Global Aesthetics Consensus: Hyaluronic Acid Fillers and Botulinum Toxin Type A—Recommendations for Combined Treatment and Optimizing Outcomes in Diverse Patient Populations

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Background: Combination of fillers and botulinum toxin for aesthetic applications is increasingly popular. Patient demographics continue to diversify, and include an expanding population receiving maintenance treatments over decades.
Methods: A multinational panel of plastic surgeons and dermatologists convened the Global Aesthetics Consensus Group to develop updated guidelines with a worldwide perspective for hyaluronic acid fillers and botulinum toxin. This publication considers strategies for combined treatments, and how patient diversity influences treatment planning and outcomes.
Results: Global Aesthetics Consensus Group recommendations reflect increased use of combined treatments in the lower and upper face, and some midface regions. A fully patient-tailored approach considers physiologic and chronologic age, ethnically associated facial morphotypes, and aesthetic ideals based on sex and culture. Lower toxin dosing, to modulate rather than paralyze muscles, is indicated where volume deficits influence muscular activity. Combination of toxin with fillers is appropriate for several indications addressed previously with toxin alone. New scientific data regarding hyaluronic acid fillers foster an evidence-based approach to selection of products and injection techniques. Focus on aesthetic units, rather than isolated rhytides, optimizes results from toxin and fillers. It also informs longitudinal treatment planning, and analysis of toxin nonresponders.
Conclusions: The emerging objective of injectable treatment is facial harmonization rather than rejuvenation. Combined treatment is now a standard of care. Its use will increase further as we refine the concept that aspects of aging are intimately related, and that successful treatment entails identifying and addressing the primary causes of each. (*Plast. Reconstr. Surg.* 137: 1410, 2016.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

Combination of hyaluronic acid fillers and botulinum toxin type A is becoming increasingly popular. Recent comparative studies have established the safety and enhanced efficacy compared with solo treatment of combined treatments for lower face rejuvenation.[1,2] A 2008 North American consensus cited combination treatment as important for the lower face and sometimes appropriate for the upper face.[3] French consensus recommendations in 2011[4,5] and a panel of five experts from Canada, Europe, and South America in 2013[6] affirmed the value of the combined approach.

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Surveys from the American Society for Aesthetic Plastic Surgery, the American Society for Dermatologic Surgery, and the International Society for Aesthetic Plastic Surgery[7–9] report steady increases in the number of toxin and hyaluronic acid filler procedures performed each year. These and other procedural surveys[10] illuminate another significant trend: the growing diversity of patients' ethnicity, sex, and age. The 2014 American Society for Aesthetic Plastic Surgery survey reported that approximately 22 percent of all cosmetic procedures were performed on ethnic minorities. Men were the recipients of approximately 11.5 percent of botulinum toxin procedures and 8 percent of hyaluronic acid filler procedures.[7] As worldwide experience accrues, another important patient group has emerged—those receiving repeated treatments over years or decades.

CONSENSUS OBJECTIVES AND METHODOLOGY

From January 17 through 19, 2014, a multidisciplinary group of key opinion leaders in the core aesthetic specialties from Asia, Australia, Europe, and North and South America convened the Global Aesthetics Consensus Group to formulate updated guidelines for aesthetic use of hyaluronic acid fillers and botulinum toxin type A. This publication provides recommendations for combined treatments. It also presents concepts for treatment planning and implementation in diverse patient populations. The Global Aesthetics Consensus Group is well suited for these objectives by virtue of its own geographic and ethnic diversity. The methodology used for determining consensus is summarized in Table 1.

EVOLVING CONCEPTS IN FACIAL AGING

Facial aging occurs at all levels. The epidermis, dermis, subcutis, and bone undergo remodeling throughout life; degradation of existing tissue is balanced with generation of new tissue. With age, regenerative properties decline and the balance of remodeling becomes disrupted, such that there is a net loss of tissue that is recognized as resorption. From a quantitative perspective, volume loss is significant from the deeper tissue layers, with deflation and descent of depleted subcutaneous fat compartments and loss of bone (Fig. 1).[11–18] Total collagen content of the skin also decreases. There is qualitative degeneration of tissue components, including dermal collagen and elastin.[19,20]

Table 1. Methodology for Global Aesthetics Consensus Group Panel Consensus: Grading of Statements and Opinions Developed during the Conference*†

Grade	Recommendation
A	Recommended
B	Reasonable choice
C	Not fully established (unclear risk/benefit, inadequate data)
D	Not recommended

Consensus is defined as ≥66% of polled panel members selecting a consensus grade (e.g., 11 of 16 polled panel members.
Minimum number of polled panel members allowed is 11.
If no statement/opinion grade reached the two-thirds level, results are reported as "no consensus reached."
Plurality or majority selection of consensus grade may be reported.

*Select results of premeeting treatment survey are included where instructive.
†For purposes of discussion, the consensus document divides the face into thirds (upper, middle, and lower). However, the panel stressed the importance of an integrative approach to both assessment and treatment.

These processes result in three-dimensional alterations in facial shape and contour; skin laxity, folds, and rhytides; and surface changes, including skin roughness and xerosis. The primary extrinsic causes of skin aging have been characterized as the "three S's"—sun (ultraviolet radiation), smoking, and stress. They increase oxidative stress by means of reactive oxygen species overload and concomitant antioxidant depletion. Multiple biochemical pathways are triggered. They promote collagen loss by inducing suppression of transforming growth factor-β receptor II; overexpression of matrix metalloproteinases, which are collagenases; and increased inflammation through the nuclear factor kappa B pathway. Ultraviolet radiation also directly damages the skin's structural proteins. Intrinsic skin aging is related to a progressive age-related decline in antioxidant capacity, coupled with increased reactive oxygen species production from oxidative metabolism in skin cells. This contributes to oxidative stress. Chromosomal analysis of aging cells reveals progressive telomere shortening, associated with tissue damage. The rates of extrinsic and intrinsic aging vary considerably, based on individual exposure to the causative factors and hereditary predisposition.[19,20]

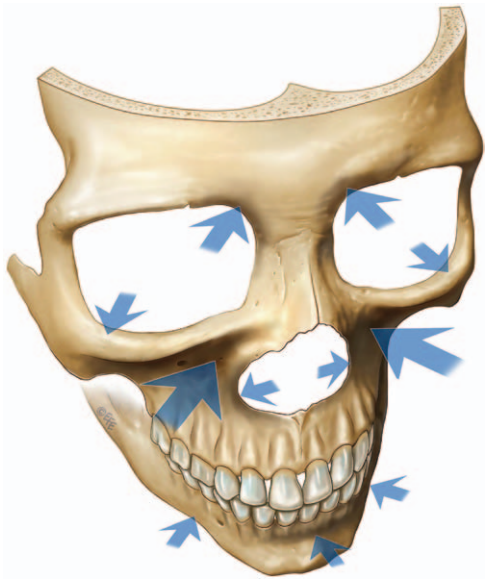

Fig. 1. Age-related bony changes are mainly in the periorbital and midcheek zones, including the superomedial and inferolateral aspects of the orbit, the medial suborbital and piriform areas of the maxilla, and the prejowl area of the mandible. *Arrows* indicate the areas of the facial skeleton susceptible to resorption with aging. The size of the *arrow* correlates with the amount of resorption. (From Mendelson B, Wong CH. Changes in the facial skeleton with aging: Implications and clinical applications in facial rejuvenation. *Aesthetic Plast Surg.* 2012;36:753–760. Reprinted with permission from Springer International Publishing AG. © EFE.)

The multifactorial cause of facial aging provides the rationale for combined treatments. The balance of fillers with toxin depends on individualized patient assessment and functional understanding of what the observations mean. In previous guidelines, toxin has been considered the foundation of treatment to the upper face, with fillers playing a larger role in the middle and lower face.[3] Increasingly, however, fillers are seen as improving the effects of toxin—and are particularly indicated as patient age increases. The consensus panel acknowledged that combined treatment has value throughout the face.

Optimizing Treatment Outcomes in Diverse Patient Populations

The objective of aesthetic treatment is often described as facial rejuvenation. A broader perspective, encompassing patient age, ethnicity, and sex, yields the more accurate objective of facial harmonization—through correction of acquired (usually age-related) disharmonies, together with modification of congenital characteristics. In recognition of growing patient diversity in clinical practice, the panel recommended enrollment of more heterogeneous subject populations in injectables studies.

Age

Surveys report that the typical age at which patients seek cosmetic procedures is between 30 and 50 years.[7] When clinically indicated, fillers

and toxin are of demonstrable benefit to older and younger patients. A retrospective review from 2008 to 2013 of a database endorsed by the American Society of Plastic Surgeons showed that patients older than 65 years had significantly more cosmetic facial procedures performed than did younger patients (62.9 percent versus 12 percent). There was no statistically significant difference in complication rates following all procedures in older patients (mean age, 69.1 years; 1.94 percent) versus younger patients (mean age, 39.2 years; 1.84 percent). This was despite the greater presence of health risks in the older group, including higher body mass index and higher incidence of diabetes mellitus.[21]

The variable time course and manifestations of aging underscore the importance of both chronologic and physiologic age when planning treatment. Individualized analysis includes assessment of tissue quality, extent and pattern of volume loss from soft and hard tissues, extent and pattern of muscular contraction, and surface skin changes. Selection of appropriate injectables to achieve the best results has been compared metaphorically to an artist's choices from a palette of paints to create a beautiful picture. As an extension of this metaphor, the face may be considered the "canvas" for aesthetic interventions.

Respect for the aging facial canvas is an evolving and fundamental principle of treatment. A paradigm shift is advocated from the youthful face as the "gold standard," toward age-appropriate facial harmonization. For example, it is inadvisable to try to restore the midface convexity (ogee curve) of a 50-year-old with depleted facial skeletal support to a level appropriate for a 25-year-old. Attempts to do so by filler injection may produce passable results in repose. But there may be undesirable effects in animation, such as impingement of the midface on the lid-cheek junction when smiling, or a discernible ledge between the submalar region and the lower face. Overvolumization is best avoided by viewing patients before, during, and after injection—not only at rest, but also in animation. A conservative approach is preferable, particularly with newer, longer lasting hyaluronic acid fillers, for which the panel agreed that "less is often more." Although these principles may seem obvious and even superfluous to state explicitly, they can become obscured if adherence to rigid algorithms and cutaneous landmarks (which shift with age) supersedes a patient-tailored approach.

There is no upper limit for age beyond which patients cease to benefit from volume restoration. Declining tissue quality and consequent skin laxity are indications for combining fillers with lasers, energy-based devices,[22] or surgery when appropriate. In older patients, fewer injection sites and smaller toxin doses at each site may be indicated if muscle mass or function is reduced.

In younger patients, age-related disharmonies are not yet prominent. Emphasis is typically on modification of congenital characteristics or of acquired disharmonies that are age-independent, such as from injuries. Treatment of younger patients is commonly described as proactive or "preventive" (e.g., when glabellar or frontal lines that were present since childhood or incipient in early adulthood are injected with toxin).

Gender

Male and female faces are governed by different treatment principles. There are considerable differences in anatomy and in what is aesthetically appealing. Harmonization of the female face entails restoring prominence to the upper and middle thirds with a lower facial taper, to achieve a heart or inverted triangle shape. In contrast, the male face is perceived as harmonious when somewhat longer, with more equal prominence of facial thirds and a well-defined jawline. The average male skull is significantly larger than that of a female skull. The frontal, maxillary, zygomatic, and mandibular bones tend to be broader, squarer, and flatter, and the supraorbital rim is more prominent. Men have greater average muscle mass and a higher density of blood vessels.[23] Gender-related differences in epidermal and dermal thickness and fat distribution are considered to be modulated by sex steroids.[24,25] Study of composite facial images indicates that greater facial symmetry confers a more gender-typical appearance for men and women.[26]

Many caveats that apply to treatment of men with injectables pertain to avoidance of facial feminization. The panel cautioned that overvolumization of the male midface produces a feminizing convexity. It is also important not to overfill the temple, as temporal hollowing is aesthetically appealing in many men. Injection of fillers into the lips may be appropriate for some men (e.g., to improve vermilion border definition), but care must be taken to avoid a feminine shape or fullness. Inappropriate elevation of the eyebrows (especially the lateral tails) with toxin will tend to feminize a male face.

Ethnicity

Clinical data with Evidence Levels I and II support the safety and efficacy of botulinum toxin

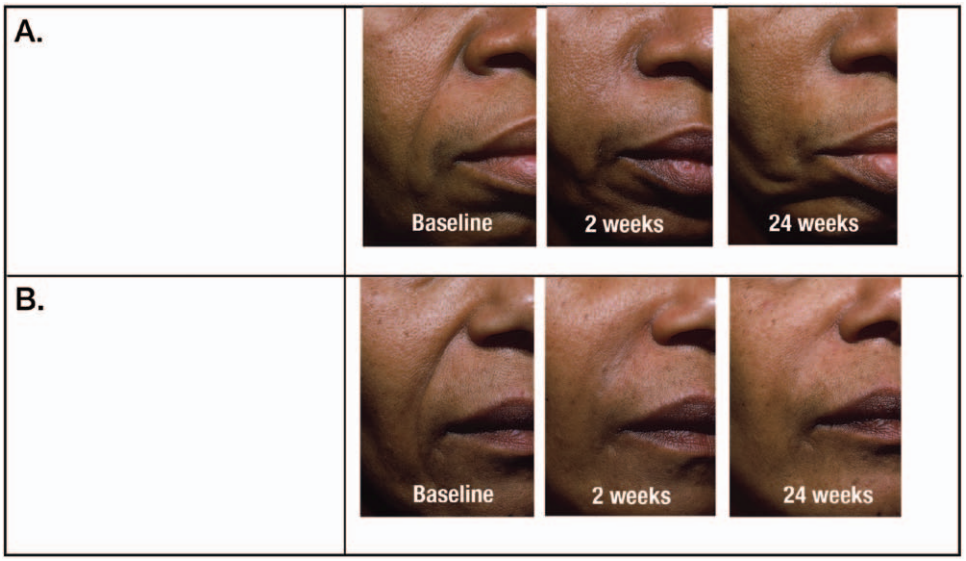

Fig. 2. Efficacy of nasolabial fold correction with crosslinked hyaluronic acid filler in patients with Fitzpatrick skin phototype VI. Nasolabial folds are shown before injection and 2 and 24 weeks after injection with Hylacross hyaluronic acid filler. (*Above*) Before and after injection of Juvéderm Ultra. (*Below*) Before and after injection of Juvéderm Ultra Plus. (From Grimes PE, Thomas JA, Murphy DK. Safety and effectiveness of hyaluronic acid fillers in skin of color. *J Cosmet Dermatol.* 2009;8:162–168. Reprinted with permission from John Wiley & Sons.)

type A and hyaluronic acid fillers in persons of color[27–30] (Fig. 2). Guidelines based on patient ethnicity should not obscure the basic tenet that ideals of beauty are largely preserved across time and cultures. Although some quantifiable congenital characteristics are commonly associated with specific ethnicities,[31–35] the general principles of individualized analysis and correction apply to every patient. Geographic variations in treatment approaches have evolved as worldwide use of injectables has expanded. This is a manifestation of ethnicity and prevalent facial morphotypes, cultural preferences, and global migration patterns.

Additional considerations pertain to immigrant patients (e.g., the cultural overlays when Asian patients consult with European or American surgeons). Asian, Latin American, African, and other patients are sometimes perceived mistakenly as uniform populations. However, there are significant physical and cultural variations within these continents. Ethnic mixing, because of intermarriage, adds to the multiplicity of facial morphotypes. These considerations inform qualitative and quantitative differences in treatment. Compared with whites, Asians are more likely to display central face retrusion; flattening of the anteromedial midface; recessed piriform fossae; flatter, broader foreheads; retrognathia; and microgenia.[34,36] These congenital characteristics account for the prevalence of filler injection to the medial midface, nose, chin, and forehead of younger Asian patients. In older patients, volumization of these regions remains a priority, in conjunction with correction of age-related disharmonies. Skeletal structure affects resting tone and contraction of the overlying musculature. A recent classification of Asian facial morphotypes proposes division into three basic categories to guide treatment strategies with botulinum toxin and fillers.[37] Validation of this classification and the associated treatment strategies is now in process.

Variations in incidence and presentation of photoaging among ethnic groups are attributable in part to physical differences, such as variations in fibroblast size and structure,[38,39] and in part to differences in lifestyle. Although all ethnic groups eventually manifest signs of photoaging, whites typically have an earlier onset and display more rhytides at a younger age. The old adage that skin of color ages more by folding than wrinkling underscores a key point—that volume loss is ubiquitous to all ethnicities. It therefore follows that restoration of volume and correction of related sequelae, including effects on associated musculature, are fundamental strategies for every patient.

Longitudinal Treatment Planning

Ongoing treatment with hyaluronic acid fillers and botulinum toxin yields cumulative

improvements. The greatest benefits are obtained if patients return for treatment when the previous results start to diminish rather than after they disappear completely. Ultimately, treatment may be required less frequently, and doses can often be reduced. A retrospective medical chart review of 194 patients who received a total of 4402 onabotulinumtoxinA treatments to glabellar lines over a mean of 9.1 years demonstrated sustained patient and physician satisfaction.[40] Greater perceived benefits were reported in patients treated for longer periods.

The long-term restorative potential of diluted (reconstituted) Hylacross hyaluronic acid filler (Juvéderm Ultra; Allergan, Inc., Irvine, Calif.) is indicated by a retrospective evaluation of more than 350 patients whose clinical improvement after superficial injection of facial fine lines persisted beyond the time frame that could be accounted for by space-filling effects alone.[41] The scientific rationale is provided by a rat study, in which enzyme-linked immunosorbent assay and reverse-transcriptase polymerase chain reaction showed up-regulation of types I and III collagen and elastin expression after intracutaneous injection of Hylacross filler, but not after control injection of saline.[42]

A recent prospective study of onabotulinumtoxinA raised the possibility of biomechanical restoration, demonstrating increased skin pliability and elastic recoil after injection of the lateral orbital, forehead, and glabellar regions of 40 women.[43] Because botulinum toxin spreads in a three-dimensional manner after injection, the mechanism of action could be intramuscular or related to the overlying skin. Previous anecdotal reports of improvement in skin texture and turgor after intradermal toxin injection[44–46] have been attributed to intracutaneous fluid retention, by means of effects on acetylcholine receptors, which exist on keratinocytes, melanocytes, and cells of the sebaceous glands.[47]

Several Global Aesthetics Consensus Group recommendations describe lower toxin doses than in previous guidelines. This is to modulate rather than obliterate muscular activity, with developing understanding that combining toxin with fillers is more appropriate for some indications in which toxin alone was advocated in the past. Some panelists expressed concern that overtreatment with toxin, especially with short retreatment intervals, could produce muscular atrophy that would exacerbate volume loss. Blinded, placebo-controlled studies of botulinum toxin type A for moderate to severe crow's feet show little clinical difference between the two most efficacious doses, although higher doses tended to provide greater patient satisfaction.[48,49] Longevity is used in studies as an endpoint of efficacy. In clinical practice, a more qualitative focus on functional and aesthetic appropriateness of the results may serve patients better. With counseling, the philosophy of more frequent visits to achieve and maintain consistently good, rather than overdone, results is readily understood by patients by extrapolation from other health and beauty arenas.

Response to Repeated Treatments with Botulinum Toxin Type A

The response rate to botulinum toxin type A for aesthetic applications is very high. In cases of apparent nonresponse or partial response to any toxin formulation, practitioners should first consider causes such as inappropriate patient selection, dosing, or placement of injection sites. If volume loss is a significant contributor to rhytides, they will respond better to combined fillers and toxin than to toxin alone. It is obvious that underdosing or incorrect placement of toxin in target muscles can impair treatment response. Overdosing with resultant recruitment of adjacent muscles can give the illusion of nonresponse, as can injection into muscles that are not the primary cause of what needs to be addressed.

From an evidence-based perspective, it is challenging to evaluate reports of secondary treatment failure with toxin, because they are typically anecdotal and retrospective. Pertinent details are likely to be missing if the practitioner who is consulted for nonresponse did not perform the treatment. Although a number of case reports describe secondary treatment failure in the presence of neutralizing antibodies, there is no high-level evidence to implicate antibodies as the actual cause.[50] Table 2 summarizes challenges in interpreting current data.[51–56] Ongoing monitoring of the increasing number of patients who receive repeated treatments will allow conclusions that are evidence-based, rather than circumstantial.

Application of Science to Optimize Clinical Efficacy and Safety

New and emerging hyaluronic acid fillers are arranged in families that are designed for layered tissue implantation. Examples include cohesive polydensified matrix (Belotero; Merz, Frankfurt am Main, Germany), Optimal Balance Technology (Emervel; Galderma, Lausanne, Switzerland), Resilient Hyaluronic Acid (Teosyal; Teoxane, Geneva, Switzerland), and Vycross (Allergan). Table 3 summarizes typical products in a filler

Table 2. Secondary Treatment Failure with Botulinum Toxin Type A for Aesthetic Indications: Evidence-Based and Experiential Analysis

Presence of neutralizing antibodies is not a predictor of nonresponse to toxin; recent publications describe both responders and nonresponders as having neutralizing antibodies.
No controlled, long-term studies have compared the immunogenicity of different botulinum toxin products.
The true clinical impact of neutralizing antibodies is difficult to determine because of limitations in antibody measurement techniques, and interclinic variability in defining secondary nonresponsiveness.*†
The incidence of neutralizing antibodies is low; meta-analysis indicates a prevalence of <0.25% for the formation of neutralizing antibodies against onabotulinumtoxinA, when injected for glabellar lines.‡
Potential risk of antibody formation is considered to have been mitigated by product reformulation to reduce protein load per dose,§‖ and the trend toward lower dosing for aesthetic applications.*¶
Consensus panelists with experience of using onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA did not note any connection between a specific product and nonresponse to treatment, or the alleviation of nonresponse.
Frequent re-treatment has been suggested as a risk factor for secondary treatment failure; however, panelists with experience performing secondary "touch-up" treatments 2–4 wk after primary toxin treatment in many patients over several years reported no emergence of nonresponders.

*Benecke R. Clinical relevance of botulinum toxin immunogenicity. *BioDrugs* 2012;26:e1–e9.
†Kamm C, Benecke R. Individualized management of cervical dystonia with different serotypes of botulinum toxin: Recent therapeutic advances and risk development of neutralizing antibodies. *Eur Neurol J.* 2010;2:49–54.
‡Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX) across multiple indications. *Mov Disord.* 2010;25:2211–2218.
§Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology* 2003;60:1186–1188.
‖Yablon SA, Brashear A, Gordon MF, et al. Formation of neutralizing antibodies in patients receiving botulinum toxin type A for treatment of poststroke spasticity: A pooled-data analysis of three clinical trials. *Clin Ther.* 2007;29:683–690.
¶Aoki KR, Merlino G, Spanoyannis A, Wheeler L. Botox (botulinum toxin type A) purified neurotoxin complex prepared from the new bulk toxin retains the same preclinical efficacy as the original but with reduced immunogenicity. Poster presented at: 51st Annual Meeting of the American Academy of Neurology; April 17–24, 1999; Toronto, Ontario, Canada. Poster 06.109.

Table 3. Typical Products in a Hyaluronic Acid Filler Family Designed for Layered Implantation, and Their Usual Implantation Depths*

Product Type	Usual Implantation Depth
Deep volumizer	Supraperiosteal and subcutaneous
Midlevel volumizer	Subcutaneous and sometimes intradermal; submucosal to lips; supraperiosteal to nasojugal folds
Superficial volumizer	Intradermal and superficial subcutis; submucosal to lips; supraperiosteal to nasojugal folds
Additional specialty products (in some filler families)	Lips, submucosal Nasojugal folds, supraperiosteal and subcutaneous

*Sundaram H. Igniting discovery, dialogue, and global innovation through international collaboration. *J Drugs Dermatol.* 2014;13:386–388.

family.[57] Complete families are available in Europe, Canada, Latin America, and parts of Asia-Pacific and the Middle East. The United States and other regions currently have partial families.

The intended clinical applications of each product are informed by its rheologic (flow-related) properties, which depend on its manufacturing process.[58,59] Deep volumizers typically have higher elasticity (G′), to confer firmness and resistance to applied force; and higher viscosity, to confer resistance to spread. For example, deep volumizer Vycross (Voluma) has higher elasticity than midlevel Vycross (Volift), which has higher elasticity than the superficial volumizer (Volbella).[59–61] Elasticity is higher in Vycross than in Hylacross products.[59,61] Complex viscosity (η*), which accurately measures whole gel behavior, is higher in deep volumizer Vycross than in Hylacross.[61]

Science-based selection of filler products and injection techniques allows a more evidence-based approach toward safety and efficacy. Treatment outcomes can be predicted by a product's scientific design, in the context of its target tissue and the techniques that are used to implant it.[57] Two controlled, split-face studies of Evidence Level II fulfill the rheologic prediction that optimal nasolabial fold correction requires a significantly smaller volume of a higher than a lower elasticity filler.[62,63] Histopathologic and ultrasonographic studies directly correlate a filler's viscosity and cohesivity to its pattern of spread and tissue integration after in vivo, intradermal implantation.[64–66]

The initial focus was on elasticity as a primary determinant of tissue "lift" when fillers were implanted deeply as boluses. It was subsequently proposed that the "lift capacity" of a hyaluronic acid filler is determined not only by elasticity but also by cohesivity.[67] A certain level of cohesivity (i.e., the tendency of the filler not to dissociate because of affinity of its molecules for each other) can be considered a prerequisite to maintain filler integrity during and after implantation. A standardized, five-point visual scale for hyaluronic acid filler cohesivity was recently developed and validated.[68] Convergence of these data with seminal studies of facial fat compartments and bony

anatomy[11–16,69–73] elucidates the primary objective of volume replacement as inflation of age-deflated soft tissues, and thus restoration of three-dimensional tissue support. A filler's elasticity, cohesivity, and water binding all contribute to this multilevel process. It is a composite of layered tissue expansion, with vertical and horizontal vectors; and tissue projection, with more vertical, bolus-type vectoring predominantly from deep tissues.[22,61]

The scientific balance of each hyaluronic acid product parallels its clinical characteristics. Higher elasticity increases tissue projection by providing firmness and resistance to muscular and gravitational forces. Cohesivity confers more three-dimensional tissue expansion. As an example of how scientific balance influences clinical behavior, it is instructive to compare Vycross and Hylacross fillers. The lower cohesivity of Vycross has been described as providing more malleability.[60] The lower water uptake of Vycross, as measured by in vitro gel swelling assay, is attributed to tighter hyaluronic acid cross-linking.[60] Additional factors contribute to tissue swelling after in vivo implantation of hyaluronic acid fillers. Dilution-reconstitution of Hylacross[41] decreases tissue swelling, presumably because of preinjection saturation of some water-binding sites.

In vitro resistance of Hylacross filler to degradation by ovine testicular hyaluronidase has been attributed to its cross-linking, cohesivity, and total hyaluronic acid concentration.[74] The longevity of Vycross filler is attributed to cross-linking, independent of concentration.[60] From a safety perspective, it is noteworthy that these fillers are degraded transarterially after implantation into cadaveric arteries—by exogenous hyaluronidase injected into surrounding soft tissue, or by immersion of closed arterial segments in hyaluronidase at therapeutic doses.[75] [**See Video, Supplemental Digital Content 1**, which demonstrates transarterial degradation of Vycross and Hylacross fillers, by injection of exogenous hyaluronidase into the surrounding soft tissues, in a fresh, frozen cadaver model in real time. In section 1 of this video, dyed Hylacross filler (Juvéderm Ultra) is injected into the facial artery lateral to the oral commissure, and product flows to the mid cheek. Digital pressure on the lower part of the vessel demonstrates that the filler gel distends and completely occludes the vessel. Ovine hyaluronidase at a concentration of 150 IU/ml (Hyalase; Sanofi-Aventis, Gentilly, France) is infiltrated around, but not directly into, the vessel containing Hylacross filler. Digital pressure and simulated tissue massage are applied. The Hylacross filler within the artery is depolymerized because of transarterial enzymatic action of the hyaluronidase. Both the vascular distention and obstruction are removed as the filler product is broken down and disperses. In section 2 of this video, dyed Vycross filler (Juvéderm Volift) is injected into the superficial temporal artery, and readily flows along the vessel to escape from the cut end of the vessel. Ovine hyaluronidase (150 IU/ml) infiltrated around, but not directly into, the artery breaks down and disperses the Vycross filler within it. In a more graphic demonstration of enzymatic depolymerization, droplets of hyaluronidase that are applied directly to extruded Vycross filler rapidly break it down and disperse it. In section 3 of this video, dyed Vycross filler (Juvéderm Volbella) is injected into the facial artery at the lower nasolabial fold, and extrudes from the cut end of a downstream arterial branch in the alar fold danger zone. This video demonstrates how injection of hyaluronic acid filler into a vessel of significant diameter can result in its spread to distant locations along the vascular tree of that vessel. The action of hyaluronidase is rapid and profound, despite infiltration into the surrounding soft tissue, rather than direct intravascular infiltration. This is demonstrated by dispersal of the filler within the vessel after a short period. Hyaluronidase also has a

Video. Supplemental Digital Content 1 demonstrates transarterial degradation of Vycross and Hylacross fillers, by injection of exogenous hyaluronidase into the surrounding soft tissues, in a fresh, frozen cadaver model in real time. Courtesy of Dr. Mark Magnusson, Dr. Tim Papadopoulos, and the Australasian Society of Aesthetic Plastic Surgery. This content was developed for the Society's Anatomical and Live Injecting Workshop, in association with the Australasian Society of Aesthetic Plastic Surgery Annual Non-Surgical Symposium. © 2014 Australasian Society of Aesthetic Plastic Surgery, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at, ***http://links.lww.com/PRS/B683.***

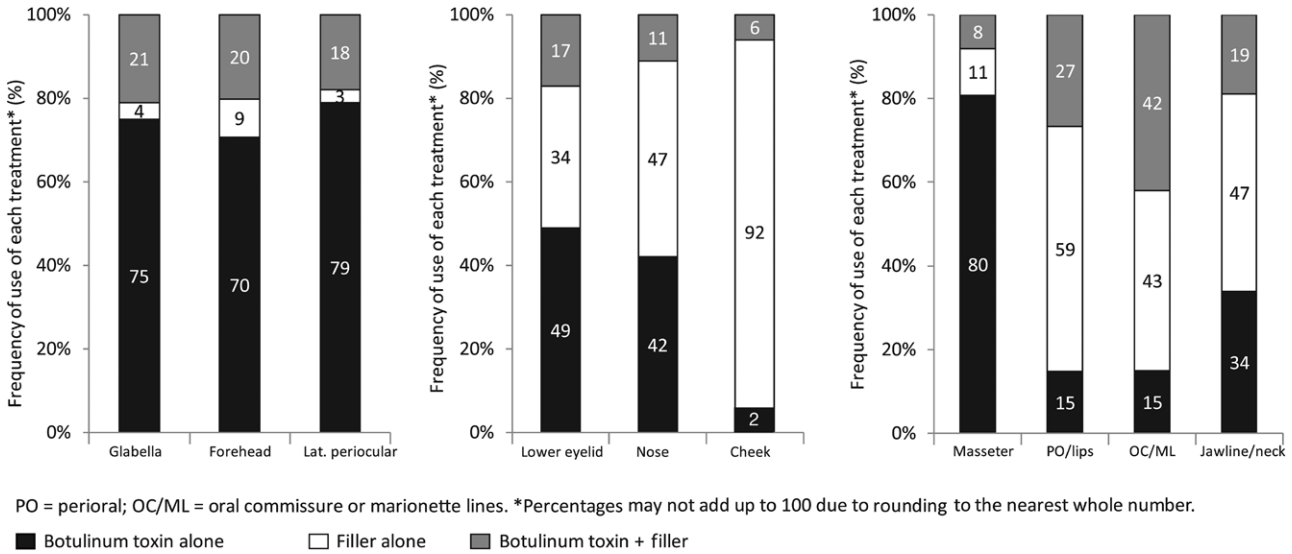

Fig. 3. Consensus panel's practice patterns in the (*left*) upper face, (*center*) midface, and (*right*) lower face, based on premeeting surveys. Percentage use of botulinum toxin alone, filler alone, and botulinum toxin plus filler are shown for each facial zone. Because percentages are rounded to the nearest whole number, they may not add up to 100 percent. *PO*, perioral; *OC*, oral commissure; *ML*, marionette lines.

Table 4. Key Points from Premeeting Panel Survey and Consensus Proceedings Regarding the Upper Face, Midface, and Lower Face

Upper face (glabella, forehead, and lateral periocular regions)
Botulinum toxin type A alone was the most common approach to treating the upper face.
Combination therapy was used for 18–21% of patients (Fig. 3, *left*).
Glabellar lines or forehead: The panel considered same-session or sequential treatments as equally viable options, with choice dependent on patient evaluation, and other considerations such as the patient's ability to return for sequential treatment.
Lateral periocular region: Sequential treatment was preferred in almost two-thirds of cases.
Sequential treatment of the upper face: Most panelists preferred initial toxin, followed by filler.
Same-session treatment: Panelists recommended injection of filler first, followed by toxin, to avoid unnecessary tissue manipulation following toxin injection. Also, filler can be more accurately implanted at the desired level if the tissue is not distended beforehand by injected toxin.
Midface (lower eyelid, nose, and cheek)
Combined treatment of the midface was used less frequently than botulinum toxin or filler alone.
The panel preferred filler alone in 92% of treatments to the cheek.
Same-session and sequential treatments were viable options when treating the lower eyelid or nose with filler and toxin.
Some panelists cautioned against same-session treatment of the infraorbital region because of increased risk of swelling.
Most panelists considered the use of toxin for nasal tip elevation to be ancillary to that of fillers, based on understanding the primary need to correct volume loss and restore support to the nasal tip.
Combined treatment of the cheek was not a common strategy but was considered appropriate in limited situations, such as hyperdynamic "accordion" cheek lines.
Lower face (oral commissure, lip, masseter, and jawline/neck regions)
Frequency of combined treatments was 42% to the oral commissure, 27% to the lips, 19% to the jawline and neck, and 8% to the masseter.
Oral commissure and marionette lines: Same-session treatment with filler followed by botulinum toxin was preferred over sequential sessions in approximately two-thirds of cases.
Same-session and sequential treatment were both considered viable options for the lips and perioral region, jawline, and neck.
The Consensus panel noted that same-session treatment with filler and then toxin was appropriate for patients with chin retrusion and consequent overactivity of mentalis; including Asians, in whom this congenital characteristic is quite common.
For the masseter, clinicians were advised to: (1) distinguish muscular hypertrophy from parotid gland hypertrophy or muscular prominence caused by volume loss and (2) rule out pathologic conditions (e.g., parotid swelling related to Sjögren syndrome or bulimia nervosa).*

*Goodman GJ. The masseters and their treatment with botulinum toxin (Botox). In: Carruthers A, Carruthers J, eds. *Botulinum Toxin (Botox).* 3rd ed. Philadelphia: Saunders; 2013.

Table 5. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Upper Face*

	Frequency of Treatment with Same versus Sequential Sessions			
	Same (%)	Sequential (%)	Typical Total Dose of OnabotulinumtoxinA (U)	Preferred Filler
Glabellar rhytides	44	56	12–40 Doses as low as 8 U may be appropriate for some patients	Superficial Vycross or Hylacross Dilution-reconstitution of Hylacross preferred by some panelists
Forehead	45	55	8–25	Rhytides: superficial Vycross or Hylacross Dilution-reconstitution of Hylacross preferred by some panelists Contouring: midlevel or diluted deep volumizer Vycross
Lateral periocular	38	62	6–15 per side	Superficial Vycross

*Botulinum toxin dosage recommendations may be extrapolated with care, and appropriate dosages, to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross (Voluma, Volift, and Volbella) and for Hylacross (Juvéderm Ultra). Selections may be extrapolated as appropriate to other hyaluronic acid filler families.

Table 6. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Middle Face*

	Same versus Sequential Sessions			
	Same (%)	Sequential (%)	Typical Total Dose of OnabotulinumtoxinA (U)	Preferred Filler
Lower eyelid	51	49	0.5–2 per side (infraorbital rhytides)	Supraperiosteal and subcutaneous contouring (e.g., nasojugal fold: superficial Vycross)
Nose	52	48	1–4 (nasal flare) 2–6 (tip elevation) 4–8 (oblique lines) Doses as high as 10 U may be appropriate for some patients	Deep volumizer or midlevel Vycross
Cheek	61	39	1–6 (intracutaneous, with caution)	Deep volumizer Vycross

*Botulinum toxin dosage recommendations may be extrapolated with care, and appropriate dosages, to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross, and for Hylacross. Selections may be extrapolated as appropriate to other hyaluronic acid filler families.

Table 7. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Lower Face*

	Same vs. Sequential Sessions			
	Same (%)	Sequential (%)	Typical Total Dose of OnabotulinumtoxinA (U)	Preferred Filler
Masseter	22	78	15–40	Deep volumizer or midlevel Vycross
Lips/perioral	54	46	1–5	Perioral rhytides: Superficial Vycross or Hylacross Dilution-reconstitution of Hylacross preferred by some panelists Lips: submucosal implantation of superficial Vycross or Hylacross
Oral commissure/marionette lines	68	32	2–4 per side (DAO); some panelists limit dose to 2 U per side	Deep volumizer Vycross
Jawline and neck	53	47	6–12 per band (platysma); maximum dose, 60 U	Deep volumizer Vycross

DAO, depressor anguli oris.
*Botulinum toxin dosage recommendations may be extrapolated with care, and appropriate dosages, to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross, and for Hylacross. Selections may be extrapolated as appropriate to other hyaluronic acid filler families.

rapid effect when applied directly to hyaluronic acid filler lying free within the soft tissue. Courtesy of Dr. Mark Magnusson, Dr. Tim Papadopoulos, and the Australasian Society of Aesthetic Plastic Surgery. This content was developed for the Society's Anatomical and Live Injecting Workshop, in association with the Australasian Society of Aesthetic Plastic Surgery Annual Non-Surgical Symposium. © 2014 Australasian Society of Aesthetic Plastic Surgery, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at, ***http://links.lww.com/PRS/B683.***]

CONSENSUS RECOMMENDATIONS FOR COMBINED TREATMENT

Figure 3 presents results of the premeeting panel surveys. Table 4 lists key points for the upper, mid, and lower face. Tables 5 through 7 provide consensus toxin dosages and representative filler product selections for combined treatment. The panel did not recommend specific changes in dosing or product selections compared to solo treatment, which is discussed in other Global Aesthetics Consensus Group publications.[76,77] They noted that the frequency of re-treatment may decrease when fillers and toxin are combined. Table 8 summarizes consensus recommendations and position statements.[78]

CONCLUSIONS

Combined treatment was originally advocated to address aspects of facial aging that were regarded as distinct. Volume restoration with fillers ameliorated facial folds and contours. Weakening of overcontracting muscles with botulinum toxin improved hyperdynamic rhytides. The lower face was viewed as most appropriate for combined treatments. The potential for

Table 8. Global Aesthetics Consensus Group Recommendations and Position Statements for Combined Treatment with Hyaluronic Acid Fillers and Botulinum Toxin Type A in Diverse Patient Populations

	Recommendation or Position Statement
Tables 5 through 7 present consensus recommendations for botulinum toxin type A dosage and hyaluronic acid product selection, in combined treatment of the upper, mid, and lower face and the neck.	R
Combined treatment with hyaluronic acid fillers and botulinum toxin is a standard of care, for which it is appropriate to consider and evaluate every patient.	R
Recommended dosing of botulinum toxin in combined treatment is the same as for botulinum toxin alone.	R
Recommendations for hyaluronic acid filler product selection are the same for combined treatment as for these fillers alone.	R
The aim of treatment with fillers and botulinum toxin may be best understood as age-appropriate harmonization of facial proportions and contours.	R
There is no upper age limit for treatment with fillers or botulinum toxin. Patient selection at all ages is based on the same safety and efficacy criteria.	R
Preventive or early treatment with botulinum toxin is a treatment option in appropriately selected younger patients.	R
Treatment of patients younger than 18 yr with fillers or botulinum toxin should be considered carefully from an ethical perspective. The appropriate objective is correction of congenital or acquired disharmonies, rather than facial enhancement.	R
Ethnically appropriate treatment with fillers and botulinum toxin entails integration of a patient-tailored approach, including analysis of facial morphotype, with individual and cultural expectations.	R
Gender-appropriate treatment with fillers and botulinum toxin requires different strategies in men than in women. In particular, feminization of the male face should be avoided.	R
A total of no more than 4 ml per treatment session is recommended for deep volumizer Vycross filler. For volume efficiency, it is best implanted by means of needle microboluses or cannula dispersion. Significant improvement in facial contours is achievable with as little as 2 ml. Reevaluation of patients after treatment can determine the necessity for injecting further product.	R
Reevaluation of patients 2–4 wk after treatment with fillers or botulinum toxin is beneficial to optimize outcomes and patient satisfaction.	R
The response rate to botulinum toxin type A is very high. Partial or complete nonresponse occurs rarely. In cases of apparent nonresponse, practitioners should first consider the possibility of inappropriate patient selection, inadequate dosing, or incorrect placement of injection sites. The Consensus panel has not noted any relationship between a specific botulinum toxin product and either nonresponse to treatment or alleviation of nonresponse.	R
Any procedures that deepithelialize the skin, or cause tissue edema, such as laser resurfacing, should be avoided on the same day as filler or botulinum toxin procedures.	PS
Diversity of ethnicity, skin type, and gender is desirable for subjects enrolled in studies to evaluate the safety and efficacy of solo and combined treatment with fillers and botulinum toxin.	PS

R, recommendation; PS, position statement.

synergy and importance of individualized treatment planning were recognized. The Global Aesthetics Consensus Group's recommendations reflect growing use of combined treatment for the lower face, and also for the upper face and certain areas of the midface. The principle of individualization has been extended to a fully patient-tailored philosophy. This integrates considerations of physiologic and chronologic age, sex, ethnicity and its associated facial morphotypes, and cultural overlays. Lower dosing of botulinum toxin modulates the activity of excessively contracting muscles rather than paralyzing them. The contribution of volume deficits in the soft and hard tissues to muscular activity is increasingly recognized. Research continues to deepen our understanding of how scientific balances in hyaluronic acid fillers influence their indications and clinical performance.

The current rationale for combining fillers and toxin is that they address intimately related processes. When viewed from this new perspective, the identification of various patterns of muscular activity (e.g., in the formation of glabellar[79] or nasal oblique lines[80]) has significant implications. Rather than serving as a mandate to target all overcontracting muscles with toxin, it provides the imperative to seek and carefully identify the primary cause of muscular recruitment. A focus on aesthetic units, rather than isolated stigmata of aging such as rhytides, is necessary to optimize results from both fillers and toxin. The evolving concepts discussed in this publication direct the clinician toward the creation of panfacial harmony and balance.

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APPENDIX: GLOBAL AESTHETICS CONSENSUS GROUP

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