# Prior Authorization Review

## Panel MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<th>Plan: Aetna Better Health</th>
<th>Submission Date: 09/04/2018</th>
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<td>Effective Date:</td>
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<td>Policy Name: Total Body Photography, Dermoscopy and Other Selected Noninvasive Dermatologic Tests</td>
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**Type of Submission – Check all that apply:**

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 188 Total Body Photography, Dermoscopy and Other Selected Noninvasive Dermatologic Tests**

Clinical content was last revised on 05/24/2017. Additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

**Revision and Update History since last PARP submission:**
- 07/17/2017 - This CPB has been updated with additional coding.
- 08/11/2017 - This CPB has been updated with additional coding.
- 07/31/2018 - This CPB has been updated with additional background information and references.
- 02/14/2019 – Tentative next scheduled review date by Corporate.

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<tr>
<th>Name of Authorized Individual (Please type or print):</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>Bernard Lewin, M.D.</td>
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Total Body Photography, Dermoscopy and Other Selected Noninvasive Dermatologic Tests

Number: 0188

Please see amendment for Pennsylvania Medicaid at the end of this CPB

Policy

I. Aetna considers total body photography (TBP) and dermoscopy (also known as total body imaging, digital epiluminescence microscopy (DELM), epiluminescence microscopy [ELM], incidence light microscopy, skin videomicroscopy, melanomography, in-vivo cutaneous surface microscopy, dermatoscopy, and magnified oil immersion diascopy) (e.g., MoleSafe) medically necessary when used for evaluation of members with a history or close family history of any of the following conditions:

   A. Atypical nevi; or
   B. Dysplastic nevi; or
   C. Melanoma; or
   D. Non-melanoma skin cancers

Repeat studies are not typically required more

Policy History

Last Review: 07/31/2018
Effective: 12/01/1997
Next Review: 02/14/2019

Definitions

A additional Information

Clinical Policy

Bulletin Notes

http://aetnet.aetna.com/mpa/cpb/100_199/0188.html
frequently than every 24 months.

Aetna considers TBP and dermoscopy experimental and investigational for all other indications because their effectiveness for indications other than the ones listed above has not been established.

II. Aetna considers computerized TBP systems (e.g., MelaFind, MoleMapCD, MoleMate) experimental and investigational because they have not been shown to provide better health outcomes than conventional TBP.

III. Aetna considers the following approaches (not an all-inclusive list) experimental and investigational for detecting and monitoring dysplastic and atypical nevi for early detection of malignant cutaneous melanomas because their clinical value for this indication has not been established.

- Confocal scanning laser microscopy
- Electrical impedance devices
- High-resolution ultrasonography
- Multi-photon laser scanning microscopy (also known as multi-photon fluorescence microscopy or multi-photon excitation microscopy)
- Multi-spectral image analysis
- Non-invasive gene expression "patch biopsy" (e.g., DermTech Pigmented Lesion Assay (PLA))
- Optical coherence tomography
- Reflectance confocal microscopy (RCM)
- Spectroscopy (impedance and optical)
- Visual image analysis
Total body photography (TBP) and dermoscopy (also known as total body imaging, digital epiluminescence microscopy (DELM), epiluminescence microscopy [ELM], incidence light microscopy, skin videomicroscopy, melanomography, in-vivo cutaneous surface microscopy, dermatoscopy, and magnified oil immersion diascopy) are established techniques for detecting and monitoring dysplastic and atypical nevi for early detection of malignant cutaneous melanomas.

A skin lesion is a nonspecific term that refers to any change in the skin surface. Skin lesions may have color (pigment), be raised, flat, large, small, fluid filled or exhibit other characteristics. A lesion may be benign, malignant or premalignant.

Skin cancers are often referred to as being nonmelanoma or melanoma, with nonmelanoma skin cancers behaving less aggressively than melanoma. The two most common types of nonmelanoma skin cancer arise from cells in layers of the epidermis (skin) for which they are named. Basal cell skin cancer originates in the basal (lowest) layer of the epidermis, while squamous cell skin cancer starts in the squamous (outer) layer of the epidermis. Most skin cancers occur on skin that is regularly exposed to sunlight or other ultraviolet radiation. Melanoma is another type of skin cancer that is less common, but more harmful.

The fact that dysplastic and atypical nevi may appear as potential precursors of cutaneous malignant melanoma (CMM) has made possible early identification of individuals who are at increased risk for developing CMM. Moreover, there is ample evidence that early resection of malignant melanoma is associated with an excellent prognosis. Thus, it is important that individuals with dysplastic or atypical nevi receive regular cutaneous examination to identify new and changing nevi.
Melanoma originates in the melanocytes and usually presents as a brown or black lesion, but can appear as pink, tan, white or nonpigmented (no color). Melanoma can appear anywhere on the body and may be difficult to detect in early phases. Surgical removal of the lesion is the standard treatment for melanoma.

Surveillance technologies have been developed in an attempt to find skin cancer, particularly melanoma, early and to assist with identifying malignant skin lesions without using a biopsy or excising (removing) the lesion. However, more than 90% of melanomas that arise in the skin can be recognized with the naked eye. Biopsy is necessary when there is a sufficient index of suspicion. Histopathologic examination remains the gold standard for skin cancer diagnosis.

Mole mapping/Total body and single lesion photography uses digital cameras for recording and storing images which can be compared over time to determine if a lesion has changed. If video images are recorded, this may be referred to as video-dermoscopy. Total body photography is helpful for patients with numerous nevi, to identify changes in these lesions during regular examinations.

Dermoscopy is a technique that may be utilized to see patterns and structures in lesions that are not perceptible to the naked eye, and is also known as dermatoscopy, digital epiluminescence microscopy (DELM), in vitro cutaneous surface microscopy, magnified oil immersion diascopy, mole mapping and melanomography. A dermoscope (handheld magnification tool) is used for examination of the skin lesions, which allows 10x or higher magnification by using high intensity light. Oil may be applied to the surface of the lesion to make the skin more transparent, but may not be necessary if a polarized light source and lens are used. DermLite is one example of a US Food and Drug Administration (FDA) approved dermoscope. Dermoscopes may be combined with
cameras, software and computerized systems that save and store images. MicroDERM is one example of a digital derscope and software system.

A dermoscope (e.g., MoleMax II™) is a specialized microscope that is used for in vivo examination of pigmented skin lesions, in order to distinguish melanocytic from non-melanocytic pigmented lesions and determine whether melanocytic pigmented lesions are likely to be malignant. Even though most malignant melanocytic lesions can be identified on the basis of unaided visual inspection alone, there are many lesions that are not readily distinguished by examination with the naked eye.

The dermoscope can also be used to visualize the subsurface layers of the skin. With the addition of the oil immersion technique, the epidermis becomes translucent, permitting macroscopic evaluation of the dero-epidermal junction. Most studies have shown that this method improves diagnostic accuracy of pigmented skin lesions by 20 % to 30 % with respect to simple clinical observation, especially by an expert dermatologist.

Since its introduction, dermoscopy has undergone extensive improvements; the instruments have become more readily available; and the diagnostic indications, benefits, and limitations have been better delineated. Dermoscopy has developed into a powerful tool to discriminate between melanocytic and non-melanocytic pigmented skin lesions, and to distinguish benign from malignant melanocytic lesions in order to avoid inopportune surgical treatments for low risk lesions. Although dermoscopy does not show 100 % sensitivity in diagnosing CMM, it is more accurate than unaided visual inspection in detecting thin CMM. Features of pigmented lesions identified by dermoscopy should be integrated with data from the history and physical examination.
The recent advent of digital imaging systems for acquiring and archiving total body skin images has resulted in greater dissemination of this technique. Although computer-based systems supposedly will provide sophisticated functionalities for automated feature extraction and lesion assessment for quantitative analysis, there is a need to better standardize computerized TBP systems if they are going to be used more extensively.

There is insufficient evidence that computerized TBP systems such as MoleMapCD provide better health outcomes than conventional TBP. In this regard, Schindewolf et al (1994) ascertained if conventional color slides or directly digitized images should be used for a reliable recognition of malignant melanoma. The authors concluded that both image acquisition techniques allow a reliable detection of malignant melanoma and both are appropriate as input for an image analysis system regarding its efficiency as a diagnostic tool. Furthermore, Brown (2002) examined the various diagnostic techniques for melanoma. A total of 6 general categories dealing with diagnostic techniques for melanoma were identified: (i) naked-eye clinical examination alone, (ii) clinical examination with the aid of TBP, (iii) epiluminescence microscopy (ELM), (iv) digital ELM, (v) computer-assisted techniques, and (vi) teledermatology. Because of the research citing the poor diagnostic accuracy (DA) of non-dermatologists, increased DA with dermatologists experienced in ELM techniques, and the importance of early melanoma diagnosis, the recommendation is to refer patients with suspicious pigmented skin lesions to experienced dermatologists, preferably those who use ELM or digital ELM.

In a review on skin imaging, Rallan and Harland (2004) stated that mole scanners are increasingly available on a commercial basis even though computer diagnosis of pigmented lesions is currently no better than diagnosis by human experts, and other
imaging techniques, such as high-resolution ultrasonography, spectroscopy and optical coherence tomography, may yet find a role in diagnosis and disease monitoring.

Starritt et al (2005) stated that the value of targeted high-resolution ultrasound (US) examination in detecting sentinel lymph node (SLN) metastases in patients with newly diagnosed primary cutaneous melanomas has not yet been fully evaluated. These investigators examined the threshold size of metastatic melanoma deposits in SLNs that are able to be detected by targeted US examination before initial melanoma surgery (n = 304). Metastatic disease was present in SLNs from 33 node fields in 31 patients. The US results in 7 of these cases were suggestive of metastatic disease; 26 node fields contained positive nodes not detected by US. Undetected deposits had diameters that are less than 4.5 mm. These researchers concluded that the findings of this study suggest that a targeted US examination of SLNs can detect metastatic melanoma deposits down to approximately 4.5 mm in diameter. They further noted that, however, most metastatic melanoma deposits in SLNs are considerably smaller than this at the time of initial staging, thus targeted high-resolution ultrasound can not be considered cost-effective in this setting.

Confocal laser scanning microscopy is similar to dermoscopy, however uses a low-power laser beam projected through a lens on a specific point on the skin and then detects the light reflected from the focal point through a filter. The reflected light is transformed into an electrical signal, which is recorded as an image by a computer. This technology purports to be capable of producing images of skin lesions at various depths below the skin's surface. One example of such technology is the VivaScope.

Gerger et al (2005) stated that in vivo confocal laser scanning microscopy (CLSM) represents a novel imaging tool that allows the examination of skin morphology in real time at a
resolution equal to that of conventional microscopes. These researchers tested the applicability of CLSM to the diagnostic discrimination of benign nevi and melanoma. Five independent observers without previous experience in CLSM received a standardized instruction about diagnostic CLSM features. Subsequently, 117 melanocytic skin tumors (90 benign nevi and 27 melanoma), imaged using a commercially available, near-infrared, reflectance confocal laser scanning microscope, were evaluated by each observer. Overall, sensitivity of 88.2 % and specificity of 97.6 % was achieved by the 5 observers. Logistic regression analysis revealed that mainly cytomorphology, architecture and keratinocyte cell borders should be taken into account for diagnostic decisions. Remarkably, using the presence or absence of monomorphic melanocytes as a single diagnostic criterion, the classification results with a sensitivity of 98.2 % and a specificity of 98.9 % were superior to the intuitive, integrative judgment of the observers. These investigators concluded that this first sensitivity and specificity study with CLSM has yielded promising results. Furthermore, Marghoob and Halpern (2005) stated that the future of CLSM looks bright; however, much work is needed before the application of this technology in routine clinical practice.

Gerger et al (2006) noted that in vivo CLSM examination appeared to be a promising method for the non-invasive assessment of melanoma and non-melanoma skin tumors. This is in agreement with the observation of Menzies (2006), who stated that the use of automated instruments for the diagnosis of cutaneous melanoma is still in an experimental phase, and its utility is dependent on the evidence that such instruments give a clinically useful expert second opinion. Currently, other non-invasive diagnostic techniques such as in vivo CLSM are reserved for clinical research settings.

Gerger and colleagues (2009) stated that in vivo confocal microscopy represents a novel imaging tool that allows the non-invasive examination of skin cancer morphology in real
time at a "quasi-histopathological" resolution viewing microanatomical structures and individual cells. Numerous morphological confocal features of melanocytic skin tumors have been described and histopathological correlates of confocal structures have been previously elucidated. Recently, several studies have evaluated the diagnostic accuracy of in vivo confocal microscopy for melanocytic skin tumors, investigating approximately 50,000 tumor images. Remarkably, sensitivity superior to the diagnostic accuracy achieved with dermoscopy could be reached by this imaging modality. These studies represented a significant contribution to the body of research necessary for the evaluation and implementation of in vivo confocal microscopy in clinical practice to avoid many currently unnecessary biopsies. In vivo confocal microscopy probably augurs a sea change in the way melanocytic skin tumors are evaluated in the future and will ultimately move the art of histological diagnosis closer to the bedside.

Psaty and Halpern (2009) noted that diagnostic aids such as TBP and dermoscopy, improve clinicians' ability to diagnose melanoma beyond un-aided visual inspection, and are considered mainstream methods for early detection. Emerging technologies such as in vivo reflectance confocal microscopy are currently being investigated to determine their utility for non-invasive diagnosis of melanoma.

Sanki et al (2009) re-assessed traditional ultrasound descriptors of SLN metastases to: (i) determine the minimum cross-sectional area (CSA) of an SLN metastasis detectable by US, and (ii) establish whether targeted, high-resolution US of SLNs identified by lymphoscintigraphy before initial melanoma surgery can be used as a substitute for excisional SLN biopsy. High-resolution US was performed on SLNs identified in 871 lymph node fields in 716 patients; SLN biopsy was performed within 24 hours of lymphoscintigraphy and US examination. The CSA of each SLN metastatic
deposit was determined sonographically and histologically. The sensitivity of targeted US in the detection of positive SLNs was 24.3 % (95 % confidence interval [CI]: 19.5 % to 28.7 %), and the specificity was 96.8 % (95 % CI: 95.9 % to 97.7 %). The sensitivity was highest for neck SLNs (45.8 %) and improved with greater Breslow thickness. The median histologic CSA of the SLN metastatic deposits was 0.39 mm(2) (12.75 mm(2) for US true-positive results and 0.22 mm(2) for US false-negative results). True-positive, US-detected SLNs had significantly greater CSAs (t-test p < 0.001) than undetected SLN metastases and were more likely to be spherical in cross-section. More than 2 sonographic descriptors of SLN metastases or rounding of the node alone were factors highly suggestive of a melanoma deposit. The authors concluded that high-resolution US is not an appropriate substitute for SLN biopsy, but it is of value in pre-operative SLN assessment and post-operative monitoring. These findings are in agreement with those of Kunte et al (2009) who reported that high resolution B-mode US can not replace SLN biopsy, especially in the detection of micrometastases, but it remains the most important method to assess the lymph node status for macrometastases pre-surgically.

Glud et al (2009) noted that dermoscopy is considered to be the gold standard for the clinical assessment of pigmented skin lesions. In expert hands, this instrument improves both sensitivity and specificity for the diagnosis of melanoma, however, the outcome is highly dependent on the skills and experience of the examiner. Spectrophotometric intracutaneous analysis (SIAscopy) is a new, commercially available method of analyzing pigmented skin lesions non-invasively. The diagnosis is based on objective features such as the presence of dermal pigment, vascularity of the lesion, and the integrity of collagen. These researchers examined the usefulness of SIAscopy for the clinical diagnosis of malignant melanoma in a prospective, unbiased manner. They enrolled 65 patients with 83 lesions, where the diagnosis of melanoma
could not be ruled out on the basis of the clinical evaluation by a non-dermatologist. All lesions were investigated by dermoscopy and SIAscopy and subsequently excised. Histopathologically, 12 lesions were diagnosed as malignant melanoma. Both dermoscopy and SIAscopy over-estimated the proportion of possible malignant lesions (n = 24 and n = 41, respectively) and had sensitivities of 92 % and 100 %, respectively. The specificity of dermoscopy in this study was 81 % against 59 % for SIAscopy. These findings showed that dermoscopy remains the best diagnostic tool for the pre-operative diagnosis of pigmented skin lesions.

An Agency for Healthcare Research and Quality's Technical Brief on "Noninvasive diagnostic techniques for the detection of skin cancers" (Parsons et al, 2011) stated that multi-photon laser scanning microscopy (also known as multi-photon fluorescence microscopy or multi-photon excitation microscopy) uses more than 1 photon excitation to illuminate endogenous fluorophores in skin tissues, which emits a fluorescence signal to be captured by a detector. Similar to CSLM, multi-photon laser scanning microscopy uses laser beam and allows imaging of tissues beyond the superficial epidermis. Unlike CSLM, this technique does not use a confocal pinhole filter. Evidence of the current application of this modality is sparse. Systematic literature search identified 3 narrative reviews and 2 diagnostic studies of multi-photon microscopy or tomography. These investigators identified 2 registered cross-sectional studies that assess the use of this technology for skin lesion evaluation. Both studies are based in Taiwan and are recruiting participants. The only commercially available device for multi-photon tomography is DermalInspect, manufactured by JenLab in Germany. The authors could not determine the FDA clearance status for this device on the FDA CDRH database; and listed multi-photon laser scanning microscopy as one of the investigational devices for the detection of skin cancers.
Marchesini et al (2002) noted that early detection and prompt excision of cutaneous melanoma is of paramount importance to improve patient survival, and the clinician should be aware of the clinical features that suggest the presence of a malignant lesion. The clinical diagnosis is mainly based on observation of the color and shape of a given skin lesion. Unfortunately, evaluation of a pigmented lesion is to a large extent subjective and is closely related to the experience of the clinician. To overcome this problem, optical imaging techniques using different instrumentation (i.e., color video camera, ELM, reflectance spectrophotometry [SPT]) and computer image analysis have been proposed in an attempt to provide quantitative measurements in an objective and reproducible fashion. The different procedures employed to perform the diagnosis automatically all have a common denominator: mimicking the eye and the brain of the clinician by image processing and computerized analysis programs, respectively. Sensitivity and specificity data reported in the literature suggest that the computer-based diagnosis of melanoma does not greatly differ from the diagnostic capability of an expert clinician, and is independent of the optical acquisition method employed to analyze the lesions. Most of the computer-processed morphometric variables useful in automated diagnosis are not recognizable nor can be objectively evaluated by the human eye, except that of lesion dimension. However, several questions should be answered before assessing the actual usefulness, including the potential and limitations, of computer-based diagnostic procedures.

Glud et al (2009) stated that spectrophotometric intra-dermal analysis (SIAscopy) is a new, commercially available method of analyzing pigmented skin lesions non-invasively. The diagnosis is based on objective features such as the presence of dermal pigment, vascularity of the lesion, and the integrity of collagen. The objective of this study was to examine the usefulness of SIAscopy for the clinical diagnosis of malignant melanoma in a prospective, unbiased manner. These investigators enrolled 65 patients with 83 lesions, where
the diagnosis of melanoma could not be ruled out on the basis of the clinical evaluation by a non-dermatologist. All lesions were investigated by dermoscopy and SIAscopy and subsequently excised. Histopathologically, 12 lesions were diagnosed as malignant melanoma. Both dermoscopy and SIAscopy over-estimated the proportion of possible malignant lesions (n = 24 and 41, respectively) and had sensitivities of 92 and 100 %, respectively. The specificity of dermoscopy in this study was 81 % against 59 % for SIAscopy. These findings showed that dermoscopy remains the best diagnostic tool for the pre-operative diagnosis of pigmented skin lesions. However, as the SIAscope in addition to the SIAgraph images produces dermoscopic images, it holds the advantages in training and archiving.

Ascierto et al (2010) stated that SPT could represent a promising technique for the diagnosis of cutaneous melanoma (CM) at earlier stages of the disease. These investigators evaluated the role of SPT in CM early detection. During a health campaign for malignant melanoma at National Cancer Institute of Naples, these researchers identified a subset of 54 lesions to be addressed to surgical excision and histological examination. Before surgery, all patients were investigated by clinical and ELM screenings; selected lesions underwent SPT analysis. For SPT, these investigators used a video SPT imaging system (Spectroshade MHT S.p.A., Verona, Italy). Among the 54 patients harboring cutaneous pigmented lesions, these researchers performed comparison between results from the SPT screening and the histological diagnoses as well as evaluation of both sensitivity and specificity in detecting CM using either SPT or conventional approaches. For all pigmented lesions, agreement between histology and SPT classification was 57.4 %. The sensitivity and specificity of SPT in detecting melanoma were 66.6 % and 76.2 %, respectively. The authors concluded that although SPT is still considered as a valuable diagnostic tool for CM, its low accuracy, sensitivity, and specificity represent the main
hamper for the introduction of such a methodology in clinical practice. Dermoscopy remains the best diagnostic tool for the pre-operative diagnosis of pigmented skin lesions.

Smith and Macneil (2011) discussed recent developments in the non-invasive imaging of skin, in particular at how such imaging may be used at present or in the future to detect CM. A Medline search was performed for articles using imaging techniques to evaluate CM, including melanoma metastasis. A total of 9 different techniques were found: dermoscopy, confocal laser scanning microscopy (including multi-photon microscopy), optical coherence tomography, high-frequency ultrasound, positron emission tomography, magnetic resonance imaging, and Fourier, Raman, and photo-acoustic spectroscopies. The authors concluded that despite the variety of techniques available for detecting melanoma, there remains a critical need for a high-resolution technique to answer the question of whether tumors have invaded through the basement membrane.

In a prospective, multi-center, blinded study, Monheit et al (2011) examined the safety and effectiveness of MelaFind, a non-invasive and objective computer-vision system designed to aid in detection of early pigmented cutaneous melanoma. The diagnostic performance of MelaFind and of study clinicians was evaluated using the histologic reference standard. Standard images and patient information for a subset of 50 randomly selected lesions (25 melanomas) were used in a reader study of 39 independent dermatologists to estimate clinicians’ biopsy sensitivity to melanoma. A total of 1,383 patients with 1,831 lesions enrolled from January 2007 to July 2008; 1,632 lesions (including 127 melanomas – 45 % in situ with median Breslow thickness of invasive lesions, 0.36 mm) were eligible and evaluable for the study end points. Main outcome measures included sensitivity of MelaFind; specificities and biopsy ratios for MelaFind and the study investigators; and biopsy sensitivities of independent dermatologists in the reader study. The measured sensitivity
of MelaFind was 98.4% (125 of 127 melanomas) with a 95% lower confidence bound at 95.6% and a biopsy ratio of 10.8:1; the average biopsy sensitivity of dermatologists was 78% in the reader study. Including borderline lesions (high-grade dysplastic nevi, atypical melanocytic proliferations, or hyperplasias), MelaFind's sensitivity was 98.3% (172 of 175), with a biopsy ratio of 7.6:1. On lesions biopsied mostly to rule out melanoma, MelaFind's average specificity (9.9%) was superior to that of clinicians (3.7%) ($p = 0.02$). The authors concluded that MelaFind is a safe and effective tool to assist in the evaluation of pigmented skin lesions. However, it is unclear if an instrument with such a low specificity is clinically useful.

In a randomized, controlled trial, Walter et al (2012) examined if adding a novel computerized diagnostic tool, the MoleMate system (SIAscopy with primary care scoring algorithm), to current best practice results in more appropriate referrals of suspicious pigmented lesions to secondary care, and to assess its impact on clinicians and patients. Subjects were 1,297 adults with pigmented skin lesions not immediately diagnosed as benign. Patients were assessed by trained primary care clinicians using best practice (clinical history, naked eye examination, 7-point checklist) either alone (control group) or with the MoleMate system (intervention group). Main outcome measures included appropriateness of referral, defined as the proportion of referred lesions that were biopsied or monitored. Secondary outcomes related to the clinicians (diagnostic performance, confidence, learning effects) and patients (satisfaction, anxiety). Economic evaluation, diagnostic performance of the 7-point checklist, and 5-year follow-up of melanoma incidence were also secondary outcomes and will be reported later. A total of 1,297 participants with 1,580 lesions were randomized: 643 participants with 788 lesions to the intervention group and 654 participants with 792 lesions to the control group. The appropriateness of referral did not differ significantly between the intervention or control groups: 56.8% (130/229) versus
64.5% (111/172); difference -8.1% (95% CI: -18.0% to 1.8%). The proportion of benign lesions appropriately managed in primary care did not differ (intervention 99.6% versus control 99.2%, p = 0.46), neither did the percentage agreement with an expert decision to biopsy or monitor (intervention 98.5% versus control 95.7%, p = 0.26). The percentage agreement with expert assessment that the lesion was benign was significantly lower with MoleMate (intervention 84.4% versus control 90.6%, p < 0.001), and a higher proportion of lesions were referred (intervention 29.8% versus control 22.4%, p = 0.001). A total of 36 histologically confirmed melanomas were diagnosed: 18/18 were appropriately referred in the intervention group and 17/18 in the control group. Clinicians in both groups were confident, and there was no evidence of learning effects, and therefore contamination, between groups. Patients in the intervention group ranked their consultations higher for thoroughness and reassuring care, although anxiety scores were similar between the groups. The authors concluded that there was no evidence that the MoleMate system improved appropriateness of referral. The systematic application of best practice guidelines alone was more accurate than the MoleMate system, and both performed better than reports of current practice. Therefore, the systematic application of best practice guidelines (including the s7-point checklist) should be the paradigm for management of suspicious skin lesions in primary care.

Longo et al (2103) stated that reflectance confocal microscopy (RCM) is a novel technique that allows visualization of the skin at nearly histological resolution although limited laser depth penetration hampers visualization of the deep dermis. These researchers examined if the diagnostic accuracy of RCM was comparable to histopathology for the diagnosis of nodular lesions, and identified possible limitations of this technique. They retrospectively evaluated 140 nodules by means of RCM while blinded from the histopathological diagnosis. At the end of the study the patient codes were broken and the evaluations
were matched with histopathological diagnosis before performing statistical analysis. The study consisted of 140 nodular lesions (23 “pure” nodular melanomas, 9 melanoma metastases, 28 basal cell carcinomas (BCCs), 6 invasive squamous cell carcinomas (SCCs), 32 naevi, 14 seborrheic keratoses, 17 dermatofibromas, 5 vascular lesions and 6 other lesions). Reflectance confocal microscopy correctly diagnosed 121 of 140 lesions (86.4 %); 8 of 140 (5.7 %) lesions revealed discordance between histopathology and confocal microscopy. Eight of the 140 (5.7 %) cases were not evaluable by means of RCM due to the presence of ulceration or hyperkeratosis and 3 cases showed a non-specific pattern. Interestingly, confocal microscopy reached a 96.5 % sensitivity and 94.1 % specificity (area under curve 0.970) (95 % CI: 0.924 to 1.015) (p < 0.001) for the diagnosis of melanoma.

The authors concluded that this study was retrospective and lesions were not included on the basis of their diagnostic difficulty. They noted that despite the limited laser depth penetration of RCM, this imaging tool represents an effective instrument in diagnosing nodular lesions; however, for fully ulcerated lesions or when a marked hyperkeratosis is present, biopsy should always be performed. They stated that prospective studies on difficult-to-diagnose nodules should be performed to analyze further the pros and cons of RCM in skin cancer diagnosis.

Mohr et al (2013) stated that previous studies have shown statistically significant differences in electrical impedance between various cutaneous lesions. Electrical impedance spectroscopy (EIS) may therefore be able to aid clinicians in differentiating between benign and malignant skin lesions. These researchers developed a classification algorithm to distinguish between melanoma and benign lesions of the skin with a sensitivity of at least 98 % and a specificity of approximately 20 % higher than the diagnostic accuracy of dermatologists. A total of 1,300 lesions were collected in a multi-center, prospective, non-randomized clinical trial from 19 centers around Europe. All lesions were excised and
subsequently evaluated independently by a panel of 3 expert dermatopathologists. From the data 2 classification algorithms were developed and verified. For the first classification algorithm, approximately 40 % of the data were used for calibration and 60 % for testing. The observed sensitivity for melanoma was 98.1 % (101/103), non-melanoma skin cancer 100 % (25/25) and dysplastic nevus with severe atypia 84.2 % (32/38). The overall observed specificity was 23.6 % (66/280). For the second classification algorithm, approximately 55 % of the data were used for calibration. The observed sensitivity for melanoma was 99.4 % (161/162), for non-melanoma skin cancer was 98.0 % (49/50) and dysplastic nevus with severe atypia was 93.8 % (60/64). The overall observed specificity was 24.5 % (116/474). The authors concluded that EIS has the potential to be an adjunct diagnostic tool to help clinicians differentiate between benign and malignant (melanocytic and non-melanocytic) skin lesions. They stated that further studies are needed to confirm the validity of the automatic assessment algorithm.

Reggiani et al (2015) stated that non-melanoma skin cancer (NMSC) is the most common malignancy in fair skinned populations. Dermoscopy, reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) are non-invasive imaging techniques that play an important role in diagnosis of skin tumors. These investigators provided new insights into the role of non-invasive techniques in the diagnosis of NMSCs, concentrating especially on dermoscopy, RCM and OCT. They performed a PubMed search concerning the role of dermoscopy, RCM and OCT in the diagnosis of NMSC. Duplicated studies, single-case report, and papers with language other than English were excluded from analysis. New and old literature about early diagnosis of NMSC through non-invasive imaging techniques were analyzed. The role and the diagnostic accuracy of dermoscopy, RCM and OCT for the diagnosis of NMSC were reported. The authors concluded that the development of non-invasive diagnostic devices (especially dermoscopy, RCM and OCT) allows tissue imaging
in-vivo contributing to a more accurate diagnosis of skin cancer, sparing time for the patient and costs for the public health system.

**MoleSafe:**

According to its website, MoleSafe is a comprehensive skin documentation system designed to expose layers of skin lesions not typically viewed during a regular examination by dermatologists. The MoleSafe system produces high-resolution diagnostic images and creates a profile for a person's skin that is monitored for any changes in lesions. The MoleSafe process involves 6 important steps:

- Meeting with a melanographer to discuss medical history and address skin concerns
- Total body photography -- A series of 25 pictures of 96% of the body's surface
- Total body dermoscopy -- A visual exam is performed and any abnormal lesion is examined with a dermatoscope
- Digital melanogram -- Images from the exam are compiled into a digital record of the skin, along with other information, including lesion coding and history
- Dermoscopist report is created -- Dermoscopist report of suspicious lesions included with recommendations for treatment and ongoing surveillance
- Patient education -- Educating patients on skin cancer risk factors and tips for protecting skin against UV radiation

**Non-Melanocytic Skin Cancer:**

Fargnoli et al (2012) noted that over the past 20 years, dermoscopy has remarkably enhanced the diagnostic accuracy of pigmented skin lesions and, more recently, of non-pigmented skin disorders, including skin cancers, inflammatory and infectious diseases. With respect to non-melanoma skin
cancers (NMSC), dermoscopy is an effective diagnostic tool for the clinical assessment of BCC, Bowen's disease, actinic keratosis (AK) and SCC. Besides its relevance for diagnostic purposes, further applications of dermoscopy in the management of NMSC have been suggested in the pre-operative evaluation, in monitoring the outcome of topical, light-based or laser treatments and in the post-treatment follow-up.

Lallas et al (2013) noted that dermoscopy has become an integrative part of the clinical examination of skin tumors. This is because it significantly improves the early diagnosis of melanoma and NMSC including BCC and keratinocyte skin cancer compared with the unaided eye. Besides its value in the non-invasive diagnosis of skin cancer, dermoscopy has also gained increased interest in the management of NMSC. Dermoscopy has been used in the pre-operative evaluation of tumor margins, monitoring of the outcomes of topical treatments and post-treatment follow-up.

Babino and associates (2015) stated that dermoscopy is a non-invasive tool that allows the identification of specific morphological features in different skin tumors, improving significantly the early diagnosis of melanoma and NMSC. This tool has also gained increased interest in the management of NMSC therapy and in the post-treatment follow-up.

Deinlein and colleagues (2016) noted that dermatoscopy is an integral part of every clinical skin examination, as it markedly enhances the early detection of melanocytic and NMSC compared to naked-eye inspection. Besides its diagnostic use, this non-invasive method is increasingly important in the selection of as well as the response assessment to various therapies used for NMSC, including BCC, AK, SCC, and also rare tumors such as Merkel cell carcinoma, angiosarcoma, or dermato-fibrosarcoma protuberans. The authors stated that
dermoscopy is a valid tool for the pre-operative assessment of tumor margins in BCC, but also for follow-up of AK after topical treatment.

Furthermore, the Canadian Cancer Society (2016) lists dermoscopy as one of the methods used for diagnosing non-melanoma skin cancer.

**Non-Invasive Gene Expression “Patch Biopsy” (e.g., DermTech Pigmented Lesion Assay (PLA)):**

According to DermTech, the Pigmented Lesion Assay (PLA; DermTech) entails non-invasive gene expression tests to aid the clinical diagnosis of skin cancer and other skin conditions. It was developed to provide physicians with a non-invasive option for the biopsy of clinically atypical pigmented lesions using an adhesive patch rather than a scalpel. The PLA is used for the detection of melanoma in atypical skin lesions or moles and utilizes a sample collected with the Adhesive Patch Skin Biopsy Kit. It provides ribonucleic acid (RNA) gene expression score for 2 genes (CMIP and LINC00518). The PLA can be used to reduce unnecessary surgical biopsy procedures by ruling out false positives based on visual assessment prior to performing a surgical removal. It may also be used to provide immediate information on lesions that require 6 to 12 months follow-up for change. This non-invasive biopsy approach has additional utility in patient populations that are anti-coagulated, at increased risk for infection and scarring, or at risk for wound complications, and for lesions in cosmetically sensitive areas.

Gerami et al (2014) developed a non-invasive genomic method using messenger RNA (mRNA) to classify pigmented skin lesions as either benign or malignant. An adhesive patch method was used to obtain cells from the surface of melanocytic lesions; mRNA was extracted and a genomic signature was formulated in a training set of benign and malignant melanocytic neoplasms and subsequently tested in
a validation set. A 2-gene signature assessing the expression levels of CMIP and LINC00518 was able to differentiate melanomas from nevi in an independent validation set of 42 melanomas and 22 nevi with a sensitivity of 97.6 % and specificity of 72.7 %. The authors concluded that these findings suggested that mRNA molecular signatures can serve as a highly useful non-invasive method of differentiating melanoma from nevi and decrease the number of unnecessary biopsies. Moreover, they stated that larger and more diverse sets of melanomas and nevi are needed for additional validation of the molecular expression profiling in various subsets of melanocytic neoplasms.

Clarke and associates (2015) identified a gene expression signature that reliably differentiated benign and malignant melanocytic lesions and evaluated its potential clinical applicability. These investigators described the development of a gene expression signature and its clinical validation using multiple independent cohorts of melanocytic lesions representing a broad spectrum of histopathologic subtypes. Using quantitative reverse-transcription polymerase chain reaction (RT-PCR) on a selected set of 23 differentially expressed genes, and by applying a threshold value and weighting algorithm, these researchers developed a gene expression signature that produced a score that differentiated benign nevi from malignant melanomas. The gene expression signature classified melanocytic lesions as benign or malignant with a sensitivity of 89 % and a specificity of 93 % in a training cohort of 464 samples. The signature was validated in an independent clinical cohort of 437 samples, with a sensitivity of 90 % and specificity of 91 %. The authors concluded that the performance, objectivity, reliability and minimal tissue requirements of this test suggested that it could have clinical application as an adjunct to histopathology in the diagnosis of melanocytic neoplasms.
Yao et al (2016) previously reported clinical performance of a novel non-invasive and quantitative PCR (qPCR)-based molecular diagnostic assay (the PLA) that differentiates primary cutaneous melanoma from benign pigmented skin lesions through 2 target gene signatures, LINC00518 (LINC) and preferentially expressed antigen in melanoma (PRAME). This study focused on analytical characterization of this PLA, including qPCR specificity and sensitivity, optimization of RNA input in qPCR to achieve a desired diagnostic sensitivity and specificity, and analytical performance (repeatability and reproducibility) of this 2-gene PLA. All target qPCRs demonstrated a good specificity (100 %) and sensitivity (with a limit of detection of 1-2 copies), which allows reliable detection of gene expression changes of LINC and PRAME between melanomas and non-melanomas. Through normalizing RNA input in qPCR, these researchers converted the traditional gene expression analyses to a binomial detection of gene transcripts (i.e., detected or not detected). By combining the binomial qPCR results of the 2 genes, an improved diagnostic sensitivity (raised from 52 % to 65 % to 71 % at 1 pg of total RNA input, and to 91 % at 3 pg of total RNA input) was achieved. The authors concluded that this 2-gene PLA demonstrated a high repeatability and reproducibility (coefficient of variation less than 3 %) and all required analytical performance characteristics for the commercial processing of clinical samples.

Gerami et al (2017) noted that clinical and histopathologic assessment of pigmented skin lesions remains challenging even for experts. Differentiated and accurate non-invasive diagnostic modalities are highly desirable. These researchers sought to provide clinicians with such a tool. A 2-gene classification method based on LINC00518 and preferentially expressed antigen in melanoma (PRAME) gene expression was evaluated and validated in 555 pigmented lesions (157 training and 398 validation samples) obtained non-invasively via adhesive patch biopsy. Results were compared with standard histopathologic assessment in lesions with a
consensus diagnosis among 3 experienced dermatopathologists. In 398 validation samples (87 melanomas and 311 non-melanomas), LINC00518 and/or PRAME detection appropriately differentiated melanoma from non-melanoma samples with a sensitivity of 91% and a specificity of 69%. These investigators established LINC00518 and PRAME in both adhesive patch melanoma samples and underlying formalin fixed paraffin embedded (FFPE) samples of surgically excised primary melanomas and in melanoma lymph node metastases. The authors concluded that this non-invasive 2-gene pigmented lesion assay classified pigmented lesions into melanoma and non-melanoma groups and may serve as a tool to help with diagnostic challenges that may be inherently linked to the visual image and pattern recognition approach. The main drawback is that this technology cannot be used on mucous membranes, palms of hands, and soles of feet.

An UpToDate review on "Clinical features and diagnosis of cutaneous melanoma" (Swetter and Geller, 2017) does not mention non-invasive gene expression test/patch biopsy as a management tool.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Melanoma” (Version 1.2017) states that “While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low versus high risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial)".

Yao and associates (2017) noted that a number of diagnoses in clinical dermatology are currently histopathologically confirmed and this image recognition-based confirmation generally requires surgical biopsies. The increasing ability of molecular pathology to corroborate or correct a clinical
diagnosis based on objective gene expression, mutation analysis, or molecular microbiome data is on the horizon and would be further supported by a tool or procedure to collect samples non-invasively. This study characterized such a tool in form of a “bladeless” adhesive patch-based skin biopsy device. The performance of this device was evaluated through a variety of complementary technologies including assessment of sample biomass, electron microscopy demonstrating the harvesting of layers of epidermal tissue, and isolation of RNA and DNA from epidermal skin samples. Samples were obtained by application of adhesive patches to the anatomical area of interest. Biomass assessment demonstrated collection of approximately 0.3 mg of skin tissue per adhesive patch and electron microscopy confirmed the nature of the harvested epidermal skin tissue. The obtained tissue samples were stored in a stable fashion on adhesive patches over a wide range of temperatures (-80 degree C to +60 degree C) and for extended periods of time (7 days or more). Total human RNA, human genomic DNA and microbiome DNA yields were 23.35 \( \pm \) 15.75 ng, 27.72 \( \pm \) 20.71 ng and 576.2 \( \pm \) 376.8 pg, respectively, in skin samples obtained from combining 4 full patches collected non-invasively from the forehead of healthy volunteers. The authors concluded that the adhesive patch skin sampling procedure was well-tolerated and provided robust means to obtain skin tissue, RNA, DNA, and microbiome samples without involving surgical biopsies. The non-invasively obtained skin samples can be shipped cost effectively at ambient temperature by mail or standard courier service, and were suitable for a variety of molecular analyses of the skin microbiome as well as of keratinocytes, T cells, dendritic cells, melanocytes, and other skin cells involved in the pathology of various skin conditions and conditions where the skin can serve as a surrogate target organ.

In a secure web-based, multiple-reader-multiple-case study, Ferris and colleagues (2017) determined the utility of the PLA for LINC00518/PRAME expression in decisions to biopsy a series of pigmented skin lesions. Board-certified
dermatologists each evaluated 60 clinical and dermoscopic images of clinically atypical pigmented lesions, first without and then with PLA gene expression information and were asked whether the lesions should be biopsied. Data were collected from March 24, 2014, through November 13, 2015. Participants were given a report for each lesion, which included the results of an assay for expression of LINC00518/PRAME and a PLA score with data on the predictive values of the information provided. Main outcomes measures were biopsy sensitivity and specificity with versus without PLA data. A total of 45 dermatologists (29 men and 16 women) performed the evaluation. After incorporating the PLA into their decision as to whether to biopsy a pigmented lesion suggestive of melanoma, dermatologists improved their mean biopsy sensitivity from 95.0 % to 98.6 % (p = 0.01); specificity increased from 32.1 % to 56.9 % (p < 0.001) with PLA data. The authors concluded that the non-invasive PLA enabled dermatologists to significantly improve biopsy specificity while maintaining or improving sensitivity. They stated that this finding may increase the number of early melanomas biopsied and reduce the number of benign lesions biopsied, thereby improving patient outcomes and reducing health care costs.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>CPT codes covered if selection criteria are met:</td>
<td></td>
</tr>
<tr>
<td>96904</td>
<td>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 family history of melanoma</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Specific Codes - Computerized TBP systems - MelaFind, MoleMapCD, MoleMate, MoleSafe, Confocal Scanning Laser Microscopy, Electrical impedance devices, High-resolution ultrasonography, Multi-photon laser scanning microscopy (also known as multi-photon fluorescence microscopy or multi-photon excitation microscopy), Multi-spectral image analysis, Spectroscopy, Visual image analysis, non-invasive gene expression “patch biopsy”</td>
<td></td>
</tr>
<tr>
<td>0400T - 0401T</td>
<td>Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia</td>
</tr>
<tr>
<td>0470T</td>
<td>Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; first lesion</td>
</tr>
<tr>
<td>0471T</td>
<td>each additional lesion (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96931 - 96936</td>
<td>Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C43.0 - C43.9</td>
<td>Malignant melanoma of the skin [not covered for multi-photon laser scanning] [not covered for DermTech Pigmented Lesion Assay]</td>
</tr>
<tr>
<td>D22.0 - D23.9</td>
<td>Melanocytic nevi and other benign neoplasms of the skin</td>
</tr>
<tr>
<td>Z80.8</td>
<td>Family history of malignant neoplasm of other organs or systems [close family history of non-melanoma skin cancers]</td>
</tr>
<tr>
<td>Z85.820</td>
<td>Personal history of malignant melanoma of skin</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>Z85.828</td>
<td>Personal history of other malignant neoplasm of skin</td>
</tr>
<tr>
<td>Z86.018</td>
<td>Personal history of other benign neoplasm [dysplastic nevus]</td>
</tr>
<tr>
<td>Z87.2</td>
<td>Personal history of diseases of the skin and subcutaneous tissue [atypical and dysplastic nevus]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


48. Parrella A. Solar Scan for diagnosis and monitoring of melanoma. Horizon Scanning Prioritization Summary -- Volume 8. Adelaide, SA: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC); February 2005;8(1).

La Plaine, France; Haute Autorite de Sante/French National Authority for Health (HAS); 2006.


80. Jaimes N, Marghoob AA. Dermoscopic algorithms for skin cancer triage. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December, 2015.


85. Lallas A, Argenziano G, Zendri E, et al. Update on non-melanoma skin cancer and the value of dermoscopy in


95. Swetter S, Geller AC. Clinical features and diagnosis of cutaneous melanoma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2017.


Amendment to
Aetna Clinical Policy Bulletin Number:
0188 Total Body Photography, Dermoscopy and Other Selected Noninvasive Dermatologic Tests

There are no amendments for Medicaid.