Multispectral Digital Skin Lesion Analysis

Policy # 00498
Original Effective Date: 01/22/2016
Current Effective Date: 01/18/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"). unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers multispectral digital skin lesion analysis to be 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.

Background/Overview
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.

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 (ie, <1.0 mm) localized stage 1 cancers the 5-year survival rate is over 90% and this decreases to around 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 suggests 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.

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Another technology that can potentially improve melanoma detection and outcomes is MSDSLA. A U.S. Food and Drug Administration (FDA) approved MSDSLA 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). The 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 (ie, high degree of morphologic disorganization) or negative (ie, 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 details in the Regulatory Status section) is intended only for suspicious pigmented lesions on intact skin and for use only by trained dermatologists.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration

A multispectral digital skin lesion analysis device called MelaFind® (MELA Sciences, Irvington, NY) was approved by the FDA in November 2011. 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 (ie, dermatologists) and only those who have additionally successfully completed training on the MelaFind device. FDA documents further note:

"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.

Centers for Medicare and Medicaid Services (CMS)

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

**Rationale/Source**

This evidence review was created with a search of the MEDLINE database through November 4, 2015. In addition, material from archived policy 00025 was incorporated. Following is a summary of the key literature to date.

This review of evidence refers to the use of MSDSLA for the evaluation of pigmented lesions that are 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.
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**MSDLSLA for Evaluating Pigmented Skin Lesions**

**Diagnostic Accuracy**

As with any diagnostic tool, assessment of MSDLSLA 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 MSDLSLA would be used in combination with clinical assessment, either based on direct visual inspection or review of photographs. Therefore, the diagnostic performance of MSDLSLA 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 MSDLSLA versus standard care (clinical assessment alone, or clinical assessment and dermatoscopy) should be evaluated.

All published studies to date on MSDLSLA were industry-sponsored and/or had authors who were employees of or consultants for MELA Sciences.

A study published by Monheit et al in 2011 contained the data submitted to the 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 the 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, andineligibility after enrollment related to scarring. Histologic analysis determined that 127 of 1632 lesions (7.8%) were melanoma. The sensitivity of MSDLSLA 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 MSDLSLA 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 the lesions into 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 MSDLSLA (p=0.02). The Monheit study only included lesions that had previously been examined clinically and were determined to be sufficiently suspicious to warrant biopsy. The study did not include patients initially presenting with pigmented lesions to see whether MelaFind can enhance the accuracy of diagnosis based on clinical examination findings alone.
Subsequently, in 2015, Winkelmann et al 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 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). A total of 99 of these lesions (85%) were considered to be “true positives” (ie, malignant melanoma, lesions with atypical melanocytic proliferation, moderately and severely dysplastic nevi). The study population included only 1 melanoma and this was categorized by MSDSLA as having high disorganization. An advantage of this study was that it was prospective and conducted in a practice setting. However, as with the Monheit study, this study did not evaluate the ability of MSDSLA to enhance the accuracy of biopsy decisions.

Clinical Utility
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 that were managed with and without the technology. RCTs would ideally compare MSDSLA to clinical examination and dermatoscopy. No studies of this type were identified.

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 study was published in 2014 by Hauschild et al 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 et al trial, previously described. All lesions met the FDA-cleared 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 result (n=107). After reviewing each case, participants completed a survey about their lesion management decision (eg, 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 devices 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. The difference in sensitivity and specificity between arms was statistically significant (p<0.001).
Some nonrandomized studies have evaluated whether use of MSDSLA leads to management changes. In 2012, Wells et al published findings of a pilot study conducted over the Internet with a convenience sample of 39 dermatologists. A total of 47 lesions (23 malignant melanomas, 24 benign lesions) were randomly selected from the repository of lesions collected by MELA Sciences. Cases may have overlapped with the data used in the Monheit study, previously described. Dermatologists were given images of the lesions taken before biopsy and case histories, but were not given MSDSLA recommendations. Participants were asked whether they would recommend biopsy. MSDSLA recommended biopsy of 22 of 23 melanoma lesions (sensitivity, 96%; lower limit of 95% CI, 83%). The average biopsy sensitivity for dermatologists was 80% (95% CI, 72% to 87%). Regarding specificity, MSDSLA did not recommend biopsy for 2 of 24 benign lesions (specificity, 8%; 95% CI, 1% to 25%). In contrast, the biopsy specificity was 43% for dermatologists (95% CI, not reported). The authors did not report p values.

Methodologic limitations of both the Hauschild et al and Wells studies include conducting the study over the Internet, not in clinical settings; clinicians were also unable to examine patients or evaluate their lesions. Lesions presented to clinicians may not have been representative of lesions seen in clinical practice. Also, clinicians participating in the studies may not have been representative of typical dermatologists. In the Wells study, participants had expressed interest in MelaFind, and, in the Hauschild et al study, participants were those who responded to invitations sent to 1200 providers by MELA Sciences. In addition, the Hauschild and Wells studies used a subset of lesions from the Monheit study.2 As previously discussed, the Monheit study included patients with lesions scheduled for biopsy rather than lesions that had not yet been examined by a clinician.

Several industry-sponsored simulation exercises were conducted at professional conferences. For example, in 2015, Winkelman et al 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 dermatoscopic 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. Potential biases in these studies include a study design (simulation exercise) that may not reflect clinical practice and study location (conferences) at which sponsorship of the sessions was likely obvious, which can result in social desirability bias. In addition, along with the information from MSDSLA, participants were
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evaluating lesions for a second or third time; this reexamination might have affected biopsy recommendations.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**

The evidence for MSDSLA in patients who have pigmented lesions being evaluated for melanoma includes 2 prospective diagnostic accuracy studies and several online studies or simulation exercises addressing clinical utility. 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 included only lesions that had already been determined by a clinician to be sufficiently suspicious to warrant excision. The online randomized controlled trial included images of a subset of lesions from the diagnostic accuracy study. The sensitivity and specificity of a correct biopsy decision was significantly higher among dermatologists who had MSDSLA results than among those who only had clinical information and digital images. Study participants did not actually examine patients. There are no studies conducted in a clinical setting that evaluate the utility of MSDSLA as a diagnostic tool in the initial evaluation of pigmented lesions. In addition, there are no studies conducted in clinical settings that compared patient management decisions and health outcomes with and without these devices. The evidence is insufficient to determine the effects of the technology on health outcomes.

**References**

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01/07/2016 Medical Policy Committee review
01/22/2016 Medical Policy Implementation Committee approval. New Policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017 Medical Policy Committee review
01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 01/2018

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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