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Original Article

Integrating Epigenetic Clocks in Aesthetic Dermatology: A New Paradigm for Personalized Skin Rejuvenation

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ABSTRACT

Background: Chronological age poorly captures biological variation in skin aging, which may contribute to inconsistent responses to aesthetic rejuvenation. DNA methylation–based epigenetic clocks provide measurable estimates of biological age and may support personalized dermatological treatment planning. Objective: To compare epigenetic-guided skin rejuvenation with standard chronological age–based treatment among adults seeking non-surgical aesthetic care. Methods: This single-center randomized controlled trial enrolled 120 adults aged 25–65 years at a tertiary dermatology setting in Punjab, Pakistan. Participants were randomized to epigenetic-guided treatment or standard care. Biological age was estimated using DNA methylation profiling and classified as accelerated, synchronous, or decelerated aging. Both groups received topical, device-based, and injectable rejuvenation over six months. Outcomes included wrinkle reduction, pigmentation improvement, elasticity enhancement, satisfaction, and epigenetic age change. Results: Of 120 randomized participants, 114 completed follow-up. Epigenetic-guided care produced greater wrinkle reduction (mean difference 0.60 PGA points, 95% CI 0.41–0.79; d=1.18; p=0.008), pigmentation improvement (12.00%, 95% CI 8.31–15.69; d=1.19; p=0.002), elasticity enhancement (12.00%, 95% CI 9.24–14.76; d=1.60; p=0.014), and epigenetic age reduction (−1.50 years, 95% CI −1.78 to −1.22; d=1.96; p=0.040). Conclusion: Epigenetic-guided rejuvenation improved clinical, patient-reported, and molecular outcomes, supporting further evaluation of biological-age-based personalization in aesthetic dermatology. Keywords: Epigenetic clock, DNA methylation, skin aging, aesthetic dermatology, personalized medicine, rejuvenation.

INTRODUCTION

Human skin is a visible and biologically active organ in which intrinsic aging, environmental exposure, lifestyle factors, and molecular senescence converge to produce wrinkles, dyspigmentation, loss of elasticity, and textural deterioration. Aesthetic dermatology has expanded rapidly because patients increasingly seek non-surgical interventions that improve appearance while preserving natural function and minimizing downtime. Current rejuvenation strategies include topical retinoids, antioxidants, sunscreens, botulinum toxin, hyaluronic acid fillers, fractional lasers, and radiofrequency-based procedures; however, clinical response remains heterogeneous even among patients of similar chronological age and comparable visible aging severity (1–6). This variability suggests that conventional treatment planning based mainly on chronological age and clinical inspection may inadequately capture the biological differences that determine treatment responsiveness.

Epigenetic aging provides a molecular framework for understanding this heterogeneity. DNA methylation changes at CpG sites accumulate with age and can be mathematically modeled through epigenetic clocks, including the Horvath pan-tissue clock, Hannum clock, PhenoAge, and GrimAge models (7–10). These clocks estimate biological age and quantify age acceleration or deceleration relative to chronological age, thereby offering a biomarker-based measure of aging burden. Unlike chronological age, biological age integrates cumulative effects of genetics, inflammation, metabolic stress, ultraviolet exposure, lifestyle, and tissue-specific molecular remodeling. In dermatology, this distinction is particularly relevant because two individuals of the same chronological age may differ substantially in collagen integrity, fibroblast activity, pigmentation behavior, epidermal repair capacity, and susceptibility to photoaging.

Skin is an appropriate model for epigenetic aging research because it is accessible, clinically measurable, and directly affected by both intrinsic and extrinsic aging pathways. Keratinocytes and dermal fibroblasts demonstrate age-related methylation changes that influence epidermal differentiation, extracellular matrix organization, collagen synthesis, barrier function, and melanogenesis (11–15). Emerging skin-specific methylation models suggest that cutaneous biological aging may not be fully represented by blood-based clocks alone, although blood-derived and pan-tissue methylation markers remain useful for estimating systemic biological age (16–18). These findings support the concept that epigenetic profiling may help identify patients with accelerated biological aging who require more intensive rejuvenation protocols, as well as biologically younger patients who may benefit from conservative collagen-supportive approaches.

The clinical problem is especially relevant in South Asian populations, where Fitzpatrick skin types III–V, high ultraviolet exposure, pigmentary disorders, and variable access to preventive skin care influence aesthetic aging patterns. Pigmentation irregularities, melasma-like changes, lentigines, and early photoaging are frequent patient concerns in Pakistan, yet most rejuvenation protocols remain guided by visible phenotype and chronological age rather than molecular aging status (19–22). This creates a risk of undertreating patients with accelerated biological aging and overtreating those whose molecular aging profile is relatively preserved. A precision approach based on biological age may improve treatment selection, reduce unnecessary procedural intensity, and align patient expectations with biologically plausible outcomes.

Although epigenetic clocks have been widely evaluated in aging biology and systemic disease prediction, their direct clinical application in aesthetic dermatology remains limited. Most existing dermatological rejuvenation studies evaluate treatment effects using clinical scales, imaging, histology, or patient-reported outcomes, but rarely integrate molecular aging markers as stratification tools or outcome measures (23–25). Therefore, it remains unclear whether epigenetic-guided treatment selection produces superior clinical outcomes compared with conventional chronological age–based planning.

The present randomized controlled trial evaluated adults aged 25–65 years seeking non-surgical aesthetic rejuvenation in a tertiary care dermatology setting. The intervention was an epigenetic-guided rejuvenation protocol in which treatment intensity and prioritization were informed by DNA methylation–derived biological age categories. The comparator was a standard rejuvenation protocol based on chronological age and physician clinical assessment. The primary outcomes were improvements in wrinkle severity, pigmentation irregularity, and skin elasticity over six months, while secondary outcomes included patient satisfaction, biological age change, and correlations between epigenetic age deviation and treatment responsiveness. The study hypothesized that epigenetic-guided personalization would produce greater clinical improvement and patient satisfaction than standard chronological age–based treatment planning.

MATERIALS AND METHODS

This study was conducted as a single-center, assessor-blinded, randomized controlled trial at the Department of Dermatology of a tertiary care hospital in Punjab, Pakistan, between January 2023 and February 2024. The trial compared an epigenetic-guided skin rejuvenation strategy with standard chronological age–based treatment planning among adults seeking non-surgical aesthetic rejuvenation. The study protocol was approved by the institutional review board before participant recruitment, and all participants provided written informed consent before enrollment. The study followed the ethical principles of the Declaration of Helsinki and was designed according to CONSORT reporting principles for randomized trials.

Patients attending the dermatology outpatient clinic with aesthetic concerns including wrinkles, pigmentation irregularities, and loss of skin elasticity were screened for eligibility. Adults aged 25–65 years who requested non-surgical skin rejuvenation, agreed to clinical follow-up, and consented to blood and skin sampling for molecular analysis were eligible. Pregnant or lactating women, patients with autoimmune disease, malignancy, chronic systemic illness, active infection, inflammatory dermatoses, keloidal tendency at the treatment site, or recent systemic retinoid, corticosteroid, or immunomodulatory use within the preceding six months were excluded. Eligible participants were recruited consecutively until the required sample size was achieved.

The planned sample size was 120 participants, with 60 allocated to each study arm. The minimum required sample size was estimated as 100 participants based on prior pilot evidence using epigenetic biomarkers, with 80% statistical power and a 95% confidence level. An additional 20 participants were recruited to compensate for anticipated dropout. Participants were randomized into two equal groups using a computer-generated random allocation sequence. Allocation concealment was maintained using sealed opaque envelopes. The experimental group received epigenetic-guided treatment planning based on biological age classification, whereas the control group received standard treatment planning based on chronological age and physician clinical judgment. Patients were aware of the procedures they received, but clinical outcome assessors and laboratory personnel remained blinded to group allocation. Physician Global Assessment scoring was performed by independent dermatologists who were blinded to treatment allocation and epigenetic results.

At baseline, all participants underwent demographic, lifestyle, clinical, imaging, patient-reported, and molecular assessment. Recorded variables included chronological age, sex, occupation, smoking status, dietary pattern, and sun exposure history. Clinical skin aging was assessed using standardized 5-point Physician Global Assessment scores for wrinkle severity, pigmentation irregularity, and elasticity loss. Dermoscopic imaging was performed to document baseline skin characteristics and monitor treatment response. Patient-reported outcomes were measured using the Dermatology Quality of Life Instrument-9. Biological sampling included 10 mL of peripheral venous blood and a 4 mm postauricular skin punch biopsy for DNA methylation analysis.

DNA was extracted using the Qiagen DNA Mini Kit. Samples were bisulfite-converted and analyzed using the Illumina Infinium MethylationEPIC BeadChip array. Epigenetic age was estimated using the Horvath pan-tissue clock, Hannum blood clock, and PhenoAge clock. Participants were classified as having accelerated biological aging when epigenetic age was at least five years older than chronological age, synchronous aging when epigenetic age was within four years above or below chronological age, and decelerated aging when epigenetic age was at least five years younger than chronological age. This classification was used only for treatment planning in the experimental group and was not disclosed to blinded outcome assessors.

All participants received a standardized non-surgical rejuvenation framework over six months. The topical regimen included broad-spectrum sunscreen SPF 50+, retinol 0.05% cream at night, and vitamin C 15% serum in the morning. Device-based interventions included non-ablative fractional laser

treatment at 1550 nm once every eight weeks and radiofrequency microneedling once every six weeks. Injectable treatments included botulinum toxin A for dynamic wrinkles and hyaluronic acid filler for midface volume loss when clinically indicated. In the experimental group, treatment intensity and prioritization were individualized according to biological aging category: participants with accelerated aging received greater emphasis on pigmentation and wrinkle-targeting interventions, those with synchronous aging received a balanced protocol across all aging domains, and those with decelerated aging received a more conservative elasticity- and collagen-supportive approach. In the control group, the same treatment modalities were available, but treatment choice and intensity were guided only by chronological age and visible clinical signs.

Participants were evaluated at baseline, three months, and six months. At each follow-up visit, PGA scoring, dermoscopic imaging, patient-reported outcome assessment, and adverse-event monitoring were performed. Adverse events included erythema, edema, bruising, infection, scarring, and persistent pigmentary change. At the six-month endpoint, repeat blood sampling was performed to assess change in DNA methylation–derived biological age.

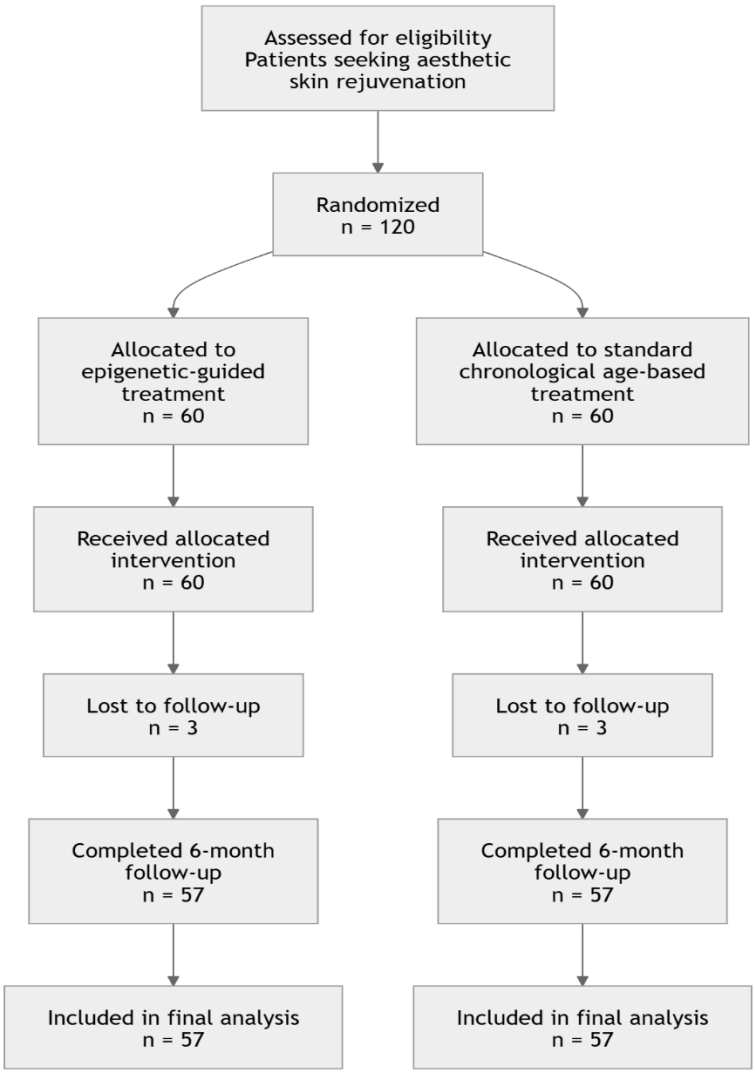

Figure 1 CONSORT Flowchart

The primary outcomes were between-group differences in wrinkle reduction, pigmentation improvement, and elasticity enhancement at six months. Secondary outcomes included patient satisfaction, change in epigenetic age, and correlations between biological age deviation and treatment responsiveness. Continuous variables were summarized as mean and standard deviation, while categorical variables were summarized as frequencies and percentages. Between-group comparisons

were performed using independent-samples t-tests and two-way analysis of variance where appropriate, and within-group changes were assessed using paired-samples t-tests. Categorical variables were compared using the chi-square test. Pearson correlation coefficients were calculated to evaluate associations between epigenetic age deviation and clinical response. Analyses were performed using SPSS version 27.0. Statistical significance was set at $\alpha=0.05$, and 95% confidence intervals were planned for point estimates. Participants who completed the six-month follow-up were included in the final analysis; no imputation was applied for participants lost to follow-up.

RESULTS

A total of 120 participants were randomized, with 60 assigned to the epigenetic-guided group and 60 to the standard-treatment group. Six participants were lost to follow-up, three from each group. Therefore, 114 participants completed the six-month assessment and were included in the final analysis, with 57 participants analyzed per group. The overall retention rate was 95.0%. Baseline demographic and clinical characteristics were comparable between groups, including sex distribution and baseline Physician Global Assessment scores for wrinkles, pigmentation, and elasticity.

At six months, the epigenetic-guided group showed greater improvement across all primary clinical outcomes. Wrinkle reduction was higher in the epigenetic-guided group than in the standard group, with a mean difference of 0.60 PGA points. Pigmentation improvement was also greater in the epigenetic-guided group, with a 12.00-percentage-point advantage over standard treatment. Elasticity enhancement followed the same pattern, with the largest standardized effect size among the primary clinical outcomes.

Table 2. Primary Clinical Outcomes at Six Months

Outcome	Epigenetic-Guided	Standard Group	Mean Difference	95% CI	Effect Size	p-value
Wrinkle reduction, PGA points	1.60 ± 0.60	1.00 ± 0.40	0.60	0.41 to 0.79	Cohen's d = 1.18	0.008
Pigmentation improvement, %	41.00 ± 11.00	29.00 ± 9.00	12.00	8.31 to 15.69	Cohen's d = 1.19	0.002
Elasticity enhancement, %	36.00 ± 8.00	24.00 ± 7.00	12.00	9.24 to 14.76	Cohen's d = 1.60	0.014

Secondary outcomes also favored epigenetic-guided treatment. Patient satisfaction was higher in the epigenetic-guided group, where 84.0% of participants reported being satisfied or very satisfied, compared with 68.0% in the standard group. Repeat DNA methylation analysis showed a greater reduction in estimated epigenetic age in the epigenetic-guided group than in the standard group.

Table 3. Secondary Outcomes at Six Months

Outcome	Epigenetic-Guided Group	Standard Group	Effect Estimate	95% CI	Effect Size	p-value
Satisfied or very satisfied, %	84.0	68.0	RR = 1.23	1.00 to 1.52	OR = 2.46	0.030
Epigenetic age change, years	−1.80 ± 0.90	−0.30 ± 0.60	Mean difference = −1.50	−1.78 to −1.22	Cohen's d = −1.96	0.040

Correlation analysis showed that epigenetic age deviation was more closely associated with treatment response than chronological age. Accelerated biological aging was positively associated with wrinkle reduction and pigmentation clearance, while elasticity enhancement showed a negative association with accelerated biological aging. Chronological age demonstrated weaker correlations with clinical response.

Table 4. Correlation Between Epigenetic Age Deviation and Treatment Response

Outcome	Direction of Association	Pearson's r	95% CI	p-value
Wrinkle reduction	Positive association with accelerated biological aging	0.62	0.43 to 0.76	<0.010
Pigmentation clearance	Positive association with accelerated biological aging	0.74	0.59 to 0.84	<0.010
Elasticity enhancement	Negative association with accelerated biological aging	−0.55	−0.71 to −0.34	<0.050

Outcome	Direction of Association	Pearson's r	95% CI	p-value
Chronological age and clinical response	Weak association	0.21–0.32		

Both treatment approaches were well tolerated. No major adverse events, including scarring, infection, or persistent pigmentary change, were reported. Minor events included transient erythema, mild swelling, and injection-site bruising, with no significant between-group difference in adverse-event frequency.

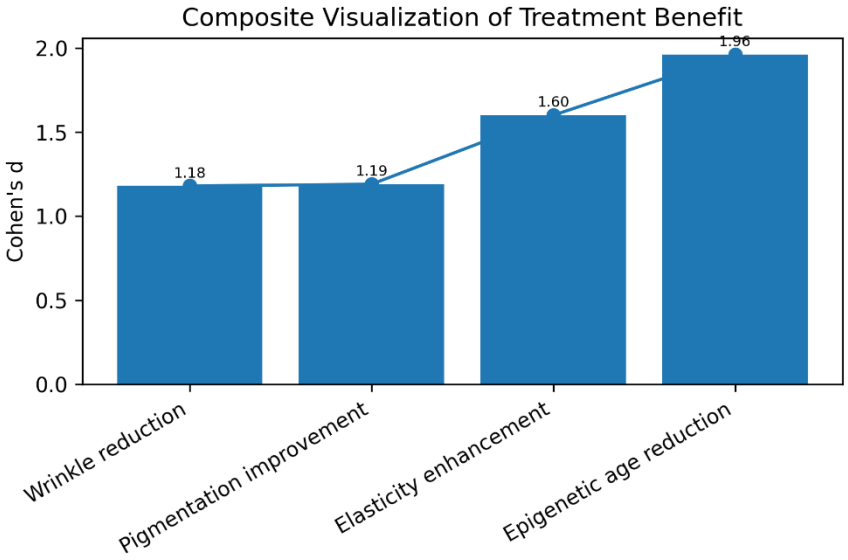

Figure 2 Composite visualization of standardized treatment benefit across clinical and molecular outcomes.

This composite figure integrates a multibar chart with a line overlay to illustrate the magnitude and trend of treatment effect sizes (Cohen's d) favoring epigenetic-guided care. The bars represent standardized effect sizes for wrinkle reduction (d = 1.18), pigmentation improvement (d = 1.19), elasticity enhancement (d = 1.60), and epigenetic age reduction (d = 1.96), while the superimposed line highlights the progressive increase in treatment benefit across outcomes. The visualization demonstrates a consistent and substantial advantage of epigenetic-guided intervention, with the strongest effect observed in molecular aging reversal and elasticity outcomes.

DISCUSSION

This randomized controlled trial found that epigenetic-guided treatment planning produced greater improvement than standard chronological age–based aesthetic care across clinical, patient-reported, and molecular outcomes. At six months, wrinkle reduction was greater in the epigenetic-guided group than in the standard group, with a mean difference of 0.60 PGA points and a large standardized effect (Cohen's d=1.18). Pigmentation improvement also favored epigenetic-guided care, with a 12.00-percentage-point greater improvement and a large effect size (d=1.19). The strongest clinical effect was observed for elasticity enhancement, where the mean between-group difference was 12.00 percentage points and the standardized effect was large (d=1.60). Patient satisfaction was also higher in the epigenetic-guided group, with approximately 23% of participants more likely to report being satisfied or very satisfied. Repeat DNA methylation analysis showed a greater reduction in estimated epigenetic age in the experimental arm, with a mean between-group difference of −1.50 years and a large, standardized effect (d=1.96), although this molecular finding should be interpreted cautiously because follow-up was limited to six months and tissue-specific mechanisms were not directly examined.

These findings are consistent with the broader aging literature showing that chronological age alone is an incomplete proxy for biological aging. DNA methylation clocks developed by Horvath, Hannum, Levine, and Lu and colleagues have demonstrated that methylation-derived biological age captures inter-individual variability in aging trajectories more precisely than chronological age alone (1–4). The

present trial extends this concept into aesthetic dermatology by showing that biological-age stratification may have practical value in treatment selection. The findings also align with skin-aging literature indicating that keratinocytes, dermal fibroblasts, collagen remodeling, pigmentation pathways, and extracellular matrix integrity are influenced by age-related molecular and epigenetic changes (8–15). The observed improvement in pigmentation and elasticity is biologically plausible, particularly because photoaging, melanogenesis, dermal matrix degradation, and fibroblast senescence are all influenced by cumulative intrinsic and extrinsic exposures. However, direct comparison with previous clinical trials is limited because most rejuvenation studies evaluate fractional lasers, radiofrequency microneedling, topical retinoids, antioxidants, fillers, or botulinum toxin using clinical and imaging endpoints rather than methylation-guided treatment allocation (19–29).

Several mechanisms may explain the observed benefit of epigenetic-guided care. Patients with accelerated biological aging may have greater cumulative molecular damage and therefore more visible clinical aging, allowing appropriately intensified protocols to produce larger measurable improvement. Conversely, patients with decelerated biological aging may retain greater fibroblast responsiveness, collagen synthetic potential, and extracellular matrix resilience, which may explain stronger elasticity gains when treatment intensity is appropriately calibrated. Fractional laser and radiofrequency microneedling create controlled dermal injury that stimulates wound-healing pathways, collagen remodeling, and neocollagenesis, while retinoids and vitamin C support epidermal turnover, collagen metabolism, and antioxidant protection (20–25). It is plausible that such interventions influence downstream molecular aging signatures, but this study cannot establish a direct causal mechanism for epigenetic age reduction. The observed methylation-age change should therefore be considered an exploratory molecular signal rather than definitive proof of biological rejuvenation.

The composite visualization demonstrates a clear gradient of treatment effectiveness favoring epigenetic-guided care across all measured outcomes. While wrinkle reduction and pigmentation improvement exhibited comparable moderate-to-large effect sizes, elasticity enhancement showed a more pronounced response, suggesting improved structural skin recovery in biologically guided interventions. The largest effect was observed in epigenetic age reduction, indicating that molecular aging markers may be more responsive to personalized treatment strategies than conventional clinical endpoints. The upward trajectory illustrated by the line overlay further reinforces the progressive increase in treatment benefit from superficial clinical improvements to deeper biological outcomes, supporting the hypothesis that integrating epigenetic profiling enhances both phenotypic and molecular dimensions of skin rejuvenation.

The study has several strengths. It used randomized allocation, balanced group sizes, blinded outcome assessment, standardized clinical follow-up, multidimensional outcome measurement, and integration of molecular biomarkers with patient-reported outcomes. The inclusion of participants from a South Asian clinical setting is also important because Fitzpatrick III–V skin types, high ultraviolet exposure, and pigmentary disorders are highly relevant to aesthetic practice in Pakistan. Nevertheless, important limitations remain. Trial registration details were not reported, and the IRB approval number was unavailable in the supplied manuscript. Although allocation concealment was described through sealed opaque envelopes, further detail on sequence generation, block size, and implementation would strengthen reproducibility. The final analysis included participants who completed follow-up rather than a clearly stated intention-to-treat population, creating potential attrition bias despite balanced dropout. The sample size was adequate for the reported outcomes but remained modest and single-center, limiting generalizability. Confidence intervals and effect sizes were not originally reported and were derived from aggregate values, not participant-level data. Finally, cost, feasibility, assay turnaround time, and access to methylation profiling were not formally evaluated (40)

Clinically, these findings suggest that biological-age-informed aesthetic planning may improve personalization beyond conventional chronological assessment. If validated in larger multicenter trials,

epigenetic profiling could help stratify patients according to treatment intensity, prioritize pigmentation- or wrinkle-targeting modalities in accelerated agers, and avoid unnecessary procedural burden in biologically younger patients. Future studies should include prospective trial registration, full CONSORT flow reporting, intention-to-treat analysis, prespecified primary endpoints, longer follow-up, skin-specific methylation clocks, standardized photography, blinded image analysis, and cost-effectiveness assessment. Multi-omics integration and machine-learning models may further improve prediction of rejuvenation response, but implementation should remain clinically cautious until molecular, economic, and ethical considerations are more clearly defined.(41).

CONCLUSION

Epigenetic-guided aesthetic treatment planning produced greater six-month improvements in wrinkle reduction, pigmentation clearance, elasticity enhancement, patient satisfaction, and estimated biological age reduction than standard chronological age–based care. These findings support the potential value of DNA methylation–derived biological age as a personalization tool in non-surgical skin rejuvenation, particularly where clinical aging patterns vary widely among patients of similar chronological age. However, the molecular findings should be interpreted cautiously because the trial was single-center, follow-up was short, and mechanistic pathways were not directly tested. Larger registered multicenter trials are needed before routine clinical implementation.

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