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Treatment of Port-Wine Stains With a Short Pulse Width 532-nm Nd:YAG laser

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ABSTRACT

Background and Objective: Pulsed dye laser treatment often results in port-wine stain (PWS) improvement; however, results vary. A frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser that allows for shorter pulse widths along with large spot sizes and high fluences has been developed for the treatment of cutaneous vascular lesions.

Study Design: A prospective, controlled study was performed in 5 adults with PWS using a frequency-doubled Nd:YAG laser (Excel V; Cutera Inc, Brisbane, CA) in 4 quadrants, using spot sizes of 6 to 10 mm, fluences of 4.8 to 9 J/cm^2, and pulse durations of 3 to 6 ms. An adjacent control area was not treated. Each was assessed immediately posttreatment for purpura and edema and at 1 month for PWS color, size, texture, and thickness. Skin biopsies obtained immediately after and at 1 month posttreatment were evaluated.

Results: All treatment quadrants displayed purpura. At 1-month follow-up, all treatment quadrants showed at least 1 grade of color improvement, from a minimum of 1% to 25% to a maximum of 51% to 75% improvement (12/20 quadrants with 1%-25% improvement, 3/20 with 26%-50%, 5/20 with 51%-75%, and 0/20 with 76%-100%). Histologic evaluation of treatment quadrants revealed vascular changes ranging 0.35 to 4 mm in depth. Immediately posttreatment, thrombi and extravasated red blood cells were observed in treatment quadrants. Histology at 1 month revealed decreased number and diameter of vessels in treatment quadrants (superficial vessels decreased by mean 1.1 vessels per section [13%], and diameter by 3.0 µm [47%], midlevel vessels decreased in number by 2.3 [20%], diameter by 2.42 µm [25%], and deep vessels decreased in number by 1.5 [83%], and diameter by 7.44 µm [88%]).

Conclusions: A single treatment with a short pulse width, frequency-doubled Nd:YAG laser resulted in safe and effective improvement of PWS, with up to 75% improvement in color observed at 1 month. Histologic evaluation demonstrated vascular injury at depths of 0.35 to 4 mm with a reduction in vessel number and size at multiple dermal levels.

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INTRODUCTION

Port-wine stains (PWS), congenital cutaneous capillary vascular malformations, occur in approximately 0.3% of the population.[1] The pathogenesis remains poorly understood; however, the resultant abnormality is the presence of a field area of dilated cutaneous vessels. Early treatment using lasers selectively targeting dilated vasculature has been recommended to provide optimal lightening and to prevent the darkening, thickening, nodularity, and/or hypertrophy that may occur with inadequate treatment.[2,3]

Vascular-specific lasers with wavelengths targeting hemoglobin in PWS vessels represent the standard of care for treatment. A fluence sufficient to induce vessel damage and a pulse width equal to or less than the thermal relaxation time of the targeted vessel has been recommended to avoid nonselective damage to surrounding structures.[4] The thermal relaxation time of PWS vessels has been estimated at 1 to 10 milliseconds (ms).[5] Given the large size of many PWS and the need for frequent treatments, larger spot sizes aid in promoting optimal treatment. High fluences in a short pulse width are also important to destroy small PWS capillaries that are often resistant to pulsed dye laser (PDL) treatment. This has presented a challenge in the treatment of PWS.

Frequency-doubled, 532-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers have been studied in a limited manner in the treatment of PWS.[6-8] A dual potassium titanyl phosphate/Nd:YAG laser (Excel V; Cutera Inc, Brisbane, CA) that allows large spot sizes up to 10 mm in diameter, along with short pulse widths of 5 to 10 ms and fluences up to 11 J/cm^2 was recently approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous vascular lesions. This laser was investigated for safety and efficacy in the treatment of PWS.

TABLE 1.

Port-Wine Stain (PWS) Subject Characteristics				
Subject No.	Age, y	Fitzpatrick Skin Type	Sex	PWS Location
01	40	II	Male	Right chest
02	27	III	Female	Right upper inner arm
03	34	III	Female	Right thigh
04	32	II	Female	Right neck
05	49	II	Female	Left neck

MATERIALS AND METHODS

A prospective, controlled study of 5 adult subjects, each with PWS of at least 16 cm^2 in size, was performed. Subjects with Fitzpatrick skin types I to III and flat (nonhypertrophic) PWS were recruited. Subjects with PWS distal to the elbows or knees or who had received PWS treatment within 6 months of the study were excluded. Subjects were asked the type and number of prior PWS treatments and for self-reported assessment of results obtained after prior treatments. Photographs were taken of the PWS areas using identical lighting and backgrounds before treatment, immediately after treatment, and 1 month after treatment.

Each PWS was treated using 532-nm Nd:YAG laser (Excel V; Cutera Inc) in four 2 × 2 cm quadrants using investigator-selected settings. An adjacent 2 × 2 cm control area was not treated. Investigators were able to perform test spots using settings of their choice in an adjacent area outside of the treatment and control quadrants to assess for optimal treatment parameters and safety immediately before continuing the full study treatment. Settings were selected by the investigator based on clinical judgment for both test spots and subsequent treatment quadrant settings. Contact cooling using a sapphire window integrated into the laser handpiece provided continuous parallel cooling at 5°C. Subject-reported pain scores were recorded according to the Wong-Baker FACES pain rating scale.

Each treatment and control quadrant was assessed by a blinded investigator before treatment, immediately after treatment, and again at 1-month follow-up. Immediately after treatment, quadrants were assessed for degree of edema and degree of purpura and for the occurrence of any adverse events. Pretreatment and at 1 month posttreatment, each area was evaluated by the blinded investigator and assigned a color grade (1 = light pink, 2 = pink, 3 = dark pink, 4 = red, 5 = light purple, 6 = purple, 7 = dark purple) and texture level (flat, hypertrophic, cobbled, or other). Also at 1-month posttreatment, subjects were evaluated clinically and compared with pretreatment photographs. A blinded investigator rated PWS improvement in each of the following: overall color, size, thickness, and texture (each quadrant rated as 0 = 0% improvement, 1 = 1%-25% improvement, 2= 26%-50% improvement, 3 = 51%-75% improvement, 4 = 76%-100% improvement). Skin biopsies (3.5-mm punch biopsy) from the control and treatment quadrants were obtained immediately after treatment, and biopsies were obtained from treatment quadrants again at 1-month follow-up. Histopathologic specimens were evaluated for vascular changes, depth of vascular injury, vessel number, and vessel diameter by a board-certified dermatopathologist.

RESULTS

Five adult subjects, ranging in age from 27 to 49 years, with Fitzpatrick skin types II and III, and PWS on the neck, trunk, or extremities were included (Table 1). In 4 of 5 subjects, the study site had not received any previous treatment, though each had received 3 to 4 PDL sessions to other areas of their PWS and felt the response was mild or unsatisfactory. All stated they had not been satisfied with the response to PDL. In the 1 patient previously treated at the study site, the site had received 4 sessions of PDL, and the patient noted mild improvement that she felt was not satisfactory.

After informed consent was obtained and the areas were photographed, treatments were delivered in four 2 × 2 cm quadrants using the 532-nm laser at spot sizes of 6 to 10 mm, fluences of 4.8 to 9 J/cm^2, and pulse durations of 3 to 6 ms (Table 2). Immediately posttreatment, all treatment quadrants showed no or mild edema. Mild to moderate purpura was present in all treatment quadrants. Control areas did not display edema or purpura. All treatments were tolerated well by the subjects. Subject-reported pain scores using the Wong-Baker FACES scale were 0 in control quadrants and ranged from 2 to 8 in treatment quadrants (Table 3).

One month posttreatment, all treatment quadrants were improved by at least 1 color grade (Table 4) (Figure 1). All treatment quadrants showed a minimum of 1% to 25% improvement in color, with a maximum of 51% to 75% improvement in color observed (12/20 [60%] quadrants showing 1% to 25% improvement, 3/20 [15%] showing 26% to 50% improvement, 5/20 [25%] showing 51% to 75% improvement, and 0/20 [0%] showing 76% to 100% improvement) (Table 5). Laser parameters at treatment quadrants showing the largest and second largest improvements in color were a spot size of 6 mm, fluence of 9 J/cm^2, and pulse duration of 4 ms, and a spot size of 9 mm, fluence of 7 J/cm^2, and pulse duration of 6 ms, respectively. The blinded investigator did not have access to the assigned pretreatment color grade when evaluating 1-month posttreatment color grade. Two of 5 control quadrants were assigned a varying color grade at 1-month (Table 4); however, upon blinded investigator comparison of the subject with pretreatment photographs, no percentage color improvement in controls was seen at 1-month (Table 5). All control and treatment quadrants were described as having a flat texture before and after treatment, and no changes in size (area), thickness, or texture were observed. Temporary hypopigmentation was observed 1 month posttreatment in 1 subject with Fitzpatrick skin type III and fully resolved after several weeks. No other adverse events were observed.

TABLE 2.

532-nm Frequency-Doubled Neodymium-Doped Yttrium Aluminum Garnet Laser Treatment Settings

	Treatment Settings	Treatment Quadrant 1	Treatment Quadrant 2	Treatment Quadrant 3	Treatment Quadrant 4
Subject 01	Epidermal cooling temp setting, °C	5	5	5	5
	Spot Size, mm	6	6	7	8
	Fluence, J/cm²	6	9	7.8	6
	Pulse duration, ms	3	4	4	4
Subject 02	Epidermal cooling temp setting, °C	5	5	5	5
	Spot size, mm	6	6	7	8
	Fluence, J/cm²	6	9	7.8	6
	Pulse duration, ms	3	4	4	4
Subject 03	Epidermal cooling temp setting, °C	5	5	5	5
	Spot size, mm	6	6	7	8
	Fluence, J/cm²	6	9	7.8	6
	Pulse duration, ms	3	4	4	4
Subject 04	Epidermal cooling temp setting, °C	5	5	5	5
	Spot size, mm	8	7	6	6
	Fluence, J/cm²	6	7.8	9	6
	Pulse duration, ms	4	4	4	3
Subject 05	Epidermal cooling temp setting, °C	5	5	5	5
	Spot size, mm	10	10	9	9
	Fluence, J/cm²	4.8	5.6	5.8	7
	Pulse duration, ms	5	6	5	6

TABLE 3.

Wong-Baker FACES Pain Rating Scores[a]

Subject	Control Quadrant	Treatment Quadrant 1	Treatment Quadrant 2	Treatment Quadrant 3	Treatment Quadrant 4
01	0	2	2	2	2
02	0	4	4	6	6
03	0	6	6	8	8
04	0	4	4	4	2
05	0	4	4	6	6

[a]0 = no hurt, 2 = hurts a little bit, 4 = hurts a little more, 6 = hurts even more, 8 = hurts a whole lot, 10 = hurts worst.

Histologic evaluation immediately posttreatment revealed vascular damage in treatment quadrants. Normal skin was seen in control quadrant biopsies. Vascular endothelial injury in treatment quadrant specimens ranged from 0.35 to 4 mm in depth. Platelet thrombi, pseudovasculitic changes, and extravasated red blood cells were also observed. Histologic evaluation at 1 month posttreatment revealed a decrease in the number and diameter of vessels in the dermis of treatment quadrant specimens. Superficial dermal vessels, defined as those vessels located at or above the superficial vascular plexus (papillary-reticular dermal junction), decreased by a mean 1.05 vessels per section (13.46% decrease in number), and mean superficial dermal vessel diameter decreased by 2.95 µm (47.3% decrease). Middermal vessels, categorized as those located between the superficial and deep vascular plexuses, were decreased by mean 2.35 vessels per section (19.58% decrease in number) and decreased in mean diameter by 2.42 µm (24.9% decrease). Deep dermal vessels located at or below the deep plexus (reticular dermal-subcutaneous fat junction) decreased in number by 1.5 vessels per section (83.3% decrease in number) and in mean diameter by 7.44 µm (87.8% decrease) (Table 6).

DISCUSSION

The PDL generally represents a first-line treatment option in PWS because of its safety and efficacy, with 70% to 80% PWS clearance typically observed over multiple sessions. Because most PWS do not display complete clearance with PDL alone, and may display resistance to PDL therapy,[6,9] other lasers, including the 532-nm frequency-doubled Nd:YAG laser, may play a beneficial role in the treatment of PWS.[6-8]

TABLE 4.

Investigator Color Assessment Pretreatment and at 1-Month Follow-up[a]

Subject	Control Quadrant		Treatment Quadrant 1		Treatment Quadrant 2		Treatment Quadrant 3		Treatment Quadrant 4	
	Pretreatment	1-month posttreatment	Pretreatment	1-month posttreatment	Pretreatment	1-month posttreatment	Pretreatment	1-month posttreatment	Pretreatment	1-month posttreatment
01	2	2	2	1	2	1	2	1	2	1
02	2	2	2	1	2	1	2	1	2	1
03	2	1	2	1	2	1	2	1	2	1
04	6	5	6	4	6	4	6	3	6	2
05	5	5	5	4	5	4	5	3	5	2

[a]1 = light pink, 2 = pink, 3 = dark pink, 4 = red, 5 = light purple, 6 = purple, 7 = dark purple.

TABLE 5.

Investigator Assessment of Overall Color Improvement[a]

Subject	Control Quadrant	Treatment Quadrant 1	Treatment Quadrant 2	Treatment Quadrant 3	Treatment Quadrant 4
01	0	3	3	3	3
02	0	1	1	1	1
03	0	1	1	1	1
04	0	2	1	2	1
05	0	1	1	2	3

[a]0 = 0% improvement, 1 = 1% to 25% improvement, 2 = 26% to 50% improvement, 3 = 51% to 75% improvement, 4 = 76% to 100% improvement.

TABLE 6.

Histologic Changes in Vessel Number and Diameter at 1-Month Posttreatment

	Mean Number of Vessels	Mean Vessel Diameter (µm)
Superficial dermis	–1.05 (–13.5%)	–2.95 (–47.3%)
Middermis	–2.35 (–19.6%)	–2.42 (–24.9%)
Deep dermis	–1.5 (–83.3%)	–7.44 (–87.8%)

[a]Negative numbers indicate a decreased number or diameter.

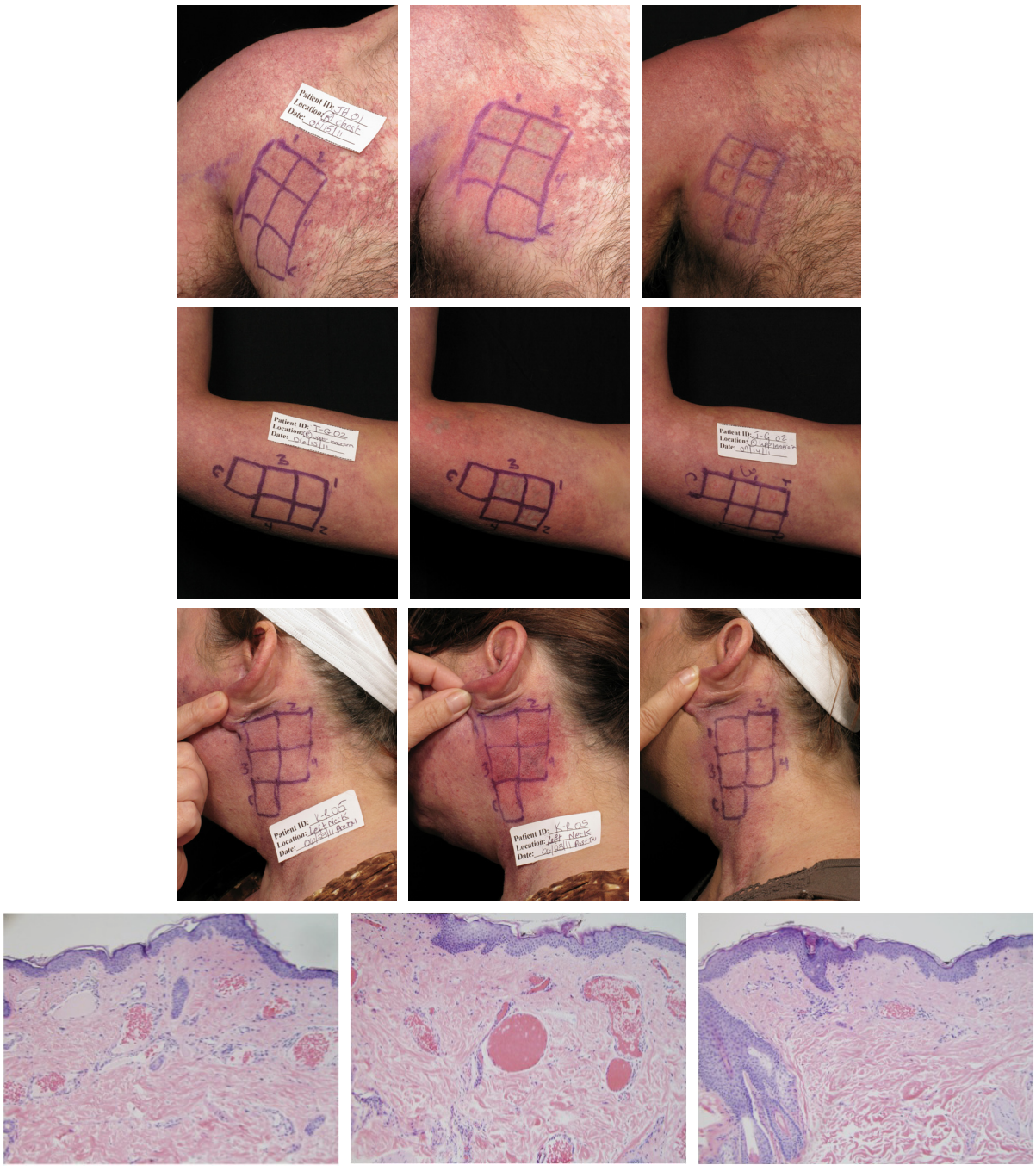
The current study demonstrates a range of 1% to 25% to 51% to 75% improvement in PWS color in individuals with a subject-reported history of mild or unsatisfactory response to PDL, after a single-session treatment using a recently FDA-approved short pulse width frequency-doubled Nd:YAG laser (Excel V; Cutera Inc). Frequency-doubled Nd:YAG 532-nm wavelengths are absorbed well by hemoglobin and display greater absorption than 585- to 595-nm wavelengths. The short pulse widths utilized (3-6 ms) more closely approach the optimal shorter pulse widths recommended for treatment of small vessels in most flat PWS.[5] These pulse widths, when combined with fluences available in the device that reach 11 J/cm^2, created purpura and vascular damage. Vessel damage was confirmed clinically by the observation of mild to moderate purpura, as well as by histologic evaluation that revealed microscopic vascular damage and extravasated erythrocytes. Color improvement at 1 month was documented through blinded assessment and histologic evaluation that showed reductions in vessel number and vessel diameter in the dermis.

Histologic vascular damage in PWS after frequency-doubled Nd:YAG laser treatment was observed at depths of 0.35 to 4.25 mm, with a mean vascular injury depth of 1.68 mm. Observed vascular changes at approximately 4-mm depth are promising and may provide benefit to patients. The laser device studied combines large spot sizes with short pulse durations, which may allow for photon scatter in all directions, as one hypothesis that could explain vascular damage in the deep dermis. Wang and Milner have previously described a 3-dimensional cutaneous vascular model that concluded 532-nm multiple scatter photons can reach the deep dermis and subcutaneous fat,[10] potentially explaining the histologic depth of injury observed.

> "These data suggest safe and effective treatment of port-wine stains in Fitzpatrick skin types I to III using a short pulse width 532-nm laser."

These data suggest safe and effective treatment of PWS in Fitzpatrick skin types I to III using a short pulse width 532-nm laser. Previous studies of frequency-doubled Nd:YAG lasers have shown varied PWS improvements and rates of adverse events. In a 2001 study by Chowdhury and colleagues of 30 PWS treated with 1 to 4 treatment sessions (mean, 2.2 sessions), 53% showed greater than 25% improvement, and 17% showed greater than 50% improvement.[8] In the current study, 40% of quadrants (8/20) showed greater than 25% improvement, and 25% of quadrants showed greater than 50% improvement. A study by Pençe and colleagues of 89 subjects with PWS treated with 1 or more sessions with a 532-nm laser reported that of 8 subjects treated with a single session (2-6 mm, 15-50 ms, 9.5-20 J/cm^2), 4/8 (50%) showed 50% to 74% clearance, 3/8 (38%) showed 75% to 94% clearance,

FIGURE 1. Subject port-wine stains before treatment (left), immediately after a single session treatment with the studied frequency-doubled 532-nm neodymium-doped yttrium aluminum garnet laser (middle), and 1 month after treatment (right, papular scars at biopsy sites evident also). Improvement in color is seen in treatment quadrants (1-4) compared with control (C). Histologic evaluation before treatment (left) shows dilated port-wine stain vessels, immediately post-treatment shows thrombi and extravasated red blood cells (middle), and 1 month posttreatment shows decreased size and number of blood vessels (right).



and 1/8 (13%) showed >94% clearance.[6] Overall, hyperpigmentation occurred in 2%, hypopigmentation in 1%, and scarring in 1%.[6] A study of PDL-resistant PWS by Woo and colleagues found 3/22 patients achieved further PWS lightening (25% or more improvement) with a 532-nm laser (VersaPulse; Lumenis, Yokneam, Isreal; a single session at 2 ms and 7 J/cm^2 or at 10 ms and 16 J/cm^2, contact cooling, 6-week follow-up).[7] Another study using the VersaPulse laser (532 nm, 2-10 ms, 2-4 mm spot, 8-20 J/cm^2, 1-8 sessions) in Chinese patients found 18% had at least 25% improvement, and 14% had at least 50% improvement, with an 11% to 33% rate of pigmentary or textural change.[11] Both the current and previous studies report side effects after use of the 532-nm laser. In the current study, adverse events consisted of a self-limited mild hypopigmentation, while the previous studies reported

incidences of hyperpigmentation and scarring.[8] In the current study, test spots were performed, and the Nd:YAG laser device utilized integrates sapphire-window contact cooling, which likely promoted the improved safety observed in Fitzpatrick skin types I to III. Melanin remains a competing chromophore with some absorption at both 532-nm and 585- to 595-nm wavelengths, making caution prudent when considering treatment of PWS in tanned skin or in Fitzpatrick skin types III and above.

In summary, the studied 532-nm, frequency-doubled Nd:YAG laser with short pulse widths, FDA approved for the treatment of cutaneous vascular lesions (Excel V; Cutera), demonstrated 1% to 25% to 51% to 75% improvement in PWS color after one treatment session in individuals with a subject-reported history of mild or unsatisfactory response to PDL. Self-limited hypopigmentation was observed in 1 patient, and no hyperpigmentation or scarring was observed. Further studies are encouraged to evaluate effects of this FDA-approved, short pulse width, 532-nm, frequency-doubled Nd:YAG laser system in improving treatment of cutaneous vascular lesions.

DISCLOSURES

Study funding was provided by the device manufacturer, Cutera Inc (Brisbane, CA).

Drs. Reddy, Brauer, Anolik, Bernstein, Brightman, Hale, Karen, Weiss, and Geronemus served as investigators for Cutera, Inc. The other authors have no relevant conflicts of interest to disclose.

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