

diseases with the decreased number and/or function of LCs.

#### CONFLICT OF INTEREST

The authors state no conflict of interest.

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#### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at [www.jidonline.org](http://www.jidonline.org), and at <https://doi.org/10.1016/j.jid.2018.10.036>.

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# Development of a Pigmented Facial Lesion Scale Based on Darkness and Extent of Lesions in Older Veterans

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#### TO THE EDITOR

Pigmented facial lesions (PFLs), including ephelides, pigmented actinic keratoses, seborrheic keratoses, and solar lentigines, are often perceived as a sign of photoaging and can increase in darkness and extent with sun exposure. Although benign, patients often seek treatment for these lesions due to their undesirable appearance. Topical medications, liquid nitrogen, chemical peels, and laser or light-based devices can all be used to clinically lighten these lesions.

Although several validated grading scales exist for photoaging, the majority of these focus on a global photoaging score, such as the Griffiths scale (Griffiths et al., 1992). Scales specific to facial rhytides also exist, where the majority of scored participants were middle-aged and female (Carruthers et al., 2008a, 2008b, 2008c; Carruthers et al., 2016a, 2016b). There remains a lack of validated scales to evaluate the darkness and extent of facial pigmented lesions, particularly in older male participants. Prior studies examining the

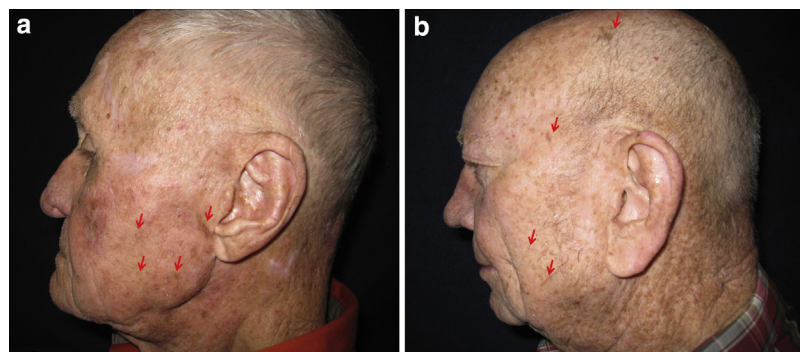
role of topical tretinoin in fading facial pigmented lesions used non-validated scales (Rafal et al., 1992). Studies of laser treatment of facial pigmented lesions also use non-validated scales (Imhof et al., 2016). Thus, this study aims to develop and validate a facial pigmented lesion scale using data from 4 of the 12 participating VA Keratinocyte Carcinoma (VAKCC) trial sites. These sites were chosen because, unlike at the other eight sites, actinic keratoses (AKs) were clinically marked and photographed by board-certified dermatologists at each study visit. There were 348 participants enrolled at baseline, of which 206 either lacked solar lentigines or demonstrated numerous papular seborrheic keratoses. Of the remaining 142 participants



Abbreviations: AK, actinic keratosis; CI, confidence interval; PFL, pigmented facial lesion; VAKCC, Veterans Affairs Keratinocyte Carcinoma Chemoprevention

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**Figure 1. Examples of pigmented facial lesion darkness and extent.** (a) Darkness: inferior medial cheek 1, superior medial cheek 2, inferior lateral cheek 3, superior lateral cheek/preauricular 4. Extent cheek: 3; extent forehead: 3. (b) Darkness: superior cheek 1, inferior cheek 2, temple 3, scalp 4. Extent cheek: 3; extent forehead: 4. Informed written consent for photograph and publication was provided by both participants.

demonstrating pigmented lesions, 31 participants had marked pigmented AKs clinically diagnosed by board-certified dermatologists, leaving 111 participants (99% males) for photographic analysis. Participants with any keratinocyte carcinomas noted on total body skin examination were excluded due to potential for confounding other VAKCC study objectives.

Two 0–4 interval subscales were developed based on the darkness and extent of PFL based on photographs of the cosmetic unit with the largest extent of pigmented lesions. Cosmetic units were defined as follows: forehead, periocular, cheeks, nose, and perioral including chin. For darkness, 0 represented normal skin without any discoloration, 1 light brown, 2 tan, 3 medium brown, and 4 dark brown/black (Figure 1a, 1b). For extent, 0 represents normal skin without any discoloration, 1 represents 1–25% involvement of the photographed area, 2 represents 26–50%, 3 represents 51–75%, and 4 represents 76–100%. Known pigmented AKs (marked by in-person clinical evaluation at study visits) were specifically excluded from pigmented lesion scale development.

Two dermatologists (KK, KL) individually graded participant photographs using both PFL subscales. Photographs were regraded at 2 weeks.

Darkness of lesions representative of grades 1–4 of the Pigmented Facial Lesion Scale are presented in Figure 1. The mean intra-class coefficient for PFL extent after round 1 was 0.86 (95% confidence interval [CI] = 0.78–0.91)

and after round 2 was 0.82 (95% CI = 0.72–0.88). Cohen's  $\kappa$  coefficient for PFL extent after round 1 was 0.81 and after round 2 was 0.79.

The mean intra-class coefficient for PFL darkness after round 1 was 0.84 (95% CI = 0.74–0.90) and after round 2 was 0.92 (95% CI = 0.87–0.95). Cohen's  $\kappa$  coefficient for PFL darkness after round 1 was 0.86 and after round 2 was 0.83.

In the comparison of rounds 1 and 2, grader 1 had an intra-class coefficient of 0.97 (95% CI = 0.95–0.98). Grader 2 had an intra-class coefficient of 0.95 (95% CI = 0.91–0.97).

We report an easy to administer photo-numeric scale looking at both extent and darkness of pigmented facial lesions in older sun-damaged males, with excellent inter- and intra-rater reliability. This scale was obtained following the exclusion of participants with papular seborrheic keratoses and pigmented AKs clinically diagnosed and marked by board-certified dermatologists.

In contrast to currently available scales focused on global photoaging or rhytides, the Pigmented Facial Lesion Scale likely distinctively measures lentigines and/or macular keratoses (Griffiths et al., 1992; Carruthers et al., 2008a, 2008b, 2008c; Carruthers et al., 2016a, 2016b; Donofrio et al., 2016; Chien et al., 2016). Typical assessments of photoaging characterize skin improvement based on the presence and degree of severity of facial rhytides or roughness on a global scale (Carruthers et al., 2008a, 2008b,

2008c; Carruthers et al., 2016a, 2016b; Donofrio et al., 2016), so there is a need for alternative measures specific for solar lentigines and other UV-related pigmented lesions for clinical monitoring and trials.

As a research tool, the Pigmented Facial Lesion Scale may be beneficial in assessing the response of field therapy agents, such as 5-fluorouracil, imiquimod, ingenol mebutate, or laser therapy, in improving PFL following standard courses of therapy.

Strengths of this study include standardized photography, freedom from commercial bias, and specific exclusion of clinically determined pigmented AKs from creation of the Pigmented Facial Lesion Scale. Limitations include a lack of predefined thresholds for clinical significance, as there are no current, validated study instruments for comparison to test responsiveness to photoaging interventions in this population; and of generalizability to younger, female, and non-Caucasian populations who are more typically represented in cosmetic studies. Further study would be useful to determine clinically relevant cutoff points, perhaps by comparing this objective measure to subjective patient-reported assessments. Another limitation is potential inaccuracy in AK diagnosis, given the lack of histologic confirmation of marked lesions, as well as a lack of histologic confirmation of scored PFLs as solar lentigines or macular seborrheic keratoses, which future studies should confirm.

The VAKCC enrolled participants at 12 nationwide sites. Participants of the VAKCC trial had a history of two or more keratinocyte carcinomas in the preceding 5 years, with at least one on the face or ears (Weinstock et al., 2018). At four of the VAKCC trial sites, all of the participants at these sites had AKs clinically marked by blinded, board-certified dermatologists and photographed at baseline and at every 6-month follow-up visit (Lee et al., 2014). The VAKCC trial was approved by the Cooperative Studies Scientific Evaluation Committee and reviewed by the VA Central Institutional Review Board and the Research and Development committees at each VA medical center (see [Supplementary Material](#)

online for further details). Written informed consent, including for photographs and publication of their images, was obtained from study participants.

Stata statistical software (version 14.0, StataCorp, College Station, TX) was used for analyses. Intra-class correlation coefficients were calculated to determine intra-rater reliability between the two raters, and Cohen's  $\kappa$  coefficients were calculated to determine the inter-rater reliability. Cohen's  $\kappa$  coefficient scores of 0–0.2 correspond to slight agreement, 0.21–0.4 correspond to fair agreement, 0.41–0.6 correspond to moderate agreement, 0.61–0.8 correspond to substantial agreement, and 0.81–1 correspond to almost perfect agreement.

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The contents of this article do not represent the views of the US Department of Veterans Affairs or the US Government.

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#### SUPPLEMENTARY MATERIAL

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# A Homozygous Nonsense Mutation in the *DSG3* Gene Causes Acantholytic Blisters in the Oral and Laryngeal Mucosa

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#### TO THE EDITOR

Keratinocytes bind to adjacent keratinocytes via desmosomes. Desmosomal cadherins, the transmembrane proteins

of desmosomes, consist of four types of desmogleins (DSG1–4) and three types of desmocollins (DSC1–3), which form heterodimers or homodimers in the

intercellular space (Delva et al., 2009). Among them, DSG1 is expressed throughout the skin epidermis, whereas DSG3 is expressed predominantly in the basal layer. In the mucosal epithelium, however, little DSG1 is expressed, whereas DSG3 is expressed throughout the epidermis (Mahoney et al., 1999). These findings explain the differential effects of DSG1 and

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