Policy Statement

Multispectral digital skin lesion analysis is considered investigational in all situations including but not limited to:

- Evaluating pigmented skin lesions
- Serially monitoring pigmented skin lesions
- Defining peripheral margins of skin lesions suspected of malignancy prior to surgical excision

Policy Guidelines

The following CPT category III codes are specific for multispectral digital skin lesion analysis:

- **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
- **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

Description

There is interest in noninvasive devices that will improve the diagnosis of malignant skin lesions. One such approach is multispectral digital skin lesion analysis (MSDLSA). This technique has the potential to improve diagnostic accuracy for suspicious skin lesions and may increase the detection rate of malignant skin lesions and/or reduce the rate of unnecessary biopsies.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In November 2011, MelaFind® (MELA Sciences, Irvington, NY, now Strata Skin Sciences, Horsham PA), a multispectral digital skin lesion analysis device, was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. Its intended use is to evaluate pigmented lesions with clinical or histologic characteristics suggestive of melanoma. It is not intended for lesions with a diagnosis of melanoma or likely melanoma. MelaFind® is intended for use only by physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) and only those who have successfully completed training on the MelaFind® device. FDA documents have further noted:
“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 nonpigmented 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., nonulcerated or nonbleeding lesions), lesions greater than 1 cm 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).”

FDA product code: OYD.

### Rationale

#### Background

Melanoma is a form of skin cancer that originates in the pigment-producing melanocytes. Most melanocytes produce melanin and the tumors are commonly pigmented brown or black. Melanoma is less common than basal and squamous cell skin cancer, but it is more likely to metastasize than other skin cancers. Prognosis is highly associated with stage of the disease at diagnosis, characterized by the depth of the tumor, the degree of ulceration, and the extent of spread to lymph nodes and distant organs. For example, for thin (i.e., <1.0 mm) localized stage I cancers the 5-year survival rate is over 90% and this decreases to 15% to 20% for metastatic stage IV cancers. Thus, early detection of disease is important for increasing survival.

Differentiating melanoma lesions from benign pigmented lesions in the clinical setting is challenging. Diagnostic aids such as the ABCDE rule have been developed to assist clinicians when they visually inspect suspicious lesions. The diagnostic accuracy of the ABCDE criteria varies depending on whether they are used singly or together. Use of a single criterion is sensitive but not specific, which would result in many benign lesions being referred or biopsied. Conversely, use of all criteria together is specific but not sensitive, meaning that a number of melanomas are missed.

There is interest in noninvasive approaches that will improve the diagnosis of malignant skin lesions. One technique is dermatoscopy (also called dermoscopy), which enables the clinician to perform direct microscopic examination of diagnostic features in pigmented skin lesions. Devices consist of a 10× magnifier lens in combination with a liquid medium or polarized light to eliminate reflection and allow for more-detailed examination of suspicious skin lesions. The available evidence from prospective randomized controlled trials and other studies has suggested that dermatoscopy used by specialists may lead to a decrease in the number of benign lesions excised and, when used by primary care physicians, may lead to fewer benign lesions being referred to specialists.

Another technology that could improve melanoma detection and outcomes is multispectral digital skin lesion analysis (MSDLSLA). A U.S. Food and Drug Administration (FDA)-approved MSDLSLA device uses a handheld scanner to shine visible light on the suspicious lesion. The light is of 10 wavelengths, varying from blue (430 nm) and near infrared (950 nm). This light can penetrate up to 2.5 mm under the surface of the skin. The data acquired by the scanner are analyzed by a data processor; the characteristics of each lesion are evaluated using proprietary computer algorithms. Lesions are classified as positive (i.e., high degree of morphologic disorganization) or negative (i.e., low degree of morphologic disorganization) according to the algorithms. Positive lesions are recommended for biopsy. For negative lesions, other clinical factors are considered in the decision of whether to refer for biopsy. The FDA-approved system (see the Regulatory Status section) is intended only for suspicious pigmented lesions on intact skin and for use by trained dermatologists.
Literature Review
This review refers to the use of multispectral digital skin lesion analysis (MSDSLA) for the evaluation of pigmented lesions suspicious for malignancy. No published evidence was identified on the use of MSDSLA for monitoring skin lesions or for evaluating cancerous lesions referred for surgery.

Use of MSDSLA devices is intended to inform decisions whether patients with pigmented lesions should undergo a biopsy. It is not clearly defined whether MSDSLA is intended to select patients for biopsy (rule in) or to select those who may undergo observation (rule out).

The evaluation of MSDSLA for diagnosis focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting the marker that is present or in excluding a marker that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease or defining prognosis); and (3) clinical utility (i.e., a demonstration that the diagnostic or prognostic information can be used to improve patient health outcomes).

Multispectral Digital Skin Lesion Analysis for Evaluating Pigmented Skin Lesions
Analytic Validity
No studies were identified on technical accuracy of MSDSLA methods for the evaluation of pigmented lesions suspicious for malignancy.

Diagnostic Accuracy
As with any diagnostic tool, assessment of MSDSLA technology involves a determination of its diagnostic accuracy compared with a reference standard and whether the results of the diagnostic tests are ultimately used to improve health outcomes. The reference standard for evaluation of pigmented skin lesions is excision with histologic diagnosis, in which, depending on the skill of the pathologist, sensitivity and specificity are considered near 100%. Clinically, noninvasive techniques such as MSDSLA would be used in combination with clinical assessment, either based on direct visual inspection or review of photographs. Therefore, the diagnostic performance of MSDSLA combined with clinical assessment should be compared with clinical assessment alone and then to the reference standard of histology. In addition, health outcomes in patients managed with MSDSLA versus standard care (clinical assessment alone, or clinical assessment and dermatoscopy) should be evaluated.

Most published studies to date on MSDSLA were industry-sponsored and/or coauthored by employees of or consultants for MELA Sciences, manufacturer of MelaFind.

A study published by Monheit et al (2011) contained the data submitted to the U.S. Food and Drug Administration (FDA) for approval of the MelaFind device. This prospective study included patients with at least 1 pigmented lesion scheduled for first-time biopsy. Lesions were between 2 mm and 22 mm in diameter. The following were exclusion criteria: anatomic site was not accessible to the device; lesion was not intact (e.g., open sores, ulcers, bleeding); lesion was on a palmar, plantar, or mucosal surface or under nails; lesion was in an area of visible scarring; and the lesion contained tattoo ink, splinter, or other foreign matter. In addition, lesions with a prebiopsy diagnosis of melanoma were excluded from analysis. Histologic diagnosis was used as the reference standard.

A total of 1393 patients with 1831 lesions were enrolled at major academic centers. Of the 1831 lesions, 1632 (90%) were eligible and evaluable. There were 165 lesions not evaluable for various reasons, including operator error, camera malfunction, and ineligible after enrollment related to scarring. Histologic analysis determined that 127 (7.8%) of 1632 lesions were melanoma. The sensitivity of MSDSLA for recommending biopsy of the melanoma lesions was 98.2% (125/127 melanomas), with a 95% lower confidence interval (CI) bound of 95.6%. The average specificity (averaged over clinicians) of MSDSLA for melanoma was 9.5%. The accuracy of clinician diagnosis was determined by randomly selecting 25 melanoma cases and matching them with 25 nonmelanoma lesions. Clinicians were asked to classify lesions into 2 categories of melanoma:
cannot rule out melanoma or not melanoma. The specificity of clinician diagnosis, as determined by the proportion of melanomas among the total number of lesions recommended for biopsy, was 3.7%, which was significantly lower than the specificity for MSDSLA (p=0.02). The Monheit study only included lesions previously examined clinically and determined to be sufficiently suspicious to warrant biopsy. The study did not include patients initially presenting with pigmented lesions to see whether MelaFind could enhance the accuracy of diagnosis based on clinical examination findings alone.

In 2016, Winkelman et al reported on further analysis of the same 1632 lesions, to correlate MSDSLA classifier scores with histopathologic severity and clinical features of melanoma. Mean classifier scores were higher for melanomas (3.5) than for high grade lesions (2.7; p=0.002), low-grade dysplastic nevi (7.1; p<0.001), nondysplastic nevi (1.6; p<0.001), and benign non-melanocytic lesions (2.0; p<0.001).

In 2015, Winkelmann et al also reported on the diagnostic accuracy of MelaFind for evaluating suspicious lesions obtained from patients undergoing routine skin examination in a community practice. Dermatologists identified suspicious lesions and selected them for biopsy. Prior to biopsy, the lesions were imaged with MelaFind (all met the FDA-approved indication for use of the device). (The study protocol did not involve reevaluation of images using MSDSLA findings.) Lesions were then biopsied and the diagnostic accuracy of MSDSLA for these lesions was determined and compared with histopathologic analysis of samples. A total of 137 consecutive lesions scheduled for biopsy were included in the study. MSDSLA categorized 21 of these lesions as having “low disorganization” (negative MSDSLA finding). All 21 of these lesions were histologically benign (11 mildly dysplastic nevi, 9 seborrheic keratosis, 1 compound nevus). The remaining 116 lesions were categorized by MSDSLA as having high disorganization (positive MSDSLA finding). Ninety-nine (85%) of these lesions were considered to be “true positives” (i.e., malignant melanoma, lesions with atypical melanocytic proliferation, moderately and severely dysplastic nevi). The study population included only 1 true melanoma and this was categorized by MSDSLA as having high disorganization. Advantages of this study were its prospective design and practice setting. However, as with the Monheit study, it did not evaluate the ability of MSDSLA to enhance the accuracy of biopsy decisions.

In 2016, Song et al reported on a smaller study comparing the diagnostic accuracy of MDLSA with reflectance confocal microscopy (RCM) in the prebiopsy detection of melanoma in 55 atypical-appearing lesions from 36 patients undergoing biopsy. MDLSA was performed with MelaFind and RCM was performed with VivaScope, by separate evaluators who were blinded to others’ evaluations. RCM was more sensitive than MDLSA (p=0.001). For the diagnosis of melanoma, MDLSA had a sensitivity of 71.4%.

Other studies have reported on the clinical performance of image-based classifiers other than MelaFind. In 2015, Ferris et al reported on the training and validation of a novel classifier. The classifier was trained on a malignant test set (105 melanomas, 29 high-grade dysplastic nevi, 23 basal cell carcinomas, 3 squamous cell carcinomas) and a benign training set (93 benign melanocytic lesions, 20 other benign lesions). In receiver operating characteristic curve analysis, with a threshold severity score of 0.4, the area under the curve was 0.818. The classifier’s performance was evaluated in a test set containing 39 melanomas, 11 basal cell carcinomas, 3 squamous cell carcinomas, and 120 benign lesions, all with available biopsy results, and 27 lesions considered not appropriate for biopsy by 2 dermatologists. The classifier’s sensitivity for melanoma was 97.4% (95% CI, 86.5% to 99.9%). Among the 120 benign lesions, 53 were correctly classified as benign (specificity, 44.2%; 95% CI, 35.1% to 53.5%); among the 27 unbiopsied lesions, 20 were classified as benign (specificity, 74.1%; 95% CI, 53.7% to 88.9%).

Section Summary: Diagnostic Accuracy
One prospective study has reported on the sensitivity and specificity of MelaFind, with high sensitivity. These results would have to be replicated in an independent sample, with appropriate confidence intervals.
Clinical Utility

Direct evidence of the clinical utility of MSDSLA would be demonstrated if its use leads to management changes that improve outcomes. This would ideally be evaluated in prospective randomized controlled trials (RCTs) examining health outcomes in patients presenting with pigmented lesions managed with and without the technology. RCTs would ideally compare MSDSLA to clinical examination and dermatoscopy. No studies of this type were identified.

Indirect evidence of clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

One RCT has been published; however, it was conducted over the Internet rather than in a clinical setting and involved retrospective analysis of lesions. The trial was published by Hauschild et al (2014) in Germany. It included 215 board-certified dermatologists selected on a first-come basis after receiving invitations to participate. Each participant was presented with information on 130 pigmented lesions; 93% had been biopsied in a prior study. Half the lesions were melanomas and half were nonmelanomas. (The lesions were a subset of evaluable lesions from the Monheit trial (previously described). All lesions met FDA indications for MelaFind.) Study participants were randomized to review clinical examination information and high-quality digital images only (n=108) or clinical information, high-quality digital images, and the MSDSLA results (n=107). After reviewing each case, participants completed a survey about their lesion management decision (e.g., recommendation for biopsy). A decision was considered correct if melanoma lesions were recommended for biopsy or if non-melanoma lesions were not recommended for biopsy. Before examining the cases, participants were shown an online slide presentation about MelaFind, including the device’s performance data.

Among dermatologists in the arm without MSDSLA findings, the sensitivity and specificity of biopsy were 69.5% (95% CI, 64.3% to 76.0%) and 55.9% (47.3% to 60.5%), respectively. In the arm with MSDSLA findings, the sensitivity and specificity were 78.0% (95% CI, 73.9% to 83.5%) and 45.8% (38.1 to 50.8%), respectively. Differences in sensitivity and specificity between arms were statistically significant (p<0.001).

Some nonrandomized studies have evaluated whether the use of MSDSLA would hypothetically lead to management changes. These studies were not conducted in clinical settings and it is unclear whether selection of lesion types and study participants (dermatologists) were representative of actual practice.

Several industry-sponsored simulation exercises have also been conducted at professional conferences. For example, Winkelman et al (2015) reported on 60 health care providers, 30 of whom were dermatologists, who participated in an exercise at a national dermoscopy conference. Participants were shown images of 12 lesions previously analyzed by MSDSLA using the MelaFind device. They were asked 3 times whether they would biopsy the lesion: (1) based on clinical images alone; (2) with the addition of high-resolution dermoscopic images; and (3) with the addition of MSDSLA classifier scores. The 12 lesions consisted of 2 melanomas in situ, 3 invasive melanomas, and 7 low-grade dysplastic nevi. Diagnostic accuracy did not increase after being shown dermoscopic images, but it did increase after getting MSDSLA scores. The proportion of dermatologists responding that they would biopsy all 5 malignant melanomas was 4% with clinical images alone, 10% after dermoscopy, and 72% after MSDSLA. Proportions among nondermatologists were 13%, 6%, and 78%, respectively. Conversely, among dermatologists, the proportion of low-grade dysplastic nevi recommended for biopsy was 53% with clinical images alone, 60% after dermoscopy, and 42% after MSDSLA. Among dermatologists, proportions were 53%, 66%, and 45%, respectively. The changes in biopsy recommendations after MSDSLA were statistically significant in all cases. Other studies conducted at conferences that used similar methodology had comparable results; biopsy decision accuracy increased significantly after clinicians were provided with MSDSLA findings.
change behavior based on medical tests, do not provide significant additional data to inform clinical utility.

**Section Summary: Clinical Utility**
No direct evidence for the clinical utility of MSDSLA in the management of pigmented lesions was identified. In addition, given the absence of firm evidence about the clinical validity of MSDSLA, a chain of inference cannot be built to support conclusions about the magnitude of benefits and harms of the use of MSDSLA in practice. Therefore, conclusions cannot be made about the clinical utility of MSDSLA.

**Summary of Evidence**
For individuals who have pigmented lesions being evaluated for melanoma who receive multispectral digital skin lesion analysis (MSDSLA), the evidence includes 2 prospective diagnostic accuracy studies of MelaFind and additional studies of other MSDSLA devices. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, and change in disease status. The diagnostic accuracy study found that MSDSLA had a sensitivity of 98.2% for recommending biopsy of melanoma lesions (8% of the pigmented lesions were melanoma). The average specificity of MSDSLA was 9.5% compared with 3.7% among clinicians. However, the study only included lesions already determined by a clinician to be sufficiently suspicious to warrant excision. No studies conducted in a clinical setting have evaluated the utility of MSDSLA as a diagnostic tool in the initial evaluation of pigmented lesions. In addition, no studies conducted in clinical settings have compared patient management decisions and health outcomes with and without MSDSLA devices. In addition, given the absence of firm evidence about the clinical validity of MSDSLA, a chain of inference cannot be built to support conclusions about the magnitude of benefits and harms of MSDSLA use in practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**
National Comprehensive Cancer Network guidelines on melanoma (v.1.2017)\(^{14}\) do not address multispectral digital skin lesion analysis.

**National Institute for Health and Care Excellence**
National Institute for Health and Care Excellence guidance on the assessment and management of melanoma\(^{15}\) does not address multispectral digital skin lesion analysis.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

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<tr>
<td>NCT01700114(^{a})</td>
<td>Post-Approval Study of MelaFind</td>
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\(^{a}\) Denotes industry-sponsored or cosponsored trial.
References


2.01.101  Multispectral Digital Skin Lesion Analysis

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.
Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.