II in remission reported by Tromme *et al*. (2014)[55] were very close to (only slightly higher than) the utility values of the UK general population aged 55 years reported by Kind *et al*. (2011)[58] and Sullivan *et al*. (2011)[90] Tromme *et al*. (2014)[55] reported that treatment duration in stages 0/Ia and Ib/II was 1 and 2 months respectively, according to expert opinion. Using the treatment and remission utility data and the treatment duration for stages 0/Ia and Ib/II, it was estimated that the reduction in utility over the year within the melanoma was treated was -0.0100 for stage 0/Ia and -0.0371 for stage Ib/II. Tromme *et al*. (2014)[55] stated that patients with stage 0 and Ia melanoma were pooled together because they had very similar management in terms of surgical treatment and follow-up, whereas patients with stage Ib and II melanoma were pooled because they had all undergone SLNB that had not been followed by elective node dissection and because of evidence that surgical resection margins did not appear to influence HRQoL. Therefore, the values of -0.0100 for stage 0/Ia and -0.0371 for stage Ib/II were considered to express the disutility associated with surgical management of early stage melanoma which involved (-0.0371) or did not involve (-0.0100) SLNB in patients with melanoma aged 55 years. These values were applied as one-off disutilities in the economic model (i.e. they were applied once, at the time of treatment of melanomas, without time adjustment), after adjusting for age by applying the age coefficient of -0.00029 reported by Sullivan *et al*. (2011),[90] for every year above 55 years of age. However, as only 50% of patients with stage Ib melanoma were assumed to undergo SLNB in the economic model, the value of -0.0100 (adjusted for age) was applied to all patients with identified melanoma of stage 0/Ia and 50% of patients with melanoma of stage Ib, and the value of -0.0371 (adjusted for age) was applied to 50% of patients with stage Ib melanoma and all patients with stage II melanoma. Apart from that disutility, which was attributed to surgical management and was applied as one-off disutility, patients with identified melanoma in stages 0-II were assumed to have the average utility of the UK general population of the same age, which was derived from Sullivan *et al*.[90] as the utility of stages 0-II in remission reported in Tromme *et al*.[55] was very close to (in fact it was higher than) the

utility of the UK general population reported in Sullivan *et al*. (2011).[90] This assumption is broadly consistent with the results of a German study, according to which the HRQoL in patients with melanoma, without recurrence within 2 years after initial therapy, was comparable to the HRQoL of the general population (Schlesinger-Raab *et al*. 2010).[62]

Patients with unidentified melanoma and people without melanoma were also assumed to have the average utility of the general UK population of the same age as reported in Sullivan *et al*. (2011).[90]

Table 28 presents the mean utility of the UK general population aged 55 years and above, as reported in Sullivan *et al*. (2011)[90] and applied in the economic model, as well as the characteristics of the US population providing responses to EQ-5D that were analysed by Sullivan et al in order to produce the catalogue of UK utility values. The mean EQ-5D utility for people 80-89 years was applied to all people aged 80 years and above in the economic model.

Table 28. Characteristics of the US population that provided EQ-5D responses and mean utility of the UK general population by age, as reported in Sullivan *et al*.[90] and applied in the economic model

Age	Number of respondents	Mean number of clinical conditions	Median EQ-5D	Mean EQ-5D	SE
50-59 years	14,333	2.4	0.796	0.798	0.0035
60-69 years	9,028	3.1	0.796	0.774	0.0039
70-79 years	6,789	4.0	0.727	0.723	0.0049
80-89 years	3,593	4.4	0.691	0.657	0.0075
Abbreviations used in table: SE, standard error					

People with metastatic melanoma disease/terminal illness (i.e. people dying due to their melanoma) were assumed to have the utility of melanoma stage IV in treatment reported in Tromme *et al*. (2014),[55] which was adjusted for age using the age coefficient of -0.00029 reported by Sullivan *et al*. (2011),[90] for every year above 55 years of age.

People undergoing surgical excision and biopsy of their lesion were assumed to experience disutility due to distress as well as anxiety while waiting for the results of the biopsy. The distress due to excision and biopsy experienced by people whose suspected lesion was melanoma was assumed to have been incorporated in the disutility associated with the surgical management of melanoma. The distress experienced by people whose suspected lesion was not melanoma (false negative), who therefore did not proceed to surgical excision with wider margins, was expressed by a one-off disutility of -0.002, which was also used to express the disutility of a diagnostic biopsy for suspected BCC in the respective economic model. As described later in Section 5.2.3.5, the disutility experienced due to surgical treatment of BCC was derived from Seidler *et al.* (2009),[60] who reported a disutility of -0.004 associated with an excision procedure due to facial non-melanoma skin cancer. The economic model on lesions suspected for BCC assumed that a diagnostic biopsy created a

disutility of -0.002 to the person, as it was expected to be a less invasive procedure than surgical treatment of BCC (excision or Mohs surgery).

In addition to the distress directly associated with excision and biopsy, people undergoing excision and biopsy for their suspected melanoma lesion were considered to experience a reduction in their HRQoL due to anxiety while waiting for the results of biopsy. The methodology used to estimate the disutility associated with anxiety while waiting for results of biopsy was adopted from a model-based economic evaluation of intraoperative tests for detecting sentinel lymph node metastases in breast cancer (Huxley *et al*., 2015)[92] that was undertaken to inform relevant NICE diagnostics guidance. In that economic model, patients who underwent histopathology experienced some level of disutility due to the associated anxiety of waiting for test results; this disutility was imputed by using the EQ-5D health state valuation equation for the UK reported by Dolan (1997),[65] which allows estimation of a person's utility based on their responses to EQ-5D classification system. The system has five dimensions (mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression) and in the version used by Dolan each dimension had 3 levels of response (no problems, moderate problems, and severe problems). Huxley *et al*. (2015)[92] used only the utility decrement due to anxiety/depression, which was expressed by the following equation:

$$Y = \alpha + AD + A2 + N3$$

where:

$\alpha = 0.081$ is the constant applied to any level of disutility in any of the 5 EQ-5D dimensions

AD = 0.071 [for each level of disutility associated with anxiety or depression]

A2 = 0.094 [for severe anxiety/depression]

N3 = 0.269 [when any of the 5 dimensions of EQ-5D is severe]

Huxley *et al*. (2015)[92] as well as the economic model on the diagnostic assessment of equivocal lesions suspected for melanoma with VivaScope, assumed that people waiting for histopathology results had already utility less than one (so the α value was not applied at the estimation of the utility decrement due to anxiety/depression), that they moved from a state of no anxiety/depression to severe anxiety/depression, and that this anxiety/depression was the only dimension of the EQ-5D they had that was severe. These assumptions resulted in a disutility of (-0.236 -0.269= -0.505).

This disutility of -0.505 was applied for only 2 weeks in the model, as clinical experts advised that biopsy results for suspected melanoma are available 2 weeks after excision and biopsy. This gave a 2-week disutility of -0.019 attributed to anxiety while waiting for the results of biopsy. This disutility

was applied in every person waiting for results of biopsy, including people who had already undergone examination with VivaScope, people undergoing routine management of equivocal lesions suspected for melanoma who had their lesions excised immediately or after 3-month monitoring, and people with missed melanomas (false negative) who had them excised at a later stage, following late identification.

A number of people in the model experienced permanent disutility due to scars on their head or neck from excision of suspected melanomas. In the economic model it was assumed that 15% of people undergoing excision of their suspected melanoma lesion on their head or neck would experience permanent disutility due to their scar over lifetime. Seidler *et al.* (2009)[60] reported a disutility of -0.016 for simple repairs/scars (granulation and primary closure) and a disutility of -0.026 for complex repairs/scars (local flap and graft) experienced by people with facial non-melanoma skin cancer. Due to lack of more relevant data, data from this study were used to express permanent disutility experienced by people with suspected melanomas on head or neck due to scars from excision. Clinical expert advice was that all initial excisions of suspected melanomas are undertaken with simple repairs/scars; wider surgical excisions of confirmed melanomas comprise 90% simple and 10% complex repairs/scars. Based on these estimates and the disutility data reported in Seidler *et al.* (2009),[60] the permanent disutility from scarring following initial excision and biopsy (people with lesions that were not melanomas) and wider surgical excision (people with melanomas) was estimated to be -0.016, and -0.017, respectively. These disutilities were applied only to people with permanent reduction in their HRQoL due to scarring on head or neck over lifetime.

Table 29 provides all utility data applied in the diagnostic economic model on equivocal lesions suspected for melanoma.

Table 29. Utility data applied to the diagnostic economic model on equivocal lesions suspected for melanoma

Type of utility	Utility value	Relevant population in the model	Source of utility data and assumptions
General utility for: 50-59 years 60-69 years 70-79 years 80 and above years	 0.798 0.774 0.723 0.657	Patients with stage 0-II melanoma (TP and FN that were identified at a later stage); patients with unidentified melanoma (FN) and people without melanoma (TN & FP)	Sullivan *et al*.;[90] applied over lifetime, according to age
Disutility due to management of melanoma	-0.010 -0.037	All patients treated for in situ or stage Ia melanoma; 50% of patients treated for stage Ib melanoma 50% of patients treated for stage Ib melanoma; all patients treated for stage II melanoma	Tromme *et al*.;[55] reported disutilities correspond to 55-year old patients and were age-adjusted in the model using an age coefficient of -0.00029;[90] applied as one-off disutilities at the time of treatment
Metastatic melanoma / terminal disease (stage IV)	0.585	All patients with identified or unidentified melanoma stage Ib or II dying due to their melanoma	Tromme *et al*.;[55] reported value corresponds to 55-year old patients and was age-adjusted in the model using an age coefficient of -0.00029;[90] applied in the year within which patients

			died due to their melanoma
Disutility due to excision and biopsy	-0.002	People without melanoma who underwent excision and biopsy (FP in VivaScope or monitoring and those undergoing excision under routine management)	Assumption used in the diagnostic model on suspected BCC lesions; value used to express distress due to diagnostic biopsy; reported disutility experienced due to surgical treatment of facial BCC was -0.004 in Seidler *et al.* (2009);[60] applied as one-off disutility
Disutility due to anxiety while waiting for results of biopsy	-0.019	Any person waiting for results of biopsy, including people who had positive results in examination with VivaScope, people undergoing routine management who had their lesions excised immediately or after 3-month monitoring, and people with missed melanomas (FN) that were excised at a later stage, following identification.	2-week disutility due to anxiety/depression estimated using the EQ-5D UK health state valuation equation,[65] assuming that people waiting for biopsy results had already utility <1, moved from no to severe anxiety/depression, and this was their only severe EQ-5D dimension.
Permanent disutility due to scarring on head or neck	-0.016 -0.017	15% of people with lesions on head or neck who underwent initial excision and biopsy (people with lesions that were not melanomas) 15% of people with lesions on head or neck who underwent wider surgical excision (people with melanomas)	Seidler *et al.* (2009);[60] initial excisions of suspected melanomas assumed to entail simple repairs/scars; wider surgical excisions of confirmed melanomas assumed to comprise 90% simple and 10% complex repairs/scars; applied over lifetime
Abbreviations used in table: FP, false positive; FN, false negative; TP, true positive; TN, true negative			

5.2.2.6 Costs

Costs considered in this economic model included the cost of diagnostic assessment of a suspected melanoma with VivaScope following an equivocal finding in dermoscopy, the cost of routine management (cost of excision or monitoring of suspected melanomas), the management cost of confirmed melanomas (true positives) following diagnostic assessment, the cost of missed melanomas (false negatives) that were identified at a later time, and costs associated with metastatic melanoma and terminal illness.

As reported in Table 25, the cost per suspected melanoma with an equivocal finding in dermoscopy examined with VivaScope was estimated to be £254 if VivaScope is exclusively used for the diagnostic assessment of suspected melanomas with an equivocal finding in dermoscopy; £63 if VivaScope is used only for diagnostic assessment of suspected melanomas giving an equivocal finding in dermoscopy and suspected BCC lesions with a positive dermoscopic finding; and £59 if the device is used not only for the diagnostic assessment of suspected melanomas and BCCs, but also for the mapping of lentigo malignas prior to surgical treatment.

The costs of all other procedures and treatments included in the model, with the exception of the cost associated with terminal illness, were taken from either the NHS reference costs for 2014[68] or the national Unit costs for Health and Social Care 2014.[67] Clinical experts advised on the appropriate

NHS service and procedure codes and unit costs corresponding to relevant healthcare resource use considered in the model.

The unit cost of excision and biopsy of a lesion suspected for melanoma was estimated to be £151, corresponding to the national unit cost of outpatient intermediate skin procedures conducted in a dermatology service for people of 13 years and over (service code 330, currency code JC42A).[68]

The unit cost of monitoring was £93 and corresponded to an outpatient, face-to-face, consultant-led dermatology follow-up attendance (service code 330, currency code WF01A).[68]

The cost of management of melanomas after identification and confirmation with excision and biopsy (i.e. both melanomas identified at initial diagnostic assessment and melanomas missed and identified at a later time) comprised:

- the cost of surgical excision with a wider and deeper margin for all melanomas (in situ, stage I and stage II), which was £943, corresponding to the national unit cost of an intermediate skin procedure treated as a day-case for people of 13 years and over (currency code JC42A).[68] Clinical experts advised that if skin grafts or flaps are required for the excision, the procedure becomes more complex and costly, however the associated additional cost was not considered due to lack of relevant data;
- the cost of SLNB for 50% of melanomas of stage Ib and all stage II melanomas. The unit cost of such a procedure was estimated to be £1,033, corresponding to a day-case procedure on the lymphatic system.[68] Clinical experts advised that this procedure is routinely carried out together with the wider excision, and therefore it might be reasonable not to apply its unit cost as a separate cost component in the model; nevertheless, other experts advised that it can be a complex procedure, especially when performed in complicated nodal sites, for example in the groin or head and neck, Consequently, it was decided to apply the unit cost of £1,033 as an extra cost in patients undergoing SLNB alongside the wide surgical excision of their melanoma;
- the cost of follow-up visits: these comprised, according to BAD guidelines:[16]
    - a single follow-up visit for patients with in-situ melanomas, after complete excision, to explain the diagnosis, check the whole skin for further primary melanomas and to teach self-examination for a new primary melanoma;
    - four 3-monthly visits in the first year after the excision of the melanoma for patients with stage Ia melanoma;
    - 3-monthly visits for 3 years and then 6-monthly visits to 5 years after the excision of the melanoma for patients with stage Ib or II melanoma.

The unit cost of a follow-up visit was £93 and corresponded to an outpatient, face-to-face, consultant-led dermatology attendance, (service code 330, currency code WF01A).[68] It should be noted, though, that clinical experts advised that in some hospitals, follow-up of patients with melanoma is nurse-led rather than consultant-led.

The healthcare resource use and associated cost of management of melanomas following excision and biopsy that was utilised in the economic model is presented in Table 30.

Table 30. Healthcare resource use and cost of management of melanoma according to stage, after excision and biopsy

	Stage			
Resource use / cost component	**In situ**	**Stage Ia**	**Stage Ib**	**Stage 2**
Surgical excision with a wider and deeper margin	£943	£943	£943	£943
Cost of SLNB	NA	NA	50% of lesions: £1,033	£1,033
Follow-up visits	One-off £93	3-monthly x 1 year £372	3-monthly x 3 years then 6-monthly x 2 years £1,488	3-monthly x 3 years then 6-monthly x 2 years £1,488
Total management cost	**£1,036**	**£1,315**	**£2,948**	**£3,464**
Abbreviations used in table: SLNB, sentinel lymph node biopsy Source of unit costs: NHS reference costs 2014[68]				

The cost of people with unidentified melanomas was assumed to be zero, unless patients died due to their melanoma (in which case they experienced terminal disease before they died and incurred respective costs) or until their melanoma was identified. Costs of identification included a GP visit at a cost of £67,[67] an outpatient, face-to-face, consultant-led first attendance at a dermatology clinic for the re-assessment of the skin lesion, costing £109 (service code 330, currency code WF01B),[68] and excision and biopsy for confirmation of the malignancy, at a cost of £151 as reported above.

The cost of terminal illness in the year within which patients died due to their melanoma (cost of management of metastatic disease and terminal care) was based on data reported in the NICE Single Technology Appraisal of Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (NICE TA 319).[93] Based on clinical expert advice, patients with metastatic melanoma and terminal disease in the model were assumed to be treated with either ipilimumab (50%), dacarbazine (15%) or vemurafenib (35%), with the proportions of patients on each drug being based on an economic analysis assessing the cost effectiveness of adding routine imaging of asymptomatic patients to current standard follow-up in patients with stage III melanoma that was undertaken for the NICE guideline update on melanoma.[18] The drug acquisition costs of ipilimumab and vemurafenib to the NHS are subject to a Patient Access Scheme discount and therefore are not known; consequently it was not possible to estimate the actual costs of chemotherapy to the NHS. The company submission for the NICE TA 319 reported the estimated total metastatic disease and terminal care costs associated with each of the 3 drugs over lifetime, as well as the average number of life-years per person for each drug, so it was possible to estimate an average annual cost associated with each drug, although it is acknowledged that costs of chemotherapy and terminal illness are unlikely to be evenly spread across life-years. However, as total life-time was not long (it did not exceed 3.5 years with any of the 3

drugs), the estimated mean annual cost was considered a reasonable approximation of metastatic disease/terminal illness cost over the last year of life of patients dying due to their melanoma in the economic model. The STA cost figures were derived from a scenario included in the Evidence Assessment Group (EAG) report that considered drugs only as first-line treatments followed by best supportive care and palliative care.[94] These costs included drug acquisition costs, costs of adverse events, costs of radiological examination, inpatient care and outpatient attendances, as well as costs of terminal and palliative care. The metastatic melanoma/terminal disease cost estimated using these data was £16,139, as shown in Table 31.

Table 31. Cost of metastatic and terminal melanoma disease

% of patients on each drug[18]	Drug	Total cost[94]	Total QALYs[94]	Total life-years gained	Total annual cost	Weighted annual cost
0.50	Ipilimumab	£57,760	2.353	3.35	£17,230	£8,615
0.15	Dacarbazine	£19,914	1.461	2.02	£9,876	£1,481
0.35	Vemurafenib	£52,346	2.166	3.03	£17,264	£6,042
Total weighted metastatic melanoma and terminal disease cost (last year of life)						**£16,139**

Abbreviations used in table: QALY, quality-adjusted life year
Note: total life-years gained estimated indirectly, based on the ratio of QALYs : life-years gained in analyses undertaken by the company[93]

All other healthcare and PSS costs incurred by the study population in the model, including the costs incurred by people with a benign lesion (i.e. people with true negative or false positive results in diagnostic assessment) were estimated to be equal between the two arms of the model and were thus omitted from the analysis.

5.2.3 Diagnostic economic model on lesions suspected for basal cell carcinoma following a positive or equivocal dermoscopic finding - methods

5.2.3.1 Study population

The study population for this model comprised people with suspected BCC lesions with a positive or equivocal result in dermoscopy. The aim of examination of the suspected BCC lesions with VivaScope was to make or confirm diagnosis, respectively, as an alternative to diagnostic biopsy.

According to NICE guidance patients with low-risk BCC lesions may be identified and managed by GPs in community care settings.[95] However, clinical experts expressed the opinion that this is not routine practice, and in reality GPs manage less than 10% of low-risk BCCs; therefore, following clinical expert advice, the economic model assumed that all patients with suspected BCC lesions are referred to (and managed by) specialist dermatologist centres.

The mean age of the study population, that is, people referred to a dermatology department with suspected BCC, was assumed to be the same with the age of people at diagnosis of BCC. BCC is

more common in older people; people aged over 75 years are about five times more likely to have a BCC than those people aged between 50-55 years.[6] According to a study that analysed trends in the demographic, clinical and socioeconomic profile of more than 50,000 cases of non-melanoma skin cancer registered between 1994 and 2011 by the Irish National Cancer Registry, the median age at diagnosis of BCC was 68 for both men and women.[78] Another study that analysed data on all cases of BCC diagnosed at a single centre of dermatopathology during 1967–96 in Strasbourg, France, reported that the mean age of people at diagnosis of BCC was 65 years.[77] Data on the mean age of patients with suspected or diagnosed BCC in the UK were not possible to identify, so the mean age of the study population (people with suspected BCC) was estimated to be 63 years based on the available data and after considering the fact that the age-specific incidence rate for BCCs has been increasing in both sexes for all age groups over the years, with the largest overall increase in BCC incidence rates being observed in the youngest age groups.[78]

Non-melanoma skin cancers are more common to males than females in the UK, with a ratio of males to females 13:10 (that translates to a proportion of 56.5% males in the total population), although the sex difference is wider for SCC than BCC.[75] Data from the Irish National Cancer Registry indicated that the proportion of men among patients with BCC between 1994 and 2011 was 52.8%.[78] This figure of 52.8%, which is overall consistent with relevant UK information on non-melanoma skin cancer, was used in the economic model, due to lack of relevant UK data on the male to female ratio specific to BCC. This figure was used to represent the percentage of men in the population with suspected (rather than confirmed) BCC following a positive or equivocal finding in dermoscopy.

The proportion of suspected and also confirmed BCC lesions on head or neck in the model was 69.4%,[80] based on information reported in Section 5.2.1 under 'annual volume of cases eligible for examination with VivaScope in a dermatology multi-disciplinary team clinic in the UK'.

Each person with suspected BCC may present in one visit with more than one lesion that has been found positive or equivocal for BCC in dermoscopy. Clinical experts advised that for non-melanoma skin cancer there is a 50% chance of a second non-melanoma skin cancer in a five year period, whereas incidental second tumours may be potentially present in about 10% of patients with BCC. The economic model assumed for simplicity that the number of suspected BCC lesions with a positive or equivocal dermoscopic finding per person is equal to the number of confirmed BCC lesions per person; the latter was estimated to be 1.09, using audit data from Teoh *et al*. (2010), who reported 926 confirmed BCC lesions in 849 patients in a retrospective single-centre audit of all BCC excisions performed in 2008.[79] The figure of 1.09 lesions per person is consistent with clinical expert advice. The study that provided the data on the diagnostic accuracy of VivaScope on suspected BCC lesions for the economic analysis reported a mean number of 1.29 lesions suspected for BCC per study participant (92 lesions in 72 patients); and a mean number of 1.40 confirmed BCC lesions per person

with BCC (45 BCCs in 32 patients).[96] The higher figure of 1.40 BCC lesions per person (suspected or confirmed) was tested in sensitivity analysis. It needs to be noted that, for purposes of simplicity in the model design, lesions in one person were assumed to be all either malignant (BCC) or not and follow the same pathway, i.e. receive the same result in examination with VivaScope, the same (necessary or unnecessary) treatment, and have the same potential impact on HRQoL.

The annual volume of lesions suspected for BCC with a positive or equivocal dermoscopic finding examined at a dermatology MDT service in the UK was estimated to be approximately 500, as reported in Section 5.2.1 under 'annual volume of cases eligible for examination with VivaScope in a dermatology multi-disciplinary team clinic in the UK'.

5.2.3.2 Intervention and comparator

The intervention assessed in this model was VivaScope 1500 (for body lesions suspected for BCC) and VivaScope 3000 (for suspected BCC lesions on head or neck) for the diagnostic assessment of skin lesions suspected for BCC. The comparator was diagnostic biopsy, which was considered to reflect routine practice following a positive or equivocal dermoscopic finding for BCC.

5.2.3.3 Model structure

A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the diagnosis of people with lesions suspected for BCC that had a positive or equivocal finding in dermoscopy. According to the model structure, which was determined by clinical expert advice and availability of relevant data, people aged 63 years, with lesions suspected for BCC following a positive or equivocal finding in dermoscopy, were either examined with VivaScope 1500 or 3000 as appropriate (according to the location of the lesion), or had a diagnostic biopsy for confirmation of BCC. The model assumed that confirmed cases of skin cancer are of the same type of cancer as initially suspected (in the case of this model, BCC), although occasionally skin cancers identified may be of different type of that initially estimated by the clinician at dermoscopy.

People whose lesions were examined with VivaScope received the results of the examination immediately. Lesions found positive under VivaScope examination were treated for BCC according to national guidelines; treatment was applied to both true positive and false positive lesions. Lesions found negative in VivaScope examination underwent diagnostic biopsy (due to the dermoscopic outcome that was suggestive of malignancy), and subsequently received treatment if BCC was confirmed (diagnostic biopsy was considered to be the gold standard for the diagnosis of BCC). The results of diagnostic biopsy were available 6 weeks after the biopsy, according to routine clinical practice in the UK. If the results of biopsy were negative, patients were discharged. It is noted that under this pathway no BCC lesions remained undiagnosed, as any false negative lesions following VivaScope examination would move on to receive a diagnostic biopsy and would eventually be

identified. On the other hand, false positive lesions following VivaScope examination received unnecessary treatment.

Lesions assessed with diagnostic biopsy following a positive or equivocal finding in dermoscopy received treatment if BCC was confirmed, otherwise patients were discharged. The results of diagnostic biopsy were received 6 weeks after the biopsy. All people in this arm of the model received treatment according to their true BCC status, and therefore none of them received unnecessary treatment.

Treatment of BCC lesions in the model comprised a mixture of surgical and non-surgical therapies, according to published guidelines.[97,98] Surgical therapies included surgical excision and Mohs surgery. Non-surgical treatments included photodynamic therapy, radiotherapy, and topical treatment with imiquimod or fluorouracil. Other overall less common treatments for BCC, such as curettage and cautery, cryotherapy and chemotherapy, were not considered in the economic model. However, it is acknowledged that curettage and cautery as well as cryotherapy are commonly used treatments for low risk BCCs, especially superficial ones. In any case, it needs to be noted that, according to clinical expert advice, there seems to be variation in clinical practice, with some of the therapies being offered more or less routinely at different dermatology centres across the country.

All people undergoing diagnostic biopsy experienced distress due to biopsy and anxiety while waiting for the results. All people receiving surgical treatment and those treated unnecessarily with any kind of treatment (surgical or non-surgical) experienced distress due to treatment. Moreover, a proportion of people undergoing diagnostic biopsy or surgical treatment for skin lesions on head or neck were assumed to experience a permanent reduction in their HRQoL due to the resulting scarring.

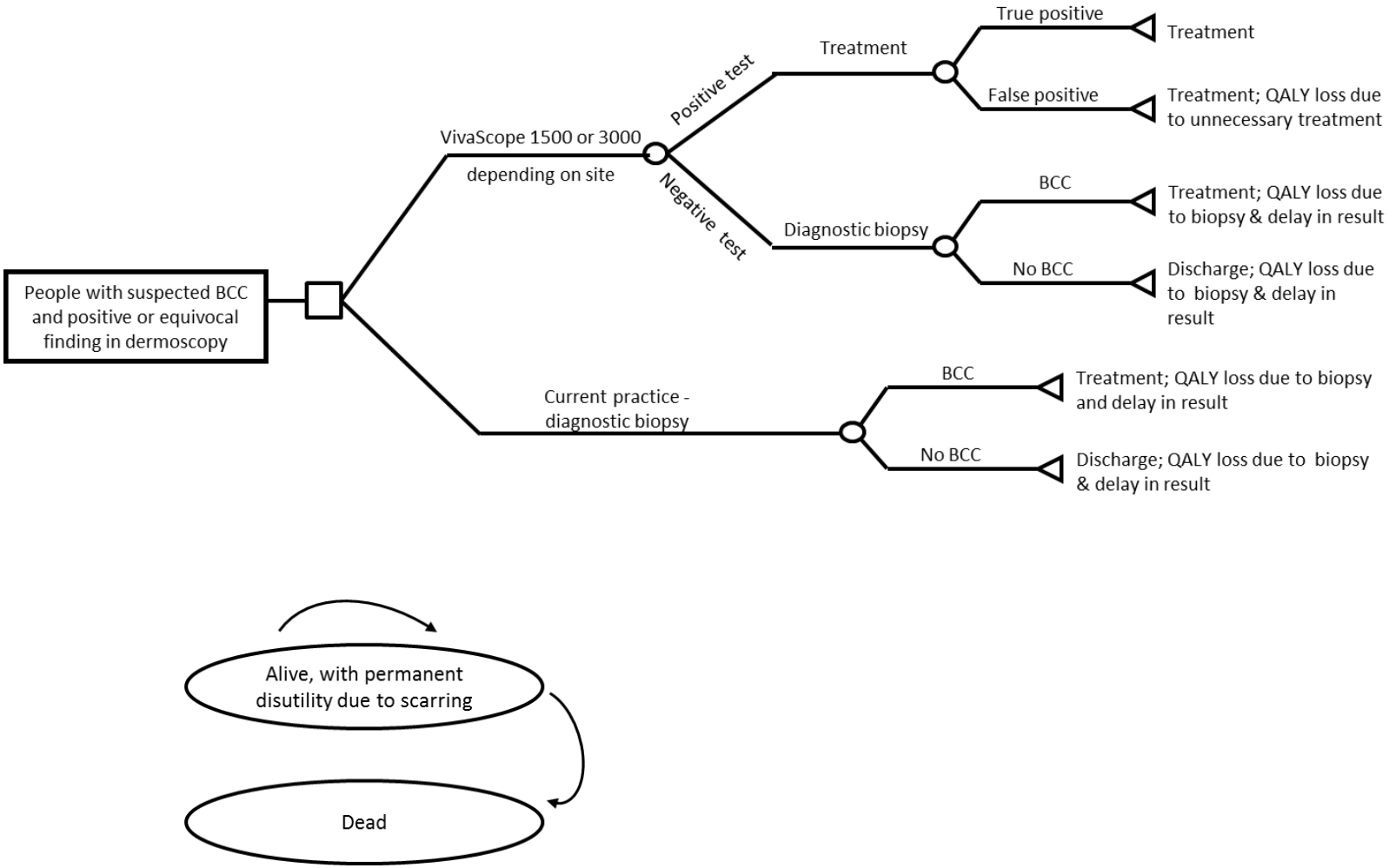
People experiencing a permanent reduction in their HRQoL due to scarring entered a very simple Markov model, consisting only of the states of alive (with permanent disutility due to scarring) and dead, in order to estimate the total disutility due to scarring experienced over life time. Apart from this permanent disutility experienced by a proportion of people in each arm of the model, the choice of diagnostic strategy (i.e. either examination with VivaScope followed by diagnostic biopsy for lesions found negative for BCC or diagnostic biopsy of all suspected BCC lesions) did not have any other impact on costs or outcomes beyond end of treatment. This is because in both arms of the model no BCC remained undiagnosed and therefore untreated. Consequently, there was no difference in tumour expansion, recurrence or mortality between the two arms of the model. For this reason, tumour expansion or future recurrence (and associated costs and impact on HRQoL) were not considered in the Markov part of the model. Thus all future costs and outcomes, with the exception of permanent disutility due to scarring experienced by a proportion of people, were estimated to be the same in both

arms of the model and were therefore omitted from the model. The cycle-length of the Markov model was 1 year and half-cycle correction was applied.

The time horizon of the economic model was over lifetime (up to 100 years of age).

A schematic diagram of the of the VivaScope diagnostics model on suspected BCC following a positive or equivocal finding in dermoscopy is shown in Figure 7.

Figure 7. Schematic diagram of the VivaScope diagnostics model on suspected BCC following a positive or equivocal finding in dermoscopy



5.2.3.4 Clinical input parameters

Diagnostic accuracy data

Diagnostic accuracy data for VivaScope were taken from the results of the systematic review of clinical evidence reported in Section 4.3. One study was found that reported the sensitivity and specificity of both VivaScope 1500 and VivaScope 3000 in the diagnosis of suspected BCC in patients presenting with at least one lesion clinically and dermoscopically suspicious for BCC that were recruited from 2 dermatology skin cancer clinics (Castro *et al*., 2014).[96] According to this study, the sensitivity of VivaScope 1500 and VivaScope 3000 was 100% and 93.3%, respectively. The specificity of both devices was 77.8%. Diagnostic biopsy was considered in the model to be the 'gold standard' for the diagnosis of BCC, that is, it was assumed to have 100% sensitivity and specificity.

Prevalence of BCC in lesions with a positive dermoscopic finding

The prevalence of BCC in lesions suspected for BCC were shown to be 83.3% in Castro *et al*. (2014).[96] Clinical expert opinion indicated that the prevalence of BCC in lesions suspected for BCC with a positive dermoscopic finding ranges from 95 to virtually 100%; when suspected BCC lesions with an equivocal finding in dermoscopy are considered, the prevalence of BCC is closer to 95%. The economic model utilised a prevalence value of BCC in lesions suspected for BCC with a positive or equivocal finding in dermoscopy of 95%.

Mortality

As BCC very rarely metastasises, it practically does not impact on patients' mortality; therefore, mortality rates in both arms of the model were assumed to equal that of the UK general population. Mortality was considered in the model only to allow estimation of the lifetime permanent disutility experienced due to scarring. Gender-and age-specific mortality rates were taken from recent UK national statistics[87] and were applied separately to men and women in every arm of the model.

5.2.3.5 Utility values

Patients in this model experienced a reduction in their HRQoL for one of the following reasons:

- due to diagnostic biopsy that caused distress as well as anxiety while waiting for the results;
- due to surgical treatment (all people undergoing surgical excision or Mohs surgery in the model) and unnecessary non-surgical treatment (people with false positive lesions);
- due to permanent scarring following surgical treatment of a lesion on head or neck.

As reported in Section 5.1.2, Seidler *et al.* (2009) estimated a disutility of -0.004 associated with an excision procedure due to facial non-melanoma skin cancer using traditional surgical excision or

Mohs surgery.[60] They also reported a disutility of -0.016 for simple repairs/scars (granulation and primary closure) and a disutility of -0.026 for complex repairs/scars (local flap and graft).

The study had many limitations and did not meet NICE criteria for use of utility data. Utility values were elicited from 5 healthy individuals in the US, who used TTO to value 2 scenarios relating to surgical excision or Mohs surgery of facial non-melanoma skin cancer. Owing to lack of better quality data, the utility values reported in this study were utilised in the economic model. The value of -0.004 was used to reflect the decrement in HRQoL (utility) experienced due to surgical treatment (either surgical excision or Mohs surgery). In the lack of any relevant data on the disutility due to unnecessary treatment received by people with lesions with a false positive result for BCC following examination with VivaScope, it was assumed that the one-off disutility of -0.004 reported in Seidler *et al.* (2009) [60] for surgical treatment applied to any (surgical or non-surgical) unnecessary treatment as well. It was assumed that a diagnostic biopsy created a disutility of -0.002 to the person, as it is expected to be a less invasive procedure than surgical excision or Mohs surgery. The disutility due to diagnostic biopsy and the disutility due to surgical/unnecessary treatment were applied as one-off disutilities (i.e. they were applied once, at the time of the respective procedure, without time adjustment). These disutilities were assumed to be additive, i.e. a lesion receiving a diagnostic biopsy followed by surgical treatment created a disutility for the patient of -0.002 + (-0.004) = -0.006 in the year within which it was biopsied and excised. Decrements in utility due to diagnostic biopsy or surgical/unnecessary treatment were applied separately to each lesion, so that a person with more than one lesion was assumed to experience a 'cumulative' disutility due to procedures experienced on each of their lesions.

In addition to the distress directly associated with diagnostic biopsy, people undergoing a diagnostic biopsy were considered to experience a reduction in their HRQoL due to anxiety while waiting for the results of biopsy. In the lack of any relevant utility data, it was assumed that people experienced moderate anxiety while waiting for a potential positive result for BCC. Moreover, people were assumed to have already utility less than one, and that they moved from a state of no anxiety/depression to moderate anxiety/depression. In the health state valuation equation provided by Dolan (1997) for EQ-5D (shown in Section 5.2.2), the disutility (coefficient) for moderate depression/anxiety was -0.071.[65] According to clinical expert advice, results of diagnostic biopsy for suspected BCC are available 6 weeks after the procedure. Therefore, the total reduction in QALYs associated with the anxiety while waiting for the results of diagnostic biopsy for suspected BCC was estimated to be -0.008. This disutility was applied in every person waiting for results, regardless of the person's number of lesions awaiting diagnosis.

A number of people may experience permanent disutility due to scars on their head or neck due to diagnostic biopsy of surgical treatment of skin lesions. In the economic model it was assumed that 5%

people undergoing a diagnostic biopsy for a skin lesion on their head or neck and 15% of people undergoing surgery for BCC on their head or neck would experience permanent disutility due to their scar over lifetime. Clinical expert advice was that 100% of diagnostic biopsies for suspected BCC are undertaken with simple repairs/scars; surgical excisions comprise 75% simple and 25% complex repairs/scars, whereas in Mohs surgery simple and complex repairs/scars comprise 50% each. Based on these estimates and the disutility data reported in Seidler *et al.* (2009),[60] the permanent disutility from scarring following diagnostic biopsy, surgical excision and Mohs surgery was estimated to be -0.016, -0.019 and -0.021, respectively. These disutilities were applied only to people with permanent reduction in their HRQoL due to scarring on head or neck over lifetime.

It needs to be noted that, as the general utility of people was not expected to differ between the two arms of the economic model (apart from the disutilities described above associated with certain procedures and resulting scars), the total number of QALYs in each arm in the model, reflecting the overall utility of each model arm from start of the model and over lifetime, was not estimated. The mean number of QALYs reported for each arm of this model is therefore negative, and reflects only the total disutility experienced by each arm of the model due to biopsy, surgery and/or scarring resulting in permanent disutility over the time horizon of the analysis.

Table 32 provides all utility data applied in the diagnostic economic model on lesions suspected for BCC.

Table 32. Utility data applied to the diagnostic economic model on lesions suspected for basal cell carcinoma

Type of utility	Utility value	Relevant population in the model	Source of utility data and assumptions
Disutility due to diagnostic biopsy	-0.002	People without BCC who underwent diagnostic biopsy (TN or FN in VivaScope examination and all people undergoing diagnostic biopsy under routine management)	Assumption; applied separately to every lesion undergoing diagnostic biopsy in each person, as one-off disutility
Disutility due to surgical treatment of a TP BCC or any unnecessary treatment of a FP BCC	-0.004	People with BCC undergoing surgical treatment (TP in VivaScope examination or identified from diagnostic biopsy) and people without BCC undergoing unnecessary treatment (FP in VivaScope examination)	Seidler *et al.* (2009);[60] disutility associated with excision procedure due to facial non-melanoma skin cancer using traditional surgical excision or Mohs surgery; applied separately to every lesion undergoing surgical treatment (or unnecessary treatment) in each person, as one-off disutility
Disutility due to anxiety while waiting for results of biopsy	-0.008	Any person waiting for results of diagnostic biopsy, including people who had negative results in examination with VivaScope and people under routine management	6-week disutility due to anxiety/depression estimated using the EQ-5D UK health state valuation equation,[65] assuming that people waiting for biopsy results had already utility <1 and moved from no to moderate anxiety/depression; applied to person (rather than lesion) as one-off disutility

Permanent disutility due to scarring on head or neck	-0.016	5% of people with lesions on head or neck who underwent diagnostic biopsy without surgical treatment (people with TN lesions in VivaScope examination who underwent diagnostic biopsy, people with FN lesions in VivaScope examination who underwent diagnostic biopsy followed by non-surgical treatment, and people with negative lesions undergoing routine management with diagnostic biopsy)	Seidler *et al.* (2009);[60] diagnostic biopsy of suspected BCCs assumed to entail simple repairs/scars; surgical excision of BCCs assumed to comprise 75% simple and 25% complex repairs/scars; Mohs surgery of BCCs assumed to comprise 50% simple and 50% complex repairs/scars; applied over lifetime
	-0.019	15% of people with BCC on head or neck who underwent surgical excision	
	-0.021	15% of people with BCC on head or neck who underwent Mohs surgery	
Abbreviations used in table: BCC, basal cell carcinoma; FP, false positive; FN, false negative; TP, true positive; TN, true negative			

5.2.3.6 Costs

Costs considered in this economic model included the cost of diagnostic assessment with VivaScope following a positive result in dermoscopy, the cost of diagnostic biopsy, and cost of treatment (including cost of unnecessary treatment for skin lesions with a false positive result in VivaScope examination).

As reported in Table 25, the cost of VivaScope per suspected BCC lesion examined was estimated to be £71 if VivaScope is exclusively used for the diagnostic assessment of suspected BCC lesions found positive in dermoscopy; £62 if VivaScope is used only for the diagnostic assessment of suspected melanomas giving an equivocal finding in dermoscopy and suspected BCC lesions with a positive dermoscopic finding; and £58 if the device is used not only for the diagnostic assessment of suspected melanomas and BCCs, but also for the mapping of lentigo malignas prior to surgical treatment.

The costs of all other procedures and treatments included in the model were taken from either the NHS reference costs for 2014[68] or the NHS National Drug Tariff for February 2015[66]. Clinical experts advised on the appropriate NHS service and procedure codes corresponding to procedures and treatments considered in the model.

The unit cost of diagnostic biopsy was estimated to be £134, corresponding to the national unit cost of outpatient minor skin procedures conducted in a dermatology service for people of 13 years and over (service code 330, currency code JC43A).[68]

Treatment comprised a mixture of surgical and non-surgical therapies. Clinical experts indicated that the proportion of BCC lesions treated surgically ranges between 66% and 90% of BCC lesions. The

economic model assumed that 75% of BCC lesions are treated surgically. Of those, 85% were assumed to undergo surgical excision and 15% to be treated with Mohs surgery (the proportion of BCC lesions undergoing Mohs surgery among those receiving surgical treatment appears to range between 10-20% across services in the UK, as indicated by clinical experts, although a wider variation may potentially exist).

Among lesions managed with non-surgical treatment, the percentage of lesions receiving each treatment was derived from a multicentre audit (7 centres in the Mersey region in Northwest England), comprising a retrospective case-note review of 50 randomly selected patients per trust who had BCCs managed non-surgically within a 12-month time period (1 January 2012 to 1 January 2013).[99] In total 246 patients were selected as being suitable for the audit. The most commonly used agent for treatment was imiquimod, used by more than 50% of patients with BCC, followed by photodynamic therapy in 21%, radiotherapy in 19% and fluorouracil in 8%. Based on these data and after consulting with clinical experts, it was assumed that non-surgical treatment of BCCs in the economic model comprised 60% topical treatment with imiquimod or fluorouracil (30% each), 21% photodynamic therapy and 19% radiotherapy. It needs to be emphasised that this is not necessarily a typical picture of non-surgical treatments across the country, as the EAG was advised that some of these treatments are not routinely used in some dermatology services, whereas others, such as cryotherapy and curettage and cautery, that were not included in the economic model, may be more frequently offered in some services for the treatment of low-risk BCC lesions, especially superficial ones. However, regarding non-surgical therapies, as these comprised only 25% of the treatment of BCC lesions, the impact of variations in relevant practice across settings on the total cost of BCC treatment was rather insubstantial.

By combining the above resource use estimates with appropriate unit costs[66,68] as recommended by clinical experts, the mean total cost of treatment per BCC lesion was estimated at £475.

All other healthcare and PSS costs incurred by people in the model were estimated to be equal between the two arms of the model and were thus omitted from the analysis.

Table 33 provides the data and assumptions used at the estimation of the mean weighted treatment cost of BCC.

Table 33. Mean weighted treatment cost of basal cell carcinoma

Type of treatment	%	Treatment	% within type	Cost	Data sources and assumptions based on clinical expert estimates
Surgical	75%	Surgical excision	85%	£388	Assuming 50% comprise minor skin procedures undertaken as day-cases (currency code JC43A, unit cost for people ≥13 years £624),[68] and 50% comprise dermatology outpatient, intermediate skin procedures (service code 330, currency code JC42A, unit cost for people ≥ 13 years £151) [68]
		Mohs surgery	15%	£943	Intermediate skin procedure undertaken as day-case (currency code JC42A, unit cost for people ≥13 years £943)[68]
Non-surgical	25%	Imiquimod	30%	£142	Imiquimod 5% cream one pack of 12 sachets £48.60[66] plus one consultant-led, dermatology outpatient follow-up visit (service code 330, currency code WF01A, unit cost £93)[68]
		Fluorouracil	30%	£126	Fluorouracil 5% cream one tube £32.90[66] plus one consultant-led, dermatology outpatient follow-up visit (service code 330, currency code WF01A, unit cost £93)[68]
		Radiotherapy	19%	£1303	Involves approximately 10 factions; cost per faction £87 plus one-off cost for the mask £433, according to clinical expert opinion
		Photodynamic therapy	21%	£753	2 sessions of photodynamic therapy offered as day cases (currency code JC46Z, unit cost £330 each)[68] plus one consultant-led, dermatology outpatient follow-up visit (service code 330, currency code WF01A, unit cost of £93)[68]
MEAN WEIGHTED TREATMENT COST				**£475**	
Note: percentages based predominantly on clinical expert opinion and published audit data[99]					

All input parameters utilised in the diagnostic economic model on lesions suspected for BCC following a positive dermoscopic finding are shown in Table 36, in Section 5.2.5.

5.2.4 Pre-surgical margin delineation economic model - methods

5.2.4.1 Study population

The study population for this model comprised patients with lentigo maligna, aged 70 years, undergoing margin delineation prior to receiving surgical treatment. The aim of examination of lentigo malignas with VivaScope prior to surgical removal was accurate definition of tumour margins. Surgical removal of lentigo malignas needs to balance between sufficiently wide margins to prevent recurrence, and minimal margins to preserve functional and aesthetic areas of face and neck. Therefore, accurate definition of the surgical margins of lentigo maligna leads potentially to a low rate of multiple excisions, sparing tissue in functional and aesthetic areas.[100]

Epidemiological data specific to lentigo maligna are rather sparse in the literature, possibly because this is a precancerous condition and it may not always recorded in cancer registries. Cases of lentigo maligna are not routinely included in UK cancer statistics. Lentigo maligna is more common in older people. A review of lentigo maligna and lentigo maligna melanoma published in 1995 indicated that patients with lentigo maligna are generally older than 40 years of age, with a mean age of 65

years.[101] Lentigo maligna most commonly affects the sun-exposed skin of the head and neck, with a predilection for the cheek.[101] A recent US study identified all adult residents with a first lifetime diagnosis of lentigo maligna between 1970 and 2007 in Olmsted County, Minnesota. The study analysed medical records in order to determine demographic, clinical and surgical data, as well as incidence and survival rates associated with lentigo maligna.[73] According to this study, the mean age of patients at lentigo maligna diagnosis was 70 years (range 33-97 years), with 64.1% being male. The proportion of lentigo malignas on head or neck were approximately 62%. However, clinical expert advice to the EAG indicated that this percentage may be much higher, and reach even 90%. Based on this information, the study population in the economic model had a mean age of 70 years, with 64% being male and 70% of them having a lentigo maligna on head or neck. Each person had only one diagnosed lentigo maligna that required surgical treatment at the time of the analysis, according to clinical expert opinion.

The annual volume of lentigo malignas examined for margin delineation at a dermatology MDT service in the UK was estimated to approximate 75, as reported in Section 5.2.1 under 'annual volume of cases eligible for examination with VivaScope in a dermatology multi-disciplinary team clinic in the UK'.

5.2.4.2 Intervention and comparator

The intervention assessed in this model was VivaScope 3000 for the margin delineation of lentigo maligna prior to surgical treatment. The comparator was routine practice, which comprised pre-surgical assessment of lentigo maligna margins with a dermoscope and/or clinical judgement.

5.2.4.3 Model structure

A decision-tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the margin delineation of lentigo malignas prior to surgical treatment. According to the model structure, which was determined by clinical expert advice and availability of relevant data, patients of 70 years of age with a lentigo maligna planned for surgical treatment either had their tumour examined with VivaScope 3000 for margin delineation prior to surgery, or underwent routine management, comprising pre-surgical assessment of lentigo maligna margins with a dermoscope and/or clinical judgement.

Following margin assessment, lentigo malignas in both arms of the model were removed either by surgical excision or by Mohs surgery. A proportion of surgical excisions were incomplete, as determined by histopathology, meaning that some pre-malignant cells were still present after treatment, despite margin delineation. Incompletely excised tumours required a second surgical excision 4-6 weeks later, after which excision was assumed to be complete and confirmed by histopathology. The proportion of lentigo malignas that were incompletely excised was determined by

the type of pre-surgical assessment of the margins (i.e. by VivaScope 3000 or dermoscope/clinical judgement). Mohs surgery is performed in surgical stages until the surgical margins are clear. The type of pre-surgical assessment of the margins (i.e. by VivaScope 3000 or dermoscope/clinical judgement) affected the number of stages of Mohs surgery.

All patients experienced distress due to surgery. Moreover, a proportion of patients with a lentigo maligna surgically removed from their head or neck experienced a permanent reduction in their HRQoL due to the resulting scarring.

After complete surgical excision or Mohs surgery, all patients in both arms of the decision-tree entered the Markov model, which was run in yearly cycles; half-cycle correction was applied. All patients entering the Markov model were at risk of recurrence of their tumour for the first 10 years (i.e. 10 years after the primary surgical removal of their lentigo maligna). The risk of recurrence depended on the type of initial pre-surgical margin delineation (i.e. with either VivaScope 3000 or dermoscope/clinical judgement) and/or the type of initial surgical treatment they had received (i.e. surgical excision or Mohs therapy). Patients experiencing a recurrence either underwent surgical excision or Mohs surgery, as according to clinical expert advice the vast majority of lentigo malignas are treated surgically; alternative therapies, such as radiotherapy and topical therapy with imiquimod are used only if the patient is unfit for surgery or there is a medical reason preventing surgery, for example, the patient is very frail and elderly. All patients experienced distress due to surgical treatment. A proportion of them with lentigo malignas on the face could experience permanent disutility due to scarring, if they were not already experiencing permanent disutility due to scarring after the initial surgical treatment.

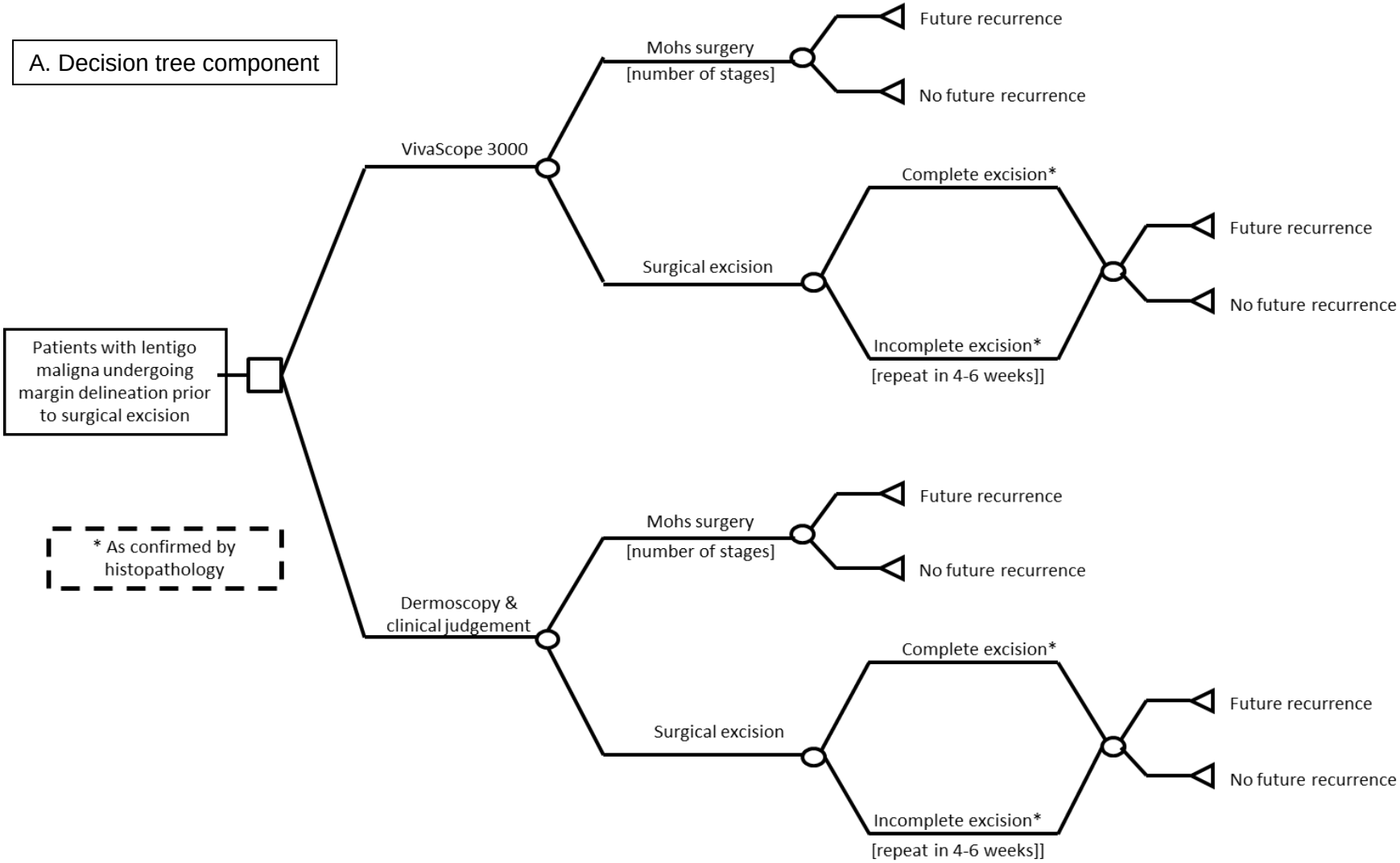
The Markov model consisted of the states of ‘no recurrence, no permanent disutility due to scarring’, ‘no recurrence, permanent disutility due to scarring’, ‘recurrence, no permanent disutility due to scarring’, ‘recurrence, permanent disutility due to scarring’, and ‘death’, which was an absorbing state. Patients moving from the decision-tree could enter one of the Markov model states, depending on whether they had already experienced permanent disutility due to scarring or not. Patients in the ‘no recurrence, no permanent disutility due to scarring’ state could remain on this state, experience a recurrence and move to ‘recurrence, no permanent disutility due to scarring’ state, experience a recurrence and a scar that created permanent disutility thus moving to ‘recurrence, permanent disutility due to scarring’ state (this was possible only for patients with lentigo maligna on head or neck), or die. Patients in the ‘no recurrence, permanent disutility due to scarring’ state (who were patients with a lentigo maligna on head or neck) could remain on this state, experience a recurrence and move to ‘recurrence, permanent disutility due to scarring’ state, or die. The two recurrence states with/without permanent disutility due to scarring were only temporary states; patients in these states could only transition to the two non-recurrence states with/without permanent disutility due to

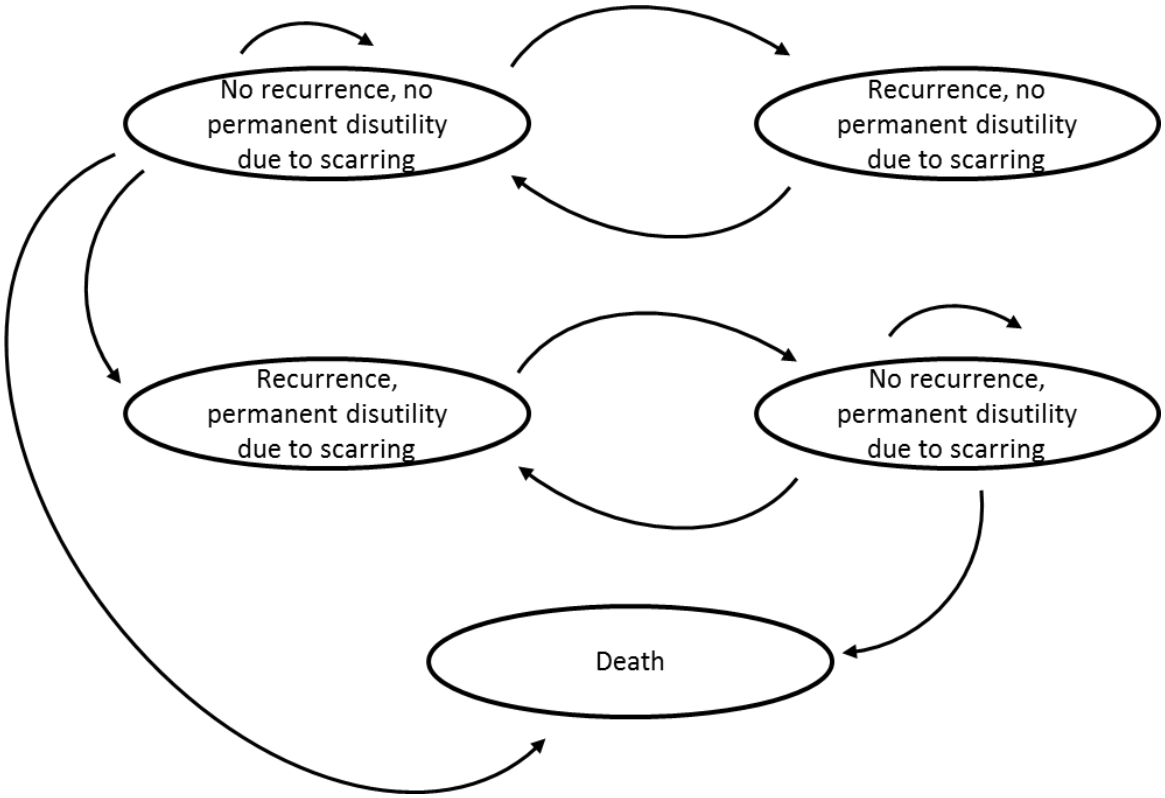
scarring, respectively, from which they could transition to a new recurrence or death in the next cycle. After the first 10 years, patients could not experience a recurrence of their tumour and therefore they could either remain in their ‘no recurrence’ state (with or without scarring) or die.

Lentigo malignas in the economic model were assumed not to progress to lentigo maligna melanomas, as the relevant risk was low, given that all lentigo malignas in the model were treated.

The time horizon of the economic model was over lifetime (up to 100 years of age). A schematic diagram of the VivaScope margin delineation model is shown in Figure 8.

Figure 8. Structure of the margin delineation model





5.2.4.4 Clinical input parameters

Impact of method of margin delineation on surgical outcomes

The impact of VivaScope on surgical outcomes following pre-surgical margin delineation of lentigo malignas was taken from the results of systematic review reported in Section 4.3. The risk of incomplete surgical excisions following margin delineation with VivaScope 3000 was taken from Guitera *et al*. (2013), who reported that out of 17 patients with lentigo maligna that was surgically excised, 2 had VivaScope-delineated margins involved after excision (12%).[38] Regarding future recurrence, the study reported that no recurrence of lentigo malignas treated surgically was observed in any of the patients by last follow up (median follow-up 37 months, range 7-66 months). However, this observation was based on a small number of lentigo malignas excised. In order to populate the economic model it was assumed that the risk of recurrence of lentigo malignas after margin delineation with the use of VivaScope 3000 was equal to the risk of recurrence of lentigo malignas following Mohs surgery, regardless of the type of surgical treatment (i.e. surgical excision or Mohs

surgery) following mapping with VivaScope 3000. This was considered by clinical experts to be a conservative assumption.

The risk of incomplete surgical excision and future recurrence following routine margin delineation with dermoscope and/or clinical judgement was based on a review of published studies and audits reporting relevant data.

A large study evaluating the outcomes of surgical excision in all lentigo maligna cases treated in Leicestershire between 1987 and 1996 reported that, out of 89 evaluable patients with lentigo maligna treated with primary excision, 8 (i.e. 9%, with 95% CI 4% to 17%) had a histologically incomplete excision.[102] The margins used by surgeons in Leicestershire were 2mm, in accordance with standard practice in the UK at the time of the study. In completely excised lesions (n = 81) the observed recurrence rate was 20% (CI: 12% to 30%) at a mean follow-up of 42 months, which was claimed to be similar to previous reports. However, Kaplan-Meier analysis undertaken by the authors estimated a probability of recurrence of 31% (CI: 19% to 50%) with time to relapse being up to 66 months

A retrospective review of all melanomas in situ referred to one hospital in Hull between 2001 and 2009 revealed that, of the 75 excisions of lentigo malignas, 22 (29.3%) were incomplete.[103] The risk of recurrence in complete excisions was 2.9% at 3 years.

A review of the clinical features, histopathology, and treatment options for lentigo maligna reported that standard excision of lentigo malignas with 5mm margins was insufficient in 50% of cases.[104] The recurrence rate with standard excision was reported to range from 8 to 20%. On the other hand, it was argued that Mohs surgery and staged excision might offer better margin control and lower recurrence rates, around 4-5%. BAD guidelines[16] reported that local recurrence of lentigo maligna occurs in about 5% of patients by 2 years.

Finally, a US retrospective study of 5-year treatment outcomes of all primary lentigo maligna cases treated with either wide local excision with 5mm margins or Mohs surgery in one dermatology setting in Minnesota between 1995 and 2005 reported that, out of 269 lesions treated with wide excision, there were 16 recurrences over 5 years (5.9%) whereas out of 154 lesions treated with Mohs surgery, there were 3 recurrences over 5 years (1.9%).[105]

The economic model used a 12% risk of incomplete excision for surgical excisions of lentigo maligna following mapping with VivaScope and a 30% risk of incomplete excision for surgical excisions after routine margin delineation with dermoscope and/or clinical judgement. The 5-year risk of recurrence of lentigo malignas mapped with VivaScope (regardless of type of subsequent surgical treatment), as well as the 5-year risk of recurrence of lentigo malignas following Mohs surgery (regardless of method of pre-surgical mapping), were 5% in the model. The 5-year risk of recurrence of lentigo

malignas after surgical excision was 15% in the model. These figures, which were based on values reported in the literature and were validated by clinical expert opinion, were converted to 1-year probabilities using exponential function and were applied over the first 10 years of the Markov model. After 10 years, it was assumed that the risk of recurrence fell at zero.

Regarding the number of stages in Mohs surgery after margin delineation of lentigo malignas, a small UK study of Mohs surgery on 16 lentigo maligna cases of which 7 had been mapped with VivaScope 3000, reported that cases that were mapped with VivaScope took an average of 1.4 stages to clear (SD 0.53) whereas those that did not undergo mapping took an average of 2.2 stages to clear (SD 1.2)[106]. These values were utilised in the economic model, due to lack of any more robust data.

Mortality

As progression of lentigo maligna to lentigo maligna melanoma is very low, in particular if treated, and in the very elderly may be unlikely within their lifespan,[16] mortality rates in both arms of the model were assumed to equal that of the UK general population. Gender-and age-specific mortality rates were taken from recent UK national statistics[87] and were applied separately to men and women in every model arm.

5.2.4.5 Utility values

Patients in this model experienced a reduction in their HRQoL for one of the following reasons:

- due to surgical treatment (either surgical excision or Mohs surgery) ;
- due to permanent scarring following surgical treatment of a lentigo maligna on head or neck.

As reported in Section 5.1.2, Seidler *et al.* (2009) estimated a disutility of -0.004 associated with an excision procedure due to facial non-melanoma skin cancer using traditional surgical excision or Mohs surgery.[60] They also reported a disutility of -0.016 for simple repairs/scars (granulation and primary closure) and a disutility of -0.026 for complex repairs/scars (local flap and graft).

The presence and surgical management of lentigo maligna was considered to have a similar impact on patients' HRQoL with that of presence and surgical management of BCC. Owing to lack of more relevant and better quality data, the value of -0.004 was used to reflect the decrement in HRQoL (utility) experienced due to surgical treatment (either surgical excision or Mohs surgery). This disutility due to surgical treatment was applied as one-off every time a person underwent surgical treatment (i.e. at first surgery, repeat surgery due to incomplete excision, or future recurrence).

Disutility due to patient waiting for a second surgery following incomplete excision was not considered, however it is acknowledged that waiting time for a second surgery may create additional distress to the patient.

The number of stages in Mohs surgery is expected to affect the patients' HRQoL, in terms of time and distress. However, the differential utility resulting from differences to the number of stages in Mohs surgery was not factored into the model as it was not possible to estimate a disutility per stage.

A number of people may experience permanent disutility due to scars on their head or neck due to surgical removal of lentigo malignas. In the economic model it was assumed that 15% of patients undergoing surgical treatment for their lentigo maligna on their head or neck (either for the first time or at a future recurrence of the tumour) would experience permanent disutility due to their scar that would last over lifetime. Clinical expert advice was that surgical removal of lentigo malignas, either by surgical excision or Mohs surgery, comprises 50% simple and 50% complex repairs/scars. Based on these estimates and the disutility data reported in Seidler *et al.* (2009),[60] the disutility associated with scarring from surgical treatment of lentigo malignas was estimated to be -0.021. This disutility was applied only to people with permanent reduction in their HRQoL due to scarring on head or neck over lifetime. A person who underwent surgical treatment for a lentigo maligna on head or neck and did not experience disutility due to scaring was at 15% risk of experiencing permanent disutility due to scarring at each potential future recurrence of lentigo maligna.

As the general utility of people in the model was not expected to differ between the two arms of the economic model (apart from the disutilities described above associated with surgical treatment and resulting scars), the total number of QALYs in each arm in the model, reflecting the overall utility of each model arm from start of the model and over lifetime, was not estimated. The mean number of QALYs reported for each arm of this model is therefore negative, and reflects only the total disutility experienced by each arm of the model due to surgery and/or scarring resulting in permanent disutility over the time horizon of the analysis.

Table 34 provides all utility data applied in the economic model on margin delineation of lentigo malignas.

Table 34. Utility data applied to the margin delineation economic model on lentigo malignas

Type of utility	Utility value	Relevant population in the model	Source of utility data and assumptions
Disutility due to surgical treatment of lentigo maligna	-0.004	People with lentigo maligna undergoing surgical treatment (surgical excision or Mohs surgery)	Seidler *et al.* (2009);[60] disutility associated with excision procedure due to facial non-melanoma skin cancer using traditional surgical excision or Mohs surgery; applied every time a person underwent surgical treatment (i.e. at first surgery, repeat surgery due to incomplete excision, or future recurrence), as one-off disutility
Permanent disutility due to scarring on head or neck	-0.021	15% of people with BCC on head or neck who underwent surgical excision or Mohs surgery at the start of the model or due to future recurrence of lentigo maligna	Seidler *et al*. (2009);[60] surgical excision and Mohs surgery of lentigo malignas assumed to comprise 50% simple and 50% complex repairs/scars; applied over lifetime
Abbreviations used in the table: BCC, basal cell carcinoma.			

5.2.4.6 Costs

Costs included the cost of pre-surgical mapping of lentigo malignas with either VivaScope 3000 or dermoscope/clinical judgement, the cost of treatment with either surgical excision or Mohs surgery and the cost of potential future treatment due to recurrence.

As reported in Table 25, the cost of margin delineation with VivaScope 3000 per lentigo maligna mapped was estimated to be £250 if VivaScope is exclusively used for pre-surgical margin delineation of lentigo malignas and £105 if the device is used for the diagnostic assessment of suspected melanomas and BCCs, as well as for the mapping of lentigo malignas prior to surgical treatment.

Routine pre-surgical margin delineation of lentigo malignas with dermoscope/clinical judgement was estimated to comprise 5 minutes of a consultant dermatologist's time. Using the unit cost of a consultant dermatologist of £140 per hour of contract,[67] the mean cost of routine pre-surgical margin delineation was estimated to be £12. The acquisition cost of dermoscope was not included in the estimation of the cost of routine pre-surgical margin delineation of lentigo malignas, as dermoscopes appear to be already in place in dermatology departments and can be used for the assessment of skin lesions.

The proportion of lentigo malignas that were treated with surgical excision in the first surgery following margin delineation and in future recurrences was estimated based on clinical expert opinion. It was assumed that 85% of the first surgical treatment of lentigo malignas comprised surgical excision and 15% Mohs surgery. After tumour recurrence, 80% of lentigo malignas were assumed to be treated with surgical excision and 20% with Mohs surgery.

The unit costs of surgical excision and Mohs surgery were taken from the NHS reference costs for 2014.[68] Clinical experts advised on the appropriate NHS service and procedure codes corresponding to these two types of surgical treatment.

Mohs surgery is undertaken in stages. The number of stages required for Mohs surgery is directly related to an opportunity cost in terms of staff time and consumables; however, it was not possible to identify a unit cost per stage of Mohs surgery. For this reason, it was assumed that the unit cost reflecting Mohs surgery corresponded to the mean number of required stages, across all skin operations requiring Mohs surgery. As relevant UK data on the mean number of stages required in Mohs surgery were not possibly to identify, this figure was derived from a US multicentre prospective cohort study, which aimed to evaluate the rate of complications and postoperative pain associated with the treatment of skin cancer using Mohs surgery.[107] The study included 1550 patients with 1792 tumours, the majority of which were BCC (61%) or SCC (31%). The authors reported that the mean number of stages was 1.6, ranging from 1 to 8. Therefore, for the purposes of costing, it was assumed that the national unit cost reflecting the cost of Mohs surgery corresponded to 1.6 Mohs stages, and that 70% of this unit cost was fixed (and independent of the number of stages involved in Mohs surgery), whereas the remaining 30% of the unit cost was variable and in linear relationship with the number of stages required for the completion of Mohs surgery. This assumption was utilised only in the first surgery following margin delineation of lentigo malignas. For Mohs surgery undertaken in future recurrences, the mean cost of Mohs surgery, without adjusting for the number of stages, was used.

All other healthcare and PSS costs incurred by people in the model were estimated to be equal between the two arms of the model and were thus omitted from the analysis.

Table 35 provides the percentages of each type of surgical treatment for lentigo maligna at first surgery following margin delineation and after recurrence, the costs of each type of surgical treatment, as well as the data sources and assumptions used for their estimation.

Table 35. Cost of surgical treatments for lentigo maligna

Treatment	% at first surgery	% after recurrence	Cost	Data sources and assumptions based on clinical expert estimates
Surgical excision	85%	80%	£388	Assuming 50% comprise minor skin procedures undertaken as day-cases (currency code JC43A, unit cost for people ≥13 years £624),[68] and 50% comprise dermatology outpatient, intermediate skin procedures (service code 330, currency code JC42A, unit cost for people ≥ 13 years £151) [68]
Mohs surgery	15%	20%	£943	Intermediate skin procedure undertaken as day-case (currency code JC42A, unit cost for people ≥13 years £943);[68] 70% assumed to be fixed and 30% assumed to be linearly determined by number of stages of Mohs surgery [this was applied only to first surgery]. Reported cost assumed to correspond to 1.6 stages of Mohs surgery.

Note: percentages based on clinical expert opinion

All input parameters utilised in the diagnostic economic model on lesions suspected for BCC following a positive dermoscopic finding are shown in Table 36, in Section 5.2.5.

5.2.5 Methods of analysis and presentation of the results

5.2.5.1 Overview of methods of analysis

A deterministic analysis, which utilised point estimates of each model input parameter, was first undertaken. This was followed by a probabilistic analysis, which was conducted to take account of the uncertainty characterising the input parameter estimates; for this analysis, all relevant input parameters were entered as probability distributions to reflect their imprecision. Probability distributions were determined by the available data or, where data were lacking, by plausible assumptions. Monte Carlo simulation was then employed to reflect this uncertainty in the models' results: 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results of the probabilistic analysis were averaged across the 10,000 iterations to provide a mean estimate of costs and QALYs for each intervention. In addition, uncertainty in the model input parameters and structural assumptions was explored through deterministic one-way and two-way sensitivity analyses.

Results have been presented in the form of incremental cost effectiveness ratios (ICERs), except in cases of dominance, which occurs when an intervention results in lower costs and a higher number of QALYs than its comparator. The results of both types of analyses (deterministic and probabilistic) have been depicted in the form of cost-effectiveness planes. The results of the probabilistic analysis have been summarised in the form of cost-effectiveness acceptability curves (CEACs), which show the probability of VivaScope being cost-effective at different cost effectiveness thresholds, in each of the analyses considered. All input parameters were tested in one-way sensitivity analysis; Tornado diagrams were produced for different analyses to show the impact of the most influential parameters on the results. The results of Tornado diagrams have been reported using incremental net monetary benefits (INMBs), estimated at a willingness to pay threshold of £20,000/QALY, rather than ICERs, because use of the whole range of some parameters tested in Tornado diagrams resulted in negative ICERs, due to dominance, which are not meaningful. Additional one-way sensitivity analyses were undertaken to estimate the impact of alternative scenarios and model assumptions on the results. Finally, two-way sensitivity analyses were carried out to test the impact of concurrently varying sensitivity and specificity of VivaScope in the diagnostic assessment of eligible skin lesions suspected for melanoma or BCC on the cost effectiveness results.

5.2.5.2 Summary of all model input parameters, probability distributions and range of values tested in sensitivity analysis

In order to run the probabilistic analysis, all relevant input parameters were entered as probability distributions to reflect their imprecision. Probability distributions were determined by the available data or, where data were lacking, by plausible assumptions.

The annual volume of the three types of lesions examined with VivaScope (i.e. suspected melanomas with an equivocal finding in dermoscopy, suspected BCCs with a positive or equivocal dermoscopic finding and lentigo malignas undergoing pre-surgical margin delineation) were given a uniform distribution, with a range of ±30% of the originally estimated volume.

The diagnostic accuracy characteristics of VivaScope and monitoring (which was part of routine management of equivocal lesions suspected for melanoma), i.e. sensitivity and specificity, were given a beta distribution. It is acknowledged that sensitivity and specificity are usually correlated, and, as such, a joint distribution should ideally be used. However, as no meta-analysis of diagnostic accuracy data was performed and no summary ROC curves that could indicate the relationship between sensitivity and specificity were possible to produce, as described in Section 4, it was considered reasonable to use a beta distribution for sensitivity and specificity, assuming that these are independent from each other, although this assumption is acknowledged as a limitation of the analysis.

All proportions and dichotomous probabilities (for example, the proportion of men in the study population, the proportion of lesions on head or neck, the probability of death associated with melanoma, the prevalence of cancer in lesions suspected for skin cancer, the probability of future recurrence of lentigo maligna, etc.) were given a beta distribution. Utilities were also given a beta distribution, using the method of moments; disutilities were given a distribution of 1 minus beta. Polychotomous transitions and variables were given a Dirichlet distribution.

Staff unit costs (radiographer, consultant dermatologist) and the required staff time to operate the VivaScope system were given a normal distribution. All other costs were assigned a gamma distribution.

Table 36 provides an overview of all input parameters, reporting deterministic values and details on the types and range of probability distributions assigned to each parameter with relevant data sources and justifications.

Table 36. Input parameters utilised in the cost effectiveness analysis of the VivaScope imaging system

Input parameter	Mean (deterministic) value	Probability distribution	Source of data - comments
PARAMETERS DETERMINING THE COST OF VIVASCOPE			
Annual volume of lesions examined with ViveScope			
Equivocal lesions suspected for melanoma	100	Uniform; range 70-130	Clinical expert advice supplemented by estimates based on national statistics and further assumptions [2,70-73]
Suspected BCCs positive/equivocal in dermoscopy	500	Uniform; range 350-650	
Lentigo malignas prior to surgical treatment	75	Uniform; range 52.5-97.5	
Purchase price of VivaScope			
VivaScope 1500	£90,224	No distribution assigned	Information provided by the company
VivaScope 3000 stand-alone device	£62,300		
VivaScope 1500 and 3000 combined	£131,824		
Annual maintenance cost of VivaScope			
VivaScope 1500	£4,100	No distribution assigned	Information provided by the company
VivaScope 3000 stand-alone device	£4,100		
VivaScope 1500 and 3000 combined	£5,500		
Useful life of VivaScope / training (years)	10	No distribution assigned	Information provided by the company / assumption
Interest rate used for annuitisation of costs	3.5%	No distribution assigned	Assumption
Costs of consumables			Including adhesive windows needed for VivaScope 1500, crodamol oil, Alcotip and ultrasound gel; based on retail prices and further assumptions
• per lesion examined with VivaScope 1500	£2.97	No distribution assigned	
• per lesion examined with VivaScope 3000	£1.50	No distribution assigned	
Cost of training (cost of staff time)	£17,816	Distribution determined by staff unit costs	Includes 1.5 day of 2 radiographers and 2 consultant dermatologists (introductory training) and 4 days of 2 consultant dermatologists (intensive expert training plus travel time) plus £2,000 travel, hotel and subsistence costs for each dermatologist attending the intensive expert training
Staff time per examination (minutes)			
Diagnosis, VivaScope 1500 – radiographer	10	Normal; SE: 0.1 x mean	Clinical expert opinion; all distributions imposed to a minimum value of 5 minutes of radiographer and 3 minutes of dermatologist for diagnosis with VivaScope 1500; 5 minutes of dermatologist for diagnosis with VivaScope 3000; 20 minutes of radiographer for mapping; distribution based on
Diagnosis, VivaScope 1500 – dermatologist	5	Normal; SE: 0.1 x mean	
Diagnosis, VivaScope 3000 – dermatologist	10	Normal; SE: 0.1 x mean	
Margin mapping, VivaScope 3000 - dermatologist	30	Normal; SE: 0.1 x mean	

Staff unit costs • Radiographer Band 7 – per hour • Clinical dermatologist – per hour of contract **Cost of VivaScope examination** **Per suspected melanoma:** • Exclusive use on suspected melanomas • Use on suspected melanomas and BCCs • Use across all 3 types of lesions **Per suspected BCC:** • Exclusive use on suspected BCCs • Use on suspected melanomas and BCCs • Use across all 3 types of lesions **Per mapped lentigo maligna:** • Exclusive use on mapping of lentigo malignas • Use across all 3 types of lesions	 £62 £140 £254 £63 £59 £70 £62 £58 £250 £105	 Normal; SE: 0.1 x mean Normal; SE: 0.1 x mean	assumption [67]; unit cost of radiographer Band 7 estimated from the unit cost of radiographer Band 5 and the ratio of salary of Band 7 to Band 5 AfC for qualified allied health professionals; distribution based on assumption Details on the estimation of these costs provided in Table 25
DIAGNOSTIC ASSESSMENT MODEL ON SUSPECTED MELANOMAS **Mean age of the study population** **Proportion of men in the study population** **Proportion of melanomas on head or neck** • Men • women **Number of suspected/diagnosed melanomas per person** **Prevalence of melanoma in equivocal lesions** **Proportion of equivocal lesions excised under routine management** **Ratio of prevalence of melanoma in equivocal lesions excised : monitored under routine management** **Prevalence of melanoma in equivocal lesions** • excised	 55 years 0.49 0.22 0.14 1 0.15 0.67 5 0.21	 N/A Beta; α=6495, β=6853 Beta; α=1429, β=5066 Beta; α=959, β=5894 No distribution assigned Beta; α=15, β=85 Beta; α=67, β=33 Normal; SD = 0.1 x mean, N = 500 Determined by relevant parameter	 [81] [75] [74] Clinical expert advice Review of studies and clinical expert opinion; distribution based on assumption Clinical expert opinion; distribution based on assumption Average between Pellacani et *al*. 2014[45] and Ferrari *et al.* 2014[47]; distribution based on assumption Determined by overall prevalence of melanoma in

• monitored	0.04	distributions	equivocal lesions, proportion of those excised under routine management, and ratio of prevalence of melanoma in lesions excised : monitored under routine management
Waiting time for biopsy results (weeks)	2	No distribution assigned	Clinical expert advice
Diagnostic accuracy of VivaScope			
Alarcon *et al.*, 2014			
Sensitivity	0.978	Beta; α=90, β=2	[33]; data for VivaScope 1500; diagnostic accuracy of VivaScope 3000 assumed to be the same
Specificity	0.948	Beta; α=238, β=13	
Pellacani *et al.*, 2014			
Sensitivity in highly suspicious lesions	1.000	Beta; α=43, β=1	[45]; data for VivaScope 1500; diagnostic accuracy of VivaScope 3000 assumed to be the same; uninformative prior distribution applied in sensitivity (both types of lesions) to deal with zero observations in β
Specificity in highly suspicious lesions	0.518	Beta; α=73, β=68	
Sensitivity in moderately/low suspicious lesions	1.000	Beta; α=26, β=1	
Specificity in moderately//low suspicious lesions	0.802	Beta; α=227, β=56	
Diagnostic accuracy of biopsy			
Sensitivity	1.000	No distributions assigned	Considered to be the gold standard for diagnosis
Specificity	1.000		
Diagnostic accuracy of monitoring			
Sensitivity	0.900	Beta; α=81, β=9	[84]
Specificity	0.734	Beta; α=1118, β=406	
Proportion of melanomas in situ among melanomas prevalent in equivocal lesions [remaining are stage I]	0.60	Beta; α=60, β=40	Review of studies and clinical expert opinion; distribution based on assumption
Sub-stages within melanoma stages			
Proportion of stage Ia melanomas among stage I	0.515	Beta; α=9,452, β=8,918	[85]
Proportion of stage IIa melanomas among stage II	0.501	Dirichlet (4,644, 3,228, 1,397)	
Proportion of stage IIb melanomas among stage II	0.348	Dirichlet (4,644, 3,228, 1,397)	
Proportion of stage IIc melanomas among stage II	0.151	Dirichlet (4,644, 3,228, 1,397)	
Transitions of people with unidentified melanomas			
Progression to next stage	0.153	Dirichlet (15.3, 35.0, 49.7)	Based on data reported in [86] and further assumptions; distribution based on assumption
Identification	0.350	Dirichlet (15.3, 35.0, 49.7)	
Remaining unidentified	0.497	Dirichlet (15.3, 35.0, 49.7)	

Mortality			
5-year mortality - melanoma stage Ia	General population	No distribution assigned	For melanoma stage Ia: UK general population mortality was assumed, based on [87]; age- and gender-specific data utilized; for all other melanoma stages: Balch et al.;[85] annual probability of death estimated assuming exponential survivor function
5-year mortality - melanoma stage stage Ib	0.920	Beta; α=8,205, β=713	
5-year mortality - melanoma stage stage IIa	0.810	Beta; α=3,762, β=882	
5-year mortality - melanoma stage stage IIb	0.700	Beta; α=2,260, β=968	
5-year mortality - melanoma stage stage IIc	0.530	Beta; α=740, β=657	
10-year mortality - melanoma stage stage Ia	General population	No distribution assigned	For melanoma stage Ia: UK general population mortality was assumed, based on [87]; age- and gender-specific data utilized; for all other melanoma stages: Balch et al.;[85] annual probability of death estimated assuming exponential survivor function and taking into account 5-year mortality
10-year mortality - melanoma stage stage Ib	0.860	Beta; α=7,669, β=1,249	
10-year mortality - melanoma stage stage IIa	0.670	Beta; α=3,111, β=1,533	
10-year mortality - melanoma stage stage IIb	0.570	Beta; α=1,840, β=1,388	
10-year mortality - melanoma stage stage IIc	0.390	Beta; α=545, β=852	
Utility values and related variables			
Melanoma-related			
Stage 0/Ia - treatment	0.687	Beta; α=271.8, β=123.8	[55]; distributions determined by method of moments using data reported in the publication; all values adjusted for age; data for stages 0/Ia and Ib/II used to estimate a disutility for stages 0-II, assuming 1 month treatment for stages 0/Ia and 2 months treatment for stages Ib/II. More details in text.
Stage 0/Ia - remission	0.809	Beta; α=381.5, β=90.1	
Stage Ib/II - treatment	0.579	Beta; α=62.4, β=45.4	
Stage Ib/II - remission	0.802	Beta; α=350.4, β=86.5	
Stage IV - treatment	0.583	Beta; α=157.1, β=112.3	
General population			
Age 50-59 years	0.798	Beta; α=10,500.0, β=2,657.9	[90]; distributions determined by method of moments using data reported in the publication
Age 60-69 years	0.774	Beta; α=8,900.7, β=2,598.9	
Age 70-79 years	0.723	Beta; α=6,029.9, β=2,310.2	
Age 80 years and over	0.657	Beta; α=2,631.4, β=1,373.8	
Age coefficient	-0.00029	Normal; 95% CI: -0.0005917 to 0.0000129	[90]
Disutility due to first excision of non-melanomas	-0.002		Based on assumption and data reported in [60]
Disutility due to anxiety while waiting for biopsy results	-0.505	1 - beta; α=827.7, β=1.66 1 - beta; α=3,787.0, β=3,863.5	Based on the UK EQ-5D valuation equation;[65] distribution based on assumption; applied for 2 weeks
% with permanent disutility from scarring (head or neck)	0.15	Beta; α=15, β=85	Clinical expert opinion; distribution based on assumption
Probability of simple closure/scar in first excision	1		Clinical expert opinion; distribution based on assumption
Probability of simple closure/scar in wider excision	0.90	No distribution assigned Beta; α=90, β=10	
Disutility due to simple closure	-0.016		[60]; distributions determined by method of moments using data reported in the publication
Disutility due to complex closure	-0.026	1 - beta; α=609.2, β=9.9	

		1 - beta; α=296.3, β=7.9	
Disutility due to scar 1st excision - permanent	-0.016		
Disutility due to scar 2nd excision - permanent	-0.017	Determined by distributions of linked variables	
Costs			
Excision & biopsy	£151		[68]; for relevant NHS reference cost codes see text; distributions based on assumptions
Monitoring or follow-up visit	£93	Gamma; SE = 0.1 x mean	
Wide excision	£943	Gamma; SE = 0.1 x mean	
Sentinel lymph node biopsy	£1,033	Gamma; SE = 0.1 x mean	
		Gamma; SE = 0.1 x mean	
Terminal disease	£16,139		Estimated using data reported in the NICE STA of ipilimumab; distribution based on assumption
		Gamma; SE = 0.1 x mean	
Newly identified melanomas			
GP visit	£67		[67], [68]; for relevant NHS reference cost codes see text; distributions based on assumptions
Dermatology first visit	£109	Gamma; SE = 0.1 x mean	
1st excision & biopsy cost	£151	Gamma; SE = 0.1 x mean	
		Gamma; SE = 0.1 x mean	
DIAGNOSTIC ASSESSMENT MODEL ON SUSPECTED BASAL CELL CARCINOMAS			
Mean age of the study population	63 years	N/A	Based on a review of studies and clinical expert advice
Proportion of men in the study population	0.53	Beta; α=2,508, β=2,240	[78]
Proportion of BCCs on head or neck	0.69	Beta; α=915, β=403	[80]
Number of suspected/diagnosed BCCs per person	1.09	Gamma; SE = 0.1 x mean	[79]; distribution based on assumption, value imposed to be ≥ 1
Prevalence of BCC in lesions found positive or equivocal in dermoscopy	0.95	Beta; α=95, β=5	Clinical expert opinion; distribution based on assumption
Waiting time for biopsy results (weeks)	6	No distribution assigned	Clinical expert advice
Diagnostic accuracy of VivaScope 1500			
Sensitivity	1.000	Beta; α=46, β=1	[96]; uninformative prior distribution applied in sensitivity to deal with zero observations in β
Specificity	0.778	Beta; α=7, β=2	
Diagnostic accuracy of VivaScope 3000			
Sensitivity	0.933	Beta; α=42, β=3	[96]

Specificity	0.778	Beta; α=7, β=2	
Diagnostic accuracy of biopsy			
Sensitivity	1.000	No distributions assigned	Considered to be the gold standard for diagnosis
Specificity	1.000		
Utility values and related variables			
Disutility due to diagnostic biopsy	-0.002	1 - beta; α=827.7, β=1.7	Based on assumption and data reported in [60];
Disutility due to surgical or unnecessary treatment	-0.004	1 - beta; α=411.7, β=1.7	estimated using method of moments
Disutility due to anxiety while waiting for biopsy results	-0.071	1 - beta; α=531.6, β=40.6	Based on the UK EQ-5D valuation equation;[65] distribution based on assumption; applied for 6 weeks
% with permanent disutility from scarring			
• due to biopsy (head or neck)	0.05	Beta; α=5, β=95	Clinical expert opinion; distributions based on assumption
• due to surgical treatment (head or neck)	0.15	Beta; α=15, β=85	
Probability of simple closure/scar			
• suspected BCC biopsy	1	No distribution assigned	Clinical expert opinion; distributions based on assumption
• BCC surgical excision	0.75	Beta; α=75, β=25	
• BCC Mohs surgery	0.50	Beta; α=50, β=50	
Disutility due to simple closure	-0.016	1 - beta; α=609.2, β=9.9	[60]; distributions determined by method of moments using data reported in the publication
Disutility due to complex closure	-0.026	1 - beta; α=296.3, β=7.9	
Disutility due to scar from biopsy - permanent	-0.016	Determined by distributions of linked variables	
Disutility due to scar from surgical treatment - permanent	-0.019		
Resource use			
<u>Surgical treatment of BCC</u>			
% of BCC treatment that is surgical	0.75	Beta; α=75, β=25	Clinical expert advice; distributions based on assumptions
% of surgical excision in BCC surgical treatment	0.85	Beta; α=85, β=15	
<u>No surgical treatment of BCC</u>			
% imiquimod	0.30	Dirichlet; (30, 21, 19, 30)	Published audit data[99] modified following clinical expert advice
% photodynamic therapy	0.21	Dirichlet; (30, 21, 19, 30)	
% radiotherapy	0.19	Dirichlet; (30, 21, 19, 30)	
% 5-fluorouracil	0.30	Dirichlet; (30, 21, 19, 30)	
Costs			
Diagnostic biopsy	£134	Gamma; SE = 0.1 x mean	Cost of procedures based on [68], except cost of radiotherapy, which was based on clinical expert opinion; cost of drugs from [66]; for details see Table
Surgical excision	£388	Gamma; SE = 0.1 x mean	
Mohs surgery	£943	Gamma; SE = 0.1 x mean	

Imiquimod 5-Fluorouracil Radiotherapy Photodynamic therapy BCC treatment cost	£142 (£49+£93) £126 (£39+£93) £753 £1,303 £475	For £93: Gamma; SE = 0.1 x mean For £93: Gamma; SE = 0.1 x mean Gamma; SE = 0.1 x mean Gamma; SE = 0.1 x mean Determined by distributions of linked variables	33
MARGIN DELINEATION MODEL ON LENTIGO MALIGNAS PRIOR TO SURGICAL TREATMENT			
Mean age of the study population	70 years	NA	Based on a review of studies and clinical expert advice
Proportion of men in the study population	0.64	Beta; α=93, β=52	[73]
Proportion of lentigo malignas on head or neck	0.70	Beta; α=70, β=30	Clinical expert opinion
Number of lentigo malilgnas per person	1	No distribution assigned	Clinical expert advice
Incomplete surgical excision • Mapping with VivaScope 3000 • Routine management	 0.12 0.30	 Beta; α=2, β=15 Beta; α=30, β=70	[38] Based on a review of studies and clinical expert opinion; distribution based on assumptions
Number of stages in Mohs surgery • Mapping with VivaScope 3000 • Routine management	 1.40 2.22	 Normal; N=7; SD=0.53 Normal; N=9; SD=1.2	[106]
Annual recurrence of lentigo maligna • Surgical excision • Mohs surgery (*applied also to recurrence after mapping with VivaScope 3000, regardless of type of surgical treatment*)	 0.032 0.010	 Beta; α=3.2, β=96.8 Beta; α=1, β=99	 Based on a review of studies, clinical expert opinion and further assumptions
Utility values and related variables Disutility due to surgical treatment	-0.004	1 - beta; α=411.7, β=1.7	[60]; estimated using method of moments
% with permanent disutility from scarring due to surgical treatment (head or neck)	0.15	Beta; α=15, β=85	Clinical expert opinion; distribution based on assumption
Probability of simple closure/scar in surgical	0.50	Beta; α=50, β=50	Clinical expert opinion; distribution based on

treatment of lentigo maligna			assumption
Disutility due to simple closure	-0.016	1 - beta; α=609.2, β=9.9	[60]; distributions determined by method of moments using data reported in the publication
Disutility due to complex closure	-0.026	1 - beta; α=296.3, β=7.9	
Disutility due to scar from surgical treatment - permanent	-0.021	Determined by distributions of linked variables	
Resource use			
Dermatologist's time for routine mapping (minutes)	5	Normal; SE: 0.1 x mean	Clinical expert opinion; distribution based on assumption, a minimum value of 3 minutes imposed
<u>% of surgical excision in surgical treatment</u>			
First surgical treatment	0.85	Beta; α=85, β=15	Clinical expert advice; distributions based on assumptions
Surgical treatment following recurrence	0.80	Beta; α=80, β=20	
Mean number of stages in Mohs surgery	1.6	No distribution assigned	[107]
Costs			
Routine mapping with dermoscopy	£12	Determined by distribution of dermatologist's time for routine mapping	
Surgical excision			
Mohs surgery (70% of cost assumed to be fixed, 30% of cost attributed to 1.6 stages)	£388 £943	Gamma; SE = 0.1 x mean Gamma; SE = 0.1 x mean	[68]; more details on relevant NHS codes provided in text; distributions based on assumptions
UK general population mortality risk (applied across all models as appropriate)	Available in [87]	No distribution assigned	Based on UK national mortality statistics UK;[87] age- and gender-specific data utilised
Annual discount rate	0.035	No distribution assigned	As recommended by NICE[64]

Abbreviations used in table: AfC, Agenda for Change; BCC, basal cell carcinoma; NA, not applicable; NHS, national health service; SE, standard error; STA, single technology appraisal

Table 37 provides the mean and the range of values of the most influential model input parameters depicted in Tornado diagrams, together with a justification of the extreme values used for each parameter.

Table 37. Most influential model input parameters depicted in Tornado diagrams, with mean values and extreme values used in one-way sensitivity analysis

Input parameter	Mean value	Low value	High value	Justification of range
Annual volume of lesions eligible for examination with VivaScope				
Suspected melanomas	100	70	130	±30% of the mean value (assumption)
Suspected BCCs	500	250	750	
Lentigo malignas prior to surgery	75	52.5	97.5	
Diagnostic assessment of suspected melanomas				
Prevalence of melanoma in equivocal lesions	0.15	0.075	0.225	±50% of the mean value (assumption)
Proportion of equivocal lesions excised under routine management	0.67	0	1	Whole plausible range tested
VivaScope sensitivity, Alarcon *et al*.	0.978	0.924	0.997	[33]; 95% CIs
VivaScope specificity, Alarcon *et al*.	0.948	0.913	0.972	
VivaScope sensitivity, highly suspicious lesions, Pellacani *et al*.	1.000	0.915	1.000	[45]; 95% CIs
VivaScope specificity, highly suspicious lesions, Pellacani *et al*.	0.518	0.432	0.6026	
VivaScope sensitivity, moderately/low suspicious lesions, Pellacani *et al*.	1.000	0.862	1.000	
VivaScope specificity, moderately/low suspicious lesions, Pellacani *et al*.	0.802	0.751	0.847	
Disutility due to first excision of non-melanomas	-0.002	-0.004	-0.001	Lower value assumed to be equal to disutility from wide excision; upper value based on assumption
Disutility due to anxiety while waiting for biopsy results	-0.505	-0.556	-0.051	Lower value assumed to be 10% lower than the mean; upper value assumed to be 10% of the mean
% with permanent disutility from scarring (head or neck)	0.15	0	1	Whole plausible range tested
Disutility due to scar 1st excision - permanent	-0.016	-0.032	-0.001	Lower value assumed to be 100% lower than the mean; upper value based on assumption
Cost of excision & biopsy	£151	£106	£196	±30% of the mean value (assumption)
Diagnostic assessment of suspected BCCs				
Number of suspected/diagnosed BCCs per person	1.09	1	1.60	Lower value lowest possible value; upper value based on [96]
Prevalence of BCC in lesions found positive or equivocal in dermoscopy	0.95	0.83	0.99	Lower value taken from [96]; upper value based on assumption
Sensitivity of VivaScope 3000	0.933	0.821	0.977	[96]; 95% CIs
Disutility due to diagnostic biopsy	-0.002	-0.004	-0.001	Lower value assumed to be equal to disutility from surgical treatment; upper value based on assumption
Disutility due to anxiety while waiting for biopsy results	-0.071	-0.142	-0.007	Lower value assumed to be 100% lower than the mean; upper value assumed to be 10% of the mean
% with permanent disutility from scarring due to biopsy (head or neck)	0.05	0	0.80	Assumption
% with permanent disutility from scarring due to surgical treatment (head or neck)	0.15	0	0.80	Assumption
Permanent disutility due to scar from biopsy	-0.016	-0.032	-0.001	Lower value assumed to be 100% lower than the mean; upper value based on

				assumption
% of BCC treatment that is surgical	0.75	0.60	0.95	Assumptions based on discussions with clinical experts
Cost of diagnostic biopsy	£134	£94	£174	±30% of the mean value (assumption)
Margin delineation of lentigo malignas				
VivaScope mapping - incomplete surgical excision	0.12	0.033	0.343	[38]; 95% CIs
Routine management - incomplete surgical excision	0.30	0.15	0.45	±50% of the mean value (assumption)
Routine management - number of Mohs stages	2.22	1.44	3.00	[106]; 95% CIs
Routine management - annual recurrence after surgical excision	0.032	0.012	0.048	Lower value based on [105]; upper value assumed to be 50% higher than the mean
VivaScope mapping - annual recurrence after surgical excision	0.010	0.002	0.015	Lower value based on [105]; upper value assumed to be 50% higher than the mean
Disutility due to surgical treatment	-0.004	-0.008	-0.001	Lower value assumed to be 100% lower than the mean; upper value based on assumption
% with permanent disutility from scar due to surgical treatment (head or neck)	0.15	0	0.80	Assumption
Permanent disutility due to scar from surgical treatment	-0.021	-0.042	-0.001	Lower value assumed to be 100% lower than the mean; upper value based on assumption
VivaScope – mapping time (min)	30	15	45	±50% of the mean value (assumption)
Cost of surgical excision	£388	£271	£504	±30% of the mean value (assumption)
Abbreviations used in table: BCC, basal cell carcinoma; CI, confidence interval				

5.2.5.3 Additional scenarios tested in one-way sensitivity analysis

Further to Tornado diagrams, which depicted the impact of the most influential input parameters on the results of the economic analysis, additional sensitivity analyses were carried out to explore the robustness of the results under alternative scenarios and model assumptions. The following alternative scenarios were explored:

Relating to the cost of VivaScope examination:

- The estimated staff time cost for diagnosis of skin lesions suspected for cancer was replaced by the NHS reference cost of £47 for a direct access ultrasound scan of less than 20 minutes, as a proxy;[68] the estimated staff time cost for mapping of skin lesions prior to surgical treatment was replaced by the NHS reference cost of £109 for a consultant-led, outpatient, dermatology first visit;[68]
- the cost associated with training was doubled, to account for the extra training required over the first few months in order for dermatologists to gain experience in the clinical interpretation of the results obtained from the examination of lesions with VivaScope. In addition, the useful time of training was reduced to 5 years.

Relating to the diagnostic model on suspected melanomas:

- People waiting for the results of biopsy were assumed to experience moderate rather severe anxiety; therefore a much lower disutility of anxiety of -0.071 was used in this scenario, as estimated from the health state valuation equation provided by Dolan (1997) for EQ-5D,[65] rather the value of -0.505 that was used in the base-case analysis.

Relating to the diagnostic model on suspected BCCs:

- Clinical experts advised that, in reality, not all suspected BCCs receive diagnostic biopsy following dermoscopy, but some move on directly to treatment. Therefore, a scenario was tested where only 70% of suspected BCCs received a diagnostic biopsy under routine care, i.e. only the 70% of the diagnostic biopsy cost was applied and only 70% of people were assumed to experience disutility associated with biopsy and permanent scarring following biopsy on head or neck (unless surgical treatment was received). For simplicity, it was assumed that the percentage of 70% of suspected BCCs that received diagnostic biopsy did not distinguish between true BCCs and no BCCs, in other words, both suspected BCC lesions that proved to be BCCs and suspected BCCs that were not actually BCCs were subject to a 0.7 probability of biopsy under this scenario.

In addition to the above scenarios, the ICERs obtained in each model were plotted against different values of the annual volume of each type of lesion examined with VivaScope (i.e. equivocal lesions suspected for melanoma, suspected BCCs that give a positive or equivocal finding in dermoscopy, and lentigo malignas prior to surgical treatment) to identify the minimum number of each type of lesions that is required to be examined with VivaScope per year, so that examination with VivaScope is a cost-effective strategy.

Finally, for the diagnostic model on suspected melanomas that utilised diagnostic accuracy data from Pellacani *et al*. (2014),[45] the impact of the percentage of the suspected melanomas with an equivocal finding in dermoscopy that were excised (i.e. because they were highly suspicious) on the results was assessed by plotting the ICER obtained in the respective analysis against the whole range of the probability of suspected melanomas being excised (i.e. 0-100%). This was decided because the percentage of the suspected melanomas that were excised on the results of the analysis had a two-fold impact:

- An increase in the percentage of suspected melanomas that were excised led to a lower diagnostic accuracy of VivaScope examination, as Pellacani *et al*. (2014)[45] reported a lower specificity for VivaScope in lesions that were chosen for excision as highly suspicious following dermoscopy than the specificity of VivaScope in less suspicious lesions that were selected for monitoring based on the results of dermoscopy. Consequently, an increase in the percentage of suspected melanomas being excised reduced the benefit of VivaScope in the model;
- at the same time, an increase in the percentage of suspected melanomas that were excised led to an increase in the cost of routine management (as the cost of excision is higher than the cost of monitoring) and an increase in the disutility due to excision, permanent disutility due

to scarring (relevant to lesions on the head or neck), and disutility due to anxiety while waiting for the results. Consequently, an increase in the percentage of suspected melanomas that being excised increased the cost of routine management and reduced its benefit.

5.2.6 Results of economic modelling

5.2.6.1 Base-case deterministic and probabilistic results

The base-case deterministic and probabilistic results for each of the economic models and analyses considered for this report are provided in Table 38 to Table 47 below. For each type of lesions different cost and cost effectiveness results are presented, depending on the type of lesions expected to be examined with VivaScope; the latter determined the cost of VivaScope, as the total cost associated with acquisition and use of the device was spread across the annual volume of lesions examined with VivaScope in order to determine a cost per lesion.

Results of the diagnostic model of suspected melanomas are presented in Table 38 and Table 39 (results derived when diagnostic data from Alarcon *et al*.[33] were utilised) and in Table 40 and Table 41 (results derived when diagnostic data from Pellacani *et al*.[45] were utilised). It can be seen that under use of the more optimistic diagnostic data from Alarcon *et al*.[33] VivaScope appears to be cost-effective in the diagnostic assessment of suspected melanomas with an equivocal finding in dermoscopy, even when VivaScope is exclusively used for this purpose (with an ICER of £8,877/QALY in deterministic analysis and £9,362/QALY in probabilistic analysis). On the other hand, use of the diagnostic data from Pellacani *et al*.[45] resulted in an ICER of £19,095/QALY in deterministic analysis and £25,453/QALY in probabilistic analysis when VivaScope was considered only for the diagnostic assessment of equivocal lesions suspected for melanoma. Nevertheless, if VivaScope is expected to be used in the diagnostic assessment of both suspected melanomas and suspected BCCs, or also in the mapping of lentigo malignas prior to surgical treatment, then VivaScope becomes dominant in the diagnostic assessment of melanomas, as the cost associated with its use is spread across a larger number of sessions, leading to the total cost associated with VivaScope examination in the economic model being lower that the total cost associated with routine management of equivocal lesions suspected for melanoma.

Table 38. Diagnostic model of suspected melanomas - results of deterministic analysis based on diagnostic data from Alarcon *et al*.[33] Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for melanoma diagnosis	£517.23	13.222
	VivaScope use for diagnosis	£326.52	
	VivaScope use for all indications	£322.28	
Routine management		£379.24	13.206
Incremental	VivaScope use only for melanoma diagnosis	£137.99	0.016
	VivaScope use for diagnosis	-£52.71	
	VivaScope use for all indications	-£56.95	
Cost effectiveness	VivaScope use only for melanoma diagnosis	£8,877/QALY	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

Table 39. Diagnostic model of suspected melanomas - results of probabilistic analysis based on diagnostic data from Alarcon *et al*.[33] Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for melanoma diagnosis	£524.82	13.222
	VivaScope use for diagnosis	£327.83	
	VivaScope use for all indications	£323.35	
Routine management		£379.52	13.206
Incremental	VivaScope use only for melanoma diagnosis	£145.31	0.016
	VivaScope use for diagnosis	-£51.69	
	VivaScope use for all indications	-£56.16	
Cost effectiveness	VivaScope use only for melanoma diagnosis	£9,362/QALY	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

Table 40. Diagnostic model of suspected melanomas - results of deterministic analysis based on diagnostic data from Pellacani *et al*.[45] Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for melanoma diagnosis	£556.27	13.215
	VivaScope use for diagnosis	£365.56	
	VivaScope use for all indications	£361.32	
Routine management		£379.24	13.206
Incremental	VivaScope use only for melanoma diagnosis	£177.03	0.009
	VivaScope use for diagnosis	-£13.67	
	VivaScope use for all indications	-£17.91	
Cost effectiveness	VivaScope use only for melanoma diagnosis	£19,095/QALY	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

Table 41. Diagnostic model of suspected melanomas - results of probabilistic analysis based on diagnostic data from Pellacani *et al*.[45] Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for melanoma diagnosis	£566.91	13.214
	VivaScope use for diagnosis	£369.63	
	VivaScope use for all indications	£365.12	
Routine management		£379.40	13.207
Incremental	VivaScope use only for melanoma diagnosis	£187.51	0.007
	VivaScope use for diagnosis	-£9.78	
	VivaScope use for all indications	-£14.29	
Cost effectiveness	VivaScope use only for melanoma diagnosis	£25,453/QALY	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

VivaScope was shown to be the dominant strategy when used for the assessment of suspected BCCs, regardless of its estimated use exclusively for this purpose or for the assessment of suspected melanomas and lentigo malignas as well (Table 42 and Table 43). Consideration of use of VivaScope for other indications, further to its use on the diagnostic assessment of suspected BCCs had little impact on the results, since the annual volume of suspected BCCs is much higher that the annual volume of other lesions expected to be examined with VivaScope, and therefore this volume of

suspected BCCs drives the cost per lesion examined with BCC and, subsequently, the cost effectiveness results.

Table 42. Diagnostic model of suspected BCCs - results of deterministic analysis. Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for BCC diagnosis	£585.82	-0.025
	VivaScope use for diagnosis	£577.50	
	VivaScope use for all indications	£572.88	
Routine management		£637.92	-0.036
Incremental	VivaScope use only for BCC diagnosis	-£52.10	0.011
	VivaScope use for diagnosis	-£60.42	
	VivaScope use for all indications	-£65.04	
Cost effectiveness	VivaScope use only for BCC diagnosis	VivaScope dominant	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

Table 43. Diagnostic model of suspected BCCs - results of probabilistic analysis. Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for BCC diagnosis	£594.93	-0.025
	VivaScope use for diagnosis	£585.85	
	VivaScope use for all indications	£580.91	
Routine management		£644.87	-0.036
Incremental	VivaScope use only for BCC diagnosis	-£49.93	0.011
	VivaScope use for diagnosis	-£59.02	
	VivaScope use for all indications	-£63.96	
Cost effectiveness	VivaScope use only for BCC diagnosis	VivaScope dominant	
	VivaScope use for diagnosis	VivaScope dominant	
	VivaScope use for all indications	VivaScope dominant	

Regarding margin delineation of lentigo malignas, mapping with VivaScope was shown to be cost-effective, even if it used exclusively for this purpose, as indicated by an ICER of £10,241/QALY obtained in deterministic analysis (Table 44) and £11,651/QALY in probabilistic analysis (Table 45). When use of VivaScope was expanded to other indications covered in this economic analysis, then VivaScope became the dominant option.

Table 44. Margin delineation model of lentigo malignas - results of deterministic analysis. Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for LM mapping	£801.98	-0.034
	VivaScope use for all indications	£657.12	
Routine management		£731.24	-0.041
Incremental	VivaScope use only for LM mapping	£70.75	0.007
	VivaScope use for all indications	-£74.12	
Cost effectiveness	VivaScope use only for LM mapping	£10,241/QALY	
	VivaScope use for all indications	VivaScope dominant	

Table 45. Margin delineation model of lentigo malignas - results of probabilistic analysis. Costs and QALYs per person.

Intervention	Total cost		Total QALYs
VivaScope examination	VivaScope use only for LM mapping	£809.69	-0.034
	VivaScope use for all indications	£659.55	
Routine management		£731.16	-0.040
Incremental	VivaScope use only for LM mapping	£78.53	0.007
	VivaScope use for all indications	-£71.60	
Cost effectiveness	VivaScope use only for LM mapping	£11,651/QALY	
	VivaScope use for all indications	VivaScope dominant	

Overall, in the analyses that combined the different 'part' models designed for this report, VivaScope was shown to be the dominant strategy over routine management in the diagnostic assessment of suspected melanomas and BCCs (Table 46) and in the diagnostic assessment of suspected melanomas and BCCs combined with margin delineation of lentigo malignas prior to surgical treatment (Table 47). The tables show the deterministic results, but probabilistic results were very similar.

Table 46. Analysis on the use of VivaScope in the diagnostic assessment of suspected melanomas and BCCs - results of deterministic analysis. Costs and QALYs per person.

Intervention	Total cost	Total QALYs
VivaScope examination	£532.56	2.347
Routine management	£591.60	2.335
Incremental	-£59.04	0.012
Cost effectiveness	VivaScope dominant	

Table 47. Diagnostics and margin delineation model, considering the use of VivaScope for the diagnostic assessment of suspected melanomas and BCCs as well as presurgical mapping of lentigo malignas - results of deterministic analysis. Costs and QALYs per person.

Intervention	Total cost	Total QALYs
VivaScope examination	£543.29	2.065
Routine management	£608.13	2.054
Incremental	-£64.84	0.011
Cost effectiveness	VivaScope dominant	

The cost-effectiveness planes of all the probabilistic analyses undertaken for this assessment are provided in Appendix 9.7.

The CEACs for each part model considered in the analysis are provided in Figure 9 to Figure 12. Figure 9 indicates that, using the diagnostic accuracy data from Alarcon *et al*.,[33] the probability of VivaScope being cost-effective in the diagnostic assessment of suspected melanomas is zero at a zero willingness-to-pay (WTP) per QALY gained, but reaches 0.99 at the lower NICE cost-effectiveness threshold of £20,000/QALY, when VivaScope is used only for this purpose (i.e. diagnostic assessment of suspected melanomas). When VivaScope is used for the diagnostic assessment of suspected melanomas and BCCs or a combination of diagnosis of suspected melanomas and BCCs

and pre-surgical margin delineation of lentigo malignas, then its probability of being cost-effective in the diagnosis of suspected melanomas is 1 and is independent of the level of WTP considered.

Figure 9. Cost-effectiveness acceptability curve – diagnostic model on suspected melanomas, diagnostic data based on Alarcon *et al*.[33]

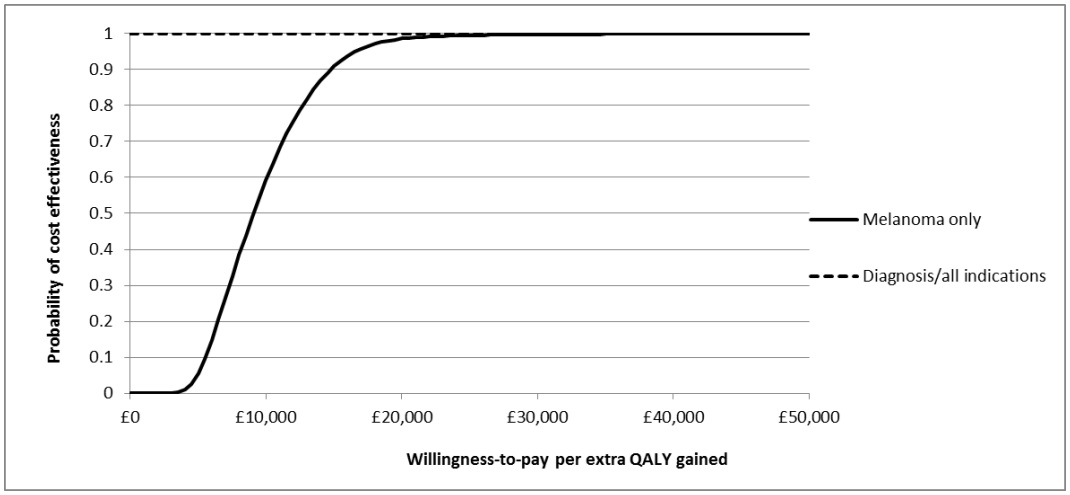
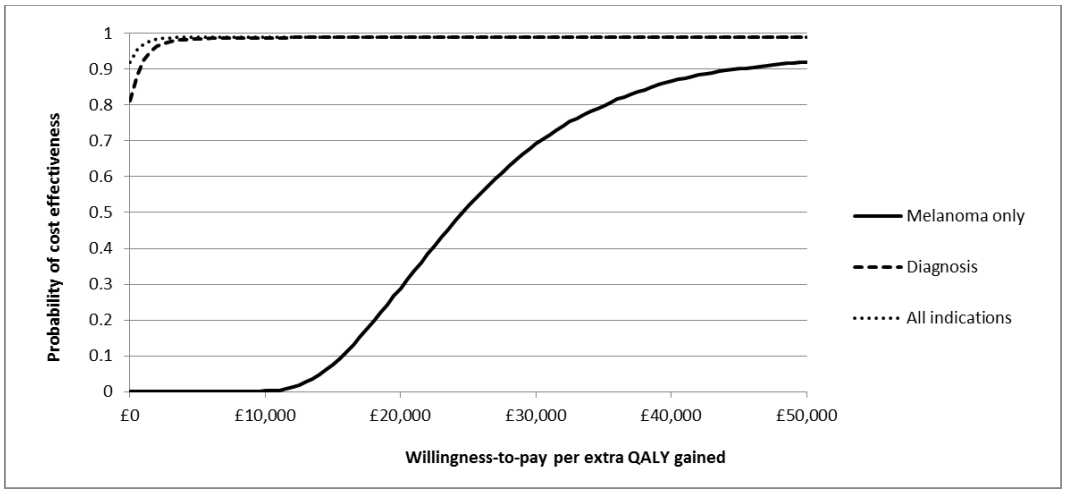


Figure 10 shows the CEAC derived when using the diagnostic accuracy data for suspected melanomas from Pellacani *et al*.[45] In this case the probability of VivaScope being cost-effective when used exclusively in the diagnostic assessment of suspected melanomas is 0.29 and 0.69 at the lower and upper NICE cost-effectiveness threshold, respectively. When the use of VivaScope is expanded to the diagnostic assessment of suspected BCCs or all indications examined in this analysis, its probability of cost-effectiveness in the diagnostic assessment of suspected melanomas reaches 0.99 at the NICE lower cost-effectiveness threshold of £20,000/QALY.

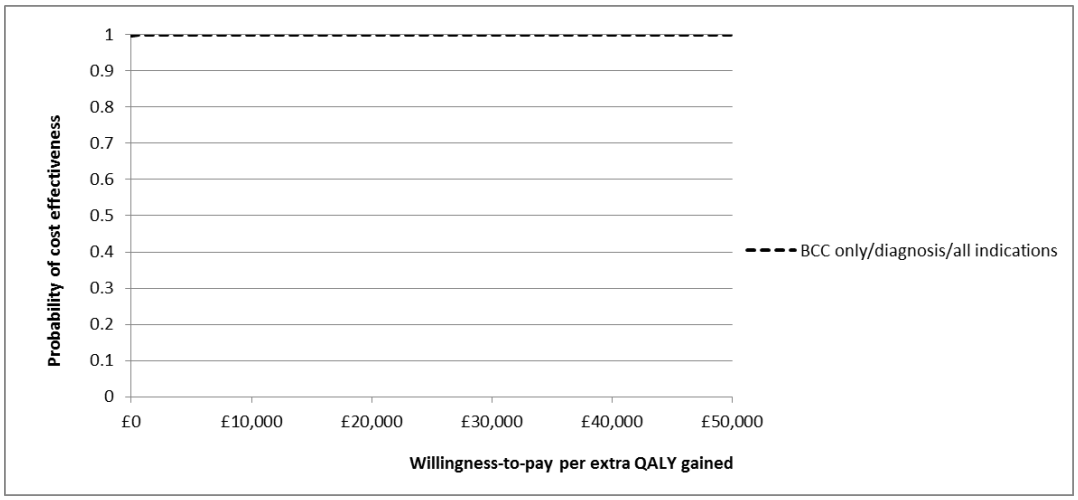
Figure 10. Cost-effectiveness acceptability curve – diagnostic model on suspected melanomas, diagnostic data based on Pellacani *et al*.[45]



Regarding the probability of cost-effectiveness of VivaScope in the diagnostic assessment of suspected BCCs, Figure 11 shows that this is 1, regardless of whether VivaScope is used exclusively

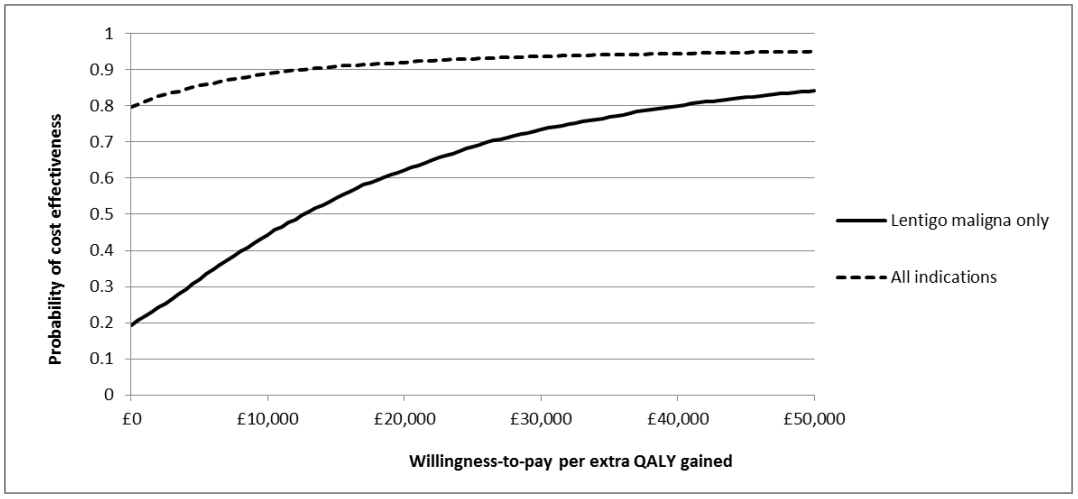
for this purpose or its use is expanded to other indications examined in this economic evaluation, and is independent of the cost-effectiveness threshold used.

Figure 11. Cost-effectiveness acceptability curve – diagnostic model on suspected BCCs



Finally, Figure 12 provides the CEAC for the model assessing the cost-effectiveness of VivaScope in the pre-surgical margin delineation of lentigo malignas. It shows that when VivaScope is used exclusively for this purpose, its probability of being cost-effective is 0.62 and 0.74 at the lower and upper NICE cost-effectiveness threshold, respectively. However, when VivaScope is used for all indications considered in economic modelling, its cost-effectiveness in the pre-surgical margin delineation of lentigo malignas improves, and its probability of being cost-effective rises up to 0.92 and 0.94 at the lower and upper NICE cost-effectiveness threshold, respectively.

Figure 12. Cost-effectiveness acceptability curve – pre-surgical margin delineation model on lentigo malignas



5.2.6.2 Results of one-way and two-way sensitivity analyses

One-way sensitivity analyses were performed on all input parameters that were given a probability distribution in the economic model. The Tornado diagrams that present the impact of the most influential input parameters on the results are shown in Appendix 9.7. It is evident that among the most influential parameters across all models are those relating to permanent disutility due to scarring (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy. Overall, the most influential parameters included:

In the diagnostic assessment of suspected melanomas:

- The percentage of people experiencing permanent disutility due to scarring;
- the disutility due to anxiety while waiting for the biopsy results;
- the percentage of equivocal lesions excised under routine management (this parameter was not considered in Tornado diagrams when Pellacani *et al*.[45] data were used, due to its two-fold impact on the results which would lead to a misleading picture in the Tornado diagram);
- the permanent disutility due to scarring from 1st excision;
- the annual volume of suspected melanomas eligible for examination for VivaScope (if VivaScope was used exclusively for examination of suspected melanomas);
- the VivaScope sensitivity and specificity;
- the prevalence of melanomas in equivocal lesions;
- the cost of first excision;
- the disutility due to first excision.

It needs to be noted that when VivaScope was assumed to be used exclusively for the diagnosis of suspected melanomas and diagnostic data from Alarcon *et al*.[33] were utilised, the only parameter that potentially resulted in negative INBs in the Tornado diagram was the disutility due to anxiety; when VivaScope was assumed to be used exclusively for the diagnosis of suspected melanomas and diagnostic data from Pellacani *et al*.[45] were utilised, then several parameters resulted in negative INBs. However, when use of VivaScope was assumed to expand to diagnosis of suspected BCCs as well, none of the influential parameters could result in a negative INMB. Tornado diagrams were not produced for the scenario of VivaScope being used for all indications suggested in this economic analysis, as results were expected to be similar to those produced when diagnosis of both suspected melanomas and suspected BCCs was informed by VivaScope.

In the diagnostic assessment of suspected BCCs:

- The percentage of people experiencing permanent disutility due to scarring from biopsy;
- the disutility due to anxiety while waiting for the results;
- the diagnostic biopsy cost;

- the prevalence of BCC in examined lesions;
- the permanent disutility due to scarring from biopsy;
- the annual volume of suspected BCCs that would be examined with VivaScope;
- the disutility due to biopsy;
- the percentage of patients treated with surgical therapy;
- the sensitivity of VivaScope 3000;
- the number of lesions per person;
- the percentage of people experiencing permanent disutility due to scarring from surgery.

However, none of the parameters had such an impact so as to turn the INMB to negative values, even when VivaScope was used exclusively in the diagnostic assessment of suspected BCCs. For this reason, Tornado diagrams relating to expansion of use of VivaScope for the assessment of other types of lesions were not produced, as expansion of use of VivaScope would only reduce the impact of influential parameters on the results even further.

In the pre-surgical mapping of lentigo malignas:

- the probability of incomplete surgical excision following routine mapping;
- the probability of annual recurrence after surgical excision;
- the probability of incomplete surgical excision following mapping with VivaScope;
- the permanent disutility due to scarring from surgical treatment;
- the percentage of people with permanent disutility from scarring;
- the probability annual recurrence following VivaScope mapping and surgical excision;
- the VivaScope mapping (staff) time;
- the cost of surgical excision;
- the number of Mohs stages under routine mapping;
- the disutility due to surgery.

As with the results for suspected melanomas, a number of influential parameters could turn the INMB into a negative value if VivaScope was used only for the mapping of lentigo malignas prior to surgical treatment. However, when a wider use of VivaScope was assumed, the INMB remained positive under any values of the influential parameters examined.

Results of the additional sensitivity analyses are shown in Table 48. It can be seen that results for suspected melanoma are negatively affected after application of relevant scenarios, when diagnostic accuracy data from Pellacani *et al.*[45] are used and VivaScope is assumed to be exclusively used for the diagnostic assessment of suspected melanomas. However, when wider use of VivaScope is assumed, the results are practically unaffected by the scenarios tested.

Table 48. Incremental cost effectiveness ratios derived from one-way sensitivity analyses testing alternative scenarios and assumptions.

Scenario	Intended use of VivaScope	ICER		
		suspected melanomas	suspected BCCs	lentigo malignas
Staff time cost for diagnosis replaced by ultrasound scan unit cost of £47; staff time cost for mapping replaced by outpatient dermatology visit of £109	Only for this purpose	£10,467/QALY (A) £21,761/QALY (P)	VivaScope dominant	£15,887/QALY
	Diagnosis	VivaScope dominant (A) £1,191/QALY (P)	VivaScope dominant	NA
	All indications	VivaScope dominant (A) £734/QALY (P)	VivaScope dominant	VivaScope dominant
VivaScope training cost doubled and its useful life reduced to 5 years	Only for this purpose	£12,451/QALY (A) £25,086/ QALY (P)	VivaScope dominant	£20,964/QALY
	Diagnosis	VivaScope dominant (A & P)	VivaScope dominant	NA
	All indications	VivaScope dominant (A & P)	VivaScope dominant	VivaScope dominant
Melanoma – moderate disutility due to anxiety while waiting for the results	Only for this purpose	£22,983/QALY (A) £40,943/QALY (P)	NA	NA
	Diagnosis	VivaScope dominant (A & P)	NA	NA
	All indications	VivaScope dominant (A & P)	NA	NA
Diagnostic biopsy assumed to be performed only in 70% of suspected BCCs	Only for this purpose	NA	VivaScope dominant	NA
	Diagnosis	NA	VivaScope dominant	NA
	All indications	NA	VivaScope dominant	NA

Abbreviations used in the table: BCC, basal cell carcinoma; NA, not applicable

(A) indicates use of diagnostic accuracy data for suspected melanomas from Alarcon *et al*. [33]

(P) indicates use of diagnostic accuracy data for suspected melanomas from Pellacani *et al*.[45]

Two-way sensitivity analyses were performed to test the impact of different combinations of sensitivity and specificity of VivaScope on its cost effectiveness in the diagnostic assessment of equivocal lesions suspected for melanoma. The results on the diagnosis of suspected melanomas are shown in Table 49 and Table 50. Results indicate that VivaScope needs to have a relatively high diagnostic accuracy in order to be cost-effective, in particular when it is used exclusively for the diagnostic assessment of suspected melanomas. A two-way sensitivity analysis for the diagnosis of suspected BCCs showed that any combination of sensitivity and specificity from values as low as 0.40 resulted in VivaScope being a cost-effective strategy (the maximum ICER, when sensitivity and specificity were 0.40, was £7,083/QALY).

Table 49. Two-way sensitivity analysis: cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas for different combinations of sensitivity and specificity – VivaScope used exclusively for this purpose

		Specificity of VivaScope										
		0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
Sensitivity of VivaScope	0.50	-£897	-£866	-£835	-£804	-£773	-£742	-£711	-£680	-£649	-£618	-£587
	0.55	-£814	-£783	-£752	-£721	-£690	-£659	-£628	-£597	-£566	-£535	-£504
	0.60	-£731	-£700	-£669	-£638	-£607	-£576	-£545	-£514	-£483	-£452	-£421
	0.65	-£649	-£618	-£587	-£556	-£525	-£494	-£463	-£432	-£401	-£370	-£339
	0.70	-£566	-£535	-£504	-£473	-£442	-£411	-£380	-£349	-£318	-£287	-£256
	0.75	-£483	-£452	-£421	-£390	-£359	-£328	-£297	-£266	-£235	-£204	-£173
	0.80	-£400	-£369	-£338	-£307	-£276	-£245	-£214	-£183	-£152	-£121	-£90
	0.85	-£317	-£286	-£255	-£224	-£193	-£162	-£131	-£100	-£69	-£38	-£7
	0.90	-£235	-£204	-£173	-£142	-£111	-£80	-£49	-£18	£13	£44	£75
	0.95	-£152	-£121	-£90	-£59	-£28	£3	£34	£65	£96	£127	£158
	1.00	-£69	-£38	-£7	£24	£55	£86	£117	£148	£179	£210	£241
All figures indicate incremental net monetary benefits of VivaScope versus routine management												

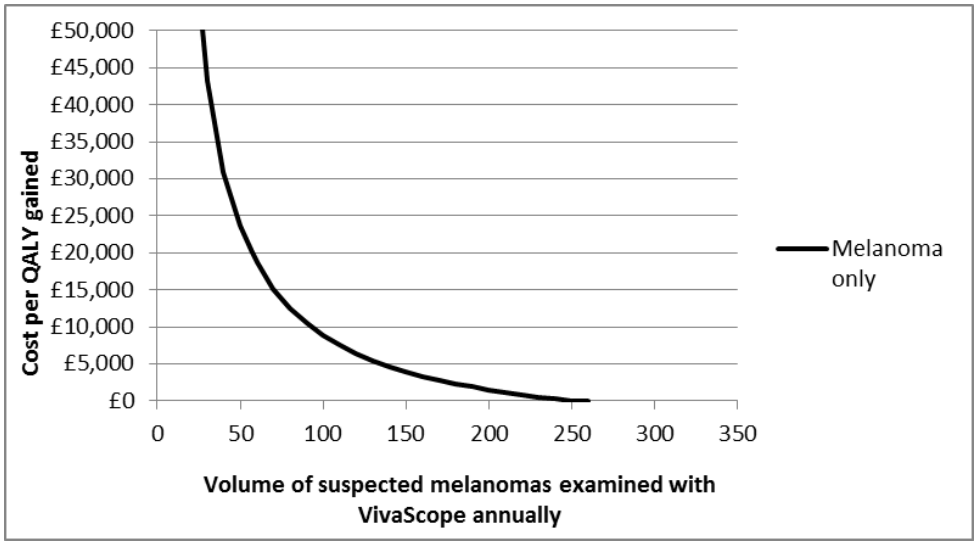
Table 50. Two-way sensitivity analysis: cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas for different combinations of sensitivity and specificity – VivaScope used for diagnosis of suspected melanomas or BCCs

		Specificity of VivaScope										
		0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
Sensitivity of VivaScope	0.50	-£706	-£675	-£644	-£613	-£582	-£551	-£520	-£489	-£458	-£427	-£396
	0.55	-£623	-£592	-£562	-£531	-£500	-£469	-£438	-£407	-£376	-£345	-£314
	0.60	-£541	-£510	-£479	-£448	-£417	-£386	-£355	-£324	-£293	-£262	-£231
	0.65	-£458	-£427	-£396	-£365	-£334	-£303	-£272	-£241	-£210	-£179	-£148
	0.70	-£375	-£344	-£313	-£282	-£251	-£220	-£189	-£158	-£127	-£96	-£65
	0.75	-£292	-£261	-£230	-£199	-£168	-£137	-£106	-£75	-£44	-£13	£18
	0.80	-£209	-£178	-£147	-£116	-£85	-£54	-£23	£8	£38	£69	£100
	0.85	-£127	-£96	-£65	-£34	-£3	£28	£59	£90	£121	£152	£183
	0.90	-£44	-£13	£18	£49	£80	£111	£142	£173	£204	£235	£266
	0.95	£39	£70	£101	£132	£163	£194	£225	£256	£287	£318	£349
	1.00	£122	£153	£184	£215	£246	£277	£308	£339	£370	£401	£432
All figures indicate incremental net monetary benefits of VivaScope versus routine management												

Figure 13, Figure 14 and Figure 15 show the ICERs obtained in each model plotted against different values of the annual volume of each type of lesion examined with VivaScope and help identify the minimum number of each type of lesions that is required to be examined with VivaScope per year, so that examination with VivaScope is a cost-effective strategy. For suspected melanomas and lentigo malignas only exclusive use of VivaScope for their examination is shown in the graphs, because consideration of wider use of VivaScope resulted in VivaScope being dominant in the diagnosis of suspected melanomas and mapping of lentigo malignas, respectively, even when a negligible number of lesions examined (close to zero) was assumed.

Figure 13. Incremental cost-effectiveness ratio plotted against annual volume of suspected melanomas examined with VivaScope – exclusive use of VivaScope for this purpose

A. Using data from Alarcon *et al*.[33]



B. Using data from Pellacani *et al*.[45]

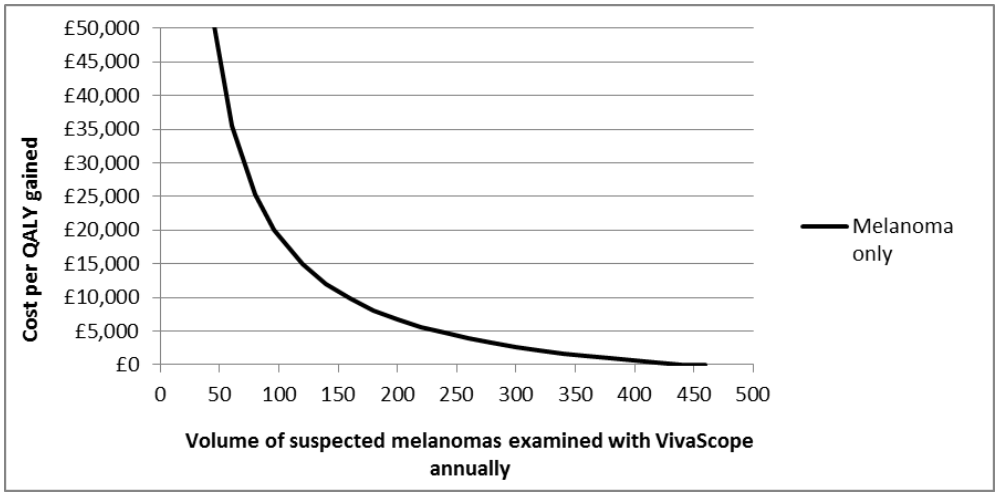


Figure 14. Incremental cost-effectiveness ratio plotted against annual volume of suspected BCCs examined with VivaScope – different uses of VivaScope considered

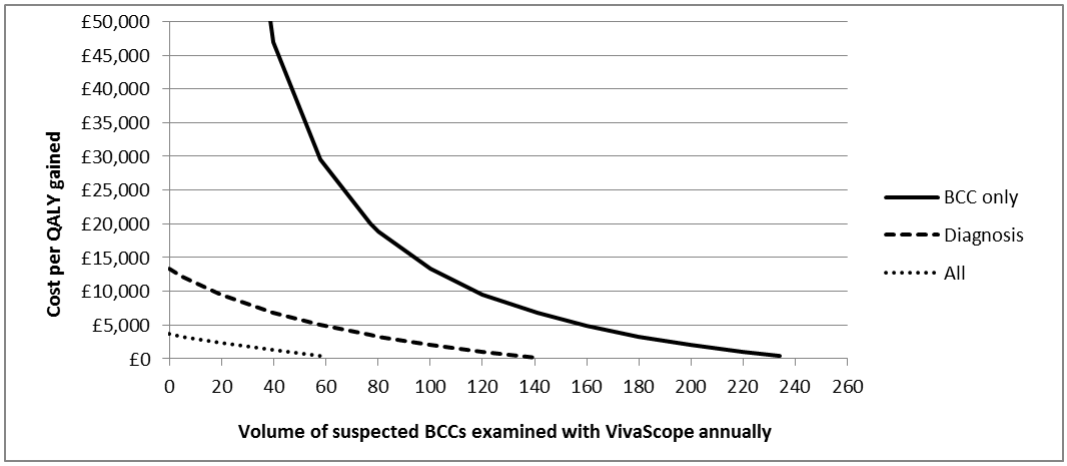
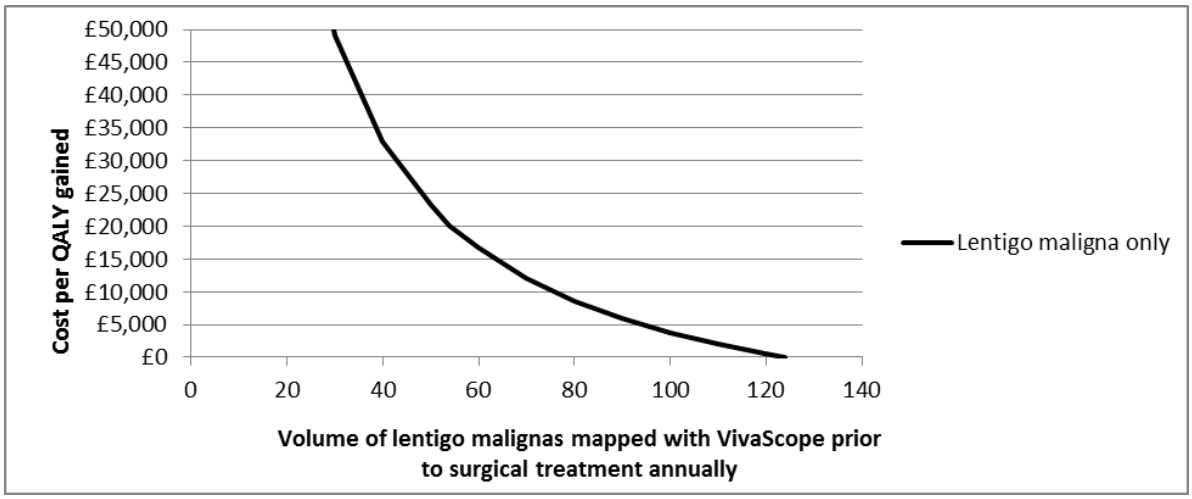
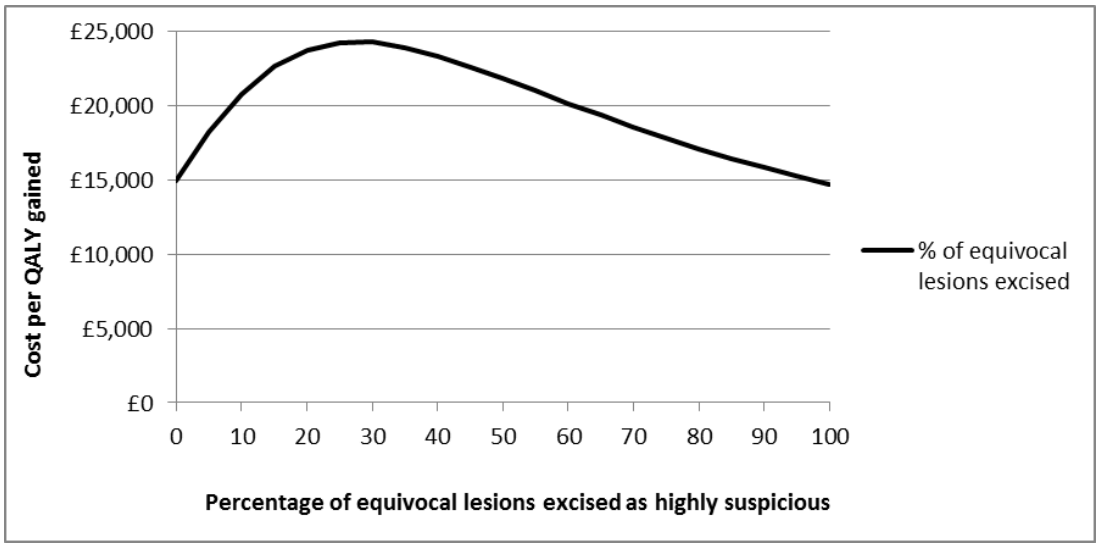


Figure 15. Incremental cost-effectiveness ratio plotted against annual volume of lentigo malignas mapped with VivaScope prior to surgical treatment – exclusive use of VivaScope for this purpose



Finally, Figure 16 shows the impact of a change in the percentage of equivocal lesions suspected for melanoma that are excised under routine management. The shape of the line is determined by the fact that the percentage of equivocal lesions sent for excision affects both the cost and disutility of routine management, but also the diagnostic accuracy of VivaScope, which differs between highly suspicious and low-moderately suspicious lesions in Pellacani *et al*.[45] The ICER is below the lower NICE cost-effectiveness threshold of £20,000/QALY when the percentage of equivocal lesions excised is approximately 10% and below, or 60% and above.

Figure 16. Incremental cost-effectiveness ratio plotted against the percentage of equivocal lesions suspected for melanoma that are excised under routine management (highly suspicious lesions) – diagnostic data from Pellacani *et al*.[45]



6 DISCUSSION

6.1 Statement of principal findings

6.1.1 Clinical effectiveness

The systematic review of clinical effectiveness identified 16 studies, 13 of which are indicated for lesion diagnosis and three for lesion margin delineation. For the index test, included studies used VivaScope 1500 or 1000 or 2500 or 3000 with or without dermoscopy as adjunctive technology or as comparator.

The majority of the included studies had low risk of bias and low applicability concerns in patient selection, conduct of the index test and reference standard. However concerning flow and timing, the risk of bias in majority of the studies was unclear due to poor reporting and/or insufficient data.

None of the included studies was conducted in the UK. The majority of the 15 included studies are from countries (Eight studies from Australia and Italy, two from Brazil and USA, two each from Spain and Australia, and one each from China and Canada) whose skin cancer rates and treatment pathways may be different from the UK setting.

Two studies (*et al.* 2014[33] conducted in Spain, and Pellacani *et al.* 2014[45] conducted in Italy) investigated lesion diagnosis and were deemed to be the most representative of clinical practice in the UK setting from the studies identified. However Alarcon was the preferred choice since it is the most representative of patients diagnosed with melanoma in the UK. This was validated by our clinical experts and therefore formed the basis of the health economic analysis for diagnosis of malignant melanoma.

One study (Guitera *et al*. 2013[38]) which investigated lesion margin delineation was also deemed to be the most representative of clinical practice in the UK setting. This was validated by our clinical experts and this trial formed the basis for the health economic analysis of VivaScope assisted margin delineation.

The most commonly reported outcome specified in the protocol was diagnostic accuracy, reported as sensitivity, specificity, PPV, NPV and in some cases number of positive or negative test results. Included studies were considered too heterogeneous to have their results combined by meta-analysis. This was due to study design (e.g. not post-dermoscopy), patient population (e.g. different prior history of melanoma) or regarding reporting of results (e.g. patient based or lesion based).

As stated in the Cochrane Handbook for Diagnostic Test Accuracy reviews[27] "in any analysis it is important to ensure that there are no differences between the studies in terms of the participants they

recruit, as this will alter the spectrum of disease and non-disease in the population, which can strongly impact on test accuracy".

6.1.1.1 Summary of key results of clinical effectiveness

1. Diagnostic accuracy of current versions of VivaScope in lesion diagnosis

- In the trial by Alarcon *et al.* 2014,[33] the addition of VivaScope 1500 to dermoscopy reduced unnecessary excisions with a high diagnostic accuracy. Based on the 264 excised lesions, combined use of dermoscopy and VivaScope was more likely to diagnose melanoma compared with dermoscopy alone (sensitivity, 97.8% *vs* 94.6%, p=0.043), and more likely to diagnose those without melanoma (non-melanoma) (specificity, 92.4% *vs* 26.74%, p<0.000001). Similar results were obtained when the analysis was based on all 343 patients who underwent RCM, assuming all the 79 patients/lesions who were followed up were TNs.
- In the study by Castro *et al.* 2014,[46] among 54 lesions imaged with both VivaScope 1500 or 3000 following dermoscopy, 45 were biopsy-proven BCCs. Comparison between VivaScope 1500 and VivaScope 3000 was as follows: sensitivity (100% *vs* 93%), specificity (78% for both RCMs), PPV (96% *vs* 95%), and NPV (100% *vs* 70%) respectively.
- Pellacani *et al*. 2014[45] prospectively assessed the potential impact of RCM when implemented in a routine melanoma workflow. Of 491 lesions, 183 underwent RCM documentation and 308 RCM consultations. In the RCM documentation group, histopathology confirmed 110 RCM positives (23 melanomas, 19 BCCs and 68 benign lesions) and 73 RCM negatives (73 benign lesions). In all melanomas and BCCs identified at histology, RCM had recommended excision. In the RCM consultation group, RCM identified 81 positives and 227 negatives. Of the 81 RCM positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 RCM negatives followed-up for 3-12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision).
- In the trial by Curchin *et al.* 2011,[34] on addition of VivaScope 1500 to dermoscope 12/13 melanomas (92.3% sensitivity, 75% specificity), 6/9 BCCs (66.7% sensitivity, 100% specificity) and 6/6 SCC and its precursors (100% sensitivity, 75% specificity) were diagnosed correctly when compared to final histopathology.
- In the trial by Rao *et al*. 2013,[42] VivaScope 1500 provided a high diagnostic accuracy in tele-consultation use. Lesions diagnosed by reader 1 (bedside trained physician, less experience) as malignant with VivaScope 1500 represented 66.7% of histologically diagnosed melanoma, 74.1% of BCC, and 37.2% of SCC. For reader 2 (distant expert, more experience), lesions diagnosed as malignant represented 88.9% of melanoma, 51.9% of BCC, and 72.1% of SCC. Out of 284 lesions evaluated by both readers, 212 were benign and 72 malignant based on histopathology.
- In the trial by Stanganelli *et al.* 2014,[48] VivaScope 1500 as additional diagnostic tool to dermoscope can improve melanoma detection and reduce unnecessary excisions. Of 30/70 lesions (43%) classified as melanoma by VivaScope 1500, 11/12 were histologically confirmed (11 TP and 1 FN), and 19 as false positives.

2. Diagnostic accuracy of older version of VivaScope in lesion diagnosis

- In the trial by Langley *et al.* 2007,[39] VivaScope 1000 had a relatively higher sensitivity than Dermoscopy, but the specificity was similar. The sensitivity of VivaScope 1000 compared with dermoscope was 97.3% *vs* 89.2% and specificity was 83.0% *vs* 84.1%.

- In the trial by Gerger *et al.* 2006[35] and Gerger *et al.* 2008,[36] VivaScope 1000 examination was a promising method for non-invasive assessment of melanoma and non-melanoma skin tumours. The overall (total of the 4 observers/readers) diagnostic differentiation of benign from malignant lesions (melanoma and BCC) reached sensitivity of 94.65%, specificity of 96.67%, PPV of 97.50%, and NPV of 92.99% based on histopathology.

3. Diagnostic accuracy of current version of VivaScope in lesion margin delineation

a. VivaScope 1500

- In the trial by Guitera *et al*. 2013[38] *in vivo* VivaScope 1500 as addition to dermoscopy provided valuable information facilitating accurate diagnosis. Out of 60 positive sites for LM confirmed by histopathology, 55 (FN=5) had been confirmed by VivaScope 1500 and 21 (FN=39) by dermoscopy, and out of 125 LM sites confirmed as negative by histopathology, 121 (FP=4) had been confirmed by VivaScope 1500 and 122 (FP=3) by dermoscopy. Both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500.
- In the trial by Pan *et al.* 2012,[40] VivaScope 1500 imaging of lesion margins demonstrated the possibility of preoperative mapping of cancer margins. In seven of 10 (70%) cases, the margins of the cancer were identified using VivaScope 1500 and confirmed by histopathological analysis. In three of 10 (30%) cases, the margin of the lesions could not be detected because of the unevenness of the surface.

b. VivaScope 2500 in lesion margin delineation

- Trial by Bennassar *et al.* 2014[44] the overall sensitivity and specificity of detecting residual BCC in surgical margins were 88% and 99%, respectively. The number of images/mosaic correctly diagnosed as TP was 79 (89%) and TN was 390 (99.7%). There was only one (0.3%) false positive. In addition average VivaScope 2500 reduced the evaluation time by 18 minutes ($p<0.001$) when compared with the processing of a frozen section.

Table 51. Summary and consistency/inconsistency of results of diagnostic accuracy

Study	Sensitivity and specificity results	Consistency/ inconsistency of results
Current versions of VivaScope in lesion diagnosis		
Alarcon *et al.* 2014[33]	The addition of VivaScope 1500 to dermoscopy reduced unnecessary excisions with a high diagnostic accuracy. Based on the 264 excised lesions, combined use of dermoscopy and VivaScope was more likely to diagnose melanoma compared with dermoscopy alone (sensitivity, 97.8% *vs* 94.6%, p=0.043), and more likely to diagnose those without melanoma (non-melanoma) (specificity, 92.4% *vs* 26.74%, p<0.000001). Similar results were obtained when the analysis was based on all 343 patients who underwent RCM, assuming all the 79	264 excisions out of 343 lesions which underwent RCM, hence reported specificity and sensitivity analysis does not reflect the total number of lesions analysed.

Study	Sensitivity and specificity results	Consistency/ inconsistency of results
	patients/lesions who were followed up were TNs.	
Castro *et al.* 2014[46]	Among 54 lesions imaged with both VivaScope 1500 or 3000, 45 were biopsy-proven BCCs. Comparison between VivaScope 1500 and VivaScope 3000 was as follows: sensitivity (100% *vs* 93%), specificity (78% for both RCMs), PPV (96% *vs* 95%), and NPV (100% *vs* 70%) respectively.	Study participants recruited from many a tertiary hospital in Brazil and a private skin cancer specialist hospital in USA, hence may not be representative.
Pellacani *et al.* 2014[45]	Of 491 lesions, 183 underwent RCM documentation and 308 RCM consultations. In the RCM documentation group, histopathology confirmed 110 RCM positives (23 melanomas, 19 BCCs and 68 benign lesions) and 73 RCM negatives (73 benign lesions). In all melanomas and BCCs identified at histology, RCM had recommended excision. In the RCM consultation group, RCM identified 81 positives and 227 negatives. Of the 81 RCM positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 RCM negatives followed-up for 3-12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision).	The comparison was between RCM documentation (documentation of lesions already qualified and scheduled for surgical excision following consistent clinical and/or dermoscopic criteria for melanoma diagnosis) and RCM consultation (an outcome decision requested from the confocal reader. In this case RCM examination determined the lesion definite outcome)
Curchin *et al.* 2011[34]	On addition of VivaScope 1500 to dermoscope, 12/13 melanomas (92.3% sensitivity, 75% specificity), 6/9 BCCs (66.7% sensitivity, 100% specificity) and 6/6 SCC and its precursors (100% sensitivity, 75% specificity) were diagnosed correctly when compared to final histopathology.	No comparator
Rao *et al*. 2013[42]	Lesions diagnosed by reader 1 (bedside trained physician, less experience) as malignant with VivaScope 1500 represented 66.7% of histologically diagnosed melanoma, 74.1% of BCC, and 37.2% of SCC. For reader 2 (distant expert, more experience), lesions diagnosed as malignant represented 88.9% of melanoma, 51.9% of BCC, and 72.1% of SCC. Out of 284 lesions evaluated by both readers, 212 were benign and 72 malignant based on histopathology.	Study had no comparator and the only comparison was between reader 1 (bedside trained physician, less experience) and reader 2 (distant expert, more experience)
Stanganelli *et al.* 2014[48]	VivaScope 1500 as additional diagnostic tool to dermoscope can improve melanoma detection and reduce unnecessary excisions. Of 30/70 lesions (43%) classified as melanoma by VivaScope 1500, 11/12 were histologically confirmed (11 TP and 1 FN), and 19 as false positives.	No comparator, and was based on retrospective study of excised lesions

Study	Sensitivity and specificity results	Consistency/ inconsistency of results
Older versions of VivaScope in lesion diagnosis		
Langley *et al.* 2007[39]	VivaScope 1000 had a relatively higher sensitivity than dermoscopy but the specificity was similar. The sensitivity of VivaScope 1000 compared with dermoscope was 97.3% *vs* 89.2% and specificity was 83.0% *vs* 84.1%.	Earlier version of VivaScope
Gerger *et al.* 2006[35] and Gerger *et al.* 2008[36]	The overall (total of the 4 observers/readers) diagnostic differentiation of benign from malignant lesions (melanoma and BCC) reached sensitivity of 94.65%, specificity of 96.67%, PPV of 97.50%, and NPV of 92.99% based on histopathology.	Earlier version of VivaScope and no comparator
Current versions of VivaScope in margin delineation		
Guitera *et al*. 2013[38]	Out of 60 positive sites for LM confirmed by histopathology, 55 (FN = 5) had been confirmed by VivaScope 1500 and 21 (FN = 39) by dermoscopy, and out of 125 LM sites confirmed as negative by histopathology, 121 (FP = 4) had been confirmed by VivaScope 1500 and 122 (FP = 3) by dermoscopy. Both the length and width of the dermoscopically visible area of the lesion were on average 60% smaller than the final corresponding dimensions determined by VivaScope 1500. Thus, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.	High risk population, 15/37 had recurrent LM, including 9 with multiple prior recurrence
Pan *et al.* 2012[40]	VivaScope 1500 imaging of lesion margins demonstrated the possibility of preoperative mapping of cancer margins. In seven of 10 (70%) cases, the margins of the cancer were identified using VivaScope 1500 and confirmed by histopathological analysis.	No comparator
Bennassar *et al.* 2014[44]	The overall sensitivity and specificity of detecting residual BCC in surgical margins were 88% and 99%, respectively. The number of images/mosaic correctly diagnosed as TP was 79 (89%) and TN was 390 (99.7%). There was only one (0.3%) false positive. In addition average VivaScope 2500 reduced the evaluation time by 18 minutes ($p<0.001$) when compared with the processing of a frozen section.	Earlier version of VivaScope and no comparator
Abbreviations used in the table: BCC, basal cell carcinoma; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive		

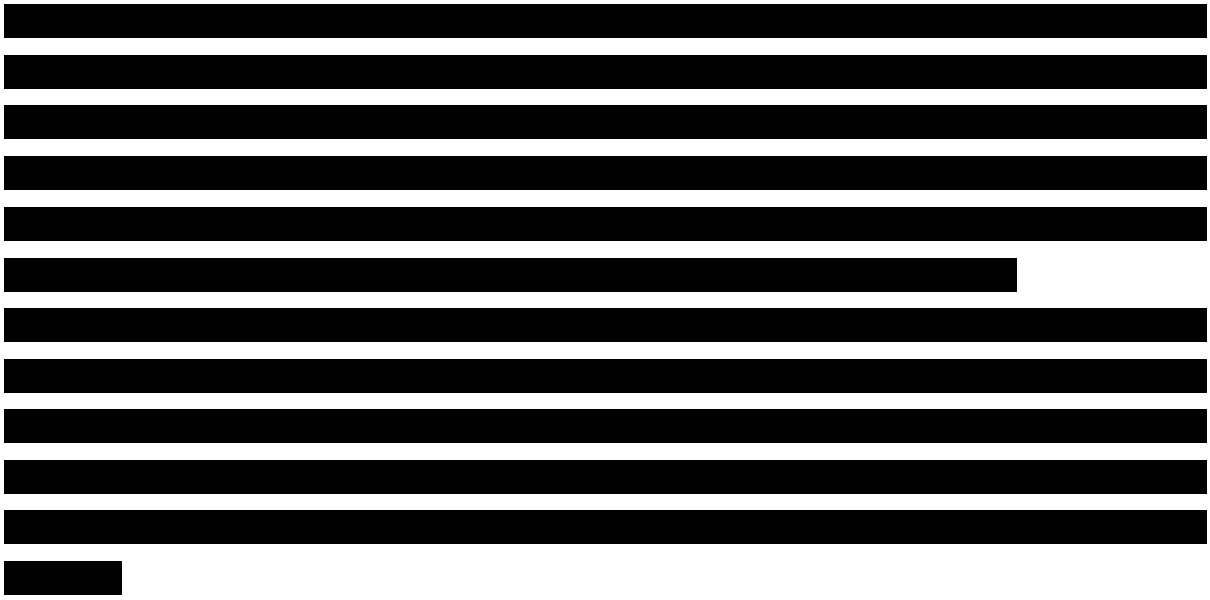
6.1.1.2 Generalisability of results

Although none of the included studies in the review of clinical effectiveness were conducted in the UK, two studies (Alarcon *et al.* 2014[33] from Spain, and Pellacani *et al.* 2014[45] from Italy) on diagnosis and one study on margin delineation (Guitera et al. 2013[38]) were deemed to be the most

representative of clinical practice in the UK setting. This was validated by our clinical experts and these trials were taken forward for the health economic analysis.

6.1.2 Cost effectiveness

Existing evidence on the cost-effectiveness of VivaScope is particularly limited. One unpublished economic evaluation



The results of primary economic modelling indicate that VivaScope is likely a cost-effective strategy in the diagnostic assessment of skin lesions suspected for cancer (suspected melanomas with an equivocal finding in dermoscopy and suspected BCCs with an equivocal or positive finding in dermoscopy) and in the margin delineation of lentigo maligna prior to surgical treatment, even when VivaScope is used exclusively for one of the three indications assessed in the economic analysis. Results were affected by the intended use of VivaScope (i.e. exclusive use on diagnostic assessment of suspected melanomas, or diagnostic assessment of suspected BCCs, or pre-surgical mapping of lentigo maligna, or combined use for the diagnosis of suspected melanomas and BCCs, or use in all of the above indications). This is because the capital, maintenance and training costs of VivaScope are spread across a different number of lesions eligible for examination, which affects the intervention cost per lesion examined, and, ultimately, the total cost associated with the use of VivaScope.

The cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas with an equivocal finding in dermoscopy was affected by the diagnostic accuracy data utilised in the model, when VivaScope was assumed to be exclusively used for this purpose. Using the more 'optimistic' diagnostic data from Alarcon *et al*. resulted in a deterministic incremental cost effectiveness ratio (ICER) of £8,877/QALY (£9,362/QALY in probabilistic analysis), while the 'less favourable' diagnostic data from Pellacani *et al*. resulted in a deterministic ICER of £19,095/QALY (£25,453/QALY in probabilistic analysis). When use of VivaScope was expanded to include other

indications assessed in the economic analysis, the use of VivaScope became the dominant strategy over routine management of equivocal lesions suspected for melanoma.

VivaScope was shown to be a dominant strategy when used for the diagnostic assessment of suspected BCCs with a positive or equivocal finding in dermoscopy, and this was independent of the intended use of the device (i.e. it was a dominant strategy when it was exclusively used for this purpose or when it was used for other indications covered by the economic analysis as well).

Regarding margin delineation of lentigo maligna, mapping with VivaScope was shown to be cost-effective, even if it was used exclusively for this purpose, as indicated by a deterministic ICER of £10,241/QALY (£11,651/QALY in probabilistic analysis). When VivaScope was used for diagnosis as well as mapping of lentigo maligna, then the intervention cost was reduced and it became a dominant strategy.

Overall, in the analyses that combined the different 'part' models designed for this report, VivaScope was shown to be a dominant strategy over routine management in the diagnostic assessment of suspected melanomas and BCCs alone or combined with margin delineation of lentigo maligna prior to surgical treatment.

One-way sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility due to scarring following surgical intervention of skin lesions on head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy.

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. All scenario analyses that were performed exclusively for the diagnostic assessment of suspected melanomas raised the ICER above the base case. However, when wider use of VivaScope was assumed, the results (VivaScope dominance) remained unaffected by the scenarios tested. Overall, the dominance of VivaScope was robust and unaffected by use of alternative data and assumptions when the system was assumed to be used for a combination of indications assessed in the economic analysis.

6.2 Strengths and limitations of the assessment

6.2.1 Clinical effectiveness

Strengths

- This systematic review provides the most up-to-date evidence of the clinical effectiveness of VivaScope 1500 and 3000 for detecting and monitoring skin cancer, and with a low likelihood of missing any key or pivotal trial.

Limitations

- There is absence of UK data in the included studies and therefore generalisability of the results. This has implications for the National Health Service (NHS).
- Apart from diagnostic accuracy and lesion recurrence rate (only reported by one study), none of the outcomes specified in the protocol were reported in the included studies.
- None of the included studies reported diagnostic accuracy results of SCC with VivaScope. This confirms evidence in the literature which suggest SCCs can be difficult to view using imaging techniques because their upper surface is often scaly, which can make it difficult to obtain sufficient resolution detail.[12] SCC will therefore not be carried through into the economic evaluation.
- In some of the studies, there was paucity and/or quality of reported data on number of patients with positive and negative test results, making it impossible to construct a 2x2 contingency table to calculate sensitivity and specificity.

6.2.2 Cost effectiveness

Strengths

- The economic analysis was based on the development of three 'part' models, each designed to simulate the care pathways of people with skin lesions eligible for examination with VivaScope that undergo assessment of their skin lesions in a dermatology MDT service. The care pathways were designed based on national guidelines and following advice from clinical experts, and were specific to each type of lesion considered in the economic analysis. Use of national guidance and consultation with clinical experts ensured that the care pathways considered in this model reflect, as close as possible, clinical practice in the NHS, although there appears to be wide variation in the management of suspected and/or confirmed skin cancer across services.
- Model input parameters were based on national guidelines and other published evidence, clinical expert opinion and national unit costs.

Limitations

- The diagnostic and mapping accuracy data that were utilised in the model were taken from studies included in the systematic literature review of clinical evidence conducted for this guideline. However, data were limited and it was not possible to synthesise the results in a meta-analysis due to heterogeneous nature of the studies identified. Moreover, none of the studies were conducted in the UK, which may have implications for the generalisability of not only the clinical, but also the economic findings, since the prevalence of the skin cancer and the population phenotype distribution may affect the diagnostic accuracy of VivaScope.
- Sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility due to scarring following surgical intervention of skin lesions on head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility due to anxiety while waiting for the results of biopsy. However, utility data relating to these events were very limited and of poor quality or non-existent, and a number of assumptions were needed in order to inform the model.
- Other complications of excision and biopsy, which was the main comparator of VivaScope in the diagnostic assessment of suspected cancerous lesions, such as bleeding, bruising, infection or allergic reaction to the topical antibiotic were not considered in the model. Clinical experts acknowledged that these are not common complications, but their omission may have potentially underestimated, to some extent, the cost-effectiveness of VivaScope.

6.3 Uncertainties

The annual volume of lesions eligible for examination with VivaScope is important in determining the cost of VivaScope per lesion examined and, ultimately, in determining its cost-effectiveness. There appears to be wide variation across dermatology in the UK in terms of the number and type of lesions examined annually. Although this parameter has been tested in sensitivity analysis in the economic model, the cost-effectiveness of VivaScope may potentially vary across different dermatology centres in the UK, depending on the volume and type of lesions assessed and managed at each service.

6.4 Other relevant factors

- Training in the use of VivaScope and the clinical interpretation of the findings is an important factor that is likely to drive the diagnostic accuracy of VivaScope in the diagnostic assessment of suspected skin cancers and the mapping of skin lesions prior to surgical treatment. The economic analysis did consider formal training costs when estimating the cost associated with the use of VivaScope. However, clinical expert advice indicated that, as expected, there is a learning curve following formal training, and the overall training required for a clinician to reach a good level of expertise comprises between 4 and 6 months' time, and approximately 1000 to 2000 cases evaluated with confocal microscopy in a setting including a sufficient number of melanomas (more than 200). This means that the benefits and cost-savings associated with VivaScope use that were suggested by the results of the economic analysis are likely to take some time to realise, as the diagnostic accuracy of VivaScope utilised in the economic analyses was taken from studies conducted in dermatology centres with expertise in the use of VivaScope, so optimal diagnostic outcomes were obtained.
- The primary economic analysis considered the costs and benefits associated with use of VivaScope in the diagnostic assessment of skin lesions suspected for melanoma or BCC and in the margin delineation of lentigo maligna prior to surgical treatment. However, evidence and clinical expert advice suggest that there may be additional benefits resulting from use of VivaScope that were not factored in the economic analysis, including:
    - Monitoring and selection of suspicious lesions for biopsy in greatly high-risk patients
    - Monitoring of less suspicious lesions by digital dermoscopy, given that a high definition digital dermoscope has been integrated into all VivaScope in vivo devices
    - Post-therapy monitoring of skin lesions
    - Margin delineation of lentigo maligna planned for non-surgical treatment
    - Contribution to the monitoring and management of benign skin tumours

7 CONCLUSIONS

7.1 Clinical effectiveness

There is a paucity of randomised controlled trial (RCT) evidence for both diagnostic accuracy and margin delineation with VivaScope 1500 and 3000. However, the systematic review provides up-to-date non-RCT evidence which indicates that the use of VivaScope subsequent to dermoscopy may improve diagnostic accuracy of equivocal skin lesions compared to dermoscopy alone, particularly for malignant melanomas. In terms of margin delineation, clinical data are extremely lacking but do suggest that VivaScope 1500 mapping for LM and LMM may improve the accuracy in terms of complete excision of lesions compared with dermoscopically determined margins.

7.2 Cost effectiveness

The use of VivaScope appears to be a cost-effective strategy in the diagnostic assessment of suspected skin cancer (more specifically, of suspected melanomas with an equivocal finding in dermoscopy and suspected BCCs with a positive or equivocal finding in dermoscopy) and the margin delineation of lentigo maligna prior to surgical treatment, in particular when VivaScope is used for all three indications considered in the economic analysis.

7.3 Implications for service provision

Although the use of VivaScope following dermoscopy may improve patient care and management, there is an absence of UK data in the included studies and therefore generalisability of the results to the UK population is unclear. However, VivaScope could potentially help to reduce the number of unnecessary excisions of benign lesions, minimise the number of patients referred for ongoing digital dermoscopy monitoring, and minimise the risk of losing patients at risk of cancer to follow-up. In addition, VivaScope may help to reduce the number of patients with incomplete excision of malignant skin lesions and thus potentially reduce the burden on both patients and the NHS in terms of further surgical procedures and ongoing surveillance.

The results of the economic analysis undertaken for this assessment indicate that use of VivaScope in dermatology MDT services is likely to reduce the patient distress and anxiety associated with diagnostic biopsy and excision of lesions suspected for skin cancer, reduce the future recurrence of lentigo maligna and the distress to the patients associated with surgical treatment, and lead to cost-savings to the NHS. However, the cost-effectiveness of VivaScope may potentially vary across different dermatology centres in the UK, depending on the volume and type of lesions assessed and managed at each service.

7.4 Suggested research priorities

High quality RCTs are required in a UK population to assess diagnostic accuracy of dermoscopy plus VivaScope compared with dermoscopy alone in people with equivocal skin lesions and margin delineation accuracy of VivaScope compared with dermoscopy alone. In addition, RCTs focusing on clinical outcomes such as time to test result; test failure rate, e.g. imaging failure; number of biopsies performed and repeat biopsies; recurrence rate and morbidity associated with surgery are required. However, this research may not be feasible due to the current lack of expertise and availability of VivaScope in the UK. In addition, research on patient specific outcomes such as patients' quality of life, adverse effects and mortality may be of interest to patients and the wider clinical community.

Further research is also needed on the impact of tools and procedures associated with the diagnostic assessment and management of potentially cancerous skin lesions on people's health-related quality of life (HRQoL), in particular the impact of the distress and anxiety associated with excision and biopsy of suspicious lesions and the disutility associated with permanent disfiguring after excision of a facial malignant lesion, in order to determine the cost effectiveness of alternative diagnostic strategies in this area with higher certainty.

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9 APPENDICES

9.1 Appendix 1: Clinical effectiveness search strategies

OVID EMBASE (searched on 14th October 2014)

#	Searches
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.
3	exp skin tumour/
4	exp amelanotic melanoma/ or exp cutaneous melanoma/ or exp melanoma/ or exp non melanoma skin cancer/ or exp melanoma skin cancer/
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.
8	exp basal cell carcinoma/
9	exp squamous cell carcinoma/
10	exp basal cell nevus syndrome/
11	exp eyelid tumour/
12	Kaposi* sarcoma*.mp.
13	Merkel* cell* carcinoma*.mp.
14	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.
15	or/1-14
16	(((CSLM or laser microscop* or confocal microscop* or confocal scanning microscop* or reflec*) adj confocal adj microscop*) or RCM or confocal laser scanning microscop* or reflectan*-mode confocal microscop*).mp.
17	exp confocal microscopy/
18	VivaScope*.mp.
19	exp epiluminescence microscopy/
20	(Dermatoscop* or dermascop* or dermoscop* or (epiluminescen* adj microscop*) or skin* surface* microscop*).mp.
21	or/16-20
22	**15 and 21**

OVID MEDLINE (searched on 14th October 2014)

#	Searches
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.
3	exp skin neoplasms/
4	exp melanoma/
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.

6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.
8	exp carcinoma, basal cell/
9	exp carcinoma, squamous cell/
10	exp Neoplasms, Basal Cell/
11	exp Basal Cell Nevus Syndrome/
12	exp eyelid neoplasms/
13	Kaposi* sarcoma*.mp.
14	Merkel* cell* carcinoma*.mp.
15	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.
16	or/1-15
17	(((CSLM or laser microscop* or confocal microscop* or confocal scanning microscop* or reflec*) adj confocal adj microscop*) or RCM or confocal laser scanning microscop* or reflectan*-mode confocal microscop*).mp.
18	exp Microscopy, confocal/
19	VivaScope*.mp.
20	exp Dermoscopy/
21	(Dermatoscop* or dermascop* or dermoscop* or (epiluminescen* adj microscop*) or skin* surface* microscop*).mp.
22	or/17-21
23	**16 and 22**

Cochrane Library (searched on 14th October 2014)

ID	Search
#1	(skin or melano* or cutaneous or sarcoma or non next melanoma) near/3 (secondar* or neoplasm or cancer or carcinoma or adenocarcinom* or tumor or tumour or malignan* or metastas or lesion)
#2	superficial near/2 melanoma or SSM or nodular next melanoma or lentigo next maligna or lentiginous next melanoma or Hutchinson* near/2 freckle or "melanoma in situ" or "acral lentiginous melanoma" or "amelanotic melanoma"
#3	MeSH descriptor: [Skin Neoplasms] explode all trees
#4	MeSH descriptor: [Melanoma] explode all trees
#5	non next melanoma or BCC or gorlin* next syndrome or rodent next ulcer or basalioma or NMSC
#6	(basal or basocellular or basosquamous) near/2 (carcinoma or cancer or neoplasm or tumor or tumour or epithelioma or malignan)
#7	(squamous near/2 (carcinoma or tumor or tumour or cancer or neoplasm or epithelioma or malignan*)) or "Bowen's disease" or "squamous cell carcinoma in situ" or SCC
#8	MeSH descriptor: [Carcinoma, Basal Cell] explode all trees
#9	MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees
#10	MeSH descriptor: [Neoplasms, Basal Cell] explode all trees
#11	MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees
#12	MeSH descriptor: [Eyelid Neoplasms] explode all trees
#13	"Kaposi's sarcoma"
#14	"Merkel cell carcinoma"
#15	"T-cell lymphoma" or "cutaneous T-cell lymphoma" or CTCL or "primary cutaneous lymphoma"
#16	{or #1-#15}
#17	CSLM or laser next microscop* or confocal next microscop* or confocal next scanning next microscop* or reflec* next confocal next microscop* or RCM or confocal next laser next scanning next microscop* or reflectan*-mode next confocal next microscop*
#18	MeSH descriptor: [Microscopy, Confocal] explode all trees
#19	vivascope

#20	MeSH descriptor: [Dermoscopy] explode all trees
#21	Dermatoscop* or dermascop* or dermoscop* or "epiluminescence microscopy" or "skin surface microscope"
#22	{or #17-#21}
#23	#16 and #22

9.2 Appendix 2: Quality assessment

Study	RISK OF BIAS Summary of risk of bias assessments of parallel RCTs included in review					APPLICABILITY CONCERNS			
	Patient selection	**Index test**	**Comparator**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Comparator**	**Reference standard**
Lesion diagnosis									
Alarcon 2014[33]	Low	Low	Low	Unclear	Low	Low	Low	Low	Low
Castro 2014[46]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Curchin 2011[34]	Unclear	Low	NC	Low	High	Unclear	Low	NC	Low
Ferrari 2014[47]	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Gerger 2006[35]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Gerger 2008[36]	Low	Low	NC	Low	Unclear	Unclear	Unclear	NC	Low
Guitera 2009[37]	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low
Guitera 2010[43]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Langley 2007[39]	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Pellacani 2007[41]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Pellacani 2014[45]	Low	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Low
Rao 2013[42]	High	High	NC	Unclear	Unclear	High	High	NC	Low
Stanganelli 2014[48]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Lesion margin delineation									
Bennassar 2014[44]	Low	Low	NC	Low	Unclear	Low	Low	NC	Low
Guitera 2013[38]	Unclear	Unclear	NC	Low	Unclear	Unclear	Unclear	NC	Low
Pan 2012[40]	Unclear	Low	NC	Low	Unclear	Unclear	Low	NC	Low
Abbreviations used in the table: NC, no comparator									

9.3 Appendix 3: Data abstraction tables

Alarcon et al 2014[33]

Reviewer: George Osei-Assibey	**Study ID: #110**	
Reference details for all refs relating to the trial:	Alarcon, I., C. Carrera C., Palou J., Alos L., Malvehy J., Puig S, Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. British journal of dermatology 2014; 170(4): 802-808.	
GENERAL		
RCT ( )	**Prospective (√)** before and after data for dermascope and VivaScope	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): Dermoscopy **Comparator(s):** dermoscope + VivaScope 1500		
Year(s) study was done: 2011 – 2012		
Setting (e.g. District General, university hospital): Melanoma Unit of the Hospital Clinic of Barcelona, Spain		
Source of funding: Fondo de Investigaciones Sanitarias, Spain; CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain; Catalan Government, Spain; European Commission (GenoMEL); the National Cancer Institute of the US National Institutes of Health		
Conflict of interest: None declared		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with dermoscopically equivocal pigmented lesions, assumed to be melanocytic. **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	1534 lesions	NR	NR
N excluded	1191	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	79	NR	NR
N completed	264 excisions	136	128

Age, Mean and Range (or data as reported): median 54.7 years (range 8-89)			
Lesion or patient level data	**Lesion ( )**	**Patient (√)**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: l Lesion site: anatomical location Head and neck = 73; Trunk = 135; Limbs = 49; Acral = 7			

Types and number of lesion excised	92 melanomas	172
Basal cell carcinoma	12	NR
Squamous cell carcinoma	NR	NR

Lentigo maligna	NR	NR
Lentigo maligna melanoma	NR	NR
Melanocytic naevi	NR	NR
Others	53	NR

Previous tests or assessments:

Dermascope test (used before VivaScope) number of lesions for excision = 343

VivaScope test (used after dermoscope) number of lesions for excision = 264

Lesions or clinical follow up 73/343 (21%)

Treatment (details of any treatments given): NR

Mortality (number of study patients reported dead): NR

INDEX TEST

Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM):

VivaScope 1500; Caliber Imaging and Diagnostics, Rochester, NY, U.S.A. Incorporates and near-infrared laser at a wavelength of 830 nm with a maximum power of 35 mW.

Image interpretation

Assessors (number of assessors): Three

Experience in using VivaScope or RCM: Images were independently reviewed by one of the three dermatologists with expertise in RCM.

Qualitative (note how positive and negative findings were defined):
Independent and blinded to the pathological outcome but not the clinical information

Quantitative diagnostic thresholds (e.g. ABCD rule): Four diagnostic features were followed to assess all of the images. The presence of two protective criteria in the basal layer with a score of -1 was considered: (i) edged papillae and (ii) presence of typical cells in the basal layer; and the presence of two risk criteria with a score of 1 was also considered: (i) presence of round pagetoid cells in upper layers of the epidermis; and (ii) presence of the nucleated cells found within the dermal papillae. A threshold score > -1 was used to obtain a diagnosis of melanoma.

Final confirmation method (e.g. histology): Optical sections were obtained of the Str Corneum, Granulosum and Spinosum dermo-epidermal junction and papillary dermis.

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): DermLite Photo; 3Gen LLC, Dana Point, CA, U.S.A.

Image interpretation

Assessors (number, expertise, experience in using comparator test): 3

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system):

Four diagnostic features were followed to assess all of the images. The presence of 2 protective criteria in a basal layer with a score of -1 was considered: (i) edged papillae and (ii) presence of typical cells in the basal layer: and the presence of risk criteria with a score of 1 was also considered: (i) presence of round pagetoid cells in the upper layers of the epidermis and (ii) presence of the nucleated cells found within the dermal papillae.

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)

Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	264
Number of re-excisions	NR
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	Breslow thickness: Median 0.5mm (0-1.3) < 1 mm = 6 >1mm = 86
Lymph node involvement or micrometastases	NR

Test interpretation: NR

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
	√	

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1500	Disease	TP=91	FP=14
	No disease	FN=2	TN=157
dermoscope	Disease	TP=87	FP=126
	No disease	FN=5	TN=46

B. Sensitivity, specificity, PPV, NPV of dermoscope and VivaScope 1500

	Demoscope (number of excised lesions, 264), % (95%CI)	**VivaScope 1500** (number of excised lesions, 264), % (95%CI)
Sensitivity	94.6 (87.2-98.0)	97.8 (91.6-99.6)
Specificity	26.74 (87.2-98.0)	92.4 (87.2-95.7)
PPV	40.8 (34.2-47.8	87.4 (79.0-92.8)
NPV	90.2 (77.8-96.3)	98.8 (95.1-99.8)

C. Number needed to treat (NNT): defined as the proportion of dermoscopically and RCM equivocal pigmented lesions, assumed to be melanocytic, excised for every melanoma.

	Lesions intended for excision	**NNT**
Dermoscopy	343	3.73
Dermoscopy + VivaScope 1500	264	2.87
VivaScope 1500	103	1.12

Abbreviations used in the table: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; NR, not reported; FN, false negative; FP, false positive; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive

<table>
<tr><td colspan="5">Quality assessment (QUADAS-2)</td></tr>
<tr><td colspan="2">Patients (setting, intended use of index test, presentation, prior testing)</td><td colspan="3">Patients with equivocal lesions attending a dedicated melanoma clinic in Barcelona</td></tr>
<tr><td colspan="2">Index test(s)</td><td colspan="3">VivaScope 1500 and dermoscope</td></tr>
<tr><td colspan="2">Reference standard and target condition</td><td colspan="3">Biopsy</td></tr>
<tr><td colspan="5">Draw a flow for the primary study</td></tr>
<tr><td colspan="5">xxxxxx</td></tr>
<tr><td rowspan="8">Domain 1: Patient selection</td><td rowspan="5">A. Risk of bias</td><td colspan="3">Describe methods of patient selection</td></tr>
<tr><td colspan="3">Consecutive patients presenting at the Melanoma Unit of the Hospital Clinic of Barcelona, Spain, with dermoscopically equivocal pigmented lesions, assumed to be melanocytic, were considered for enrolment. Dermoscopic criteria for diagnosing
melanoma and the criteria were used to establish the eligibility of lesions</td></tr>
<tr><td></td><td>Yes</td><td>No</td><td>Unclear</td></tr>
<tr><td>Was a consecutive or random sample of patients enrolled?</td><td>√</td><td></td><td></td></tr>
<tr><td>Was a case-control design avoided?</td><td>√</td><td></td><td></td></tr>
<tr><td>Did the study avoid inappropriate exclusions?</td><td>√</td><td></td><td></td></tr>
<tr><td></td><td>Low risk</td><td>High risk</td><td>Unclear risk</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>√</td><td></td><td></td></tr>
<tr><td rowspan="3">B. Concerns regarding applicability</td><td colspan="3">Describe included patients (prior testing, presentation, intended use of index test and setting)</td></tr>
<tr><td colspan="3">Patients with equivocal lesions were tested with dermoscope then Viva Scope® 1500, The aim of the study was to assess the therapeutic impact of Viva Scope ® 1500 on the number of excisions of lesions deemed equivocal using dermoscope</td></tr>
<tr><td></td><td>Low risk</td><td>High risk</td><td>Unclear risk</td></tr>
<tr><td>Is there concern that the included patients do not match the review question?</td><td>√</td><td></td><td></td></tr>
<tr><td rowspan="2">Domain 2: Index test(s)</td><td rowspan="2">A. Risk of bias</td><td colspan="3">Describe the index test and how it was conducted and interpreted</td></tr>
<tr><td colspan="3">In vivo confocal microscopy was performed with a VivaScope 1500. Four diagnostic features were followed to assess all images. The presence of two protective criteria in the basal layer with a score of -1 was considered: (i) edged papillae and (ii) presence of typical cells in the basal layer; and the presence of two risk criteria with a score of 1 was also considered: (i) presence of round pagetoid cells in upper layers of the epidermis; and (ii) presence of the nucleated cells found within the dermal papillae. A threshold score > -1 was used to obtain a diagnosis of melanoma.</td></tr>
</table>

			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		Performed by certified dermatopathologists			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?		√	
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?			√
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		All lesion data is included in the 2x2 tables			
		Describe the time interval and any interventions between index test(s) and reference standard			
		Immediately, one after the other			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	√		
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		

			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?	√		
Notes/comments:					

Bennassar *et al.* 2014[44]

Reviewer: George Osei-Assibey	**Study ID:**	
Reference details for all refs relating to the trial:	Bennassar A, Vilata A, Puig S, Malvehy J. Ex vivo fluorescence confocal microscopy for fast evaluation of tumour margins during Mohs surgery. British Journal of Dermatology. 2014;170(2):360-5.	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Margin delineation		
Intervention(s): VivaScope 2500 **Comparator(s):** NR		
Year(s) study was done: October 2010 and November 2011		
Setting (e.g. District General, university hospital): Mohs Surgery Unit at the Hospital Clinic, Barcelona, Spain		
Source of funding: Personal grants to A.B. from Hospital Clinic de Barcelona 'Emili Letang' and is partially supported by Fondo de Investigaciones Sanitarias (FIS) grant 09/1393; CIBERER U-726, ISCIII.		
Conflict of interest: The VivaScope_ 2500 was borrowed from Lucid Inc. for 8 months (now Caliber Imaging and Diagnostics).		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: 80 BCCs (≥5 mm in diameter) which have undergone classical Mohs surgery **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	74 (80 lesions)	44	30
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	74 (80 lesions)	44	30

Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: Lesion location: head and neck, 73 (91%); trunk, 7 (9%) Status of lesions: Primary, 63 (79%); recurrent, 17 (21%)			

Types and number of lesion excised	80	
Basal cell carcinoma	80	NR

Squamous cell carcinoma	NR	NR
Lentigo maligna	NR	NR
Melanocytic naevi	NR	NR
Others		

Previous tests or assessments: NR

Treatment (details of any treatments given):

Mortality (number of study patients reported dead): NR

INDEX TEST

Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM):

VivaScope 2500; Caliber Imaging and Diagnostics, Rochester, NY, USA); this FCM version is specially designed for ex vivo imaging of freshly excised tissue samples.

Image interpretation

Assessors (number of assessors): One

Experience in using VivaScope or RCM: NR

Qualitative (note how positive and negative findings were defined):
Eight criteria, namely presence of fluorescence, tumour demarcation, nuclear crowding, peripheral palisading, clefting, nuclear pleomorphism, increased nuclear–cytoplasm ratio and the presence of stroma, were described, evaluated and validated. These criteria have been demonstrated to be useful in distinguishing BCC nests and strands from adnexal structures. In RCM mosaics, a well-circumscribed mass or lobule of pleomorphic hyperfluorescent bright dots, with a striking tendency to arrange with peripheral palisading next to the clefting, is very likely to be a BCC.

Quantitative diagnostic thresholds (e.g. ABCD rule): NR

Final confirmation method (e.g. histology): Histopathology

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR

Image interpretation

Assessors (number, expertise, experience in using comparator test): NR

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)

Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	80
Number of re-excisions	NR
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR

Lymph node involvement or micrometastases		NR	
Test interpretation: NR			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):		**<6 weeks**	**>6 weeks**
		NR	NR
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 2500	Disease	TP=79	FP=1
	No disease	FN=10	TN=390
B. Sensitivity, specificity, PPV, NPV of detecting BCC margins			
Sensitivity, %	88		
Specificity, %	99		
PPV	98		
NPV	97		
C. Change in evaluation time			
The mean time to obtain VivaScope mosaics in the first Mohs stage (two samples per stage) was 10.1 ± 1.22 min, while it took a mean of 28.2 ± 2.2 min to process the samples with frozen haematoxylin and eosin-stained slides. Thus on average VivaScope 2500 reduced the evaluation time by 18 minutes ($p<0.001$)			
Abbreviations used in the table: BCC, basal cell carcinoma; FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive			
Quality assessment (QUADAS-2)			

Patients (setting, intended use of index test, presentation, prior testing)		Eighty consecutive BCCs from 74 patients were prospectively collected and the margins scanned with VivaScope 2500			
Index test(s)		VivaScope 2500			
Reference standard and target condition		Histopathology			
Draw a flow for the primary study					
xxxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Eighty consecutive BCCs from 74 patients were prospectively collected and the margins scanned with VivaScope 2500			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		NR			

	applicability		Low risk	High risk	Unclear
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Confocal mosaics were acquired using a modified version of a commercially available ex vivo laser scanning RCM (VivaScope 2500; Caliber Imaging and Diagnostics, Rochester, NY, USA); this RCM version is specially designed for ex vivo imaging of freshly excised tissue samples. All samples were directly immersed in a 1 mmol L^{-1} solution of acridine orange to provide a strong nuclear–dermis contrast, as it specifically stains nuclear DNA.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?			√
			Low risk	High risk	Unclear
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear

		Could the patient flow have introduced bias?			√
Notes/comments:					

Castro *et al.* 2014[46]

Reviewer: George Osei-Assibey	**Study ID: Handsearch**	
Reference details for all refs relating to the trial:	Castro R.P. SA, Fraga-Braghiroli N.A., Oliviero M.C., Rezze G.G., H. Rabinovitz H., Scope A. Accuracy of in vivo confocal microscopy for diagnosis of basal cell carcinoma: a comparative study between handheld and wide-probe confocal imaging. Journal of European Academy of Dermatology and Venereology. 2014; Oct 22. doi: 10.1111/jdv.12780. [Epub ahead of print].	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Lesion diagnosis		
Intervention(s): VivaScope 1500 and 3000 **Comparator(s):** NR		
Year(s) study was done: NR		
Setting (e.g. District General, university hospital): Outpatient dermatology clinic at a tertiary cancer centre in Sao Paulo, Brazil and at a private practice that specializes in skin cancer treatment in South Florida, USA.		
Source of funding: NR		
Conflict of interest: Dr Rabinovitz is an investigator in a study coordinated by Lucid Inc., manufacturer of a commercial confocal microscope. He has received funding for a fellowship programme and equipment from Lucid Inc. He is also a consultant and has received equipment from 3-Gen, manufacturer of a polarized dermoscope. MC Oliviero is a consultant, speaker for Caliber ID, 3Gen LLC, Canfield and MelaSciences. The other authors have no conflicts of interest to declare.		
PARTICIPANT CHARACTERISTICS		

Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with one or more skin lesions that were deemed suspicious for BCC based on clinical and dermoscopic examination. **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	73	44	30
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	73	NR	NR

Age, Mean and Range (or data as reported): Mean 65 years (range 30-89)			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**

Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: 38 (41%) of the lesions were mostly facial; 24 (75%) of the patients had skin phototype II and 8 (25%) skin phototype III. The anatomic distribution of these 45 BCCs was head and neck 9 (20%), torso 26 (58%), upper extremities 4 (9%) and lower extremities 6 (13%)		
Types and number of lesion excised		
Basal cell carcinoma	92	NR
Squamous cell carcinoma	NR	NR
Lentigo maligna	NR	NR
Melanocytic naevi	NR	NR
Others	NR	NR
Previous tests or assessments: Dermoscopy		
Treatment (details of any treatments given): NR		
Mortality (number of study patients reported dead): NR		
INDEX TEST		
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1500 and 3000		
Image interpretation		
Assessors (number of assessors): 2		
Experience in using VivaScope or RCM: All examinations, including clinical, dermoscopic and RCM imaging, were made by a dermatologist experienced with RCM examination with supervision by a skin cancer expert		
Qualitative (note how positive and negative findings were defined): Images were evaluated for the presence of previously-published RCM criteria for identification of BCC including: the presence of neoplastic aggregates, seen as 'dark silhouettes' or as 'bright tumour islands' at the level of the DEJ or upper dermis; 'streaming' polarization of nuclei in neoplastic aggregates along the same axis of orientation; 'peripheral palisading' of nuclei at the tumour islands' periphery; dark 'peritumoral clefts' around the tumour islands; fibrotic stroma with 'thickened collagen bundles'; dilated and tortuous 'linear blood vessels' and 'coiled blood vessels'; 'bright dendritic structures' within tumour islands; and 'bright round cells' in the stroma		
Quantitative diagnostic thresholds (e.g. ABCD rule): A threshold of ≥3 RCM criteria to identify BCC, whereby at least one of the criteria had to be the presence of 'dark silhouettes' or 'bright tumour islands'; these latter criteria denote the presence of neoplastic aggregates of BCC and hence need to be observed in all cases identified as BCC by RCM		
Final confirmation method (e.g. histology): Histopathology		
Technical failures (number and reasons): NR		
COMPARATOR TEST		
Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR		
Image interpretation		
Assessors (number, expertise, experience in using comparator test): NR		
Qualitative (note how positive and negative findings were qualitatively defined): NR		
Quantitative diagnostic thresholds (e.g. ABCD system): NR		
Quantitative diagnostic thresholds (e.g. ABCD system): NR		
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR		

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)	
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	92
Number of re-excisions	NR
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR
Lymph node involvement or micrometastases	NR

Test interpretation: NR

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
	NR	NR

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1500	Disease	TP=45/47	FP=2
	No disease	FN=	TN=
VivaScope 3000	Disease	TP=42/44	FP=2
	No disease	FN=	TN=

B. Sensitivity, specificity, PPV, NPV of detecting BCC margins

	VivaScope 1500	**VivaScope 3000**
Sensitivity, %	100	93
Specificity, %	78	78
PPV	96	95
NPV	100	70

Abbreviations used in the table: BCC, basal cell carcinoma; FN, false negative; FP, false positive; NR, not reported; NPV, negative predictive value; PPV, positive predictive value; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Patients with one or more skin lesions that were deemed suspicious for BCC based on clinical and dermoscopic examination, recruited from outpatient dermatology clinic at a tertiary cancer centre in Sao Paulo, Brazil and at a private practice that specializes in skin cancer treatment in South Florida, USA
Index test(s)		VivaScope 1500 and 3000
Reference standard and target condition		Histopathology
Draw a flow for the primary study		
xxxxxxx		
Domain 1:	**A. Risk of bias**	Describe methods of patient selection

Patient selection		Patients included in the study were recruited from the population of women and men who underwent skin cancer screening at the outpatient dermatology clinic at a tertiary cancer centre in Sao Paulo, Brazil and at a private practice that specializes in skin cancer treatment in South Florida, USA. Patients recruited were those presenting with one or more skin lesions that were deemed suspicious for BCC based on clinical and dermoscopic examination. Informed consent was obtained from each study participant.			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Included patients had been clinically and dermoscopically tested			
			Low risk	High risk	Unclear
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Handheld reflectance confocal microscopy imaging was performed with commercially -available in vivo RCM system (Vivascope3000; CaliberID). TWP-RCM imaging was performed with a commercially available in vivo RCM system (Vivascope1500; CaliberID)			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear
		Could the reference standard, its conduct, or its interpretation have	√		

		introduced bias?			
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear
		Could the patient flow have introduced bias?	√		√
Notes/comments:					

Curchin *et al.* 2011[34]

Reviewer: George Osei-Assibey	**Study ID: #643**		
Reference details for all refs relating to the trial:	Curchin, C. E., E. M. Wurm E.M., Lambie D.L., Longo C., Pellacani G., Soyer H.P. First experiences using reflectance confocal microscopy on equivocal skin lesions in Queensland." Australasian Journal of Dermatology 2011; 52(2): 89-97.		
GENERAL			
RCT ( )	**Prospective (√)**	**Retrospective ( )**	
Indication for test (diagnosis or margin delineation or both): Diagnosis			
Intervention(s): VivaScope 1500 with a dermoscopic camera **Comparator(s):** NR			
Year(s) study was done: January 2010 to May 2010			
Setting (e.g. District General, university hospital):): Princess Alexandra Hospital Dermatology Department, Queensland, Australia			
Source of funding: NR			
Conflict of interest: NR			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Consecutive patients with equivocal lesions recruited from the dermatology departments booking list **Exclusion criteria:** NR			

	Total	Men	Women
N enrolled	42 (50 lesions)	NR	NR
N excluded	0	NR	NR
N withdrawn	0	NR	NR
N lost to follow up	0	NR	NR
N completed	42 (50 lesions)	NR	NR
Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: NR			
Types and number of lesion excised			
Basal cell carcinoma		9	NR
Squamous cell carcinoma		6	NR
Lentigo maligna		NR	NR
Melanoma		13	NR
Benign naevus		22	NR
Others			
Previous tests or assessments: NR			
Treatment (details of any treatments given): NR			
Mortality (number of study patients reported dead): NR			
INDEX TEST			
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1500 (Lucid Inc, Rochester, NY, USA)			
Image interpretation			
Assessors (number of assessors): One			
Experience in using VivaScope or RCM: Assessor was a novice who had completed a course in RCM			
Qualitative (note how positive and negative findings were defined): Confidence level in diagnosis (low confidence 1, medium confidence 2, high confidence 5) each image also evaluated for the presence and degree of artefact			
Quantitative diagnostic thresholds (e.g. ABCD rule): Superficial layer scrutinised for 3 possible pattern: honey combed pattern formed by 10-20 µm polygonal cells with dark nuclei and bright thin cytoplasm; cobble-stone pattern consisting of small polygonal cells refractive cytoplasm. Presence of pagetoid cells, and refractive cells in the basal layer and epidermal junction. Size of the basal cells was also considered >250 μm^2 measured. IN the papillary dermis melanocytic nest features were divided into 3 different types of cellular clusters.			
Final confirmation method (e.g. histology): Images blind to the histopathology result.			
Technical failures (number and reasons): NR			
COMPARATOR TEST			

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR			
Image interpretation			
Assessors (number, expertise, experience in using comparator test): NR			
Qualitative (note how positive and negative findings were qualitatively defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR			
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)			
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR		
Diameter of excisions (e.g. 2mm)	NR		
Number of excisions	50		
Number of re-excisions	NR		
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR		
Lymph node involvement or micrometastases	NR		
Test interpretation: NR			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**	
	NR	✓Pts @ excision clinic	
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:	**Reference standard**		
	Disease	**No disease**	
Test – Disease	**TP**	**FP**	
Test – No disease	**FN**	**TN**	
B. Diagnostic accuracy of VivaScope 1500			
	Number correctly diagnosed after histopathology	**Sensitivity**	**Specificity**
Melanomas	12/13	92.3%	75%
BCC	6/9	66.7%	100%
SCC	6/6	100%	75%
Benign naevi	19/22	86%	95%
Abbreviations used in table: FP, false positive; FN, false negative, NR, not reported; RCM, reflectance confocal microscopy; TP, true positive; TN, true negative;			
Quality assessment (QUADAS-2)			
Patients (setting, intended use of	Consecutive patients attending a dermatology department minor excision		

<table>
<tr><td colspan="2">index test, presentation, prior testing)</td><td colspan="4">clinic</td></tr>
<tr><td colspan="2">Index test(s)</td><td colspan="4">VivaScope 1500</td></tr>
<tr><td colspan="2">Reference standard and target condition</td><td colspan="4">Histopathology</td></tr>
<tr><td colspan="6">Draw a flow for the primary study</td></tr>
<tr><td colspan="6">xxxxxx</td></tr>
<tr><td rowspan="8">Domain 1: Patient selection</td><td rowspan="5">A. Risk of bias</td><td colspan="4">Describe methods of patient selection</td></tr>
<tr><td colspan="4">Consecutive patients already on the dermatology excision clinic list</td></tr>
<tr><td></td><td>Yes</td><td>No</td><td>Unclear</td></tr>
<tr><td>Was a consecutive or random sample of patients enrolled?</td><td>√</td><td></td><td></td></tr>
<tr><td>Was a case-control design avoided?</td><td>√</td><td></td><td></td></tr>
<tr><td>Did the study avoid inappropriate exclusions?</td><td></td><td></td><td>√</td></tr>
<tr><td></td><td>Low risk</td><td>High risk</td><td>Unclear risk</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td></td><td></td><td>√</td></tr>
<tr><td rowspan="3">B. Concerns regarding applicability</td><td colspan="4">Describe included patients (prior testing, presentation, intended use of index test and setting)</td></tr>
<tr><td colspan="4">Previous tests not reported, indication = equivocal lesions</td></tr>
<tr><td></td><td>Low risk</td><td>High risk</td><td>Unclear risk</td></tr>
<tr><td>Is there concern that the included patients do not match the review question?</td><td></td><td></td><td>√</td></tr>
<tr><td rowspan="2">Domain 2: Index test(s)</td><td rowspan="2">A. Risk of bias</td><td colspan="4">Describe the index test and how it was conducted and interpreted</td></tr>
<tr><td colspan="4">The dermoscopic and RCM images were aligned over the top of each other so that correlation between the two could be made. RCM images were taken as blocks (a series of
individual RCM images digitally stitched together to form a larger mosaic) in the horizontal plane at depths of 30, 60 and 90 mm, approximate levels of the epidermis, dermal–
epidermal junction and dermis, respectively. Individual features of interest were identified from the blocks and were imaged further with vertical stacks (a series of individual
RCM images taken at the same position but at increasing depths in the vertical plane). Vertical stacks were taken from depths of 0 to 120 mm, 10 mm apart.</td></tr>
</table>

			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		Histopathological analysis, details of method not reported			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		The patients were already on the excision clinic list and received RCM prior to the excision			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	√		
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			√
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?		√	
Notes/comments:					

Ferrari *et al.* 2014[47]

Reviewer: George Osei-Assibey	**Study ID: Obtained from updated search**		
Reference details for all refs relating to the trial:	Ferrari B, Pupelli G,Farnetani F, De Carvalho N.T, Longo C, Reggiani C,Argenziano G, Pellacani G. Dermoscopic difficult lesions: an objective evaluation of reflectance confocal microscopy impact for accurate diagnosis. J Eur Acad Dermatol Venereol. 2014 Oct 10. doi: 10.1111/jdv.12769. [Epub ahead of print]		
GENERAL			
RCT ( )	**Prospective ( )**	**Retrospective (√)**	
Indication for test (diagnosis or margin delineation or both): Diagnosis			
Intervention(s): VivaScope 1500 **Comparator(s):** dermoscope			
Year(s) study was done: 2010			
Setting (e.g. District General, university hospital): Department of Dermatology, University of Modena and Reggio Emilia, Italy			
Source of funding: None declared.			
Conflict of interest: None declared.			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** ( )	**No** (√)	**Unclear** ( )
Inclusion criteria: Only lesions with high quality dermoscopic images, a complete set of confocal images and histopathology report available were included. **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	322 lesions	NR	NR
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	322 lesions	NR	NR

Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: Among 322 lesions, 70 were melanomas and 252 were naevi			

Types and number of lesion excised	322	
Basal cell carcinoma	NR	NR
Squamous cell carcinoma	NR	NR
Lentigo maligna	NR	NR
Lentigo maligna melanoma	NR	NR
naevi	252	NR

Melanoma	70	NR
Previous tests or assessments: Histopathology		
Treatment (details of any treatments given): NR		
Mortality (number of study patients reported dead): NR		
INDEX TEST		
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): Confocal imaging was performed with near-infrared reflectance-mode confocal laser scanning microscope (VivaScope1500; MAVIG GmbH, Munich, D).		
Image interpretation		
Assessors (number of assessors): One		
Experience in using VivaScope or RCM: Dermatologist trained in RCM		
Qualitative (note how positive and negative findings were defined): In the superficial layer it was evaluated the presence of pagetoid cells, the cell shape (roundish or dendritic) and their number (<5 or ≥5 cells per mm^2). At the dermal–epidermal junction lesion's architecture was evaluated for the presence of the following patterns: ringed, meshwork, clods and non-specific pattern, according with previous definition;16 architectural disorder, corresponding to irregular alternation of different RCM patterns, non-edged papillae extended over the 10% of lesion, and/or tangled filaments/dendrites crossing the papillae; presence of cytological atypia (≥5 cells per mm2). In the superficial dermis, the presence of atypical nucleated cells arranged in nests was analysed. Presence of five or more roundish pagetoid cells, architectural disorder at the junction, atypical cells at the junction, and atypical nucleated cells arranged in nests were considered melanoma clues upon RCM examination.		
Quantitative diagnostic thresholds (e.g. ABCD rule): NR		
Final confirmation method (e.g. histology): Histopathological analysis		
Technical failures (number and reasons): NR		
COMPARATOR TEST		
Equipment : Comparator (e.g. dermoscope); (note machine name and manufacturer and the specification): dermoscope		
Image interpretation		
Assessors (number, expertise, experience in using comparator test): Dermatologist trained in dermoscopy		
Qualitative (note how positive and negative findings were qualitatively defined): The 7-point checklist score was calculated for each case12 as well as the frequencies of each distinct dermoscopic feature accounting for the score. Afterwards, lesions were classified according the 7-point checklist score into three categories: 'featureless' lesions for score ranging between 0 and 2, 'positive-borderline' lesions for score between 3 and 4 and 'positive- clear cut' lesions for score from 5 to 10.		
Quantitative diagnostic thresholds (e.g. ABCD system): The 7-point checklist score was calculated for each case12 as well as the frequencies of each distinct dermoscopic feature accounting for the score. Afterwards, lesions were classified according the 7-point checklist score into three categories: 'featureless' lesions for score ranging between 0 and 2, 'positive-borderline' lesions for score between 3 and 4 and 'positive- clear cut' lesions for score from 5 to 10.		
Quantitative diagnostic thresholds (e.g. ABCD system): NR		
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR		
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)		
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR	

Diameter of excisions (e.g. 2mm)	NR
Number of excisions	322
Number of re-excisions	NR
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	Mean ± SD: 1.05 ± 2.16 mm; range 0–10 mm
Lymph node involvement or micrometastases	NR

Test interpretation: NR

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
	NR	NR

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
Test	Disease	TP	FP
	No disease	FN	TN

B. Sensitivity and specificity with VivaScope 1500

VivaScope 1500:

- In the population with score 0-2, logistic regression analysis identified ≥5 round pagetoid cells (B=2.464, P=0.049) and architectural disorder (B=2.806, P=0.015) as independently significant parameters to distinguish between melanomas and naevi for lesions with 7-point checklist score ranging 0-2. Presence of at least one of the two independent parameters accounted for the detection of all six melanomas (100% sensitivity), with a specificity of 82.3%

- In the population with borderline score (3-4), logistic regression analysis identified presence of round pagetoid cells, any number (B =1.346, P=0.043) and five or more atypical cells at the junction (B=2.920, P<0.000) for lesions with 7-point checklist score ranging 3-4. Presence of at least one of the two independent parameters accounted for the detection of 16 of 17 melanomas (94.1% sensitivity), with a specificity of 62.4%.

- Number (%) of lesions positive for at least one independent parameter identified using VivaScope 1500 by logistic regression
  - For score 0-2: Melanoma, 6/6 (100%); naevi, 30/124 (17.7%)
  - For score 3-4: Melanoma, 16/17 (94.1%); naevi, 32/85 (37.6%)

Dermoscope:

- In the population with score 0–2, 2/6 melanomas were not showing any positive dermoscopic clue and four presented one positive feature.
- In the population with score 3-4, the most representative dermoscopic features were atypical network (70.6% of melanomas), irregular pigmentation (76.5% of melanomas), irregular dots and globules (58.8% of melanomas)

Abbreviations used in the table: FN, false negative; FP, false positive; NR, not reported; SD, standard deviation; RCM, reflectance confocal microscopy

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)	322 melanocytic lesions obtained from the Department of Dermatology, University of Modena and Reggio Emilia, Italy
Index test(s)	VivaScope 1500
Reference standard and target condition	Histopathological analysis
Draw a flow for the primary study	

xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Only lesions with high quality dermoscopic images, a complete set of confocal images and histopathology report available were included in the study			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?			√
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Study samples included all melanocytic lesions excised on the basis of equivocal clinical and/or dermoscopic features. Before excision, all lesions were recorded by means of digital dermoscopy and RCM. Only lesions with high quality dermoscopic images, a complete set of confocal images and histopathology report available were included in the study			
			Low risk	High risk	Unclear
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Confocal imaging was performed with VivaScope 1500. A minimum of three mosaics, with a maximum area of 8x8 mm, were obtained per lesion, one in the superficial epidermis (stratum granulosum/spinosum), one at the dermoepidermal junction and one in papillary dermis, to analyse the overall architectural and cytological aspects			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?			
		Yes			
			Low risk	High risk	Unclear
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		The histopathological analysis was performed by a Board Certified Pathologist			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear

		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear
		Could the patient flow have introduced bias?			√
Notes/comments:					

Gerger *et al.* 2006[35]

Reviewer: George Osei-Assibey		**Study ID: #962**	
Reference details for all refs relating to the trial:		Gerger, A., Koller, S., Weger, W., Richtig, E., et al. (2006). "Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumours." Cancer 107(1): 193-200.	
GENERAL			
RCT ( )		**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Diagnosis			
Intervention(s): VivaScope 1000 **Comparator(s):** NR			
Year(s) study was done: NR			
Setting (e.g. District General, university hospital): Dermato-oncology Clinic at the Department of Dermatology, Medical University of Graz, Austria			
Source of funding: Fond zur Forderung der wissenschaftlichen Forschung" (Project 16206-B05			
Conflict of interest: NR			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with melanocytic and non-melanocytic skin tumours were selected. **Exclusion criteria:** NR			
	Total	**Men**	**Women**

N enrolled	119	62	57
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	NR	NR	NR
Age, Mean and Range (or data as reported):			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: One hundred seventeen melanocytic skin lesions and 45 non-melanocytic skin lesions (90 benign naevi, 27 malignant melanomas, 15 BCC, and 30 seborrheic keratoses)			
Types and number of lesion excised			
Basal cell carcinoma		NR	NR
Squamous cell carcinoma		NR	NR
Lentigo maligna		NR	NR
Lentigo maligna melanoma		NR	NR
Melanocytic naevi		NR	NR
Previous tests or assessments: NR			
Treatment (details of any treatments given): NR			
Mortality (number of study patients reported dead): NR			
INDEX TEST			
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1000; Lucid Inc., Rochester, NY			
Image interpretation			
Assessors (number of assessors): Four			
Experience in using VivaScope or RCM: Four independent dermato-oncologists without previous experience in CLSM received a standardized instruction about diagnostic RCM features of malignant melanoma, benign naevi, BCC, and seborrheic keratosis for 1 hour as a Power-Point presentation. Diagnostic criteria were explained, and 26 image examples were demonstrated for training purposes.			
Qualitative (note how positive and negative findings were defined): Morphologic features of melanocytic skin tumours were assessed according to identification of melanocytic cytomorphology and architecture, keratinocyte cell borders, and complex branching dendrites as highly diagnostic criteria. For BCC, vascular architecture, tumour cells in a streaming pattern, and collagen fibre bundles were taken into account for diagnostic decisions. In contrast, SK features were assessed solely based on well known, standard criteria used in conventional histopathology			
Quantitative diagnostic thresholds (e.g. ABCD rule): NR			
Final confirmation method (e.g. histology): NR			
Technical failures (number and reasons): NR			
COMPARATOR TEST			

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR				
Image interpretation				
Assessors (number, expertise, experience in using comparator test): NR				
Qualitative (note how positive and negative findings were qualitatively defined): NR				
Quantitative diagnostic thresholds (e.g. ABCD system): NR				
Quantitative diagnostic thresholds (e.g. ABCD system): NR				
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR				
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)				
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR			
Diameter of excisions (e.g. 2mm)	NR			
Number of excisions	72			
Number of re-excisions	NR			
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR			
Lymph node involvement or micrometastases	NR			
Test interpretation: NR				
Technical failures: NR				
Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**		
	NR	NR		
RESULTS				
A. Test accuracy: label all tables as appropriate (add more tables as necessary)				
Note threshold(s) where appropriate:	**Reference standard**			
	Disease	**No disease**		
Test – Disease	**TP**	**FP**		
Test – No disease	**FN**	**TN**		

B. Diagnostic differentiation between lesions				
	Sensitivity	**Specificity**	**PPV**	**NPV**
Melanoma and all other lesions based solely on VivaScope 1000 examination	90.74%	98.8%	94.22%	98.17%
Benign versus malignant skin tumours lesions based solely on VivaScope 1000 examination	94.05%	98.75%	96.3%	97.94%
Benign versus malignant lesions classification based on only the biopsy documented lesions	94.65%	96.67%	97.50%	92.99%
Overall	97.5%	99%	97.5%	99%

C. Correlation between VivaScope 1000 diagnosis and the assessed pathologic or clinical diagnosis		
	Pathologic diagnosis	
VivaScope 100 diagnosis	**Malignant melanoma**	**Basal cell carcinoma**

Malignant melanoma	98	0
Basal cell carcinoma	2	58
Benign naevus	3	0
Seborrheic keratosis	5	2
Abbreviations used in the table: BCC, basal cell carcinoma; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; NR, not reported; reflectance confocal microscopy; TP, true positive; TN, true negative		
Quality assessment (QUADAS-2)		

Patients (setting, intended use of index test, presentation, prior testing)		One hundred nineteen patients (62 males and 57 females) recruited prospectively from the Dermato-oncology Clinic at the Department of Dermatology, Medical University of Graz, Austria over 2 years.			
Index test(s)		VivaScope 1000			
Reference standard and target condition		Histopathology			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		One hundred nineteen patients (62 males and 57 females) recruited prospectively from the Dermato-oncology Clinic at the Department of Dermatology, Medical University of Graz, Austria			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		One hundred nineteen patients (62 males and 57 females) with 117 melanocytic skin lesions and 45 non-melanocytic skin tumours, including malignant melanoma, benign naevi, BCC, and SK, were imaged consecutively by using a confocal microscope			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Morphologic features of melanocytic skin tumours were assessed according to the results of published investigations. The identification of melanocytic cytomorphology and architecture, keratinocyte cell borders, and complex branching dendrites were rated as highly diagnostic criteria. The set of confocal BCC features was selected based on qualitatively described criteria from previously published studies. Vascular architecture, tumour cells in a streaming pattern, and collagen fibre bundles were taken into account for diagnostic decisions. In contrast, SK features were assessed solely based on well known, standard criteria used in conventional histopathology.			

			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?		√	
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?			√
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments:					

Gerger *et al.* 2008[36]

Reviewer: George Osei-Assibey	**Study ID: #961**	
Reference details for all refs relating to the trial:	Gerger, A., Hofmann-Wellenhof R., Langsenlehner U., Richtig E., Weger W., et al. "In vivo confocal laser scanning microscopy of melanocytic skin tumours: diagnostic applicability using unselected tumour images." British journal of dermatology, 2008; 158(2): 329-333.	
GENERAL		
RCT ( )	**Prospective ( )**	**Retrospective (√)**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): VivaScope 1000 **Comparator(s):** NR		
Year(s) study was done: study conducted over 10 months		
Setting (e.g. District General, university hospital): Dermato-oncology clinic, Medical University of Graz, Austria		
Source of funding: Fond zur Forderung der wissenschaftlichen Forschung		
Conflict of interest: NR		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with melanocytic skin tumours **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	60	32	28
N excluded	0	0	0
N withdrawn	0	0	0
N lost to follow up	0	0	0
N completed	0	32	28

Age, Mean and Range (or data as reported): NR

Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**

Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: NR

Types and number of lesion excised	70	NR
Malignant melanoma	20	NR
Basal cell carcinoma	NR	NR
Squamous cell carcinoma	NR	NR
Lentigo maligna	NR	NR
Benign naevi	50	NR

Previous tests or assessments: Dermoscope		
Treatment (details of any treatments given): NR		
Mortality (number of study patients reported dead): NR		
INDEX TEST		
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1000; Lucid Inc., Rochester, NY). The VivaScope 1000 had a diode laser at 830 nm wavelength and a power of <35 mW at the tissue level. (Reported in reference 14 Gerger British J Dermatology 2006; 107:193-200		
Image interpretation		
Assessors (number of assessors): Four independent clinical dermato-oncologists		
Experience in using VivaScope or RCM: Four independent clinical dermato-oncologists with moderate experience in confocal laser scanning micrioscopy who have received a standardized instruction about diagnostic CLSM features of melanocytic skin tumours assessed the images		
Qualitative (note how positive and negative findings were defined): Blind to the dermoscope and biopsy results.		
Quantitative diagnostic thresholds (e.g. ABCD rule): Morphological features of melanocytic skin tumours were selected and assessed according to recently published studies. Melanocytic cytomorphology and architecture and keratinocyte cell borders were taken into account for diagnostic decisions. All morphological features were defined a priori without reference to the image set of the present study.		
Final confirmation method (e.g. histology): Biopsy		
Technical failures (number and reasons): NR		
COMPARATOR TEST		
Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR		
Image interpretation		
Assessors (number, expertise, experience in using comparator test): NR		
Qualitative (note how positive and negative findings were qualitatively defined): NR		
Quantitative diagnostic thresholds (e.g. ABCD system): NR		
Quantitative diagnostic thresholds (e.g. ABCD system): NR		
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR		
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)		
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR	
Diameter of excisions (e.g. 2mm)	NR	
Number of excisions	34	
Number of re-excisions	NR	
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	Mean ± SD, 1.48 ± 1.60 mm	
Lymph node involvement or micrometastases	NR	
Test interpretation: NR (All 20 MM received biopsy but only 14/50 naevi received biopsy)		
Technical failures: NR		
Interval between index test and reference standard (excision of	**<6 weeks**	**>6 weeks**

the histological specimen):		NR	NR
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1000	Disease	TP = 15	FP = 0 V
	No disease	FN = 0	TN = 45

B. Diagnostic differentiation of benign naevi and malignant melanoma using RCM				
	Sensitivity	**Specificity**	**PPV**	**NPV**
VivaScope 1000	97.5%	99%	97.5%	99%
Abbreviations used in the table: FP, false positive; FP, false negative; PPV, positive predictive value; NPV, negative predictive value; NR, not reported; TP, true positive; TN, true negative; SD, standard deviation				

Quality assessment (QUADAS-2)					
Patients (setting, intended use of index test, presentation, prior testing)		Patients were recruited from the dermato-oncology clinic, Medical University of Graz, Austria over a period of 10 months. The intended use of the index test was to validate diagnostic confocal examination of melanocytic skin tumours using unselected tumour images.			
Index test(s)		VivaScope 1000			
Reference standard and target condition		Histopathological analysis			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Patients were recruited from the dermato-oncology clinic over a period of 10 months. The tumour set in the present study was randomly selected from a consecutively imaged and previously published study set. Overall, 70 melanocytic skin tumours including 50 benign naevi and 20 malignant melanomas (60 patients: 32 male and 28 female) were selected.			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?			√
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?			√
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		The test set comprised 70 melanocytic skin tumours, including 20 melanomas (all histologically verified) and 50 benign naevi (14 histologically verified) obtained from 60 patients.			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?			√

Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Index test was carried out using confocal laser scanning microscopy. All images obtained in the horizontal plane. From individual tumours, a minimum of 17 and a maximum of 170 images per tumour were obtained. Morphological features of melanocytic skin tumours were selected and assessed according to published studies. Melanocytic cytomorphology and architecture and keratinocyte cell borders were taken into account for diagnostic decisions. All morphological features were defined a priori without reference to the image set of the present study.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?		√	
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?			√
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		Histopathology was performed by well-trained dermato-pathologists, without diagnostic difficulties.			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?			√
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?		√	

		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			√
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments:					

Guitera *et al.* 2009[3]

Reviewer: George Osei-Assibey	**Study ID: #1057**		
Reference details for all refs relating to the trial:	Guitera, P., Pellacan G., Longo C., Seidenari S., Avramidis M., Menzies S.W. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. Journal of Investigative Dermatology 2009; 129(1): 131-138.		
GENERAL			
RCT ( )	**Prospective (√)**	**Retrospective ( )**	
Indication for test (diagnosis or margin delineation or both): Diagnosis			
Intervention(s): VivaScope 1000 and VivaScope 1500 **Comparator(s):** Dermoscope			
Year(s) study was done: September 2004 to August 2007			
Setting (e.g. District General, university hospital): Two referral centres, Sydney melanoma diagnostic centre, University of Sydney, University of Modena.			
Source of funding: Study partially supported by a grant from, the Fondazione Cassa di Risparmio di Moderna and Cancer Institute New South Wales.			
Conflict of interest: NR			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Melanocytic lesions that required excision following standard clinical practices. **Exclusion criteria:** Lentigo maligna and lesions of the soles and palms			

	Total	**Men**	**Women**
N enrolled	326	177	149
N excluded	Unclear		
N withdrawn	Unclear		
N lost to follow up	Unclear		
N completed	Unclear		

Age, Mean and Range (or data as reported): Median, 47; range, 6-90 years			
Lesion or patient level data	**Lesion ( )**	**Patient ( )**	**Both (√)**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: **Naevi:** compound = 127; Dermal = 9; Junctional = 42; Spitz n = 25; Light coloured = 13; Pigmented lesions = 172			

Malignant Melanoma: Median Breslow thickness 0.54mm (IQ 0 – 0.98); 34 in situ**;** 86 superficial spreading**;** 3 nodular**;** Light coloured n= 13**;** Pigmented lesions n= 110

12.2% did not display dermoscopic features of MM and 68% of naevi displaying dermoscopic features of malignancy.

Types and number of lesion excised		
Malignant melanoma	123	NR
Basal cell carcinoma	NR	NR
Squamous cell carcinoma	NR	NR
Lentigo maligna	Excluded	NR
Melanocytic naevi	203	NR

Previous tests or assessments: NR

Treatment (details of any treatments given): NR

Mortality (number of study patients reported dead): NR

INDEX TEST

Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM):

VivaScope 1000 and 1500 Lucid Inc, Henrietta, NY. 830 laser source.
Images correspond to field of view: 500x500 µm; Lateral resolution: 1.0 µm; Axial resolution; 3-5 µm

Image interpretation

Assessors (number of assessors): 2 image assessors working blind to the dermoscopy and histology results but not the age or site of the lesion. Images from Sydney were judged in Modena and vice-versa.

Experience in using VivaScope or RCM: NR

Qualitative (note how positive and negative findings were defined): Six diagnostic features were scored: non-edged papillae and cytological atypia at the dermal–epidermal junction were given a score of 2 each, whereas the presence of round pagetoid cells intraepidermally, widespread pagetoid infiltration in the epidermis, nucleated cells found within the dermal papillae, and cerebriform nests in the dermis all scored 1 each. A score greater than 3 corresponded to the threshold for the diagnosis of melanoma

Quantitative diagnostic thresholds (e.g. ABCD rule): NR

Final confirmation method (e.g. histology): Biopsy

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment: Comparator (e.g. dermoscope); (note machine name and manufacturer and the specification): In Sydney: High resolution digital oil immersion dermoscope dermoscopy camera (Sentry polytechnics Ltd, Sydney NSW, Australia).

In Modena: hand held dermascope (Delta 10 Heine, Herrsching, Germany)

Image interpretation

Assessors (number, expertise, experience in using comparator test): NR

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)	
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	NR
Number of re-excisions	NR
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	median Breslow thickness of 0.54mm
Lymph node involvement or micrometastases	NR

Test interpretation: NR

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
	NR	NR

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	No disease
Dermoscope (nevus)	Disease	TP = 138	FP
	No disease	FN	TN = 65
VivaScope 1500 (nevus)	Disease	TP = 65	FP
	No disease	FN	TN = 138
Dermoscope (malignant melanoma)	Disease	TP = 108	FP
	No disease	FN	TN = 15
VivaScope 1500 (malignant melanoma)	Disease	TP = 112	FP
	No disease	FN =11	TN = 11

B. Diagnostic accuracy of dermoscope and RCM in the biopsied set

		Diagnosed as benign by dermoscopy	**Diagnosed as malignant melanoma by dermoscopy**	**Diagnosed as benign by RCM**	**Diagnosed as malignant melanoma by RCM**
Nevus (n=203)	n	65	138	138	65
	%	(32%)[a]	(68%)	(68%)[a]	(32%)
Malignant melanoma (n=123)	n	15	108	11	112
	%	(12.2%)	(88%)	(8.9%)	(91%)
Odds ratio		3.4[b]	NR	27.5[b]	NR
95% CI		1.8-6.3[b]	NR	14.5-52.3[b]	NR

[a]Specificities of the two methods were significantly different (p<0.01).

[b]Odds ratio (95% CIs) for the diagnosis of MM when the method diagnosed the lesion as malignant were significantly different between RCM and dermoscopy (p<0.01)

C. Misdiagnosis of lesions

• A total of 15 melanomas (12%) were misclassified by dermoscopy • Eleven melanomas (9%) were misclassified by the RCM method • Only 2.4% of MMs being misclassified by both techniques
Abbreviations used in the table: CI, confidence interval; MM, malignant melanoma; n, number of lesions; FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive
Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Lesions (203 naevi and 123 melanomas with a median Breslow thickness of 0.54mm) recruited from two referral centres in Sydney (Australia) and Modena (Italy) to assess whether in vivo RCM enhances secondary evaluation of melanocytic lesions			
Index test(s)		RCM (VivaScope 1000 and VivaScope 1500, Lucid Inc., Henrietta, NY)			
Reference standard and target condition		Biopsy of suspected malignant melanoma			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Melanocytic lesions (203 naevi and 123 melanomas with a median Breslow thickness of 0.54mm) were recruited from two referral centres in Sydney (Australia) and Modena (Italy)			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		No prior testing is reported. Index test used to detect MM, no information about the presentation given			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?			√
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		RCM images were acquired by means of reflectance confocal laser scanning microscopes (VivaScope 100 and VivaScope 1500, Lucid Inc., Henrietta, NY).A sequence of montage images was acquired for each lesion. Confocal images were scored by experts, retrospectively and blinded to dermoscopy and pathological diagnosis. Six diagnostic features were scored: non-edged papillae and cytological atypia at the dermal-epidermal junction were given a score of 2 each, whereas the presence of round pagetoid cells intra-epidermally, widespread pagetoid infiltration in the epidermis, nucleated cells found within the dermal papillae, and cerebriform nests in the dermis all scored 1 each. A score greater than 3 corresponded to the threshold for the diagnosis of melanoma.			

			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?			√
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?			√
		Did patients receive the same reference standard?			√
		Were all patients included in the analysis?			√
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced	√		

		bias?			
Notes/comments:					

Guitera *et al.* 2013[43]

Reviewer: George Osei-Assibey	**Study ID: #1465**	
Reference details for all refs relating to the trial:	Guitera, P., Moloney F.J., Menzies S.W., Stretch J.R., Quinn M.J., Hong A., Fogarty G., Scolyer R.A.. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. JAMA dermatology 2013; 149(6): 692-698.	
GENERAL		
RCT ( )	**Prospective ()**	**Retrospective (√)**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): Dermoscope + VivaScope 1500 **Comparator(s):** Dermoscope		
Year(s) study was done: 2013		
Setting (e.g. District General, university hospital): Two tertiary referral melanoma centres (Sydney melanoma diagnostic centre & The melanoma institute Australia		
Source of funding: Melanoma Institute Australia, the Melanoma Foundation of the University of Sydney, Cancer Institute New South Wales, and the Australian and New Zealand Melanoma Trials Group.		
Conflict of interest: NR		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with one or more of the following: facial involvement of an LM lesion larger than 5 cm that would require complex reconstructive surgery; recurrent LM; or lightly pigmented or poorly delineated LM **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	37	11	26
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	NR	NR	NR

Age, Mean and Range (or data as reported): mean, 71; range, 47-88 years			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: 10 LM lesions were ametanotic, (including 9 lesions invisible to the naked eye or dermascopic assessment and 1 pink lesion. Nine were partially lightly pigmented 27 were in the cheek, 5 on the nose 2 on the temple, 1 on the eyebrow, 1 on the shoulder and 1 on the lower leg.			

Types and number of lesion excised	37	
Basal cell carcinoma	0	
Squamous cell carcinoma	0	

Lentigo maligna	32	
Lentigo maligna melanoma	5	
Melanocytic nevi	0	

Previous tests or assessments: NR

Treatment (details of any treatments given): NR

Mortality (number of study patients reported dead): NR

INDEX TEST

Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM):

VivaScope 1500; Lucid Inc 830-nm laser beam with a maximum power of 35mW

Image interpretation

Assessors (number of assessors): A team of at least 1 dermatologist, 1 plastic surgeon, 1 radiation oncologist

Experience in using VivaScope or RCM: All patients were assessed by a multidisciplinary team (usually at a specialized multidisciplinary LM clinic) including at least 1 dermatologist

Qualitative (note how positive and negative findings were defined):
When the lesion was visible clinically the RCM field of view was centred in the middle of the lesion. Confocal images were obtained in 4 radial directions allowing for anatomical barriers for margin determination until no evidence of LM was seen.

Quantitative diagnostic thresholds (e.g. ABCD rule): The length and width of the visible area were measured retrospectively from the clinical photograph and compared with the length and width of the lesion determined by RCM on the same photograph. The ratio of the RCM and clinical lengths and widths were then calculated. Images were evaluated and the differences were assessed as being greater or less than 5 mm.

Final confirmation method (e.g. histology): Each of the 37 patients had at least 1 positive site and 1 negative site biopsied to obtain histopathologic correlation. Targeted 2-3 mm punch biopsies were performed at the margins of the lesion, in particular when they were considered equivocal by RCM. Pathologic assessment of all biopsy specimens included examination of multiple tissue sections (typically 12 sections per 2-mm punch biopsy).

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification):
Dermoscope **(**Nikon D1X digital camera, and with a Nikon F401s camera with a 60-mm lens with dermatophot attachment)

Image interpretation

Assessors (number, expertise, experience in using comparator test): NR

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)

Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	2-3 mm

Number of re-excisions	Total number of biopsies per patient ranged from 2 to 12; median, 5; mean, 5
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	median Breslow thickness for the invasive melanomas was 0.62 mm (0.20–7.92 mm).
Lymph node involvement or micrometastases	NR

Test interpretation: NR
.

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
		√

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1500	Disease	TP = 55	FP = 4
	No disease	FN = 5	TN = 121
Dermoscope	Disease	TP = 21	FP = 3
	No disease	FN = 39	TN = 122

B. Pathologic, RCM, and dermoscopic correlations

	Pathologic analysis	Dermoscopic evaluation	VivaScope 1500
Number of sites positive for lentigo maligna	60	21 (39 FN)	55 (5 FN)
Number of sites negative for lentigo maligna	125	122 (3 FP)	121 (4 FP)

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Patients with suspicious pigmented lesions prospectively recruited from the Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics at the Queen Elizabeth II Health Sciences Centre (Canada) to undergo a clinical, dermoscopic and CSLM examination			
Index test(s)		VivaScope 1000			
Reference standard and target condition		Histopathological analysis			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Patients with suspicious pigmented lesions prospectively recruited from the Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics at the Queen Elizabeth II Health Sciences Centre (Canada)			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low risk	High risk	Unclear risk

		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Male and female patients aged ≥16 years and scheduled for biopsy of their lesions due to clinical suspicion of malignancy determined by clinical appearance or a history of change in the lesion after clinical, dermoscopic and vivo CSLM diagnosis			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		The lesion as well as adjacent, uninvolved, clinically normal, and control skin were imaged with VivaScope 1000. A drop of oil was applied to the control/lesional skin, followed by a metal adaptor ring with a tape adhesive. The confocal scanning laser microscope was scanned with a field of view of 450 x 400 µm which was scanned repeatedly over a total area of 13 mm. A single observer with experience in CSLM performed the imaging and examined all images in real-time. For the diagnosis of melanoma, the architectural and cytological features included: epidermal disarray with loss of the normal honeycomb pattern; a grainy image; pagetoid cells in the epidermis; complex branching dendrites or dendritic cells; atypical and pleomorphic refractile cells, and presence of bright, highly refractile particles. For the diagnosis of naevi, the architectural and cytological features included: a normal epidermal architecture with a regular honey combed pattern; the presence of junctional or dermal nests, and monomorphic refractile cells. For benign melanocytic lesions, it was expected that dendrites, if present, would be rare and not have complex branching patterns.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?		√	
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		

	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?			√
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?			√
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments: NR					

Langley *et al.* 2007[39]

Reviewer: George Osei-Assibey	**Study ID: #1465**	
Reference details for all refs relating to the trial:	Langley, R. G., Walsh, N., Sutherland, A. E., Propperova, I., Delaney, L., Morris, S. F., et al. (2007). "The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: a prospective study." Dermatology 215(4): 365-372.	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): VivaScope 1000 **Comparator(s):** Dermoscope		
Year(s) study was done: 2002-2005		
Setting (e.g. District General, university hospital): Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics at the Queen Elizabeth II Health Sciences Centre, Dalhousie University, Canada		
Source of funding: Canadian Dermatology Foundation, Nova Scotia Health Research Foundation and the University Internal Medicine Research Foundation.		

Conflict of interest: NR			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Male and female patients aged ≥16 years and scheduled for biopsy of their lesions due to clinical suspicion of malignancy determined by clinical appearance or a history of change in the lesion. **Exclusion criteria:** Patients were excluded from the study if their lesions were not amenable to CSLM (i.e. physically inaccessible site), or if they had a previous diagnostic biopsy done on the lesion.			

	Total	**Men**	**Women**
N enrolled	125	NR	NR
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	125	NR	NR

Age, Mean and Range (or data as reported): Mean 44.2 years (range from 16-84)			
Lesion or patient level data	**Lesion ( )**	**Patient ( )**	**Both (√)**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: The study included 125 patients with 125 lesions (88 melanocytic naevi and 37 melanomas).			

Types and number of lesion excised	125	NR
Basal cell carcinoma=	NR	NR
Squamous cell carcinoma=	NR	NR
Lentigo maligna=	NR	NR
Melanoma	37	NR
Melanocytic naevi=	88	NR

Previous tests or assessments: Clinical diagnosis
Treatment (details of any treatments given): NR
Mortality (number of study patients reported dead): NR
INDEX TEST
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1000, Lucid Inc., Henrietta, N.Y., USA
Image interpretation
Assessors (number of assessors): Single reviewer
Experience in using VivaScope or RCM: A single observer with experience in CSLM performed the imaging and examined all images in real-time
Qualitative (note how positive and negative findings were defined): For the diagnosis of melanoma, the architectural and cytological features included: epidermal disarray with loss of the normal honey comb pattern; a grainy image; pagetoid cells in the epidermis; complex branching dendrites or dendritic cells; atypical and pleomorphic refractile cells, and the presence of bright, highly refractile particles.

For the diagnosis of naevi, the architectural and cytological features included: a normal epidermal architecture with a regular honeycombed pattern; the presence of junctional or dermal nests, and monomorphic refractile cells. For benign melanocytic lesions, it was expected that dendrites, if present, would be rare and not have complex branching patterns.			
Quantitative diagnostic thresholds (e.g. ABCD rule): NR			
Final confirmation method (e.g. histology): Biopsy			
Technical failures (number and reasons): NR			
COMPARATOR TEST			
Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): Dermoscope **(**Nikon D1X digital camera, and with a Nikon F401s camera with a 60-mm lens with dermatophot attachment)			
Image interpretation			
Assessors (number, expertise, experience in using comparator test): Single reviewer			
Qualitative (note how positive and negative findings were qualitatively defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR			
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)			
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR		
Diameter of excisions (e.g. 2mm)	NR		
Number of excisions	125		
Number of re-excisions	NR		
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	median Breslow thickness for the invasive melanomas was 0.62 mm (0.20–7.92 mm).		
Lymph node involvement or micrometastases	NR		
Test interpretation: NR .			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**	
	NR	NR	
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:	**Reference standard**		
	Disease	**No disease**	
VivaScope 1000 — Disease	TP=36.96	FP=14.79	
VivaScope 1000 — No disease	FN=1.03	TN=72,23	

B. Specificity, sensitivity, PPV, NPV of dermoscopic and RCM						
Diagnostic test	**Number of benign lesions correctly diagnosed (total 88)**	**Number of malignant melanomas correctly diagnosed (total 37)**	**Specificity, %**	**Sensitivity, %**	**PPV, %**	**NPV, %**
Dermoscopy	74	33	84.1	89.2	70.2	94.9
RCM	73	36	83.0	97.3	70.6	98.6

- No significant difference (p=0.3932) was found between the sensitivities or specificities between the two methods
- RCM had a higher sensitivity compared to dermoscopy. The difference was 8.11% (95%CI: -3.15 to 19.35%; p=0.1797)
- Dermoscopy had a higher specificity with a difference of 1.14% (95%CI: –7.39 to 9.67%; p=0.7963).

C. Misdiagnosis of lesions

- Diagnosis made using dermoscopy and RCM together agreed on 73 out of 88 total benign naevi, and on 32 out of 37 malignant melanomas.
- There were 5 melanomas for which RCM and dermoscopy produced differing diagnoses. In these cases, RCM correctly classified 4 of the melanomas, whereas dermoscopy correctly classified the other melanoma.
- There were no cases where melanoma was misdiagnosed when RCM and dermoscopy were used together.
- There were 15 benign naevi for which the diagnoses made by dermoscopy and RCM differed. Of these, dermoscopy provided the correct diagnosis 9 times, and RCM made the correct diagnosis 6 times.
- There were 7 benign naevi for which both diagnoses were incorrect. Two of the melanomas were misdiagnosed by the investigator using dermoscopy, but correctly diagnosed by RCM were amelanotic/hypomelanotic melanomas.

Abbreviations used in the table: CI, confidence inreval; FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Patients with suspicious pigmented lesions prospectively recruited from the Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics at the Queen Elizabeth II Health Sciences Centre (Canada) to undergo a clinical, dermoscopic and CSLM examination			
Index test(s)		VivaScope 1000			
Reference standard and target condition		Histopathological analysis			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Patients with suspicious pigmented lesions prospectively recruited from the Division of Dermatology Pigmented Lesion Clinic and the Plastic Surgery Clinics at the Queen Elizabeth II Health Sciences Centre (Canada)			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low risk	High risk	Unclear risk
		Could the selection of patients have	√		

		introduced bias?			
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Male and female patients aged ≥16 years and scheduled for biopsy of their lesions due to clinical suspicion of malignancy determined by clinical appearance or a history of change in the lesion after clinical, dermoscopic and vivo CSLM diagnosis			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		The lesion as well as adjacent, uninvolved, clinically normal, and control skin were imaged with VivaScope 1000. A drop of oil was applied to the control/lesional skin, followed by a metal adaptor ring with a tape adhesive. The confocal scanning laser microscope was scanned with a field of view of 450 x 400 µm which was scanned repeatedly over a total area of 13 mm. A single observer with experience in CSLM performed the imaging and examined all images in real-time. For the diagnosis of melanoma, the architectural and cytological features included: epidermal disarray with loss of the normal honeycomb pattern; a grainy image; pagetoid cells in the epidermis; complex branching dendrites or dendritic cells; atypical and pleomorphic refractile cells, and presence of bright, highly refractile particles. For the diagnosis of naevi, the architectural and cytological features included: a normal epidermal architecture with a regular honey combed pattern; the presence of junctional or dermal nests, and monomorphic refractile cells. For benign melanocytic lesions, it was expected that dendrites, if present, would be rare and not have complex branching patterns.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?		√	
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?			√
			Low risk	High	Unclear

				risk	risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?			√
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments: NR					

Pan *et al.* 2012[40]

Reviewer: George Osei-Assibey	**Study ID: #1903**	
Reference details for all refs relating to the trial:	Pan ZY, Lin JR, Cheng TT, Wu JQ, Wu WY, Pan ZY, et al. In vivo reflectance confocal microscopy of Basal cell carcinoma: feasibility of preoperative mapping of cancer margins. Dermatologic Surgery. 2012;38(12):1945-50.	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): margin delineation		
Intervention(s): VivaScope 1500 **Comparator(s):** NR		
Year(s) study was done: NR		
Setting (e.g. District General, university hospital): Dermatology department		
Source of funding: NR		
Conflict of interest: None		
PARTICIPANT CHARACTERISTICS		

Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with lesions clinically suggestive of BCC			

Exclusion criteria: NR			
	Total	**Men**	**Women**
N enrolled	10	NR	NR
N excluded	0	NR	NR
N withdrawn	0	NR	NR
N lost to follow up	0	NR	NR
N completed	10	NR	NR
Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms:			
Types and number of lesion excised		13	
Basal cell carcinoma		13	
Squamous cell carcinoma		0	
Lentigo maligna		0	
Others		0	
Previous tests or assessments: NR			
Treatment (details of any treatments given): NR			
Mortality (number of study patients reported dead): NR			
INDEX TEST			
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1500; Lucid Technologies, Henrietta, NY), which uses a diode laser with a wavelength of 830 nm and power of less than 15 mW			
Image interpretation			
Assessors (number of assessors): NR			
Experience in using VivaScope or RCM: NR			
Qualitative (note how positive and negative findings were defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD rule): NR			
Final confirmation method (e.g. histology): Histopathology (surgical excision)			
Technical failures (number and reasons): NR			
COMPARATOR TEST			
Equipment : Comparator (e.g. dermoscope); (note machine name and manufacturer and the specification): NR			
Image interpretation			
Assessors (number, expertise, experience in using comparator test): NR			

Qualitative (note how positive and negative findings were qualitatively defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR			
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)			
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR		
Diameter of excisions (e.g. 2mm)	NR		
Number of excisions	13		
Number of re-excisions	NR		
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR		
Lymph node involvement or micrometastases	NR		
Test interpretation: NR			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**	
	NR	NR	
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:	**Reference standard**		
	Disease	**No disease**	
VivaScope 1500 – Disease	NR	NR	
VivaScope 1500 – No disease	NR	NR	
B. Histologic confirmation of margins correctly delineated			
	N (%) of cases/margins correctly delineated		
VivaScope 1500	7 (70%)		
Abbreviations used in the table: BCC, basal cell carcinoma; N, number of cases/patients; NR, not reported; RCM, reflectance confocal microscopy			
Quality assessment (QUADAS-2)			

Patients (setting, intended use of index test, presentation, prior testing)	Ten patients with lesions clinically suggestive of BCC and then biopsy proven were recruited randomly from the dermatology department for the margin study				
Index test(s)	VivaScope 1500				
Reference standard and target condition	Histopathologoical analysis				
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Patients with lesions clinically suggestive of BCC and then biopsy proven were recruited randomly from the dermatology department for the margin study. Thirteen patients with biopsy-proven BCC were recruited for surgical excision.			
			Yes	No	Unclear

		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?			√
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Ten patients with lesions clinically suggestive of BCC and then biopsy proven were recruited randomly from the dermatology department to investigate the feasibility of RCM in defining the margins of basal cell carcinoma before surgery.			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Confocal imaging was performed using VivaScope 1500; Lucid Technologies, Henrietta, NY), which uses a diode laser with a wavelength of 830 nm and power of less than 15 mW. This system provides high-resolution images (horizontal resolution 1.0 µm, vertical optical section thickness 3.0 µm) from a depth of 0 to 250 lm in vivo (from the epidermis to the papillary dermis). Blocks of 2- by 2-mm mosaic image mode were used to detect the margins.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of results of reference?	√		
		If a threshold was used, was it pre-specified?			√
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		Biopsy specimens were routinely processed with formalin fixation and paraffin embedding followed by vertical sectioning and hematoxylin and eosin staining. Slides were also examined for findings that appeared to correlate best with RCM structures under analysis.			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		

Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?	√		
Notes/comments:					

Pellacani *et al.* 2007[41]

Reviewer: George Osei-Assibey	**Study ID: #1952**	
Reference details for all refs relating to the trial:	Pellacani, G., Guitera, P., Longo, C., Avramidis, M., Seidenari, S., Menzies, S., et al. (2007). "The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions." Journal of Investigative Dermatology 127(12): 2759-2765.	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): Dermoscope + VivaScope 1000 or VivaScope 1500 **Comparator(s):** NR		
Year(s) study was done: NR		
Setting (e.g. District General, university hospital): Sydney Melanoma Diagnostic Centre of the Royal Prince Alfred Hospital, University of Sydney, Australia; and the Department of Dermatology of the University of Modena and Reggio Emilia, Italy		
Source of funding: Partially supported by grants from the Fondazione Cassa di Risparmio di Modena, Italy, the CNR (Centro Nazionale per la Ricerca), Italy, and the Cancer Institute New South Wales, Sydney, Australia.		
Conflict of interest: Authors have no conflict of interest		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with melanoma and equivocal melanocytic lesions. **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	332	174	158
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	NR	NR	NR

Age, Mean and Range (or data as reported): Median 47.7 years (interquartile range: 35.9-60.4)			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: NR			

Types and number of lesion excised	351	
Malignant melanoma	351	NR
Melanoma	136	NR
Melanocytic naevi	215	NR
Lentigo maligna melanoma	NR	NR

Previous tests or assessments: clinical and dermoscopic assessments	
Treatment (details of any treatments given): NR	
Mortality (number of study patients reported dead): NR	
INDEX TEST	
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1000 and VivaScope 1500, Lucid Inc., Henrietta, New York	
Image interpretation	
Assessors (number of assessors): 2	
Experience in using VivaScope or RCM: Two expert observers, blinded from anamnestic information, dermoscopy, and clinical aspects, but not for the location and the patient's age.	
Qualitative (note how positive and negative findings were defined): Morphological features of RCM images were evaluated for the presence/absence (binary non-parametric data), with the exception of the number and size of pagetoid cells that were dichotomized for statistics considering the presence of more than three pagetoid cells in five 0.5 x 0.5mm images and pagetoid cells larger than 20 µm, respectively	
Quantitative diagnostic thresholds (e.g. ABCD rule): The total RCM score was also calculated for each lesion evaluating the presence of two major features (non-edged papillae and cellular atypia at dermal-epidermal junction), each scored two points, and four minor ones (roundish pagetoid cells, widespread pagetoid infiltration, cerebriform nests, nucleated cells within the papilla), each scored 1 point, and compared with new models obtained by statistical analysis.	
Final confirmation method (e.g. histology): Biopsy	
Technical failures (number and reasons): NR	
COMPARATOR TEST	
Equipment : Comparator (e.g. dermoscope); (note machine name and manufacturer and the specification): NR	
Image interpretation	
Assessors (number, expertise, experience in using comparator test): NR	
Qualitative (note how positive and negative findings were qualitatively defined): NR	
Quantitative diagnostic thresholds (e.g. ABCD system): NR	
Quantitative diagnostic thresholds (e.g. ABCD system): NR	
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR	
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)	
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	NR
Number of re-excisions	NR
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR
Lymph node involvement or micrometastases	NR
Test interpretation: NR .	
Technical failures: NR	

Interval between index test and reference standard (excision of the histological specimen):	<6 weeks	>6 weeks
	NR	NR

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		Reference standard	
		Disease	**No disease**
Test	Disease	TP	FP
	No disease	FN	TN

B. Sensitivity and specificity for RCM score with different thresholds

RCM score threshold	Sensitivity	Specificity
≥1	96.3%	49.3%
≥2	96.3%	52.1%
≥3	91.9%	69.3%
≥4	79.4	77.2%
≥5	66.9%	82.3%
≥6	49.3%	91.6%
≥7	23.5%	98.1%
≥8	2.2%	100

Total RCM score was calculated for each lesion evaluating the presence of two major features (non-edged papillae and cellular atypia at dermal–epidermal junction), each scored two points, and four minor ones (roundish pagetoid cells, widespread pagetoid infiltration, cerebriform nests, nucleated cells within the papilla), each scored 1 point, and compared with new models obtained by statistical analysis.

Abbreviations used in the table: FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Patients with malignant melanomas recruited from the Sydney Melanoma Diagnostic Centre of the Royal Prince Alfred Hospital, University of Sydney (Australia) and the Department of Dermatology of the University of Modena and Reggio Emilia (Italy) were evaluated for 37 confocal features			
Index test(s)		VivaScope 1000 and VivaScope 1500			
Reference standard and target condition		Histopathology			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		A total of 351 melanocytic lesions from 332 patients with 351 melanomas, recorded by means of RCM at the Sydney Melanoma Diagnostic Centre (156 lesions) and at the Department of Dermatology of the University of Modena and Reggio Emilia (195 lesions) were included			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low	High	Unclear

			risk	risk	risk
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		351 melanocytic lesions from 332 patients (158 female and 174 males, median age of 47.7, interquartile range 35.9–60.4), of which 136 were melanomas, 215 were melanocytic naevi (49 junctional, 132 compound, nine intradermal and 25 Spitz naevi), recorded by means of RCM. The lesions were located on the head/neck region in 15 cases, on the abdomen and chest in 68, on the back in 135, on the upper limbs in 50, and on the lower limbs in 83, without significant differences between the site distribution of melanomas and naevi			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		RCM images were acquired by means of near-infrared reflectance confocal laser scanning microscopes (VivaScope 1000 and VivaScope 1500. A sequence of montage images (‘‘block’’ images) were acquired for each lesion at the level of the dermo-epidermal junction to explore a 4x4mm field of view per lesion. For large lesions, not completely comprised within the field of view, the device was centered on the lesion or on the portion with the most suspicious dermoscopic features, according to pattern analysis and standard second step melanoma diagnostic methods. Confocal sections, beginning at the stratum corneum and ending inside the papillary dermis, were recorded at areas of interest. More than 100 capture images per lesion were recorded.			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?		√	
		If a threshold was used, was it pre-specified?	√		
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low	High	Unclear

			risk	risk	risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			√
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments:					

Pellacani *et al.* 2014[45]

Reviewer: George Osei-Assibey	**Study ID: Obtained from updated search**	
Reference details for all refs relating to the trial:	Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. Br J Dermatol. 2014 Nov;171(5):1044-51. doi: 10.1111/bjd.13148. Epub 2014 Oct 19	
GENERAL		
RCT ( )	**Prospective (√)**	**Retrospective ( )**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): Dermoscope + VivaScope 1500 (RCM consultation) **Comparator(s):** Dermoscope (RCM documentation)		
Year(s) study was done: January 2010 - December 2010		
Setting (e.g. District General, university hospital): Melanoma-Pigmented Lesion Outpatient Clinic of the Dermatology Department, University of Modena and Reggio Emilia, Italy		
Source of funding: NR		
Conflict of interest: NR		
PARTICIPANT CHARACTERISTICS		

Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with the request of a mole check and/or with a suspect of melanoma **Exclusion criteria:** Clinical and/or dermtoscopic clear-cut epithelial tumours were not enrolled			
	Total	**Men**	**Women**
N enrolled	1005	443	562
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	NR	NR	NR
Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion ( )**	**Patient ( )**	**Both (√)**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: Patients referred for RCM consultation had a higher number of naevi (>100 naevi; 19%) and of atypical naevi (>5; 15%), compared to patients referred for RCM documentation and patients without RCM referral (p<0.0001). Personal and/or familial history of melanoma was recorded in approximately 8% of patients			
Types and number of lesion excised		292	NR
Basal cell carcinoma		38	NR
Melanoma		29	NR
Lentigo maligna		NR	NR
Spitz naevi		13	NR
Clark's naevi		192	NR
Other benign lesions		9	
Previous tests or assessments: Clinical dermoscopic examinations			
Treatment (details of any treatments given): NR			
Mortality (number of study patients reported dead): NR			
INDEX TEST			
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1500, MAVIG GmbH, Munich, Germany), which uses an 830 nm laser beam with a maximum power of 20 mW.			
Image interpretation			
Assessors (number of assessors): One			
Experience in using VivaScope or RCM: Confocal reader			
Qualitative (note how positive and negative findings were defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD rule): NR			
Final confirmation method (e.g. histology): Biopsy			

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): Dermoscopy examinations were conducted using the Dermlite HR (3Gen® LLC, San Juan Capistrano, CA, U.S.A).

Image interpretation

Assessors (number, expertise, experience in using comparator test): NR

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR

REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)

Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR
Diameter of excisions (e.g. 2mm)	NR
Number of excisions	292
Number of re-excisions	NR
Tumor staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR
Lymph node involvement or micrometastases	NR

Test interpretation: NR

Technical failures: NR

Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**
	NR	NR

RESULTS

A. Test accuracy: label all tables as appropriate (add more tables as necessary)

Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
Test	Disease	TP	FP
	No disease	FN	TN

B. Number (%) of lesions histologically proven

	RCM Referral				
Diagnosis	**Dermoscope (RCM documentation)**	**RCM proposed outcome**	**Dermoscope + VivaScope 1500 (RCM consultation)**	**RCM proposed outcome**	**Total**
Histopathology proven cases					
Melanoma	23 (79.3%)	Excised: 23; Follow up: 0	6 (20.7%)	Excised: 6; Follow up: 0	29
Basal cell carcinoma	19 (50%)	Excised: 19; Follow up: 0	19 (50%)	Excised: 19; Follow up: 0	38

Clark's naevi	121 (63%)	Excised: 57; Follow up: 64	71 (37%)	Excised: 46; Follow up: 25	192
Spitz naevi	8 (61.5%)	Excised: 6; Follow up: 2	5 (38.5%)	Excised: 3; Follow up: 2	13
Other benign lesions	12 (60%)	Excised: 5; Follow up: 7	8 (40%)	Excised: 7; Follow up: 1	19

RCM Documentation lesions: Histopathology results identified 23 melanomas; 19 BCC; 121 Clark's naevi, 11 Spitz naevi; and 12 other benign lesions.
In all melanoma and basal cell carcinomas identified at histology, RCM had recommended excision. In 82.6% of the melanoma (19/23) and in 94.7% of the BCC (18/19), RCM had proposed the same diagnosis as those confirmed at histopathology.
RCM Consultation lesions: Excision was recommended at RCM in all 6 cases of melanoma, in all 19 cases of BCC, and in 56 benign lesions (46 Clark's naevi, 3 Spitz naevi, and 7 benign non-melanocytic lesions.

C. Confocal-histopathology concordance

- Overall, RCM proposed diagnosis was concordant with histopathologic diagnosis in 216 out of 283 evaluated cases (76.3%)
- Most misdiagnoses were of naevi classified as melanomas (42 cases)
- BCC was the most accurate diagnosis (97.4%; 37/38), followed by melanoma (85.7%; 24/28)
- Spitz nevus was the most frequently misclassified diagnosis (accurate diagnosis 30.8%; 4/13); 6 were misclassified as Clark's naevi and 3 as melanoma

D. Number needed to Excise (NNE)

	NNE	**Benign:Melanoma**
NNE after RCM examination	6.8	197:29
NNE after follow-up (end of the study)	7.7	225:29
Estimated NNE values:		
a) Without RCM (overall) -Documentation group -Consultation group	14.6 ($p<0.05$ vs. actual value) 6.1 47.2 ($p<0.05$ vs. actual value)	424:29 141:23 283:6
b) Using RCM in all cases (before follow-up) -Documentation group -Consultation group	4.3 ($p<0.05$ vs. actual value) 2.9 ($p<0.05$ vs. actual value) 47.2 (significant vs. estimated NNE without RCM)	124:29 68:23 56:6

Immediate NNE was 6.8, and NNE after the follow-up period was 7.7. In the first hypothesis where RCM evaluations were not considered, the estimated NNE was 14.6 (6.1 for the RCM Documentation subgroup, and 47.2 for RCM Consultation subgroup, $p<0.05$). In the second hypothesis, considering RCM evaluations (in both RCM Documentation subgroup and lesions changed after follow-up) the NNE was 4.3 (2.9 for RCM Documentation subgroup, and 9.3 for RCM Consultation subgroup, $p<0.05$).

Abbreviations used in the table: BCC, basal cell carcinoma; FN, false negative; FP, false positive; NR, not reported; NNE, number needed to excise; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		Patients referred to a single Melanoma Clinic were consecutively enrolled.
Index test(s)		VivaScope 1500
Reference standard and target condition		Histopathology
Draw a flow for the primary study		
xxxxxx		
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection
		Patients with the request of a mole check and/or with a suspect of melanoma were included but patients with clinical and/or dermoscopic clear-cut epithelial tumours were excluded

			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?	√		
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?	√		
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		Patients had a request of a mole check and/or with a suspect of melanoma. The purpose of the index test was to prospectively determine its potential impact when implemented in a routine melanoma diagnosis workflow			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Confocal images were acquired using a near-infrared reflectance confocal microscope (VivaScope 1500, MAVIG GmbH, Munich, Germany), which uses an 830 nm laser beam with a maximum power of 20 mW			
			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?		√	
		If a threshold was used, was it pre-specified?		√	
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?			√
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?		√	
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		

		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?		√	
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?		√	
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√
Notes/comments:					

Rao *et al.* 2013[42]

Reviewer: George Osei-Assibey	**Study ID: #2108**		
Reference details for all refs relating to the trial:	Rao, B. K., Mateus R., Wassef C., Pellacani G. "In vivo confocal microscopy in clinical practice: comparison of bedside diagnostic accuracy of a trained physician and distant diagnosis of an expert reader." Journal of the American Academy of Dermatology, 2013; 69(6): e295-e300.		
GENERAL			
RCT ( )	**Prospective (√)**	**Retrospective ( )**	
Indication for test (diagnosis or margin delineation or both): Diagnosis			
Intervention(s): Dermoscope + VivaScope 1500 **Comparator(s):** NR			
Year(s) study was done: June 2010 – September 2011			
Setting (e.g. District General, university hospital): Tele-consultation			
Source of funding: NR			
Conflict of interest: Drs Pellacani and Rao are both consultants for CaliberID. Dr Mateus and Ms Wassef have no conflicts of interest to declare.			
PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: Patients with lesions that had been selected for removal for either cosmetic or medical reasons.			

Exclusion criteria: NR			
	Total	**Men**	**Women**
N enrolled	340	NR	NR
N excluded	6	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	17	NR	NR
N completed	334	NR	NR
Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion (√)**	**Patient ( )**	**Both ()**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: Images captured at the superficial spinous /granualar layer, dermoepidemo junction, papillary dermis and more reticular dermis. The lesions were on the trunk (n =135), face (n=90), upper limbs (n=70), lower limbs (n=39)			
Types and number of lesion excised		334	
Melanoma		9	NR
Basal cell carcinoma		27	NR
Squamous cell carcinoma=		43	NR
Lentigo maligna=		NR	NR
Lentigo maligna melanoma=		NR	NR
Melanocytic naevi=		182	
Actinic keratosis		26	
Seborrheic keratosis (and Solar Lentigo)		24	
Others		23	
Previous tests or assessments: NR			
Treatment (details of any treatments given): NR			
Mortality (number of study patients reported dead): NR			
INDEX TEST			
Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM): VivaScope 1500, CaliberID, Rochester, NY			
Image interpretation			
Assessors (number of assessors): Two			
Experience in using VivaScope or RCM: Images were reviewed by 2 confocal readers, one in New York, NY (reader 1), and the other in Modena, Italy (reader 2). Reader 1 at the start of the study had less experience reading RCM images compared with reader 2, who had over 9 years of experience with RCM.			
Qualitative (note how positive and negative findings were defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD rule): 2 viva stacks from the Stratum corneum to			

the stratum corneum to the dermis were taken.			
Final confirmation method (e.g. histology): Histopathological analysis, method not reported			
Technical failures (number and reasons): NR			
COMPARATOR TEST			
Equipment : Comparator (e.g. Dermoscope); (note machine name and manufacturer and the specification): NR			
Image interpretation			
Assessors (number, expertise, experience in using comparator test): NR			
Qualitative (note how positive and negative findings were qualitatively defined): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Quantitative diagnostic thresholds (e.g. ABCD system): NR			
Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR			
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)			
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)	NR		
Diameter of excisions (e.g. 2mm)	NR		
Number of excisions	334		
Number of re-excisions	NR		
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)	NR		
Lymph node involvement or micrometastases	NR		
Test interpretation: NR .			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):	**<6 weeks**	**>6 weeks**	
	NR	NR	
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1500	Disease	TP = 79	FP = 60
	No disease	FN = 20	TN = 175
B. Comparison of RCM diagnosis by a trained physician vs. distant diagnosis by an expert			
	Reader 1 (bedside trained physician) evaluated 317 of 334 cases (94.9%)	**Reader 2 (distant expert) evaluated 323 of 334 cases (96.7%)**	**Combined sensitivity and specificity**
Sensitivity	93.1%	97.4%	98.6%

Specificity	64.1%	80.5%	44%

Diagnostic performance of the readers (percent of lesions correctly diagnosed)

- For reader 1, RCM diagnosis was in agreement with histopathological diagnosis in 83.2% of naevi, 58.3% of seborrheic keratosis, and 17.3%% of other benign lesion, 66.7% of melanomas, 74.1% of BCC, and 37.2% of SCC.
- RCM diagnosis of reader 2 was the same as the histopathological diagnosis in 83% of naevi, 66.7% of seborrheic keratosis, 21.7% of other benign lesions, 88.9% of melanomas, 51.9% of BCC, and 72.1% of SCC.

Abbreviations used in the table: FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; SCC, squamous cell carcinoma; TN, true negative; TP, true positive

Quality assessment (QUADAS-2)

Patients (setting, intended use of index test, presentation, prior testing)		The study sought to assess RCM diagnostic accuracy in a support teleconsultation setting in lesions had been selected for removal for either cosmetic or medical reasons			
Index test(s)		VivaScope 1500			
Reference standard and target condition		Histopathological analysis			
Draw a flow for the primary study					
xxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Patients selected were from the United States and had lesions that had been selected for removal for either cosmetic or medical reasons. A total of 340 lesions were imaged between June 2010 and September 2011. Six cases were excluded from the study because of insufficient information.			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?			√
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?			√
			Low risk	High risk	Unclear risk
		Could the selection of patients have introduced bias?		√	
	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		The intended test was to assess its diagnostic accuracy in a support teleconsultation			
			Low risk	High risk	Unclear risk
		Is there concern that the included patients do not match the review question?		√	
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		Lesions were imaged using VivaScope 1500. An imaging protocol allowed for the capture of 1 dermoscopic image and 4 RCM images for each lesion. Series of consecutive high resolution images starting from the stratum corneum to the dermis were taken. The images were reviewed by 2 confocal readers. Diagnosis was based on the dermoscopic image and confocal microscopy evaluation before excision.			

			Yes	No	Unclear
		Were the index test results interpreted without knowledge of the results of the reference standard?			√
		If a threshold was used, was it pre-specified?		√	
			Low risk	High risk	Unclear risk
		Could the conduct or interpretation of the index test have introduced bias?		√	
	B. Concerns regarding applicability		Low risk	High risk	Unclear risk
		Is there concern that the index test, its conduct, or interpretation differ from the review question?		√	
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Unclear
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?			√
			Low risk	High risk	Unclear risk
		Could the reference standard, its conduct, or its interpretation have introduced bias?			√
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Unclear
		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?			√
			Low risk	High risk	Unclear risk
		Could the patient flow have introduced bias?			√

Notes/comments:

Stanganelli *et al.* 2014[48]

Reviewer: George Osei-Assibey	**Study ID: Handsearched**	
Reference details for all refs relating to the trial:	Stanganelli I, Longo C, Mazzoni L, Magi S, Medri M, Lanzanova G, Farnetani F, Pellacani G. Integration of reflectance confocal microscopy in sequential dermoscopy follow-up improves melanoma detection accuracy. Br J Dermatol. 2014 Aug 25. doi: 10.1111/bjd.13373.	
GENERAL		
RCT ( )	**Prospective ( )**	**Retrospective (√)**
Indication for test (diagnosis or margin delineation or both): Diagnosis		
Intervention(s): Dermoscope + VivaScope 1500 **Comparator(s):**		
Year(s) study was done: July 2010 to July 2012		
Setting (e.g. District General, university hospital): Skin Cancer Unit at the 'Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori' (IRST IRCCS), in Ravenna/Forli and Meldola, Italy		
Source of funding: No external funding		
Conflict of interest: None declared		

PARTICIPANT CHARACTERISTICS			
Consecutive sample	**Yes** (√)	**No** ( )	**Unclear** ( )
Inclusion criteria: (i) lesion excised after change at the follow-up visit; (ii) availability of baseline and follow-up dermoscopic images; (iii) availability of a complete standard set of RCM images;21,22 (iv) availability of histopathology report and slides. **Exclusion criteria:** NR			

	Total	**Men**	**Women**
N enrolled	70	38	32
N excluded	NR	NR	NR
N withdrawn	NR	NR	NR
N lost to follow up	NR	NR	NR
N completed	70	NR	NR

Age, Mean and Range (or data as reported): NR			
Lesion or patient level data	**Lesion ( )**	**Patient ( )**	**Both (√)**
Lesion characteristics if known at the time VivaScope or RCM was performed and duration of symptoms: Most common skin phototype was type III (n = 50), followed by II (n = 18), I (n = 1) and IV (n = 1). Twenty-six patients (37%) had a history of melanoma. Regarding total naevus counts, 27 patients (39%) had more than 50 melanocytic naevi, 33 patients (47%) had 10–50 naevi and 10 patients (14%) had fewer than 10 naevi.			
Types and number of lesion excised	70		

Melanoma	12
Benign	58
Lentigo maligna	NR
Lentigo maligna melanoma	NR
Melanocytic naevi	NR

Previous tests or assessments: NR

Treatment (details of any treatments given): NR

Mortality (number of study patients reported dead): NR

INDEX TEST

Equipment: (note machine name and manufacturer of VivaScope 1500 or 3000 or RCM):

RCM with VivaScope 1500 (Lucid Inc., MAVIG GmbH, Munich, Germany) using an 830-nm laser at a maximum power of 20 mW

Dermoscopy with Leica Wild M-650 stereo microscope with a Sony 3CCD DXC-930P colour video camera connected to a workstation with DERMOX application software (Tesi Imaging, Milan, Italy

Image interpretation

Assessors (number of assessors): Three

Experience in using VivaScope or RCM: RCM images were evaluated jointly by three expert dermatologists who had no knowledge of the clinical, dermoscopic or histopathology information, and reached a consensus or majority opinion for feature evaluation and diagnostic classification.

Qualitative (note how positive and negative findings were defined):
RCM - Each lesion was classified considering the main melanoma features and weighted according to extent and distribution for differential diagnosis with dysplastic naevus.

Dermoscopy - Baseline morphological features of each lesion were determined from the digital dermoscopy images using the standard seven-point checklist of melanoma-specific criteria for pigmented skin lesions20 and focusing on the global pattern and symmetry of both colour and structure. Lesions were evaluated for each of the following variables: (i) symmetrical or asymmetrical changes in structural dermoscopy features; (ii) symmetrical or asymmetrical chromatic changes; (iii) appearance of melanoma-specific features (e.g. blue-white veil, atypical or negative pigment network, atypical vascular patterns, irregular dots and globules, streaks, irregular blotches, peripheral pigmented structureless areas and regression).

Quantitative diagnostic thresholds (e.g. ABCD rule):

RCM –NR

Dermoscopy - A score of ‘no change’ was assigned if all variables remained constant, with a tolerance of major axis change of 2 mm; ‘minor change’ if there was only symmetrical change in structural or chromatic pattern; ‘moderate change’ if either structural or chromatic changes were asymmetrical, but there were no melanoma-specific criteria; and ‘major change’ if there were asymmetrical structural and chromatic changes, or the appearance of melanoma-specific criteria

Final confirmation method (e.g. histology): Histopathology

Technical failures (number and reasons): NR

COMPARATOR TEST

Equipment : Comparator (e.g. Dermascope); (note machine name and manufacturer and the specification): NR

Image interpretation

Assessors (number, expertise, experience in using comparator test): NR

Qualitative (note how positive and negative findings were qualitatively defined): NR

Quantitative diagnostic thresholds (e.g. ABCD system): NR

Technical failures (number and reasons e.g. lesion site inaccessible with equipment): NR			
REFERENCE STANDARD (Test: Biopsy (used for confirmation and staging) note any details)			
Method of preparation of the specimen (immunohistochemistry - antibodies -; S100, HMB 45 and Melan A)		NR	
Diameter of excisions (e.g. 2mm)		NR	
Number of excisions		70	
Number of re-excisions		NR	
Tumour staging: Thickness of the melanoma (Breslow thickness, Clark level, TNM system)		Median 0.4 mm (range 0.2-1.0 mm)	
Lymph node involvement or micrometastases		NR	
Test interpretation: NR			
Technical failures: NR			
Interval between index test and reference standard (excision of the histological specimen):		**<6 weeks**	**>6 weeks**
		NR	NR
RESULTS			
A. Test accuracy: label all tables as appropriate (add more tables as necessary)			
Note threshold(s) where appropriate:		**Reference standard**	
		Disease	**No disease**
VivaScope 1500	Disease	TP=11	FP=19
	No disease	FN=1	TN=39
Abbreviations used in the table: FN, false negative; FP, false positive; NR, not reported; RCM, reflectance confocal microscopy; TN, true negative; TP, true positive;			
Quality assessment (QUADAS-2)			

Patients (setting, intended use of index test, presentation, prior testing)		Data on 70 patients with 70 lesions obtained from a database at the Skin Cancer Unit at the 'Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori' (IRST IRCCS), in Ravenna/Forli and Meldola, Italy			
Index test(s)		VivaScope 1500			
Reference standard and target condition		Histopathology			
Draw a flow for the primary study					
xxxxxxxx					
Domain 1: Patient selection	**A. Risk of bias**	Describe methods of patient selection			
		Inclusion criteria included (i) lesion excised after change at the follow-up visit (ii) availability of baseline and follow-up dermoscopic images (iii) availability of a complete standard set of RCM images (iv) availability of histopathology slides.			
			Yes	No	Unclear
		Was a consecutive or random sample of patients enrolled?			√
		Was a case-control design avoided?	√		
		Did the study avoid inappropriate exclusions?	√		
			Low risk	High risk	Unclear
		Could the selection of patients have introduced bias?	√		

	B. Concerns regarding applicability	Describe included patients (prior testing, presentation, intended use of index test and setting)			
		The population included 32 women (46%), mean age 39 years, and 38 men (54%), mean age 40 years. The index test was conducted to determine whether combining it with sequential dermoscopy imaging can improve melanoma detection and reduce the burden of unnecessary excisions			
			Low risk	High risk	Uncle ar
		Is there concern that the included patients do not match the review question?	√		
Domain 2: Index test(s)	**A. Risk of bias**	Describe the index test and how it was conducted and interpreted			
		RCM images of 0.5x0.5 mm were acquired with a lateral resolution of 1 µm and an axial resolution of 3-5 µm and assembled into composite images that covered 4-8 mm^2 mosaics. Images were evaluated jointly by 3 expert dermatologists who had no knowledge of the clinical, dermoscopic or histopathology information, and reached a consensus or majority opinion for feature evaluation and diagnostic classification. Each lesion was classified considering the main melanoma features			
			Yes	No	Uncle ar
		Were the index test results interpreted without knowledge of the results of the reference standard?	√		
		If a threshold was used, was it pre-specified?			
		NR			
			Low risk	High risk	Uncle ar
		Could the conduct or interpretation of the index test have introduced bias?	√		
	B. Concerns regarding applicability		Low risk	High risk	Uncle ar
		Is there concern that the index test, its conduct, or interpretation differ from the review question?	√		
Domain 3: Reference standard	**A. Risk of bias**	Describe the reference standard and how it was conducted and interpreted			
		NR			
			Yes	No	Uncle ar
		Is the reference standard likely to correctly classify the target condition?	√		
	B. Concerns regarding applicability	Were the reference standard results interpreted without knowledge of the results of the index test?	√		
			Low risk	High risk	Uncle ar
		Could the reference standard, its conduct, or its interpretation have introduced bias?	√		
		Is there concern that the target condition as defined by the reference standard does not match the review question?	√		
Domain 4: Flow and timing	**A. Risk of bias**	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)			
		NR			
		Describe the time interval and any interventions between index test(s) and reference standard			
		NR			
			Yes	No	Uncle ar

		Was there an appropriate interval between index test(s) and reference standard?			√
		Did all patients receive a reference standard?	√		
		Did patients receive the same reference standard?	√		
		Were all patients included in the analysis?	√		
			Low risk	High risk	Unclear
		Could the patient flow have introduced bias?			√
Notes/comments:					

9.4 Appendix 4: Table of excluded studies with rationale on clinical effectiveness

Full reference details	Reason for exclusion
Gurgen J, Gatti M. Epiluminescence microscopy (dermoscopy) versus visual inspection during Mohs' microscopic surgery of infiltrative basal cell carcinoma. Dermatologic surgery. 2012;38(7 Pt 1):1066-9.	Dermoscopy *vs.* visual inspection
Guardiano RA, Grande DJ. A direct comparison of visual inspection, curettage, and epiluminescence microscopy in determining tumour extent before the initial margins are determined for Mohs' micrographic surgery. Dermatologic surgery. 2010;36(8):1240-4.	Visual inspection *vs.* curettage *vs.* dermoscopy
Binder M, Schwarz M, Winkler A, Steiner A, Kaider A, Wolff K, et al. Epiluminescence microscopy. A useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. Archives of Dermatology. 1995;131(3):286-91.	Trained *vs.* non-trained experts in dermoscopy
Argenziano G, Puig S, Zalaudek I, Sera F, Corona R, Alsina M, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. Journal of clinical oncology. 2006;24(12):1877-82.	Accuracy of referrals using Dermoscope
Blum A, Hofmann-Wellenhof R, Luedtke H, Ellwanger U, Steins A, Roehm S, et al. Value of the clinical history for different users of dermoscopy compared with results of digital image analysis. Journal of the European Academy of Dermatology & Venereology. 2004;18(6):665-9.	Trained *vs.* untrained clinicians in dermoscopy
Blum A, Rassner G, Garbe C, Blum A, Rassner G, Garbe C. Modified ABC-point list of dermoscopy: A simplified and highly accurate dermoscopic algorithm for the diagnosis of cutaneous melanocytic lesions. Journal of the American Academy of Dermatology. 2003;48(5):672-8.	Accuracy of ABCD point list in dermoscopy
Carli P, De GV, Crocetti E, Mannone F, Massi D, Chiarugi A, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. British Journal of Dermatology. 2004;150(4):687-92.	Dermoscope users *vs.* non-users
Chiacchio N, Hirata SH, Enokihara MY, Michalany NS, Fabbrocini G, Tosti A. Dermatologists' accuracy in early diagnosis of melanoma of the nail matrix. Archives of dermatology. 2010;146(4):382-7.	Clinicians agreement of nail melanomas with dermoscopy
Dolianitis C, Kelly J, Wolfe R, Simpson P, et al. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. Archives of Dermatology. 2005;141(8):1008-14.	Comparison of 4 dermoscopic algorithms
Dreiseitl S, Binder M, Hable K, Kittler H, Dreiseitl S, Binder M, et al. Computer versus human diagnosis of melanoma: evaluation of the feasibility of an automated diagnostic system in a prospective clinical trial. Melanoma Research. 2009;19(3):180-4.	Experts *vs.* non-experts in the use of computer-based diagnostic systems
Elbaum M, Kopf AW, Rabinovitz HS, Langley RG, Kamino H, Mihm MC, Jr., et al. Automatic differentiation of melanoma from melanocytic naevi with multispectral digital dermoscopy: a feasibility study. Journal of the American Academy of Dermatology. 2001;44(2):207-18.	Differentiation between melanoma and melanocytic naevi
Fruhauf J, Leinweber B, Fink-Puches R, Ahlgrimm-Siess V, Richtig E, Wolf IH, et al. Patient acceptance and diagnostic utility of automated digital image analysis of pigmented skin lesions. Journal of the European Academy of Dermatology & Venereology. 2012;26(3):368-72.	Patients acceptance of dermoscopy
Garcia Arroyo JL, Garcia ZB, Garcia Arroyo JL, Garcia Zapirain B. Detection of pigment network in dermoscopy images using supervised machine learning and structural analysis. Computers in Biology & Medicine. 2014;44:144-57.	Only dermoscopy, no RCM
Garnavi R, Aldeen M, Bailey J, Garnavi R, Aldeen M, Bailey J. Computer-aided diagnosis of melanoma using border and wavelet-based texture analysis. IEEE Transactions on Information Technology in Biomedicine. 2012;16(6):1239-52.	Only dermoscopy, no RCM
Garnavi R, Aldeen M, Celebi ME, Varigos G, Finch S, Garnavi R, et al. Border detection in dermoscopy images using hybrid thresholding on optimized color channels. Computerized Medical Imaging & Graphics. 2011;35(2):105-15.	Only dermoscopy, no RCM

Gilmore S, Hofmann-Wellenhof R, Soyer HP, Gilmore S, Hofmann-Wellenhof R, Soyer HP. A support vector machine for decision support in melanoma recognition. Experimental Dermatology. 2010;19(9):830-5.	Only dermoscopy, no RCM
Haenssle HA, Krueger U, Vente C, Thoms KM, Bertsch HP, Zutt M, et al. Results from an observational trial: digital epiluminescence microscopy follow-up of atypical naevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. Journal of Investigative Dermatology. 2006;126(5):980-5.	Only dermoscopy, no RCM
Henning JS, Dusza SW, Wang SQ, Marghoob AA, et al. The CASH (color, architecture, symmetry, and homogeneity) algorithm for dermoscopy. Journal of the American Academy of Dermatology. 2007;56(1):45-52.	Accuracy of dermoscopy algorithm
Hoffmann K, Gambichler T, Rick A, Kreutz M, Anschuetz M, Grunendick T, et al. Diagnostic and neural analysis of skin cancer (DANAOS). A multicentre study for collection and computer-aided analysis of data from pigmented skin lesions using digital dermoscopy. British Journal of Dermatology. 2003;149(4):801-9.	Only dermoscopy, no RCM
Iyatomi H, Oka H, Celebi ME, Ogawa K, Argenziano G, Soyer HP, et al. Computer-based classification of dermoscopy images of melanocytic lesions on acral volar skin. Journal of Investigative Dermatology. 2008;128(8):2049-54.	Classification of dermoscopy images
Iyatomi H, Oka H, Saito M, Miyake A, Kimoto M, Yamagami J, et al. Quantitative assessment of tumour extraction from dermoscopy images and evaluation of computer-based extraction methods for an automatic melanoma diagnostic system. Melanoma Research. 2006;16(2):183-90.	Only dermoscopy, no RCM
Kockara S, Mete M, Yip V, Lee B, Aydin K, Kockara S, et al. A soft kinetic data structure for lesion border detection. Bioinformatics. 2010;26(12):i21-i8.	Assessment of dermoscopic images
Lorentzen H, Weismann K, Petersen CS, Larsen FG, Secher L, Skodt V, et al. Clinical and dermatoscopic diagnosis of malignant melanoma. Assessed by expert and non-expert groups. Acta Dermato-Venereologica. 1999;79(4):301-4.	Only dermoscopy, no RCM
Lorentzen H, Weismann K, Secher L, Petersen CS, Larsen FG, Lorentzen H, et al. The dermatoscopic ABCD rule does not improve diagnostic accuracy of malignant melanoma. Acta Dermato-Venereologica. 1999;79(6):469-72.	Accuracy of ABCD rule in dermoscopy
Lorentzen HF, Eefsen RL, Weismann K, Lorentzen HF, Eefsen RL, Weismann K. Comparison of classical dermatoscopy and acrylic globe magnifier dermatoscopy. Acta Dermato-Venereologica. 2008;88(2):139-42.	Classical dermoscopy *vs.* acrylic globe magnifier dermoscopy
MacKie RM, Fleming C, McMahon AD, Jarrett P, MacKie RM, Fleming C, et al. The use of the dermatoscope to identify early melanoma using the three-colour test. British Journal of Dermatology. 2002;146(3):481-4.	Only dermoscopy, no RCM
Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions. Journal of the American Academy of Dermatology. 1994;30(4):551-9.	Accuracy of ABCD rule in dermoscopy
Piccolo D, Ferrari A, Peris K, Diadone R, Ruggeri B, et al. Dermoscopic diagnosis by a trained clinician vs. a clinician with minimal dermoscopy training vs. computer-aided diagnosis of 341 pigmented skin lesions: a comparative study. British Journal of Dermatology. 2002;147(3):481-6.	Trained clinician *vs.* clinician with minimal dermoscopy training *vs.* computer-aided diagnosis
Soyer HP, Argenziano G, Zalaudek I, Corona R, Sera F, Talamini R, et al. Three-point checklist of dermoscopy. A new screening method for early detection of melanoma. Dermatology. 2004;208(1):27-31.	Experts vs. non-experts in dermoscopy
Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Three-point checklist of dermoscopy: an open internet study. British Journal of Dermatology. 2006;154(3):431-7.	Only dermoscopy, no RCM
Cosgarea RU. Our 9 years digital dermoscopy experience in the diagnosis of early melanoma. JDDG - Journal of the German Society of Dermatology. 2013 Conference (var.pagings):July.	Only dermoscopy, no RCM
Gereli MCO. Comparison of two dermoscopic techniques in the melanoma diagnosis: 3-Point checklist and 7-point checklist. Turkderm Deri Hastaliklari ve Frengi Arsivi. 2008;42(2):45-50.	Comparison of two dermoscopic techniques

9.5 Appendix 5: List of ongoing trials on clinical effectiveness

Title, study and identifier and link	Type of RCM	Study design	Indication	Status (ongoing or completed
Sensitivity/Specificity Study of Non-invasive Imaging for Melanoma Diagnosis (NCT 01556503) https://clinicaltrials.gov/ct2/show/NCT01556503?term=vivascope&rank=1	VivaScope 1500 and 2500	Prospective observational	Lesion diagnosis	Ongoing (April 2011 to August 2015)
Treatment of Basal Cell Carcinoma Using a One-stop-shop With Reflectance Confocal Microscopy: a Randomized Controlled Multicenter Trial (NCT02285790) https://clinicaltrials.gov/ct2/show/NCT02285790?term=vivascope&rank=2	VivaScope 1500	RCT	Lesion diagnosis	Ongoing (January 2015 to February 2016)
Reflectance confocal microscopy of wounds during Mohs' surgery: feasibility testing of a mosaicing algorithm for intraoperative imaging of cancer margins (NCT01872130) https://clinicaltrials.gov/ct2/show/NCT01872130?term=reflectance+confocal+ microscopy&rank=4	Not reported	Prospective observational	Margin delineation	Ongoing (May 2013 to May 2015)
VivaNet Study. A Multicenter Study of Confocal Reflectance Microscopy in Telemedicine (NCT01385943) https://clinicaltrials.gov/ct2/show/NCT01385943?term=reflectance+confocal+microscopy&rank=8	Not reported	Prospective observational	Lesion diagnosis	Ongoing (April 2011 to December 2015)
Evaluation of optical imaging for margin delineation of non-melanoma skin cancer (NCT00432471) https://clinicaltrials.gov/ct2/show/NCT00432471?term=reflectance+confocal+microscopy&rank=14	Not reported	Prospective observational	Margin delineation	Ongoing (January 2007 to January 2016)

9.6 Appendix 6: Health Economics search strategy

Search 1: Economic evaluations

Medline

Full database title: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

Date of search: 21st October 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	175861
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	4241
3	exp skin neoplasms/	99460
4	exp melanoma/	76818
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	7559
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	19588
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	134054
8	exp carcinoma, basal cell/	14918
9	exp carcinoma, squamous cell/	107922
10	exp Neoplasms, Basal Cell/	16143
11	exp Basal Cell Nevus Syndrome/	1083
12	exp eyelid neoplasms/	3914
13	Kaposi* sarcoma*.mp.	11949
14	Merkel* cell* carcinoma*.mp.	1974
15	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.	1645
16	or/1- 15	344314
17	Health economics.mp.	2317
18	Economic evaluation.mp.	5602
19	exp "Costs and Cost Analysis"/	188506
20	exp Cost-Benefit Analysis/	62754
21	exp Models, economic/	10609
22	exp "Fees and Charges"/	27778
23	exp Budgets/	12298
24	Cost Effectiveness Analysis.mp.	6038
25	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	23117
26	Cost Minimi?ation Analysis.mp.	489
27	Cost Utility Analysis.mp.	1327
28	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.	104630
29	(decision adj1 (tree* or analys* or model*)).tw.	9424
30	(econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic*	638050

	or pharmaco-economic*).tw.	
31	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.	4538
32	Markov*.tw.	14886
33	or/17-31	864990
34	16 and 33	5004
35	(letter or editorial or comment or case report or review).pt.	3334906
36	(animals not humans).sh.	3983385
37	34 (not 35 or 36)	3682
38	(((CSLM or laser microscop* or confocal microscop* or confocal scanning microscop* or reflec*) adj confocal adj microscop*) or RCM or confocal laser scanning microscop* or reflectan*-mode confocal microscop*).mp.	10172
39	exp Microscopy, confocal/	44436
40	vivascope*.mp.	22
41	exp Dermoscopy/	2067
42	(Dermatoscop* or dermascop* or dermoscop* or (epiluminescen* adj microscop*) or skin* surface* microscop*).mp.	3210
43	or/38-42	53228
44	43 not (35 or 36)	30492
45	37 and 44	38

Embase

Full database title: 1974 to 2014 October 20
Date of search: 21st October 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	285165
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	5818
3	skin tumor/ or exp skin cancer/	214794
4	exp melanoma/ or exp non melanoma skin cancer/ or exp melanoma skin cancer/ or exp amelanotic melanoma/ or exp cutaneous melanoma/	268360
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	10211
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	25252
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	143567
8	exp basal cell carcinoma/	21007
9	exp squamous cell carcinoma/	101150
10	exp basal cell nevus syndrome/	1954
11	exp eyelid tumor/	3553
12	Kaposi* sarcoma*.mp.	18521
13	Merkel* cell* carcinoma*.mp.	2589
14	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.	18117
15	or/1-14	485211
16	exp "cost utility analysis"/	5618
17	exp "cost benefit analysis"/	65480
18	exp "cost effectiveness analysis"/	100676

19	exp "cost minimization analysis"/	2538
20	health economics.mp.	35999
21	economic evaluation.mp.	13996
22	statistical model/	103962
23	exp fee/	34213
24	exp budget/	19880
25	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	31850
26	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.	134581
27	(decision adj1 (tree* or analys* or model*)).tw.	11939
28	(econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.	768319
29	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.	5823
30	Markov*.tw.	16453
31	or/16-30	1124796
32	15 and 31	9954
33	(letter or editorial or comment or case report or review).pt.	3302908
34	(animal$ not human$).sh,hw.	3787830
35	32 not (33 or 34)	7260
36	(((CSLM or laser microscop* or confocal microscop* or confocal scanning microscop* or reflec*) adj confocal adj microscop*) or RCM or confocal laser scanning microscop* or reflectan*-mode confocal microscop*).mp.	11941
37	exp confocal microscopy/	40535
38	vivascope*.mp.	155
39	exp epiluminescence microscopy/	3889
40	(Dermatoscop* or dermascop* or dermoscop* or (epiluminescen* adj microscop*) or skin* surface* microscop*).mp.	4476
41	or/36-40	54904
42	41 not (33 or 34)	36364
43	35 and 42	80

HTA database (HTA)

Date of search	14/10/2014
Search terms (and fields searched)	#1 (skin or melano* or cutaneous or sarcoma or non next melanoma) near/3 (secondar* or neoplasm or cancer or carcinoma or adenocarcinom* or tumor or tumour or malignan* or metastas or lesion) #2 superficial near/2 melanoma or SSM or nodular next melanoma or lentigo next maligna or lentiginous next melanoma or Hutchinson* near/2 freckle or "melanoma in situ" or "acral lentiginous melanoma" or "amelanotic melanoma" #3 MeSH descriptor: [Skin Neoplasms] explode all trees #4 MeSH descriptor: [Melanoma] explode all trees #5 non next melanoma or BCC or gorlin* next syndrome or rodent next ulcer or basalioma or NMSC #6 (basal or basocellular or basosquamous) near/2 (carcinoma or cancer or neoplasm or tumor or tumour or epithelioma or malignan) #7 (squamous near/2 (carcinoma or tumor or tumour or cancer or neoplasm or epithelioma or malignan*)) or "Bowen's disease" or "squamous cell carcinoma in situ" or SCC #8 MeSH descriptor: [Carcinoma, Basal Cell] explode all trees #9 MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees #10 MeSH descriptor: [Neoplasms, Basal Cell] explode all trees #11 MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees #12 MeSH descriptor: [Eyelid Neoplasms] explode all trees #13 "Kaposi's sarcoma"

	#14 "Merkel cell carcinoma" #15 "T-cell lymphoma" or "cutaneous T-cell lymphoma" or CTCL or "primary cutaneous lymphoma" #16 {or #1-#15} #17 CSLM or laser next microscop* or confocal next microscop* or confocal next scanning next microscop* or reflec* next confocal next microscop* or RCM or confocal next laser next scanning next microscop* or reflectan*-mode next confocal next microscop* #18 MeSH descriptor: [Microscopy, Confocal] explode all trees #19 vivascope #20 MeSH descriptor: [Dermoscopy] explode all trees #21 Dermatoscop* or dermascop* or dermoscop* or "epiluminescence microscopy" or "skin surface microscope" #22 {or #17-#21} #23 #16 and #22
Number of hits	5

NHS Economic Evaluations Database (NHS EED)

Date of search	14/10/2014
Search terms (and fields searched)	#1 (skin or melano* or cutaneous or sarcoma or non next melanoma) near/3 (secondar* or neoplasm or cancer or carcinoma or adenocarcinom* or tumor or tumour or malignan* or metastas or lesion) #2 superficial near/2 melanoma or SSM or nodular next melanoma or lentigo next maligna or lentiginous next melanoma or Hutchinson* near/2 freckle or "melanoma in situ" or "acral lentiginous melanoma" or "amelanotic melanoma" #3 MeSH descriptor: [Skin Neoplasms] explode all trees #4 MeSH descriptor: [Melanoma] explode all trees #5 non next melanoma or BCC or gorlin* next syndrome or rodent next ulcer or basalioma or NMSC #6 (basal or basocellular or basosquamous) near/2 (carcinoma or cancer or neoplasm or tumor or tumour or epithelioma or malignan) #7 (squamous near/2 (carcinoma or tumor or tumour or cancer or neoplasm or epithelioma or malignan*)) or "Bowen's disease" or "squamous cell carcinoma in situ" or SCC #8 MeSH descriptor: [Carcinoma, Basal Cell] explode all trees #9 MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees #10 MeSH descriptor: [Neoplasms, Basal Cell] explode all trees #11 MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees #12 MeSH descriptor: [Eyelid Neoplasms] explode all trees #13 "Kaposi's sarcoma" #14 "Merkel cell carcinoma" #15 "T-cell lymphoma" or "cutaneous T-cell lymphoma" or CTCL or "primary cutaneous lymphoma" #16 {or #1-#15} #17 CSLM or laser next microscop* or confocal next microscop* or confocal next scanning next microscop* or reflec* next confocal next microscop* or RCM or confocal next laser next scanning next microscop* or reflectan*-mode next confocal next microscop* #18 MeSH descriptor: [Microscopy, Confocal] explode all trees #19 vivascope #20 MeSH descriptor: [Dermoscopy] explode all trees #21 Dermatoscop* or dermascop* or dermoscop* or "epiluminescence microscopy" or "skin surface microscope" #22 {or #17-#21} #23 #16 and #22
Number of hits	2

FIRST PASS

Potential economic evaluations reviewed at second pass (n=5):

#	Study
1	Morton, C. A., et al. (2011). "Community photo-triage for skin cancer referrals: An aid to service delivery." Clinical and Experimental Dermatology 36(3): 248-254.

2	Stratigos, A. J. and A. D. Katsambas (2009). "The value of screening in melanoma." Clinics in Dermatology 27(1): 10-25.
3	Tromme, I., et al. (2014). "Selective use of sequential digital dermoscopy imaging allows a cost reduction in the melanoma detection process: a belgian study of patients with a single or a small number of atypical nevi." PLoS ONE [Electronic Resource] 9(10): e109339.
4	Watts, C., et al. (2013). "Using multiple data sources to determine the cost of managing individuals in a clinic for individuals at high risk of primary melanoma." JDDG - Journal of the German Society of Dermatology Conference: 8th World Congress of Melanoma, 9th Congress of the European Association of Dermatology, EADO, 7th Interdisciplinary Melanoma/Skin Cancer Meeting, 3rd European Post-Chicago Melanoma Meeting 2013 Hamburg Germany. Conference Start: 20130717 Conference End: 20130720. Conference Publication: (var.pagings). 20130711 (pp 20130771-20130772).
5	Wilson, E. C., et al. (2013). "The cost-effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model." Value in Health 16(2): 356-366.

SECOND PASS

Summary of reasons for exclusion, economic evaluations

Bibliographic reference	Reasons for exclusion
Wilson, E. C., et al. (2013)	Clinical experts advised the TAG that the MoleMate system (SiaScopy) is not a relevant intervention; SiaScopy produces images at surface features, whereas the VivaScope can image cells of a histological quality
Tromme, I., et al. (2014)	Digital dermascopy is not a diagnostic test of interest
Watts, C., et al. (2013)	Interventions not relevant
Stratigos, A. J. and A. D. Katsambas (2009)	Not an economic evaluation or costing study
Morton, C. A., et al. (2011)	Interventions not relevant

Search 2: Resource use and cost-of-illness studies

Medline

Full database title: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present
Date of search: 17th December 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	177999
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	4293
3	exp skin neoplasms/	100649
4	exp melanoma/	77456
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	7658
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	20007
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	135631
8	exp carcinoma, basal cell/	15250
9	exp carcinoma, squamous cell/	108973

10	exp Neoplasms, Basal Cell/	16501
11	exp Basal Cell Nevus Syndrome/	1089
12	exp eyelid neoplasms/	3991
13	Kaposi* sarcoma*.mp.	12016
14	Merkel* cell* carcinoma*.mp.	2022
15	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.	1659
16	or/1- 15	348258
17	(UK or United Kingdom or England or Wales or Scotland or GB or Great Britain).tw.	160549
18	exp Great Britain/	312045
19	(NHS or National Health Service or DOH or Department of Health or PSSRU or Personal Social Services Research Unit).tw.	35310
20	or/17-19	412613
21	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	23706
22	(econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.	647359
23	exp "cost of illness"/	19141
24	or/21-23	675466
25	16 and 20 and 24	110
26	(letter or editorial or comment or case report or review).pt.	3373280
27	(animals not humans).sh.	4004891
28	25 not (26 or 27)	83

Embase

Full database title: 1974 to 2014 December 16th
Date of search: 17th December 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	288557
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	5905
3	skin tumor/ or exp skin cancer/	216673
4	exp melanoma/ or exp non melanoma skin cancer/ or exp melanoma skin cancer/ or exp amelanotic melanoma/ or exp cutaneous melanoma/	262555
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	10400
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	25557
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	145113
8	exp basal cell carcinoma/	21264
9	exp squamous cell carcinoma/	102063
10	exp basal cell nevus syndrome/	1973
11	exp eyelid tumor/	3589
12	Kaposi* sarcoma*.mp.	18669
13	Merkel* cell* carcinoma*.mp.	2642
14	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous*	18384

	lymphoma*).mp.	
15	or/ 1-14	487558
16	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	32693
17	(econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.	777455
18	exp "cost of illness"/	14591
19	or/16-18	806927
20	(UK or United Kingdom or England or Wales or Scotland or GB or Great Britain).tw.	279911
21	exp United Kingdom/	338464
22	(NHS or National Health Service or DOH or Department of Health or PSSRU or Personal Social Services Research Unit).tw.	45706
23	or/20-22	523277
24	15 and 19 and 23	291
25	(letter or editorial or comment or case report or review).pt.	3322723
26	(animal$ not human$).sh,hw.	3800224
27	24 not (25 or 26)	194

First pass

Resource use and cost-of-illness studies reviewed at second pass (n=9):

#	Study
1	Brown, B., et al. (2008). "An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy, Switzerland, and the United Kingdom." Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 11(5): 791-799.
2	Dixon, S., et al. (2006). "Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial." British journal of cancer 94(4): 492-498.
3	Johnston, K., et al. (2012). "Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study)." European journal of cancer (Oxford, England: 1990) 48(14): 2175-2182.
4	Kim, K., et al. (2011). "Economic burden of resected squamous cell carcinoma of the head and neck in an incident cohort of patients in the UK." Head & neck oncology 3: 47.
5	Morris, S., et al. (2009). "Cost of skin cancer in England." The European journal of health economics: HEPAC: health economics in prevention and care 10(3): 267-273.
6	Parthan, A., et al. (2009). "Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck." Head & neck 31(10): 1255-1262.
7	Ramrakha-Jones, V. S. and R. M. Herd (2003). "Treating Bowen's disease: a cost-minimization study." The British journal of dermatology 148(6): 1167-1172.
8	Vallejo-Torres, L., et al. (2014). "Measuring current and future cost of skin cancer in England." Journal of public health (Oxford, England) 36(1): 140-148.
9	Wilson, E. C. F., et al. (2013). "The cost-effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model." Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 16(2): 356-366.

Second pass

Summary of reasons for exclusion, resource use and cost-of-illness studies

Study	Reasons for exclusion
Brown, B., et al. (2008)	Irrelevant population: SCC of the head and neck*
Dixon, S., et al. (2006)	Only total incremental costs are reported
Johnston, K., et al. (2012)	Irrelevant population: unresectable melanoma treatment pattern used to estimate the cost per user or per patient
Kim, K., et al. (2011)	Irrelevant population: SCC of the head and neck*
Parthan, A., et al. (2009)	Irrelevant population: SCC of the head and neck*
Ramrakha-Jones, V. S. and R. M. Herd (2003)	Irrelevant population: Bowen's disease (provisionally included as a proxy for skin cancer, but later excluded as sources of melanoma and non-melanoma skin cancer were identified)
*comprising cancers of the oral cavity, nasopharynx, pharynx and larynx which are outside of the population specified in the protocol Abbreviations used in the table: SCC, squamous cell carcinoma.	

Search 3: Health related quality of life (HRQoL) studies

Medline

Full database title: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present
Date of search: 10st October 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	175702
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	4237
3	exp skin neoplasms/	99426
4	exp melanoma/	76777
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	7537
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	19570
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	133902
8	exp carcinoma, basal cell/	14912
9	exp carcinoma, squamous cell/	107853
10	exp Neoplasms, Basal Cell/	16136
11	exp Basal Cell Nevus Syndrome/	1080
12	exp eyelid neoplasms/	3914
13	Kaposi* sarcoma*.mp.	11933
14	Merkel* cell* carcinoma*.mp.	1976
15	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.	1643
16	or/ 1-15	343965
17	((quality adj3 life) or life quality or QOL).ti,ab.	165058
18	(HRQL or HRQOL or HRQol).ti,ab.	10741

19	(value adj2 life).ti,ab. or exp "Value of Life"/	6494
20	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/	11098
21	(disabilit$3 adj2 life).ti,ab.	2298
22	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	17444
23	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	1413
24	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).ti,ab.	488
25	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.	3126
26	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	24
27	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.	349
28	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	4590
29	(hye or hyes or health$ year$ equivalent$).ti,ab.	65
30	(willing$ adj2 (pay or accept)).tw.	4195
31	standard gamble$.tw.	708
32	(health adj3 (utilit$3 or value$2 or preference$2)).tw.	7607
33	(visual analog$3 scale or VAS).tw.	41882
34	(person$ trade-off or person$ trade off or PTO).ti,ab.	626
35	(contingent value or contingent valuation).ti,ab.	440
36	discrete choice.ti,ab.	736
37	((quality adj3 wellbeing index) or QWB).ti,ab.	181
38	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.	1263
39	(utility or utilities).ti,ab.	129244
40	disutil$.ti,ab.	255
41	((quality of adj (wellbeing or well-being or well being)) or qwb).ti,ab.	191
42	(health utilities index or HUI or hui$1).ti,ab.	1388
43	or/17-42	353292
44	16 and 43	5517
45	(letter or editorial or comment or case report or review).pt.	3331203
46	(animals not humans).sh.	3981381
47	44 not (45 or 46)	4394
48	limit 47 to yr="1997 -Current"	3812

Embase

Full database title: 1974 to 2014 October 16
Date of search: 17st October 2014

#	Terms	Hits
1	((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.	285106
2	((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.	5815
3	skin tumor/ or exp skin cancer/	214761

4	exp melanoma/ or exp non melanoma skin cancer/ or exp melanoma skin cancer/ or exp amelanotic melanoma/ or exp cutaneous melanoma/	268303
5	(non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.	10210
6	((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.	25248
7	((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.	143535
8	exp basal cell carcinoma/	21004
9	exp squamous cell carcinoma/	101134
10	exp basal cell nevus syndrome/	1954
11	exp eyelid tumor/	3551
12	Kaposi* sarcoma*.mp.	18518
13	Merkel* cell* carcinoma*.mp.	2588
14	(T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.	18116
15	or/ 1-14	485109
16	((quality adj3 life) or life quality or QOL).ti,ab.	234577
17	(HRQL or HRQOL or HRQol).ti,ab.	14935
18	(value adj2 life).ti,ab.	698
19	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp quality adjusted life year/	16541
20	(disabilit$3 adj2 life).ti,ab.	2667
21	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	24039
22	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	1537
23	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).ti,ab.	743
24	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.	4495
25	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.	35
26	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.	334
27	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	7421
28	(hye or hyes or health$ year$ equivalent$).tw.	110
29	(willing$ adj2 (pay or accept)).tw.	5611
30	standard gamble$.tw.	800
31	(health adj3 (utilit$3 or value$2 or preference$2)).tw.	9274
32	(visual analog$3 scale or VAS).tw.	59137
33	(person$ trade-off or person$ trade off or PTO).ti,ab.	641
34	(contingent value or contingent valuation).ti,ab.	565
35	discrete choice.ti,ab.	935
36	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.	1598
37	(utility or utilities).ti,ab.	158757
38	disutil$.ti,ab.	390
39	((quality of adj (wellbeing or well-being or well being)) or qwb).ti,ab.	207
40	(health utilities index or HUI or hui$1).ti,ab.	1858
41	or/16-40	464862

42	15 and 41	10334
43	(letter or editorial or comment or case report or review).pt.	3302060
44	(animal$ not human$).sh,hw.	3786854
45	42 not (43 or 44)	8001
46	limit 45 to yr="1997 -Current"	7400

HTA database (HTA)

Date of search	14/10/2014
Search terms (and fields searched)	#1 (skin or melano* or cutaneous or sarcoma or non next melanoma) near/3 (secondar* or neoplasm or cancer or carcinoma or adenocarcinom* or tumor or tumour or malignan* or metastas or lesion) #2 superficial near/2 melanoma or SSM or nodular next melanoma or lentigo next maligna or lentiginous next melanoma or Hutchinson* near/2 freckle or "melanoma in situ" or "acral lentiginous melanoma" or "amelanotic melanoma" #3 MeSH descriptor: [Skin Neoplasms] explode all trees #4 MeSH descriptor: [Melanoma] explode all trees #5 non next melanoma or BCC or gorlin* next syndrome or rodent next ulcer or basalioma or NMSC #6 (basal or basocellular or basosquamous) near/2 (carcinoma or cancer or neoplasm or tumor or tumour or epithelioma or malignan) #7 (squamous near/2 (carcinoma or tumor or tumour or cancer or neoplasm or epithelioma or malignan*)) or "Bowen's disease" or "squamous cell carcinoma in situ" or SCC #8 MeSH descriptor: [Carcinoma, Basal Cell] explode all trees #9 MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees #10 MeSH descriptor: [Neoplasms, Basal Cell] explode all trees #11 MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees #12 MeSH descriptor: [Eyelid Neoplasms] explode all trees #13 "Kaposi's sarcoma" #14 "Merkel cell carcinoma" #15 "T-cell lymphoma" or "cutaneous T-cell lymphoma" or CTCL or "primary cutaneous lymphoma" #16 {or #1-#15}
Number of hits	151

NHS Economic Evaluations Database (NHS EED)

Date of search	14/10/2014
Search terms (and fields searched)	#1 (skin or melano* or cutaneous or sarcoma or non next melanoma) near/3 (secondar* or neoplasm or cancer or carcinoma or adenocarcinom* or tumor or tumour or malignan* or metastas or lesion) #2 superficial near/2 melanoma or SSM or nodular next melanoma or lentigo next maligna or lentiginous next melanoma or Hutchinson* near/2 freckle or "melanoma in situ" or "acral lentiginous melanoma" or "amelanotic melanoma" #3 MeSH descriptor: [Skin Neoplasms] explode all trees #4 MeSH descriptor: [Melanoma] explode all trees #5 non next melanoma or BCC or gorlin* next syndrome or rodent next ulcer or basalioma or NMSC #6 (basal or basocellular or basosquamous) near/2 (carcinoma or cancer or neoplasm or tumor or tumour or epithelioma or malignan) #7 (squamous near/2 (carcinoma or tumor or tumour or cancer or neoplasm or epithelioma or malignan*)) or "Bowen's disease" or "squamous cell carcinoma in situ" or SCC #8 MeSH descriptor: [Carcinoma, Basal Cell] explode all trees #9 MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees #10 MeSH descriptor: [Neoplasms, Basal Cell] explode all trees #11 MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees #12 MeSH descriptor: [Eyelid Neoplasms] explode all trees #13 "Kaposi's sarcoma" #14 "Merkel cell carcinoma" #15 "T-cell lymphoma" or "cutaneous T-cell lymphoma" or CTCL or "primary cutaneous

	lymphoma" #16 {or #1-#15}
Number of hits	134

First pass

Potential studies reporting utility data reviewed at second pass (n=41):

#	Study
Published studies	
1	Askew, R. L., et al. (2011). "Mapping FACT-melanoma quality-of-life scores to EQ-5D health utility weights." Value in Health 14(6): 900-906.
2	Barzey, V., et al. (2013). "Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis." Journal of Medical Economics 16(2): 202-212.
3	Beusterien, K. M., et al. (2009). "Societal preference values for advanced melanoma health states in the United Kingdom and Australia." British Journal of Cancer 101(3): 387-389.
4	Brown, B., et al. (2008). "An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy, Switzerland, and the United Kingdom." Value in Health 11(5): 791-799.
5	Chan, A. L., et al. (2011). "Cost effectiveness of cetuximab concurrent with radiotherapy for patients with locally advanced head and neck cancer in Taiwan: a decision-tree analysis." Clinical Drug Investigation 31(10): 717-726.
6	Chen (2008). "Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma (Archives of Dermatology (2007) 143, 11, (1386-1392))." Archives of Dermatology 144(2).
7	Cormier, J. N., et al. (2007). "Cost effectiveness of adjuvant interferon in node-positive melanoma." Journal of Clinical Oncology 25(17): 2442-2448.
8	Crott, R., et al. (2004). "Cost-utility of adjuvant high-dose interferon alpha therapy in stage III cutaneous melanoma in Quebec." Value in Health 7(4): 423-432.
9	Dixon, S., et al. (2006). "Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial." British Journal of Cancer 94(4): 492-498.
10	Essers, B. A., et al. (2006) Cost-effectiveness of Mohs micrographic surgery vs surgical excision for basal cell carcinoma of the face (Structured abstract). Archives of Dermatology 142, 187-194
11	Freedberg, K. A., et al. (1999) Screening for malignant melanoma: a cost-effectiveness analysis. J Am Acad Dermatol 41: 738-45.
12	Hannouf, M. B., et al. (2012). "Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer." PLoS ONE [Electronic Resource] 7(6): e38557.
13	Hengge, U. R., et al. (2007). "Cost-effectiveness of reduced follow-up in malignant melanoma." Journal der Deutschen Dermatologischen Gesellschaft 5(10): 898-907.
14	Hillner, B. E. et al. (1998). "Cost-effectiveness assessment of interferon alfa-2b as adjuvant therapy of high-risk resected cutaneous melanoma." European Journal of Cancer 34 Suppl 3: S18-S21.
15	Hillner, B. E., et al. (1997). "Economic analysis of adjuvant interferon alfa-2b in high-risk melanoma based on projections from Eastern Cooperative Oncology Group 1684." Journal of Clinical Oncology 15(6): 2351-2358.
16	Hirst, N. G., et al. (2012). "Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use." Value in Health 15(2): 261-268.
17	Hollenbeak, C. S., et al. (2001). "The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the N0 neck." Cancer 92(9): 2341-2348.
18	Kansal, A. R., et al. (2013). "Cost-effectiveness of a FISH assay for the diagnosis of melanoma in the USA." Expert Review of Pharmacoeconomics & Outcomes Research 13(3): 371-380.
19	King, S. M., et al. (2011). "Melanoma quality of life: pilot study using utility measurements." Archives of Dermatology 147(3): 353-354.
20	Ko, C. Y., et al. (2003). "Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment." Journal of Surgical Research 114(1): 1-5.

21	Lear, W., et al. (2008). "Measurement of utility in nonmelanoma skin cancer." Journal of Cutaneous Medicine & Surgery 12(3): 102-106.
22	Losina, E., et al. (2007). "Visual screening for malignant melanoma: a cost-effectiveness analysis." Archives of Dermatology 143(1): 21-28.
23	Morton, R. L., et al. (2009). "The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma." Annals of Surgical Oncology 16(4): 929-940.
24	Parthan, A., et al. (2009). "Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck." Head & Neck 31(10): 1255-1262.
25	Seidler, A. M., et al. (2009). "Mohs versus traditional surgical excision for facial and auricular nonmelanoma skin cancer: an analysis of cost-effectiveness." Dermatologic Surgery 35(11): 1776-1787.
26	Shingler, S. L., et al. (2013). "Utilities for advanced basal cell carcinoma." Journal of Medical Economics 16(6): 777-783.
27	Wilson, E. C., et al. (2013). "The cost-effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model." Value in Health 16(2): 356-366.
28	Wilson, L. S., et al. (2002). "Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma." Melanoma Research 12(6): 607-617.
29	Skin cancer prevention: information, resources and environmental changes (PH32)
Conference papers	
30	Amdahl, J., et al. (2014). "Cost effectiveness of trametinib as first-line (1l) treatment for braf v600 positive advanced or metastatic melanoma - a canadian societal perspective." Value in Health Conference: ISPOR 19th Annual International Meeting Montreal, QC Canada. Conference Start: 20140531 Conference End: 20140604. Conference Publication: (var.pagings). 20140517 (20140533) (pp A20140583).
31	Dalgard, F., et al. (2014). "The psychological burden of common skin diseases in 13 European countries." British Journal of Dermatology Conference: 94th Annual Meeting of the British Association of Dermatologists Glasgow United Kingdom. Conference Start: 20140701 Conference End: 20140703. Conference Publication: (var.pagings). 20140171 (pp 20140703).
32	Delea, T. E., et al. (2014). "Cost-utility analysis of dabrafenib/trametinib combination (d+t) for BRAFV600 mutation-positive metastatic melanoma (MM) from the united kingdom (UK) national health service (NHS) perspective." Value in Health Conference: ISPOR 19th Annual International Meeting Montreal, QC Canada. Conference Start: 20140531 Conference End: 20140604. Conference Publication: (var.pagings). 20140517 (20140533) (pp A20140588).
33	Klein, J., et al. (2013). "Health-related quality of life in head-and-neck cancer treated with radiation therapy with or without chemotherapy: A systematic review." International Journal of Radiation Oncology Biology Physics Conference: 55th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2013 Atlanta, GA United States. Conference Start: 20130922 Conference End: 20130925. Conference Publication: (var.pagings). 20130987 (20130922 SUPPL. 20130921) (pp S20130605-S20130606).
34	Radford, M., et al. (2013). "Cost-effectiveness of ipilimumab in previously treated patients for advanced melanoma in portugal." Value in Health Conference: ISPOR 18th Annual International Meeting New Orleans, LA United States. Conference Start: 20130518 Conference End: 20130522. Conference Publication: (var.pagings). 20130516 (20130513) (pp A20130139).
35	Sebaratnam, D., et al. (2013). "Cost effectiveness analysis of Mohs micrographic surgery versus traditional surgical excision for head and neck basal cell carcinoma." Journal of the American Academy of Dermatology Conference: 71st Annual Meeting of the American Academy of Dermatology Miami Beach, FL United States. Conference Start: 20130301 Conference End: 20130305. Conference Publication: (var.pagings). 20130368 (20130304 SUPPL. 20130301) (pp AB20130159).
36	Seubring, I., et al. (2013). "Cost-effectiveness and quality of life on mal-pdt versus imiquimod and simple surgical excision in basal cell carcinoma; A decision tree model." Nederlands Tijdschrift voor Dermatologie en Venereologie Conference: 14th Annual Scientific Meeting of the Nederlandse Vereniging voor Experimentele Dermatologie, NVED 2013 Lunteren Netherlands. Conference Start: 20130131 Conference End: 20130201. Conference Publication: (var.pagings). 20130123 (20130131) (pp 20130150-20130151).
37	Shih, V., et al. (2014). "Braf targeted therapies for the treatment of metastatic melanoma: A cost-effectiveness analysis." Value in Health Conference: ISPOR 19th Annual International Meeting Montreal, QC Canada. Conference Start: 20140531 Conference End: 20140604. Conference Publication: (var.pagings). 20140517 (20140533) (pp A20140584).
Technology Appraisals	
38	Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321)
39	Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319)

40	Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268)
41	Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269)

SECOND PASS

From the references lists of those 17 cost-effectiveness studies identified from the database search, 17 sources of utility values were identified. Of those, 3 studies were previously identified from the database search and met the criteria for full-text review at second pass (Hillner 1997; Beusterien 2009; Freedberg 1999), 12 studies were not considered to meet the inclusion criteria based on a review of the title and abstract (Killbridge 2001; Mooney 1997; Killbridge 2002; Beusterien 2003; Jani 2003; Lafuma 2001; Van de Hout 2003; NICE 2009), or publication date (Hutton 1996; Torrance 1988; Goodwin 1988; Weeks 1994), and the remaining 2 studies were ordered for a full-text review (Bendeck 2004; Bendeck 2004b).

Source of utility values applied in cost-effectiveness studies identified from the HRQoL search, October 2014

Reference identified from the search	Source of utility values
Cormier et al., 2007	Killbridge et al., 2001*; Mooney et al., 1997***; Hillner et al., 1997
Crott et al., 2004	Killbridge et al., 2002*
Barzey et al., 2013	Beusterien et al., 2009
Hannouf et al., 2012	NICE (2009) Manufacturer's submission: cetuximab for the treatment of recurrent or metastatic head and neck cancer **
Hillner 1998	Goodwin et al., 1988****; Weeks et al., 1994****
Hirst et al., 2012	Bendeck et al., 2004a; Beusterien et al., 2003*****; Killbridge et al., 2001*; Hillner et al., 1997
Kansal et al., 2013	Beusterien et al., 2009
Losina et al., 2007	Bendeck et al., 2004a
Morton et al., 2009***	Killbridge et al., 2001*; Bendeck et al., 2004a; Torrance et al., 1989****; Jani et al., 2003; Lafuma et al., 2001; Hutton et al., 1996****; Van de Hout et al., 2003; Hillner et al., 1997; Mooney et al., 1997
Wilson et al., 2013	Bendeck et al., 2004b
Wilson et al., 2002	Killbridge et al., 2001*
Sebaratnam et al., 2013	Not reported
PH32	Freedberg et al., 1999
TA321	Beusterien et al., 2009
TA319	Beusterien et al., 2009
TA268	Beusterien et al., 2009
TA269	Beusterien et al., 2009

*Killbridge et al., 2001 and Killbridge et al., 2002 assessed utilities for health states associated with adjuvant IFN therapy

**SCC of the head and neck comprises of cancers of the oral cavity, nasopharynx, pharynx and larynx which are outside of the population specified in the protocol

***Lafuma 2001, Van de Hout 2003, Mooney 1997 and Jani 2003 focused on adjuvant IFN therapy, bone metastasis, lung metastasis and breast cancer, respectively; the TAG considers these populations to be irrelevant to that specified in the protocol.

****Excluded based on criteria (published pre 1997)

*****Beusterien 2003 collected utility data from a trial comparing subcutaneous histamine plus IL-2 and IL-2 alone

Summary of reasons for exclusion, HRQoL

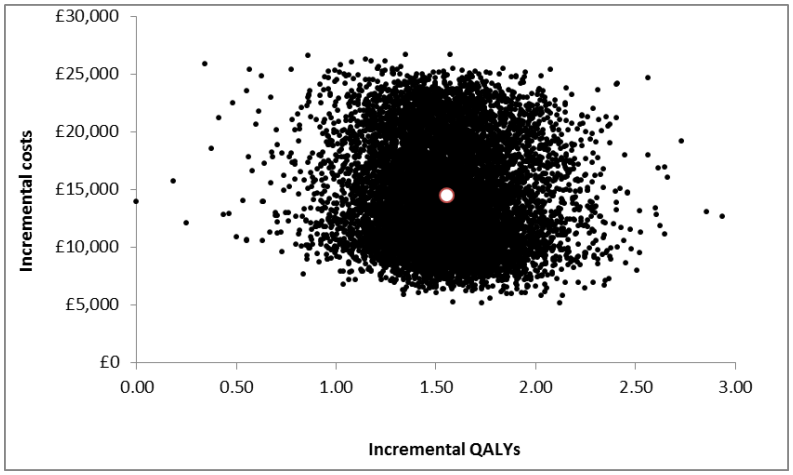
Study	Reasons for exclusion
Identified through database search	
Dixon *et al*., 2006	Utilities are reported separately for the placebo arm (which are not influenced by patients receiving interferon therapy), but these change over time and cannot be connected to stages in the model. In addition malignant melanoma is not defined
Ko *et al*., 2003	Utilities reported for melanoma, but melanoma is not defined
Chan *et al*., 2011	Modified utility values from Brown , B., et al. 2008 with the incidence rate observed in a recent Chinese clinical trial
Chen 2008	Utility values not reported
Essers *et al*., 2006	Utility values not reported
Hengge *et al*., 2007	Utility values not reported
Hollenbeak *et al*., 2001	Health states not applicable to the model (report values for modified neck dissection and/or radiation)
Hillner *et al*., 1997	Method used to estimate utility values not reported, appear to be subjective estimates
Klein et al., 2013	Irrelevant population*; utility values not reported; patients within the studies are treated with radiation therapy
Parthan *et al*., 2009	Irrelevant population*; completed the QLQ-C30 questionnaire at different time points (crossing walking algorithm to EQ-5D utility scores)
Brown *et al*., 2008	Irrelevant population*; health states considered are not applicable to model (UK oncology nurse completed the EQ-5D)
Lear *et al.,* 2008	Methods to estimate utility values were not robust which resulted in unrealistic utility values for BCC i.e. 0.999
Dalgard *et al*., 2014	Utility values not reported; insufficient methodological detail
Radford *et al*., 2013	Utility values not reported; insufficient methodological detail
Shih *et al*., 2014	Unable to access full-text
Seubring *et al*., 2013	Unable to access full-text
Amdahl *et al*., 2014	Utility values based on patients receiving trametinib, dacarbazine or vemurafenib
Delea *et al*. 2014	Utility values based on patients receiving vemurafenib or dacarbazine.
Freedberg *et al*., 1999	Report quality adjustment values obtained from dermatologists using the VAS technique which is not the preferred method specified in the protocol but was considered following relaxation of inclusion criteria regarding valuation method; however, study reports decrements (in days) from the projected total quality-adjusted life expectancy, which not allow straightforward estimation of utility values.
Identified through reference list search	
Bendeck *et al*., 2004a	Conference papers published pre January 2014 – the TAG reviewed the full texts of these papers due to the large number of citations from the cost-effectiveness studies
Bendeck *et al*., 2004b	
*SCC of the head and neck comprises of cancers of the oral cavity, nasopharynx, pharynx and larynx which are outside of the population specified in the scope Abbreviations used in the table: BCC, basal cell carcinoma; QLQ-C30, Quality of Life Questionnaire-Core 30; SCC, squamous cell carcinoma; TAG, technology assessment group.	

9.7 Appendix 7: Detailed results of economic modelling

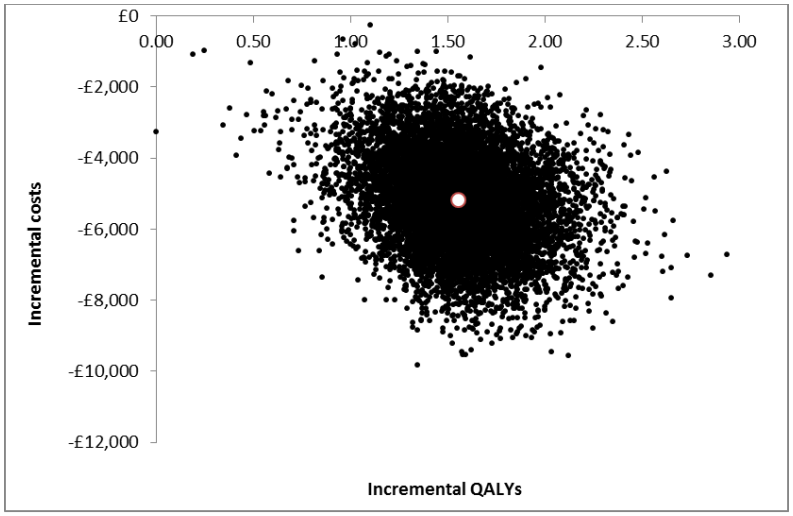
Cost effectiveness planes – all probabilistic analyses

Diagnosis of suspected melanomas using the Alarcon *et al*.[33] diagnostic accuracy data.

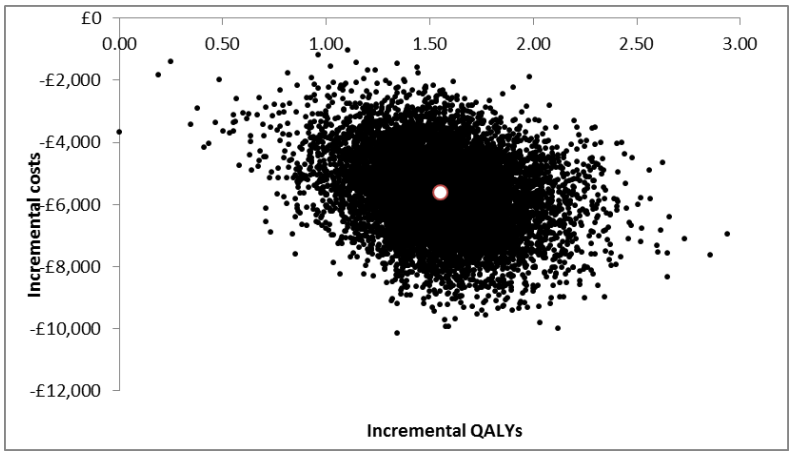
A. VivaScope use only for melanoma diagnosis



B. VivaScope use for the diagnosis of suspected melanomas and BCCs

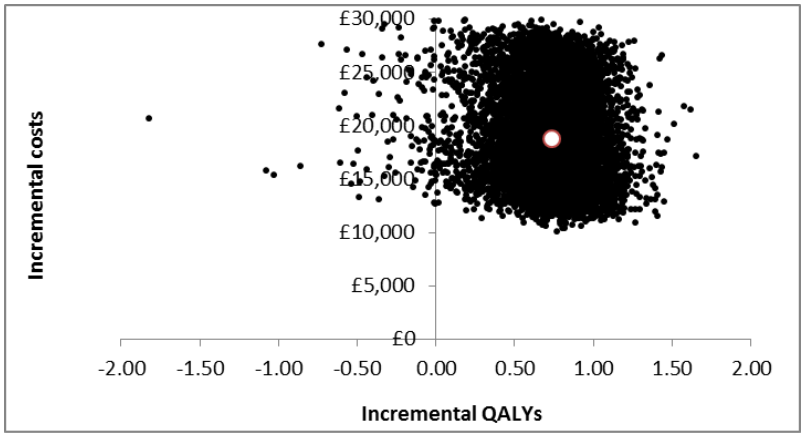


C. VivaScope use for all indications assessed in the economic modelling

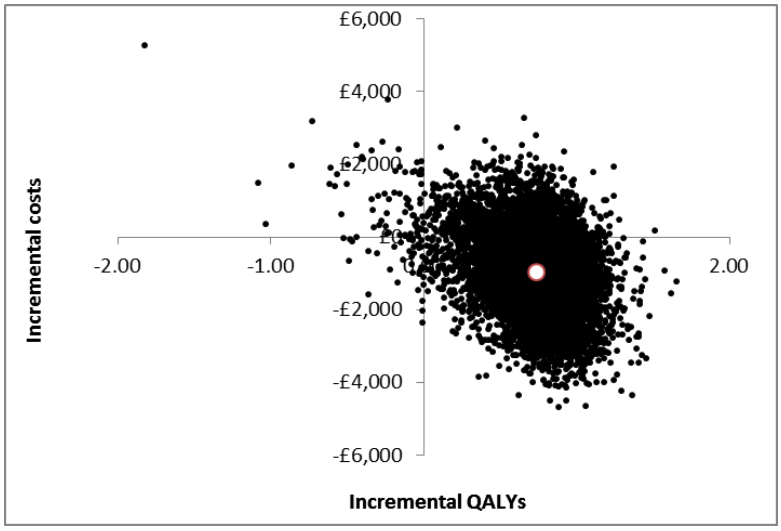


Diagnosis of suspected melanomas using the Pellacani *et al*.[45] diagnostic accuracy data.

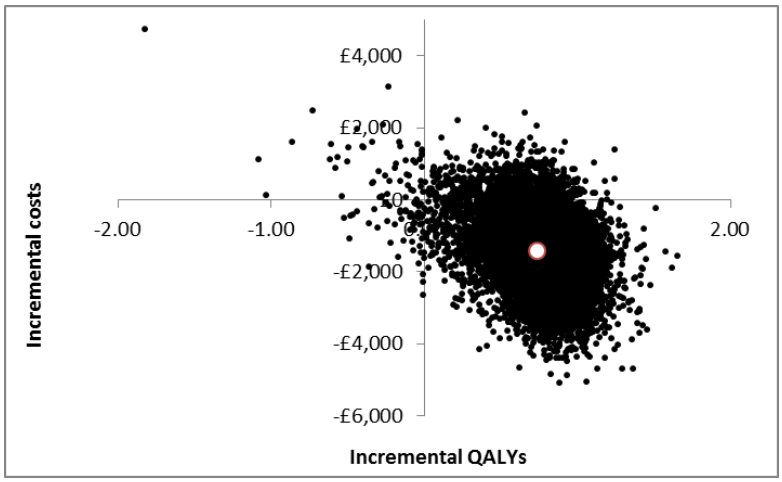
A. VivaScope use only for diagnosis of suspected melanomas



B. VivaScope use for diagnosis of suspected melanomas and BCCs

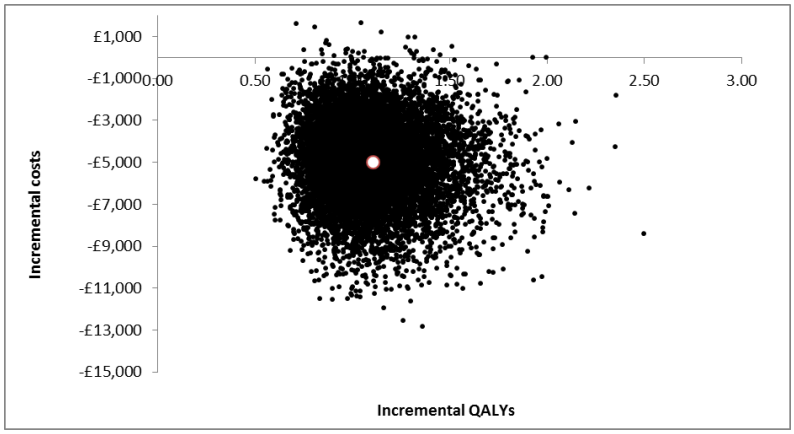


C. VivaScope use for all indications assessed in the economic modelling

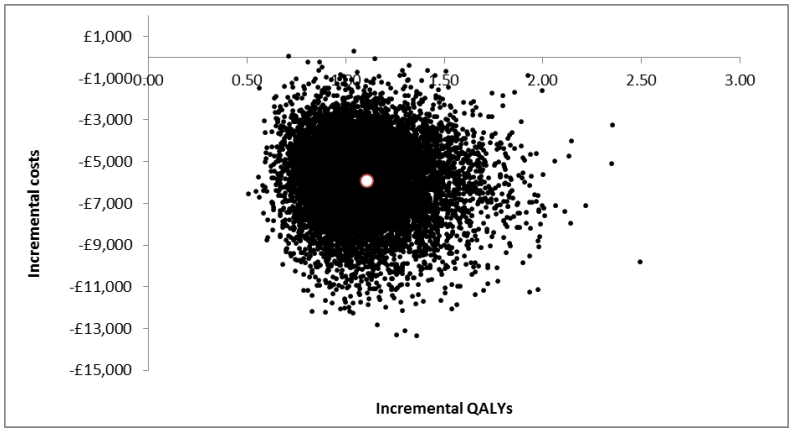


Diagnosis of suspected BCCs

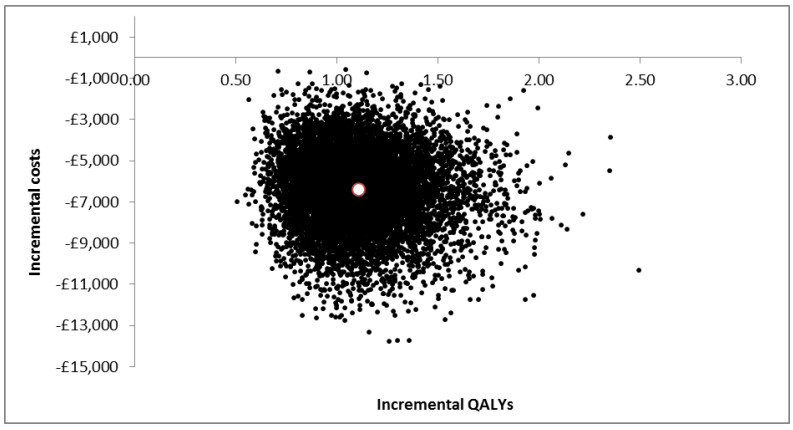
A. VivaScope use only for the diagnosis of suspected BCCs



B. VivaScope use for the diagnosis of suspected melanomas and BCCs

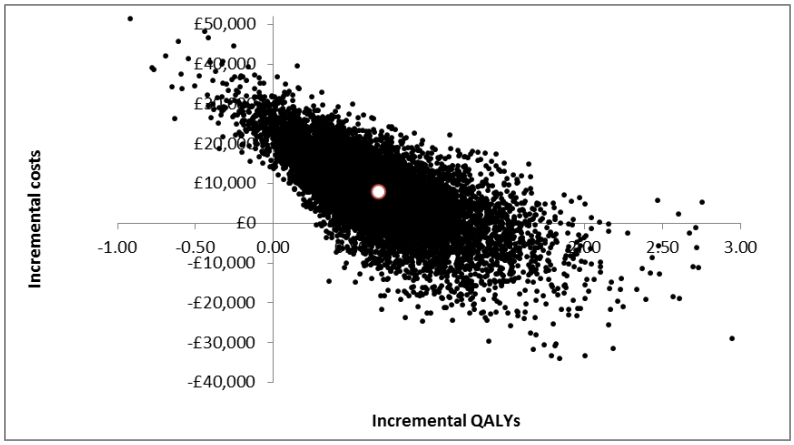


C. VivaScope use for all indications assessed in the economic modelling

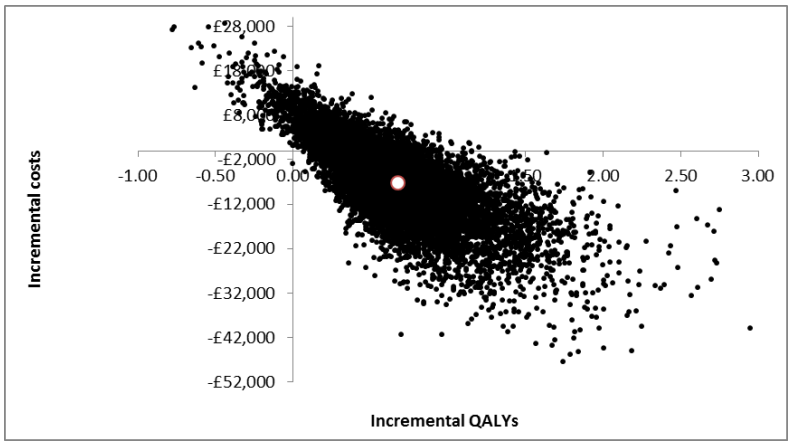


Pre-surgical margin delineation of lentigo malignas

A. VivaScope use only for the pre-surgical margin delineation of lentigo malignas



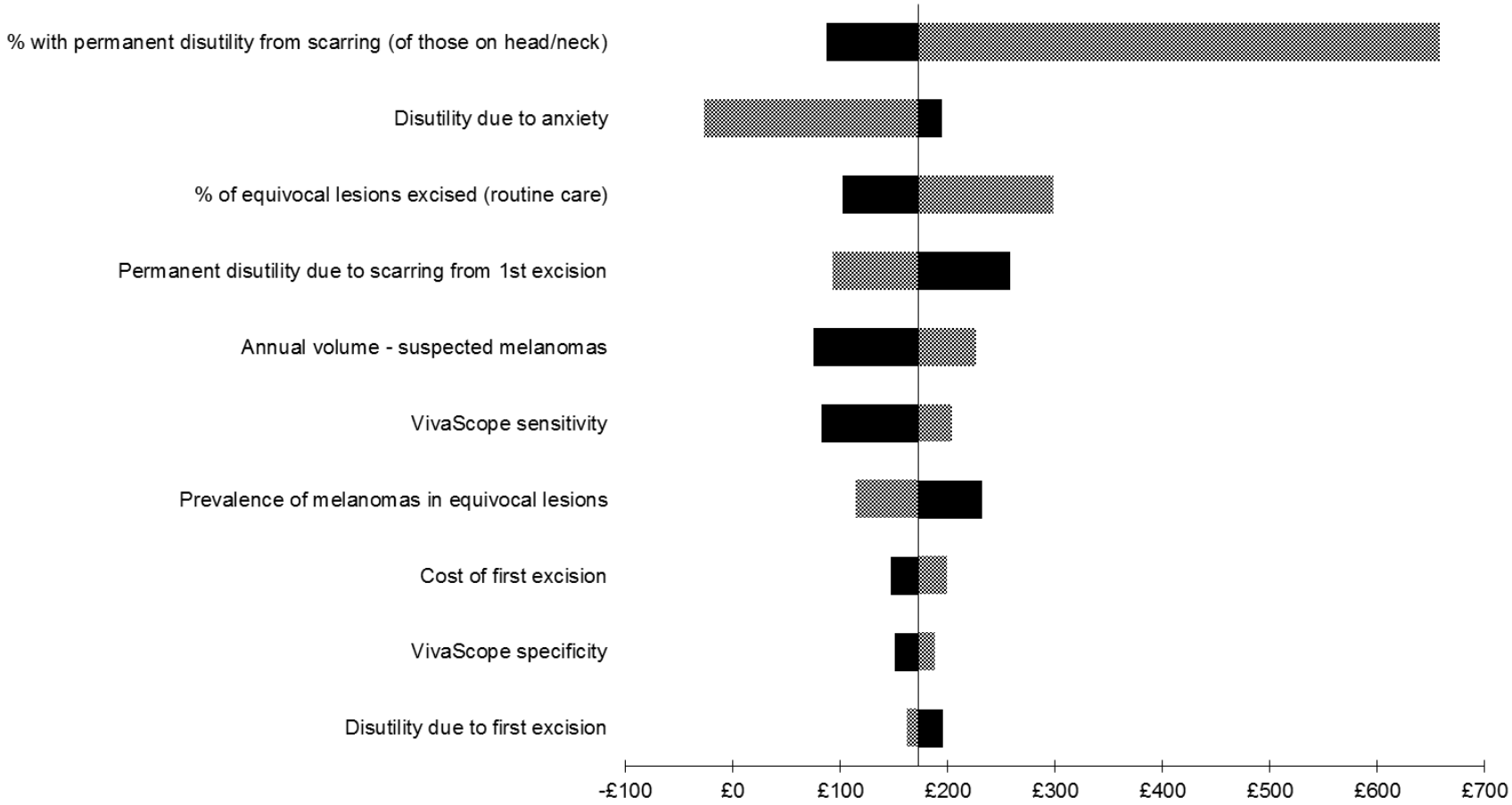
B. VivaScope use for all indications assessed in the economic modelling



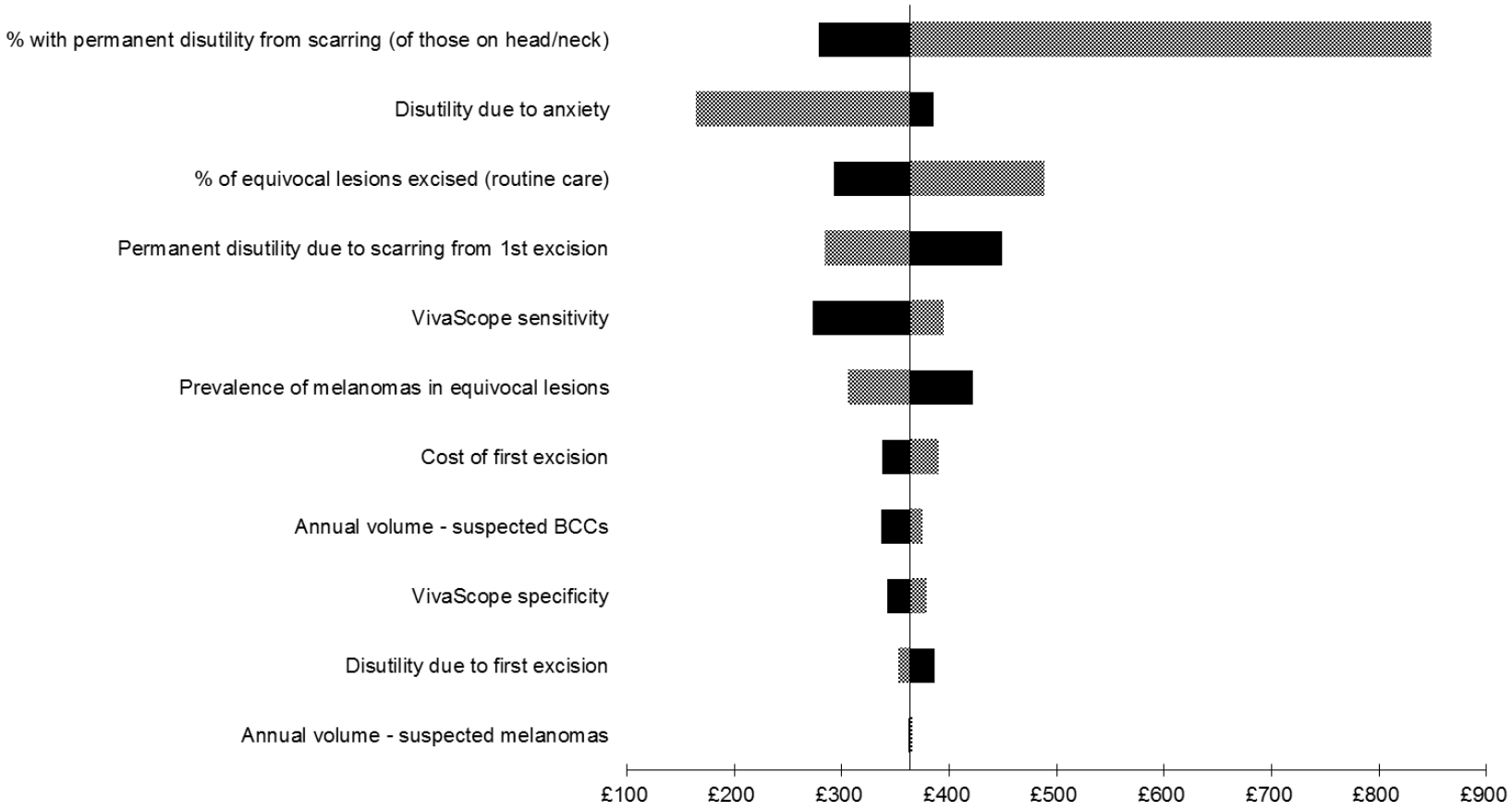
Tornado diagrams – all analyses

Diagnosis of suspected melanomas using the Alarcon *et al*.[33] diagnostic accuracy data.

A. VivaScope use only for melanoma diagnosis

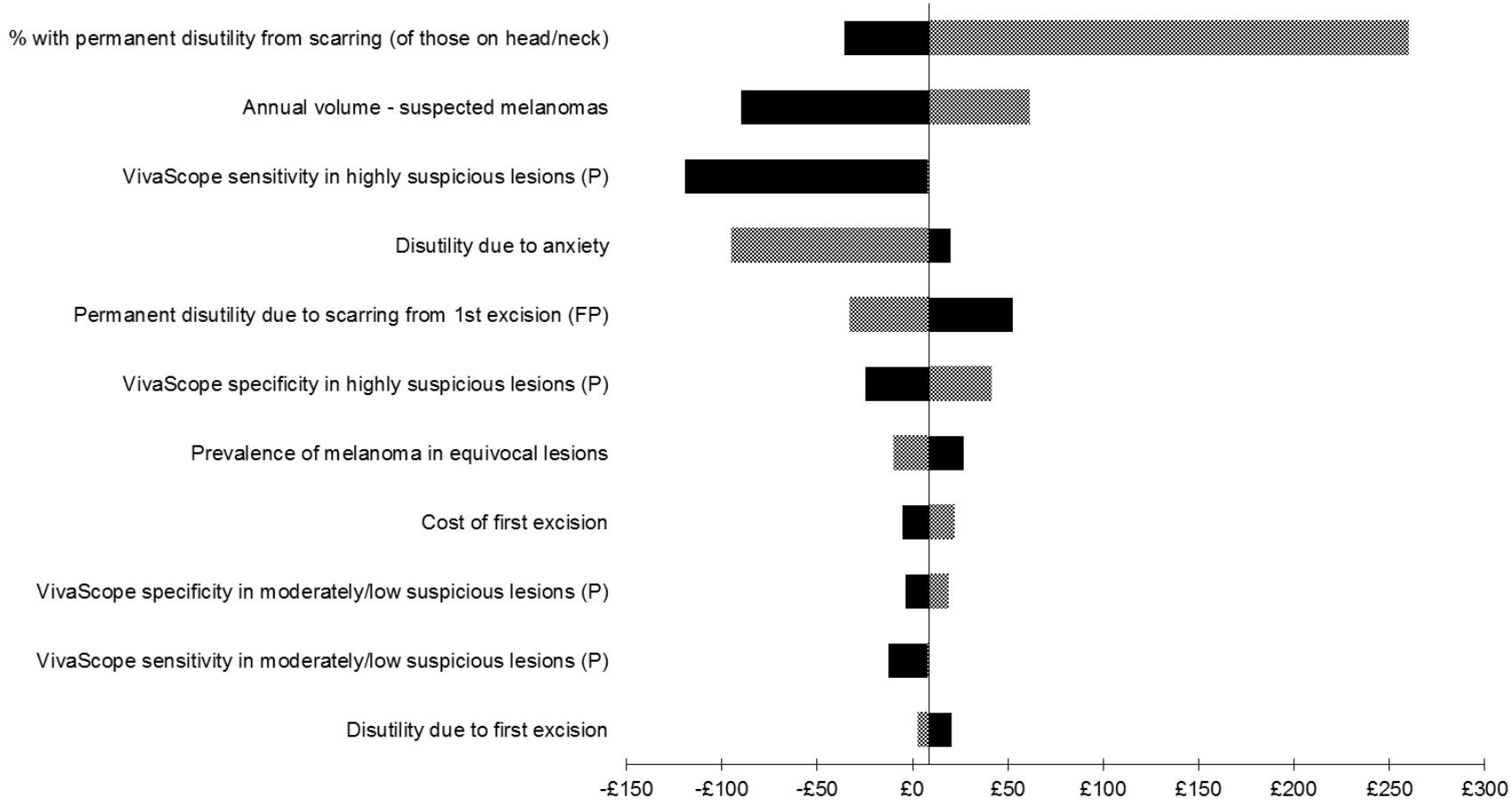


B. VivaScope use for the diagnosis of suspected melanomas and BCCs

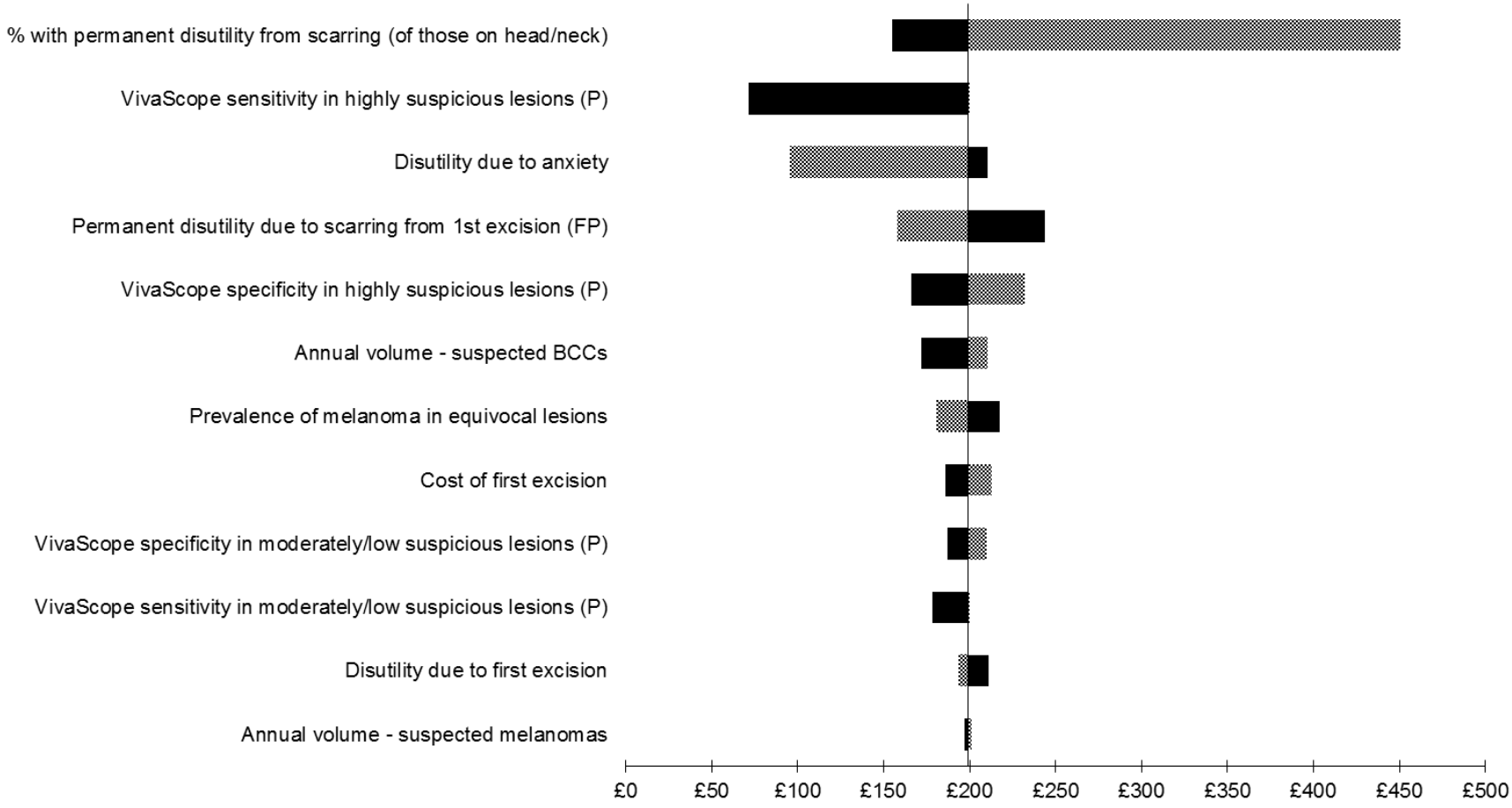


Diagnosis of suspected melanomas using the Pellacani *et al*.[45] diagnostic accuracy data.

A. VivaScope use only for diagnosis of suspected melanomas

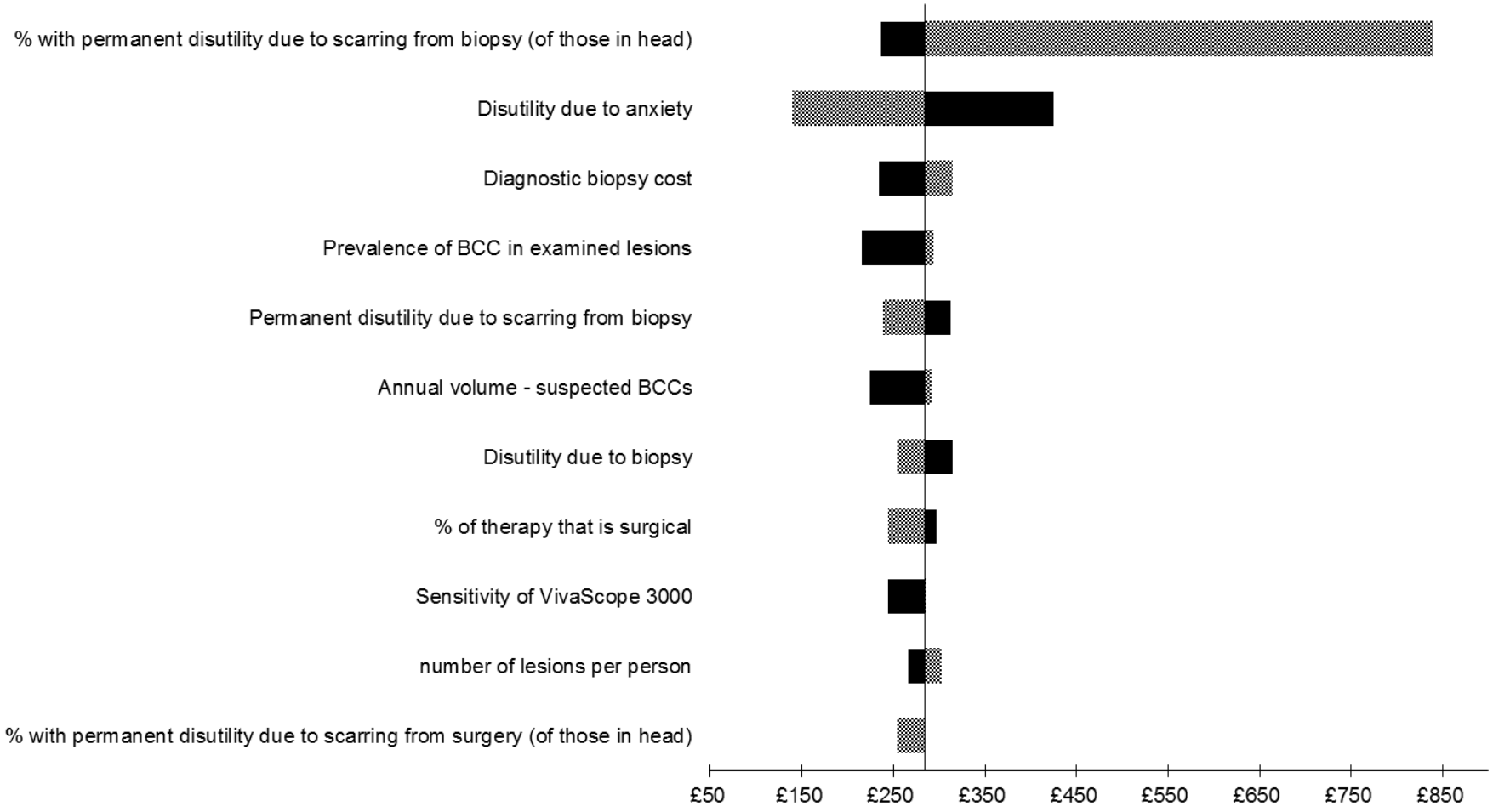


B. VivaScope use for the diagnosis of suspected melanomas and BCCs



Diagnosis of suspected BCCs

VivaScope use only for the diagnosis of suspected BCCs



NICE National Institute for Health and Care Excellence

Skin cancer: the VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	Response
British Association of Dermatologists / Royal College of Physicians	**1.**		General	It is unclear why there was selection of this particular confocal laser scanning microscopy system for review over others, or over a wider assessment of confocal microscopy in general.	NICE determined the final scope of this DAR based on stakeholder feedback.
	2.		General	At the workshop, our nominated expert highlighted the need for further evidence on the technology's usefulness as compared against, - well trained or experienced dermatologists' clinical acumen, and - other modalities for skin imaging, before going ahead with the positioning of this particular technology.	At the workshop, NICE advised the EAG that training is a feature of implementation. The DAR does attempt to address the cost of training but the use of VivaScope by inexperienced dermatologists was not formally assessed. The positioning of VivaScope was specified in the NICE final scope.
	3.		General	We have also been informed that NICE was aware, following the consultation for the draft scope, of an NIHR programme (in Birmingham) looking at evaluating all diagnostic tests for melanoma and non-melanoma skin cancers through a suite of over 20 systematic reviews.	The EAG were not made aware of the NIHR programme referred to but the scope of the DAR was the use of VivaScope following dermoscopy.
	4.		General	Overall, there is very limited evidence available for this systematic review (all observational studies); the evidence for clinically relevant benefits from these technologies over and above standard clinical practice is very weak – an RCT is really required to demonstrate this [redacted]	The EAG identified the best available evidence for the use of VivaScope within the NICE scope by conducting a systematic review of the clinical literature. It is not uncommon for the only available evidence for diagnostic tests to be based on observational studies.
	5.		General	We are most concerned about the ambiguous language used in the conclusions in this systematic review indicating that this tool may be useful, whilst at the same time saying the evidence is lacking.	As the evidence base is limited, the EAG is not in a position to make clear statements for clinical and cost effectiveness. The available evidence suggests VivaScope *may be* clinically and cost-

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				[redacted] for example: "There is a paucity of randomised controlled trial (RCT) evidence for both diagnostic accuracy and margin delineation with VivaScope 1500 and 3000. However, VivaScope subsequent to dermoscopy ***may improve*** diagnostic accuracy of equivocal skin lesions compared to dermoscopy alone, particularly for malignant melanomas. In terms of margin delineation, VivaScope 1500 mapping for LM and LMM ***may improve*** the accuracy in terms of complete excision of lesions compared with dermoscopically determined margins. In addition, use of VivaScope ***appears to be*** a cost-effective strategy in the diagnostic assessment of suspected skin cancer (more specifically, of suspected melanomas with an equivocal finding in dermoscopy and suspected BCCs with a positive or equivocal finding in dermoscopy) and the margin delineation of lentigo maligna prior to surgical treatment, in particular when VivaScope is used for all three indications considered in the economic analysis."	effective. The statements in the DAR are consistent with the limited available evidence.
	6.		General	The criteria for use of this technology must be appraised very carefully. The rigor of the analysis was low and based on 'crude' health economic data. We would be very interested to learn the funding body for the one, unpublished cost-effectiveness article submitted and later included following relaxation of the pre-determined	The unpublished cost effectiveness study did not play any role in the EAG's conclusions. The DAR states, "[redacted]

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				inclusion criteria.	[redacted]".
	7.		General	At present, this is a very time-consuming technique which may have a significant impact on the number of patients per hour able to be assessed, and consequently lead to an increased waiting list.	As stated in the DAR, the EAG's clinical experts suggested that, ". . . examination of skin lesions suspected for cancer with VivaScope 1500 requires 10 minutes of radiographer's time (from the time patient enters the consultation room until end of visit, including radiographer's time for attaching the adhesive window and obtaining the image) plus 5 minutes of a dermatologist's time for evaluation of images. Examination of skin lesions suspected for cancer with VivaScope 3000 requires 10 minutes of dermatologist's time (from the time patient enters the consultation room until end of visit, including dermatologist's time for obtaining and interpreting the image) . . . Mapping of lentigo malignas with VivaScope 3000 prior to surgical treatment requires 30 minutes of dermatologist's time." The EAG does not consider the times suggested by its clinical experts to be indicative of, "a very time-consuming technique". Moreover, the cost effectiveness analysis is based on an *annual volume of 675 lesions* anticipated to be examined/mapped with VivaScope. Based on 253 working days per year,

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					this equates to an assessment of 2.67 lesions per working day. The DAC will need to assess if the estimated annual volume is accurate and whether the anticipated annual volume would create increased waiting lists, considering also the alternatives to such assessments and the required time/expected volume (e.g., as advised by the EAG's clinical experts, alternatives include excision of suspected melanomas, biopsy of suspected BCCs; mapping has no alternative procedure but standard care is anticipated to result in need for more stages of Mohs surgery or repeat surgical excision).
	8.		General	[redacted]	This is a consideration for the DAC.
	9.		General	We would recommend that NICE investigates the full range of technologies available for diagnostic scanning of the skin, perhaps even including 1) optical cohesive tomography and 2) infrared spectroscopy, and justify why this particular VivaScope system warrants such detailed assessment.	This is beyond the NICE final scope for the DAR.
	10.		Conclusion	We would also recommend that the sentence "However, this research may not be feasible due to the current lack of expertise and availability of VivaScope in the UK" is deleted or reworded. If VivaScope cannot be evaluated in a properly set up multi-centre RCT in the UK, then it will be difficult to see how its introduction into UK-wide dermatology centres could be validated. Proponents of this technology feel it has the potential for wider clinical use in the future, once validation is achieved and training courses for dermatologists have been set up.	The conclusions of the DAR reflect the opinions of the EAG based on the available evidence and consultation with its clinical experts.

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Mavig GmbH	**11.**	93	5.2.1.6	We revised the report and we have only one point we would like to comment. We think that the number of cases assumed for confocal examination are very conservative compared to the use we see here. In the report it is assumed that the annual volume of cases eligible for examination with Vivascope in a dermatology multidisciplinary team (MDT) clinic in the UK are 675. This number doesn´t reflect the current use we see over here. We screened the publications in order to find an objective average and the best one which reflects an realistic estimate is the one of Prof. Pellacani with the title : “Reflective confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excision: A longitudinal prospective study” In this study it is described that in 66 days a total of 491 lesion underwent confocal examination. The daily number of examination would therefore be 7,4 which represent the average number of current dermatology clinic using this technology. If we assume that the yearly working days are 220-230	

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				days we can estimate that the yearly average number currently undergoing confocal examination with the Vivascope ranges in between 1628-1702 per year which reflects also our experience. As this number has a big impact on the economic cost effectiveness it might be interesting for the assessment group to have also this information.	