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ORIGINAL ARTICLE

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# The erythema Q-score, an imaging biomarker for redness in skin inflammation

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## Abstract

Physician rating of cutaneous erythema is central to clinical dermatological assessment as well as quantification of outcome measures in clinical trials in a number of dermatologic conditions. However, issues with inter-rater reliability and variability in the setting of higher Fitzpatrick skin types make visual erythema assessment unreliable. We developed and validated a computer-assisted image-processing algorithm (EQscore) to reliably quantify erythema (across a range of skin types) in the dermatology clinical setting.

Our image processing algorithm evaluated erythema based upon green light suppression differentials between affected and unaffected skin. A group of four dermatologists used a 4-point Likert scale as a human evaluation of similar erythematous patch tests. The algorithm and dermatologist scores were compared across 164 positive patch test reactions. The intra-class correlation coefficient of groups and the correlation coefficient between groups were calculated. The EQscore was validated on and independent image set of psoriasis, minimal erythema dose testing and steroid-induced blanching images. The reliability of the erythema quantification method produced an intra-class correlation coefficient of 0.84 for the algorithm and 0.67 for dermatologists. The correlation coefficient between groups was 0.85. The EQscore demonstrated high agreement with clinical scoring and superior reliability compared with clinical scoring, avoiding the pitfalls of erythema underrating in the setting of pigmentation. The EQscore is easily accessible (http://lab.rockefeller.edu/krueger/EQscore), user-friendly, and may allow dermatologists to more readily and accurately rate the severity of dermatological conditions and the response to therapeutic treatments.

Software Download Available: http://lab.rockefeller.edu/krueger/EQScore.

KEYWORDS
biomarkers, inflammation, inflammatory skin diseases

## 1 | BACKGROUND

Physician assessment and measurement of cutaneous erythema are central to the assessment of a number of dermatological conditions including psoriasis, acne, atopic dermatitis and irritant/allergic contact dermatitis.[1,2] Erythema is defined as skin redness as a result of injury or irritation causing dilatation of the superficial capillaries and is highly subjective when assessed through visual inspection.[1-3] Erythema is also an essential component in the quantification of clinical outcome measures including the PASI and EASI scores[3,4] used in therapeutic clinical trials of new pharmacotherapies in psoriasis and atopic dermatitis respectively. Despite its clinical significance and role in outcome measures for clinical trials, a highly reliable, objective measurement system for erythema is lacking.[1-4] The most common system used in formal outcome measurements includes the 4-point Likert scale, with a grade of 1 to indicate mild, 2- moderate, 3- severe and 4- very severe.[1,2] Subjective assessment with this scale is prone to variation based upon color perception, training and psychological factors.[2-4] Scales with continuous measurement or a greater number of discrete measurement points are more prone to wide inter-rater variation.[1,2] Other factors such as illuminating light, intensity, saturation, brightness and background Fitzpatrick skin type[4] can also affect the way in which colors are perceived.[3] Hence, the inter-rater reliability of erythema between physicians is only moderate.[5,6]

Objective assessment of erythema using image analysis technologies overcomes the issues with subjective measurement bias and poor reliability, but can be dependent upon the camera used and circumstantial conditions, such as illumination and distance from objects.[7] Scanning reflectance spectrophotometers, tri-stimulus colorimetric instruments and narrow band simple reflectance meters do not vary based upon illumination and other situational factors, but can be costly, cumbersome and are not implementable on a large scale in clinical settings.[8] The wide and rapid proliferation of smartphones provide opportunity for a relatively standardized imaging technology to be utilized for the objective assessment of dermatologic variables such as erythema.[9,10] Imaging processing algorithms can analyse the ratio of red light to green light reflecting from the skin (which is higher for inflamed areas than for normal skin), ratios and variables which are independent from situational factors complicating other image analysis technologies.[7]

## 2 | AIM

Our aim was to develop and validate an image-processing algorithm to reliably quantify erythema (across a range of skin types) in the dermatology clinical setting.

The theoretical underpinnings of the algorithm were based upon the comparison of green light suppression in the lesion to green light suppression in the surrounding normal skin. The relative strength of the red channel of the Red/Green/Blue color image over the green channel was calculated. As melanin absorption is strong in the blue light range, but relatively, and consistently, small across the green and red ranges. So analysis of the green and red channels makes the measurement largely insensitive to the presence or absence of melanin.

## 3 | METHODS

### 3.1 | Algorithm development

A computer program was written to interface with erythema ratings. This algorithm has been made available for public use at http://lab.rockefeller.edu/krueger/EQScore. On the original color image, the user was prompted to select a rectangular area including only unobstructed skin (i.e. no pen marks) that contains both the erythematous lesion and as much normal surrounding skin as possible. The user was then prompted to select a rectangular area containing equal amounts of the lesion and normal tissue. Finally, the user was prompted to select a rectangular area containing only normal, non-erythematous skin. The EQCI was then automatically computed as in Equation 1.

To enable image processing, the clinical image of the reaction was first loaded into the Matlab (Mathworks) computing environment. A grey-scale image, called ratio_red, was created by dividing the red layer of the color image by the green layer. The selected area containing equal amounts of lesion and normal tissue served as a distribution on which the algorithm could draw a threshold that defined the lesion border. The median value of ratio_red in the gradient region was chosen as a threshold that identifies the lesion segment. If ratio_red was larger than the threshold for any particular pixel, than that pixel was included in the lesion segment. The mean value of ratio_red in the lesion segment, called lesion_red, indicated the lesion's erythema intensity. The mean value of ratio_red in a second selected area containing only normal skin was extracted and called norm_red to specify background redness. The EQCI was then derived:

$$\mathrm{EQCI} = 10 \times \left( \frac{\mathrm{lesion\_red}}{\mathrm{norm\_red}} - 1 \right) \quad (1)$$

A linear transformation of the EQCI was performed in order to produce a continuous scaled erythema quantification score (EQCIs) in the typical range between 1 and 4. It was evaluated as a tool in standardizing the assessment of erythema.

**TABLE 1** Statistical properties of the erythema quantification indices

| Index | μ | σ | Pearson | Pearson CI | Agreement | ICC | ICC CI |
|---|---|---|---|---|---|---|---|
| EQHI | 2.08 | 0.38 | 0.91 | [0.83,0.88] | 33.54% | 0.68 | [0.62,0.74] |
| EQCIs | 1.57 | 0.18 | | | 63.82% | 0.88 | [0.84,0.90] |

Considering minimum (min) and maximum (max) observed values as good estimates of the population's minimum and maximum, we linearly scaled the EQCI from [min,max] to [0.5,4.5] using the general linear transformation to scale values from an interval [*a*,*b*] to another interval [*c*,*d*]:

$$f(x) = \frac{d-c}{b-a}x + c - \frac{a(d-c)}{b-a} \quad (2)$$

### 3.2 | Participants and clinical photography

Clinical photographs of positive patch test reactions from a sample of 164 subjects were used for the development of the algorithm. All subjects had suspected ACD, were patch tested with the North American Contact Dermatitis Group (NACDG) panel in line with published best practice techniques.[11] The NACDG 80 panel utilizes common allergens,[17] such as nickel and fragrance mix (Table S1). We also tested for dust mite using Dermatophagoide Farinae mix of chemotechnique diagnostic. The areas that showed positive patch tests reactions were separated into 1 × 1-inch area with a marker, and subsequently photographed with a standard digital camera.

### 3.3 | Contact dermatitis image evaluation

Image evaluation was undertaken independently and in a blinded manner by four expert dermatologists, and four non-dermatologist technicians. The expert dermatologists independently assessed the images using a 1–4 Likert scale to assign integer assessment values of erythema reddening as per published guidelines.[11] A score of 1 was used for mild reactions and a score of 4 was reserved for very severe reactions. 0 was not an option since all lesions depicted positive reactions. These measurements were termed the "erythema quantification human index" (EQHI). The non-dermatologist technicians independently assessed the same images using the developed image-processing algorithm (detailed below). These measurements were termed the "erythema quantification computer index" (EQCI).

### 3.4 | Statistical methods and development of the EQ score

Since the minimum and maximum EQCI observed were 0.3 and 7.73 respectively we used the following equation to transform EQHI to EQCIs:

$$\text{EQCIS} = \frac{4.5-0.5}{7.73-0.3}\text{EQCI} + 0.5 - \frac{0.3(4.5-0.5)}{7.73-0.3} = 0.34 + 0.54\text{EQCI} \quad (3)$$

We statically compared EQHI and EQCIs. When integers values were required, an approximation to the closer integer of the EQCIs was used. For each patient, the mean of EQCIs ratings (μEQCIs) were calculated across the 4 technician scores and across the 4 dermatologist EQHI ratings (μEQHI) on the interval 1–4. A comparison of the means between the two groups was performed using a two-tail paired t test as well as the Pearson correlation coefficient was measured for correlation between groups. The percentage of agreement and intra-class correlation coefficient (ICC) were calculated within groups. A 0.05 significance level was considered for all analyses. To simulate EQHI, a polynomial general linear model was estimated to predict EQHI by using EQCIs as predictor. For model estimation, the means μEQHI and μEQCIs were used as dependent and independent variables, respectively. The final EQscore was derived using a polynomial general linear model based upon the distributional qualities of the EQHI and EQCI.

### 3.5 | Algorithm validation using independent clinical image sets

After the development of EQscore, independent validation was undertaken using a compilation of images of psoriasis and minimal erythema dose testing, as well as public domain images from other published studies.[12-15] Each image was scored using the EQscore software only once for exploratory investigation. This method was chosen as appropriate over repeated use and presentation of the statistical distribution of the results in order to demonstrate a single user's consistency. Exploratory analysis of the inverse of the EQ score (expressed as a negative number) was also performed upon patients with topical corticosteroid-induced cutaneous blanching.

## 4 | RESULTS

### 4.1 | Contact dermatitis image evaluation and development of EQscore

The μEQHI and μEQCIs means were 2.08 and 1.57 respectively, with statistically significant differences between them ($P < .0001$). The **σ**EQHI and **σ**EQCIs means were 0.38 and 0.16, respectively, with statistically significant differences between them too ($P < .0001$). The Pearson correlation between μEQHI and μEQCIs was 0.91. For ECHI and EQCIs discretized to the closest integer, the percentage of agreement was 34% and 65% within each group and the intra-class correlation coefficients for agreement were 0.68 and 0.88 respectively (Table 1). Figure 2A shows the relationship between the μEQHI

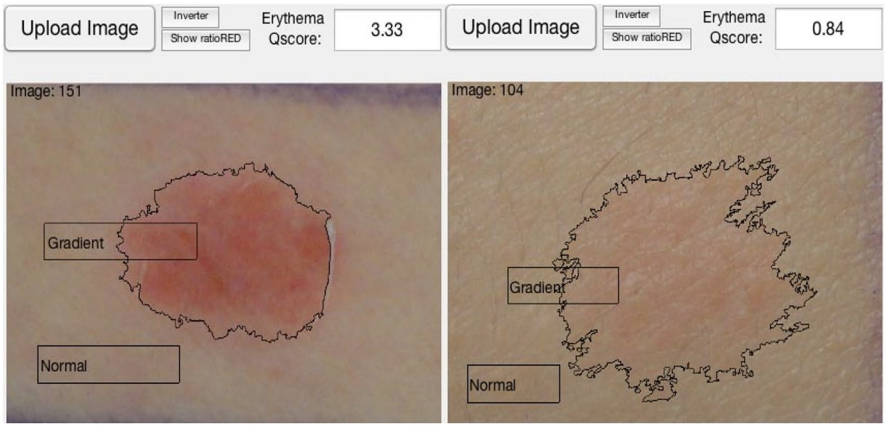


**FIGURE 1** Sample EQscore analyses. The original images for a severe reaction from mascara and mild reaction from dust mite. The rectangular regions, set by 4 user coordinate inputs, show the technician-generated choice areas for the gradient-containing and normal regions. The text above the images was not available to the technicians during review. The EQ score of each lesion is output to the display box above each image, illustrating the online application resource provided

and μEQCIs. Based on that relationship, the polynomial general linear model (Figure 2B) estimate is given by the following equation.

$$\text{EQscore} = -0.35 + 1.9 \times \text{EQCIs} - 0.2 \times \text{EQCIs}^2 \quad (4)$$

Equation 4 gives the erythema q-score (EQscore), a semi-automatic erythema quantification method in units that best match the dermatologists' evaluations. Fisher tests for ANOVA contrast and t tests for each coefficient have $P < .001$ with adjusted $R^2 = 0.78$, supporting the fit of the proposed model. To test the agreement between the final EQscore metric and the initial human assessment (EQHI), we discretized the mean of the EQscores to the nearest integer and compared directly to the EQHI. The erythema quantification indices EQHI and EQCIs have means and standard deviations equal to 2.08/0.38 and 1.57/0.18 respectively, while Pearson correlation between them is equal to 0.91 [0.83,0.98]. Agreement is quantitatively higher for EQCIs than for EQHI (63.82% vs. 33.54%). The ICC index is significantly different between both indices: 0.68 [0.62,0.74] and 0.88[0.84,0.90] for QHI and EQCIs respectively.

## 4.2 | EQscore applied beyond patch testing

The EQscores generated from minimal erythema dose testing images are shown in Figure 3.[16-19] Multiple linear relationships are

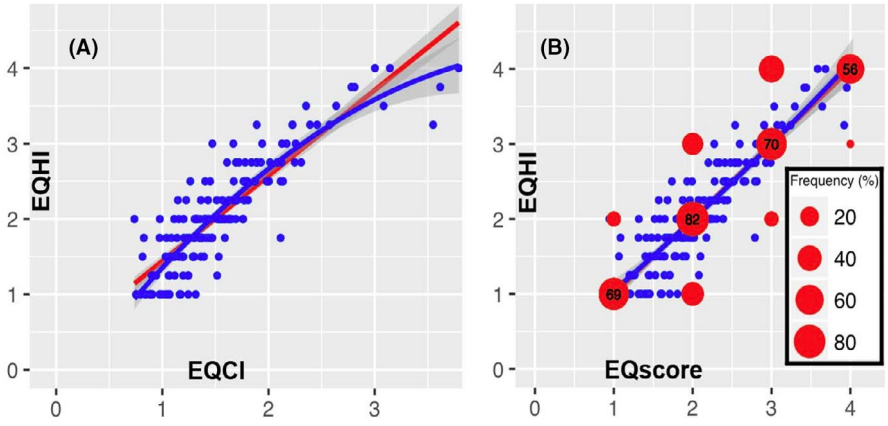


**FIGURE 2** Correlation between human and computer metrics. (A) Each blue data point plots the mean erythema score assigned by the group of four dermatologists as a function of the mean erythema score assigned by the group of four technicians using the semi-automated technique. While any value was possible for the continuous EQCI, the EQHI was the mean of 4 integers that were strongly corelated (due to the visual sensory cue being the same driving the cue), so they appear in increments of 0.25. The blue curve, which is the second-degree polynomial fit, shows that a polynomial of order 2 fits the data better than a linear fit (red line). The correlation between the EQHI and EQCIs scores is characterized by the correlation coefficient r = 0.88, while the inter-observer agreement is characterized by the inter-class correlation agreement ICC = 0.64. These data show that although the EQHI does not agree with the EQCIs, with only AP = 45% of the EQHI scores agreeing with the EQCIs, the EQCIs can be used to predict the EQHI using the second order polynomial. B, Correlation between the erythema Q-score (EQscore), which is a transformation of the EQCIs, and erythema quantification human index. All the lesions that received each EQHI index (eg. green oval marks those that received EQHI = 2) were stratified into the per cent that received each integer-discretized EQscore. The example highlighted (green oval) shows that 82% of the lesions that received a mean EQHI = 2 across the 4 expert dermoscopists also received an integer-discretized mean EQscore of 2 across the technicians, and thus were in agreement. The overall fraction of agreements, where was AP = 76% and the inter-class agreement coefficient was ICC = 0.88

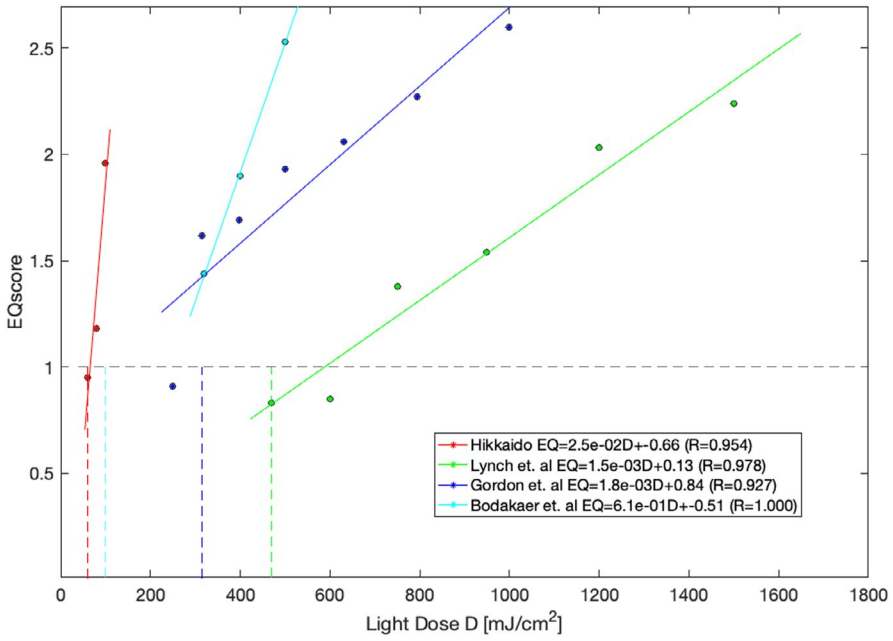


**FIGURE 3** EQscore on minimal erythema dose (MED[21]) tests by processing published figure images. The chart shows the results of our QEscore algorithm versus images from the literature[16-19]. Each literature image leads to a color-coded data set. Vertical dashed coloured lines indicated MED stated in the literature. The x-axis for the Bodakaer data is$D = 100$ times the standard erythema dose (SED) such that$D = 100 \times \text{SED}$ for the purposes of graphing the data together. The slope of the linear fit is an imaging biomarker that quantifies the incremental erythema per incremental light dose and quantitates, for instance, sunburn risk.

demonstrated between EQscore and light dose for various patients. The slope of the linear fit is broadly consistent with the Fitzpatrick skin type of participants in the respective studies.[16-19] The greater the slope, the lower the Fitzpatrick skin type. EQscores from a single user for a psoriasis patient (Figure 4A) demonstrate the ability for quantification of different degrees of erythema from within one contiguous area (Figure 4A insets).

The EQscore was also able to quantify vasoconstriction after application of clobetasol in a healthy volunteer (Figure 4B). Vasoconstriction images from publicly available literature (reference 20) demonstrated scores of −0.91 for Figure 1 (of reference 20), site 1, −1.08 for Figure 1 (of reference 20), site 2 and −0.95 for Figure 1(of reference 20), site 4. As an example of extreme blanching, an EQscore of −2.94 was generated from the left index finger of a typical Raynaud's episode.[16]

## 5 | DISCUSSION

The semi-automated image-processing algorithm that produces the EQscore provides a reasonable 4-point scale grading system for erythema quantification (Figure 2B). The precision is calculated at 0.01 based on Statistical Method, which is 100× finer than the expert dermatologist's integer scale, although the clinical relevance of such precision requires further investigation. The similarity between the means of the EQHI scores and EQscores demonstrates that the software is able to generate a score that can be translated to an equivalent human analysis, suggestive of a high degree of face validity in the assessment of erythema.

Given the relationship between Fitzpatrick skin type and EQscore (Figure 3), one potential application is evaluation of a set of various light doses as a surrogate measurement of the patient's tendency to sunburn. This has been previously achieved using a spectrophotometer is in

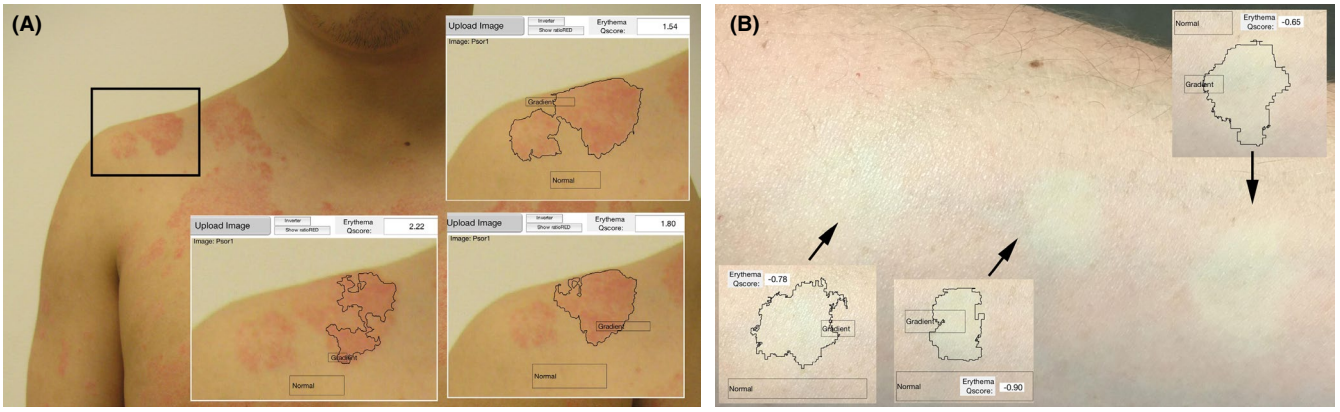


**FIGURE 4** EQscore of Psoriatic Skin (A) and Topical Steroid applied skin (B). A, Psoriatic lesion analysed with three different choices of the gradient region, illustrating that within a lesion, there can be different erythema severity regions. B, Topical steroid application of a pea-sized amount of clobetasol 0.05% in three locations at 4 h . The EQscore analysis was executed with the "Inverter" (see Figure 1) button selected, thereby achieving a quantitative measurement of blanching caused by the agent.

MED tests[17,18] although the EQscore has the potential to replicate such measurements without the need for specialized equipment. Further studies must be undertaken to directly compare the validity and reliability of EQscore compared with spectraphotometric measurements prior to any definitive statements regarding measurement equivalence. In addition to this potential application and applications shown in Figure 4, another potential application is in rosacea, the most common type being erythematotelangiectatic. Laser treatments remove vessels and thus redness. The EQscore could be a good assay to test the efficacy of vascular lasers, to use in clinical trials of said lasers or simply for use to measure topical treatments for the redness in rosacea.

Given the known issues with inter-rater reliability in physician erythema measurements, the smaller degree of variation between computer-aided analysis compared with human analysis suggests EQscore is superior in terms of reliability than the traditionally used Likert scale ratings of clinical erythema. Computer-assisted erythema quantification using the EQscore eliminates reliability issues and provides a standardized platform for the assessment of erythema in the clinical trial and research setting. The technology could easily be applied to a smartphone or tablet application, which would further expand its accessibility and ease of use as part of integrated mobile medicine. The next stage of validation would involve validating EQscore alongside accepted gold standard clinical outcome measures such as the PASI and EASI scores in order to assess the changes over time which equate to clinically significant outcomes. This would also enable the validation of EQ scores alongside in-person clinical evaluation which has been shown to be superior to assessment of clinical features via photography.

Additionally, other areas of medicine, such as immunology, can benefit from the image-processing algorithm. For example, topical sensitizers such as diphenylcyclopropenone can be applied to the skin of HIV patients in order to assess their immune competence. Positive skin reactions, including erythema, induration, bullae and vesicles, imply good immune function.[22] Studies have shown that the severity of these cutaneous reaction directly correlates with CD4 count and viral load, both key indicators of immune status. This functional assessment of immunity in HIV individuals is a non-invasive, cost efficient method to monitor HIV patient status, assess their response to treatments, and help guide further management.[23] Incorporation of EQscore may help to assess these skin reactions and their important implications.

Limitations of the EQscore image-processing algorithm are the inability to identify vesicles and blisters, induration and papules. Because the EQscore only quantifies redness and not other morphological features, these must still be scored manually. Additionally, in order to comprehensively validate the EQ score, independent validation against existing gold standard measurements (Such as SCORAD, EASI, etc.) is required in large cohorts in specific disease states. The cohort employed in this study is enough to establish proof-of-concept validity of the EQ score generally, but further validation is required to establish the level of evidence needed for the EQ score to be considered a gold standard measurement of erythema. Such work is currently underway.

## 6 | CONCLUSIONS

The EQ score is a highly reliable computer-assisted quantification algorithm for the assessment of erythema as well as corticosteroid-induced blanching of skin. The algorithm uses a technique which ensures erythema quantification is independent of pigmentation and hence has benefits above visual inspection and rating. The elevated reliability of the EQscore indicates it holds potential as a reliable alterative to erythema scoring in clinical research and trial settings. Future directions include validation against gold standard clinical outcomes and defining the clinical relevance of the EQscore in longitudinal clinical and interventional settings.

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### CONFLICT OF INTEREST

All authors have no conflict of interest to report.

### AUTHOR CONTRIBUTION

D.G. initiated this project and conceived, designed and implemented the image analysis framework, graphic-user interface and computer application to quantify the EQscore. J.F. led the writing of the manuscript, and L.P and C.B contributed to the writing. The statistics team (Co-Authors S.G. and M.S.F.) chose the statistical analyses and carried out the associated computations. P.B, T. C., J.K., R.F., I.C., J.F.D., H.O., T.L. and V.Y. served as users of the EQscore computer application written by D.G. and provided estimates of the erythema severity. E.G.Y. and her clinical team provided the clinical images used in this study. J.G.K. and E.G.Y. provided guidance of the project and critical review of the manuscript during the process of revisions.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**Table S1** Patch Test Allergens Used in the study

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