Medical Coverage Policy

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Malignant Melanoma Surveillance Technologies

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Related Coverage Resources

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Overview

This Coverage Policy addresses technologies that have been proposed for the early detection, screening or surveillance of malignant melanoma.

Coverage Policy

Total body photography, once every five years, is considered medically necessary in an individual age 18–45 years for ANY of the following indications:

- personal history of primary melanoma
- presence of atypical or dysplastic nevi
- family history of melanoma

Total body photography is considered not medically necessary for ANY other indication.

Each of the following technologies for the early detection, screening or surveillance of melanoma is considered experimental, investigational or unproven:

- visual image analysis
- electrical impedance devices
- multispectral image analysis
- ultrasound
- optical coherence tomography [OCT]
- reflectance confocal microscopy [RCM]
- multiphoton microscopy
- Raman spectroscopy
- 3D imagery
- photoacoustic microscopy
- 3D color histogram mapping
- stepwise two-photon-laser spectroscopy
- quantitative infrared imaging
- multiphoton tomography
- thermal imaging
- molecular fluorescent imaging

Dermoscopy is considered to be an integral part of a normal evaluation of a pigmented skin lesion and not separately reimbursable.

General Background

Melanoma, also called cutaneous melanoma or malignant melanoma, is a malignant disease of the skin and one of the most dangerous forms of skin cancer. Although melanoma accounts for less than 5% of skin cancer cases, it accounts for approximately three-fourths of all skin cancer deaths. Early detection and treatment are the best strategies to reduce the mortality and morbidity associated with melanoma. Only 20 to 30 percent of melanomas are found in existing moles, while 70 to 80 percent arise on normal skin with no associated nevus (Cymerman, 2016). Moles are common with the average person having 10–40. Puberty is a time when the size and number of nevi increase with very few moles developing after the age of 40 (Hooper and Goldman, 1999).

Risk factors for the development of single or multiple primary melanomas include male sex, age >60 years, phenotypic predisposition, personal medical history/comorbidities and environmental factors (National Comprehensive Cancer Network® [NCCN], 2021; National Cancer Institute [NCI], 2021). High-risk individuals for melanoma include those with a personal history of prior primary melanoma, presence of pigmented lesions (e.g., atypical nevi, dysplastic nevi) or a first-(i.e. parent, sibling or child) or second-degree relative with melanoma (NCCN, 2021; NCI, 2021; Goodson, et al., 2010; Banky, et al., 2005; Oliveria, et al., 2004; Haenssle, et al., 2004). There are certain characteristics that place patients at higher risk of dying from melanoma. Despite there being a lower incidence of melanoma in Black patients, the five-year relative survival is lower than for white patients (69% vs. 93%) (Geller and Swetter, 2021; Cormier, et al., 2006). This trend has been observed in the Hispanic American population and is thought to be due to a greater likelihood of presenting with advanced disease compared to non-Hispanic white individuals (Cockburn, et al., 2006). The greater mortality in patients with skin of color may be due to several factors including delayed diagnosis due to a lower perceived risk of disease or lower rates of skin examinations, locations of melanoma in atypical non-sun-exposed areas (eg, leg, hip, and feet), a higher proportion of acral and nodular subtypes, and a decreased ability to seek care for localized disease (Carter, et al., 2021; Coups, et al., 2012; Myles, et al., 2012; Pollitt, et al., 2011). Almost 50 percent of melanoma deaths in the United States occur in white men over the age of 50 (Geller and Swetter, 2021). The poor survival rate in men may be due to differences in tumor biology and by differences in skin awareness, self-examination, and other early detection practices.

The assessment of suspicious skin lesions begins with a physical examination and visual inspection of the skin with the naked eye. Dermoscopy including digital epiluminescence microscopy (DELM) has evolved into an established technology used as an adjunct to a normal eye exam and is considered to be an integral part of the exam depending on the lesions being examined. Additional noninvasive technologies are proposed to provide better examination of lesions and assist the examiner in deciding whether a lesion should be biopsied. None of these devices can diagnosis skin cancer. Biopsy is considered the diagnostic “gold standard”. Noninvasive

technologies include: total-body photography (TBP); visual image analysis; electrical impedance devices; multispectral image analysis; ultrasound, optical coherence tomography [OCT]; and reflectance confocal microscopy (RCM). There is insufficient evidence in the peer-reviewed literature to support the use of these noninvasive technologies for the evaluation and surveillance of melanoma.

Total Body Photography (TBP)
TBP, also known as whole body photography, surveillance photography, total body mapping, has been proposed for screening and monitoring for the early detection of skin cancers, especially for people at high risk for melanoma. A proposed disadvantage of TBP is the poor resolution of images and loss of follow-up in noncompliant patients. The majority of melanomas are pigmented, but 2–8% are hypopigmented and detection by a TBP imaging system may be less reliable than with pigmented lesions. Historically, TBP has been performed via 2D imaging and is now evolving into 3D capabilities. The intent is that 3D imaging will improve diagnostic accuracy, be time and cost efficient and more accessible to patients. TBP involves a series of multiple photographs (25–40) of head-to-toe images of the patient's entire cutaneous (skin) surface and is proposed for high-risk patients with multiple lesions. The photographs may be enlarged to show the details of lesions. New photographs can be compared with previous photographs to determine if a lesion has changed. Photographs are generally useful for 5–8 years. Available software can automatically match lesions on two standardized photographs and highlight new or changed lesions. Examples of this software are the Fotofinder™ bodystudio LITE (FotoFinder Systems Inc. Columbia, MD) and MIRROR™ Body Mapping Module (Digitale Photographie Gmbh, Fairfield, NJ). (Rayner, et al., 2018; Mayer, et al., 2014; Guitera and Menzies, 2011). Total body photography has evolved into an accepted surveillance technique for individuals with an increased risk of subsequent primary melanomas, such as prior multiple primary melanomas, family history of melanoma, and the presence of atypical/dysplastic nevi (NCCN, 2021).

US Food and Drug Administration (FDA): Because the cameras used for surveillance are not considered medical devices, they are not regulated by the FDA.

Literature Review: Watts et al. (2015) conducted a systematic review of published international clinical practice guidelines for the identification, screening and follow-up of individuals at high risk for primary cutaneous melanoma. Thirty-four guidelines from 20 countries were included. Consistently reported high-risk characteristics included: many melanocytic nevi, dysplastic nevi, family history, large congenital nevi, and Fitzpatrick Type I and II skin types. Monitoring of high risk individuals was recommended but only half of the guidelines recommended screening based on level of risk. There were high levels of evidence for targeted, regular monitoring using dermoscopy and sequential digital dermoscopy imaging (SDDI) but low levels of evidence for the use of total-body photography (TBP).

Salerni et al. (2011) reported surveillance of 618 patients at high risk for melanoma using digital total body photography and digital dermatoscopy. A total of 11,396 lesions were monitored (mean 18.44/patient) during a median follow-up of 96 months (median 10 visits/patient).Data analysis revealed that older age at inclusion and higher number of lesions excised during follow-up were the variables most associated with melanoma diagnosis during surveillance ($p=0.003$ and $p<0.001$, respectively). A total of 98 melanomas (8.5% of excised lesions) were diagnosed in 78 patients (12.6%). No conclusions regarding the impact of TBP on long-term health outcomes can be drawn from this study as there were no control groups.

In a prospective trial, Goodson et al. (2010) sought to determine whether biopsy rate, rate of melanoma detection, and melanoma derivation (nevus derived versus de novo) differed, using total body and digital epiluminescence microscopy (DELM) photography. A total of 889 new patients and 187 established patients were included. Most patients had one or more of the following melanoma risk factors: three or more clinically atypical nevi, more than 50 nevi, personal history of melanoma, and two or more family members with history of melanoma. Follow-ups occurred for 6-12 months. A total of 110 patients were lost to follow-up. The patients underwent total body photography and were monitored using photographs obtained at the initial visit. Risk factors and median monitoring periods for these patients were comparable with those of patients previously monitored using DELM photography. A total of 275 biopsies were performed on 467 patients on follow-up visits. The authors cited low biopsy rates on follow-up visits with both approaches (0.59 biopsies per patient with total body photography versus 1.1 per patient with DELM photography, statistically significant). The significantly higher biopsy rate with DELM photography may be a consequence of the greater sensitivity for detecting

morphologic changes in nevi because of higher resolution of these photographs and the fact that lesions exhibiting photographic change were more likely to be biopsied.

Banky et al. (2005) conducted a prospective case series (n=309) to assess the effectiveness of total body photography and dermoscopy in the evaluation of new, changed and regressed nevi and melanomas. Included patients were referred to a dermatologist for clinical examination and had at least one of the following risk factors for melanoma: four or more clinically dysplastic nevi, 100 or more melanocytic nevi, a personal history of melanoma, or a family history of melanoma. Individuals with one of these risk factors underwent total body photography. Biopsy specimens were not obtained of all changed and new pigmented lesions. If melanoma could not be confidently excluded by clinical examination and dermoscopy, an excisional biopsy was performed. The median number of follow-up visits following photography was three. The median length of follow-up was 34 months. A total of 311 changed nevi and 262 new pigmented lesions were detected. Eighty-six nevi regressed completely. Eighteen melanomas were detected in 16 patients. The benign-malignant ratio of biopsied specimens was almost 3:1.

Visual Image Analysis
Visual image analysis involves image acquisition, segmentation (a step that often has to be overseen by the human operator), extraction of morphological data and numeric conversion of the data. A classification by mathematical algorithm is used to give a diagnosis. To date, no mechanized systems have proven to be reliable enough to produce a fully automated diagnosis with high diagnostic accuracy. Image-based systems require the lesion to be pigmented which means light-colored lesions are usually poorly diagnosed (Guitera and Menzies, 2011).

Electrical Impedance Devices
These devices utilize resistance or impedance measured between two electrodes in contact with the epidermis and provides a score based on the cellular irregularity of the skin. Different tissues have different electrical impedance spectra. Normalized conductivity and capacitance recorded on growing skin tumors have been shown to change relative to the lesion. Necrosis, present in larger lesions, is associated with a decrease in the electrical conductivity. Studies are still investigating the role of electrical impedance in the diagnosis of melanoma.

US Food and Drug Administration (FDA): The Nevisense™ (Scibase AB, Stockholm, Sweden) received FDA PMA approval in June 2017. The device is indicated for use on "cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Nevisense should not be used on clinically obvious melanoma. The Nevisense result is one element of the overall clinical assessment. The output of Nevisense should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy. Nevisense is indicated only for use on:

- primary skin lesions with a diameter between 2 mm and 20 mm;
- lesions that are accessible by the Nevisense probe;
- lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions);
- lesions that do not contain a scar or fibrosis consistent with previous trauma;
- lesions not located in areas of psoriasis, eczema, acute sunburn or similar skin conditions;
- lesions not in hair-covered areas;
- lesions which do not contain foreign matter;
- lesions not on special anatomic sites (i.e., not for use on acral skin, genitalia, eyes, mucosal areas)."

The device includes a control unit, probe and probe cable.

Literature Review: Malvehy et al. (2014) conducted a prospective multicenter case series to assess the safety and effectiveness of the Nevisense system in the distinction of benign skin lesions from melanoma with electrical impedance spectroscopy (EIS). There were multiple exclusion criteria including: age <◦18 years, metastases or recurrent lesions, lesions <◦2 mm or >◦20 mm in diameter, location of lesion, and skin conditions. All eligible skin lesions were examined with the EIS-based Nevisense system, photographed, removed by excisional biopsy and subjected to histopathological evaluation. A total of 1951 patients with 2416 lesions were enrolled in the study

and 473 lesions were excluded. A total of 265 lesions were diagnosed as melanomas (112 in situ and 153 invasive). Compared to histopathology, the observed sensitivity of Nevisense was 96.6% (256 of 265 melanomas), observed specificity was 34.4% (would not have been biopsied), positive predictive value was 21.1% and the negative predictive value was 98.2%. The observed sensitivity for nonmelanoma skin cancer was 100% (55 of 48 BCCs and seven SCCs). A high proportion of seborrheic keratoses were inaccurately classified as positive by the system. It was proposed that a trained dermatologist would not apply Nevisense to these lesions. Nine melanoma lesions were classified as a false negative by Nevisense. No serious adverse events were reported. Additional studies are needed to validate the outcomes of this study and establish the clinical utility of Nevisense.

In a multi-center study, Har-Shai et al. (2005) prospectively evaluated the ability of electrical impedance scanning to differentiate between benign and malignant skin lesions in 382 patients (449 lesions), including 53 melanomas from the trunk and extremities. Results were correlated with histopathologic findings. Electrical impedance scanning detected melanomas of the trunk and extremities with 91% sensitivity and 64% specificity. Visual examination identified 67% of small, thin malignant lesions (n=27) compared to 100% by electrical impedance scanning (p=0.002). Clinical examination detected 96% of larger or thicker melanomas (n=26) compared to 81% by electrical impedance scanning.

Multispectral Image Analysis
Computer-aided multispectral imaging analysis or scanning technique is proposed to allow analysis of sequences of images taken at different wavelengths. With similar segmenting and image analysis as the first devices, they may also provide information on skin chromophores (mostly collagen, melanin and hemoglobin). In a review article, Winklemann et al. (2017) reported an overall sensitivity of 62%–94%, specificity 25%–79% and biopsy accuracy of 65%–80% using multispectral digital skin lesion analysis. Studies evaluating spectrophotometric intracutaneous analysis (SIA) scope (SIAscope, Biocompatibles, Farnham, Surrey, UK) reported a sensitivity of 80%–100% with a specificity of 76%–91%. The authors noted that the risk of missing melanomas using multispectral analysis has prevented these devices from being routinely used in clinical practice. Biopsies are still required.

U. S. Food and Drug Administration (FDA): An example of a multispectral device is the MelaFind® (Strata Skin Sciences, Inc., Horsham, PA) which received FDA pre-market approval (PMA) for “use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma”. The device is proposed to help a dermatologist make a decision to biopsy. It is not to be used alone for making biopsy decisions. MelaFind is indicated “only for use on lesions with a diameter between 2 mm and 22 mm, lesions that are accessible by the MelaFind imager, lesions that are sufficiently pigmented (i.e. not for use on non-pigmented or skin-colored lesions), lesions that do not contain a scar or fibrosis consistent with previous trauma, lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions), lesions greater than one centimeter away from the eye, lesions which do not contain foreign matter, and lesions not on special anatomic sites (i.e., not for use on acral, palmar, plantar, mucosal, or subungual areas). MelaFind is not designed to detect pigmented non-melanoma skin cancers, so the dermatologist should rely on clinical experience to diagnose such lesions” (FDA, 2011).

SIAScope II® (Astron Clinica Ltd., Cambridge, UK), a Class II device, is a non-invasive skin analysis system proposed to show the location of blood, collagen and pigment. Using spectrophotometric intracutaneous analysis (SIAscopy) to identify and graphically display the separate components of the skin, the device provides color bitmaps called SIAscans. SIAscopy uses a digital camera and light (both visible and near-infrared) to investigate the skin's interior structure.

Literature Review: Monheit et al. (2011) conducted a prospective multicenter study to evaluate the safety and effectiveness of MelaFind (n=1612 lesions; 114 melanomas). The pooled data on melanoma reported a sensitivity of 98.4%, specificity ranged from 0%–25% (average 9%), negative predictive value was > 98%, and biopsy ratio of 10.8:1. MelaFind had an average specificity of 9.5% which was significantly higher than that of investigators (3.7%) (p=0.02). The study also included a pilot study of biopsy sensitivity (reader study) using 25 randomly selected melanomas and 25 nonmelanomas which showed that dermatologists misdiagnosed thin melanomas. The average biopsy sensitivity of 39 dermatologist readers was 78%. An author noted limitation of the study was that only pigmented lesions were scheduled for biopsy and these benign lesions are not

representative of lesions in the general population. Thus, the specificity in this study is not applicable to the general population for clinicians or MelaFind.

In a prospective study, Haniffa et al. (2007) evaluated the ability of the spectrophotometric device, SIAscope, to aid in the diagnosis of melanomas. The investigator's diagnosis before and after spectrophotometry were compared to the histological diagnosis where available or with the expert's clinical diagnosis. Of 860 patients, 179 biopsies were performed, with 31 melanomas diagnosed. Sensitivity and specificity for melanoma diagnosis before and after spectrophotometry were 94% and 91% vs. 87% and 91%, respectively, with no significant difference in the area under the receiver operating characteristic curves.

Ultrasound
Ultrasound/reflex transmission imaging relies on the properties of reflected sound waves through tissue. The ultrasound impulsion is administered by a probe and transmitted to the skin. The probe acts as a receptor that will collect the backscattered or diffused ultrasound and transform it into an electric signal. Ultrasound creates an image of the strain on the tissue imposed by presence of an abnormal growth. Ultrasound is not currently a widely accepted technology for evaluating melanomas due to the lack of resolution in the epidermis and dermis which does not allow for the differentiation of tumors. Refinement of the technology and equipment and its clinical utility are still being investigated (Welzel and Schuh, 2017).

U.S. Food and Drug Administration (FDA): Ultrasounds are approved by the FDA as a Class II, 510(k) device. An example of an approved device is the DermaScan C Ultrasonic System (Cortex Technology, Denmark). The device is intended "to be used to visualize the layers of the skin, including blood vessels, and to make approximate measurements of dimensions in the layers of the skin and blood vessels by ultrasonic means" (FDA, 1999).

Literature Review: Dinnes et al. (2018) conducted a Cochrane review to assess the accuracy of high-frequency ultrasound (HFUS) in the diagnosis of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, cutaneous squamous cell carcinoma (cSCC), and basal cell carcinoma (BCC) in adults. Studies were included if they evaluated HFUS (20MHz or more) in adults with lesions suspicious for melanoma, cSCC or BCC versus histological confirmation or clinical follow-up. Six studies met the inclusion criteria. The authors noted that half of the studies were not designed to establish test accuracy and all could be considered preliminary experiments on the potential value of high-frequency ultrasound. Sensitivities for HFUS started at 83% for the detection of melanoma. Analysis combining three features of lesions (i.e. hypoechoic, homogenous and well defined) demonstrated 100% sensitivity in two studies with specificities of 33% and 73%. Due to the scarcity of data and the poor quality of the studies, no meta-analysis was performed. Author noted limitations included: study heterogeneity, unclear to low methodological quality, limited volume of evidence, selective study populations, and small patient populations. There is insufficient data to support the efficacy of HFUS in the diagnosis of melanoma or BCC.

Rallan et al. (2007) conducted a prospective study (n=87) to determine if high-resolution ultrasound reflex transmission imaging (RTI) could differentiate common benign pigmented lesions (BPLs) from melanoma. RTI was used to determine the lesion attenuation properties. The study also assessed if the "lesional backspatter image" (LBI) which depicts intralesional sound reflection characteristics and the "entry echo image" (EEI), which depicts surface sound reflectance characteristics, could aid in diagnosis. Twenty-five malignant melanomas (MM) and 62 noncancerous lesions, as classified by a dermatologist, were analyzed by RTI. Of the noncancerous lesions, 24 were seborrheic keratosis (SK) and 38 were BPLs. When the sensitivity of diagnosing melanoma was set at 100%, RTI, LBI, and EEI were compared in the diagnosis of SK. A total of nine of the 24 SK were detected by RTI and LBI for a specificity of 38%. EEI detected seven out of 24 for a specificity of 29%. Each of the three methods was compared in its ability to diagnose BPLs (with sensitivity set at 100%). The specificity of EEI, LBI, and RTI were 30%, 15%, and 10%, respectively.

Reflectance Confocal Microscopy
Reflectance confocal microscopy (RCM), also known as confocal scanning laser microscopy (CSLM), uses a near infrared laser that emits near-infrared light (830 nm) to obtain images of the top layers of the skin. The images are magnified and information regarding cell structure and the architecture of the surrounding tissues is evaluated. Combinations of features are assessed to give a positive or negative diagnosis of melanoma. RCM is

proposed to be comparable to conventional histology and proposed for use as an adjunctive diagnostic tool to examination and dermoscopy in difficult to diagnose lesions and therefore, aid in determining if a lesion is benign or is a melanoma. It enables high-resolution, noninvasive, real-time imaging of the epidermis and upper dermis at cellular resolution. Its primary field of application is the differential diagnosis of pigmented lesions. Studies evaluating the accuracy of confocal scanning laser RCM/CSLM in assessing skin lesions for melanoma have reported sensitivity, specificity, positive and negative predictive values ranging from 90.74% to 97.5%, 83% to 99%, 70.6% to 97.5%, and 98.17% to 99%, respectively.

RCM is considered an evolving technology with several limitations. The depth of imaging is confined to the epidermis and papillary dermis which may result in false negatives. Penetration of RCM light may be hampered by hyperkeratosis, reflective creams and surface particles. Another limitation is the challenge that the interpreter has of distinguishing between cells with similar reflection index and shape (e.g., Langerhans cells versus dendritic melanocytes at the spinous layer). RCM is a time consuming exam taking an average of seven minutes per lesion. Clinical-dermatoscopic skills are required, as well as adequate training and experience to read RCM images and make the correct interpretation. It has yet to be determined if the advantages of the clinical utility of RCM as an adjunctive diagnostic tool are greater than the risk of over-excising benign lesion and misdiagnosing melanomas as benign. In some cases RCM may be used for cosmetically sensitive areas to avoid excision (Hayes, 2019; Que, et al., 2016; Stevenson, et al., 2013; Gerger, 2008; Langley, 2007; Gerger, 2006). There is insufficient evidence to support the clinical utility of RCM.

U.S. Food and Drug Administration (FDA): Confocal microscopes are approved by the FDA 510(k) as a class II device. Examples of these devices include the VivaScope System 1500 and the handheld VivaScope 3000 (Lucid, Inc., Rochester, New York). The VivaScope is intended “to acquire, store, retrieve, display and transfer in vivo images of tissue, including blood, collagen and pigment, in exposed unstained epithelium and the supporting stroma for review by physicians to assist in forming a clinical judgment”. The VivaScope 3000 is a hand-held device designed to access hard to reach areas such as nose, ears, or eyes. The 1500 and 3000 systems can be used alone or together. The SIAscope II (Astron Clinica Limited, Crofton MD) is FDA approved as a “non-invasive skin analysis system, which provides a synthesized ‘image’ showing the relative location of blood collagen and pigment” (FDA, 2008; 2003).

Literature Review: Pezzini et al. (2020) conducted a systematic review and meta-analysis to assess the accuracy of reflectance confocal microscopy (RCM) in diagnosing cutaneous malignant melanoma (MM) according to study design, lesion type and diagnostic modality. The meta-analysis included 32 studies (n=7352 lesions) that met the criteria of reporting RCM lesion classifications and included either histopathology diagnoses or long-term clinical follow-up data that verified the accuracy of the original diagnosis with evaluations that were performed by an expert/trained RCM investigator. Seven studies were prospective-non interventional, three were prospective interventional studies and 22 were retrospective reviews. Studies were excluded if they were case series/case reports with <10 lesions; pertained to special sites such as oral mucosa, lips, eyes, or genital area; or were for other types of skin cancers. The secondary outcome measure was a comparison of diagnostic accuracy to dermoscopy. The length of follow up was not reported. The pooled sensitivity was 92% with a pooled specificity of 70%. In regards to study design, the diagnostic sensitivity was high for all study types. The specificity was lower for prospective interventional studies. Diagnostic accuracy was high for all lesion types with the highest specificity reported in consecutive lesions (77%) highly suspicious for MM (65%). RCM diagnostic accuracy was 56% vs. dermoscopy at 38%. No serious adverse events were reported. Author noted limitations of the meta-analysis include heterogeneity of the inclusion and exclusion criteria of the studies, wide range of study designs, use of algorithms or scoring systems, and the range of RCM investigator expertise. Additional high quality studies with large patient populations and long term follow up are needed to validate the outcomes of this analysis and establish the clinical utility of RCM in the diagnosis of MM.

Edwards et al. (2016) conducted a systematic review and health technology assessment on the clinical effectiveness of the VivaScope 1500 and 3000 systems in the diagnosis of equivocal skin lesions. VivaScope 3000 was also evaluated for the assessment of lesion margin delineation prior to surgical excision of lesions. Eleven prospective observational studies and five retrospective reviews were included. No randomized controlled trials (RCTs) were found. One study suggested that VivaScope used subsequent to dermoscopy may improve diagnostic accuracy of equivocal skin lesions compared with dermoscopy alone, especially for malignant melanomas. Another study reported that the sensitivity for dermoscopy plus VivaScope 1500 were the same

(100%). Clinical data regarding margin delineation are scarce. The studies were too heterogeneous to be used in a meta-analysis. The authors noted that apart from diagnostic accuracy and lesion recurrence rate (only reported by one study), none of the outcomes specified in the protocol were reported in the outcomes and in some of the studies, there was paucity of reported data on number of patients with positive and negative test results. Other limitations of the studies included: lack of a comparator; retrospective study design; small patient populations; heterogeneity in cancer types (melanoma, basal cell and squamous cell carcinoma); and variation in reporting results as patient based or lesion based. The authors suggested that high-quality RCTs are required to assess diagnostic accuracy of dermoscopy plus VivaScope compared with dermoscopy alone in people with equivocal skin lesions, as well as the margin delineation accuracy of VivaScope compared with dermoscopy alone. RCTs focusing on clinical outcomes, test failure rates, number of biopsies performed, repeat biopsies, recurrence rates and morbidity associated with surgery are required.

Pellacani et al. (2014) conducted a prospective case series (n=1005) to assess the impact of reflectance confocal microscopy (RCM) in the routine diagnosis of melanoma. Patients had atypical moles and were initially referred to either no further examination or to RCM. The RCM group was further subdivided into RCM documentation (suspicious lesions already qualified for excision) or RCM consultation (i.e., RCM would determine if the lesion was excised or monitored with digital dermoscopy). RCM did not affect the outcome in patients already scheduled for excision. Patients referred for RCM had a higher number of nevi (>100 nevi; 19%) and atypical nevi (>5; 15%) compared to patients referred for RCM documentation and patients without RCM referral ($p<0.0001$). Personal and/or familial history of melanoma was recorded in approximately 8% of patients. A total of 493 lesions were referred to RCM of which 183 underwent RCM documentation and 308 RCM consultations. Histopathology identified 23 melanomas. RCM proposed the same diagnosis as histopathology in 82.6% of melanomas. A total of 109 of 308 RCM consultation lesions were excised, six cases of melanoma were diagnosed and five cases were confirmed as melanomas. Twenty-eight lesions deferred to follow-up were excised based on dermoscopic changes. Overall RCM proposed diagnosis was concordant with histopathological diagnosis in 76.3% of cases and reduced the number of excision by 46.5%. Limitations of the study include: 12.3% of patients were lost to follow-up; 11 patients either refused RCM or were unable to undergo RCM; and the study population was a low risk group referred for screening.

Stevenson et al. (2013) conducted a systematic review of the literature to determine the diagnostic accuracy of reflectance confocal microscopy (RCM) as an adjunctive tool to dermoscopy for the evaluation of melanoma. No systematic reviews or meta-analysis were found. Studies were primarily in the form of case series, case reports, and descriptive correlation studies that only described RCM features and narrative reviews. Five studies (n=909 lesions) met inclusion criteria and were eligible for meta-analysis. Meta-analysis returned a per lesion sensitivity of 93% (range 91%–97%) and a specificity of 76% (range 68%–86%). The average prevalence of melanoma was 36%. The authors noted that a weakness of the study was that the studies may not have focused on the pertinent patient populations to test the ability of RCM as an add-on test to dermoscopy. Limitations of the studies included use of various types of melanoma scoring systems and outcome measures, heterogeneity of lesion locations, and two studies did not list number of patients evaluated.

Other Noninvasive Technologies

Multiple other noninvasive technologies have been proposed for use in melanoma diagnosis and surveillance. To date, some of these technologies have not been FDA approved nor has the accuracy and/or clinical utility been established. Other proposed noninvasive diagnostic surveillance techniques include: optical coherence tomography (OCT), ultra-high resolution/high-definition OCT (HD-OCT), multiphoton microscopy, Raman spectroscopy, 3D imageries, photoacoustic microscopy system, and 3-D histograms of color mapping or color histogram analysis. Additional evolving technologies include molecular fluorescent imaging, stepwise two-photon-laser spectroscopy, multiphoton tomography, and quantitative dynamic infrared imaging proposed for assessment of preselected lesions. Thermal imaging measures differences in the infrared emission between healthy tissue and the lesion during the thermal recovery process after the removal of a cooling stress. These technologies are in the investigative phase and clinical utility has not been established (Fink and Haenssle, 2017; Godoy, et al., 2017; Fink, et al., 2016; Menge and Pellacani, 2016; Gurjarpadhye, et al., 2015; Wachsman, et al., 2011; Guitera and Menzies, 2011; Stanley, et al., 2007).

There is insufficient evidence to support the accuracy and clinical utility of other noninvasive technologies for the screening, diagnosis and surveillance of melanoma. Studies are primarily in the form of small case series, case reports and retrospective reviews with conflicting outcomes.

Xiong et al. (2018) conducted a meta-analysis to evaluate the accuracy of optical coherence tomography (OCT) for the diagnosis of skin cancer. Retrospective and prospective studies were included if they investigated the accuracy of OCT for the diagnosis of skin cancer, collected sufficient data for statistical analysis and confirmed diagnosis with histopathology. Fourteen studies (n=813 patients, 1958 lesions) including eight prospective studies and six retrospective reviews met the inclusion criteria. Included studies covered one or more of the following types of skin cancer: malignant melanoma (MM), actinic keratosis (AK), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Studies were excluded if they were comment papers, small case series, case reports, reviews, or guideline articles. Five studies used VivoSight OCT, five used Skintell high definition-OCT, two used polarized sensitivity-OCT and one used full field-OCT. Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were included in the meta-analysis. The pooled data on the diagnostic accuracy of OCT for skin cancer (n=12 studies, n=1740 lesions) reported a sensitivity range of 66.7%–100.0% with a specificity from 64.4%–100.0%. Pooled sensitivity and specificity were 91.8% and 86.7% respectively. The pooled PLR and NLR were 6.94 and 0.12, respectively. The data on diagnostic accuracy of OCT for BCC (n=9 studies, n=1386 lesions) reported a pooled sensitivity of 92.4%, specificity of 86.9%, PLR of 6.07 and NLR of 0.12. Data on diagnostic accuracy of OCT for SCC (n=3 studies) reported a pooled sensitivity and specificity of 92.3% and 99.5%, respectively. The pooled PLR and NLR were 68.01 and 0.11, respectively. The data on diagnostic accuracy of OCT for AK (n=3 studies) reported a pooled sensitivity of 73.8% and specificity of 91.5%. The pooled PLR and NLR were 7.67 and 0.17, respectively. Data on diagnostic accuracy of OCT for MM (n=2 studies) were 81.0% pooled sensitivity, 93.8% specificity, 11.82 PLR and 0.18 NLR. Author noted limitations of the studies included the variations in the study designs, the inclusion and exclusion criteria, type of OCT devices used and clinical experience of the user. Additional limitations of the study include the small patient populations and retrospective study design. Additional randomized control trials with large patient populations are needed to establish the clinical value of OCT.

Ferrante di Ruffano et al. (2018) conducted a Cochrane review to assess the diagnostic accuracy of optical coherence tomography (OCT) in the detection of malignant melanoma (MM), basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC) in adults. Five studies (four prospective and one unknown) met inclusion criteria (n=529 cutaneous lesions). Two studies investigated OCT for melanoma and three for BCC. Patient selection (3/5), recruitment (2/5) and study design (1/5) were unclear or not described in some of the studies. Comparators included visual inspection alone and visual inspection plus dermoscopy. Results were verified by histopathology. Meta-analysis for the diagnosis of melanoma or cSCC was not performed due to the paucity of data and differences in thresholds used to define test positivity. Statistical pooling for the diagnosis of BCC reported a sensitivity of 95% and specificity of 77%. It was noted these studies limited participant inclusion to only those with erythematous/pink lesions. Author-noted limitations included: a paucity of studies, small sample sizes, different OCT technologies used and differences in the degree of testing performed prior to OCT. There is insufficient data available on the use of OCT for the detection of melanoma or cSCC. Prospective comparative studies are required to determine accuracy of OCT in diagnosing skin cancer and clinical applicability.

Meyer et al. (2014) conducted a single-center prospective study (n=131 patients; 138 lesions) to evaluate the accuracy and reliability of high-frequency ultrasonography (HFUS) and 930-nm optical coherence tomography (OCT) compared to histopathological measurements in assessing the thickness of melanoma lesions. The objective of the study was to test whether these two imaging methods could improve preoperative management of skin melanoma by estimating lesion thickness and allowing a single-step excision with defined surgical margins. Each lesion underwent OCT and HFUS assessments twice (at least one week apart) before excision and pathological examination. HFUS was conducted on a Dermcup 2020 scanner (Atys Medical, Soucieu en Jarrest, France) and OCT was conducted on a Ganymede 930 (Thorlabs, Newton, NJ). A total of 67 lesions were diagnosed as melanoma by histopathology. OCT measurements were not obtained on 11 patients due to technical issues. The mean difference between OCT and histopathological assessments was high at 0.53 mm. In a subgroup analysis of melanomas with a Breslow index below 1 mm, the mean difference was 0.62 showing that OCT underestimated melanoma thickness. The repeatability and inter-rater reproducibility of HFUS were high (G=0.99 and G=0.97, respectively). The mean difference between HFUS and pathological assessment of

tumor thickness was 0.01 mm. The difference between OCT and HFUS vs. histopathology increased with tumor thickness for both devices. The study was limited by the small patient population, lack of comparison of results between the devices, heterogeneity of lesions and the number of lesions not measured by OCT. The authors noted that these outcomes are inconsistent with similar studies.

Professional Societies/Organizations
American Academy of Dermatology (AAD): In the guidelines for the management of primary cutaneous melanoma, AAD (2019) states that biopsy is the first step for a definitive diagnosis of cancer. In the discussion on emerging diagnostic technologies, the Academy notes that the use of noninvasive imaging/electrical data acquisition and evaluation tools including RCM, electrical impedance spectroscopy combined with digital dermoscopy, optical coherence tomography, cross-polarized light and fluorescence photography, and high-frequency ultrasound are being investigated to further classify melanocytic lesions as either benign or malignant. AAD makes no recommendation on their use as evidence regarding effectiveness, clinical utility, and competing strategies is needed.

In a position statement on reflectance confocal microscopy (RCM), the American Academy of Dermatology (ADA) (2019) states their support for "the use of RCM as a modality for in vivo microscopic examination of suspicious epidermal and superficial dermal skin lesions for diagnosing skin pathology when clinically appropriate." However, they recommend that additional research be conducted about the utility and efficacy of RCM in the diagnosis of skin lesions. The ADA's disclaimer states that the position statement is provided for educational and informational purposes only to offer physicians guiding principles and policies regarding the practice of dermatology not to establish a legal or medical standard of care.

National Cancer Institute (NCI): According to NCI (2021), risk factors for melanoma include sun exposure, pigmentary characteristics, multiple nevi, family and personal history of melanoma, immunosuppression and environment exposures. Fair-skinned individuals exposed to the sun are at high risk and certain types of pigmented lesions (dysplastic or atypical nevi), with several large nondysplastic nevi, with many small nevi, or with moderate freckling have a twofold to threefold increased risk of developing melanoma. Familial dysplastic nevus syndrome or the presence of several dysplastic or atypical nevi increases the risk of developing melanoma greater than fivefold. NCI stated that the only widely proposed screening procedure for skin cancer is visual examination of the skin, including both self-examination and clinical examination. More than 90% of melanomas can be recognized with the naked eye. A biopsy should be performed for any suspicious lesion.

National Comprehensive Cancer Network® (NCCN®): In the discussion for follow-up following diagnosis and treatment of melanoma, NCCN's Clinical Practice Guidelines in Oncology™ (2021) states that patients cured of an initial primary melanoma are at increased risk for a second melanoma. Patients with risk factors that increase the chance for recurrence (e.g., prior multiple primary melanomas, family history of melanoma and presence of atypical/dysplastic nevi) should be enrolled in a more intensive surveillance program and may benefit from adjuncts such as high-resolution total body photography. These risk factors include multiple primary melanomas, positive family history and the presence of multiple dysplastic nevi.

U.S. Preventive Services Task Force (USPSTF): The USPSTF published a 2016 updated systematic review on visual screening for skin cancer. Thirteen studies, mostly observational cohort studies and retrospective reviews (n=10), met inclusion criteria. Acceptable screening tests were defined as whole or partial visual skin examination with or without tools to aid examination (e.g., dermatoscopy, whole body photography). The report noted that definitive diagnosis of non-melanoma and melanoma skin cancer is made by shave, punch or excision biopsy depending on the type of skin cancer. The authors concluded that due to the limited evidence, no firm conclusions on skin cancer screening and melanoma mortality could be made. Noted limitations of the fair-quality studies included: various follow-up times; short-term follow-ups; noncomparative study design; subjects tended to be younger women even though the incidence of skin cancer is highest in older men; lack of complete data presented; and lack of rigorous studies on skin cancer screening conducted in the United States with an application in primary care or internal medicine settings.

Use Outside of the US
It has been reported that there has been a global trend of increasing melanoma incidence in people of European descent. One of the highest incidences is in Croatia which has had a four-fold increase in the past 40 years.

Central and Eastern Europe had the largest share of deaths (35.5%) among the four geographic European regions. Melanoma mortality remains the highest in Australia and New Zealand (Mayer et al., 2014). The Nevisense has been CE Marked since 2013, and is currently commercially available in Europe including Sweden, Germany, Switzerland, Australia, United Kingdom, Belgium, and Austria. Nevisense has Therapeutic Goods Administration TGA in Australia.

Brazilian Dermatology Society: The Brazilian guidelines on the diagnosis and treatment of primary cutaneous melanoma included recommendations on total body photography with digital dermoscopy (body mapping [BM]). The recommendations stated that follow-up with BM has benefits for patients with an increased risk of melanoma (grade A - experimental or observational studies of higher consistency). BM is not typically indicated for low-risk individuals (grade B - experimental or observational studies of lower consistency) but may be indicated in a low-risk individual who has an isolated suspicious lesion without specific criteria for melanoma (grade A). Follow-up with BM complements but does not replace clinical and dermoscopic examination of the entire skin surface. The Society noted that isolated BM, not aimed at follow-up, is frequently used in Brazil as a diagnostic test to replace/complement dermoscopic examination during dermatological consultations and stated that this indication is far from ideal. BM may be justified in situations where dermoscopy of the entire body surface cannot be performed (grade D recommendation - opinion without critical evaluation, based on consensus, physiological studies or animal models) (Castro, et al., 2016).

European Society for Medical Oncology (ESMO): In their 2015 (updated 2019) clinical practice guidelines for the diagnosis, treatment and follow-up of cutaneous melanoma, ESMO stated that dermoscopy by an experienced physician enhances diagnostic accuracy. Another technology identified to improve early detection is full body imaging with high-resolution pictures. The Society does not discuss the use of other photographic surveillance techniques.

National Institute for Health and Clinical Excellence (NICE): The 2015 NICE guidelines (United Kingdom) on the assessment and management of melanoma included a review of the literature on dermoscopy and other visualization techniques. NICE stated that dermoscopy is an accepted practice but the accuracy and clinical utility depends on the experience of the practitioner who is using it and recommended its use in the assessment of lesions when performed by a trained professional. Based on the literature review, NICE did not recommend the routine use of confocal microscopy or computer-assisted diagnostic tools. NICE recommended that baseline photography (preferably dermoscopic) be used for a clinically atypical melanocytic lesion that does not need excision and to review the clinical appearance with the images every three months. NICE noted that photography (mole mapping), might help to identify changes in moles but the quality is variable. The Guideline Development Group was uncertain about the most appropriate timing for sequential photography to detect significant changes in pigmented lesions to aide in the diagnosis of early melanoma.

Based on a systematic review of the literature, NICE stated that there is insufficient evidence to recommend the routine use of VivaScope 1500 and 3000 imaging systems to help decide whether to biopsy and excise skin lesions in people with suspected melanoma. Thirteen studies (randomized, prospective cohort and retrospective) met inclusion criteria and reported on the use of VivaScope or reflectance confocal microscopy (RCM) in diagnosing suspected or equivocal melanoma lesions and three reported its use in lesion margin delineation. Six studies used VivaScope 1500 and one used VivaScope 1500 or 3000. Six studies used earlier versions of VivaScope. Comparators included dermoscopy and histopathology. Meta-analysis could not be performed due to the heterogeneity of the studies including: study design; patient population (e.g., prior history of melanoma); and variation in reporting results as patient based or lesion based (NICE, 2015, updated 2020).

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD	Novitas	Reflectance Confocal Microscopy (L37375)	Retired 8/27/2020

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
96904	Whole body integumentary photography, for monitoring of high risk patients with dysplastic nevus syndrome or a history of dysplastic nevi, or patients with a personal or familial history of melanoma

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
96931	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition and interpretation and report, first lesion
96932	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition only, first lesion
96933	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, first lesion
96934	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition and interpretation and report, each additional lesion (List separately in addition to code for primary procedure)
96935	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition only, each additional lesion (List separately in addition to code for primary procedure)
96936	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, each additional lesion (List separately in addition to code for primary procedure)
96999†	Unlisted special dermatological service or procedure
0400T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; one to five lesions (Code deleted 01/01/2021)
0401T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; six or more lesions (Code deleted 01/01/2021)
0470T	Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; first lesion
0471T	Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; each additional lesion (List separately in addition to code for primary procedure)
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score
0700T	Molecular fluorescent imaging of suspicious nevus; first lesion (Code effective 01/01/2022)
0701T	Molecular fluorescent imaging of suspicious nevus;each additional lesion (List separately in addition to code for primary procedure) (Use 0701T in conjunction with 0700T) (Code effective 01/01/2022)

†**Note: Considered Experimental/Investigational/Unproven when used to report multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia.**

Not separately reimbursable when dermoscopy is performed as part of a normal evaluation of a pigmented skin lesion.

CPT®* Codes	Description
96999	Unlisted special dermatological service or procedure

***Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.**

References

1. Aberg P, Birgersson U, Elsner P, Mohr P, Ollmar S. Electrical impedance spectroscopy and the diagnostic accuracy for malignant melanoma. Exp Dermatol. 2011 Aug;20(8):648-52.

2. Alarcon I, Carrera C, Palou J, Alos L, Malvehy J, Puig S. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. Br J Dermatol. 2014 Apr;170(4):802-8.

3. American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. Updated 2019. Accessed Sep 8, 2021. Available at URL address: http://www.aad.org/education/clinical-guidelines

4. American Academy of Dermatology (AAD). Position statement on reflectance confocal microscopy (RCM). 2019. Accessed Sep 8, 2021. Available at URL address: https://www.aad.org/search/?k=position+statement+RCM&sort=

5. Argenziano G, Puig S, Zalaudek I, Sera F, Corona R, Alsina M, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006 Apr 20;24(12):1877-82.

6. Banky JP, Kelly JW, English DR, Yeatman JM, Dowling JP. Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. Arch Dermatol. 2005 Aug;141(8):998-1006.

7. Botar-Jid CM, Cosgarea R, Bolboacă SD, Şenilă SC, Lenghel LM, Rogojan L, Dudea SM. Assessment of cutaneous melanoma by use of very- high-frequency ultrasound and real-time elastography. AJR Am J Roentgenol. 2016 Apr;206(4):699-704.

8. Braun RP, Mangana J, Goldinger S, French L, Dummer R, Marghoob AA. Electrical Impedance Spectroscopy in Skin Cancer Diagnosis. Dermatol Clin. 2017 Oct;35(4):489-493.

9. Calin MA, Parasca SV, Savastru R, Calin MR, Dontu S. Optical techniques for the noninvasive diagnosis of skin cancer. J Cancer Res Clin Oncol. 2013 Jul;139(7):1083-104.

10. Castro LGM, Bakos RM, Duprat J, Bittencourt FV, Di Giacomo THB, Serpa SS, Messina MCL, Loureiro WR, Macarenco RS, Stolf HO, Gontijo G. Brazilian guidelines for diagnosis, treatment and follow-up of primary cutaneous melanoma - Part II. An Bras Dermatol. 2016; 91(1):49-58.

11. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Sep 8, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx?Cntrctr=373&ContrVer=1&CntrctrSelected=373*1&DocType=Active%7cFuture&s=All&bc=AggAAAQAAAAA&

12. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Sep 8, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx.

13. Cinotti E, Labeille B, Debarbieux S, Carrera C, Lacarrubba F, Witkowski AM, Moscarella E, Arzberger E, Kittler H, Bahadoran P, Gonzalez S, Guitera P, Agozzino M, Farnetani F, Hofmann-Wellenhof R, Ardigò M, Rubegni P, Tognetti L, Łudzik J, Zalaudek I, Argenziano G, Longo C, Ribero S, Malvehy J, Pellacani G, Cambazard F, Perrot JL. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. Journal of the European Academy of Dermatology and Venereology. 2018;32(8):1284-1291.

14. Cymerman RM, Shao Y, Wang K, Zhang Y, Murzaku EC, Penn LA, Osman I, Polsky D. De Novo vs Nevus-Associated Melanomas: Differences in Associations With Prognostic Indicators and Survival. J Natl Cancer Inst. 2016 May 27;108(10):djw121. doi: 10.1093/jnci/djw121. PMID: 27235387; PMCID: PMC5939856.

15. Diebele I, Kuzmina I, Lihachev A, Kapostinsh J, Derjabo A, Valeine L, Spigulis J. Clinical evaluation of melanomas and common nevi by spectral imaging. Biomed Opt Express. 2012 Mar 1;3(3):467-72.

16. Dinnes J, Bamber J, Chuchu N, Bayliss SE, Takwoingi Y, Davenport C, Godfrey K, O'Sullivan C, Matin RN, Deeks JJ, Williams HC; Cochrane Skin Cancer Diagnostic Test Accuracy Group. High-frequency ultrasound for diagnosing skin cancer in adults. Cochrane Database Syst Rev. 2018 Dec 4;12:CD013188. doi: 10.1002/14651858.CD013188.

17. Edwards SJ, Mavranezouli I, Osei-Assibey G, Marceniuk G, Wakefield V, Karner C. VivaScope® 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. Health Technol Assess. 2016 Jul;20(58):1-260.

18. Edwards SJ, Osei-Assibey G, Patalay R, Wakefield V, Karner C. Diagnostic accuracy of reflectance confocal microscopy using VivaScope for detecting and monitoring skin lesions: a systematic review. Clin Exp Dermatol. 2017 Apr;42(3):266-275. doi: 10.1111/ced.13055.

19. Esmaeili A, Scope A, Halpern AC, Marghoob AA. Imaging techniques for the in vivo diagnosis of melanoma. Semin Cutan Med Surg. 2008 Mar;27(1):2-10.

20. European Society of Clinical Oncology (ESMO). Cutaneous melanoma: ESMO clinical practice guidelines. 2015; updated Sep 2019. Accessed Sep 8, 2021. Available at URL address: http://www.esmo.org/Guidelines/Melanoma/Cutaneous-Melanoma

21. Ferrante di Ruffano L, Dinnes J, Deeks JJ, Chuchu N, Bayliss SE, Davenport C, Takwoingi Y, Godfrey K, O'Sullivan C, Matin RN, Tehrani H, Williams HC; Cochrane Skin Cancer Diagnostic Test Accuracy Group. Optical coherence tomography for diagnosing skin cancer in adults. Cochrane Database Syst Rev. 2018 Dec 4;12:CD013189. doi: 10.1002/14651858.CD013189.

22. Ferrante di Ruffano L, Takwoingi Y, Dinnes J, Chuchu N, Bayliss SE, Davenport C, Matin RN, Godfrey K, O'Sullivan C, Gulati A, Chan SA, Durack A, O'Connell S, Gardiner MD, Bamber J, Deeks JJ, Williams HC; Cochrane Skin Cancer Diagnostic Test Accuracy Group. Computer-assisted diagnosis techniques (dermoscopy and spectroscopy-based) for diagnosing skin cancer in adults. Cochrane Database Syst Rev. 2018 Dec 4;12:CD013186. doi: 10.1002/14651858.CD013186.

23. Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. Br J of Dermatol. 2004 Apr;150(4):706-14.

24. Ferris LK, Harris RJ. New diagnostic aids for melanoma. Dermatol Clin. 2012 Jul;30(3):535-45.

25. Fink C, Jaeger C, Jaeger K, Haenssle HA. Diagnostic performance of the MelaFind device in a real-life clinical setting. J Dtsch Dermatol Ges. 2017 Apr;15(4):414-419.

26. Fink C, Haenssle HA. Non-invasive tools for the diagnosis of cutaneous melanoma. Skin Res Technol. 2017 Aug;23(3):261-271. doi: 10.1111/srt.12350.

27. Fink C, Hofmann M, Jagoda A, Spaenkuch I, Forschner A, Tampouri I, Lomberg D, Leupold D, Garbe C, Haenssle HA. Study protocol for a prospective, non-controlled, multicentre clinical study to evaluate the diagnostic accuracy of a stepwise two-photon excited melanin fluorescence in pigmented lesions suspicious for melanoma (FLIMMA study). BMJ Open. 2016 Dec 19;6(12):e012730.

28. Friedman RJ, Gutkowicz-Krusin D, Farber MJ, Warycha M, Schneider-Kels L, Papastathis N, et al. The diagnostic performance of expert dermoscopists vs a computer-vision system on small-diameter melanomas. Arch Dermatol. 2008 Apr;144(4):476-82.

29. Gambichler T, Regeniter P, Bechara FG, Orlikov A, Vasa R, Moussa G, et al. Characterization of benign and malignant melanocytic skin lesions using optical coherence tomography in vivo. J Am Acad Dermatol. 2007 Oct;57(4):629-37.

30. Gambichler T, Schmid-Wendtner MH, Plura I, Kampilafkos P, Stücker M, Berking C, Maier T. A multicentre pilot study investigating high-definition optical coherence tomography in the differentiation of cutaneous melanoma and melanocytic naevi. J Eur Acad Dermatol Venereol. 2014 Jul 30.

31. Gerger A, Koller S, Weger W, Richtig E, Kerl H, Samonigg H, et al. Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer. 2006 Jul 1;107(1):193-200.

32. Gerger A, Hofmann-Wellenhof R, Langsenlehner U, Richtig E, Koller S, Weger W, et al. In vivo confocal laser scanning microscopy of melanocytic skin tumours: diagnostic applicability using unselected tumour images. Br J Dermatol. 2008 Feb;158(2):329-33.

33. Godoy SE, Hayat MM, Ramirez DA, Myers SA, Padilla RS, Krishna S. Detection theory for accurate and non-invasive skin cancer diagnosis using dynamic thermal imaging. Biomed Opt Express. 2017 Mar 22;8(4):2301-2323.

34. Goodson AG, Florell SR, Hyde M, Bowen GM, Grossman D. Comparative analysis of total body and dermatoscopic photographic monitoring of nevi in similar patient populations at risk for cutaneous melanoma. Dermatol Surg. 2010 Jul;36(7):1087-98.

35. Guitera P, Menzies SW. State of the art of diagnostic technology for early-stage melanoma. Expert Rev Anticancer Ther. 2011 May;11(5):715-23.

36. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and Basal cell carcinoma using a two-step method: analysis of 710 consecutive clinically equivocal cases. J Invest Dermatol. 2012 Oct;132(10):2386-94.

37. Gulia A, Massone C. Advances in dermoscopy for detecting melanocytic lesions. F1000 Med Rep. 2012;4:11.

38. Gurjarpadhye AA, Parekh MB, Dubnika A, Rajadas J, Inayathullah M. Infrared Imaging Tools for Diagnostic Applications in Dermatology. SM J Clin Med Imaging. 2015;1(1):1-5.

39. Haenssle HA, Vent C, Bertsch HP, Rupprecht R, Abuzahra F, Junghans V, et al. Results of a surveillance programme for patients at high risk of malignant melanoma using digital and conventional dermoscopy. Eur J Cancer Prev. 2004 Apr;13(2):133-8.

40. Haniffa MA, Lloyd JJ, Lawrence CM. The use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma in the setting of a melanoma screening clinic. Br J Dermatol. 2007 Jun;156(6):1350-2.

41. Har-Shai Y, Glickman YA, Siller G, McLeod R, Topaz M, Howe C, et al. Electrical impedance scanning for melanoma diagnosis: a validation study. Plast Reconstr Surg. 2005 Sep;116(3):782-90.

42. Hayes, Inc. Evidence Analysis Research Brief. Reflectance confocal microscopy for diagnosis of melanoma. Lansdale, PA: Hayes, Inc. Dec 20, 2019.

43. Hawryluk EB, Liang MG. Pediatric melanoma, moles, and sun safety. Pediatr Clin North Am. 2014 Apr;61(2):279-91. doi: 10.1016/j.pcl.2013.11.004. Epub 2014 Jan 28. PMID: 24636646.

44. Hooper BJ and Goldman MP. Primary Dermatologic Care. St. Louis: Mosby, 1999. Chapter 6, Pigmentary Disorders, p. 286-288.

45. Kardynal A, Olszewska M. Modern non-invasive diagnostic techniques in the detection of early cutaneous melanoma. J Dermatol Case Rep. 2014 Mar 31;8(1):1-8.

46. Kelly JW, Yeatman JM, Regalia C, Mason G, Henham AP. A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. Med J Aust. 1997 Aug 18;167(4):191-4. PMID: 9293264.

47. Kleinerman R, Whang TB, Bard RL, Marmur ES. Ultrasound in dermatology: Principles and applications. J Am Acad Dermatol. 2012 Sep;67(3):478-87.

48. Kuzmina I, Diebele I, Jakovels D, Spigulis J, Valeine L, Kapostinsh J, Berzina A. Towards noncontact skin melanoma selection by multispectral imaging analysis. J Biomed Opt. 2011 Jun;16(6):060502.

49. Lallas A, Apalla Z, Chaidemenos G. New trends in dermoscopy to minimize the risk of missing melanoma. J Skin Cancer. 2012;2012:820474. doi: 10.1155/2012/820474.

50. Langley RG, Walsh N, Sutherland AE, Propperova I, Delaney L, Morris SF, Gallant C. The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: a prospective study. Dermatology. 2007;215(4):365-72.

51. Lan J, Wen J, Cao S, Yin T, Jiang B, Lou Y, Zhu J, An X, Suo H, Li D, Zhang Y, Tao J. The diagnostic accuracy of dermoscopy and reflectance confocal microscopy for amelanotic/hypomelanotic melanoma: a systematic review and meta-analysis. Br J Dermatol. 2020 Aug;183(2):210-219. doi: 10.1111/bjd.18722. Epub 2019 Dec 22. PMID: 31747045.

52. Levine A, Wang K, Markowitz O. Optical Coherence Tomography in the Diagnosis of Skin Cancer. Dermatol Clin. 2017 Oct;35(4):465-488. 9.

53. Lui H, Zhao J, McLean D, Zeng H. Real-time Raman spectroscopy for in vivo skin cancer diagnosis. Cancer Res. 2012 May 15;72(10):2491-500.

54. Lucas CR, Sanders LL, Murray JC, Myers SA, Hall RP, Grichnik JM. Early melanoma detection: nonuniform dermoscopic features and growth. J Am Acad Dermatol. 2003 May;48(5):663-71.

55. Malvehy J, Hauschild A, Curiel-Lewandrowski C, Mohr P, Hofmann-Wellenhof R, Motley R, Berking C, Grossman D, Paoli J, Loquai C, Olah J, Reinhold U, Wenger H, Dirschka T, Davis S, Henderson C, Rabinovitz H, Welzel J, Schadendorf D, Birgersson U. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol. 2014 Nov;171(5):1099-107.

56. Marghoob AA, Charles CA, Busam KJ, Rajadhyaksha M, Lee G, Clark-Loeser L, et al. In vivo confocal scanning laser microscopy of a series of congenital melanocytic nevi suggestive of having developed malignant melanoma. Arch Dermatol. 2005 Nov;141(11):1401-12.

57. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc. 2007 Mar;82(3):364-80.

58. Mayer JE, Swetter SM, Fu T, Geller AC. Screening, early detection, education, and trends for melanoma: current status (2007-2013) and future directions: Part I. Epidemiology, high-risk groups, clinical strategies, and diagnostic technology. J Am Acad Dermatol. 2014 Oct;71(4):599.e1-599.e12.

59. Menge TD, Pellacani G. Advances in noninvasive imaging of melanoma. Semin Cutan Med Surg. 2016 Mar;35(1):18-24. doi: 10.12788/j.sder.2016.003.

60. Meyer N, Lauwers-Cances V, Lourari S, Laurent J, Konstantinou MP, Lagarde JM, Krief B, Batatia H, Lamant L, Paul C. High-frequency ultrasonography but not 930-nm optical coherence tomography reliably evaluates melanoma thickness in vivo: a prospective validation study. Br J Dermatol. 2014 Oct;171(4):799-805.

61. Monheit G, Cognetta AB, Ferris L, Rabinovitz H, Gross K, Martini M, et al. The performance of MelaFind: a prospective multicenter study. Arch Dermatol. 2011 Feb;147(2):188-94.

62. National Cancer Institute (NCI). Heath Professional. Melanoma treatment (PDQ®). Updated Jul 23, 2021. Accessed Sep 7, 2021. Available at URL address: https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#section/all

63. National Cancer Institute (NCI). Heath Professional. Skin Cancer Screening (PDQ®). Updated Aug 6, 2021. Accessed Sep 7, 2021. Available at URL address: https://www.cancer.gov/types/skin/hp/skin-screening-pdq

64. National Comprehensive Cancer Network® (NCCN®). Clinical Practice Guidelines in Oncology™. Melanoma: cutaneous V.2.2021. Feb 19, 2021. Accessed Sept 3, 2021. Available at URL address: https://www.nccn.org/professionals/physician_gls/default.aspx#site

65. National Institute for Health and Clinical Excellence (NICE). Melanoma: assessment and management [NG14]. Jul 2015. Accessed Sep 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/ng14

66. National Institute for Health and Clinical Excellence (NICE). Diagnostic guidance. VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions. Nov 2015, updated Jan 2020. Accessed Sep 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/dg19

67. Nehal KS, Gareau D, Rajadhyaksha M. Skin imaging with reflectance confocal microscopy. Semin Cutan Med Surg. 2008 Mar;27(1):37-43.

68. Oliveria SA, Dusza SW, Phelan DL, Ostroff JS, Berwick M, Halpern AC. Patient adherence to skin self-examination. effect of nurse intervention with photographs. Am J Prev Med. 2004 Feb;26(2):152-5.

69. Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. Br J Dermatol. 2014 May 29.

70. Pezzini C, Kaleci S, Chester J, Farnetani F, Longo C, Pellacani G. Reflectance confocal microscopy diagnostic accuracy for malignant melanoma in different clinical settings: systematic review and meta-

analysis. J Eur Acad Dermatol Venereol. 2020 Jan 29. doi: 10.1111/jdv.16248. Epub ahead of print. PMID: 31997465.

71. Psaty EL, Halpern AC. Current and emerging technologies in melanoma diagnosis: the state of the art. Clin Dermatol. 2009 Jan-Feb;27(1):35-45.

72. Psaty EL, Scope A, Halpern AC, Marghoob AA. Defining the patient at high risk for melanoma. Int J Dermatol. 2010 Apr;49(4):362-76.

73. Que SK, Fraga-Braghiroli N, Grant-Kels JM, Rabinovitz HS, Oliviero M, Scope A. Through the looking glass: Basics and principles of reflectance confocal microscopy. J Am Acad Dermatol. 2015 Aug;73(2):276-84.

74. Que SK, Grant-Kels JM, Longo C, Pellacani G. Basics of Confocal Microscopy and the Complexity of Diagnosing Skin Tumors: New Imaging Tools in Clinical Practice, Diagnostic Workflows, Cost-Estimate, and New Trends. Dermatol Clin. 2016 Oct;34(4):367-375.

75. Rallan D, Bush NL, Bamber JC, Harland CC. Quantitative discrimination of pigmented lesions using three-dimensional high-resolution ultrasound reflex transmission imaging. J Invest Dermatol. 2007 Jan;127(1):189-95.

76. Rathmore, B. Melanoma. In: Ferri's Clinical Advisor 2021. Philadelphia: Elsevier, 2021. p 875-877.

77. Rayner JE, Laino AM, Nufer KL, Adams L, Raphael AP, Menzies SW, Soyer HP. Clinical Perspective of 3D Total Body Photography for Early Detection and Screening of Melanoma. Front Med (Lausanne). 2018 May 23;5:152.

78. Risser J, Pressley Z, Veledar E, Washington C, Chen SC. The impact of total body photography on biopsy rate in patients from a pigmented lesion clinic. J Am Acad Dermatol. 2007 Sep;57(3):428-34.

79. Salerni G, Carrera C, Lovatto L, Puig-Butille JA, Badenas C, Plana E, et al. Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma. J Am Acad Dermatol. 2011 Jun 15. [Epub ahead of print]

80. Scope A, Benvenuto-Andrade C, Agero AL, Halpern AC, Gonzalez S, Marghoob AA. Correlation of dermoscopic structures of melanocytic lesions to reflectance confocal microscopy. Arch Dermatol. 2007 Feb;143(2):176-85.

81. Solivetti FM, Elia F, Guerrisi A, Desiderio F, Santaguida M, Sperduti I, Cavallotti C, Di Carlo A. Cutaneous melanoma follow-up: appropriateness of requests for ultrasound tests--the S.Gallicano National Referral Centre Experience. J Exp Clin Cancer Res. 2013 Oct 9;32:73.

82. Stanley RJ, Stoecker WV, Moss RH. A relative color approach to color discrimination for malignant melanoma detection in dermoscopy images. Skin Res Technol. 2007 Feb;13(1):62-72.

83. Stevenson AD, Mickan S, Mallett S, Ayya M. Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. Dermatol Pract Concept. 2013 Oct 31;3(4):19-27.

84. Stimpfle DW, Serra AL, Wüthrich RP, French LE, Braun RP, Hofbauer GF. Spectophotometric intracutaneous analysis: an investigation on photodamaged skin of immunocompromised patients. J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1141-7.

85. Tucker MA. Melanoma epidemiology. Hematol Oncol Clin North Am. 2009 Jun;23(3):383-95, vii.

86. U.S. Food and Drug Administration (FDA). 510(k) premarket notification database. Accessed Sep 7, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

87. U.S. Food and Drug Administration (FDA). Premarket approval (PMA) database Accessed Sep 7, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

88. U.S. Food and Drug Administration (FDA). Nevisense. Premarket approval (PMA) database. Product code ONV. Accessed Sep 7, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

89. U.S. Preventive Services Task Force (USPSTF). Skin cancer: screening. Wernli KJ, Henrikson NB, Morrison CC, Nguyen M, Pocobelli G, Whitlock EP. Screening for skin cancer in adults: an updated systematic evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 137. AHRQ Publication No. 14-05210-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2016. Accessed Sep 8, 2021. Available at URL address: https://www.uspreventiveservicestaskforce.org/BrowseRec/Index

90. Vestergaard ME, Menzies SW. Automated diagnostic instruments for cutaneous melanoma. Semin Cutan Med Surg. 2008 Mar;27(1):32-6.

91. Wachsman W, Morhenn V, Palmer T, Walls L, Hata T, Zalla J, Scheinberg R, Sofen H, Mraz S, Gross K, Rabinovitz H, Polsky D, Chang S. Noninvasive genomic detection of melanoma. Br J Dermatol. 2011 April; 164(4): 797–806. doi: 10.1111/j.1365-2133.2011.10239x.

92. Wang Y, Maslov K, Zhang Y, Hu S, Yang L, Xia Y, Liu J, Wang LV. Fiber-laser-based photoacoustic microscopy and melanoma cell detection. J Biomed Opt. 2011 Jan-Feb;16(1):011014.

93. Watts CG, Dieng M, Morton RL, Mann GJ, Menzies SW, Cust AE. Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. Br J Dermatol. 2015 Jan;172(1):33-47.

94. Welzel J, Schuh S. Noninvasive diagnosis in dermatology. J Dtsch Dermatol Ges. 2017 Oct;15(10):999-1016.

95. Winkelmann RR, Farberg AS, Glazer AM, Rigel DS. Noninvasive Technologies for the Diagnosis of Cutaneous Melanoma. Dermatol Clin. 2017 Oct;35(4):453-456.

96. Witkowski AM, Łudzik J,2, Arginelli F, Bassoli S, Benati E, Casari A, De Carvalho N, De Pace B, Farnetani F, Losi A, Manfredini M, Reggiani C, Malvehy J, Pellacani G. Improving diagnostic sensitivity of combined dermoscopy and reflectance confocal microscopy imaging through double reader concordance evaluation in telemedicine settings: A retrospective study of 1000 equivocal cases. PLoS One. 2017 Nov 9;12(11):e0187748.

97. Xiong YQ, Ma SJ, Mo Y, Huo ST, Wen YQ, Chen Q. Comparison of dermoscopy and reflectance confocal microscopy for the diagnosis of malignant skin tumours: a meta-analysis. J Cancer Res Clin Oncol. 2017 Mar 13. doi: 10.1007/s00432-017-2391-9. [Epub ahead of print]

98. Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. J Eur Acad Dermatol Venereol. 2016 Aug;30(8):1295-302.

99. Xiong YQ, Mo Y, Wen YQ, Cheng MJ, Huo ST, Chen XJ, Chen Q. Optical coherence tomography for the diagnosis of malignant skin tumors: a meta-analysis. J Biomed Opt. 2018 Feb;23(2):1-10. doi: 10.1117/1.JBO.23.2.020902.

100. Zhang J, Fan Y, Song Y, Xu J Accuracy of Raman spectroscopy for differentiating skin cancer from normal tissue. Medicine (Baltimore). 2018 Aug;97(34):e12022.