Anthem

Medical Policy

Subject: Noninvasive Imaging Technologies for the Evaluation of Skin Lesions
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Description/Scope

This document addresses the use of photographic, optical, video, and other imaging technologies for the evaluation of skin lesions.

For other documents addressing skin lesions, please see:

- CG-SURG-90 Mohs Micrographic Surgery

Position Statement

Not Medically Necessary:

Dermatoscopy (also known as dermoscopy, epiluminescence microscopy [ELM], or digital epiluminescence microscopy [DELM], skin surface microscopy, skin videomicroscopy, or incidence light microscopy) using either direct inspection, digitization of images, or computer-assisted analysis is considered **not medically necessary** in all cases.

Reflectance confocal microscopy for the evaluation of skin lesions is considered **not medically necessary** in all cases.

Investigational and Not Medically Necessary:

Whole body integumentary photography, including melanomagram, is considered **investigational and not medically necessary** in all cases.

The following technologies are considered **investigational and not medically necessary** for the evaluation of skin lesions:

A. Confocal scanning laser microscopy
B. Electrical impedance spectroscopy
C. Elastic scattering spectroscopy
D. Molecular fluorescent imaging
E. Multi-spectral image analysis
F. Multiphoton laser scanning microscopy
G. Optical coherence tomography
H. Photoacoustic microscopy
I. Quantitative infrared imaging
J. Raman spectroscopy
K. Ultrasonography
L. Visual image analysis

Rationale

Dermatoscopy

While there is extensive literature regarding dermatoscopy, the literature is inconclusive regarding its clinical role in the management of pigmented skin lesions, for instance, as a technique to select or deselect lesions for excision. At this time, there is insufficient evidence to support the use of this technology to improve outcomes either by reducing the frequency of unnecessary biopsies or by improving early detection of malignant melanoma.

The diagnostic performance of dermatoscopy combined with clinical assessment must be compared with clinical assessment alone and with the “gold standard,” histology. There are three clinical scenarios in which dermatoscopy might be of benefit:

> (1) Use of dermatoscopy to evaluate a lesion with low pretest possibility of malignancy to determine if excisional biopsy is necessary. In this scenario, the negative predictive value is the most relevant diagnostic parameter.
> (2) Use of dermatoscopy to evaluate multiple suspicious pigmented lesions to determine which of the multiple lesions are most clinically suspicious and in need of excision. In this scenario, the positive predictive value of dermatoscopy is the relevant diagnostic parameter. and
> (3) Serial assessment of lesions over time, as a means to prompt excision when a lesion changes in character in an individual with multiple pigmented lesions, or for lesions in a location difficult to excise. In this scenario, both the positive and negative predictive values of the results of serial imaging and clinical assessment are relevant.

Early prospective studies reported the sensitivity, specificity, and positive and negative predictive values with some conflicting results (Argenziano, 2006; Carli, 2003; Cristofolini, 1994; Wollina, 2007).

In 2018, Cochrane published a review on dermoscopy with and without visual inspection for diagnosing melanoma in adults (Dinnes, 2018a). The review included a literature search from the introduction of dermoscopy to August 2016. All studies that evaluated dermoscopy for diagnosing melanoma in adults compared with either clinical follow-up or histological confirmation were included. There were 104 studies with 42,788 lesions included in the analysis. Studies on the diagnosis being made face-to-face were separated from those based on remote assessment. Face-to-face diagnosis accuracy was significantly higher than remote assessment (relative diagnostic odds ratio [RDOR] 4.6; 95% confidence interval [CI], 2.4 to 9.0; $p<0.001$). The evaluators found dermoscopy to be more accurate than visual inspection alone during face-to-face assessments (RDOR 4.6; 95% CI, 3.0 to 7.5; $p<0.001$), and during remote assessments (RDOR 5.6; 95% CI, 3.7 to 8.5; $p<0.001$). For face-to-face assessments with dermoscopy, the predicted difference in sensitivity at a fixed specificity of 80% was 16% (95% CI, 8% to 23%; 92% for dermoscopy with visual inspection versus 76% for visual inspection), and predicted difference in specificity at a fixed sensitivity of 80% was 20% (95% CI, 7% to 33%; 95% for dermoscopy with visual inspection versus 75% for visual inspection). For remote assessment of dermoscopy, the predicted difference in sensitivity was 34% (95% CI, 24% to 46%; 81% for dermoscopy versus 47% for visual inspection), at a fixed

specificity of 80%, and predicted difference in specificity was 40% (95% CI, 27% to 57%; 82% for dermoscopy versus 42% for visual inspection), at a fixed sensitivity of 80%. While these findings are significant, there are concerns with the applicability. Most of the studies included were either case-control or case-series studies. Other areas of concern as noted by the evaluators include “selective participant recruitment, lack of reproducibility of diagnostic thresholds and lack of detail on observer expertise” (Dinnes, 2018a).

Another Cochrane review published in 2018 reported on visual inspection and dermoscopy, alone or in combination, for diagnosing keratinocyte skin cancers in adults (Dinnes, 2018b). The literature search, which included studies from the introduction of dermoscopy to August 2016 that evaluated dermoscopy, visual inspection, or both in adults with lesions suspicious for skin cancer compared with either clinical follow-up or histological confirmation, yielded 24 studies with 27 visual inspection datasets (8805 lesions; 2579 malignancies) and 33 dermoscopy datasets (6855 lesions; 1444 malignancies). Studies on the diagnosis being made face-to-face were separated from those based on remote assessment; however, no significant difference was found between the accuracy of the two. Face-to-face evaluations of dermoscopy was more accurate than visual inspection alone in the detection of basal cell carcinoma (RDOR of 8.2, 95% CI, 3.5 to 19.3; p<0.001). “This corresponds to predicted differences in sensitivity of 14% (93% versus 79%) at a fixed specificity of 80% and predicted differences in specificity of 22% (99% versus 77%) at a fixed sensitivity of 80%” (Dinnes, 2018b). The data showed very similar results for the remote assessments. There was insufficient data in the included studies to draw conclusions on the accuracy of dermoscopy through face-to-face or remote assessment for the detection of cutaneous squamous cell carcinomas. Limitations to this review and the applicability of the results include most of the studies included being either case-control or case-series studies, potential bias participant recruitment due to selection processes, lack of reproducibility of diagnostic thresholds, and unclear observer expertise.

There are no conclusive data regarding the role of serial dermatoscopic monitoring compared to serial clinical monitoring. In addition, there is insufficient data to assess the impact of dermatoscopy on skin cancer-related morbidity and mortality.

Reflectance confocal microscopy

The peer-reviewed literature investigating reflectance confocal microscopy (RCM) as a technology for the evaluation of skin lesions mainly consists of case-series and retrospective studies. There have been multiple combined systematic reviews and meta-analyses conducted to evaluate RCM for melanoma, basal cell carcinoma [BCC], and cutaneous squamous cell carcinoma [cSCC]), either alone or with dermoscopy (Dinnes, 2018b, 2018c, 2018d; Edwards, 2017; Pezzini, 2020; Xiong, 2016). These studies reported widely varying sensitivity and the specificity results, and the authors noted significant flaws in the body of evidence, including significant risk of bias, wide variation in study design, lack of reporting on provider training, and unclear study details such as population eligibility. The majority of studies were assessed to have high or unclear potentials for bias in relation to the applicability of the evidence.

To date, the most robust study was published by Pellacani (2022), who reported the results of a prospective RCT involving 3165 participants with dermascopically equivocal skin lesions. Participants were assigned to follow-up with RCM (n=1583) or to standard care without RCM (n=1582). Participants whose skin lesions did not have unequivocal clinical or RCM features of malignancy were referred to short (3-6 month) or long (≥ 12 months) dermoscopic digital follow-up based on their physicians’ level of uncertainty about the malignant potential of their lesion. The mean follow-up period for participants who did not receive immediate excision was 9.6 months. In the RCM group, 45.5% were sent for immediate excision. RCM group members who did not receive immediate excision were assigned to short-term dermoscopic digital follow-up. Within this group, 17.9% eventually had their lesion excised. Melanoma was confirmed in 33.2% of excised lesions assessed with adjunctive RCM, with 51.8% of those being melanoma in situ. All participants in the control group (except 8 who declined) received lesion excision and histopathology. Melanoma was detected in 18.6% of those lesions, with 60.5% classified as melanoma in situ. In the overall study population, melanoma was identified in 23.9% of lesions, with a number needed to excise determined to be 4.2 and overall positive predictive value (PPV) of 23.9%. Compared with standard care only, the adjunctive use of RCM was associated with a significantly lower excision rate (52.8% vs. 98.4%) with a lower rate of benign lesion excisions (benign-to-malignant ratio 1.8 with RCM vs 3.7 without RCM). The number of lesions needed to excise to detect one malignancy was also reduced by 43.2% (3.0 with RCM vs 5.3 without). The authors concluded, “…adjunctive use of RCM for suspect lesions reduces unnecessary excisions and assures the removal of aggressive melanomas at baseline in a real-life, clinical decision-making application for referral centers with RCM.” However, as they noted, this study does not address overdiagnosis or the generalizability of their findings to centers without extensive RCM experience. The short follow up in this study does not permit conclusions about the long-term effects of this diagnostic method on health outcomes.

Overall, the current published literature on RCM for the evaluation of skin lesions lacks credible data that permits reasonable conclusion concerning effect of this technology on health outcomes. Well-designed and executed prospective RCTs are needed in order to assess the clinical utility of this technology.

Whole body integumentary photography

The body of evidence addressing the use of whole body integumentary photography (also known as whole body photography or TBP) is limited. Only three peer-reviewed articles discuss the results of clinical trials using TBP (Feit, 2004; Menon, 2006; Risser, 2007). The first two studies lack control groups, do not address specificity or sensitivity issues, and do not report any data regarding alterations in health outcomes as a result of the use of this technique. The third study, by Risser and colleagues, retrospectively investigated the impact of TBP on the clinical treatment of individuals seen in a pigmented lesion clinic. The authors reviewed the charts of 64 subjects who had undergone TBP and 64 who had not. The authors report that TBP had no impact on the number of biopsies or on the number of dysplastic nevi diagnosed in the first year of the clinic. As such, the clinical utility is questionable. Further evidence from well-controlled prospective trials is needed to properly evaluate the net health outcomes of TBP.

Another device, the DZ-D100 DERMOCAMERA™ and the DZ-S50 scope (Casio America, Inc., Dover, NJ) obtained FDA clearance in 2022 for skin observation and delivers both standard sized and close-up shots of an affected area with a single unit. It can be used with the D'z IMAGE Viewer, a free downloadable software that manages the captured images. According to the manufacturer, the unit can capture polarized, non-polarized and UV photos at the same viewpoint with a single click of the shutter button. According to the user’s manual, “This product is not a diagnostic device and should only be used for observing skin lesions. This product is a digital camera for dermal observations and is intended for photographing the surface of the skin over the entire body.” Given this statement, the role of this device in clinical practice is unclear, and warrants robust evaluation in well-designed and conducted trials that permit reasonable conclusions concerning the effect of the device on health outcomes.

Ultrasonography

Ultrasonography (US) has been proposed for use in the assessment of skin tumors. US has been described as a tool for differentiation of common benign pigmented skin lesions from melanoma. There are only a few weak RCTs currently available in the literature describing this technique. US has also been used in the preoperative measurement of melanoma thickness in preparation for lesion excision. The studies addressing this procedure have been small nonrandomized controlled studies and the impact of US assistance in melanoma excision planning was not addressed in relation to any potential decrease in repeat excisions or other outcome measures. Other studies have investigated the use of US in the assessment of inflammatory skin lesions and connective tissue diseases. The evidence is limited to poorly designed and conducted case series studies that do not evaluate the impact of US

on net health outcomes or on clinical management. Additional research is needed to establish the clinical utility of US for evaluation and management of skin lesions.

Electrical Impedance Spectroscopy (EIS)

The Nevisense™ System (Scibase AB, Stockholm, Sweden) is a non-invasive test proposed for early detection of malignant melanoma. This test uses EIS to measure resistance between two electrodes in contact with the epidermis to detect irregularities in electrical conductivity that are associated with skin tumors. In June 2017, the FDA granted premarket approval for the Nevisense system for the following indications:

> 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 (that is, 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 (that is, not for use on acral skin, genitalia, eyes, mucosal areas).

There is very little published evidence regarding this technology, and studies are still investigating the role of EIS in the diagnosis of melanoma.

Malvehy (2014) reported the results of a large multicenter blinded study involving 1943 lesions suspected of being melanoma and scheduled for excision. The lesions represented a mix of clinically designated low-, medium-, and high-risk lesions. All lesions were evaluated with EIS, dermoscopy, photography, histopathology, and reviewed by blinded panels of experts. An EIS score ≥ 4 was considered EIS positive, indicating higher risk for melanoma. The authors reported 265 histopathology identified melanomas (13.2%) and 55 non-melanoma skin cancers (2.8%). EIS correctly identified 256 melanomas and all 55 non-melanoma malignant lesions resulting in a sensitivity of 96.6% for melanoma and 100% for non-melanoma lesions. The authors identified 157 nevi with severe dysplasia, of which 132 were identified as malignant by EIS. Additionally, 7 out of 8 actinic keratoses were identified by EIS. A single Merkel cell carcinoma was included and correctly identified by EIS as malignant. EIS resulted in 9 false negatives for melanoma. Out of the remaining 1457 lesions, 501 were diagnosed as negative, yielding an observed specificity of 34.4%. The authors reported a PPV for EIS of 21.1% and negative predictive value (NPV) of 98.2%. For ABCD (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter > 6 mm) dermoscopy, the specificity of melanoma detection with cut-offs of 4.75 and 5.45 was reported to be 54.2% and 47.1%, respectively. Sensitivity was 90.1% and 94%, respectively. The authors concluded that EIS was safe and effective, and should be used in conjunction with clinical risk assessment for the evaluation of melanoma. The results of this study are of interest but did not address the incremental benefit of the addition of EIS to clinical risk assessment. Further, this study involved the use of lesions suspected of malignancy and already chosen for excision. It did not involve the identification of equivocal lesions, where the use of this adjunctive technology would be most helpful.

Rocha (2017) reported the results of a prospective case series study involving 118 subjects presenting with 171 suspicious lesions during routine dermatological visits. A total of 160 lesions were evaluated with both short-term sequential digital dermoscopy imaging and EIS. Eleven lesions were not included in the study due to features unfavorable to the use of EIS. Both dermoscopy and EIS were conducted at the first visit and all lesions were assigned an EIS score. A score of < 4 was considered low risk for melanoma, a score of 4-6 was considered to indicate intermediate risk with a positive predictive value of melanoma estimated to be 9-18%, and score ≥ 7 indicating a high probability of melanoma. Lesions with a score ≥ 7 were excised immediately. Lesions with score of 0-6 were monitored for 3 months with sequential dermoscopy. Lesions that changed during the monitoring period were excised. Continued monitoring was performed for other lesions. A total of 31 lesions had an EIS score ≥ 7 and were immediately excised. Five (16.1%) of these lesions were diagnosed as melanoma, 22 (71.1%) as dysplastic nevi, and 4 (12.9%) as benign nevi. Out of the 154 benign lesions found, 128 had an EIS score 0-6, resulting in a specificity of EIS to diagnosing melanoma at the ≥ 7 cut-off of 83.1%. Five of the 6 melanomas (83.3%) found in this study had an EIS score ≥ 7. The single melanoma lesion not scored at least a 7 was scored a 6 and was identified as melanoma by dermoscopy near the end of the trial period. Of the lesions with an intermediary score, 61 lesions did not change on further dermoscopy. Of the 24 that did have subsequent changes and were excised, only 1 (4.2%) was a melanoma. The remaining were dysplastic nevi (n=17) and benign nevi (n=6). Of the 44 lesions that had an EIS score of 0-3, none were melanoma. Three lesions underwent subsequent changes identified by dermoscopy and were identified as nevi on histology. Overall, only 3 of 43 (7.0%) nevi with an EIS score of 0-3 changed on follow-up dermoscopy compared to 21 of 82 (25.6%) nevi with an EIS score of 4-6 (p=0.01). The authors reported that the sensitivity and specificity of combined short-term sequential digital dermoscopy imaging and EIS for the diagnosis of melanoma was 100% and 69.5% and that it significantly reduced the need for short-term sequential digital dermoscopy in routine practice by 46.9%. Limitations of this study include the short 3-month follow-up period, lack of blinding, small study size, and the lack of power needed to accurately assess sensitivity. The authors concluded, “Further studies in other centers with larger samples are also needed to confirm the role of EIS in investigating suspicious melanocytic lesions using this protocol.”

Zakria (2023) reported the results of a survey-based study involving 231 dermatologists who were shown images of 49 skin lesions including melanoma, severe dysplastic nevi, and benign pigmented skin lesions. The study’s goal was to assess whether the addition of EIS can improve correct biopsy choices beyond clinical and dermoscopic evaluations. Participants were provided with clinical photographs, dermoscopic images, and EIS results for all 49 skin lesions and asked to determine if they would biopsy the lesion after each viewing, resulting in 33,957 decisions in total. The results indicated that the addition of dermoscopic images significantly improved the correct biopsy choice above clinical photographs alone (85.2% vs. 79.9%, respectively for melanoma [p<0.01]; and 69.3% vs. 59.7% respectively for severely dysplastic nevi [p<0.01]). Addition of EIS scores further significantly improved correct biopsy choices beyond the result of clinical photographs plus dermoscopic images (91.1% vs. 85.2% respectively for melanoma [p<0.01]; and 79.1% vs. 69.3%, for severely dysplastic nevi [p<0.01]). Selection of correct choice for benign lesions was likewise significantly improved (40.2% vs. 35.0%, p<0.01). Selection of incorrect choice was similarly improved as well with the addition of the EIS score to dermoscopy and clinical image compared to dermoscopy and clinical image for melanoma (8.9% vs. 14.8%, p<0.01), benign dysplastic nevi (20.9% vs. 30.7%, p<0.01) and benign lesions (58.5% vs. 65.1%, p<0.01). The authors noted that up to one-third of early melanomas may be initially undetected, even by dermatologists with experience in managing pigmented skin lesions and assert that the addition of dermoscopy and EIS may improve clinical decision-making processes. This paper is a “short communication” published without extensive description of materials and methods. Participating dermatologists were recruited at a single clinical conference. The qualifications of the participating dermatologists are not described. There is no description of objective

diagnostic criteria or inter-rater assessments. Additionally, this study did not involve the evaluation of actual lesions and the authors state that “actual biopsy behavior could be different in the clinical setting.” Further study involving prospective evaluation of the utility of EIS in a variety of actual clinical settings is needed to confirm this study’s results.

Two similarly designed studies were published as letters in the Journal of the American Academy of Dermatology. The first, by Svoboda (2019), involved 164 dermatology trainees evaluating 45 lesions. They reported that the addition of EIS improved biopsy decisions of dermatology trainees in 24.3% of cases, resulting in 402 fewer missed melanomas and a net decrease of 376 benign biopsies ($p<0.001$). The addition of EIS score improved the mean sensitivity of respondents for ruling out melanoma from 80.7% to 95.2% ($p<0.001$) and mean specificity from 50.4% to 58.6% ($p<0.001$). A study by Litchman (2021) involved 267 practicing dermatologists evaluating 43 lesions. They reported that incorporation of EIS scores significantly improved the number needed to biopsy from 6.3 to 5.3 ($p<0.001$), sensitivity from 84% to 98% ($p<0.001$), and specificity from 34% to 44% ($p<0.001$). They reported that addition of EIS resulted in an additional 581 melanomas correctly selected for biopsy and 782 unnecessary biopsies avoided. Finally, EIS resulted in a significant increase in biopsies for melanomas with the fewest ABCD characteristics and a similar significant decrease in biopsies for benign lesions with the greatest number of ABCD characteristics. As with the Zakria study discussed above, these two additional studies shared similar shortcomings, including lack of publication in full-text format with a thorough description of the material and methods, not using lesions in situ, lack of an inter-rater assessment, and no objective diagnostic criteria. The Svoboda study involved the online recruitment of dermatology residents, with no description of stage of training or at what facilities they were located. The Litchman study involved practicing dermatologists but provided no description of their qualifications. While these studies provide interesting results, they should be confirmed in studies that permit reasonable conclusions concerning the effect of the device on health outcomes and published in a format that allows full evaluation of their quality.

Overall, the available evidence does not permit reasonable conclusions about the effect of EIS testing on health outcomes. The clinical utility of EIS in clinical practice has not been prospectively demonstrated in rigorously designed and conducted clinical trials. Specifically, it is not known whether the use of EIS results in decreased biopsy rates and, more importantly, improved health outcomes such as decreased mortality. Data regarding the use of EIS used without dermoscopy is needed to establish the utility of this technology outside of the investigational and specialist dermatological settings.

Raman Spectroscopy

The use of Raman spectroscopy has primarily been limited to the experimental and laboratory settings. However, a limited number of clinical trials have been published addressing the use in the clinical setting.

Lui (2012) described the results of a single-center study involving 518 discrete skin lesions amenable to spectral characterization. Lesions included in the study were malignancies and premalignancies that required treatment, malignant melanoma, BCC, SCC, actinic keratosis, and benign conditions that can visually mimic skin cancer. Definitive diagnosis for each lesion was established via clinical evaluation and/or histopathologic analysis when a biopsy sample was available. All lesions suspected of being cancerous were confirmed by skin biopsy. Dermoscopy was not used for final diagnosis in this study. A total of 313 lesions (60%) underwent subsequent treatment, including 44 malignant melanomas, 47 SCCs, 109 BCCs, and 32 actinic keratoses. The authors observed an ROC (Receiver Operating Characteristic) AUC (Area Under the Curve) of 0.879 for Raman spectroscopy when used to distinguish cancerous and precancerous skin lesions from benign skin lesions ($p<0.001$). At a sensitivity of 90%, specificity was 64%, PPV was 67% and NPV was 89%. An analysis done reclassifying actinic keratosis as benign found an AUC of the ROC curve of 0.863 with a sensitivity of 90%, specificity 63%, PPV of 60%, and NPV of 91%. When used to discriminate between malignant melanoma and nonmelanoma pigmented skin lesions, Raman spectroscopy resulted in an ROC AUC of 0.823 with sensitivities between 99% to 90% and specificities from 15% to 68%. When used to discriminate between malignant melanoma and seborrheic keratosis, Raman spectroscopy resulted in an AUC ROC of 0.898 and sensitivities ranging from 99% to 90% and specificities of 25% to 68%. The authors concluded that Raman spectroscopy can distinguish malignant melanoma from benign skin lesions with accuracy comparable to other optical based methods. However, it should be noted that this study was limited to the use of highly selected lesions for which treatment was already determined and reviewers were not blinded. The results of this study need to be confirmed in a more rigorous trial with blinded evaluators in a variety of clinical settings and using direct comparison to histopathology.

At this time, the clinical utility of Raman spectroscopy has yet to be determined and investigation in rigorous, well designed and conducted trials that permit reasonable conclusions concerning the effect of the device on health outcomes is needed.

Optical Coherence Tomography (OCT)

OCT has been investigated as a tool for the evaluation of suspicious skin lesions in several studies. Ulrich (2015) assessed the sensitivity and specificity of OCT in a prospective multicenter case series study involving 164 subjects with 256 nonpigmented pink lesions suspected of BCC and requiring biopsy. All lesions were examined clinically. Clinically suspicious lesions were then examined with dermoscopy, photography, and OTC before progressing to biopsy, histology, and excision when warranted. Sensitivity for clinical examination only was calculated to be 90.0%, 90.6% with the addition of dermoscopy, and 95.7% with the addition of OCT. Specificity for clinical examination alone was 28.6%, 54.3% for dermoscopy, and 75.3% with the addition of OCT ($p<0.001$ between clinical exam and OCT). Overall, the accuracy of diagnosis for BCC increased from 65.8% for clinical examination alone to 87.4% with the addition of OCT. Given that all suspicious lesions need biopsy, sensitivity is more important than specificity for this test. Sensitivity was not significantly different between clinical evaluation, dermoscopy, and OTC. Another limitation of this study is its observational nature without randomized comparison of diagnostic approaches.

Holmes (2018) evaluated factors influencing OCT performance. A total of 100% of the 12 infiltrative BCC lesions were correctly identified as BCC by clinical examination, dermoscopy and OCT. However clinical diagnosis correctly identified only 39% of actinic keratosis as not BCC vs. 81% with OCT. They also reported that OCT image quality was correlated with improved diagnostic performance, and lesions with mediocre image quality were reported to still be better than either clinical examination or dermoscopy. The authors noted that the sample size for several types of lesions that can mimic BCC was too small to draw conclusions about OCT performance in their diagnosis. They also noted that the study was conducted by specialized dermatologists and that the results may not represent performance that would be seen in more general practice. Since 66% of histology findings were obtained from biopsies, rather than excisions, it is possible that the true number of BCC lesions was underrecognized.

Adan (2022) reported the results of a prospective investigator-blinded non-inferiority RCT involving 598 subjects who underwent diagnosis of BCC via OTC or biopsy ($n=299$ for each group). All participants had a BCC-suspected lesion identified by both clinical examination and dermoscopy. Lesions with obvious BCC on clinical examination or dermoscopy, lesions in the H (high risk) zone of the face, and locally advanced lesions were excluded from the study. Participants were randomized to be evaluated by punch biopsy (standard care group), or by OTC. One expert dermatologist performed all OTC assessments and graded diagnostic confidence on a 5-point Likert scale. Confidence was considered insufficient for 103 of the 299 participants in the OCT group. These participants had further treatment guided by biopsy. For participant safety, all members of the OTC group received punch biopsies, but the biopsy result was withheld unless confidence in the OCT result was considered insufficient, or unless an independent monitor not otherwise involved in the study determined that urgent treatment was needed. Reexamination of the lesion site was done at a mean of 12 months following evaluation. In the OCT group, a high confidence diagnosis of BCC and BCC subtype could be made in 66% of

subjects. The remaining 34% of subjects still required a biopsy to establish a diagnosis. The primary outcome was the proportion of subjects remaining free from recurrent or residual lesions 12 months after initiation of treatment. At follow-up, the biopsy group retained 93.6% of subjects while the OTC only group had 57.5% of the original subjects. For the OTC plus biopsy group, 88.3% of original subjects were retained. Histopathology identified BCC in 75% of subjects in the OCT group and 72% of subjects in biopsy group. A total of 45% of subjects in the OCT group and 51% in the biopsy group received non-invasive treatment with imiquimod for histologically superficial BCC. The modified intent-to-treat (ITT) analysis included 553 subjects who had primary endpoint data available (n=268 in the OCT group and n=285 in the biopsy group). At the 12-month follow-up, 94% of OCT group subjects were free from a recurrent or residual lesion vs. 93% of biopsy group subjects (p=0.30). Malignant recurrent or residual lesions were reported in 60% of OTC subjects and 79% of biopsy group subjects. In the per-protocol population 95% of OCT group subjects and 94% of biopsy group subjects were free from a residual or recurrent lesion (p=0.34). Malignant recurrent or residual lesions were reported in 61.5% of OTC subjects and 82.3% of biopsy group subjects. In the OCT group there were 225 histologically verified BCCs with 192 detected with OTC with high confidence, corresponding to a sensitivity of 85.3%, specificity of 94.6%, positive predictive value of 98%, and negative predictive value of 68.0%. The authors concluded that the findings of this study showed that “OCT-guided diagnosis and treatment is non-inferior to regular care and does not compromise patient safety". However, the authors noted that “… the result strongly hinge on the OCT diagnoses made by a single, experienced physician, who had evaluated 500 scans before the start of the study”, indicating that success was potentially highly correlated with OCT operator experience. The study also excluded subjects with large lesions and lesions located on the H-zone of the face, which are at high risk of BCC.

Overall, the use of OCT in the evaluation of BCCs is promising, but further investigation in large, population-based studies is warranted. OTC has not yet been accepted as standard practice for diagnosis of BCC, nor for any other type of skin lesion.

Other Technologies

A wide variety of other non-invasive technologies have been proposed for the evaluation of skin lesions, including the following:

- Confocal scanning laser microscopy
- Elastic scattering spectroscopy
- Molecular fluorescent imaging
- Multi-spectral image analysis
- Multiphoton laser scanning microscopy
- Photoacoustic microscopy
- Quantitative infrared imaging
- Visual image analysis

At this time, there are no rigorous, well-designed, and conducted trials evaluating the accuracy, clinical utility, or safety of these technologies. Such investigations are needed to adequately assess these factors before they should be used in routine clinical care outside the investigational setting.

Use of Artificial Intelligence (AI)

The use of AI-powered skin image (dermoscopy) analytics for evaluation of skin lesions is an area of ongoing investigation. Available technologies (e.g., Belle Dermoscopy AI) involve the use AI software to compare dermoscopy images of pigmented lesions obtained via pocket dermatoscope or smartphone to possible similar dermoscopy reference text and images including actinic keratosis, angioma and vascular lesions, squamous cell carcinoma. basal cell carcinoma, melanoma, and atypical moles. Use of the technology is proposed to provide an improved ability to detect abnormalities, classify lesion types, and assess lesion risks of malignancy. Such devices may be used by a lay person, non-dermatologist healthcare provider, or a dermatologist.

Menzies (2023) reported a multicenter, prospective study evaluating two experimental mobile-phone-based AI algorithms, the 7-class AI algorithm and the International Skin Imaging Collaboration (ISIC) AI algorithm. Use of a simple optical attachment was required during the trial. The study had two parts. The first was a diagnostic trial involving participants undergoing routine excision or biopsy of one or more suspicious pigmented skin lesions bigger than 3 mm in the longest diameter. The second part was a management trial involving participants who had baseline total-body photographs taken within 1-4 years. All participants had a modified Fitzpatrick I-III skin type. The diagnostic portion of the report included 172 suspicious pigmented lesions (84 malignant) from 124 participants. The management portion included 5696 pigmented lesions (18 malignant) from the whole body of 66 high-risk participants. Algorithm results were compared to the decisions of both specialist and novice clinicians. The authors reported that use of the 7-class AI algorithm in the diagnostic portion was equivalent to specialists' decisions (absolute accuracy difference 1.2%), and significantly superior to the novices' decisions (21.5%). The diagnoses of the ISIC algorithm were significantly inferior to the specialists' decisions (-11.6%) but significantly superior to the novices' decisions (8.7%). In the management portion of the trial, the best 7-class result was significantly inferior to specialists' management (0.5% in cases where the decision was to monitor or dismiss the case, and -0.4% in cases where biopsy was indicated). Compared with the novices' management, the 7-class algorithm was significantly inferior in cases where the decision was to monitor or dismiss the case (-0.4%) but significantly superior (0.4%) in cases where the decision was to biopsy. The authors observed, “An AI algorithm that was superior in experimental studies was significantly inferior to specialists in a real-world scenario, suggesting that caution is needed when extrapolating results of experimental studies to clinical practice.” These findings emphasize the need for caution with regard to adoption and use of such technologies.

Finally, an important issue not yet evaluated in the literature is whether performance of such algorithms varies depending on skin tone or other factors, and result in systematic false-positive or false-negative results. Overall, additional data is needed to establish whether this technology improves net health outcomes.

Authoritative Organization Recommendations

The American Academy of Dermatology (AAD) in its guideline on 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 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 and to guide the need for further biopsy…The AAD makes no recommendation on their use as evidence regarding effectiveness, clinical utility, and competing strategies is needed.

The National Comprehensive Cancer Network (NCCN) only addresses these technologies in their guideline on cutaneous melanoma (V2.2023). They state:

> Pre-diagnostic clinical modalities (ie, dermoscopy, total-body photography and sequential digital dermoscopy), noninvasive imaging and other technologies (eg, reflectance confocal microscopy, electrical impedance

spectroscopy) may aid in surveillance for new primary melanoma, particularly in patients with high mole count and/or presence of clinically atypical nevi.

However, this is not a strong recommendation, and they do not provide an evidentiary basis for this statement.

In 2023 Kashani-Sabet published a consensus statement from the Melanoma Prevention Working Group (MPWG) addressing the early detection and prognostic assessment of cutaneous melanoma. Among 42 respondents involved in the modified Delphi method process, the majority reported experience using dermoscopy (81%) and all respondents supported the use of dermoscopic examination to evaluate patients with no new, changing, or unusual skin lesions or with a new lesion that is not visually concerning. It was also supported for new, but not visually concerning, lesions, and a new and visually concerning lesions. For RCM, the majority of panelists did not have experience with that technology (14%) and there was not majority support for the use of RCM as a first-line technique for the evaluation new or suspicious lesions. They did reach consensus that clinically suspicious lesion with likely benign RCM findings would not need a biopsy and could be followed with repeated visual examination. None of the respondents reported experience using EIS, and the majority did not support its use for any indication.

Background/Overview

Of the three main types of skin cancer, melanoma is the most aggressive and accounts for approximately 75% of all skin cancer related deaths. Treatment of melanoma is highly successful if caught early. The gold standard for evaluation of pigmented skin lesions is excision with examination of the lesion under a microscope for diagnosis. The sensitivity and specificity are nearly 100% for a skilled pathologist. The early phase of malignant melanoma can be particularly difficult to identify since malignant melanomas of skin can share many clinical features with atypical birthmarks, moles, or other benign skin lesions. Because of this diagnostic difficulty, multiple tools have been proposed in order to improve the accuracy of diagnosis of malignancies in pigmented skin lesions and therefore improve health outcomes, without necessarily requiring biopsy or excision of lesions for testing.

Dermatoscopy, epiluminescence microscopy (ELM), and the other techniques mentioned in this document have been introduced as non-invasive aids in the visual examination of pigmented skin lesions in-vivo (on the individual's body). While dermatoscopy is extensively used in Western Europe, it has gained only limited acceptance in the U.S. It is considered to be an extraneous diagnostic step in the work-up of suspected melanoma.

In addition, the use of the dermatoscope requires adequate training and experience to use it effectively and studies have shown that its use by practitioners without adequate training actually decreases diagnostic accuracy below that obtained from clinical examination alone. The brand names of epiluminescence microscopes that are available include, but are not limited to, the Nevoscope$^{\hat{O}}$, the Episcope$^{\hat{O}}$, the Dermascope$^{\hat{O}}$, and MoleMax$^{™}$.

Dermatoscopy and all its forms use magnification of in vivo skin lesions for better visualization of surface and subsurface structures without requiring excision. This diagnostic tool permits the recognition of morphologic structures not visible to the naked eye. The technique involves placing mineral oil, alcohol or water on the skin lesion and inspecting it using a hand-held lens, a hand-held scope, a stereomicroscope, a camera, or a digital imaging system. The magnifications of these various instruments range from 6x up to 100x. The most commonly used dermatoscope has a 10x magnification. The fluid placed on the lesion eliminates surface reflection and renders the hardened external layer translucent, thus allowing a better visualization of pigmented structures within the epidermis, the dermoepidermal junction and the superficial dermis. Moreover, size and shape of vessels of the superficial vascular plexus can be easily visualized by this procedure. Dermatoscopy is proposed to increase the accuracy of the clinical diagnosis of pigmented lesions and particularly to aid in the early recognition of malignant melanoma.

Reflectance confocal microscopy (RCM), which is also known as confocal laser scanning microscopy and confocal microscopy, is a microscopic technique that visualizes deep layers of the skin and provides a more detailed, magnified evaluation of potential lesions than other microscopic techniques. It has been evaluated as a possible alternative or adjunct to dermoscopy for the evaluation of skin lesions. While RCM is painless, it is more time consuming and requires additional training than other microscopic technologies.

Whole body integumentary photography involves photographing an individual's entire body surface. Photographs may be taken using either conventional or digital photography. The purpose of this procedure is to attain a visual record of the skin with the hope of being able to compare with future examinations to assist in the identification of new or changed skin lesions. This technology has been proposed as a tool in the management of individuals at high risk for skin cancer.

Ultrasound (US) imaging is a method of obtaining images from inside the body through the use of high frequency sound waves. Sound waves are emitted by a handheld probe and penetrate the body without any discomfort or sensation. These sound waves are reflected by the structures inside the body and received by a receiver in the probe. The echoes are then processed by a computer and displayed as a real-time visual image on a monitor. The image that is displayed shows movement of internal structures of the body as they occur, including blood flow in the veins and arteries, aiding diagnosis of a variety of conditions. US for use in evaluating skin lesions has been proposed as a method to allow assessment of blood supply, thickness, and depth of the growth into the skin.

Electrical Impedance Spectroscopy (EIS) utilizes an electrical current run between two electrodes when in contact with a skin lesion. EIS devices evaluate the resistance between the electrodes and irregularities in electrical conductivity to detect potential skin cancers and other types of lesions.

A wide variety of other light-based spectrograph-based technologies have been proposed for the evaluation of skin lesions. Such technologies are based on the premise that light is scattered differently by cancerous and pre-cancerous skin cells compared to normal cells. The use of these types of technologies involve the use of a specialized light source, a light-detecting sensor, and computer to evaluate light scattering patterns in the evaluated lesions.

Definitions

Dermatoscope: A hand-held device used for the examination of the structures of the epidermis and epidermal-dermal junction using magnification of about 10x.

Dermatoscopy (Dermascopy, Dermoscopy, DS): A family of noninvasive techniques (skin videomicroscopy, epiluminescence microscopy [ELM], incident light microscopy, skin surface microscopy) that allow microscopic examination of skin lesions. These techniques are intended to help distinguish between benign and malignant pigmented skin lesions using a dermatoscope, stereomicroscope, camera, or a digital imaging system. The magnifications of these various instruments range from 6x to 40x and up to 100x.

Dermoscopy (DS): Another name for Dermatoscopy; see Dermatoscopy.

Digital epiluminescence microscopy (D-ELM): A version of dermatoscopy that involves using digital photography of the dermatoscopic images; the computerized digital images are stored for comparison of the skin lesion(s) at a later date.

Epiluminescence microscopy (ELM): Another dermatoscopic technique that allows microscopic examination of skin lesions directly on the person, without requiring excision.

Incidence or incident light microscopy: Another term sometimes used for dermatoscopy, dermoscopy or ELM.

Melanomagram: A whole-body image produced by using a digital-picture dermatoscope (MoleMax). A full set of digital computer images are evaluated for the presence of skin lesions and then digitally archived for future use. These images are used to do side-by-side comparisons of past and current images to determine changes in size, color, or other skin cancer risk factors.

Reflectance confocal microscopy: A technique performed with a hand-held device that uses infrared light to visualize deeper layers of the skin than compared to other microscopy technologies.

Skin fluorescent imaging (SFI): Refers to the Orlucent® System (Orlucent, Inc. Los Gatos, CA), which is a hand-held molecular-based imaging system that is intended for in-office use in the clinical assessment of suspicious moles prior to biopsy. The Orlucent system uses a novel fluorescent biotag that is topically applied to non-invasively detect a biomarker of early tissue changes that occur during a mole's transition from benign to atypia. Full FDA clearance for this device is pending.

Skin surface microscopy: Another name for dermatoscopy.

Ultrasonography: The diagnostic or therapeutic use of ultrasound, which uses sound waves to create two-dimensional images used for the examination and measurement of body structures and the detection of abnormalities.

Videomicroscope, videomicroscopy, or videodermatoscopy: A technique that uses a video-microscope linked to a computer that generates a melanomagram of the whole body or body region.

Whole body integumentary photography**:** A procedure where the entire skin surface of an individual is photographed. The purpose of this procedure is to provide a reference source of skin lesions over time; pictures may be conventional pictures or digital images stored electronically; also see melanomagram.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.

When services are Not Medically Necessary:

CPT	
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
96935	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition only, each additional lesion
96936	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, each additional lesion
96999	Unlisted special dermatological service or procedure [when specified as dermatoscopy techniques such as dermoscopy, epiluminescence microscopy, or digital epiluminescence microscopy, skin surface microscopy, skin videomicroscopy, incidence light microscopy or reflectance confocal microscopy not generating mosaic images]

ICD-10 Diagnosis	
	All diagnoses

When services are Investigational and Not Medically Necessary:

CPT	
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
96999	Unlisted special dermatological service or procedure [when specified as other technologies such as confocal scanning laser microscopy, elastic scattering spectroscopy, multi-spectral image analysis, multiphoton laser scanning microscopy, OCT, photoacoustic microscopy, quantitative infrared imaging, Raman spectroscopy, ultrasonography or visual image analysis of the skin for skin lesions]
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score
0700T	Molecular fluorescent imaging of suspicious nevus; first lesion
0701T	Molecular fluorescent imaging of suspicious nevus; each additional lesion

ICD-10 Diagnosis	
	All diagnoses

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Electrical Impedance Spectroscopy (EIS)
Epiluminescence Microscopy
Episcope
Incident Light Microscopy
International Skin Imaging Collaboration (ISIC) AI algorithm
MelaFind®
Melanomagram
MicroDERM®
Mirror Body Mapping
MoleMap
MoleMax
Molesafe™
Nevisense System
Nevoscope
Orlucent system
Reflectance Confocal Microscopy
Skin Imaging Collaboration (ISIC) AI algorithm
Skin Surface Microscopy
SIAScope II®
Total Body Photography
Ultrasound
Video Microscopy
VivaScope®

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale, References, Websites, and Index sections.
Revised	05/11/2023	MPTAC review. Revised document title. Added additional technologies to INV and NMN section. Updated Description/Scope, Rationale, Background, Coding and References sections.
Reviewed	05/12/2022	MPTAC review. The Rationale, Definitions, References and Index sections were updated.
	12/29/2021	Updated Coding section with 01/01/2022 CPT changes; added 0700T, 0701T effective 01/01/2022.
Revised	05/13/2021	MPTAC review. A new position statement was added for electrical impedance spectroscopy which is considered INV and NMN. The Rationale, References and Index sections were updated. Updated Coding section with 07/01/2021 CPT changes; added 0658T.
Revised	05/14/2020	MPTAC review. Added reflectance confocal microscopy to the Not Medically Necessary section of the Position Statement. Removed Cosmetic and Not Medically Necessary statement on ultrasonographic evaluation of photoaging, intrinsic aging and skin rejuvenation techniques from the Position Statement. Updated Description, Rationale, Background, Definitions, References, Websites, and Index sections. Updated Coding section; added CPT code range 96931-96936.
Reviewed	02/20/2020	MPTAC review. Updated References and Websites sections.
Reviewed	03/21/2019	MPTAC review. Updated Rationale, References, and Websites sections.
Reviewed	03/22/2018	MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Rationale, References, and Websites sections.
Reviewed	05/04/2017	MPTAC review. Updated References and Websites sections.
Reviewed	05/05/2016	MPTAC review. Updated Reference section. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review. Updated Rationale and Reference sections.
Reviewed	05/15/2014	MPTAC review. Updated Reference section.
Reviewed	05/09/2013	MPTAC review. Updated Reference section.
Reviewed	05/10/2012	MPTAC review. Updated Reference section.
Reviewed	05/19/2011	MPTAC review. Updated Reference section.
Reviewed	05/13/2010	MPTAC review. Updated Reference section,
Reviewed	05/21/2009	MPTAC review. Updated Reference section
Reviewed	05/15/2008	MPTAC review. The phrase “cosmetic/not medically necessary” was clarified to read “cosmetic and not medically necessary.” Updated Coding and Reference sections.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Revised	05/17/2007	MPTAC review. Added investigational/not medically necessary statement regarding whole body photography. Updated Rationale, Reference Coding and Index sections.
	01/01/2007	Updated Coding section with 01/01/2007 CPT/HCPCS changes; removed CPT codes 0044T, 0045T deleted 12/31/2006.
Reviewed	06/08/2006	MPTAC annual review. References updated.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organization	Last Date Reviewed	Document Number	Title

Anthem, Inc.	01/28/2004	MED.00004	Technologies for the Evaluation of Skin Lesions (including Dermatoscopy, Epiluminescence Microscopy, Videomicroscopy and Ultrasonography)
WellPoint Health Networks, Inc.	09/23/2004 06/24/2004	2.02.03 4.02.02	Dermatoscopy Ultrasonographic Evaluation of Skin Lesions

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

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 eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.