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ORIGINAL RESEARCH

# Epigenetic Skin Aging and Its Reversal to Improve Skin Longevity across Ethnicities and Phototypes Using a Dihydromyricetin-Containing Serum: Results from a Prospective, Single-Cohort Study

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## ABSTRACT

***Introduction***: Skin aging is driven by intrinsic and extrinsic factors. Epigenetic alterations are one primary hallmark of aging and powerful biomarkers of biological skin age. To investigate epigenetic skin aging mechanisms and their regulation as a skin longevity approach across diverse ethnicities and phototypes, we assessed epidermal methylomes from white, African, and Asian donors.

***Methods***: We collected epidermis samples from 17 multi-ethnic donors with diverse phototypes using a newly established tape-stripping method followed by array-based DNA methylation profiling to investigate the robustness of DNA methylation clocks across diverse ethnic backgrounds. Additionally, we conducted a clinical study with 60 participants representing Fitzpatrick phototypes I–VI. Diverse clinical parameters and biological skin age of the volunteers were determined at baseline and after applying a serum containing the natural epigenetic inhibitor dihydromyricetin (DHM) for 8 weeks to investigate skin longevity effects across phototypes.

***Results***: Data analysis revealed that age-dependent DNA hypermethylation is conserved across populations and affects genes essential for keratinocyte vitality and longevity. A newly developed epidermal methylation clock accurately predicted biological age in multi-ethnic cohorts, confirming the robustness of epigenetic

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age estimation across phototypes. Topical application of a DHM-containing serum significantly reduced epidermal DNA methylation age. Epigenetic rejuvenation was associated with clinical improvements, including reduced skin roughness and wrinkle visibility and occupancy, and increased dermal echogenicity.

***Conclusions***: Together, these findings establish that epigenetic aging signatures are conserved across ethnicities and that targeted modulation using a DHM-containing topical formulation can reverse biological skin age while improving structural and visible signs of aging. This work provides the clinical evidence supporting epigenetic rejuvenation as a viable strategy for skin longevity across diverse populations.

**Keywords:** Dihydromyricetin; DNA methylation; Epigenetic age clock; Rejuvenation; Skin of color

| **Key Summary Points** |
|---|
| *Why carry out this study?* |
| Epigenetic alterations are one primary hallmark of aging. However, most studies investigating age-related epigenetic changes in human skin are conducted in white populations. |
| We hypothesized that epigenetic skin aging mechanisms are shared across diverse ethnicities and phototypes and that these epigenetic alterations can be positively addressed with epigenetic compounds such as dihydromyricetin (DHM), independent of phototype. |
| *What was learned from the study?* |
| We showed that epigenetic aging signatures are conserved across ethnicities, and that a topical formulation containing DHM reverses the biological skin age while improving visible and structural signs of aging. |
| We propose epigenetic rejuvenation as a viable strategy for skin longevity across diverse ethnicities and phototypes. |

## INTRODUCTION

Skin aging is a complex process that is influenced by numerous intrinsic and extrinsic factors [1, 2]. Traditional skin aging research has mostly focused on populations with white skin. However, more recent approaches have started to include other ethnicities. A democratization of diverse knowledge is necessitated both by demographic changes and by marked, ethnicity-related differences in skin-aging phenotypes. While the increased pigmentation of skin of color renders it less susceptible to photoaging and more prone to hyperpigmentation, other features are specific for white, African, or Asian skin [3]. A better understanding of key mechanisms of skin aging across ethnicities is urgently needed to develop antiaging intervention strategies that are both optimized for specific ethnicities and effective across different phenotypes, phototypes, and skin types.

The hallmarks of aging provide a general framework for understanding the underlying mechanisms that drive aging and age-related diseases. These hallmarks were first proposed in 2013 and updated in 2023 to reflect new discoveries [4]. They are grouped into three categories. Primary hallmarks (causes of damage) are the initial triggers of aging-related decline. Antagonistic hallmarks (response to damage) are compensatory responses that can become harmful. Integrative hallmarks (culprits of the aging phenotype) result from the interaction of the above.

Epigenetic changes are defined as a primary hallmark, with DNA methylation being the longest known and best understood epigenetic modification of the human genome, and being recognized as an important biomarker and functional component of skin aging [5]. A prominent example is provided by skin DNA methylation clocks that can accurately predict donor age on the basis of DNA methylation patterns [6]. More recently, this approach has been extended to second-generation age clocks that can predict specific skin aging phenotypes from white skin, including wrinkle grade and visual age, just on the basis of the epigenetic

pattern [7]. As such, the different types of age clocks offer a holistic view on skin aging and its associated phenotypes. Although they can serve as valuable diagnostic tools, they make a particularly significant contribution to advancing the understanding of the biological and molecular mechanisms underlying skin aging [8]. Finally, it has been shown that DNA methylation levels in regulatory regions in the human epidermis increase with age [6, 9, 10], and this hypermethylation is associated with a reduced expression of corresponding skin-aging genes [11, 12]. DNA methylation has been established as an attractive target for skin longevity interventions [5], and a natural ingredient, dihydromyricetin (DHM), showed noticeable rejuvenating effects on epigenetic and phenotypical levels in human skin models [12]. However, the effect has not been analyzed in vivo yet.

Furthermore, the analysis of epigenetic skin aging has been largely focused on white skin. The only published DNA methylation analysis of skin samples from different ethnicities was performed more than 10 years ago [13]. Initial data analysis suggested the presence of stable DNA methylation differences related to different ethnic backgrounds [13]. However, more detailed analyses were not feasible at the time of the initial publication, because the computational tools for the analysis of complex DNA methylation patterns were only beginning to be developed.

We hypothesize that epigenetic skin aging mechanisms are shared among multiple ethnic populations and phototypes. Accordingly, the presented study aimed to investigate whether epigenetic skin aging mechanisms are conserved across diverse ethnicities and phototypes and whether they can be used as robust biomarkers of biological skin age for skin samples of multiple ethnic backgrounds. Following our hypothesis, in the second part of our study, we evaluated whether targeting epigenetic alterations as a primary hallmark of aging by applying a cream containing the natural epigenetic inhibitor dihydromyricetin can induce skin longevity effects across all phototypes.

# METHODS

### Volunteers

The pilot study comprised a total of 17 male and female participants from diverse ethnic backgrounds and different phototypes between the broad age range of 24 and 69 years (see Supplementary Table S1 for details). The product-use study comprised 60 volunteers from a diverse Brazilian population in the age range of 40–70 years with an average age of 55 years, including all Fitzpatrick phototypes and both genders (see Supplementary Table S2 for details). Details about volunteers' health condition and exclusion criteria can be found in the Supplementary Methods.

### Ethical Approval

Both studies were conducted in accordance with ethics requirements. The pilot study was approved by the Ethics Committee of the Faculty of Medicine at the University of Heidelberg (ref. S-783/2024), and all participants provided written, informed consent. Specifically, consent was obtained for the storage and processing of biosamples at the German Cancer Research Center (DKFZ) and for the processing and use of data for biomedical research, including publication. The product-use study was conducted in accordance with the principles of the Declaration of Helsinki, applicable regulatory requirements, including Resolution CNS no. 466/12, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6: Good Clinical Practices and Document of the Americas. This study was approved by the Independent Ethics Committee (IEC) of Investiga-Institutos de Pesquisa, registered by the National Research Ethics Commission (CONEP) (CEP approval no. CAAE 90155525.9.0000.5599). All participants provided written, informed consent for the collection of clinical data, biological samples, and facial images, as well as consent for the publication of anonymized data and images in scientific media.

### Epidermal Tape Stripping

Epidermal samples were collected via adhesive tape strips, as described previously [14], with minor adaptations (details can be found in the Supplementary Methods).

### In Vivo Topical Application of DHM-Containing Serum

Volunteers were provided with a facial serum containing DHM as the key active ingredient, in addition to antioxidants and hyaluronic acid (product code: E004079A-01) and sunscreen with SPF 50+ (product code: E004079A-01). The DHM-containing serum was topically applied twice a day, morning and night, for 8 weeks on the entire face and neck (clean and dry), avoiding contact with the eyes. After complete absorption of the serum, the volunteers applied the sunscreen on the entire face and neck, and it was reapplied throughout the day as needed. The compliance of the participants was validated by weighing both products before the first application, after 4 weeks of application, and at the end of the study. Additionally, the clinical and self-perception skin structure parameters (complete details can be found in the Supplementary Methods) were measured at those time points (before first application, at 4 weeks, and at 8 weeks), and skin samples of the volunteers were collected via tape stripping at the beginning and the end of the study. All analyzed volunteers used ≥ 10 g of DHM-containing serum after 4 weeks.

### DNA Methylation Age Determination

Genomic DNA isolation was performed as described previously [14] and further processed for Methylation EPIC version 2.0 BeadChip arrays (Illumina). Methylation data analysis was performed as described previously [14]. DNA methylation age was determined via the published TapeLift clock from Rodríguez-Paredes et al. [14] or the newly trained 23 k epidermis clock (details about clock training can be found in the Supplementary Methods).

## RESULTS

### Conserved Age-Dependent DNA Hypermethylation and Robust Epigenetic Age Prediction in Human Skin across Ethnicities

In an initial analysis, we used published datasets to investigate age-related epigenetic changes across ethnicities in more detail. Our results strongly suggest that age-dependent DNA hypermethylation is enriched in bivalent regions across ethnicities (Supplementary Fig. S1). Small interfering RNA (siRNA) knockdown experiments of genes affected by age-related hypermethylation confirmed a role of these genes in cellular longevity (Supplementary Fig. S2).

To further investigate whether the biological age prediction using epigenetic age clocks trained on white individuals is applicable across ethnicities, we analyzed the published multi-ethnic 27 k dataset of epidermis samples [13]. We identified 23,845 probes that are shared between the 27 k methylation array used for the original multi-ethnic study, and the more comprehensive 450 k methylation array used to establish the first DNA methylation clock for the human epidermis [6]. We then trained a methylation clock on the basis of these 23,845 probes and the epidermis methylation dataset from 108 white female donors aged 18–78 years [6]. This established a novel "23 k epidermis clock" based on 173 cytosine-guanine dinucleotides (CpGs) and with a cross-validation error (type measure = "mse") of 5.66 years. When this clock was applied to the published multi-ethnic dataset, it predicted donor ages with a mean absolute error of 4.88 years and without any detectable ethnic bias (Fig. 1A), suggesting that DNA methylation clocks are robust across diverse ethnic backgrounds.

To further confirm the robustness of DNA methylation clocks across diverse ethnic backgrounds, we collected additional epidermis samples from 17 multi-ethnic donors with diverse phototypes (Supplementary Table S1) using tape stripping (see Methods for details). DNA from these samples was isolated and subsequently processed on Infinium EPICv2 methylation

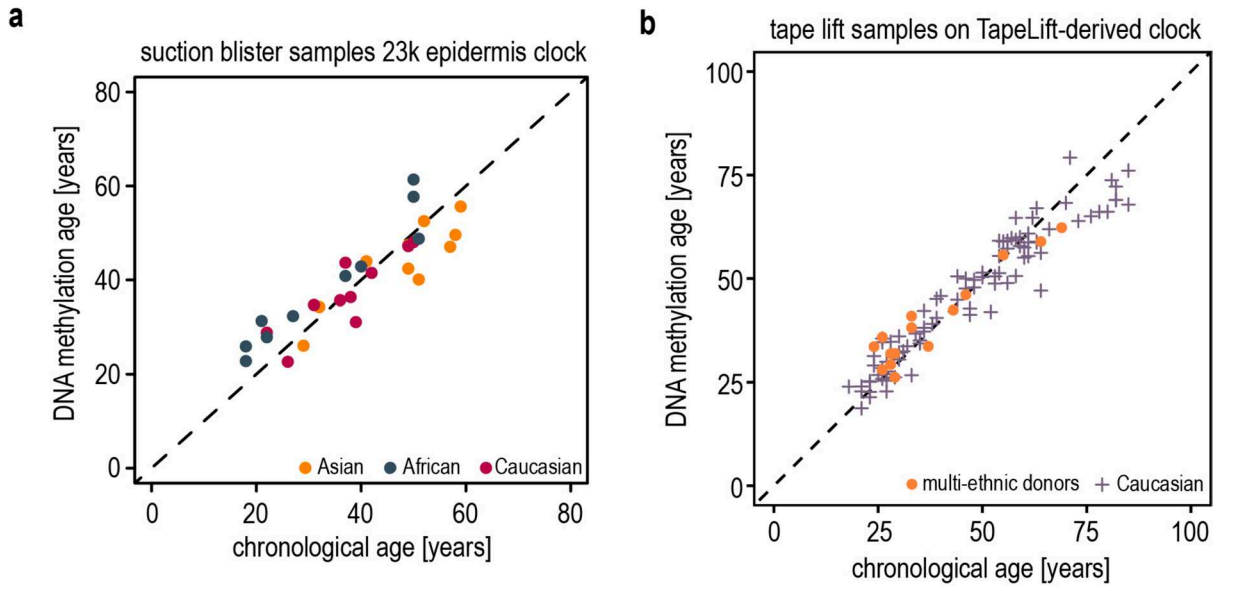


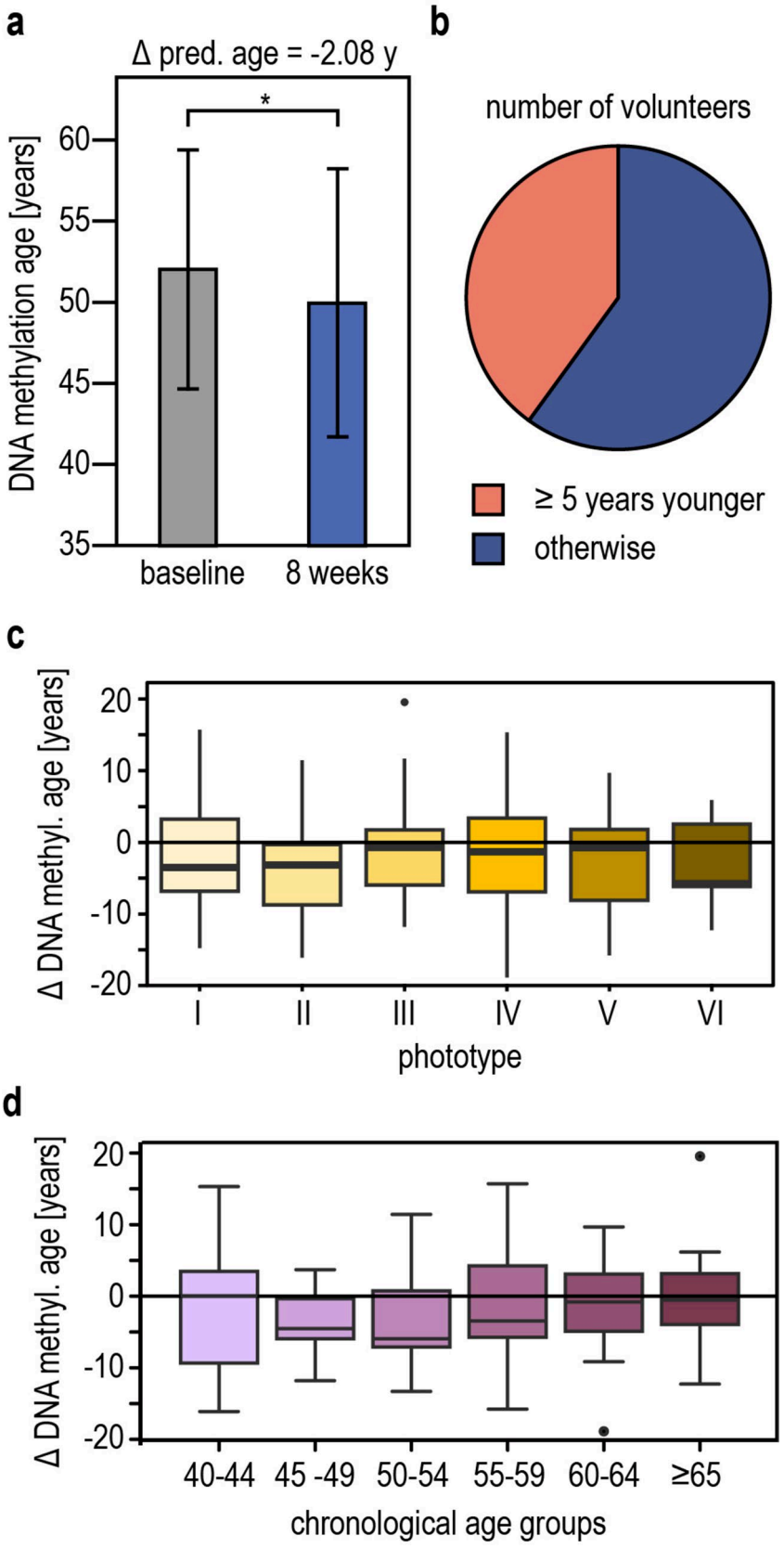

**Fig. 1** Epigenetic skin aging is conserved across ethnicities and phototypes. **a** Comparison of chronological age and DNA methylation age in a multi-ethnic epidermis dataset, based on the 23 k epidermis clock. **b** Comparison of chronological age and DNA methylation age in a TapeLift dataset, based on a published TapeLift-derived clock [14]. Samples from multi-ethnic donors are shown as orange dots

arrays. Furthermore, when we used a DNA methylation clock that was specifically trained with tape strip samples [14], we did not observe any bias for the non-white samples (Fig. 1B). These findings further confirm that DNA methylation clocks provide accurate predictions for skin samples from diverse ethnicities and with diverse phototypes.

## A DHM-Containing Serum Induces Rejuvenating Effects in the Epidermal DNA Methylation Patterns across Diverse Phototypes and Age Groups

The natural compound dihydromyricetin has been qualified as a promising candidate for cosmetic antiaging applications, showing a well-defined safety profile [12] and no reactivation of skin-related oncogenes (Supplementary Fig. S3). To further investigate the rejuvenating effect of DHM in vivo, we analyzed 60 volunteers (male and female) from an ethnically diverse population, including all Fitzpatrick phototypes (Supplementary Fig. S4 and Supplementary Table S2). A DHM-containing serum was topically applied to the face and neck twice a day, morning and night. Sunscreen with SPF 50+was additionally applied. Skin samples were obtained by tape stripping in the periorbital (crow's feet) area before and after an 8-week treatment period. Baseline analyses revealed that the mean absolute error of the predicted donor age before product usage was 6.2 years and that no bias due to different phototypes was observable (Supplementary Fig. S5).

Subsequent analyses of the epidermal DNA methylation profiles before and after product treatment revealed a significantly ($p = 0.029$, paired Wilcoxon test) reduced mean epigenetic age of around 2.1 years (Fig. 2A), with 40% of participants showing a reduction of ≥ 5 years (Fig. 2B). Notably, when we stratified the results according to phototype, no detectable difference in the response to the treatment could be observed (Fig. 2C). Similar observations were made for the stratification by chronological age groups in 5-year intervals (Fig. 2D). These findings strongly suggest that the rejuvenating effect of the DHM-containing serum is independent of phototype and chronological age.


a
Δ pred. age = -2.08 y
*
DNA methylation age [years]
60
55
50
45
40
35
baseline
8 weeks
b
number of volunteers
≥ 5 years younger
otherwise
c
Δ DNA methyl. age [years]
20
10
0
-10
-20
I
II
III
IV
V
VI
phototype
d
Δ DNA methyl. age [years]
20
10
0
-10
-20
40-44
45 -49
50-54
55-59
60-64
≥65
chronological age groups

◂**Fig. 2** Biological age reduction after topical application of DHM-containing serum for 8 weeks. **a** Average reduction of the biological age across all 60 volunteers, which is significant ($p = 0.029$). **b** Proportion of volunteers with a biological age reduction of ≥ 5 years. **c** Biological age reduction across phototypes I–VI and **d** age groups in 5-year intervals, respectively. ΔDNA methyl. age and Δpred. age = predicted DNA methylation age at week 8 − predicted DNA methylation age at baseline; *y* years

To exclude confounding effects from sunscreen application, a partial correlation analysis was conducted correcting for the applied quantity of products. The results showed a significant positive ($R = 0.25$, $p = 0.05$, Pearson correlation) correlation between the biological age reduction and the amount of epigenetic serum used, after correction for the amount of SPF-containing product used (Supplementary Table S3). In contrast, the correlation between the biological age reduction and the amount of sunscreen used, after correction for DHM-containing serum used, was not significant ($p = 0.29$) and even showed a slightly negative ($R = -0.14$, Pearson correlation) trend (Supplementary Table S3). A similar result was also obtained for the uncorrected correlation (Supplementary Table S4). These results further confirm that the observed rejuvenating effect is induced by DHM-containing serum, rather than SPF application. This is in line with the recently published observation that SPF application alone does not lead to a reduction of the biological age but rather prevents epigenetic aging upon sun exposure [15]. In conclusion, these findings provide the first evidence for an in vivo rejuvenating effect of a DHM-containing serum that is independent of the phototype.

### A DHM-Containing Serum Improves Clinical Skin Structure Parameters

To investigate the impact of the DHM-containing serum on functional parameters of skin structure, validated clinical assessment methods were applied at baseline and after 4 and 8 weeks of product application (see Methods for details). Standardized facial imaging was used for the quantification of wrinkle visibility and occupancy rate (Fig. 3A). In parallel, three-dimensional profilometry of the skin surface (Fig. 3B) provided objective metrics of surface roughness, and dermal echogenicity (Fig. 3C) was used to assess dermal density. Finally, expert clinical grading was used for standardized tactile and visual evaluations of face and neck skin aging markers at baseline, week 4, and week 8 (Fig. 3D).

Quantitative image analysis revealed a statistically significant reduction ($p < 0.001$, pairwise Wilcoxon signed-rank test) in the coefficient of visibility and occupancy rate of periorbital wrinkles (crow's feet) at both 4 and 8 weeks compared with baseline (Table 1). At week 8, image analysis quantification demonstrated that 86.4% of subjects exhibited improvement in wrinkle visibility, with a mean reduction of 13.9% from baseline, and 81.4% an improvement in occupancy rate, corresponding to an average reduction of 12.3%, indicating decreased wrinkle prominence and reduced spatial extent of wrinkle presentation compared with baseline (Supplementary Fig. S6 and Table 1). Analysis of skin microtopography data showed a statistically significant reduction in skin roughness parameters, with −4.3% (arithmetic mean roughness [SPa]) and −5.4% (root mean square roughness [SPq]), respectively ($p < 0.05$), consistent with improvements in surface smoothness and texture homogeneity (Table 1). Ultrasound analysis showed a significant increase in dermal echogenicity of +7.7% at week 4 and +10.4% at week 8 ($p < 0.001$), suggesting enhanced dermal density and structural remodeling (Table 1). These findings were corroborated by expert clinical grading. Statistically significant improvements ($p < 0.05$) were observed across multiple parameters, including global facial wrinkles, skin texture (face and neck), elasticity, firmness, radiance/luminosity, and horizontal neck wrinkles. Notably, neck elasticity and firmness also improved, indicating a consistent treatment effect across multiple anatomical sites (Table 2). Taken together, these results demonstrate clinically and statistically significant improvements in both superficial and structural signs of skin aging, in agreement with a holistic rejuvenation effect of the DHM-containing serum on the skin phenotype. Self-grading (Fig. 3D) and self-assessment outcomes reinforce the clinical findings, indicating that volunteers

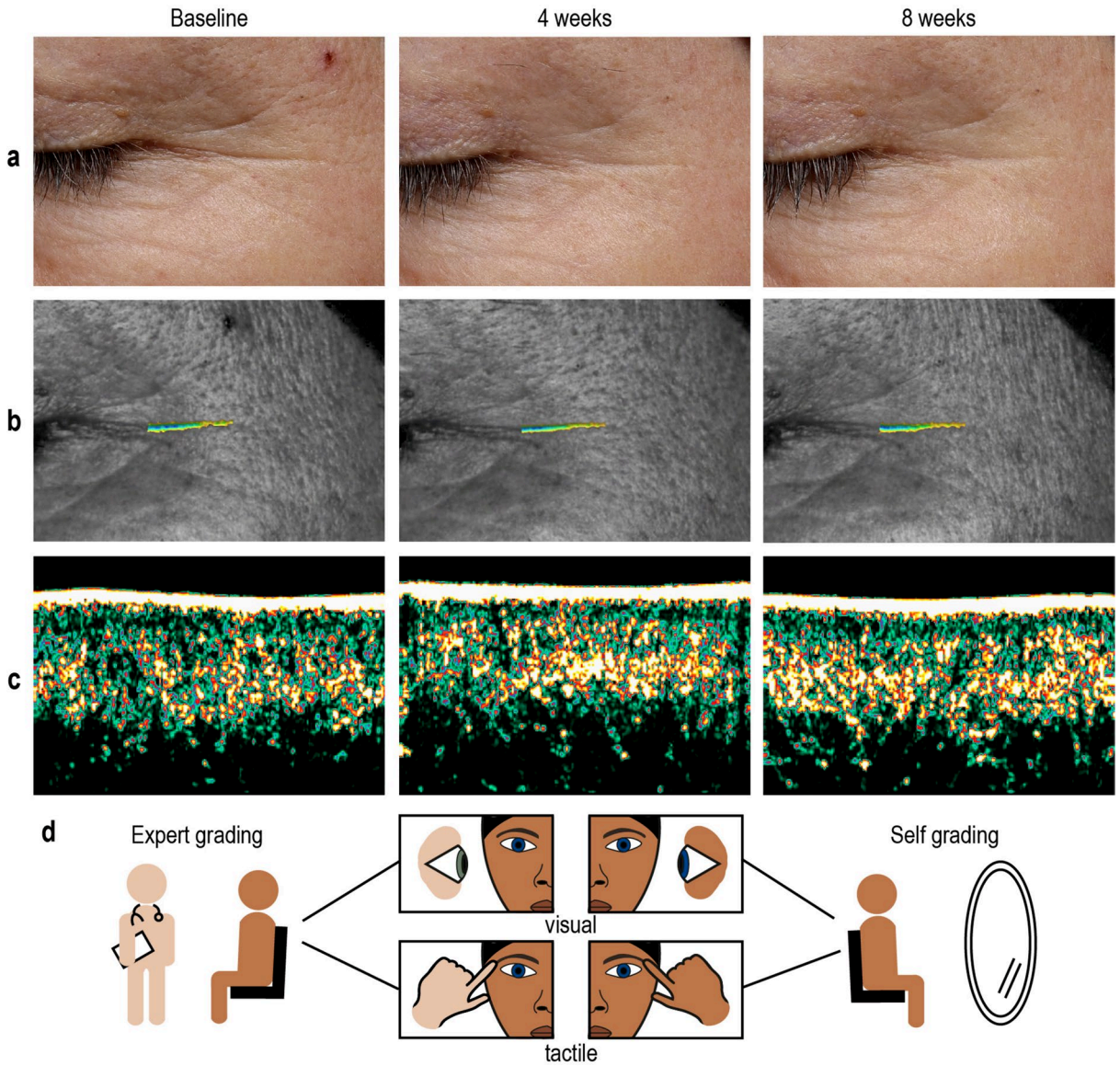



**Fig. 3** Applied clinical assessment tools to determine clinical skin structure parameters before, after 4 weeks, and after 8 weeks of applying DHM-containing serum twice a day exemplified on the best-case improvement. **a** Representative images of wrinkle measurements via high-resolution images. **b** Representative images of skin surface roughness measurements based on three-dimensional profilometry of the skin surface with deep profiles colored in blue to less deeper profiles in red. **c** Representative images of dermis density measurements via dermal echogenicity with low density colored in green/black and denser structures in red/white. **d** Scheme of clinical expert- and self-grading performing tactile and visual evaluations. An average case for high-resolution images for wrinkle measurements is depicted in Supplementary Fig. S7

perceived overall improvements in signs of aging, which significantly contributed to enhanced quality of life (Supplementary Tables S5–7, respectively). Finally, the above-described improvements in clinical parameters were observable irrespective of phototype, gender, and ethnicity (Fig. 4), suggesting that the rejuvenating effect of the DHM-containing serum is perceivable across gender, ethnicity, and phototypes, while showing

**Table 1** Summary of instrumentally measured clinical skin structure parameters after 4 weeks and 8 weeks of topical application of DHM-containing serum twice daily

| Instrument | Area | Parameter | No. of subjects | Percentage (%) improvement (on mean) | | | |
|---|---|---|---|---|---|---|---|
| | | | | 4 weeks | | 8 weeks | |
| Standardized facial imaging^ | Periorbital wrinkles | Coefficient of visibility | 59 | 12.6 ↓ | *** | 13.9 ↓ | *** |
| | | Occupancy rate | 59 | 8.6 ↓ | *** | 12.3 ↓ | *** |
| 3D profilometry^ | Periorbital skin surface | SPa | 51 | 2.6 | n.s | 4.3 ↓ | * |
| | | SPq | 51 | 1.2 | n.s | 5.4 ↓ | * |
| | | Volume | 51 | 1.7 | n.s | −1.6 | n.s |
| Dermal echogenicity° | Malar region | Intensity | 60 | 7.7 ↑ | *** | 10.4 ↑ | *** |

Percentage improvement on mean of periorbital wrinkles (crow's feet) detected via standardized facial imaging, dermal density measured via echogenicity, and skin roughness measured via three-dimensional (3D) profilometry, including SPq (root mean square roughness) and SPa (arithmetic mean roughness). ↓ indicates a decrease in periorbital wrinkles and skin roughness, while ↑ indicates an increase in dermal density. Significance is depicted as n.s. = not significant, * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ (^ indicates pairwise Wilcoxon signed-rank test and ° pairwise *t*-test)

**Table 2** Summary of expert clinical grading results after 4 weeks and 8 weeks of topical application of DHM-containing serum twice daily

| Type of grading | Score | Percentage (%) improvement (on mean) | | | |
|---|---|---|---|---|---|
| | | 4 weeks | | 8 weeks | |
| Visual | Wrinkles (global) | 3.5 ↓ | ** | 7.0 ↓ | *** |
| | Facial sagging | 0.7 ↓ | n.s | 4.4 ↓ | ** |
| | Skin plumpness | 2.4 ↓ | * | 3.8 ↓ | ** |
| | Radiance/luminosity | 8.2 ↓ | *** | 19.6 ↓ | *** |
| | Horizontal wrinkles—neck | 2.0 ↓ | n.s | 6.3 ↓ | *** |
| | Skin texture—neck | 5.5 ↓ | ** | 9.5 ↓ | *** |
| | Skin age | 2.4 ↓ | ** | 6.5 ↓ | *** |
| Tactile | Skin texture | 14.6 ↓ | *** | 23.6 ↓ | *** |
| | Skin elasticity | 8.1 ↓ | *** | 14.2 ↓ | *** |
| | Skin firmness | 3.9 ↓ | ** | 9.8 ↓ | *** |
| | Skin firmness—neck | 0.3 ↓ | n.s | 6.3 ↓ | ** |
| | Skin elasticity—neck | 5.3 ↓ | *** | 11.5 ↓ | *** |

Percentage improvement on mean in visual and tactile parameters of skin aging assessed by dermatologists in a blinded setting. ↓ indicates a reduction in the score, which equals an improvement of the parameter (score range [0–9], with 0 = "good" and 9 = "bad"). Significance is depicted as n.s. = not significant, * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ (pairwise Wilcoxon signed-rank test)

good tolerability with no described adverse events related to investigational product use.

### Improved Clinical Skin Structure Parameters Correlate with Reduced Epigenetic Age after DHM-Containing Serum Usage, Substantiating Skin Longevity Effects

In further analyses, we also investigated the relationship between clinical skin parameters and DNA methylation age. Correlation analyses revealed a significant positive correlation ($R$=0.31, $p$<0.05, Pearson correlation) between the change in the epigenetic age and the change in wrinkle volume, indicating that the reduced biological age after product usage is associated with a reduction of wrinkle expression (Fig. 5A). To holistically assess the effect of the topical treatment on the skin aging phenotype, we defined a multiparameter score (see Supplementary Methods for details), which integrates the following representative measurements of the skin aging phenotype (Supplementary Fig. S8): expert-assessed global wrinkles, tactile skin firmness, and tactile skin texture, as well as the instrumentally measured occupancy rate. A high score corresponds to a mature skin phenotype and a low score to a juvenile skin phenotype. Of note, the score significantly correlated with the biological age change related to product usage (Supplementary Fig. S9). Further analysis also revealed a significant positive correlation ($R$=0.30, $p$<0.05, Pearson correlation) between the reduction in the epigenetic age and improvement in the score (Fig. 5B). Taken together, these results demonstrate that the DHM-containing serum reduces the DNA methylation age of facial skin, and that the rejuvenating effect correlates with an overall improvement of clinical skin structure parameters, especially wrinkle formation.

## DISCUSSION

### Population Diversity and Relevance

Most skin aging trials to date have enrolled predominantly white populations, limiting generalizability, as clinical manifestations across skin types differ owing to biological variations, particularly epidermal melanin content. Darker skin contains two to six times more melanin, with larger, more persistent melanosomes [16, 17], resulting in markedly reduced ultraviolet (UV) penetration and an inherent photoprotection equivalent to SPF 13.4 in Black skin, leading to a 15–33 times higher minimal erythema dose compared with lighter skin [18]. Studies show 70–75% lower UVA and UVB penetration in Black versus white skin [19] and significantly less UV-induced DNA damage across darker tones, alongside more efficient apoptotic clearance of damaged cells [20–22]. These features delay wrinkle formation but increase susceptibility to hyperpigmentation [3]. Although the clinical manifestations and time of onset of photoaging differ by skin type, the underlying mechanisms, including DNA methylation, are present across all skin types [23].

Skin of color refers to a heterogeneous group of populations, typically falling under Fitzpatrick skin types IV–VI, who may belong to racial and ethnic groups such as Africans, African Americans, African Caribbeans, Native Americans, Chinese, Japanese, Indians, and Hispanics [24]. The Brazilian population, however, represents one of the most genetically admixed in the world, comprising approximately 68% European, 19% African, and 11% Native American ancestries [25]. The present study included male and female participants across a broad age range (20–59 years) and Fitzpatrick phototypes I–VI, thereby reflecting this ethnic and phenotypic diversity. While applying the epigenetic clock introduced by Horvath (2013) to other tissues—such as blood, saliva, and brain—revealed race-specific aging rates [26], the skin-specific TapeLift clock appears to capture broader, more general age-related mechanisms across ethnicities, as our clock analyses showed robust predictive accuracy across all phototypes and ancestries, thereby confirming their validity in a heterogeneous population.

### Clinical and Biological Implications

Current skin aging management encompasses topical, oral, injectable, and device-based

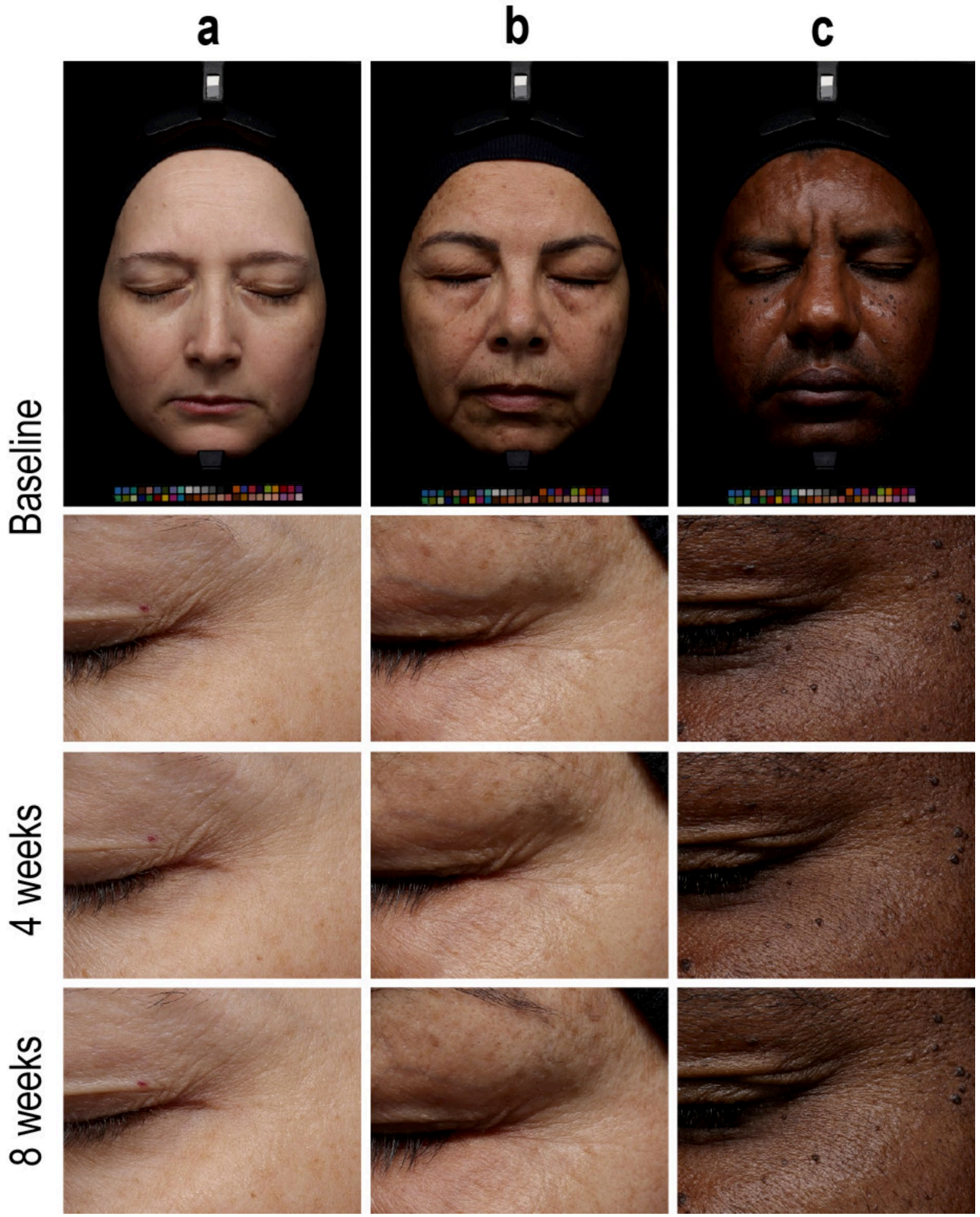



**Fig. 4** Improvement of wrinkle measurements after topical application of DHM-containing serum twice daily for 8 weeks across phototypes, ethnicities, and genders exemplified on the best-case improvement. **a** White female volunteer with phototype I. **b** Asian female volunteer with phototype III. **c** African male volunteer with phototype V

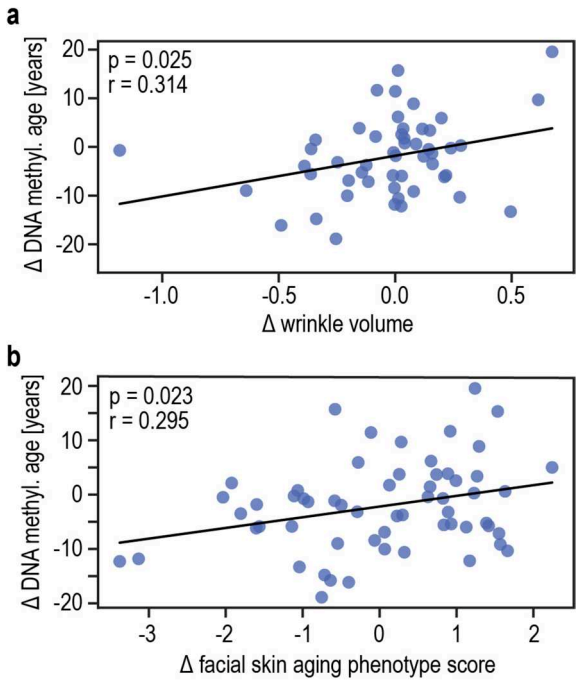



**Fig. 5** Correlation of biological age reduction with improvement of clinical signs of aging. **a** Significant ($p < 0.05$) correlation of improved wrinkle volume with biological age reduction. **b** Significant ($p < 0.05$) correlation of improved multi-clinical parameter facial skin aging phenotype score with biological age reduction

interventions, with daily photoprotection as the only proven preventive measure and topical tretinoin as the gold standard pharmacologic treatment, with robust evidence demonstrating improvements in fine wrinkles, pigmentation, and skin texture [27–29]. Its efficacy has been consistently supported by multiple systematic reviews and randomized clinical trials [27–29]. For cosmetic (nonprescription) formulations, retinol, retinaldehyde, and retinyl esters are effective alternatives, although their clinical effects are generally less pronounced than those of tretinoin [30]. Indubitably, tolerability remains a key limitation of retinoids, particularly among older individuals, whose thinner and more fragile skin increases susceptibility to irritation [31–34].

Currently, in aesthetic dermatology, a paradigm shift of antiaging treatments is underway [35, 36]: Rather than merely treating visible symptoms, longevity principles are now being applied to the skin. These approaches aim to address primary hallmarks of aging as root causes of aging to improve and preserve skin functionality. Among these hallmarks, epigenetic silencing of key genes plays a critical role. Several of our identified marker genes, which are hypermethylated and downregulated in aged skin, are essential for maintaining keratinocyte vitality and regenerative capacity (Supplementary Fig. S2). Epigenetic treatments that reduce this hypermethylation (Supplementary Fig. S10) and thus reactivate these genes can therefore contribute to skin cell longevity. To validate the efficacy of longevity-focused topical treatments, Klinngam et al. [37] proposed a dual assessment strategy: combining traditional cosmetic endpoints (e.g., hydration, elasticity, and pigmentation) with biomarker-driven longevity evaluations [37]. To our knowledge, this study is the first to show that a DHM-containing topical capable of reactivating silenced longevity-related genes can reduce biological skin age, as measured by DNA methylation clocks, within 8 weeks—independent of chronological age or phototype and unaffected by sunscreen use. Beyond molecular endpoints, these changes are correlated to measurable clinical improvement. After 4 and 8 weeks, wrinkle visibility and occupancy decreased significantly, accompanied by reductions in surface roughness and textural irregularity. High-frequency ultrasound analysis demonstrated a 10.4% increase in dermal echogenicity after 8 weeks, reflecting enhanced dermal density, exceeding the improvements reported for oral collagen supplementation [38], highlighting the efficacy of a topical, noninvasive approach. The DHM serum demonstrated an excellent safety profile and tolerability across all phototypes and age groups. Its formulation—combining low- and high-molecular-weight hyaluronic acid (HA) (52 kDa and 2000 kDa), bioactive glycine saponin (which upregulates dermal HA, collagen, and elastin), and enoxolone (which inhibits hyaluronidase-mediated degradation)—may further contribute to skin hydration, elasticity, and structural recovery. The concordance between biological and clinical improvements suggests that reversing epigenetic

aging is not merely a molecular phenomenon but also clinically meaningful.

### Limitations

While this study provides valuable insights, several aspects offer opportunities for further refinement. In the product-use study, Asian and male volunteers were less represented, and the follow-up period was limited to 8 weeks; extending the observation window and incorporating additional time points could enable a more detailed understanding of the temporal dynamics of epigenetic alterations. Moreover, although previous verum/vehicle-controlled work has demonstrated that DHM can upregulate epigenetically silenced genes, the present product-use study did not include a vehicle-controlled arm, which could be integrated into future designs to further strengthen causal interpretation. Finally, the epigenetic analyses focused on biological age predictions, and expanding the approach to include complementary omics layers, such as transcriptomics, may provide a more comprehensive view of DHM-associated molecular effects.

## CONCLUSIONS

Taken together, the findings of this study suggest that targeting epigenetic mechanisms represents a new direction in approaching skin longevity in dermatology. By acting upstream of conventional biochemical and structural pathways, epigenetic modulation offers the potential not only to improve clinical appearance but also to restore a more youthful molecular phenotype of the skin. Future investigations should include longer follow-up periods, additional omics-based analyses, and comparative studies versus established gold standard treatments to confirm the durability and mechanistic pathways underlying these effects.

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***Data Availability.*** Datasets analyzed in this study are available in the ArrayExpress database under the accession no. E-MTAB-4385 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-4385) and E-MTAB-625 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-625) or from the corresponding author on reasonable request.

### *Declarations*

***Conflict of Interest.*** Authors Minyue Qi, Paula Pitta, Katrin Wegner, Boris Kristof, Julia Gallinger, Marc Winnefeld, Cassandra Falckenhayn, and Elke Grönniger were employed by the company Beiersdorf AG. Lilia Guadanhim, Cheri Frey, and Frank Lyko received consultation fees from Beiersdorf AG. Manuel Rodríguez-Paredes received speaker fees from Beiersdorf SA. The remaining authors Günter Raddatz, Yan Feng, and Rungsima Wanitphakdeedecha declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

***Ethical Approval.*** Both studies were conducted in accordance with ethics requirements. The pilot study was approved by the Ethics Committee of the Faculty of Medicine at the University of Heidelberg (ref. S-783/2024), and all participants provided written, informed consent. Specifically, consent was obtained for the storage and processing of biosamples at the German Cancer Research Center (DKFZ) and for the processing and use of data for biomedical research, including publication. The product-use study was conducted in accordance with the principles of the Declaration of Helsinki, applicable regulatory requirements, including Resolution CNS no. 466/12, and ICH E6: Good Clinical Practices and Document of the Americas. This study was approved by the Independent Ethics Committee (IEC) of Investiga-Institutos de Pesquisa, registered by the National Research Ethics Commission (CONEP) (CEP approval no. CAAE 90155525.9.0000.5599). All participants provided written, informed consent for the collection of clinical data, biological samples, and facial images, as well as consent for the publication of anonymized data and images in scientific media.

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