



Consensus Opinion

Value and Benefits of the Polynucleotides HPT™ Dermal Priming Paradigm A Consensus on Practice Guidance for Aesthetic Medicine Practitioners and Future Research

Cavallini M^{1*}, Bartoletti E², Maioli L³, Palmieri IP⁴, Papagni M⁵, Priori M⁶, Trocchi G⁷

¹Unit Chief, Operative Unit of Dermatology and Dermatologic and Plastic Surgery, CDI Hospital, Milan, Italy.

²Director, Esthetic Medicine Outpatient Service, Fatebenefratelli Hospital, Rome, Italy.

³Maioli Private Practice Sassari, Italy.

⁴Tutor, Master Diploma in Morphofunctional Polydistrectual Surgery, University of Padua Medical School, Padua, Italy; Contract Professor, Master Diploma in Aesthetic Medicine, University of Naples Medical School, Naples, Italy.

⁵Senior Trainer and Member of the Board, Agorà, Italian Scientific Society of Aesthetic Medicine, Milan, Italy.

⁶President, SIES, Esthetic Medicine and Surgery Society, Florence, Italy.

⁷Member of the Board, International School of Aesthetic Medicine, Fondazione Internazionale Fatebenefratelli, Rome, Italy.

*Corresponding author: Maurizio Cavallini, Operative Unit of Dermatologic and Plastic Surgery, CDI Hospital, Via Simone Saint Bon 20, 20147 Milan, Italy.

Citation: Cavallini M, Bartoletti E, Maioli L, Palmieri IP, Papagni M, et al. (2024) Value and Benefits of the Polynucleotides HPT™ Dermal Priming Paradigm A Consensus on Practice Guidance for Aesthetic Medicine Practitioners and Future Research. Clin Exp Dermatol Ther 9: 224. DOI: <https://doi.org/10.29011/2575-8268.100224>

Received Date: 02 June, 2024; **Accepted Date:** 18 June, 2024; **Published Date:** 20 June, 2024

Abstract

Background: Polynucleotides High Purification Technology (PN HPT™), a highly biocompatible functional ingredient without protein contaminants and no pharmacological or allergic potential, demonstrated a reconditioning effect on the dermal environment. Might dermal cells react with improved responses to other skin revitalisation strategies after, or concomitantly with, a PN HPT™ priming treatment that makes them more metabolically reactive? A digital survey of dermatologists, plastic surgeons, and aesthetic physicians investigated the rationale of such a “PN HPT™ dermal priming paradigm”. A meeting by distinguished experts to discuss the survey outcomes led to this consensus paper, which provides a rationale for the confirmatory studies currently planned and launched and a set of practical recommendations for the proposed priming paradigm. **Methods of consensus development:** Three years after their first 2020 consensus meeting on PN HPT™ in aesthetic medicine as the only ingredient of medical devices for intradermal injection or combined with hyaluronic acid, the PN HPT™ Priming Board of eight distinguished experts in cosmetic medicine and plastic surgery convened once again. The purpose of the 2023 Board meeting was to produce a guidance document on the PN HPT™ benefits on skin quality in sequential or combined treatment protocols

with other skin revitalisation strategies and the framework for a clinical research program to support the concept. The paper originated from the Board's digital and face-to-face discussions on the outcomes of the digital survey (16 questions), designed by the Board's experts and filled out by 51 surveyed specialists. **Results:** The Board reached a "Recommendation" (consensus of more than 80%) about the value and scope of the PN HPT™ dermal priming paradigm before or concomitantly to all secondary treatments-skin resurfacing and stretch mark treatment with ablative CO₂ and Er:YAG lasers, volume-enhancement with fillers in perioral, cheeks, lips and other areas, carboxytherapy, chemical peels, needling, Intense Focused Ultrasound and radiofrequency, and LED treatment of the scalp area. The Board's orientation was for a "Consensus statement" (agreement level, 71%) only for carboxytherapy. The Board's suggestions included details of doses and volumes to inject and the ideal number of priming sessions. **Conclusions:** The Consensus document illustrates the rationale behind the PN HPT™ dermal priming paradigm and provides practical guidance for its application in different skin areas. It also lays the foundations for the ongoing clinical research program, conceived to provide new evidence supporting the PN HPT™ dermal priming paradigm.

Keywords: Dermal priming Polynucleotides; Polynucleotides High Purification Technology; PN HPT™; Skin Quality.

Background

Conditioning priming of the dermal environment—reasonable or delusion?

"Priming" and "to prime" are ancient words, decanted from religious Medieval Latin into Anglo-Saxon Old English ("prima" was the first office recited in the early morning, first cited in the Rule of St. Benedict). The Old French word "prime" imported by Normans definitively established them in Middle English [1].

The word is ancient, but priming is a biological concept in full blossom. For instance, consider seed priming, a recent technology of controlled seed hydration before sowing. Imbibed "primed" seeds undergo their first germination stage without radical protrusion through the seed coat, helping them to tide over environmental stresses during germination like salinity, drought, cold and heavy metal contamination, and lifting crop performance in fragile lands [2,3]. Or consider how fragile the *in vivo* survival of multipotent mesenchymal stromal cells (MSCs) is in inhospitable microenvironments during cell-based therapies of immune-mediated, inflammatory, and degenerative disorders. Exposure to cytokines and growth factors, hypoxia, pharmacological drugs, biomaterials, and different culture conditions are all MSC priming strategies currently explored [4] Are skin priming strategies conceivable in cosmetic dermatology and micro-invasive procedures to enhance aesthetic benefits and their persistence? Let us think of some iconic examples.

The skin's failure to elongate under low-intensity forces and mechanical stretching is the ultimate determinant of striae albae. The end-stage outcomes in mature striae albae are atrophy, elastic disruption, blunting of rete ridges, sparse dermal vessels, and voluminous collagen bundles, densely packed and oriented according to mechanical forces [5,6]. The outcomes of all proposed treatment strategies are conflicting and inconclusive, be they energy and light-emitting devices, platelet-rich plasma,

glycolic and trichloroacetic acids chemical peels, aluminium oxide microdermabrasion, micro-needling, carboxytherapy, or galvanopuncture [7-9]. Interestingly, combining bipolar radiofrequency with topical tretinoin offers the best outcomes; conversely, topical tretinoin monotherapy appears to be the worst option [5].

A different example

Hyaluronic acid fillers correct the soft tissue losses that, in the ageing facial middle third, translate into dark shadows, malar area concavities, and unmasking of the inferior orbital rim over the zygomatic arch. Unfortunately, the favourable outcomes are fleeting in a few months [10]. Might some preliminary or simultaneous conditioning treatment reverse or improve such short-persistence liability?

A third still different example is the botulinum toxin treatment of glabellar lines. Here, the problems are the variable anatomy of the corrugator supercilii and frontalis muscles, the risk of eyebrow ptosis and asymmetry, and, in general, local neurotoxic side effects [11]. Might a glabellar conditioning (priming) strategy improve the aesthetic outcomes and lessen the risk of ptosis and unpleasant gaze? In all such situations, which preliminary or concomitant treatment might improve the aesthetic benefits or, at least, slow their reversal? Based on which rationale? Could the background conditioning treatment improve the underlying skin quality in agreement with the holistic concept of 360-degree skin quality? [12] Could the rationale be the same for the three outlined iconic conditions and the others that might benefit from improved or persistent outcomes?

The Polynucleotides HPT™ (PN HPT™) dermal priming paradigm

The gonads of trouts bred for human consumption are the natural source of Polynucleotides High Purification Technology (PN HPT™). A pure, highly biocompatible functional ingredient without protein contaminants and no pharmacological or allergic potential is the end-product of high-tech purification and

sterilisation procedures that respect world-class Quality Assurance and Good Manufacturing Practice standards [13] PN HPT™ are available in Italy, Europe, and several extra-European markets as Class-III CE-marked medical devices for intradermal injection. The face and periocular area, the décolleté and neck, hands, scalp, and stretch marks are the targets of the current collection of specifically designed PN HPT™ devices (single-ingredient formulations or co-formulations with hyaluronic acid) [13].

Intradermally injected PN HPT™ have tissue hydrating and volume-enhancing actions similar to hyaluronic acid. *In vivo*, PN HPT™ and the water dipoles of the PN HPT™ hydration cuff reorganise into an elastic three-dimensional gel with short-term hyaluronate-like tissue volumizing effects [13,14].

Moreover, PN HPT™ are scavengers of oxygen-derived free radicals [15]. Over the short term, the hydrated dermal environment facilitates the fibroblast production of collagen, hyaluronic acid, tropoelastin, and other extracellular matrix components. Moreover, the reduced oxidative stress level in the dermal environment antagonises the degradation of hyaluronic acid and the physiological depletion of tissue antioxidants with ageing [13,14,16]. Untoward effects, if any, are minor and ephemeral [13].

At least as interesting are the long-term PN HPT™ functional effects in the dermis environment. Damaged, hypoxic, and dying cells release polynucleotide derivatives in extracellular spaces [17,18]. Similarly, intradermal PN HPT™ act (non-pharmacologically) as pro-fibroblast primers by passively replenishing the fibroblast pool of nitrogen bases, nucleosides, and nucleotide precursors [14,17].

Based on these considerations, the PN HPT™ dermal priming paradigm is easily conceptualised while waiting for the supporting demonstrations in the ongoing program of clinical studies: does supporting the metabolic efficiency and resilience of dermal cells recondition (prime) the dermal environment, with more robust and faster responses to further skin revitalisation strategies? Has skin preliminary soil tilling by PN HPT™ any role before or concomitantly with other aesthetic treatments like fillers, CO₂ laser and other energy-based therapies, carboxytherapy, chemical peels, or needling? [13].

A Board convened to define and validate the PN HPT™ dermal priming paradigm

A group of distinguished Italian experts in dermatology, plastic surgery, and aesthetic medicine with extensive experience in improving skin quality and preserving acquired benefits over time (The Polynucleotides HPT™ Priming Board) first convened in Sanremo, Italy, in September 2019. The Board's primary purpose was to elaborate evidence-based recommendations for the safe and effective use of PN HPT™; the Board also aimed to discuss the first ideas about the PN HPT™ dermal priming paradigm and its

rationale. The same eight-member expert panel convened again in Rome in May 2023 to further elaborate on the PN HPT™ dermal priming paradigm and provide expert guidance to national and international practitioners.

The first clinical pieces of evidence about the priming potential supported the initiative. An example is an exploratory yet well-designed randomised study with PN HPT™ as a skin priming agent before cross-linked hyaluronic acid for correcting moderate to severe nasolabial folds [19]. The citation from the paper's abstract and the graph from the Results section describe the sequence of priming events and outcomes. The authors hypothesised that PN HPT™ conditioning of the skin to react more intensely to hyaluronic acid would exalt and prolong the overall aesthetic benefits compared to hyaluronic acid alone [19].

This consensus report summarises the recommendations arising from the Board's collective discussions.

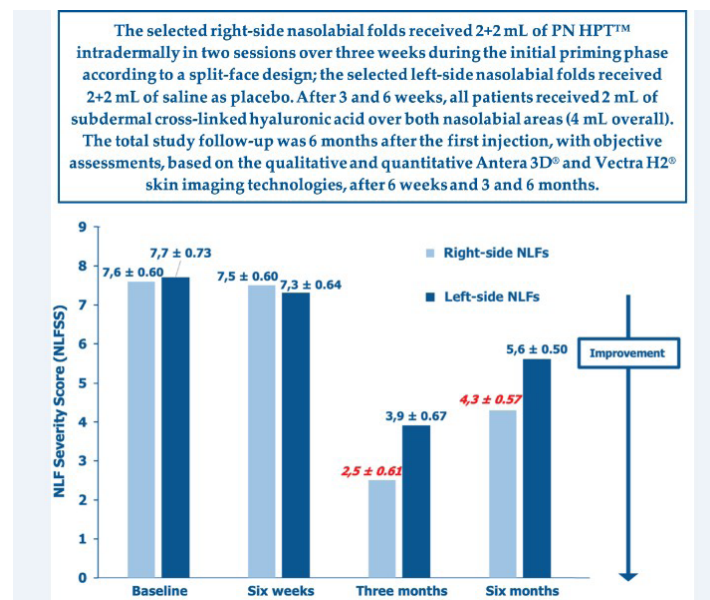


Figure 1: Comparison of nasolabial folds (NLFs) severity mean scores (NLFSS) in treated right-side and left-side nasolabial folds at baseline and after six weeks (PN HPT™ vs saline placebo monotherapy) and 3 and 6 months (PN HPT™ priming + concomitant hyaluronic acid consolidation); outcomes in red and Italics: $p < 0.05$ vs. baseline—outline of the study design in the text box. Abstract citation (partially modified) and graph reproduced with permission by the paper's authors and Editor (License Number 5701861471265 issued on January 4, 2024) [19].

Methods of Consensus Development

Preliminary activities before the consensus meeting

In the first phase of the Board's activities, the eight experts searched

and reviewed the literature, indexed on PubMed/MEDLINE and other leading databases, on PN HPT™ treatments combined with other skin rejuvenating techniques to improve skin quality. The experts shared the manuscripts online among them for initial idea-sharing.

Those preliminary online discussions also helped the Board to develop a digital 16-item multiple-choice survey questionnaire about the relevance, personal attitudes, and everyday behaviour of surveyed specialists regarding the proposed PN HPT™ dermal priming paradigm. For the list of the digital survey's sixteen questions, please refer to Supplemental File A. All survey questions were multiple-choice.

A representative sample of aesthetic medicine practitioners in Italy, 51 experienced practitioners of both genders (29 female and 22 male specialists; mean age 58 years old, min 44, max 69), completed the questionnaire independently of each other on a secure, dedicated website. The survey cohort comprised six dermatologists (11.8%), twelve plastic surgeons (23.5%), and thirty-three certified aesthetic medicine practitioners (64.7%). All operations, including tabulation and descriptive analysis of survey outcomes, were over and ready for discussion before the consensus event.

The last preliminary activity by the Board was formulating a series of suggestions, presented in summary tables, about how to decline the PN HPT™ dermal priming paradigm in different face and body areas: PN HPT™ injection techniques, PN HPT™ priming doses and gel volumes, number of priming sessions, and intervals between priming sessions before or in combination with other treatments. The suggested treatment schedules will also be the foundations for the developing clinical research program to confirm and substantiate the PN HPT™ dermal priming paradigm.

The suggestions were discussed, modified, voted upon, and accepted or refused at the Rome meeting. A set of modified Delphi rules was the basis of the voting process: an expert consensus of at least 80% was the threshold to accept the indication/proposal as a "Recommendation"; an agreement between 60% and 80% was the threshold to qualify the indication/proposal as a "Consensus statement". The final "Recommendations" needed not to agree rigidly with survey outcomes.

Results

PN HPT™ dermal priming PARADIGM, general considerations

The Scientific Board expressed a Recommendation for all statements but one. Waiting for definitive support from the clinical studies now being planned and launched, the Board did

not support a rigidly sequential formulation of the PN HPT™ dermal priming paradigm. The Board agreed that, likely, PN HPT™ priming does not need a previous conditioning PN HPT™ treatment; a simultaneous intradermal administration should also be acceptable, as demonstrated in the first published study of the clinical research program [19]. Confirming the indications of the last Consensus meeting and waiting for confirmation in clinical studies, the Board stated again that aesthetic outcomes are likely to be better if the background priming cycle with PN HPT™ starts before the second treatment, even by only a week. Suggested technique: a 30-32 gauge 13-mm needle and a microdroplet or linear retrograde intradermal injection strategy [13].

For rigorous preliminary skin priming in young individuals, the Scientific Board confirmed the 2020 suggestions of using single-ingredient PN HPT™, usually 20 mg/mL (for instance, the Plinest™ brand, dosed at 40 mg in 2 mL) or 7.5 mg/mL in more delicate, thinner skin areas, the hands and the scalp (for example, the Plinest Fast™ and the Plinest Hair™ brands, both dosed at 15 mg in 2 mL).

Low-concentration, single-agent PN HPT™ formulations in delicate areas like the periorcular area minimise the risk of persistent wheals occasionally occurring with more concentrated formulations with or without hyaluronic acid [13].

The Board recommended, in real-world use and the clinical research program, single-ingredient PN HPT™ devices like Plinest One™ (8 mg in 4 mL) or combined PN HPT™/hyaluronic acid devices like Newest One™ (4+4 mg in 4 mL) as priming options in adult-age skin. In areas of advanced photoaging or severely disrupted skin integrity, the Board recommended almost unanimously using PN HPT™ with hyaluronic acid (e.g., the Newest™ brand, 10+10 mg in 2 mL). In severely disrupted skin, the hydrating effect of hyaluronic acid, which markedly enhances the indirect PN HPT™ dermal stimulating effect, is distinctly beneficial [13,14,20]. Table 1 summarises the general Board's suggestions for office practice and the clinical research program.

In experienced hands, more extensive areas may be more straightforwardly treated with cannulas and infiltrations in the deep dermis and hypodermis: fewer injections mean reduced trauma, although at the cost of less precise intradermal infiltrations [22].

Recommendations were detailed for the two treatment strategies, single-agent PN HPT™ or PN HPT™ combined with hyaluronic acid. Please refer to Supplemental File B for the details of the response outcomes to the survey questions. Whatever the injection technique, the studies investigating safety demonstrated that the PN HPT™ toxicological liabilities are nil at the administered doses [21].

	Young subjects (according to the clinical picture)	Severely damaged skin	Periocular areas	Scalp	Body in adult-age subjects
PN HPT™ + HA: concentrations	7.5 mg/mL PN HPT™ (delicate areas) or 20 mg/mL PN HPT™	10 mg/mL PN HPT™ + 10 mg/mL HA	7.5 mg/mL PN HPT™	PN HPT™	2 mg/mL PN HPT™ or 1 mg/mL PN HPT™ + 1 mg/mL HA

Table 1: PN HPT™ dermal priming: suggested intradermal doses according to skin area and severity of skin derangement. HA: hyaluronic acid.

As suggestions for real-world office practice and the ongoing clinical research program, the following sections highlight examples of sequential or simultaneous PN HPT™ dermal priming strategies before some of the most frequently performed aesthetic medicine procedures and the supporting rationale for the Board’s proposals.

Suggested PN HPT™ priming procedures according to secondary treatments

Skin resurfacing and stretch mark treatment with ablative CO₂ and Er:YAG lasers

The Board’s recommendation, with an overall estimated agreement of 88% over the whole set of questions, was that the candidate subjects should receive a preliminary PN HPT™ priming cycle of at least two to three sessions (suggested dose: one syringe or vial per priming session). The priming cycle should begin at least one month before the laser session, with suspension at least one week before. Indications are photoaging, facial wrinkles, keloids, xanthelasma, actinic and seborrheic keratoses, moles and other nevi, and other superficial skin lesions (Table 2).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the (first) ablative laser session End: at least one week before the (first) ablative laser session	At least two or three	Usually, the content of one syringe-vial fractioned over the treated areas (forehead, temples, eyelids, nose, cheeks, lips, chin) during the laser session

Table 2: Suggested intradermal PN HPT™ priming procedure before skin resurfacing with ablative CO₂ or Er:YAG laser.

The rationale for PN HPT™ priming before skin resurfacing is to improve dermal hydration and priming the fibroblasts in the exposed papillary dermis to react promptly to the laser trauma with increased collagen and extracellular matrix production. The Board emphasised that the increased fibroblast production of vasoactive cytokine may help control the pinpoint bleeding, oedema, crusting, and oozing. A 2020 study of stretch mark treatment with PN HPT™ and CO₂ laser ablation and quantitative Antera® 3D CS supported the PN HPT™ priming paradigm even before the Board tentatively formulated it in the 2020 Consensus meeting [13,23]. That early study concluded that combining the resurfacing efficacy of CO₂ laser treatment PN HPT™ may improve aesthetic outcomes [23].

The Board agreed that the primed dermal environment should likely preserve the accrued resurfacing benefits over the long term, but demonstration by targeted clinical studies is desirable.

Based on available evidence, the suggested PN HPT™ dermal priming strategy might be somewhat different before ablative laser treatment for acne and traumatic scars and stretch marks, which microscopically appear as dermal scars. While waiting for confirmation from clinical studies, the advice is for at least four sessions before the second treatment, starting at least one month before the (first) laser ablative session. The suggested priming protocol envisions up to eight PN HPT™ infiltration sessions, with four sessions after the ablative laser treatment.

The Board recommended infiltrating one to two syringe vials per stretch mark area per session (overall estimated agreement over the whole set of questions, 86%; Table 3).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the (first) ablative laser session	From four to eight (suggestion: four sessions after the end of the ablative CO ₂ laser cycle)	Content of one to two prefilled syringes or vials over the scarred area

Table 3: Suggested intradermal PN HPT™ priming procedure before ablative CO₂ or Er:YAG laser treatment of stretch marks.

Before volume enhancement with fillers in the perioral, cheeks, lips, and other skin areas

Stabilising the evanescent volume-enhancing benefits allowed by fillers is the rationale for preliminary dermal priming and indirect activation of metabolic vitality. The available evidence about the PN HPT™ dermal priming paradigm supports the concept by demonstrating the slower resorption of volumes in the areas with nasolabial folds (cf. Figure 1) [19]. The study’s authors concluded that PN HPT™ recondition the biological substrate for the consolidating action of later administered hyaluronic acid, enhancing and prolonging the benefits for tissue volumes. Moreover, in the authors’ words,

“the women who underwent the (sequential) PN HPT™ hyaluronic acid treatment perceived a significantly superior subjective aesthetic benefit after three and six months despite the lack of microstructural differences with nasolabial fold treated with hyaluronic acid alone”[19].

Waiting for the evidence-based outcomes of the clinical research program, the Board agreed that the PN HPT™ priming program should start at least one month before the last planned filler treatment, with two to four PN HPT™ personalised infiltration sessions depending on the patient’s age, phototype, skin hydration, elasticity, and areas undergoing treatment.

The Board’s Recommendation (overall estimated agreement, 92%) was for one prefilled syringe or vial per treated area at each filler session (Table 4).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the (first) filler session	From two to four	One syringe vial per treated area (per infiltration session)

Table 4: Suggested intradermal PN HPT™ priming procedure before filler volume enhancement.

Carboxytherapy

Vasodilatation and collagen reorganisation are the goals of intradermal and subcutaneous microinjections of sterile, purified carbon dioxide [24]. Indications are several dermatologic and cosmetic conditions like skin ageing, striae distensae, atrophic scar, cellulite, fibro-lipodystrophy adhesions after liposuction, localised fat deposits, lymphedema, alopecia areata, psoriasis, morphea, and vitiligo [24].

How carboxytherapy acts is still unclear: improving oxygenation, interacting with tissue perfusion regulators, and disrupting adipose cell membranes are the leading suggestions [25]. Acting synergically with carboxytherapy by priming fibroblasts to increase vasoactive cytokine and extracellular matrix production and improve overall tissue oxygenation and hydration is the rationale for preliminary PN HPT™ priming. The ongoing clinical research program will dispel ambiguities once and for all.

Due to the unclear situation about how the synergy between carboxytherapy might develop, the Board’s suggestions remained at the level of a “Consensus statement” with an overall estimated agreement of 71%. The suggested preliminary or concomitant PN HPT™ priming cycle is analogous to what the Board proposed before ablative laser procedures (Table 5).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the (first) carboxytherapy session	At least four before the carboxytherapy treatment cycle	One or two before each carboxytherapy session

Table 5: Suggested intradermal PN HPT™ priming procedure before the carboxytherapy treatment cycle.

Chemical peels

With chemical peels, the cosmetic outcomes and incidence of complications directly relate to how deeply peels induce desquamation of the stratum corneum and skin remodelling [26,27]. Superficial peels with low- or higher-molecular-weight alpha-hydroxy acids like glycolic, lactic, malic, citric, tartaric or mandelic and benzilic acid or beta-hydroxy acids like salicylic acid, trichloroacetic acid 10%-35%, Jessner solution, tretinoin stimulate keratinocyte renewal from the basal layer; the concomitant reactive inflammation in the upper dermis ignites neocollagenesis with preserved basement membrane integrity [26,27].

The production of type-I collagen and tropoelastin fibres might benefit from PN HPT™ priming. The case for preliminary priming is especially compelling for medium peels (trichloroacetic acid 35%-50%, pyruvic acid 40%-70%), which arrive at the papillary and upper reticular dermis and the follicular epithelium, and deep peels (trichloroacetic acid >50%, phenol 88%), which eliminate the epidermis, penetrate the mid-reticular dermis and induce protein coagulation appearing as frosting [26,27].

The biosynthesis of dermal fibres can persist for years as a permanent effect of deep peels [26,27]. PN HPT™ dermal priming may act synergically with superficial and medium peels to enhance neocollagenesis; conversely, PN HPT™ priming and fine-tuning of the fibroblast activity before deep chemical peels is likely to antagonise atrophic scarring.

Skin hydration drives the intradermal PN HPT™ priming protocol for superficial and medium peels. If the skin is severely dehydrated, the Board's Recommendation waiting for definitive (overall estimated agreement, 81%), even if still tentative due to the lack of solid confirmation from the ongoing studies, is for two preliminary PN HPT™ priming infiltrations before the chemical peel session (repeated over time). With regular skin hydration, the suggested priming protocol envisions alternating sessions-a PN HPT™ priming session and a chemical peel session (Table 6).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the (first) chemical peeling session End: at least one week before the (first) chemical peeling session	Dehydrated skins: two PN HPT™ priming sessions, one chemical peeling session Normal skins: one chemical peeling, one intradermal PN HPT™ priming session	One syringe or vial per treated area per infiltration session

Table 6: Suggested intradermal PN HPT™ priming procedure before each superficial or medium peel session.

Needling

Needling applications (micro-needling, meso-needling) are extensive: scars, skin rejuvenation in general, and androgenetic alopecia [28-30]. Skin remodelling follows fibroblast stimulation with increased collagen and elastin production reaching up to 400% after six months, with an increase in the thickness of the stratum granulosum for up to one year [29]. The Board believes needling might be an almost iconic application of the PN HPT™ dermal priming paradigm to exploit the synergism on fibroblasts [29]. Waiting for the progressing, confirmatory clinical studies, the Board's Recommendation for office practice (overall estimated agreement, 88%) is to start low-dose PN HPT™ priming at least one month before the needling session (Table 7).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the micro-needling session	At least two before superficial/middle needling; three before deep needling	One per skin area to infiltrate per needling session

Table 7: Suggested intradermal PN HPT™ priming procedure before needling.

Intense Focused Ultrasound and Radiofrequency

Energy-transferring and heat-generating devices share the dermal fibroblast target with other skin-tightening technologies. Heat-induced denaturalisation of dermal collagen with the production of new networks of collagen and tropoelastin, the decrease of total tissue elastin content, and skin tightening follow the thermal effect in the sub-epidermal and sub-epithelial layers [31-33]. The Board's Recommendation (overall agreement, 83%) is to perform two to four priming sessions of PN HPT™ infiltrations, starting at least one month before the Intense Focused Ultrasound or Radiofrequency procedure (Table 8).

While waiting for the confirmatory clinical studies, the suggestions could tentatively apply to non-ablative "sub-surfacing" laser technologies that induce dermal collagen remodelling without damaging the epidermis and dermis. Examples are the Q-switched Neodymium-doped yttrium aluminium garnet (Nd:YAG) laser device emitting at a wavelength of 1064 nm, the Nd:YAG laser device emitting at 1320 nm, and the diode laser device emitting at 1450 nm [34,35].

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the skin tightening session	From two to four	One before each skin tightening session (if more than one)

Table 8: Suggested intradermal PN HPT™ priming procedure before Intense Focused Ultrasound, radiofrequency, and non-ablative skin tightening laser procedures.

LED treatment of the scalp area

The Federal Drug Administration and other regulatory authorities have cleared low-level light therapy via light-emitting diodes (LEDs) to treat male and female pattern hair loss. LEDs are semiconductor diodes that glow when a voltage is applied and emit red light or near-infrared radiation at 633 and 830 nm wavelengths. Applied to the scalp, the penetration of energy-producing packets of light deep into the scalp stimulates the hair follicles, increases their size, and slows hair from entering catagen, the end phase of the hair growth cycle [36]. The Board’s suggestions (overall estimated agreement, 85%) were to perform at least four PN HPT™ priming sessions with one to two PN HPT™ infiltrations per session at the reduced dose of 15 mg/mL, starting at least one month before the light treatment (Table 9).

Suggested timing of the priming protocol	Preliminary priming sessions	Prefilled syringe/vials per priming session
Start: at least one month before the LED session	At least four	One or two PN HPT™ intradermal infiltrations (dose: 15 mg/mL) at each priming session

Table 9: Suggested intradermal PN HPT™ priming procedure before LED for scalp.

PN HPT™ dermal priming paradigm: any risk of adverse events?

The Board stated once again that local injection site reactions like bruises, erythema, and burning are expected and the most frequent adverse events that may occasionally follow preliminary PN HPT™ intradermal injections. These transient adverse events, influenced by the needle size, site of injection, technique, and speed of injection, appear about twelve hours after the PN HPT™ injection.

Several strategies may help prevent or manage adverse events after skin priming with PN HPT™ gels. The main recommendations are to avoid exposure to natural sunlight or sun lamps for 48 hours and apply soothing creams and ice packs. Topical anaesthetics may help reduce discomfort.

Discussion

The value of multiple concomitant options to maximise skin quality benefits is well documented [37-39]. However, the founding rationale behind the PN HPT™ dermal priming paradigm is somewhat different and not simply additive, based on the potent non-pharmacological reactivation of mesenchymal cells like dermal fibroblasts by natural-origin PN HPT™ [13]. Administered preliminarily or concomitantly, PN HPT™ act as a plough that tills the dermal environment, conditioning it to amplify the response to further skin rejuvenation strategies. The developing clinical research program will hopefully substantiate the concept in several body districts and indications, as already shown for nasolabial folds and hyaluronic acid as post-priming treatment [19].

This Consensus document, born out of long online and face-to-face discussions by a run-in group of distinguished experts and waiting for definitive confirmation from ongoing clinical studies, outlines what the Board believes might be the most effective PN HPT™ priming strategies in different skin areas. The first three questions to the surveyed specialists and the related answers distinctly supported the PN HPT™ dermal priming paradigm. The first one - “For which outcome may Polynucleotides HPT™ (PN HPT™) formulations be used as skin primers before further treatment?” - was the cornerstone of the whole survey and overcame the statement acceptance threshold (80%) without trouble. Like the first survey question, the second and third ones - “For which of the following skin treatments is a preliminary PN HPT™ priming treatment advisable?” and “What may be the main benefits of preliminary PN HPT™ priming before a further skin treatment?” - also had a general perspective and overcame the acceptance threshold.

In summary, the most prominent endorsement for the PN HPT™ dermal priming paradigm in office practice and the developing clinical research program came from those first three survey questions, all accepted as statements. The following survey questions cast light on

more specific details of the PN HPT™ priming paradigm.

Admittedly, the Board's proposals may sometimes appear tentative because some aspects of the PN HPT™ priming paradigm are only currently being tested in clinical studies. Still, the already available extensive evidence-based body of preclinical and clinical papers on the PN HPT™ properties and foreseeable clinical value is already a reasonable foundation for the proposed non-pharmacological priming paradigm [13,40,41].

The hydrophilic PN HPT™ have short-term hydrating and volume-enhancing properties like hyaluronic acid [13]. Unsurprisingly, PN HPT™ are often co-formulated with hyaluronans. However, the paradigm's long-term core value lies in the PN HPT™ reconditioning properties of dermal fibroblasts and, generally, mesenchymal cells. By passively replenishing the dermal cells' nucleotide and nitrogen base pools, PN HPT™ fine-tune the metabolic performance of dermal cells. The increased production of fibres and extracellular matrix favourably impacts all four perceptual categories of skin quality—skin tone evenness, skin surface evenness, skin firmness, and skin glow [12,13,40].

Metabolic fine-tuning also means that mesenchymal cells might be more reactive to other skin-quality treatments—the core bulwark of the PN HPT™ dermal priming paradigm that evidence-based clinical studies begin to substantiate [19]. The priming strategy will likely need individualisation founded on skin hydration and elasticity, another goal of the clinical research program now in progress.

The long-term benefits of the PN HPT™ dermal priming paradigm might also favourably impact the long-term maintenance phase of acquired improvements. Thanks to the high degree of acceptance that the Board repeatedly highlighted, PN HPT™ infiltrations are readily repeatable, thus preserving a steady fibroblast reactivity to other treatments over time. The study by Araco and collaborators has shed light on the value of the PN HPT™ dermal priming paradigm for maintenance; [19] hopefully, the progressing clinical study program will confirm those early suggestions.

Conclusions

The Consensus document illustrates the rationale behind the PN HPT™ dermal priming paradigm and provides practical guidance for its application in different skin areas. It also lays the foundations for the ongoing clinical research program, conceived to provide new evidence supporting the PN HPT™ dermal priming paradigm.

Conflicts Of Interest Statement

All the members of the Scientific Board received grants from aesthetic medicine/surgery companies as consultants for research and medical education activities or for participating as investigators in national and international clinical studies in aesthetic medicine

and surgery. Mastelli S.r.l., Sanremo, Italy, producer of the PN HPT™-based medical devices, was a former sponsor of the Board members. All members of the Board avoided conflicts of interest related to the development of this Consensus document; Mastelli S.r.l., the producer of the brands cited in the paper, supported only the Scientific Board's secretarial and logistic costs. Moreover, Mastelli S.r.l. will sustain the publication costs of the Consensus manuscript.

Ethical and Financial Disclosures/CoI Statement

The authors declare that all activities leading to the Consensus manuscript were spontaneous, arising from scientific curiosity and published literature.

The manuscript's authors state they have no conflict of interest, they received no funds or utility, and they have no paid or unpaid relations with industry manufacturers, publishers, or other companies in some way related to the submitted Consensus manuscript.

Maurizio Cavallini received research grants as an R&D steering board member and a lecturer and tutor in continuous medical education activities, mainly for Allergan and Mastelli S.r.l. Similarly, Marco Papagni, Gloria Trocchi, and Mauro Raichi (overview) declare they received fees in the former year and a half from Mastelli S.r.l. and other producers of fillers and aesthetic medicine/plastic surgery products as lecturers at Continuous Medical Education activities and other sponsored educational meetings or producers of educational materials. All performed activities reviewed in the manuscript were within the regulatorily accepted indications stated in the Patient Information leaflets of administered devices. According to accepted regulatory requirements (i.e., Article 62 to Article 82 of the European Union regulation MDR 2017/745 and Article 16 of the Legislative Decree 137/2022), these considerations would have allowed waiving the requirement for formal approval by an Ethical Committee when absent—even more so for Polynucleotides HPT™-based medical devices still regulatorily classified in the MDD category (The Medical Device Directive — Council Directive 93/42/EEC of 14 June 1993).

Acknowledgements

The authors acknowledge the overview and medical writing support by Dr Mauro Raichi.

References

1. Online Etymology Dictionary.
2. Devika OS, Singh S, Sarker D, Barnwal P, Suman J, et al. (2021) Seed priming: A potential supplement in integrated resource management under fragile intensive ecosystems. *Front Sustain Food Syst* 5: 654001.

3. Paul S, Dey S, Kundu R (2022) Seed priming: an emerging tool towards sustainable agriculture. *Plant Growth Regulation* 97: 215-234.
4. Noronha NC, Mizukami A, Caliári-Oliveira C, Cominal JG, M Rocha LJ, et al. (2019) Priming approaches to improve the efficacy of mesenchymal stromal cell-based therapies. *Stem Cell Res Ther* 10: 131.
5. Lu H, Guo J, Hong X, Chen A, Zhang X, et al. (2020) Comparative effectiveness of different therapies for treating striae distensae: A systematic review and network meta-analysis. *Medicine (Baltimore)* 99: e22256.
6. Alsharif SH, Alghamdi AS, Alhumaidi WA, AlRobaish OA, Al Hamoud MH, et al. (2023) Treatment of striae distensae with filler injection: A systematic review. *Clin Cosmet Investig Dermatol* 16: 837-845.
7. Ross NA, Ho D, Fisher J, Mamalis A, Heilman E, et al. (2017) Striae distensae: Preventative and therapeutic modalities to improve aesthetic appearance. *Dermatol Surg* 43: 635-648.
8. Hague A, Bayat A (2017) Therapeutic targets in the management of striae distensae: A systematic review. *J Am Acad Dermatol* 7: 559-568.
9. Borrelli MR, Griffin M, Ngaage LM, Longaker MT, Lorenz HP (2021) Striae distensae: Scars without wounds. *Plast Reconstr Surg* 48: 77-87.
10. Muzaffar AR, Mendelson BC, Adams WP Jr (2002) Surgical anatomy of the ligamentous attachments of the lower lid and lateral canthus. *Plast Reconstr Surg* 110: 873-884.
11. Cavallini M, Dell'Avanzato R, Fundarò SP, Urdiales Gálvez F, Papagni M, et al. (2024) Treating glabellar lines with botulinum toxin: does your patient need to frown steadily? *Aesthet Surg J* 44: 421-427.
12. Goldie K, Kerscher M, Fabi SG, Hirano C, Landau M, et al. (2021) Skin Quality – A holistic 360° view: consensus results. *Clin Cosmet Investig Dermatol* 14: 643-654.
13. Cavallini M, Bartoletti E, Maioli L, Massirone A, Palmieri LP, et al. (2021) on behalf of The Polynucleotides HPT™ Priming Board. Consensus report on the use of PN HPT™ (Polynucleotides Highly Purified Technology) in aesthetic medicine. *J Cosmet Dermatol* 20: 922-928.
14. Colangelo MT, Govoni P, Belletti S, Squadrito F, Guizzardi S, et al. (2021) Polynucleotide bio gel enhances tissue repair, matrix deposition and organisation. *J Biol Regul Homeost Agents* 35:355-362.
15. Alma Universitas Studiorum Parmensis, Medical School, Embryology and Histology Laboratory report, Parma (Italy). Valutazione dell'attività di scavenger di PN, HA e PN+HA in risposta all'ossidazione indotta da H₂O₂.
16. Schwartz E, Cruickshank FA, Christensen CC, Perlish JS, Lebwohl M (1993) Collagen alterations in chronically sun-damaged human skin. *Photochem Photobiol* 58: 841-844.
17. Guizzardi S, Uggeri J, Belletti S, Cattarini G (2013) Hyaluronate increases polynucleotides effect on human cultured fibroblasts. *J Cosmet Dermatol Sci Appl* 3: 124-128.
18. Simmonds H.A., NUCLEIC ACIDS - Physiology, Editor: Benjamin Caballero, Encyclopedia of Food Sciences and Nutrition (Second Edition), Academic Press, 2003, Pages 4152-4163, ISBN 9780122270550, <https://doi.org/10.1016/B0-12-227055-X/00837-3>
19. Araco A, Araco F, Raichi M (2023) Clinical efficacy and safety of polynucleotides highly purified technology (PN HPT®) and cross-linked hyaluronic acid for moderate to severe nasolabial folds: A prospective, randomised, exploratory study. *J Cosmet Dermatol* 22: 146-155.
20. Moisturising properties of hyaluronic acid (HA) and polynucleotides (PN), Mastelli Srl Internal R&D Report, Sanremo (Italy), 2021
21. Injectable gel medical devices toxicological assessment, KROS BioScience Healthcare, Pomezia (Italy), February 9th, 2023
22. Pavicic T, Frank K, Erlbacher K, Neuner R, Targosinski S, et al. (2017) Precision in dermal filling: a comparison between needle and cannula when using soft tissue fillers. *J Drugs Dermatol* 16: 866-872.
23. Matera G, Dodici N, Raichi M (2020) Improving on laser: biorevitalization of stretch marks, the polynucleotides infiltrations combined with CO2 laser option. *Aesth Med* 6:17-24.
24. Bagherani N, Smoller BR, Tavoosidana G, Ghanadan A, Wollina U, et al. (2023) An overview of the role of carboxytherapy in dermatology. *J Cosmet Dermatol* 22: 2399-2407.
25. Ahramiyanpour N, Shafie'ei M, Sarvipour N, Amiri R, Akbari Z (2022) Carboxytherapy in dermatology: A systematic review. *J Cosmet Dermatol* 21: 1874-1894.
26. Truchuelo M, Cerdá P, Fernández LF (2017) Chemical peeling: A useful tool in the office. *Actas Dermosifiliogr* 108: 315-322.
27. Lee KC, Wambier CG, Soon SL, Sterling JB, Landau M, et al. (2019) on behalf of the International Peeling Society. Basic chemical peeling: Superficial and medium-depth peels. *J Am Acad Dermatol* 81: 313-324.
28. Juhasz MLW, Cohen JL (2020) Microneedling for the treatment of scars: An update for clinicians. *Clin Cosmet Investig Dermatol* 13: 997-1003.
29. Pająk J, Szepletowski JC, Nowicka D (2022) Prevention of ageing—The role of micro-needling in neck and cleavage rejuvenation: a narrative review. *Int J Environ Res Public Health* 19: 9055.
30. English RS Jr, Ruiz S, DoAmaral P (2022) Microneedling and its use in hair loss disorders: A systematic review. *Dermatol Ther (Heidelb)* 12: 41-60.
31. Suh DH, So BJ, Lee SJ, Song KY, Ryu HJ (2015) Intense focused ultrasound for facial tightening: histologic changes in 11 Patients. *J Cosmet Laser Ther* 17: 200-203.
32. El-Domyati M, El-Ammawi TS, Medhat W, Moawad O, Brennan D, et al. (2011) Radiofrequency facial rejuvenation: Evidence-based effect. *J Am Acad Dermatol* 64: 524-535.
33. Austin GK, Struble SL, Quatela VC (2022) Evaluating the effectiveness and safety of radiofrequency for face and neck rejuvenation: A systematic review *Lasers Surg Med* 54: 27-45.
34. Grema H, Greve B, Raulin C (2003) Facial rhytides--subsurfacing or resurfacing? A review. *Lasers Surg Med* 32: 405-412.
35. Papadavid E, Katsambas A (2003) Lasers for facial rejuvenation: a review. *Int J Dermatol* 42: 480-487.
36. Sorbellini E, Rucco M, Rinaldi F (2018) Photodynamic and photobiological effects of light-emitting diode (LED) therapy in dermatological disease: an update. *Lasers Med Sci* 33: 1431-1439.

37. Carruthers J, Burgess C, Day D, Faby SG, Goldie K, et al. (2016) Consensus recommendations for combined aesthetic interventions in the face with botulinum toxin, fillers, and energy-based devices. *Dermatol Surg* 42: 586-597.
38. Fabi SG, Burgess C, Carruthers A, Carruthers J, Day D, et al. (2016) Consensus recommendations for combined aesthetic interventions using botulinum toxin, fillers, and microfocused ultrasound in the neck, décolletage, hands, and other areas of the body. *Dermatol Surg* 42: 1199-1208.
39. Brandi C, Cuomo R, Nisi G, Grimaldi L, D'Aniello C (2018) Face rejuvenation: a new combined protocol for biorevitalization. *Acta Biomedn* 89: 400-405.
40. Bartoletti E, Cavallini M, Maioli L, et al. (2020) Introduction to polynucleotides highly purified technology. *Aesth Med* 6: 43-47.
41. Massirone A (2021) Polynucleotides highly purified technology and the face skin, a story of innovative skin priming. *Aesth Med* 7: 35-40.

In memory of Professor Alberto Massirone, President, Agorà, Italian Scientific Society of Aesthetic Medicine, member of The Polynucleotides HPT™ Priming Board.