NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG19: VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions

This guidance was issued in November 2015.

The review date for this guidance is November 2018.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Transfer the guidance to the 'static guidance list'.

At the Guidance Executive meeting of 14 January 2020 the proposal to transfer the guidance to the static list without consultation was agreed. A list of the options that were considered, and the consequences of each option is provided in Appendix 2 at the end of this paper.

2. Rationale

No new evidence was found which could have a material impact on the guidance recommendations, the guidance will therefore be transferred to the static guidance list. In addition, there have been no fundamental changes to the VivaScope 1500 or the VivaScope 3000 devices, therefore a technical supplement is not necessary.

During development of the original guidance the committee were concerned about generalisability of the clinical data to the NHS in England. None of the new studies reporting diagnostic accuracy were conducted in the UK, so the uncertainty around generalisability remains. Changes to the care pathway include an updated staging system for melanoma and new immunotherapies and targeted treatments that have been recommended by NICE. However, these changes are likely to have limited impact on the results from the economic model.

3. Implications for other guidance producing programmes

No implications for other guidance producing programmes were identified.

4. Original objective of guidance

To assess the clinical and cost effectiveness of VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions.

5. Current guidance

Adoption recommendations

1.1. The VivaScope 1500 and 3000 imaging systems show promise but there is currently insufficient evidence to recommend their routine adoption in the NHS for:

- deciding whether to biopsy and excise skin lesions in people with suspected melanoma (equivocal lesions), basal cell carcinoma or lentigo maligna, or
- defining margins of skin lesions in people with lentigo maligna and basal cell carcinoma.

1.2. Further research (see section 7) on using the VivaScope 1500 and 3000 imaging systems is recommended in the following areas:

- the impact on clinical workflows for melanoma and basal cell carcinoma assessment in secondary care settings
- the proportion of people with melanoma referred into secondary care under the 2-week wait rule, and the outcomes achieved
- the number of confirmatory diagnostic biopsies needed for people with a clinical diagnosis of basal cell carcinoma, before definitive treatment is started
- the comparative clinical effectiveness of using these imaging systems to define margins of lentigo maligna and basal cell carcinoma
- epidemiological research on lentigo maligna diagnosed in England.

1.3. The VivaScope 1500 and 3000 imaging systems are not recommended for:

- helping decide whether to biopsy and excise skin lesions in people with suspected invasive squamous cell carcinoma, or
- defining margins of skin lesions in people with melanoma or invasive squamous cell carcinoma.

Research recommendations

7.1. The committee recommended that robust evidence is generated to demonstrate the impact of using the VivaScope 1500 and 3000 imaging systems in the clinical workflow of melanoma and basal cell carcinoma assessment in secondary care in England. The impact on excision rates, diagnostic accuracy, health-related quality of life and associated NHS costs should be reported.

7.2. The committee recommended the collection of data on the proportion of people with melanoma who are referred into secondary care under the 2-week wait rule, the proportion of equivocal moles that are excised and the proportion that are monitored.

7.3. The committee recommended the collection of data on the number of confirmatory diagnostic biopsies before definitive treatment, in people who have a clinical diagnosis of basal cell carcinoma. Data on the different modalities used to treat basal cell carcinoma should also be collected.

7.4. The committee recommended the generation of robust evidence to demonstrate the clinical effectiveness of using the VivaScope 1500 and 3000 imaging systems to define margins of lentigo maligna and basal cell carcinoma compared with histological margins determined by Mohs surgery.

7.5. The committee recommended the collection of data on the incidence of lentigo maligna diagnosed in England. Data on the different therapies used to treat lentigo maligna should also be collected."

6. New evidence

The search strategies on clinical effectiveness, economic evaluation and cost of illness from the original diagnostics assessment report were re-run on Embase, Medline (MEDLINE[R] and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), and Cochrane Library. References published since January 2015 were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

Both the VivaScope 1500 and VivaScope 3000 technologies are still available in the UK and are CE marked. Since the publication of NICE's guidance, there have been changes to the hardware and software of the technologies. A clinical expert noted that this has led to higher quality images. Specifically, regarding the VivaScope 1500 system (now 4th generation), the following changes have been made:

- New generation scan stage, 6x speed
- Improved dermatoscope: Vivacam HD
- Potential to add total body mapping
- Potential to connect to the network, VivaNet, allowing remote viewing and diagnosis of images.
- Capability to securely send images to experts via VivaTeach
- Buffering function to prevent network breakdowns.

The company provided up-dated costs of the VivaScope systems. These are listed in Table 1, alongside the original costs from the diagnostics assessment report.

Table 1 Costs relating to the VivaScope devices

Cost of technology (and associated parameters)	Current costs provided by company	Costs used in DG19	% difference
List price of technology VS1500 (dermoscopy included)	£97,000	£90,224	+7.5%
List price of technology VivaScope 3000 stand alone	£44,000	£41,600	+5.8%
List price of technology VivaScope 3000 add-on (dermoscopy included)	£73,000	£62,300	+17.2%
Service / maintenance	£4400	£4380	+0.5%
Anticipated life span of technology	25 years	10 years	
Average length of use per treatment	5 minutes	10 to 15 minutes	
Average frequency of use	15 to 20 per day	15 to 20 per day	
Total cost per treatment / patient	£125	Diagnosis Costs range from £254 (exclusive use of device for suspected melanomas) to £58 (use across 3 lesion types, Table 25 of DAR).	
		Margin mapping Exclusive use of device for mapping of lentigo maligna: £250 Use of device across all 3 types of lesions: £105	

The direct costs of the technologies and consumables used with the VivaScope systems do not appear to have increased appreciably above inflation. Other cost inputs in the diagnostics assessment report related to the downstream consequences of diagnosis and management following the use of VivaScope, for example, the management cost of confirmed melanomas (true positives) and the cost of missed melanomas (false negatives) that were identified later. Most of these costs were calculated using standard reference cost or tariffs and would not be expected to have changed significantly above inflation since DG19 was published. A possible exception to this may be the use of drugs to treat invasive and metastasising melanoma.

6.2 Clinical practice

No substantial changes to the diagnostic pathways for suspected skin cancer have been identified. NICE's guideline on melanoma was published shortly before DG19 (July 2015) and states 'do not routinely use confocal microscopy or computer-assisted diagnostic tools to assess pigmented skin lesions'. This guideline has recently undergone surveillance and will be updated to consider the latest staging system for melanoma from the American Joint Committee on Cancer, but it has not been scheduled yet.

In terms of the management of diagnosed melanoma there have been important changes to the pathway; new immunotherapies and targeted treatments are now recommended by NICE, including:

- Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (2019) NICE technology appraisal guidance 558
- Nivolumab in combination with ipilimumab for treating advanced melanoma (2016) NICE technology appraisal guidance 400
- Nivolumab for treating advanced (unresectable or metastatic) melanoma (2016) NICE technology appraisal guidance 384
- Pembrolizumab for advanced melanoma not previously treated with ipilimumab (2015 updated 2017) NICE technology appraisal guidance 366
- Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (2015 updated 2017) NICE technology appraisal guidance 357
- Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (2019) NICE technology appraisal guidance 562
- Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (2016) NICE technology appraisal guidance 396
- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (2012 updated 2015) NICE technology appraisal guidance 269

6.3 New studies

A total of 16 relevant studies that have been published since DG19 were identified. Of these, 14 addressed the diagnosis of equivocal skin lesions and 2 addressed the determination of excision margins.

Diagnosis of equivocal skin lesions

Of 14 studies identified, 13 were observational studies reporting diagnostic accuracy outcomes (8 retrospective and 5 prospective) and 1 was a randomised controlled trial (RCT). Most studies were of VivaScope 1500 but some used VivaScope 3000. Sample sizes of the observational studies ranged from 55 lesions to 1279 lesions. None of the studies were done in the UK. Summary results from the studies are provided in Table 2 in appendix 1.

A strength of most observational studies was that the diagnostic accuracy of the VivaScope devices was compared with a suitable reference standard test; histopathology through punch excision or whole-lesion excision. However, all the studies had important methodological limitations. The retrospective studies were most limited because they did not use dynamic in vivo imaging but relied on the assessment of historical static images which does not reflect real-life practice. In some studies, it was unclear how patients or lesions had been selected for analysis, which could potentially introduce selection bias. There were also problems with the generalisability, as most studies focused on specific subsets of equivocal lesions, such as those of a certain pigmentation or in a specific anatomical location. None of the studies reported the effect of the use of VivaScope on clinical management or clinical outcomes.

Results of the studies were heterogeneous: sensitivity ranged from 46% to 100%, with similar ranges in specificity. This wide range in diagnostic values highlights the differences in study methodologies and lesion types assessed.

The RCT (Kadouch et al. 2017) was set in 2 tertiary hospitals in the Netherlands, which may not be generalizable to the NHS setting in England. The authors reported that 100 consecutive patients with clinically suspected basal cell carcinoma (BCC) were randomised into 1 of 2 clinical pathways; standard care (punch biopsy, n = 50), and 'one-stop-shop' (VivaScope followed by direct surgical excision, n = 48 [2 people excluded because they declined to participate or the device malfunctioned]). It was not clear how patients were randomised. In all cases, the lesions were excised and analysed using histopathology as a reference standard. The study reported that VivaScope had a sensitivity of 100.0% (95% CI 90.8 to 100.0%) compared with 93.9% (95% CI 78.0 to 99.3%) for punch biopsy. However, specificity of VivaScope for diagnosing BCC was 37.5% (95% CI 8.5 to 75.5%) compared with 78.6% (95% CI 49.2 to 95.3%) for punch biopsy. The wide confidence intervals may due to the

low number of true negatives in the sample, with VivaScope incorrectly identifying 5 lesions as BCC.

Determination of excision margins

Two studies were identified on defining the margins of skin lesions. Summary results from the studies are provided in Table 3 in appendix 1. The study by Pellicani et al. (2018) assessed the feasibility of using the VivaScope 3000 device for improved precision in the removal of lentigo maligna. This was a single-armed study that measured the diagnostic utility of VivaScope in patients with proven lentigo maligna following successive excision steps. The study was small (n = 23) and did not provide comparative data. The study by Venturini et al. (2016) used the VivaScope 1500 device to assess the proportion of lesions that had features of basal cell carcinoma beyond the margins identified by dermoscopy only. The VivaScope evaluation showed presence of basal cell carcinoma features beyond the dermoscopy defined margins in 3 of 10 lesions, which was confirmed with histology.

Economic studies

There were 3 economic studies identified which reported on reflectance confocal microscopy (RCM; assumed to be a variant of VivaScope) for the diagnosis of skin cancer. Summary results from the studies are provided in Table 4 in appendix 1. Of these, 2 were reported as conference abstracts only. Unlike the economic model in the NICE diagnostics assessment report, these studies appear to include short-term costs only, that is, cost savings from a reduction in biopsies but not costs associated with management of confirmed skin cancers and missed skin cancers.

The study by Sinha et al. (2016) used a combination of epidemiological data from local audit and diagnostic accuracy data from published evidence. It estimated that RCM could potentially save £20,000 over a 4-month period in a specialised dermatology setting in the UK through reduced follow-ups and biopsies. The study by Thng et al. (2016) reported diagnostic accuracy data for RCM in Singapore. The authors estimated RCM could release resources of S$600,000 through a reduction in the number of biopsies, assuming it is used for 3000 cases a year, and has a sensitivity of 98.6% and specificity of 95.7%.

Pellacani et al. (2016) reported a cost-benefit analysis of RCM compared with current practice (dermoscopy) from the perspective of the Italian health service. It reported number of benign lesions needed to excise a melanoma in terms of outcomes and costs per patient. The authors reported a large reduction in benign lesions excised when RCM was used compared with use of dermoscopy alone; the numbers needed to excise were 6.25 for RCM and 19.41 for dermoscopy. Authors concluded that malignant melanoma removal using an RCM approach cost €2133 compared with €2932 for standard care. This could lead to a potential saving of

€262,314 per 1 million inhabitants per year. However, the authors acknowledged that the generalisability of these results was limited.

Similar to these published models, the NICE assessment of VivaScope included a reduction in the number of biopsies when VivaScope was used. This resulted in cost savings compared with current practice, but the committee noted uncertainty in the number of biopsies that would be avoided in clinical practice in the NHS.

Cost of illness studies

In total, 155 cost of illness studies were identified from the focused literature search. However, none of the studies were directly relevant to the decision question or economic analysis.

6.4 NICE's research commissioning activities

A research project was commissioned by NICE to address the research recommendations in DG19 VivaScope. A protocol was designed and published as part of this project, but funding was not awarded (Herz et al. 2018).

7. Summary of new evidence and implications for review

No new evidence was found which could have a material impact on the guidance recommendations. During development of the original guidance the committee were concerned about generalisability of the clinical data to the NHS in England. None of the new studies reporting diagnostic accuracy were conducted in the UK, so the uncertainty around generalisability remains. In addition, the new studies identified were heterogeneous and many had methodological limitations. None of the ongoing studies identified are expected to address the research recommendations made in DG19 – only 1 small observational study is ongoing in the UK.

Changes to the care pathway include an updated staging system for melanoma and new immunotherapies and targeted treatments that have been recommended by NICE. However, these changes are likely to have limited impact on the results from the economic model. The costs relating to the use of the VivaScope devices have not increased much beyond inflation.

There have not been any fundamental changes to the VivaScope 1500 or the VivaScope 3000 devices, however, small changes to hardware and software have been made to increase the scan speed, improve the quality of the images and improve the connectivity. In term of additional technologies, clinical experts advise that optical coherence tomography was being trialled in the UK and entering routine practice abroad, but a recent Cochrane review concluded that there is currently 'insufficient data available on the use of optical coherence tomography for the detection of melanoma or cutaneous squamous cell carcinoma'.

8. Equality issues

During guidance development it was noted that people with white skin, older people, immunocompromised people and people with HIV are at a higher risk of developing skin cancers. The committee considered the evidence on the clinical effectiveness of VivaScope 1500 and 3000 systems and did not identify any issues relating to differential accuracy or outcomes in these subgroups.

Paper sign off by: Rebecca Albrow, Associate Director, 17 January 2020

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Appendix 1

Table 2 Summary of included studies on the diagnosis of equivocal skin lesions

<table>
<tr><th>Reference, design, setting</th><th>Population and sample size</th><th>Intervention</th><th>Comparators</th><th>Outcomes</th><th>Key results</th><th>Comments</th></tr>
<tr>
<td>Scope et al. (2019)

Prospective DAS

Multicentre tertiary care</td>
<td>Patients with equivocal skin lesions (n=92).

100/439 lesions randomly selected for analysis.</td>
<td>VivaScope 1500 through tele-consultation.

3 clinicians performing assessment.</td>
<td><u>Reference standard:</u>
histopathology.</td>
<td>Inter-rater agreement.

Identification of RCM specific features.</td>
<td><u>Reader agreement</u>:
<table>
<tr><th></th><th>Se</th><th>Sp</th><th>DA</th></tr>
<tr><td>Reader 1</td><td>74%</td><td>67%</td><td>70%</td></tr>
<tr><td>Reader 2</td><td>46%</td><td>84%</td><td>69%</td></tr>
<tr><td>Reader 3</td><td>72%</td><td>46%</td><td>56%</td></tr>
</table>
Kappa statistic: 0.34</td>
<td>RCM image assessed through simulated tele-consultation (static images), thus may lack generalisability.
Conclusion: RCM “may be associated with limited diagnostic accuracy and inter-observer agreement”</td>
</tr>
<tr>
<td>Gomez-Martin et al. (2019) (27)

Prospective DAS

Single tertiary centre, Spain</td>
<td>Patients with “pink flat lesions on the legs” (n=85).

114 lesions assessed (34 benign, 80 malignant).</td>
<td>VivaScope 1500.</td>
<td>Clinical evaluation.
Dermoscopy.
<u>Reference standard:</u>
histopathology through 4mm punch biopsy.</td>
<td>DA outcomes.

Dermoscopic features associated with malignancy.</td>
<td><u>Diagnostic accuracy</u>
<table>
<tr><th>Technique</th><th>DA</th><th>Se</th><th>Sp</th></tr>
<tr><td>Clinical evaluation</td><td>49.1 %</td><td>68.7 %</td><td>73.5 %</td></tr>
<tr><td>Dermoscopy</td><td>59.6 %</td><td>85.0 %</td><td>67.6 %</td></tr>
<tr><td>RCM (blinded)</td><td>71.9 %</td><td>90.0 %</td><td>73.5 %</td></tr>
<tr><td>RCM (not blinded)</td><td>85.1 %</td><td>97.5 %</td><td>88.2 %</td></tr>
</table>
DA to detect malignancy: 94.7%</td>
<td>Specific lesion morphology and anatomical location limits generalisability.
Conclusion: “Confocal microscopy may improve diagnostic accuracy, sensitivity and specificity as a secondary evaluation after dermoscopy”</td>
</tr>
<tr>
<td>Ahlgrimm-Siess et al. (2019)

Retrospective DAS.

Single-centre, Austria</td>
<td>People with facial skin lesions (n=148).

160 equivocal consecutive lesions (60% malignant, 40% benign).</td>
<td>VivaScope 1500 as adjunctive to dermoscopy.</td>
<td>Clinical and dermoscopic evaluation.

<u>Reference standard:</u>
histopathology biopsy.</td>
<td>DA outcomes.

Simulated excision rates.</td>
<td>RCM Se: 93%
RCM Sp: 58%

Dermoscopy Se: 95%
Dermoscopy Sp: 28%

Simulation showed RCM had the potential to reduce excisions.</td>
<td>Images not assessed in real time.

Conclusion: “unnecessary biopsies in this cosmetically sensitive area could be reduced by one third without missing a melanoma”.</td>
</tr>
</table>

Reference, design, setting	Population and sample size	Intervention	Comparators	Outcomes	Key results	Comments
Mandel *et al.* (2018) Retrospective DAS (case control). Single tertiary care centre, Italy.	People retrospectively identified with at least 1 confirmed malignant (cases) or benign melanocytic lesion (controls) of the breast area (n=55)	Images captured with VivaScope 1500.	Dermoscopy. Reference standard: histopathology	Features of malignancy DA outcomes	Combined dermoscopy and RCM to detect malignancy: Se: 95.2% Sp: 82.4% AUC 0.904	Images not assessed in real time. Case control design subject to spectrum bias. Limited to breast area. Conclusion: "The combined use of dermoscopy and confocal microscopy in the triage of pigmented lesions of the breast area may help in increasing the diagnostic accuracy and avoiding unnecessary excisions"
Borsari *et al.* (2018) Retrospective DAS Single tertiary centre, Italy	Patients with lesions with histological diagnosis of MM(n=314) or nevi (n=333)	Images from VivaScope 1500.	Reference standard: histopathology results from excision.	Predictors of malignancy (ORs) NNE (retrospective calculation).	Se (*in situ* MM): 92.5% Sp: 61% Validations: Se: 92% Sp: 58%	DA parameters were reported following development of an algorithm. Retrospective nature of studies limits internal validity and generalisability.
Cinotti *et al.* (2019) Retrospective DAS Single centre, France	People with clinically equivocal facial lesions (suspected LM or LMM, n=201). 223 lesions evaluated.	VivaScope 3000. 21 independent clinical assessors.	Dermoscopy. Reference standard: histopathology.	DA outcomes (detection of malignancy or classification into LM or LMM). Investigator agreement.	RCM Se: 80% RCM Sp: 81% RCM AUC ROC: 0.965 Dermoscopy Se: 61% Dermoscopy Sp 92% Dermoscopy AUC ROC: 0.857	Image assessment not performed in real-time. Conclusion: "Reflectance confocal microscopy and dermoscopy are both useful techniques for the diagnosis of facial lesions and in particular LM/LMM".

Reference, design, setting	Population and sample size	Intervention	Comparators	Outcomes	Key results	Comments
Kadouch et al, (2017). Prospective RCT. 2 tertiary centres, Netherlands.	Patients with clinically suspected BCC on chest, extremity, or head/neck. (n=100)	VivaScope 1500 2 clinical assessors.	Punch biopsy (standard care). Reference standard: histopathology confirmation following excision.	DA outcomes in each arm (n=50)	Detection BCC RCM Se: 100% RCM Sp: 38% Punch biopsy Se: 94% Punch biopsy Sp: 79% Inter-rater agreement RCM ranged from 50% to 85% depending on the BCC subtype.	Also reported in Kadouch *et al.* (2017) Conclusion: "Reflectance confocal microscopy and punch biopsy have comparable diagnostic accuracy to diagnose and subtype BCC depending on RCM experience".
Gomez-Martin *et al.* (2017) Prospective DAS Single centre, Spain	People with pigmented facial macule (n=61). 63 equivocal lesions with 12 controls.	VivaScope 1500	Dermoscopy Reference standard: histopathology (mainly by punch excision)	DA outcomes Identification of confocal characteristics in LM and LMM lesions. Correlation between techniques	Diagnosis of pigment facial macules with RCM: Se: 91.7% Sp: 86.8%	Conclusion: "Reflectance confocal microscopy improves LM diagnosis in photo-damaged skin with good histopathologic correlation although false-positive and false-negative cases exist".
Witkowski *et al.* (2016) Retrospective DAS Single tertiary centre, Italy	260 lesions selected from 3869 consecutive cases. Lesions were "equivocal non-pigmented 'pink' cutaneous"	VivaScope 1500	Dermoscopy. Reference standard: Histopathology report.	DA outcomes (classification of lesion type). Differential diagnosis of BCC.	RCM Se: 85.1% RCM Sp: 93.8% RCM PPV: 91.5% Dermoscopy Se: 85.1% Dermoscopy Sp: 92.4% Dermoscopy PPV: 89.8% Dermoscopy/RCM Se: 77.2% Dermoscopy/RCM: 96.6% Dermoscopy/RCM: 94.6%	Lesions for analysis were retrospectively selected for analysis (not real-time). May not be generalisable to real-life practice.

Reference, design, setting	Population and sample size	Intervention	Comparators	Outcomes	Key results	Comments
Menge *et al.* (2016) Prospective DAS Single tertiary centre, USA	People with known or suspected LM (n=17). 63 equivocal areas of skin.	VivaScope 3000, real-time video. 2 assessors using Guitera LM identification algorithm.	Dermoscopy. Reference standard: histopathology.	DA outcomes (detection of LM). Concordance with dermoscopy.	RCM Se: 100% RCM Sp: 71% RCM PPV: 85% RCM NPV: 100% 89% concordance with dermoscopy.	Small sample size. Conclusion: "RCM shows excellent sensitivity for detecting LM although features of benign macules on a background of actinically damaged skin can obscure diagnosis and limit its specificity"
Ludzik *et al.* (2016) Retrospective DAS Single tertiary centre, Italy.	316 consecutive patients with 316 "dermoscopically equivocal pink cutaneous lesions".	VivaScope 3000. "Double reader concordance"	Dermoscopy (1 reader) Reference standard: excision for histopathological analysis.	DA outcomes.	Combined RCM (reader 2 and 3): Overall Se: 98.3% Overall Sp: 42.7% AMM Se: 100% BCC Se: 98.6% Nevi (not Spitz) Se: 44.6% Dermoscopy (reader 1): Overall Se: 95.9% Overall Sp: 33.6% AMM Se: 91.7% BCC Se: 95.7% Nevi (not Spitz) Se: 35.7%	Retrospective study, no live imagery. Conclusion: "Evaluation of dermoscopy-RCM image sets of equivocal pink lesions by a single reader in telemedicine settings is limited by the potential for misdiagnosis of dangerous malignant lesions".
Ludzik *et al.* (2016) Retrospective DAS Single tertiary centre, Italy	Retrospective analysis of 100 dermoscopically equivocal skin lesions.	VivaScope 1500. "Double reader concordance". .	Reference standard: excision for histopathological analysis.	DA outcomes (detection of MM). Decision to excise.	Combined RCM (2 readers): Overall Se: 98.1% Overall Sp: 56.3% AMM Se: 100% BCC Se: 97.2% Nevi (not Spitz) Se: 53.5%	Similar to Ludzik *et al.* (2016), but on MM and different recruitment periods and intervention, so likely unique patients.
Guitera *et al.* (2016)	Consecutive lesions identified with "lightly	VivaScope 1500. Analysis of	Amelanotic dermoscopy (reports).	DA outcomes (detection of	Malignancy detection Dermoscopy Se: 83% Dermoscopy Sp: 18%	Retrospective analysis of population that may not be representative.

Reference, design, setting	Population and sample size	Intervention	Comparators	Outcomes	Key results	Comments
Retrospective DAS 3 tertiary centres, Italy and Australia	coloured and amelanotic lesions with a differential diagnosis of melanoma" 191 lesions (45 MM, 48 BCC, 10 SCC, 78 benign).	historical static images. 3 independent readers.	Reference standard: diagnosis by histopathology report.	MM and BCC). Decision to excise (reader confidence).	RCM Se (MM): 67% RCM Se (BCC): 73% RCM Sp (non-malignancy): 56% RCM recommended biopsy in 84% of MM. Avoided biopsy in 47% of benign lesions. "All melanomas misclassified by either dermoscopy or RCM were detected by the other tool".	Conclusions: "Dermoscopy and RCM represent complementary/synergistic methods for diagnosis of amelanotic/light-coloured skin lesions".
Borsari *et al.* (2016) Prospective DSA Single tertiary centre, Italy.	Consecutive patients (n=1147) with "at least 1 clinically and/or dermoscopically equivocal skin lesion referred to RCM imaging". 1279 lesions.	VivaScope 1500 used in standard clinical practice.	Reference standard: histopathology	Identification of features significantly correlated with RCM outcome (ORs). NNE.	RCM Se (detection skin cancer): 95.3% RCM Sp: 83.9%. NNE: 2.4 Surgical removal/biopsy recommended in 53.2% of cases. Excision on RCM assessment: 229/243 MM cases 131/134 non-MM skin cancer.	Essentially an audit of people already referred for RCM assessment. No comparator data in this setting. Conclusion: "Lesions located on the head and neck, damaged by chronic sun-exposure, and dermoscopically typified by regression represent best indications for the use of RCM".
Abbreviations: AMM, amelanotic/hypomelanotic melanoma; AUC, area under curve; BCC, basal cell carcinoma; DA, diagnostic accuracy; DAS, diagnostic accuracy study; LM, lentigo maligna; LMM, lentigo maligna melanoma; MM, malignant melanoma; NNE, number needed to excise; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RCM, reflectance confocal microscopy; RCT, randomised controlled trial; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity.						

Table 3 Summary of included studies on defining the margins of skin lesions

Reference, design, setting	Population, sample size	Intervention	Comparators	Outcomes	Key results	Comment
Pellacani *et al.* (2018) Single armed observational study Two academic centres, Italy.	23 patients with biopsy proven LM or clear signs of MM.	Evaluation of margin limits of lesion using VivaScope 3000 to guide excision (SMART approach).	No comparator. Margins determined by histopathology and 1 year follow up for recurrence.	Proportion of negative RCM margins at progressive steps. Recurrence after 1 year. Agreement between bedside operator and remote assessor (telemedicine).	6 cases negative at 1st step. 11 negative at 2nd step. 4 negative at third step. 2 margins could not be determined by RCM. No recurrence of MM in patients followed up at 1 year (n=15). Remote reader: Se 92%, Sp 57%.	This was a small study (n=23) which may not be generalisable to clinical practice. Conclusion: "Margin mapping of LM with hand-held-RCM, using superficial skin cuts, appears feasible".
Venturini *et al.* (2016) Observational study Single tertiary centre, Italy.	Consecutive patients with lesions clinically suggestive of non-pigmented BCC with ill-defined margins. 10/45 screened patients with lesion eligible for study (suspected BCC).	VivaScope 1500 used to create mosaic to determine if delineated border area is BCC free.	No comparator.	Proportion of lesion with features of BCC beyond surgical margin.	RCM evaluation showed BCC foci beyond the pre-surgical marker in 3/10 (30%) lesions.	Small study (n=10), may not be generalisable to UK clinical practice. Conclusion: "new procedure helped to improve the identification of proper margins for surgical excision in non-pigmented BCC with clinically and dermoscopically ill-defined margins".

Abbreviations: BCC, basal cell carcinoma; LM, lentigo maligna; MM, malignant melanoma; RCM, reflectance confocal microscopy; Se, sensitivity; Sp, specificity; SMART, Superficial Margin Assessment with handheld Reflectance confocal microscopy Technology.

Table 4 Summary of economic evidence

Reference, study type, aims	Population, perspective, time horizon	Intervention	Comparators	Key results	Comment
Sinha *et al.* (2016) "Epidemiological data study" Assessment of how RCM could impact management of MM and BCC in a skin cancer clinic.	People with equivocal moles (239/1549 in a skin cancer clinic). NHS perspective (skin cancer clinic). Data collected over 4 months (2 in summer, 2 in winter).	RCM (VivaScope not specified but highly likely to be this technology).	Current standard care (referral for biopsy using current methods of diagnosis). Reference standard: biopsy and photographic monitoring.	32% of suspected BCC did not have histological evidence of BCC. 270 cases of suspected BCC and equivocal moles where RCM may have been useful. RCM could have saved £20,000 over 4 months through reduced follow ups and biopsy.	No data collected on DA of RCM (instead DA was estimated from literature). Reported as conference abstract so insufficient detail to appraise methodology.
Thng *et al.* (2016) Prospective observer-blinded study. "Cost-effectiveness of RCM for diagnosis of skin cancer in Singapore".	People (n=121) with clinically suspicious lesions (n=131). Perspective not stated Time period and horizon not stated.	RCM (VivaScope not specified but highly likely to be this technology).	Reference standard: histopathology.	RCM Se: 98.6% RCM Sp: 95.7% Potential cost savings of $600,000 from 3000 annual cases.	Conference abstract so insufficient detail to appraise methodology. Authors stated that Se and Sp of RCM was much superior to previously reported European studies.
Pellacani *et al.* (2016) Cost benefit analysis (retrospective data) "The influence of RCM on number of benign lesions needed to excise a melanoma, in terms of clinical outcomes and costs"	People with suspected MM (i.e. equivocal lesions). Italian health service (costed in Euros). Annual savings.	Addition of RCM (VivaScope not specified but highly likely to be this technology).	Current practice (dermatological examination with dermoscopy, or total body digital dermoscopy). Reference standard: histopathology	Reduction in unnecessary excisions: • NNE (university hospital) 6.25 • NNE (district hospital): 19.41 • 4320 reduction in unnecessary excisions/1 million inhabitants/year • Cost MM removal (standard care): €2932 • Cost MM removal (RCM): €2133 • €262,314 saving per 1 million inhabitants/year	Conference abstract so insufficient detail to appraise methodology. Unlikely to be generalisable to NHS in England and Wales.

Abbreviations: BCC, basal cell carcinoma; DA, diagnostic accuracy; MM, malignant melanoma; NNE, number needed to excise; RCM, reflectance confocal microscopy; Se, sensitivity; Sp, specificity.

Appendix 2 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to N/A	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 3 – supporting information

Relevant Institute work

Published

Suspected cancer: recognition and referral (2015, updated 2017) NICE guideline 12

Melanoma: assessment and management (2015) NICE guideline 14

Improving outcomes for people with skin tumours including melanoma (2010) NICE cancer service guideline CSG8

Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (2019) NICE technology appraisal guidance 562

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (2019) NICE technology appraisal guidance 558

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (2018) NICE technology appraisal guidance 553

Avelumab for treating metastatic Merkel cell carcinoma (2018) NICE technology appraisal guidance 517

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (2018) NICE technology appraisal guidance 517

Vismodegib for treating basal cell carcinoma (2017) NICE technology appraisal guidance 489

Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (2017) NICE technology appraisal guidance 473

Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2016) NICE technology appraisal guidance 414

Talimogene laherparepvec for treating unresectable metastatic melanoma (2016) NICE technology appraisal guidance 410

Nivolumab in combination with ipilimumab for treating advanced melanoma (2016) NICE technology appraisal guidance 400

Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (2016) NICE technology appraisal guidance 396

Nivolumab for treating advanced (unresectable or metastatic) melanoma (2016) NICE technology appraisal guidance 384

Pembrolizumab for advanced melanoma not previously treated with ipilimumab (2015, updated 2017) NICE technology appraisal guidance 366

Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (2015, updated 2017) NICE technology appraisal guidance 357

Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2014) NICE technology appraisal guidance 321

Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (2014) NICE technology appraisal guidance 319

Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (2012, updated 2015) NICE technology appraisal guidance 269

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (2012) NICE technology appraisal guidance 268

Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (2008) NICE technology appraisal guidance 145

Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma (2014) NICE interventional procedures guidance 478

Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (2013) NICE interventional procedures guidance 446

Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions) (2006) NICE interventional procedures guidance 155

Ambulight PDT for the treatment of non-melanoma skin cancer (2011) NICE medical technologies guidance 6

Skin cancer (2016) NICE quality standard 130

Suspected cancer (2016, updated 2017) NICE quality standard 124

In progress

Melanoma: assessment and management. NICE guideline. Publication date to be confirmed. (*Update proposed by ongoing surveillance consultation – March 2019)*

Improving outcomes for people with skin tumours including melanoma. NICE guideline. Publication date to be confirmed. (*Update proposed by ongoing surveillance consultation – March 2019)*

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]. NICE technology appraisals guidance. Publication expected July 2019

Nivolumab with ipilimumab for treating squamous cell carcinoma of the head and neck ID1355. NICE technology appraisals guidance. Publication expected August 2020

Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck (ID1140). NICE technology appraisals guidance. Publication expected August 2020

Atezolizumab with cobimetinib for untreated BRAF wild-type metastatic melanoma ID1470. NICE technology appraisals guidance. Publication date to be confirmed.

Carotuximab with pazopanib for treating advanced angiosarcoma ID1503. NICE technology appraisals guidance. Publication date to be confirmed.

Details of new technologies

Optical coherence tomography is being trialled in the UK and is entering routine practice in other countries. It was the subject of a Cochrane review (Ferrante di Ruffano et al. 2018; search date August 2016) which included five studies with 529 cutaneous lesions (282 malignant lesions). The authors concluded that there was "Insufficient data available on the use of optical coherence tomography for the detection of melanoma or cutaneous squamous cell carcinoma".

Registered and unpublished trials

Trial name and registration number	Details
Peppelman *et al.* (2016) Reflectance Confocal Microscopy in Basal Cell Carcinoma NCT02623101	A randomised controlled trial set in the Netherlands in patients with lesions suspicious of basal cell carcinoma. Expected number of patients: 322 Intervention: VivaScope 1500 Comparator: Punch biopsy Reference standard: histopathology Outcomes: diagnostic accuracy, quality-of-life, costs, cost-effectiveness Expected primary completion: December 2018
Confocal Microscopy Evaluation of Margin Clearance in Basal Cell Carcinomas in Mohs Surgery (FCM-P) NCT03610620	An observational study set at Norfolk and Norwich University Hospitals NHS Foundation Trust in patients undergoing Mohs surgery for basal cell carcinoma. Expected number of patients: 30 Intervention: VivaScope 2500 Reference standard: histopathology Outcomes: diagnostic accuracy, time taken Estimated primary completion: October 2019
Pellacani et al. (2019) Protocol provided by clinical expert	A randomised controlled trial set in Italy in 3 different populations: patients with equivocal skin lesions; patients with possible “featureless melanoma”; patients with suspected basal cell carcinoma. Expect to screen 30,000 patients Interventions: VivaScope 1500 and VivaScope 3000 Comparator: standard care (excision or biopsy) Reference standard: histopathology Outcomes: diagnostic accuracy, costs, economic analysis Estimated primary completion: unknown

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