# HTE temp withdrawn

Highly specialised technologies guidance

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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

# Contents

# 1 Recommendations

This guidance considers the use of VivaScope 1500 and 3000 imaging systems to help decide whether to biopsy and excise skin lesions, and to map lesion margins in people with skin cancer.

The VivaScope 1500 and 3000 imaging systems are novel technologies that can image tissue at a cellular level in real time.

The 4 types of skin cancer considered were melanoma, basal cell carcinoma, squamous cell carcinoma and lentigo maligna.

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.

# 2 The technologies

2.1      The VivaScope 1500 and 3000 imaging systems (MAVIG) are non-invasive, high resolution, reflectance laser confocal microscope systems that are designed to help assess potentially malignant skin lesions. They aim to provide quasi-histological resolution (a highly magnified image) of skin cells that is reportedly comparable to microscopic examination of a skin specimen. The VivaScope imaging systems are designed to be used with dermoscopy to help diagnose potentially malignant skin lesions, to delineate tumour margins for excision or to monitor healing after treatment.

2.2      The 2 CE-marked VivaScope imaging systems were identified during scoping as relevant to this assessment. No other commercially available laser confocal microscopes with real-time imaging functionality were identified.

# 3 Clinical need and practice

## The problem addressed

3.1    The purpose of this assessment is to assess the clinical and cost effectiveness of the VivaScope 1500 and 3000 imaging systems to:

- help decide whether to biopsy and excise skin lesions in people with suspected skin cancer

- define the margins of skin lesions for excision in people with skin cancer.

## The condition

3.2    Skin cancer is commonly classified into 2 main categories, which include over 95% of all reported skin cancers: melanoma skin cancer and non-melanoma skin cancer. Melanoma skin cancers develop from melanocytes, the skin cells in the deeper layers of the epidermis that produce the skin-darkening pigment known as melanin. Non-melanoma skin cancers develop from keratinocytes, the cells that produce the skin structural protein called keratin.

## Melanoma skin cancers

3.3    Although uncommon, melanoma incidence rates increased 7-fold between 1976 and 2009. In the UK, it is most common in people 50 years and over. A fifth of cases occur in young adults. The rise in incidence may be a result of increased surveillance, but it is estimated that more than 80% of cases are linked to UV exposure related to recreational behavioural change involving sun exposure and sunbeds (Cancer Research UK 2014). The incidence of melanoma is lower in lower socio-economic groups.

3.4    Melanoma can invade nearby tissue and spread to other parts of the body. It is responsible for most skin cancer deaths; in the UK in 2010 there were

approximately 2200 deaths and 12,818 new cases. Survival has improved substantially in recent decades and the survival rate is among the highest of any cancer, largely because of increased awareness, earlier diagnosis and better treatments (Cancer Research UK 2014).

3.5 Treatment is more likely to be successful when melanoma is detected in its early stages. In the UK, most melanomas are diagnosed at an early stage: 82% in men and 87% in women presented at stages 1 or 2 in 2010. In men, most melanomas present on the trunk (41%), head and neck (22%) or arms (19%). In women the most common sites for presentation are legs (39%), arms (24%) and trunk (20%).

3.6 Melanomas may be classified into broad types (superficial spreading melanomas, nodular melanomas, lentigo maligna melanomas, acral lentiginous melanomas) depending on their growth characteristics, appearance and location on the body.

# Non-melanoma skin cancer

3.7 Non-melanoma skin cancers are a group of common cancers, estimated to be about a third of all cancers detected in the UK. In 2011, 102,628 cases of non-melanoma skin cancer were recorded in the UK. However, the true number of cases may be higher because not all cancers are recorded by the cancer registries. The 2 most common types of non-melanoma skin cancer are basal cell carcinoma and squamous cell carcinoma. Basal cell carcinoma develops in keratinocytes deep in the epidermis and around the hair follicles; squamous cell carcinoma develops from keratinocytes elsewhere in the skin. Other types of cell in the epidermis may also become malignant, although they are far less common and include Kaposi's sarcoma, Merkel cell carcinoma and T-cell lymphoma.

3.8 Of the 2 types of non-melanoma skin cancer, squamous cell carcinoma is the more serious; basal cell carcinoma is rarely fatal. However, if basal cell carcinoma is not diagnosed early enough, or is not properly treated, it can destroy parts of the body such as the nose, eyes, ears and lips, which can be more difficult to treat and may become inoperable. Squamous cell carcinomas can also be disfiguring and, if they spread, fatal.

## Squamous cell carcinoma

3.9   Squamous cell carcinoma is the second most common skin cancer with 26,000 cases in the UK in 2011, and its incidence is increasing. Chronic ultraviolet light exposure is a key risk factor and squamous cell carcinoma is commonest in people with sun-damaged skin. This cancer most often develops in areas that have been exposed to the sun, such as the head, neck, forearms and the backs of the hands. Some squamous cell carcinomas can be difficult to view using imaging techniques because their upper surface is often scaly, which can make it hard to get sufficient resolution (detail).

## Basal cell carcinoma

3.10   Basal cell carcinoma is the most common skin cancer. About 75 out of every 100 cases of non-melanoma skin cancers diagnosed are this type – approximately 76,000 cases in the UK in 2011. It is most likely to develop in sun-exposed areas of skin, such as the nose, forehead, cheeks, back or lower legs, and is most often diagnosed in people in middle or older age.

3.11   Basal cell carcinomas (also known as rodent ulcers) may begin as a small lump and usually have shiny or pearly looking edges with a depressed center, which may become crusty or ulcerate. If untreated the ulcer can grow, becoming wider and deeper and affecting more skin tissue. Rodent ulcers can also affect other types of tissue, such as cartilage or bone. However, advanced rodent ulcers are uncommon in the UK because most people get treatment at an early stage.

3.12   There are different subtypes of basal cell skin cancers, including nodular (the most common – around 50% of all basal cell carcinomas), superficial, morphoeic and pigmented. Each of these subtypes looks and behaves differently.

3.13   It is unusual for basal cell skin cancer to spread to another part of the body to form a secondary cancer but it is possible to have more than 1 basal cell skin cancer at any 1 time. People who have already had 1 basal cell carcinoma are at greater risk of developing subsequent basal cell carcinomas.

# The diagnostic and care pathways

3.14    Most skin lesions will first be examined in a primary care setting. Because melanoma is still a relatively infrequent cancer in primary care, the initial diagnosis of suspicious skin lesions in primary care should follow the British Association of Dermatologists' ABCD-Easy guide to checking your moles (2011). NICE's guideline on the recognition and referral of suspected cancer (2015) includes a 7-point checklist that helps clinicians decide whether a person should be urgently referred to a specialist for an appointment under the 2-week rule, (where urgent referrals to a specialist should be seen within 2 weeks).

3.15    Any lesions that cannot be considered definitively or unequivocally non-cancerous should be referred to a skin specialist. NICE guidance on improving outcomes for people with skin tumours including melanoma (2010), recommends that health professionals who knowingly treat people with any type of skin cancer should be members of a multidisciplinary skin cancer team (local hospital skin cancer multidisciplinary teams or specialist skin cancer multidisciplinary teams).

3.16    NICE's guideline on the recognition and referral of suspected cancer (2015) recommends that a person with suspected non-melanoma skin cancer presenting in primary care should be referred for specialist opinion either under the 2-week rule (squamous cell carcinoma) or as a routine referral. All people who present in primary care with a possible cutaneous squamous cell carcinoma should be referred urgently under the 2-week rule to a skin specialist, as in the case of suspected melanoma. Basal cell carcinoma should be referred as a routine referral, although low-risk basal cell carcinoma can be managed in a community setting by a suitably qualified level 1 practitioner (GP).

## Management of melanoma

3.17    The management of cutaneous melanoma is outlined in the British Association of Dermatologists' revised UK guidelines (Marsden et al. 2010). When a person with a suspicious skin lesion presents and there is a need to exclude melanoma, the lesion will usually be examined using a dermatoscope (a handheld, specialised magnifying device). The lesion is photographed and then the whole lesion,

together with a clinical margin of 2 mm of normal skin, is completely removed (excision biopsy). This allows tumour staging by measuring the thickness of the tumour in the tissue (Breslow thickness).

3.18    Shave biopsies, which only remove part of the lesion, may be done on large lesions, but this can increase the risk of sampling error and may make staging the tumour difficult. Punch biopsy or incisional biopsy is occasionally used, for example, in the differential diagnosis of lentigo maligna or of acral melanoma. These types of biopsy are only carried out by the skin cancer multidisciplinary team.

3.19    All suspected melanoma lesions that are removed should be sent for histopathological review to the pathologist associated with the specialist skin cancer team. Histological reporting should follow the requirements set out in the British Association of Dermatologists' guidelines for managing cutaneous melanoma (Marsden et al. 2010).

3.20    If it is not possible to distinguish pathologically between a melanoma and a benign melanocytic lesion, the person should be referred to the specialist multidisciplinary team for clinical and pathological review.

3.21    Surgery is the only curative treatment for melanoma and, if there is histopathological confirmation of malignancy, a wider and deeper margin is excised to ensure complete removal. The lateral margins for excision depend on the tumour thickness.

3.22    Lentigo maligna and other in situ melanomas with no potential for metastatic spread should be excised completely with a clear histological margin. No further treatment is necessary. Complete removal is recommended because of the risk of sub-clinical microinvasion. Incisional biopsy may miss this because of sampling error. Lentigo maligna can present a diagnostic challenge because it can cover a large area on sites such as the face, and have varied histology and diffuse boundaries. In older people the risk of progression may be low, so treatments other than surgery such as radiotherapy or observation may be more appropriate. About 5% of people have a local recurrence within 2 years, possibly caused by incomplete removal of cancer cells around the margin of the excision.

# Management of non-melanoma

## Squamous cell carcinoma

3.23    Diagnosis is established histologically after biopsy and the margins of excised tissues may be stained before histological preparation to determine the peripheral and deep margins. Most squamous cell carcinomas are low risk and respond to several treatments. However, identifying the high-risk cases needs to be managed by a specialist skin team.

3.24    The aim of treatment is to remove the primary tumour and any metastases. This needs accurate margin assessment. The gold standard for margin identification is currently histology. However, most treatments rely on clinical judgement, which may not accurately predict the extent of the tumour if there is no well-defined margin.

3.25    The British Association of Dermatologists' guidelines for managing primary squamous cell carcinoma (Motley et al. 2009) state that, when feasible, surgical excision techniques (including Mohs surgery) should be considered as the first choice for treating squamous cell carcinoma, because these techniques provide histological confirmation of tumour removal. Mohs microsurgery involves the removal of tumours to predefined margins, carefully mapped to match the histopathology. The tissue removed from the tumour is histologically examined to identify the further areas of tissue to be removed. This process is repeated until the margins are shown to be clear of cancer cells, and it needs well-integrated surgical and histological services.

3.26    In surgical excision, a minimum margin of 4 mm is recommended for clinically well-defined, low-risk tumours. A narrower margin is more likely to leave residual cancer cells, which can cause recurrence. Ill-defined tumours more than 2 cm in diameter, tumours that are moderately or poorly differentiated, or tumours on the ear, lip, scalp, eyelid or nose should be removed with a wider margin of 6 mm or more or with Mohs surgery. The concept of clinical margin is important in predicting successful excision.

## Basal cell carcinoma

3.27    Low-risk nodular basal cell carcinoma may be removed in community settings by suitably qualified GPs. However, if there is uncertainty in the diagnosis or the appropriate treatment cannot be provided in primary care, referral should be made to the specialist skin cancer team according to the NICE guideline on improving outcomes for people with skin tumours including melanomas. Basal cell carcinomas would usually be referred from primary care as a non-urgent referral rather than by the 2-week wait rule.

3.28    After diagnosis, basal cell carcinoma may be treated non-surgically through medical treatments such as imiquimod, or by curettage, cautery or laser ablation. However, higher-risk basal cell carcinomas may need a more aggressive approach involving surgical removal to clear margins, either by excision or by Mohs surgery. Incomplete excision increases the risk of recurrence. Mohs surgery is a successful treatment for high-risk basal cell carcinoma and for high-risk recurrent basal cell carcinoma.

# 4 The diagnostic tests

## The interventions

### VivaScope 1500 imaging system

4.1     The VivaScope 1500 imaging system is a non-invasive reflectance confocal microscope system that uses a near-infrared point-laser light to get images of the top layers of the skin. These images are intended to be so highly magnified that they are quasi-histological (comparable with microscopic examination of skin cells). The VivaScope 1500 system is console based and operates at a single wavelength of 830 nm.

4.2     The VivaScope 1500 imaging system includes software designed to analyse, store and display real-time images of skin tissue in vivo, including skin cells, blood vessels, collagen and pigment. The images present a surface-down view of the skin and may give information about the skin lesion's cell structure and the architecture of the surrounding tissues. This may help a clinician to make a clinical judgement and provide a positive or negative diagnosis of a cancerous skin lesion. Because the images do not give a transverse view of the skin, tumour thickness would typically need to be determined by histological examination of a biopsy.

4.3     The VivaScope 1500 imaging system is fixed to the skin by a magnetic ring attachment with a disposable adhesive window and a transparent, low-refractive index medium between the skin and lens system. The system automatically scans the area of skin to which it is attached and is reported to give an image of the superficial reticular dermis (upper layer of the skin) to a depth of 250 micrometres at a resolution (ability to distinguish detail) of 1.25 micrometres. Overall, the set-up time to attach the system and get an image is about 10 minutes, although this may vary depending on the experience of the user. The system is intended for diagnosing skin cancers and identifying lesions needing surgery, identifying the margins of lesions before and after surgery, and in monitoring the impact of non-invasive treatments.

4.4      Another version of the VivaScope 1500 imaging system is the VivaScope 1500ML (Multilaser) system. This system is intended for use with fluorescent dyes for imaging skin in vivo or ex vivo, and is currently used in research settings.

## VivaScope 3000 imaging system

4.5      The VivaScope 3000 imaging system is a handheld unit and is technically similar to the VivaScope 1500 imaging system. It operates with a single laser (830 nm) and images the superficial reticular dermis at a resolution of 1.25 micrometres. The handheld device is designed for imaging lesions in more difficult to reach areas, such as around the nose, eyes, ears, lips and gums. Unlike the VivaScope 1500 imaging system, the VivaScope 3000 imaging system is not attached to the skin surface but can be moved freely across the surface. The VivaScope 3000 imaging system is also intended for diagnosing skin cancers and identifying lesions needing surgery, identifying the margins of lesions before and after surgery, and in monitoring the impact of non-invasive treatments.

## The comparators

4.6      The comparators used in this assessment are current clinical practices used in the NHS to diagnose skin cancer and determine skin cancer tumour margins. These are:

- examining skin using dermoscopy and clinical judgement to detect potentially cancerous lesions

- examining skin using dermoscopy and clinical judgement to determine tumour margins.

# 5 Outcomes

The Diagnostics Advisory Committee (section 11) considered evidence from a number of sources (section 12).

## How outcomes were assessed

5.1      The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of using the VivaScope 1500 and 3000 imaging systems with dermoscopy and clinical judgement to:

- help decide whether to biopsy and excise skin lesions in people with suspected skin cancer

- define the margins of skin lesions for excision in people with skin cancer.

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

## Clinical effectiveness

5.3      The External Assessment Group identified 16 studies that met the inclusion criteria for the review. Of the 16 included studies, 13 reported the use of VivaScope or reflectance confocal microscopy (RCM) in diagnosing suspected or equivocal lesions, and 3 reported its use in lesion margin delineation.

5.4      Of the 13 studies reporting lesion diagnosis, 7 used VivaScope 1500 or 3000 imaging systems. Of these 7 studies, 6 used VivaScope 1500 and 1 used VivaScope 1500 and 3000. Four of the studies that used VivaScope 1500 did not include dermoscopy as a comparator. The remaining 6 of the 13 studies used earlier versions of the VivaScope imaging system. Of these, 3 used VivaScope 1000 (2 of which did not include dermoscopy as a comparator), 2 used VivaScope 1000 and 1500 (1 did not include dermoscopy as a

comparator), and 1 used VivaScope 2500.

5.5 In 10 of the 13 studies reporting lesion diagnosis, consecutive patients were prospectively enrolled from settings including melanoma or dermatology clinics in tertiary or university hospitals, and 1 study retrospectively selected previously imaged lesions or excised lesions.

5.6 Two of the 3 studies reporting lesion margin delineation used VivaScope 1500 with or without dermoscopy as a comparator and the remaining study used VivaScope 2500.

5.7 Of the 3 studies on lesion margin delineation, 1 retrospectively assessed and interpreted lesion images in patients previously enrolled in 2 university-based clinics or hospitals and 2 prospectively and randomly recruited patients with lesions from a dermatology department or Mohs surgery unit.

5.8 None of the included studies was conducted in the UK. Most of the 16 included studies were from countries whose skin cancer rates and treatment pathways may be different from the UK settings (8 studies from Australia and Italy, 2 from Brazil and the USA, 2 each from Spain and Australia, and 1 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 3 studies to be the most representative of clinical practice in the UK.

5.9 Most of the included studies had low risk of bias and low applicability concerns regarding patient selection (11 studies), conduct of the index test (13 studies) and reference standard (13 studies). However, the risk of bias for flow and timing was unclear in most of the studies (13 studies) because of poor reporting and insufficient data. Included studies were considered too heterogeneous to have their results combined by meta-analysis. This was because of study design, patient population, or insufficient reporting of results. Of the outcomes defined in the scope, only diagnostic accuracy and lesion recurrence rate were reported in the included studies.

# Diagnostic accuracy in lesion diagnosis

5.10    Diagnostic accuracy was the most commonly reported outcome in studies, reported as sensitivity, specificity, positive predictive value and negative predictive value. Other diagnostic accuracy data such as false positive, false negative and true negative were rarely reported so had to be estimated and calculated using other reported diagnostic data when possible.

## Dermoscopy plus VivaScope 1500 compared with dermoscopy

5.11    Three studies compared dermoscopy plus VivaScope 1500 with dermoscopy.

5.12    Alarcon et al. (2014) assessed the impact of RCM analysis on dermoscopically equivocal pigmented lesions. Of the 343 lesions examined using RCM, only 264 were excised and analysed using histopathology (79 lesions were followed up for 1 year without any melanoma diagnosed). The 92 melanomas diagnosed using dermoscopy also had independent VivaScope 1500 examination. Histopathology showed that there were 6 false negatives using dermoscopy alone, and 2 false negatives with dermoscopy plus VivaScope 1500. When dermoscopy plus VivaScope 1500 and dermoscopy alone were compared using the histopathology findings for the 264 excised lesions, there were statistically significant differences in sensitivity in the diagnosis of melanoma (97.8% versus 94.6%; $p=0.043$ respectively) and specificity in non-melanoma (92.4% versus 26.7%; $p<0.000001$ respectively). Using a 2×2 contingency table to compare RCM with dermoscopy and assuming the 79 lesions followed up were true negatives, the sensitivity was 97.8% and 93.5% respectively and the specificity was 94.8% and 49.0% respectively. Therefore, although 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% versus 49.0%) compared with analysis based on 264 excised lesions.

5.13    Pellacani et al. (2014) prospectively assessed the potential impact of RCM when implemented in a routine melanoma workflow. At dermoscopy, patients were referred to 1 of the following pathways:

- no further examination

- referral to RCM:

  — RCM documentation (lesions with consistent suspicious clinical or dermoscopic criteria, already qualified and scheduled for surgical excision)

  — RCM consultation for equivocal lesions, followed by either excision or digital follow-up.

5.14 In the Pellacani et al. (2014) study, 493 lesions were referred for RCM examination, but 2 patients refused RCM imaging so lesions were excised, and histopathology reported 1 basal cell carcinoma (BCC) and 1 benign lesion. Of the remaining 491 lesions, 183 had RCM documentation and 308 RCM consultations. In the RCM documentation group, histopathology confirmed 110 positives using RCM (23 melanomas, 19 BCCs and 68 benign lesions) and 73 negatives using RCM (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 6 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. Assuming that all of the 21 RCM negatives lost to follow-up in the RCM consultation group were true negatives, for RCM documentation and RCM consultation the sensitivity was 100% and 100% respectively; the specificity was 51.77% and 78.6% respectively. However, when the 21 RCM negatives lost to follow-up were excluded, the sensitivity was 100% and specificity was 80.2% for RCM consultation.

5.15 Ferrari et al. (2014) evaluated the most relevant RCM features for melanomas that were difficult to detect 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 1 of the 2 independent parameters accounted for the detection of all 6 melanomas (100% sensitivity; 82.3% specificity). Similarly, in the population with a dermoscopic score of 3–4, the presence of at least 1 of the 2 independent parameters accounted for the detection of 16 of 17 melanomas (94.1% sensitivity; 62.4% specificity).

## Dermoscopy plus VivaScope 1500

5.16    There were 4 studies that reported the diagnostic accuracy of VivaScope 1500 after dermoscopy without a comparator.

5.17    Curchin et al. (2011) reported sensitivity and specificity data on 50 equivocal lesions in 42 patients. With VivaScope 1500 after dermoscopy, 12 of 13 melanomas (92.3% sensitivity; 75% specificity), 19 of 22 benign naevi (86% sensitivity; 95% specificity), 6 of 9 BCCs (66.7% sensitivity; 100% specificity) and all 6 squamous cell carcinomas (SCCs) and its precursors (100% sensitivity; 75% specificity) were correctly diagnosed.

5.18    Guitera et al. (2010) assessed which RCM features could distinguish lentigo maligna (LM) from benign macules of the face such as solar lentigo, actinic keratosis and seborrheic keratosis, and tested different algorithms for diagnosing LM. A LM score of 2 or more resulted in a sensitivity of 85% and specificity of 76% for the diagnosis of LM (odds ratio [OR] for LM 18.6; 95% confidence interval [CI] 9.3 to 37.1).

5.19    Rao et al. (2013) assessed the accuracy of VivaScope 1500 compared with histopathology in the diagnosis of 284 cutaneous lesions by 2 readers with different degrees of experience. Malignant lesions diagnosed with VivaScope 1500 by reader 1 represented 66.7%, 74.1% and 37.2% of histologically diagnosed melanoma, BCC and SCC respectively. For reader 2, lesions diagnosed as malignant represented 88.9%, 51.9% and 72.1% of histologically diagnosed melanoma, BCC and SCC respectively. Of the 284 lesions evaluated by both readers, 212 were benign and 72 were malignant based on histopathology.

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

## Dermoscopy plus VivaScope 1000 compared with dermoscopy

5.21    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 after dermoscopy compared with dermoscopy alone was 97.3% and 89.2% respectively, and the specificity was 83.0% and 84.1% respectively. Using a 2×2 contingency table to estimate histologically proven positive and negative diagnostic tests, the numbers of patients or lesions correctly and incorrectly diagnosed were similar using VivaScope 1000 after dermoscopy compared with dermoscopy alone.

## VivaScope 1000

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

5.23    In the trial by Gerger et al. (2006), 117 melanocytic skin lesions and 45 non-melanocytic skin lesions were consecutively sampled and examined by 4 independent observers using VivaScope 1000. The overall (total of the 4 observers) diagnostic differentiation of benign from malignant lesions (melanoma and BCC) reached a sensitivity of 94.65%, specificity of 96.67%, positive predictive value of 97.50%, and negative predictive value of 92.99% based on histopathology. In a supplementary publication to Gerger et al. (2006), Gerger et al. (2008) retrospectively evaluated 3709 selected images of 70 lesions (20 malignant melanomas and 50 benign naevi) using VivaScope 1000. The overall performance of the 4 observers who reviewed the images showed a sensitivity of 97.5%, specificity of 99.0%, positive predictive value of 97.5%, and a negative predictive value of 99.0%.

## VivaScope 1000 or 1500 compared with dermoscopy

5.24    In a trial by Guitera et al. (2009), the possible additive value of VivaScope 1000 and 1500 in managing melanocytic lesions was evaluated at 2 centres. For the diagnosis of melanoma, there was no significant difference in sensitivities between VivaScope 1000 or 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 or 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

5.25    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 or 1500 demonstrated optimal sensitivity for a score of 2 or more (96.3%), with 52.1% specificity.

## Dermoscopy plus VivaScope 1500 compared with dermoscopy plus VivaScope 3000

5.26    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 after dermoscopy and VivaScope 3000 after dermoscopy showed: sensitivity (100% versus 93%), specificity (78% for both RCMs), positive predictive value (96% versus 95%), and negative predictive value (100% versus 70%) respectively.

# Misdiagnosis of lesions

## VivaScope 1000 or 1500 compared with dermoscopy

5.27    In the trial by Guitera et al. (2009), 15 melanomas (12%) were misclassified by dermoscopy, 11 melanomas (9%) were misclassified by the VivaScope 1000 or 1500, and only 3 (2.4%) by both techniques.

## Dermoscopy plus VivaScope 1000 compared with dermoscopy

5.28    In the trial by Langley et al. (2007), there were 5 out of 37 melanomas for which VivaScope 1000 after dermoscopy and dermoscopy alone produced different diagnoses. VivaScope 1000 after dermoscopy correctly classified 4 out of 5 melanomas, whereas dermoscopy alone correctly classified 1 out of 5 melanomas. Additionally, there were 7 benign naevi for which both diagnoses

were incorrect. Of the melanomas, 2 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

5.29    In the trial conducted by Pellacani et al. (2014), overall the VivaScope 1500 proposed diagnosis was concordant with histopathological diagnosis in 216 of 283 (76.3%) evaluated cases. BCC was the most accurate diagnosis (37 of 38; 97.4%), then melanoma (24 of 28; 85.7%). Spitz nevus was the most frequently misclassified diagnosis (accurate diagnosis: 4 of 13; 30.8%); 6 were misclassified as Clark's naevi and 3 as melanoma.

# Diagnostic accuracy in margin delineation

## Dermoscopy plus VivaScope 1500 compared with dermoscopy

5.30    Guitera et al. (2013) analysed patients with LM and lentigo maligna melanoma to determine whether VivaScope 1500 mapping might alter patient care and lesion management. Out of 60 positive sites for LM confirmed by histopathology, 55 (5 false negatives) had been confirmed by VivaScope 1500 and 21 (39 false negatives) by dermoscopy. Of 125 LM sites confirmed as negative by histopathology, 121 (4 false positives) had been confirmed by VivaScope 1500 and 122 (3 false positives) by dermoscopy. Histopathology also showed 17 of 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. Therefore, the visible area was on average less than 40% of the area that was treated based on VivaScope 1500 mapping findings.

## VivaScope 1500

5.31    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 7 of 10 (70%) cases, the margins of the cancer were identified using VivaScope 1500 and confirmed by histopathological analysis. In 3 of 10 (30%) cases, the margins of the lesions could not be detected because of the unevenness of the surface.

### VivaScope 2500

5.32    Bennassar et al. (2014) evaluated the sensitivity and specificity of ex vivo imaging with fluorescence confocal microscopy for detecting residual BCC in Mohs tissue excisions, and calculated the time invested up to the diagnosis for both fluorescence confocal microscopy and frozen sections. The overall sensitivity and specificity of detecting residual BCC in surgical margins was 88% and 99% respectively. The number of images or mosaic correctly diagnosed as true positive was 79 (89%) and true negative was 390 (99.7%). There was only 1 (0.3%) false positive. In addition, on average VivaScope 2500 reduced the evaluation time by 18 minutes (p<0.001) when compared with the processing of a frozen section.

## Lesion recurrence in margin delineation

5.33    The trial conducted by Guitera et al. (2013) reported that of 17 patients with LM that was surgically excised, 2 (12%) had re-excisions (margins were confirmed by histopathology). Regarding future recurrence, the study reported that no recurrence of LMs treated surgically was observed in any patient by last follow-up (median follow-up 37 months; range 7–66 months). However, this observation was based on a small number of LMs excised.

## Change in management in margin delineation

5.34    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 of 37 patients.

# Cost effectiveness

## Systematic review of cost-effectiveness evidence

5.35    The External Assessment Group conducted a search to identify economic studies investigating the cost effectiveness of VivaScope 1500 and 3000 in the diagnosis of skin lesions suspected as skin cancer and in the margin delineation of malignant skin lesions, including LM, before surgical treatment. No studies were considered eligible for inclusion in the systematic review.

5.36    During the development of this report, the company made available to the External Assessment Group an unpublished study of the cost effectiveness of RCM in the diagnosis of skin lesions suspected as skin cancer. The study had a retrospective design, and therefore did not meet the inclusion criteria for economic evaluations. However, because there was a lack of relevant economic evidence on the cost effectiveness of VivaScope, this study was accepted in the systematic literature review. This study is academic in confidence at the time of writing this draft guidance.

## Economic analysis

5.37    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 as skin cancer and in the margin delineation of malignant skin lesions, including LM, before surgical treatment.

5.38    According to the study populations that were identified as relevant for the economic evaluation of VivaScope, 3 separate 'part' economic models were developed:

- Use of VivaScope in the diagnosis of equivocal lesions suspected as melanoma. This model assessed the cost effectiveness of

VivaScope 1500 and 3000 as 1 integrated system, assuming that both devices would be available for the diagnosis of equivocal lesions but that each would 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 after a positive or equivocal finding in dermoscopy. As with the previous model, this model assessed the cost effectiveness of VivaScope 1500 and 3000 as 1 integrated system, assuming that both devices would be available for the diagnosis of suspected BCC lesions but that each would be used as appropriate according to the location of the skin lesion to be examined.

- Use of VivaScope for the margin delineation of LM before surgery. This model assessed the cost effectiveness of VivaScope 3000 as a stand-alone device, because only this device is appropriate for margin delineation.

5.39    Five economic analyses were carried out, examining the cost effectiveness of VivaScope:

- Diagnostic assessment of equivocal lesions suspected as melanoma (integrated use of VivaScope 1500 and 3000).

- Diagnostic assessment of lesions suspected as BCC after a positive or equivocal result in dermoscopy (integrated use of VivaScope 1500 and 3000).

- Diagnostic assessment of skin lesions suspected as skin cancer, either melanoma (after an equivocal finding in dermoscopy) or BCC (after a positive or equivocal finding in dermoscopy) – this analysis combined the results of the 2 respective 'part' models.

- Margin delineation of LM before surgical treatment (using VivaScope 3000 as a stand-alone device).

- Diagnostic assessment of skin lesions suspected as either melanoma or BCC, and the margin delineation of LMs (integrated use of VivaScope 1500 and 3000) – this analysis combined the results of all 3 'part' models.

5.40    The final economic analysis synthesised all cost and effectiveness data from
each of the 'part' economic models to give 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 multidisciplinary team service.

# Diagnostic economic model for suspected melanoma lesions after an equivocal finding in dermoscopy

## Model structure

5.41    A decision tree followed by a Markov model was constructed to assess the cost
effectiveness of VivaScope in the diagnosis of lesions suspected as melanoma
after an equivocal finding in dermoscopy. The model structure was determined by
clinical expert advice and the availability of relevant data. Dermoscopically
equivocal lesions suspected as melanoma in people aged 55 years were either:
examined with VivaScope 1500 or 3000 followed by excision and biopsy or
discharge; or managed in routine clinical practice, comprising excision and biopsy
of the suspicious lesions and monitoring of equivocal lesions.

## Model inputs

5.42    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. Because 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 as
melanoma from Alarcon et al. (2014) and Pellacani et al. (2014) in 2 separate
analyses, because these 2 studies were considered to be the most
representative of the UK setting.

## Costs

5.43 Costs considered in this economic model included:

- Cost of diagnostic assessment of a suspected melanoma with VivaScope after an equivocal finding in dermoscopy.

- Cost of routine management (cost of excision or monitoring of suspected melanomas).

- Cost of managing confirmed melanomas (true positives) after diagnostic assessment.

- Cost of missed melanomas (false negatives) that were identified at a later time.

- Cost associated with metastatic melanoma and terminal illness.

## Health-related quality of life

5.44 The utility values applied to each health state were derived from the published literature. People in the model experienced utility (or disutility) associated with 1 or more of the following:

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

- Disutility due to permanent scarring after 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).

## Base-case results

5.45 For the purposes of decision-making, the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained or lost were considered. The

following assumptions were applied in the base-case analysis:

- The model assumed that confirmed skin cancer lesions were of the same type of cancer as initially suspected (in the case of this model, melanoma), although occasionally skin cancers identified might be of a different type to that initially identified by the clinician at dermoscopy.

- People whose lesions were shown not to be a melanoma on biopsy were assumed to have a benign tumour that did not need treatment and were discharged after the (unnecessary) excision and biopsy.

- The diagnostic accuracy of VivaScope 3000 in equivocal lesions suspected as melanoma was assumed to be equal to that of VivaScope 1500 in the economic model, because of 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.

5.46 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 used in the model, when VivaScope was assumed to be exclusively used for this purpose. Using the more 'optimistic' diagnostic data from Alarcon et al. (2014) resulted in a probabilistic ICER of £9362 per QALY gained. The 'less favourable' diagnostic data from Pellacani et al. (2014) resulted in an ICER of £25,453 per QALY gained. When using VivaScope was expanded to include other indications assessed in the economic analysis, VivaScope became the dominant strategy, that is, it was more effective and less costly than routine management of equivocal lesions suspected as melanoma.

## Sensitivity analyses

5.47 One-way sensitivity analyses were performed on all input parameters that were given a probability distribution in the economic model. The results of the one-way sensitivity analyses were reported as the incremental net monetary benefit associated with the VivaScope imaging systems, assuming a maximum acceptable ICER of £20,000 per QALY gained.

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

- percentage of people experiencing permanent disutility due to scarring

- disutility due to anxiety while waiting for the biopsy results

- percentage of equivocal lesions excised under routine management

- permanent disutility due to scarring from first excision

- annual volume of suspected melanomas eligible for examination for VivaScope (if VivaScope was used exclusively for examination of suspected melanomas)

- VivaScope sensitivity and specificity

- prevalence of melanomas in equivocal lesions

- cost of first excision

- disutility due to first excision.

5.49    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. (2014) were used in the model, the only parameter that potentially resulted in a negative incremental net benefit was the disutility due to anxiety. When VivaScope was assumed to be used exclusively for the diagnosis of suspected melanomas and when diagnostic data from Pellacani et al. (2014) were used in the model, several parameters resulted in negative incremental net benefits. 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.

5.50    When diagnostic accuracy data from Pellacani et al. (2014) were used and VivaScope was assumed to be exclusively used for the diagnostic assessment of suspected melanomas, the use of VivaScope became less cost effective in the different scenarios. However, when wider use of VivaScope was assumed for all indications, the results were unaffected by the scenarios tested.

5.51 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 as melanoma. The results indicated that VivaScope needs to have a relatively high diagnostic accuracy in order to be cost effective, particularly when it is used exclusively for the diagnostic assessment of suspected melanomas.

5.52 The effect of a change in the percentage of equivocal lesions suspected as melanoma that are excised under routine management was also analysed. The ICER was less than £20,000 per QALY gained when the percentage of equivocal lesions excised was approximately 10% and below, or 60% and above.

# Diagnostic economic model on lesions suspected as basal cell carcinoma after a positive or equivocal dermoscopy finding

## Model structure

5.53 A decision tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in the diagnosis of lesions suspected as 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 after a positive or equivocal finding in dermoscopy, were either examined with VivaScope 1500 or 3000 followed by treatment or diagnostic biopsy or had a diagnostic biopsy for confirmation of BCC. The model assumed that confirmed cases of skin cancer were of the same type of cancer as initially suspected (in the case of this model, BCC), although occasionally skin cancers identified might be a different type to that initially identified by the clinician at dermoscopy.

## Model inputs

5.54 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. 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 1 suspicious lesion for BCC (clinically and dermoscopically) who 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 systems was 77.8%.

## Costs

5.55    Costs considered in this economic model included the cost of diagnostic assessment with VivaScope after 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).

## Health-related quality of life

5.56    The utility values applied to each health state were derived from the published literature.

5.57    Patients in this model experienced a reduction in their health-related quality of life for one of the following reasons:

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

- surgical treatment (all people having surgical excision or Mohs surgery in the model) and unnecessary non-surgical treatment (people with false positive lesions)

- permanent scarring after surgical treatment of a lesion on head or neck.

## Base-case results

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

- Confirmed cases of skin cancer were of the same type of cancer as initially
  suspected (in the case of this model, BCC), although occasionally skin
  cancers identified might be of a different type to that initially identified 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.

5.59    VivaScope was the dominant strategy, that is, it was more effective and less
        costly, when used for assessing suspected BCCs, regardless of whether it was
        used exclusively for assessing BCCs or all indications (suspected melanomas and
        LMs).

## Sensitivity analyses

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

- percentage of people experiencing permanent disutility due to scarring from
  biopsy

- disutility due to anxiety while waiting for the results

- diagnostic biopsy cost

- prevalence of BCC in examined lesions

- permanent disutility due to scarring from biopsy

- annual volume of suspected BCCs that would be examined with VivaScope

- disutility due to biopsy

- percentage of patients treated with surgery

- sensitivity of VivaScope 3000

- number of lesions per person

- percentage of people experiencing permanent disutility due to scarring from surgery.

5.61 However, none of the parameters had an impact great enough to turn the incremental net benefit to negative values, even when VivaScope was used exclusively in the diagnostic assessment of suspected BCCs.

5.62 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 £7083 per QALY gained).

# Pre-surgical margin delineation economic model

## Model structure

5.63 The study population for this model comprised patients with LM, aged 70 years, having margin delineation before surgery. The aim of examination of LMs with VivaScope before surgical removal was the accurate definition of tumour margins. A decision tree followed by a Markov model was constructed to assess the cost effectiveness of VivaScope in margin delineation of LMs before surgical treatment. The model structure was determined by clinical expert advice and availability of relevant data. Patients aged 70 years with a LM planned for surgical excision either had their tumour examined with VivaScope 3000 for margin delineation before surgery, or had routine lesion management, comprising pre-surgical assessment of LM margins with dermoscopy or clinical judgement.

## Model inputs

5.64 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.

5.65  The impact of VivaScope on surgical outcomes after pre-surgical margin delineation of LMs was taken from the results of the systematic review of clinical effectiveness. The values used in the model were taken from Guitera et al. (2013) and are described in section 5.34.

## Costs

5.66  Costs included the cost of:

- pre-surgical mapping of LMs with either VivaScope 3000 or dermoscopy or clinical judgement

- treatment with either surgical excision or Mohs surgery

- potential future treatment due to recurrence.

## Health-related quality of life

5.67  The utility values applied to each health state were derived from the published literature. Patients in this model experienced a reduction in their health-related quality of life for one of the following reasons:

- surgical treatment (either surgical excision or Mohs surgery)

- permanent scarring after surgical treatment of a LM on the head or neck.

## Base-case results

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

- LMs did not progress to lentigo maligna melanomas, because the relative risk

was low as a result of all LMs in the model being treated.

- The risk of recurrence of LMs after margin delineation using VivaScope 3000 was equal to the risk of recurrence of LMs after Mohs surgery, regardless of the type of surgical treatment (surgical excision or Mohs surgery) after mapping with VivaScope 3000 (this was considered by clinical experts to be a conservative assumption).

- After 10 years, the risk of recurrence was zero.

5.69 Regarding margin delineation of LMs, mapping with VivaScope was cost effective, even if it was used exclusively for this purpose, as indicated by an ICER of £11,651 per QALY gained. When use of VivaScope was expanded to other indications covered in this economic analysis, VivaScope became the dominant option, that is, it was more effective and less costly.

## Sensitivity analyses

5.70 The following inputs had the most impact on the cost effectiveness of pre-surgical mapping of LMs using VivaScope:

- probability of incomplete surgical excision after routine mapping

- probability of annual recurrence after surgical excision

- probability of incomplete surgical excision after mapping with VivaScope

- permanent disutility due to scarring from surgical treatment

- percentage of people with permanent disutility from scarring

- probability of annual recurrence after VivaScope mapping and surgical excision

- VivaScope mapping (staff) time

- cost of surgical excision

- number of Mohs stages under routine mapping

- disutility due to surgery.

5.71 When it was assumed that VivaScope was used only for the mapping of LMs before surgical treatment, negative incremental net benefits were possible for several parameters. However, when a wider use of VivaScope was assumed, the incremental net benefit remained positive under any values of the influential parameters examined.

# 6 Considerations

6.1    The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of using the VivaScope 1500 and 3000 imaging systems, to help decide whether to biopsy and excise skin lesions in people with suspected skin cancer, and to define the margins of skin lesions for excision in people with skin cancer, compared with current practice.

6.2    The Committee considered the quality of the studies included in the systematic review of clinical effectiveness. It noted that the External Assessment Group generally considered the studies to be at unclear risk of bias because insufficient information was reported in the publications. The Committee also discussed how clinical practice had advanced and heard from a clinical expert that older studies may not be representative of current NHS clinical practice. The Committee noted that more recent studies, from 2013 onwards, included care that was more representative of current clinical practice, and considered the impact of introducing confocal microscopy on clinical workflow. The Committee concluded therefore that studies from 2013 onwards were most relevant to the assessment: Alarcon et al. (2014), Pellacani et al. (2014), Ferrari et al. (2014), Castro et al. (2014), Stanganelli et al. (2014) and Rao et al. (2013).

6.3    The Committee considered the evidence on using the VivaScope systems to image different types of lesion. The Committee noted that there was a lack of available evidence on using the VivaScope systems in diagnosing lentigo maligna (LM) and in defining lesion margins in melanoma. The Committee heard from clinical experts that VivaScope is not useful in clinical practice for defining lesion margins in melanoma because the margins of melanomas are clearly defined and can easily be completely excised. The Committee also noted that no evidence was available on imaging squamous cell carcinoma (SCC) and recognised that improving diagnosis of this cancer is important. The Committee heard from clinical experts that SCCs can be difficult to view using imaging techniques because the upper surface is often scaly, which can make it hard to get sufficient penetration of the beam for effective imaging. The Committee also heard that confocal microscopes, including the VivaScope systems, do not currently have the technical capability to measure to a depth sufficient for accurately diagnosing invasive SCC. However, confocal microscopes may improve the diagnosis of in

situ SCC if the carcinoma cells are confined to the epidermis and have not invaded the deeper dermis. The Committee concluded that the VivaScope 1500 and 3000 systems were not technically suitable for imaging invasive SCC and therefore, further research was not appropriate.

6.4     The Committee discussed the different types of biopsy used in the diagnosis and treatment of skin cancer. It heard that a punch biopsy is used in the diagnosis of skin cancers before treatment and that this type of biopsy is most commonly used for basal cell carcinoma (BCC) and LM. The Committee also heard that an excision biopsy is often used for melanoma and it can be used to diagnose and treat skin cancers simultaneously, or that it can be performed after diagnosis just for treatment purposes. The Committee concluded that it is important to understand the different types of biopsy used for different skin lesions to fully understand the different clinical pathways.

# Diagnosis

6.5     The Committee considered the evidence on using the VivaScope systems after dermoscopy, to inform decisions on biopsy and excision of equivocal skin lesions in people with suspected melanoma and in people with suspected BCC. The Committee noted that the 2 studies (Alarcon et al. 2014, see section 5.12; Pellacani et al. 2014, see section 5.13) considered most representative of NHS clinical practice for melanoma diagnosis reported similar sensitivity values, but higher specificity values for the VivaScope systems compared with dermoscopy alone. However, the Committee also noted that the reported specificity values differed substantially between the 2 studies. The Committee considered the 1 representative study (Castro et al. 2014, see section 5.26) for BCC diagnosis and noted that although the reported sensitivity and specificity values were good, the study was small and at risk of bias because of patient recruitment and the lack of independent reviews of images. The Committee concluded that the evidence suggested that imaging using the VivaScope systems after dermoscopy had a higher negative predictive value than dermoscopy alone, but there is uncertainty in the actual accuracy values, particularly for BCC.

6.6     The Committee discussed the findings of a systematic review by Stevenson et al. (2013) that reported lower sensitivity and specificity values than those identified

in this assessment. It heard from the External Assessment Group that the systematic review had been excluded from this assessment because it considered the accuracy of using the VivaScope systems in all people with suspected melanoma not just those with equivocal lesions post dermoscopy, as in this assessment. The Committee noted that this difference in population could explain the higher specificity values in this assessment. It also heard from the External Assessment Group that there is uncertainty in the accuracy values in the systematic review because the meta-analysis combined patient- and lesion-level data. The Committee concluded that it was not appropriate to include the systematic review in this assessment.

6.7     The Committee discussed the importance of training and experience in using the VivaScope systems and the impact on clinical effectiveness. The Committee heard from clinical experts that diagnosing skin cancer is dependent on experience and that there is considerable variation in the accuracy of diagnosis using current techniques. The Committee concluded that training on using the VivaScope systems in settings with sufficient numbers of skin lesions to ensure competency would be vital to achieving the higher negative predictive values reported in the studies compared with dermoscopy alone.

6.8     The Committee discussed the prevalence of BCC in people with positive or equivocal lesions. The Committee noted that in this group the prevalence was approximately 95% and the pre-test probability was therefore high. It discussed the value of an additional diagnostic technology, such as the VivaScope system, in this population and noted that there was likely to be limited benefit and marginal improvement in accuracy. The Committee heard from clinical experts that for a person with BCC to begin treatment, a diagnostic biopsy is normally needed to confirm the diagnosis. The Committee concluded therefore, that using the VivaScope system may offer benefit in people with BCC by avoiding the need for a diagnostic biopsy, although the number of biopsies that would be avoided in clinical practice is uncertain.

6.9     The Committee considered the utility values used in the cost-effectiveness model in diagnosing melanoma and BCC. It heard from the External Assessment Group that there were limited data available regarding utility values associated with anxiety from waiting for results, scarring from removing a lesion and getting a false positive result. The Committee noted that the utility loss associated with a

skin biopsy or excision was lower than the disutility associated with the anxiety from waiting for results. The Committee discussed the plausibility of the size of the difference between these 2 values and noted there was considerable uncertainty around the utility values. The Committee noted that changes in these utility values could substantially affect the cost effectiveness of the VivaScope systems, which consequently results in substantial uncertainty in the ICERs.

6.10    The Committee considered the cost effectiveness of VivaScope in diagnosing melanoma and BCC in people with equivocal skin lesions. The Committee discussed the evidence and noted that there is uncertainty in the specificity of the VivaScope systems in diagnosing melanoma and in the accuracy of diagnosing BCC. It also noted the uncertainty in the number of biopsies that could be avoided and in the utility values used in the model. Overall, the Committee concluded that although the VivaScope systems show promise, there is too much uncertainty in the evidence for it to be confident that using the VivaScope systems represents a cost-effective use of NHS resources.

# Margin delineation

6.11    The Committee considered the clinical evidence for using the VivaScope systems to delineate margins of LM and noted that only 1 study had been identified and it had small patient numbers. It heard from clinical experts that lower recurrence rates could be inferred from the study but noted that the study was not comparative and had short (6 months) follow-up, which limits the robustness of the findings. The Committee concluded that the VivaScope systems showed promise but further research was needed to determine their clinical effectiveness in defining margins of LM.

6.12    The Committee discussed the cost effectiveness of using the VivaScope systems to map margins of LM. The Committee noted that the ICERs suggest that using the VivaScope systems is cost effective (see section 5.69). However, it also considered the evidence informing the model and noted that there is substantial uncertainty in the diagnostic accuracy of the VivaScope systems and in the impact that their use has on lesion recurrence rates. The Committee concluded therefore, that there is too much uncertainty in the clinical evidence to determine if using the VivaScope systems is a cost-effective use of NHS resources.

6.13 The Committee considered potential implementation issues of using the VivaScope systems to map the margins of LM. It heard from clinical experts that it took about 1 hour to map margins of LM using the VivaScope systems and the Committee noted that this was time consuming. However, clinical experts also informed the Committee that LM often needs very complex management and that spending time on accurate mapping can make treatment decisions more efficient, so the time spent mapping can effectively be offset. The Committee heard that people having surgery to remove a LM lesion may need to have up to 7 surgeries under local anaesthetic, spread over a number of weeks. This can result in people having open wounds between surgeries, which are at risk of infection. The Committee concluded that more accurate pre-surgical mapping using the VivaScope systems could offer substantial benefits to people by reducing the number of surgeries.

# General considerations

6.14 The Committee considered the training needed to accurately interpret the images produced by the VivaScope systems. It heard from the company that it currently provides training in Italy but is considering setting up a training site in the UK. The Committee heard from clinical experts that dermatopathologists are more familiar with interpreting cellular images than dermatologists and therefore, working together as a team may greatly help in developing the necessary skills and experience to interpret the images. The Committee concluded that effective training was vital to the clinical effectiveness of the VivaScope systems and was encouraged that training in the UK was being considered. The Committee considered the quality control of using the VivaScope systems in the NHS. It heard from clinical experts that there are currently no official quality control measures in place because the VivaScope systems are only being used in 1 hospital trust in England. The company informed the Committee that a Europe-wide network of VivaScope users is being set up and that this would include quality control. The Committee concluded that a quality control scheme would need to be established to support widespread use of the VivaScope systems in the NHS.

6.15 The Committee discussed the numbers of people who would be examined using VivaScope for melanoma, BCC and LM. It noted that the greatest number of

people would be examined for BCC, and that when VivaScope use included BCC the cost of the system spread across each lesion examined was greatly reduced. It also noted that the cost effectiveness of VivaScope was sensitive to the annual volume of suspected melanomas examined, if VivaScope was used exclusively for this purpose. It also heard from clinical experts that there is a lack of good quality data for the numbers of people following the different clinical pathways for melanoma, BCC and LM. The Committee concluded that there was uncertainty in the number of people who would be examined using VivaScope for the different skin lesions and consequent uncertainty in the number of biopsies and excisions avoided.

6.16    The Committee considered the impact of skin cancer on people. It heard from a patient expert that people can experience substantial anxiety about scarring and invasive procedures, particularly on the face and neck. People can also be shocked when first seeing a wound on their face, and the consequent scarring can lead to low self-esteem and withdrawal from social activities. The patient expert also highlighted that because skin cancer can be fatal in some people, the anxiety associated with biopsies, excision and the risk of skin cancer from their moles can be substantial and long-term. The Committee also heard that anxiety can be even greater in people who have many moles. The Committee noted the points highlighted by the patient expert and acknowledged the substantial impact that skin cancer has on the lives of patients and their families.

6.17    The Committee considered the innovative nature of the VivaScope 1500 and 3000 systems and noted that the ability to provide images at a cellular level (quasi-histological) in real-time and in a near-patient setting could offer substantial benefits to clinical practice. The Committee heard from a clinical expert that the technologies were promising and may lead to fewer biopsies, which would reduce the burden on pathology laboratories. The Committee also noted that pathology expertise is vital to interpreting images produced by the VivaScope systems and thought that the use of these technologies could encourage multidisciplinary decision-making and the sharing of expertise, potentially improving the efficiency of the patient pathway. The Committee concluded that the VivaScope systems show promise but further research is needed to determine whether they are a cost-effective use of NHS resources.

# Research considerations

6.18    The Committee considered the lack of evidence on the disutility of anxiety, skin biopsy and scarring from excisions, and noted that it is unlikely that current estimates fully capture the disutility. The Committee encouraged further research on the disutility of skin biopsies and excisions and the associated anxiety.

6.19    The Committee heard from clinical experts that the VivaScope imaging systems may have potential for monitoring the incomplete response rate of topical chemotherapy and photodynamic therapy for treating BCCs. The Committee encouraged further research in this area.

# 7 Recommendations for further research

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.

# 8 Implementation

NICE will support this guidance through a range of activities to promote the recommendation for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 7 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

# 9 Related NICE guidance

## Published

- Melanoma: assessment and management (2015) NICE guideline NG14

- Suspected cancer: recognition and referral (2015) NICE guideline NG12

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

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

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

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

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

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

- Endoscopic radical inguinal lymphadenectomy (2011) NICE interventional procedure guidance 398

- Skin cancer prevention (2011) NICE guideline PH32

- Improving outcomes for people with skin tumours including melanoma (2010) Cancer service guidance

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

# Under development

NICE is developing the following guidance (details available from the NICE website):

- Melanoma (BRAF V600E mutation positive, unresectable, metastatic) – dabrafenib and trametinib. NICE technology appraisal guidance (publication expected August 2016)

# 10 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Andrew Dillon
Chief Executive
November 2015

# 11 Diagnostics Advisory Committee members and NICE project team

## Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

## Standing Committee members

**Professor Adrian Newland**
Chair, Diagnostics Advisory Committee

**Dr Mark Kroese**
Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

**ProfessorRonAkehurst**
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

**Dr Phil Chambers**
Research Fellow, Leeds Institute of Cancer & Pathology, University of Leeds

**Dr Sue Crawford**
GP Principal, Chillington Health Centre

**Professor Erika Denton**
National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

**Mr David Evans**
Lay member

**Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

**Mr John Hitchman**

Lay member

**Professor Chris Hyde**

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

**Mr Matthew Lowry**

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

**Dr Michael Messenger**

Deputy Director and Scientific Manager, NIHR Diagnostic Evidence Co-operative, Leeds

**Dr Peter Naylor**

GP, Chair Wirral Health Commissioning Consortia

**Dr Dermot Neely**

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

**Ms Gail Norbury**

Consultant Clinical Scientist, Guy's Hospital

**Dr Simon Richards**

Vice President Regulatory Affairs, EME (Europe and Middle East), Alere Inc.

**Dr Deirdre Ryan**

Consultant Cellular Pathologist, Royal London Hospital

**Professor Mark Sculpher**

Professor of Health Economics, Centre for Health Economics, University of York

**Dr Steve Thomas**

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation

Trust

**Mr Paul Weinberger**
Chief Executive Officer, DiaSolve Ltd, London

**Professor Anthony Wierzbicki**
Consultant in Metabolic Medicine and Chemical Pathology, St Thomas' Hospital

## Specialist Committee members

**Dr Andy Coleman**
Head of Non-ionising Radiation Physics, Guy's and St Thomas' NHS Foundation Trust

**Dr Emma Craythorne**
Consultant Dermatologist and Dermatological Surgeon, Guy's and St Thomas' NHS
Foundation Trust

**Dr Navaid Alam**
GP, TG Medical Centre, West Kirby, Merseyside

**Dr Jennifer Garioch**
Consultant Dermatologist, Norfolk and Norwich University Hospital NHS Foundation Trust

**Dr Rakesh Patalay**
Consultant Dermatologist, Chelsea and Westminster Hospital NHS Foundation Trust

**Mrs Patricia Fairbrother**
Lay member

# NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who
acts as the topic lead), a Technical Adviser and a Project Manager.

**Brendan Mullaney**
Topic Lead

**Sarah Byron**

Technical Adviser

**Robert Fernley**
Project Manager

# 12 Sources of evidence considered by the Committee

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

- Edwards SJ, Mavranezouli I, Osei-Assibey G et al. VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. A Diagnostic Assessment Report. April 2015.

# Registered stakeholders

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

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

- MAVIG GmbH

## Other commercial organisations:

- Michelson 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

# About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost-effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products that might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE diagnostic technologies guidance process.

We have produced a summary for patients and carers. Information about the evidence it is based on is available.

**Your responsibility**

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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