

# Assessment and Monitoring Challenges Among Patients With Moderate-to-Severe Atopic Dermatitis Across Fitzpatrick Skin Types: A Photographic Review and Case Series

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**Abstract:** Atopic dermatitis (AD) is a common, chronic, inflammatory skin condition that affects people of all ages, races, and ethnicities. The condition is heterogeneous in both clinical presentation (phenotype) and underlying pathobiology (endotype). Atopic dermatitis diagnosis, assessment, and monitoring rely on clinical evaluation because there are no definitive biomarkers for AD. This review addresses variation in the clinical presentation of AD across the spectrum of Fitzpatrick skin types, with an emphasis on clinical evaluation challenges in patients with skin of color. We present photographs from phase 3 clinical trials that evaluated the safety and efficacy of upadacitinib among patients with moderate-to-severe AD and demonstrate the challenges in evaluating the clinical signs of AD (erythema and excoriation in patients with dark skin types and lichenification in those with light skin types) by illustrating the changes in clinical signs and symptoms that can be achieved with targeted systemic therapies.

## INTRODUCTION TO ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common inflammatory skin condition in the developed world.<sup>1</sup> According to data from the Global Burden of Disease Study 1990–2017, regions with the highest AD burden include Andean Latin America, North America, Asia Pacific, Western Europe, and Southern Sub-Saharan Africa.<sup>2</sup> The estimated prevalence of adult patients with AD in the United States is approximately 10%,<sup>3</sup> which equates to more than 33.4 million people (based on 2020 US

census data).<sup>4</sup> Atopic dermatitis affects people of all races and ethnicities<sup>5</sup> but disproportionately affects people with skin of color (SOC), particularly African Americans.<sup>6,7</sup> Analysis of data from 2 US multiethnic, longitudinal studies (N = 92,360) indicates that African Americans of all ages are more likely to have AD (odds ratio [OR], 2.06; 95% confidence interval [CI], 1.70–2.48) and experience poorer disease control (OR, 2.02; 95% CI, 1.71–2.37), compared with White patients.<sup>6</sup>

Atopic dermatitis is heterogeneous in terms of its prevalence,<sup>8</sup> clinical presentation (ie, phenotype),<sup>9</sup> disease and symptom severity,<sup>10</sup>

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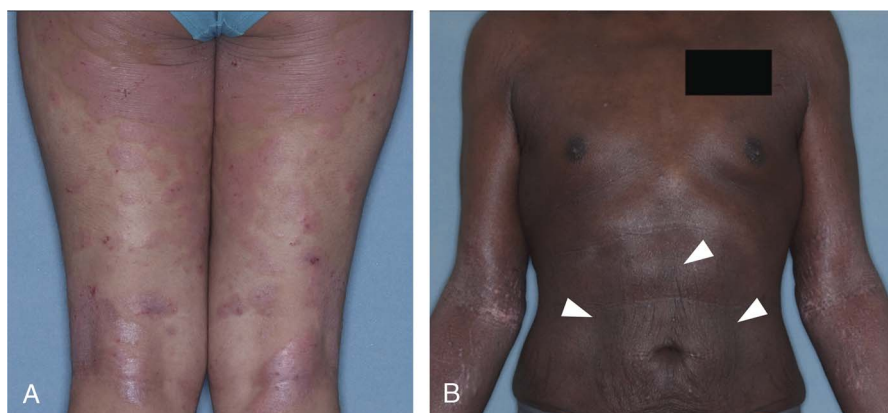


**Figure 1.** Erythema (redness) in patients with light and dark skin tones. Erythema is readily apparent in light skin (A). It is more difficult to identify in dark skin and often appears violaceous (B; white arrows) or in other shades, depending on the background skin tone and the presence of postinflammatory hyperpigmentation.

and treatment response.<sup>10</sup> Each of these aspects of AD varies by race/ethnicity<sup>11,12</sup> and geographic location.<sup>13</sup> Atopic dermatitis presents with different clinical phenotypes in certain populations based on age,<sup>14–16</sup> disease duration,<sup>14,15</sup> immunoglobulin E status,<sup>14,15,17</sup> mutations in genes associated with skin barrier function (eg, the filaggrin gene),<sup>14,15,17</sup> race/ethnicity,<sup>14,15,17</sup> and underlying molecular and immunologic mechanisms (ie, endotype).<sup>14,15,17,18</sup> For example, patients with AD and SOC often present clinically with extensor involvement and are more likely to develop lichenification and/or prurigo nodularis than White patients.<sup>14</sup> Notably, Black patients with AD experience more severe pruritus compared with those of other races/ethnicities because of molecular and structural skin differences,<sup>19</sup> which may contribute to the increased incidence of lichenification and prurigo nodularis in this patient population.<sup>14</sup>

Consequential racial/ethnic treatment disparities exist among both adults<sup>20</sup> and children<sup>21,22</sup> with AD. Black children with either uncontrolled AD or limited disease control are significantly less likely to have been seen by a dermatologist, compared with White children.<sup>21</sup> Similarly, patients with SOC are more likely to use urgent or emergency care for their AD<sup>20,21</sup> (compared with White patients),

suggesting inadequate routine ambulatory care for disease management. A better understanding of disease severity and improved clinical evaluation and monitoring of patients with AD and SOC may be a step toward reducing racial/ethnic treatment disparities. We review some challenges often encountered regarding assessment and monitoring of AD among patients with SOC and present photographic evidence. Our intent is to aid clinicians in overcoming these challenges, thereby contributing to improved AD management in this disproportionately affected patient population.

## CHALLENGES IN ASSESSMENT AND MONITORING OF AD ACROSS FITZPATRICK SKIN TYPES

Atopic dermatitis diagnosis, assessment, and monitoring are accomplished by clinical evaluation, including a detailed medical history and physical examination. A skin biopsy specimen may be obtained in some instances, although there are no pathognomonic histologic findings that confirm a diagnosis of AD. Similarly, certain laboratory tests may support or suggest a diagnosis of AD, but there are no definitive biomarkers for AD.<sup>23</sup>

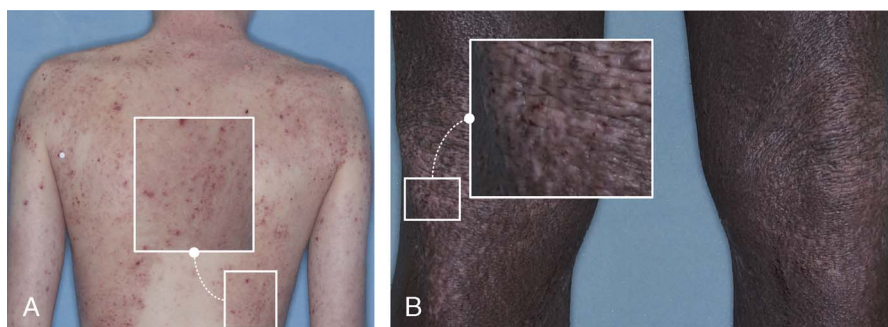


**Figure 2.** Excoriation (scratching) assessment in different skin tones. Excoriation is usually easily identified in light skin (A). In very dark skin (B), excoriations may be masked by background skin pigmentation or dyschromia. Note the significant dyschromia of the knees (right worse than left) and noticeable lichenification involving all the lower extremity skin shown.

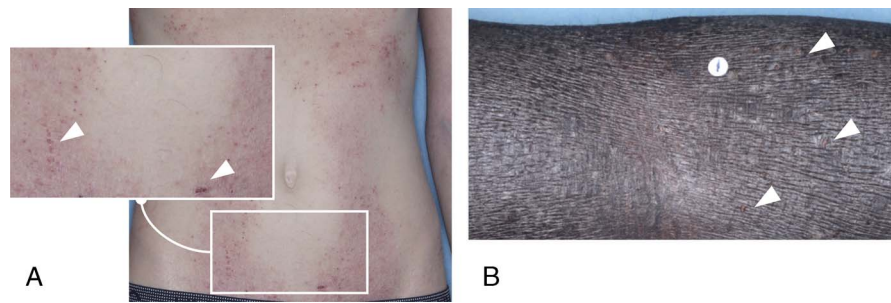


**Figure 3.** Lichenification (thickness) assessment in different skin tones. Lichenification is often challenging to identify in light skin (A) and is typically more easily identified in dark skin (B). Again, note the challenge of identifying excoriations (white arrows) in very dark skin (B) compared with light skin (A).

Patients' constitutional (inherited) skin types are typically categorized using the Fitzpatrick categories (I–VI). Fitzpatrick skin types IV, V, and VI are commonly referred to as SOC.<sup>24</sup> Assessing clinical signs of AD is more challenging in patients with SOC compared with those whose skin contains less epidermal melanin. This challenge may put patients with SOC and AD at an increased risk for misdiagnosis or underestimation of their AD severity. Failure to accurately recognize disease extent and intensity of inflammatory signs may lead to inadequately controlled disease and greater disease burden<sup>25</sup> with possible exacerbation of comorbidities. Undertreatment may, in turn, result in potentially avoidable sequelae such as postinflammatory hyperpigmentation, which is associated with decreased quality of life (QoL) as measured by the Dermatology Life Quality Index (DLQI) or the Patient-Oriented Eczema Measure (POEM).<sup>26</sup> Findings from a notable study suggest that the adverse effects of postinflammatory hyperpigmentation on QoL are associated with Fitzpatrick skin type; patients with the darkest skin tones (type V or VI) experience a greater reduction in QoL related to postinflammatory hyperpigmentation compared with patients with

the lightest skin tones (type I or II).<sup>26</sup> Prurigo nodularis is another possible sequela of undertreated AD, particularly among Black patients.<sup>19</sup> Undertreated AD also drives pruritus, pain, reduced QoL,<sup>27</sup> and susceptibility to skin infections.<sup>28</sup> Photographs presented in the following section depict a subgroup of patients with moderate-to-severe AD who participated in randomized clinical trials. These images provide an opportunity to discuss the challenges of clinical assessment among patients with SOC and AD.

### Clinical Signs of AD Across Fitzpatrick Skin Types in the Context of Eczema Area and Severity Index Assessment

The Eczema Area and Severity Index (EASI) is a validated scoring system used for grading the physical signs of AD.<sup>29</sup> The EASI reflects the extent and severity of 4 common clinical signs of AD: erythema, edema/papulation, excoriation, and lichenification. Extent assessment involves determining the percentage involvement of 4 body areas; severity is rated as none, mild, moderate, or severe.



**Figure 4.** Edema/papulation (swelling) assessment in different skin tones. For better evaluation of edema in light skin, a side-by-side comparison at baseline (A) and after 16 weeks of upadacitinib 15-mg treatment (B) is provided. For better evaluation of edema in dark skin, a top-bottom comparison at baseline (C) and after 16 weeks of upadacitinib 30-mg treatment (D) is provided. Note the marked dyschromia (white boxes), lichenification (white arrows), and grayish discoloration (C) in the patient with dark skin at baseline. Note that excoriations are difficult to assess in the patient with dark skin, whereas both excoriations and erythema are easily identifiable in the patient with light skin (A, B).

The EASI is reported as a number (0–72), which correlates to 1 of 6 AD severity strata: 0, clear; 0.1 to 1.0, almost clear; 1.1 to 7.0, mild; 7.1 to 21.0, moderate; 21.1 to 50.0, severe; and greater than 50.0, very severe.<sup>30</sup> The global Harmonizing Outcome Measures for Eczema initiative recommends EASI as the preferred core outcome measure for assessing the clinical signs of AD in all clinical trials.<sup>29</sup> In clinical trials, efficacy end points are based on the proportion of patients achieving at least a threshold reduction in EASI (ie,  $\geq 50\%$ ,  $\geq 75\%$ , or  $\geq 90\%$  reduction in EASI from baseline [EASI 50, EASI 75, or EASI 90, respectively]).

Data from studies published in 2015<sup>31</sup> and 2002<sup>32</sup> suggest poor reliability of disease severity scoring among patients with highly pigmented skin and varied subjective perceptions of erythema as a

contributing factor. In contrast, data from a 2017 study conducted among 25 patients with AD (11 light skin and 14 SOC) who were assessed by 5 physician evaluators suggest excellent EASI intrarater and interrater reliability for all Fitzpatrick skin types.<sup>33</sup> Although this study was critical to the Harmonizing Outcome Measures for Eczema initiative consensus recommendation to use EASI as the core outcome measure for clinical AD signs, there were limitations. These include small sample size,<sup>33</sup> categorization of skin type into only 2 broad groups (fair skin [types I, II, and III] or SOC [types IV, V, and VI]),<sup>34</sup> and use of extensively experienced evaluators, which may have reduced scoring variability. Additional large-scale studies are needed to further evaluate outcome measures among patients with SOC and AD.

**TABLE 1. Case 1: Clinician- and Patient-Reported Outcomes**

|                                       | Baseline                           | Week 2             | Week 16             |
|---------------------------------------|------------------------------------|--------------------|---------------------|
| Clinician-reported outcomes           |                                    |                    |                     |
| vIGA-AD                               | 4, severe                          | 2, mild            | 2, mild             |
| EASI                                  | 45.5, severe                       | 3.9, mild          | 8.4, moderate       |
| Erythema                              |                                    |                    |                     |
| Head/neck                             | Severe                             | Mild               | Moderate            |
| Lower limb                            | Severe                             | Moderate           | Mild                |
| Trunk                                 | Severe                             | Mild               | Moderate            |
| Upper limb                            | Moderate                           | Mild               | Moderate            |
| Lichenification                       |                                    |                    |                     |
| Head/neck                             | Mild                               | None               | Moderate            |
| Lower limb                            | Moderate                           | Moderate           | None                |
| Trunk                                 | Moderate                           | None               | Moderate            |
| Upper limb                            | Moderate                           | Mild               | Moderate            |
| Excoriation                           |                                    |                    |                     |
| Head/neck                             | Severe                             | Mild               | Moderate            |
| Lower limb                            | Severe                             | None               | Moderate            |
| Trunk                                 | Mild                               | None               | Moderate            |
| Upper limb                            | Moderate                           | None               | None                |
| Edema/papulation                      |                                    |                    |                     |
| Head/neck                             | Mild                               | Mild               | Moderate            |
| Lower limb                            | Moderate                           | Moderate           | None                |
| Trunk                                 | Mild                               | Mild               | Moderate            |
| Upper limb                            | Moderate                           | Mild               | Moderate            |
| Patient-reported outcomes             |                                    |                    |                     |
| DLQI                                  |                                    |                    |                     |
| Sore, painful, or stinging            | A lot                              | A little           | Very much           |
| Embarrassed                           | Very much                          | A little           | A little            |
| Interfered with ADL                   | Very much                          | Not at all         | Not at all          |
| Affected social or leisure activities | A lot                              | Not at all         | Not at all          |
| Prevented working or studying         | Very much                          | Not at all         | Not at all          |
| POEM                                  |                                    |                    |                     |
| Days skin has been itchy              | Every day                          | 3–4 d              | Every day           |
| PGIT                                  |                                    |                    |                     |
| Severity                              | Moderately severe                  | Mild               | Moderate            |
| Change                                |                                    | Very much improved | Very much improved  |
| Treatment                             | Neither dissatisfied nor satisfied | Very satisfied     | Extremely satisfied |

ADL, activities of daily living; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PGIT, Patient Global Impression of Treatment; POEM, Patient-Oriented Eczema Measure; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

The challenge in using EASI to assess AD disease severity centers on the variable appearance of its component clinical signs among patients with different Fitzpatrick skin types. Some clinical signs are more difficult to assess in patients with SOC (erythema and excoriations), whereas others are easier (lichenification and prurigo nodules). In the subsequent section, we explore challenges associated with the assessment of each of the 4 clinical signs included in EASI using a photographic review. A subset of patients with moderate-to-severe AD and different Fitzpatrick skin types who participated in phase 3 clinical trials that evaluated the safety and efficacy of upadacitinib monotherapy (Measure Up 1 [NCT03569293] and Measure Up 2 [NCT03607422])<sup>35</sup> consented to have their AD skin lesions photographed at baseline and during treatment as part of an exploratory photographic substudy. The photographs demonstrate some of the nuances and challenges of assessing clinical signs of AD in light versus dark skin.

### Erythema

Erythema is defined as redness of the skin (or mucous membranes) caused by a localized increase in cutaneous blood flow. It is an indicator of underlying skin inflammation and a hallmark sign of AD. Erythema is usually easily identified in light skin (Fig. 1A) but can be more challenging to assess in dark skin (Fig. 1B). The increase in cutaneous blood flow with erythema equates to a higher concentration of

oxyhemoglobin in the superficial skin imparting a pink/red tone. Hues in the pink/red color group are easily perceived in patients with light skin because of the relatively low concentration of melanin. In patients with SOC, however, higher levels of epidermal melanin make appreciating the intensity of erythema more difficult. The affected skin can appear as any of a variety of hues in the red, brown, purple (violaceous), or gray color groups.

In Figure 1B, the normal skin tone of the patient's midchest region is contrasted with the violaceous color of the patient's abdominal skin. Notably, patients with SOC are at an increased risk for the development of hyperpigmentation, hypopigmentation, and/or dyschromia (ie, skin discoloration or patches of uneven color) secondary to a skin inflammatory process, such as AD.<sup>36</sup> Inflammatory mediators and reactive oxygen species can stimulate cutaneous melanocytes, triggering increased melanin production and deposition.<sup>36</sup> This may result in darkening or discoloration of the affected skin, making the assessment of erythema during AD flares more challenging. Marked dyschromia of the antecubital fossa skin can be seen in Figure 1B.

### Excoriation

Excoriation refers to abrasion of the epidermis with exposure (and possibly partial loss) of the underlying dermis. In patients with AD, excoriations occur because of vigorous scratching triggered by



**Figure 5.** Case 1 at baseline, week 2, and week 16 of upadacitinib treatment. Patient experienced improvement in clinical signs after 2 weeks of upadacitinib 15-mg treatment, moving from EASI severe at baseline (A, D) to mild at week 2 (B, E) and moderate at week 16 (C, F).

pruritus and characteristically appear as linear or punctate pink/red marks covered by serous crusts. Excoriations are easily identified in people with light skin (Fig. 2A) but may be difficult to identify in patients with very dark skin (type VI) because of the background skin tone or dyschromia (Fig. 2B).

Because pruritus is a hallmark feature of AD,<sup>37</sup> scratching and subsequent excoriations are exceedingly common with active disease. A recent systematic review and meta-analysis of studies from across the globe reported pruritus as the most common clinical characteristic of AD, with an overall prevalence of 94%.<sup>38</sup>

## Lichenification

Over time, chronic pruritus and associated scratching may result in lichenification, a process wherein the epidermis thickens because of

irregular hyperplasia of the stratum spinosum (ie, irregular acanthosis) in response to rubbing and long-standing disease. Characteristic features include thick leathery skin and exaggerated skin lines.<sup>39</sup> In contrast to excoriations, lichenification is more challenging to identify in patients with light skin (Fig. 3A) compared with patients with dark skin (Fig. 3B). Lichenification is a common clinical finding among patients with AD; a recent systematic review and meta-analysis reported an overall prevalence of 66%.<sup>38</sup> However, lichenification presents more frequently in patients with SOC—specifically those of Southeastern Asian or African descent<sup>38</sup>—than in patients of other races/ethnicities, possibly because of more prolonged<sup>19</sup> and/or more severe pruritus.<sup>14,40</sup> The more prominent lichenification presentation among patients with SOC may be due to genetic differences in epidermal biology

**TABLE 2. Case 2: Clinician- and Patient-Reported Outcomes**

|                                       | Baseline               | Week 16             |
|---------------------------------------|------------------------|---------------------|
| Clinician-reported outcomes           |                        |                     |
| vIGA-AD                               | 4, severe              | 1, almost clear     |
| EASI                                  | 44.8, severe           | 1.6, mild           |
| Erythema                              |                        |                     |
| Head/neck                             | Mild                   | None                |
| Lower limb                            | Severe                 | Mild                |
| Trunk                                 | Severe                 | None                |
| Upper limb                            | Severe                 | None                |
| Lichenification                       |                        |                     |
| Head/neck                             | Mild                   | None                |
| Lower limb                            | Severe                 | Mild                |
| Trunk                                 | Severe                 | None                |
| Upper limb                            | Severe                 | Mild                |
| Excoriation                           |                        |                     |
| Head/neck                             | Mild                   | None                |
| Lower limb                            | Severe                 | None                |
| Trunk                                 | Severe                 | Mild                |
| Upper limb                            | Severe                 | None                |
| Edema/papulation                      |                        |                     |
| Head/neck                             | Mild                   | None                |
| Lower limb                            | Moderate               | None                |
| Trunk                                 | Severe                 | Mild                |
| Upper limb                            | Severe                 | None                |
| Patient-reported outcomes             |                        |                     |
| DLQI                                  |                        |                     |
| Sore, painful, or stinging            | A lot                  | A little            |
| Embarrassed                           | Very much              | A little            |
| Interfered with ADL                   | A lot                  | A little            |
| Affected social or leisure activities | A lot                  | A little            |
| Prevented working or studying         | Yes                    | No                  |
| POEM                                  |                        |                     |
| Days skin has been itchy              | Every day              | Every day           |
| PGIT                                  |                        |                     |
| Severity                              | Moderately severe      | Minimal             |
| Change                                |                        | Very much improved  |
| Treatment                             | Extremely dissatisfied | Extremely satisfied |

ADL, activities of daily living; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PGIT, Patient Global Impression of Treatment; POEM, Patient-Oriented Eczema Measure; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

or immune deviation, both of which have been reported among Black patients with AD.<sup>41–44</sup>

### Edema/Papulation

There is a lack of literature addressing potential challenges of assessing edema/papulation in patients with AD. Perhaps because of the predominantly 3-dimensional nature of these signs, assessment might be accomplished with equivalent ease across the spectrum of Fitzpatrick skin types (Fig. 4), although edema may be difficult to identify in patients with severe lichenification. Edema/papulation is generally best assessed and rated by palpation.

### Addressing Challenges in the Clinical Evaluation of AD

Honing clinical evaluation skills requires adequate training and practice. There is an unmet need in dermatologic training among medical students as well as early-career and experienced dermatologists regarding awareness and recognition of the unique presentations of a variety of skin diseases in patients with SOC.<sup>45–51</sup> Addressing the shortage of images depicting skin lesions in patients with SOC is a key aspect of meeting this educational need. The historic scarcity of educational photographic images of patients with SOC may be due, in part, to limitations of film photography to accurately capture what is observed with the human eye.<sup>52</sup> The advent of digital photography, however, has mitigated many of these obstacles.<sup>52</sup> The International Skin Imaging Collaboration technical guidelines<sup>53</sup> provide recommendations to help clinicians and medical photographers take high-quality patient photographs, addressing issues such as appropriate lighting, background color, field of view, image orientation, focus and depth of field, resolution, and scale and color calibration.

Improving clinical training regarding the nuanced presentation of AD and increasing the availability of photographs depicting AD-related skin lesions in patients with SOC—such as those presented

herein—can aid dermatologists in both clinical trials and clinical practice. Enhancing the capacity to accurately assess disease severity in patients with SOC and AD to avoid possible underestimation of disease activity is of particular educational importance, because such underestimation may adversely affect monitoring and effective management of patients with SOC and AD. Accurate assessment of AD disease severity is also crucial to ensure the scientific integrity of clinical trials, given that the EASI is a core outcome measure and the Validated Investigator Global Assessment for AD (vIGA-AD) is based on clinical signs of the disease, including erythema. It is also important to enroll sufficient numbers of patients with SOC into AD clinical trials to ensure adequate statistical power to identify potential differences in response to treatment among specific racial/ethnic populations, something that has been lacking historically.<sup>54</sup> Selection of clinical research organizations, clinical trial investigators, and groups that have an informed understanding of the need for more diversity in clinical trials is critically important.

Additional studies are required to further evaluate the potential implications of subjective perceptual differences in identifying and accurately assessing the clinical signs of AD.<sup>34</sup> Looking ahead, ongoing research into new optical science technologies (eg, handheld colorimeters and pocket-sized spectral imaging devices) may one day offer clinicians a more objective mechanism by which to measure certain features of AD (eg, erythema, hypopigmentation, hyperpigmentation, and dyschromia) across the full diverse spectrum of skin tones.<sup>55</sup> Some preliminary, but potentially promising, proof-of-concept research examining the feasibility of conducting EASI assessments using convolutional neural networks (a form of artificial intelligence) is also underway.<sup>56</sup> Importantly, the development of accurate assessments using artificial intelligence requires training data sets depicting the full spectrum of skin tones, particularly images from persons with SOC.

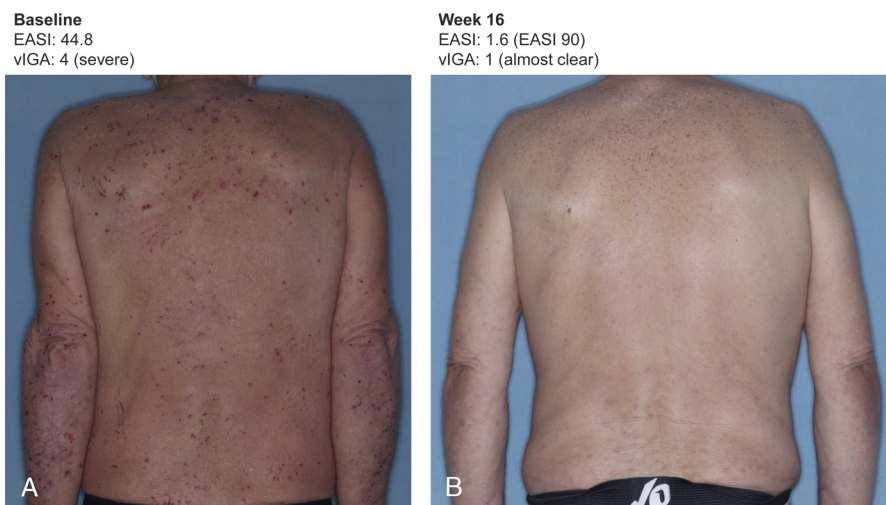


**Figure 6.** Case 2 at baseline and week 16 of upadacitinib treatment. Patient went from EASI severe at baseline (A) to mild (B) with 16 weeks of upadacitinib 15-mg treatment.

## EXAMPLES OF BASELINE AND LONGITUDINAL ASSESSMENTS OF AD ACROSS FITZPATRICK SKIN TYPES

In the following photographic case series, we present baseline and longitudinal treatment images from 4 patients who participated in phase 3, randomized, double-blind, placebo-controlled clinical trials (Measure Up 1 and Measure Up 2) conducted to assess the efficacy and safety of once-daily oral upadacitinib for the treatment of adolescents (12 years or older) and adults with moderate-to-severe AD. Results from these trials demonstrate the potential of upadacitinib as a treatment option for adolescents and adults with moderate-to-severe AD.<sup>35</sup> The photographs depict a range of moderate-to-severe AD disease at baseline (EASI, 32.7–66.8) and visually illustrate

EASI responses among patients with different estimated Fitzpatrick skin types, alongside patient-reported outcomes collected at the corresponding visits.

### Case 1

Case 1 is a male patient aged 21 years with estimated Fitzpatrick skin types I to II and a history of moderate-to-severe AD for more than 20 years. Previous AD medications included topical and oral steroids, methotrexate, and cyclosporine. At baseline, the patient's AD was rated as severe per the vIGA-AD (Table 1). His baseline EASI was 45.5 (severe; Table 1; Figs. 5A, D). Patient-reported outcomes at baseline reflected a substantial burden of AD on the patient's QoL (Table 1). After 2 weeks of systemic upadacitinib therapy (15 mg

**TABLE 3. Case 3: Clinician- and Patient-Reported Outcomes**

|                                       | Baseline                           | Week 16             |
|---------------------------------------|------------------------------------|---------------------|
| Clinician-reported outcomes           |                                    |                     |
| vIGA-AD                               | 4, severe                          | 1, almost clear     |
| EASI                                  | 42.0, severe                       | 0.6, almost clear   |
| Erythema                              |                                    |                     |
| Head/neck                             | Mild                               | None                |
| Lower limb                            | Mild                               | None                |
| Trunk                                 | None                               | None                |
| Upper limb                            | Mild                               | None                |
| Lichenification                       |                                    |                     |
| Head/neck                             | Severe                             | None                |
| Lower limb                            | Severe                             | Mild                |
| Trunk                                 | Severe                             | None                |
| Upper limb                            | Severe                             | Mild                |
| Excoriation                           |                                    |                     |
| Head/neck                             | Moderate                           | None                |
| Lower limb                            | Moderate                           | None                |
| Trunk                                 | Mild                               | None                |
| Upper limb                            | Moderate                           | None                |
| Edema/papulation                      |                                    |                     |
| Head/neck                             | Severe                             | None                |
| Lower limb                            | Severe                             | None                |
| Trunk                                 | Severe                             | None                |
| Upper limb                            | Severe                             | None                |
| Patient-reported outcomes             |                                    |                     |
| DLQI                                  |                                    |                     |
| Sore, painful, or stinging            | Very much                          | Not at all          |
| Embarrassed                           | A lot                              | Not at all          |
| Interfered with ADL                   | A little                           | Not at all          |
| Affected social or leisure activities | A lot                              | Not at all          |
| Prevented working or studying         | No                                 | No                  |
| POEM                                  |                                    |                     |
| Days skin has been itchy              | Every day                          | No days             |
| PGIT                                  |                                    |                     |
| Severity                              | Moderately severe                  | Minimal             |
| Change                                |                                    | Very much improved  |
| Treatment                             | Neither dissatisfied nor satisfied | Extremely satisfied |

ADL, activities of daily living; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PGIT, Patient Global Impression of Treatment; POEM, Patient-Oriented Eczema Measure; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

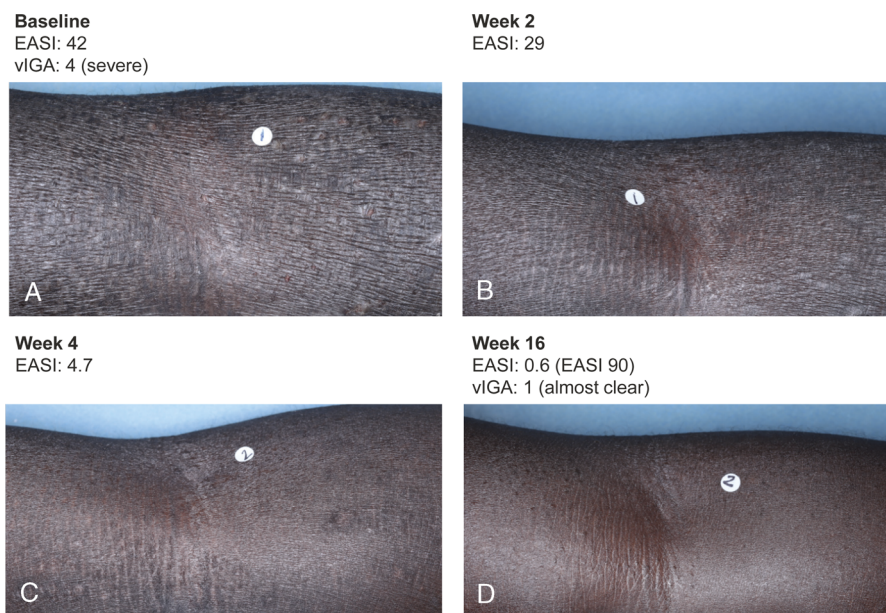


**Figure 7.** Case 3 at baseline and weeks 2, 4, and 16. The EASI was severe at baseline (A) and week 2 (B), mild at week 4 (C), and almost clear after 16 weeks of upadacitinib 30-mg treatment (D).

daily), his EASI decreased to 3.9 (mild), an improvement of more than 90% compared with baseline (achieved EASI 90; Figs. 5B, E). At week 16, his EASI was 8.4 (moderate; Table 1; Figs. 5C, F). Improvements in patient-reported DLQI, POEM, and the Patient Global Impression of Treatment (PGIT) were noted (Table 1).

## Case 2

Case 2 is a male patient aged 65 years with an estimated Fitzpatrick skin types III to IV and a history of moderate-to-severe AD for more

than 4 years. Previous AD medications included topical steroids and topical calcineurin inhibitors. The patient's AD was rated as severe at baseline per the vIGA-AD (Table 2). His baseline EASI was 44.8 (severe; Table 2, Fig. 6A). Patient-reported outcomes at baseline reflected a substantial burden of AD on the patient's QoL (Table 2). After 16 weeks of systemic upadacitinib therapy (15 mg daily), his EASI decreased to 1.6 (mild), an improvement of more than 96% compared with baseline (achieved EASI 90; Table 2, Fig. 6B). Improvements in patient-reported DLQI and PGIT were noted (Table 2).

**TABLE 4. Case 4: Clinician- and Patient-Reported Outcomes**

|                             | Baseline          | Week 16      | Week 40   |
|-----------------------------|-------------------|--------------|-----------|
| Clinician-reported outcomes |                   |              |           |
| vIGA-AD                     | 4, severe         | 3, moderate  | 2, mild   |
| EASI                        | 65.2, very severe | 27.9, severe | 4.8, mild |
| Erythema                    |                   |              |           |
| Head/neck                   | Severe            | Moderate     | None      |
| Lower limb                  | Severe            | Severe       | Moderate  |
| Trunk                       | Severe            | Moderate     | None      |
| Upper limb                  | Severe            | Moderate     | None      |
| Lichenification             |                   |              |           |
| Head/neck                   | Severe            | None         | None      |
| Lower limb                  | Severe            | Moderate     | Mild      |
| Trunk                       | Severe            | Mild         | None      |
| Upper limb                  | Severe            | Moderate     | None      |
| Excoriation                 |                   |              |           |
| Head/neck                   | Moderate          | None         | None      |
| Lower limb                  | Severe            | Severe       | Moderate  |
| Trunk                       | Moderate          | None         | None      |

(Continued on next page)

**TABLE 4.** (Continued)

|                                       | Baseline           | Week 16               | Week 40            |
|---------------------------------------|--------------------|-----------------------|--------------------|
| Upper limb                            | Severe             | Mild                  | None               |
| Edema/papulation                      |                    |                       |                    |
| Head/neck                             | Severe             | Mild                  | None               |
| Lower limb                            | Severe             | Moderate              | Mild               |
| Trunk                                 | Severe             | Moderate              | None               |
| Upper limb                            | Severe             | Moderate              | None               |
| Patient-reported outcomes             |                    |                       |                    |
| DLQI                                  |                    |                       |                    |
| Sore, painful, or stinging            | Very much          | Very much             | A little           |
| Embarrassed                           | Very much          | Very much             | A little           |
| Interfered with ADL                   | Very much          | Very much             | A little           |
| Affected social or leisure activities | Very much          | Very much             | A little           |
| Prevented working or studying         | Yes                | Yes                   | No                 |
| POEM                                  |                    |                       |                    |
| Days skin has been itchy              | Every day          | Every day             | 3–4 d              |
| PGIT                                  |                    |                       |                    |
| Severity                              | Moderate           | Moderately severe     | Moderate           |
| Change                                |                    | Minimally improved    | Minimally improved |
| Treatment                             | Somewhat satisfied | Somewhat dissatisfied | Somewhat satisfied |

ADL, activities of daily living; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PGIT, Patient Global Impression of Treatment; POEM, Patient-Oriented Eczema Measure; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

### Case 3

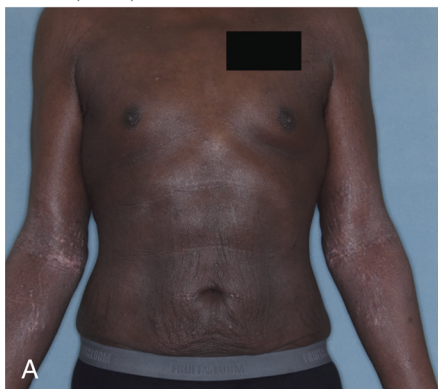
Case 3 is a male patient aged 18 years with estimated Fitzpatrick skin type VI and a history of moderate-to-severe AD for more than 15 years. Previous AD medications included topical steroids. The patient's AD was rated severe at baseline per the vIGA-AD (Table 3). His baseline EASI was 42.0 (severe; Table 3, Fig. 7A). Patient-reported outcomes at baseline reflected a substantial burden of AD on the patient's QoL (Table 3). Figures 7B to D show the patient's skin after 2, 4, and 16 weeks of treatment with systemic upadacitinib therapy (30 mg daily). By week 16, his EASI decreased to 0.6 (almost clear), an improvement of more than 98% compared

with baseline (achieved EASI 90; Table 3, Fig. 7D). Improvements in patient-reported DLQI, POEM, and PGIT were noted (Table 3).

### Case 4

Case 4 is a male patient aged 41 years with estimated Fitzpatrick skin type VI and a history of moderate-to-severe AD for more than 10 years. Previous AD medications included topical steroids. The patient's AD was rated as severe at baseline per the vIGA-AD (Table 4). His baseline EASI was 65.2 (very severe; Table 4, Fig. 8A) compared with 27.9 (severe; Table 4, Fig. 8B) at treatment week 16. At baseline, multiple shades of erythema

**Baseline**  
EASI: 65.2  
vIGA: 4 (severe)



**Week 16**  
EASI: 27.9 (EASI 50)  
vIGA: 3 (moderate)

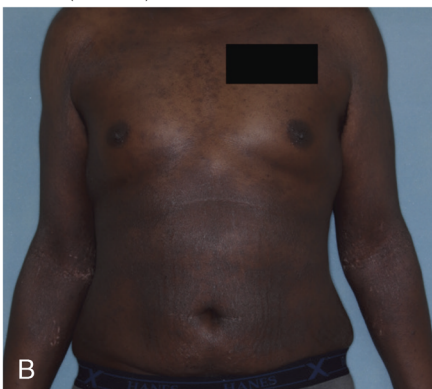


**Figure 8.** Case 4 at baseline and week 16. Patient went from EASI very severe at baseline (A) to severe (EASI 50) after 16 weeks of upadacitinib 30-mg treatment (B).

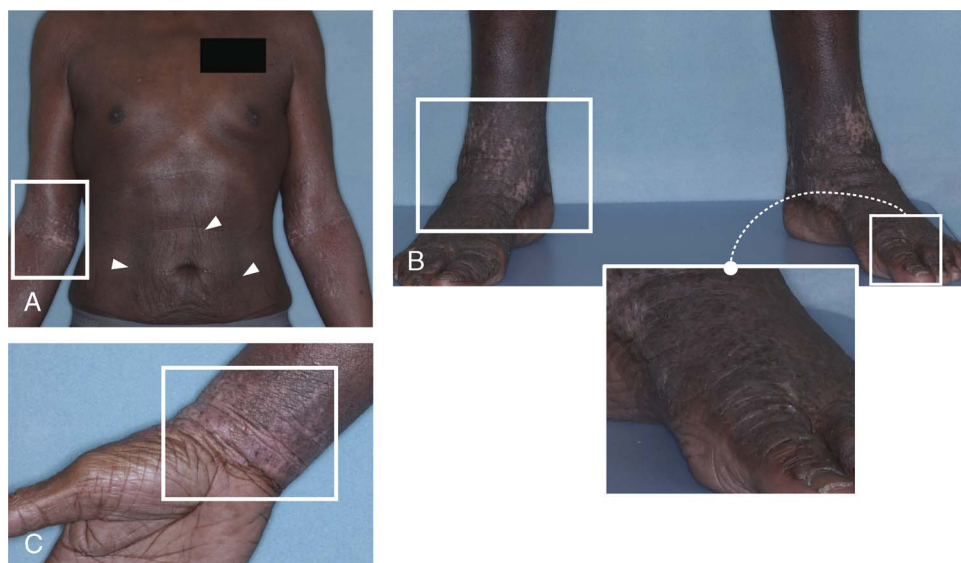


**Figure 9.** Case 4 baseline erythema, lichenification, and dyschromia. At baseline, the patient exhibited multiple shades of erythema including violaceous discoloration of the abdominal skin (A, white arrows); grayish discoloration of the dorsal feet (B, inset); and profound lichenification of the elbows (A, white boxes), lower extremities (B), and wrist (C).

can be seen in this patient, including violaceous discoloration of the abdominal skin (Fig. 9A) and grayish discoloration on the dorsal feet (Fig. 9B). The cause of the grayish discoloration has not been elucidated but may represent an optical effect of xerosis on dark background skin pigmentation and/or postinflammatory hyperpigmentation. Although hyperpigmentation and xerosis are

not signs of active disease, it is important for treating physicians to recognize the adverse effects of these findings on patients' QoL. Substantial lichenification and dyschromia can be observed on the elbows, lower extremities, and wrists (Figs. 9A–C). Patient-reported outcomes at baseline reflected a substantial burden of AD on the patient's QoL (Table 4). After 16 weeks of treatment with systemic

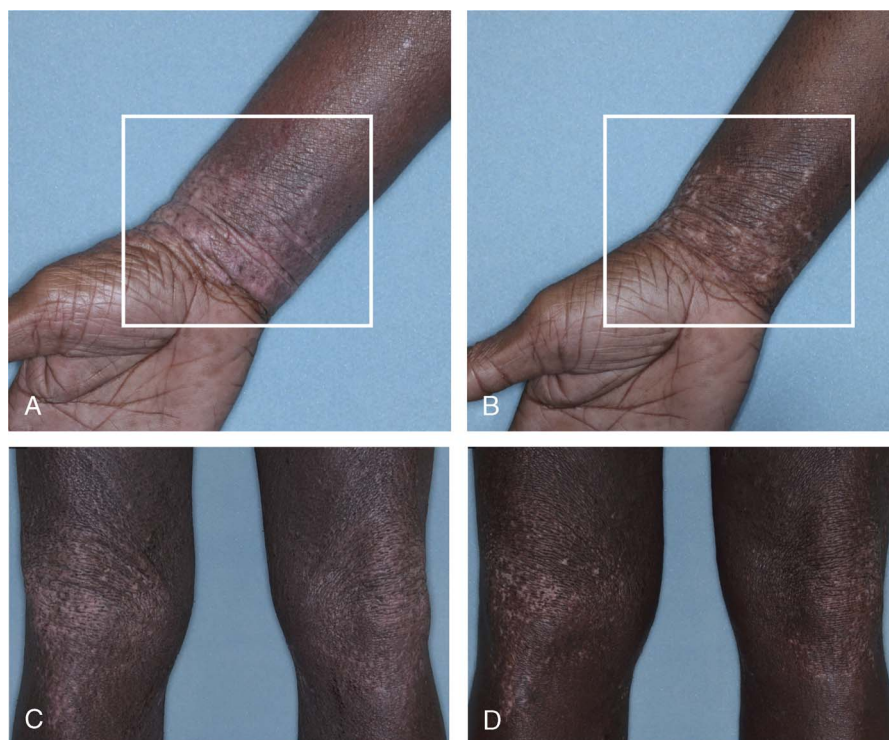


**Figure 10.** Case 4 dyschromia at baseline and week 16. Significant improvement was observed in dyschromia from baseline (A, C) to week 16 on upadacitinib 30-mg treatment (B, D).

upadacitinib therapy (30 mg daily), his EASI decreased to 27.9 (severe), an improvement of more than 55% compared with baseline (achieved EASI 50). Compared with baseline (Figs. 10A, C), notable improvement in this patient's dyschromia was observable at week 16 (Figs. 10B, D).

Despite the reduction in EASI, this patient did not achieve the primary end point of greater than or equal to 75% decrease from baseline in EASI (EASI 75) at week 16. There were no improvements in patient-reported DLQI or POEM at week 16 (Table 4), and assessment of patient satisfaction using the PGIT indicated that the patient was somewhat dissatisfied with treatment at week 16. At treatment week 40 (no photographs available), the EASI was 4.8 (mild) and the patient's AD was rated as mild per the vIGA-AD (Table 4). Patient-reported improvements in DLQI, POEM, and PGIT were also noted (Table 4). The patient reported substantial improvement regarding activities of daily living such as working, studying, and sleeping, although he still experienced significant pruritus 3 to 4 days per week.

## SUMMARY

Atopic dermatitis is a common, chronic inflammatory skin condition that confers a substantial disease burden. It is phenotypically and endotypically heterogeneous across age and race/ethnicity. The clinical presentation of AD commonly differs between patients with SOC and patients with light skin, particularly with respect to some EASI components (ie, erythema, excoriations, and lichenification), as demonstrated in the photographic review. These differences pose challenges for clinicians in terms of accurate assessment and monitoring of disease activity, as discussed in the case series presentations. Data suggest that patients with SOC are at an increased risk for moderate-to-severe AD, highlighting the importance of diverse Fitzpatrick skin type representation in clinical trials and educational materials. Notably, some of the clinical features of AD may take longer to resolve in patients with SOC compared with patients with lighter skin. Therefore, it is important to consider patient-related outcomes alongside clinical features of AD when assessing and monitoring response to treatment. We present this report for training purposes to aid medical students, dermatologists in training, experienced dermatologists, and other clinicians in their ability to accurately assess clinical signs of AD across a diverse spectrum of Fitzpatrick skin tones in both clinical practice and clinical trial settings.

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## REFERENCES

- Weidinger S, Beck LA, Bieber T, et al. Atopic dermatitis. *Nat Rev Dis Primers* 2018;4(1):1.
- Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. *Br J Dermatol* 2021;184(2):304–309.
- Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013;132(5):1132–1138.
- United States Census Bureau. 2020 Census apportionment news conference transcript. Available at: <https://www.census.gov/newsroom/press-kits/2021/2020-census-apportionment-counts.html>. Accessed May 14, 2021.
- Karimkhani C, Dellavalle RP, Coffeng LE, et al. Global skin disease morbidity and mortality: an update from the Global Burden of Disease Study 2013. *JAMA Dermatol* 2017;153(5):406–412.
- Abuabara K, You Y, Margolis DJ, et al. Genetic ancestry does not explain increased atopic dermatitis susceptibility or worse disease control among African American subjects in 2 large US cohorts. *J Allergy Clin Immunol* 2020;145(1):192–198.e11.
- Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131(1):67–73.
- Odhambo JA, Williams HC, Clayton TO, et al. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. *J Allergy Clin Immunol* 2009;124(6):1251–1258.e23.
- Giolomoni G, de Bruin-Weller M, Aoki V, et al. Nomenclature and clinical phenotypes of atopic dermatitis. *Ther Adv Chronic Dis* 2021;12:20406223211002979.
- Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups—variations in epidemiology, genetics, clinical presentation and treatment. *Exp Dermatol* 2018;27(4):340–357.
- Tackett KJ, Jenkins F, Morrell DS, et al. Structural racism and its influence on the severity of atopic dermatitis in African American children. *Pediatr Dermatol* 2020;37(1):142–146.
- Vachiramon V, Tey HL, Thompson AE, et al. Atopic dermatitis in African American children: addressing unmet needs of a common disease. *Pediatr Dermatol* 2012;29(4):395–402.
- Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol* 2017;13(1):15–26.
- Nomura T, Wu J, Kabashima K, et al. Endophenotypic variations of atopic dermatitis by age, race, and ethnicity. *J Allergy Clin Immunol Pract* 2020;8(6):1840–1852.
- Czarnowicki T, He H, Krueger JG, et al. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol* 2019;143(1):1–11.
- Silverberg JI, Vakharia PB, Chopra R, et al. Phenotypical differences of childhood- and adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract* 2018;6(4):1306–1312.
- Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. *Ann Allergy Asthma Immunol* 2019;122(5):449–455.
- Bakker DS, Nierkens S, Knol EF, et al. Confirmation of multiple endotypes in atopic dermatitis based on serum biomarkers. *J Allergy Clin Immunol* 2021;147(1):189–198.
- McColl M, Boozalis E, Aguh C, et al. Pruritus in black skin: unique molecular characteristics and clinical features. *J Natl Med Assoc* 2021;113(1):30–38.
- Silverberg JI, Gelfand JM, Margolis DJ, et al. Atopic dermatitis in US adults: from population to health care utilization. *J Allergy Clin Immunol Pract* 2019;7(5):1524–1532.e2.
- Wan J, Oganisian A, Spieker AJ, et al. Racial/ethnic variation in use of ambulatory and emergency care for atopic dermatitis among US children. *J Invest Dermatol* 2019;139(9):1906–1913.e1.
- Fischer AH, Shin DB, Margolis DJ, et al. Racial and ethnic differences in health care utilization for childhood eczema: an analysis of the 2001–2013 Medical Expenditure Panel Surveys. *J Am Acad Dermatol* 2017;77(6):1060–1067.

23. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol* 2014;70(2):338–351.
24. Taylor SC, Cook-Bolden F. Defining skin of color. *Cutis* 2002;69(6):435–437.
25. Wei W, Anderson P, Gadkari A, et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. *J Dermatol* 2018;45(2):150–157.
26. Maymone MBC, Neamah HH, Wirya SA, et al. The impact of skin hyperpigmentation and hyperchromia on quality of life: a cross-sectional study. *J Am Acad Dermatol* 2017;77(4):775–778.
27. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol* 2020;156(1):44–56.
28. Wang V, Boguniewicz J, Boguniewicz M, et al. The infectious complications of atopic dermatitis. *Ann Allergy Asthma Immunol* 2021;126(1):3–12.
29. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014;134(4):800–807.
30. Leshem YA, Hajar T, Hanifin JM, et al. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol* 2015;172(5):1353–1357.
31. Zhao CY, Wijayanti A, Doria MC, et al. The reliability and validity of outcome measures for atopic dermatitis in patients with pigmented skin: a grey area. *Int J Womens Dermatol* 2015;1(3):150–154.
32. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in Black children compared with their white counterparts. *Br J Dermatol* 2002;147(5):920–925.
33. Zhao CY, Hao EY, Oh DD, et al. A comparison study of clinician-rated atopic dermatitis outcome measures for intermediate- to dark-skinned patients. *Br J Dermatol* 2017;176(4):985–992.
34. Chansky PB, Mittal L, Werth VP. Dermatological evaluation in patients with skin of colour: the effect of erythema on outcome measures in atopic dermatitis. *Br J Dermatol* 2017;176(4):853–854.
35. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet* 2021;397:2151–2168.
36. Callender VD, St Surin-Lord S, Davis EC, et al. Postinflammatory hyperpigmentation: etiologic and therapeutic considerations. *Am J Clin Dermatol* 2011;12(2):87–99.
37. Galli E, Cinicola B, Carello R, et al. Atopic dermatitis. *Acta Biomed* 2020;91(11-S):e2020011.
38. Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *J Am Acad Dermatol* 2019;80(2):390–401.
39. Glazenburg EJ, Mulder PG, Oranje AP. A statistical model to predict the reduction of lichenification in atopic dermatitis. *Acta Derm Venereol* 2015;95(3):294–297.
40. Shaw FM, Luk KMH, Chen KH, et al. Racial disparities in the impact of chronic pruritus: a cross-sectional study on quality of life and resource utilization in United States veterans. *J Am Acad Dermatol* 2017;77(1):63–69.
41. Alexis AF, Woolery-Lloyd H, Williams K, et al. Racial/ethnic variations in skin barrier: implications for skin care recommendations in skin of color. *J Drugs Dermatol* 2021;20(9):932–938.
42. Wongvibulsin S, Sutaria N, Kannan S, et al. Transcriptomic analysis of atopic dermatitis in African Americans is characterized by T<sub>H</sub>2/T<sub>H</sub>17-centered cutaneous immune activation. *Sci Rep* 2021;11(1):11175.
43. Girardeau-Hubert S, Deneuve C, Pigeon H, et al. Reconstructed skin models revealed unexpected differences in epidermal African and Caucasian skin. *Sci Rep* 2019;9(1):7456.
44. Muizzuddin N, Hellemans L, Van Overloop L, et al. Structural and functional differences in barrier properties of African American, Caucasian and East Asian skin. *J Dermatol Sci* 2010;59(2):123–128.
45. Alvarado SM, Feng H. Representation of dark skin images of common dermatologic conditions in educational resources: a cross-sectional analysis. *J Am Acad Dermatol* 2021;84(5):1427–1431.
46. Bellicoso E, Quick SO, Ayoo KO, et al. Diversity in dermatology? An assessment of undergraduate medical education. *J Cutan Med Surg* 2021;25:409–417.
47. Perlman KL, Williams NM, Egbeto IA, et al. Skin of color lacks representation in medical student resources: a cross-sectional study. *Int J Womens Dermatol* 2021;7(2):195–196.
48. Fenton A, Elliott E, Shahbandi A, et al. Medical students' ability to diagnose common dermatologic conditions in skin of color. *J Am Acad Dermatol* 2020;83(3):957–958.
49. Perlman KL, Klein EJ, Park JH. Racial disparities in dermatology training: the impact on Black patients. *Cutis* 2020;106(6):300–301.
50. Nijhawan RI, Jacob SE, Woolery-Lloyd H. Skin of color education in dermatology residency programs: does residency training reflect the changing demographics of the United States? *J Am Acad Dermatol* 2008;59(4):615–618.
51. Ebade T, Papier A. Disparities in dermatology educational resources. *J Am Acad Dermatol* 2006;55(4):687–690.
52. Scheinfeld N. Film photography's limitations in imaging skin of color underlies racial imaging disparities; new digital photography features facilitate the imaging of skin of color. *J Am Acad Dermatol* 2008;59(2):351–352.
53. Finnane A, Curiel-Lewandrowski C, Wimberley G, et al. Proposed technical guidelines for the acquisition of clinical images of skin-related conditions. *JAMA Dermatol* 2017;153(5):453–457.
54. Montgomery SNB, Elbuluk N. A quantitative analysis of research publications focused on the top chief complaints in patients with skin of color. *J Am Acad Dermatol* 2021;85(1):241–242.
55. Abdlaty R, Hayward J, Farrell T, et al. Skin erythema and pigmentation: a review of optical assessment techniques. *Photodiagnosis Photodyn Ther* 2021;33:102127.
56. Bang CH, Yoon JW, Ryu JY, et al. Automated severity scoring of atopic dermatitis patients by a deep neural network. *Sci Rep* 2021;11(1):6049.