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ANTI-AGING BREAKTHROUGHS: FUTURE OF THE AESTHETICS MARKET

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KEY TAKEAWAYS

- A convergence of several factors is expected to continue to drive the rapid growth of the multibillion dollar aesthetics market, including improved technologies with better efficacy and patient tolerability, a growing segment of the population with adequate disposable income and willing to undergo aesthetic procedures, lack of third-party reimbursement impediments, and a growing segment of the clinician workforce seeking to enhance profitability in their practices through provision of aesthetic procedures.

- From an investor perspective, innovative technologies to provide less invasive and more effective means for body contouring and to enhance skin rejuvenation procedures are showing the greatest promise. For the purposes of this report, we are focusing on private companies that are addressing these highly attractive markets.

- With respect to body contouring, non-invasive technologies to address cellulite and subcutaneous fat reduction (LipoSonix, SmoothShapes, UltraShapes, Cabochon Aesthetics, Juniper Medical, Kythera Biopharmaceuticals) merit attention.

- On the skin rejuvenation side, longer-acting and better tolerated dermal fillers (BioForm, FibroGen, FzioMed, Kythera Biopharmaceuticals), photo-pneumatic devices (Aesthera), fractionated laser devices (Reliant Technologies), ultrasound-based skin tightening technologies (Ulthera, Julia Therapeutics), and plasma resurfacing (Rhytec) are the areas and companies to watch.

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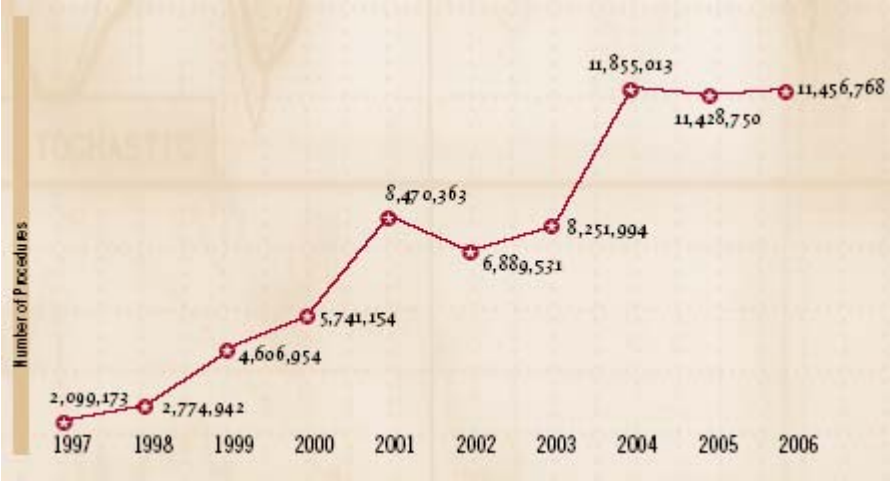
INTRODUCTION

According to the American Society for Aesthetic Plastic Surgery (ASAPS), there were approximately 11.5 million cosmetic procedures performed in the U.S. in 2006, and nonsurgical procedures accounted for 83% of the total. While the overall number of procedures grew only slightly compared to 2005 (~1%), since 1997, this market has expanded 446%, and the number of nonsurgical procedures has increased by 747% (Figure 1).

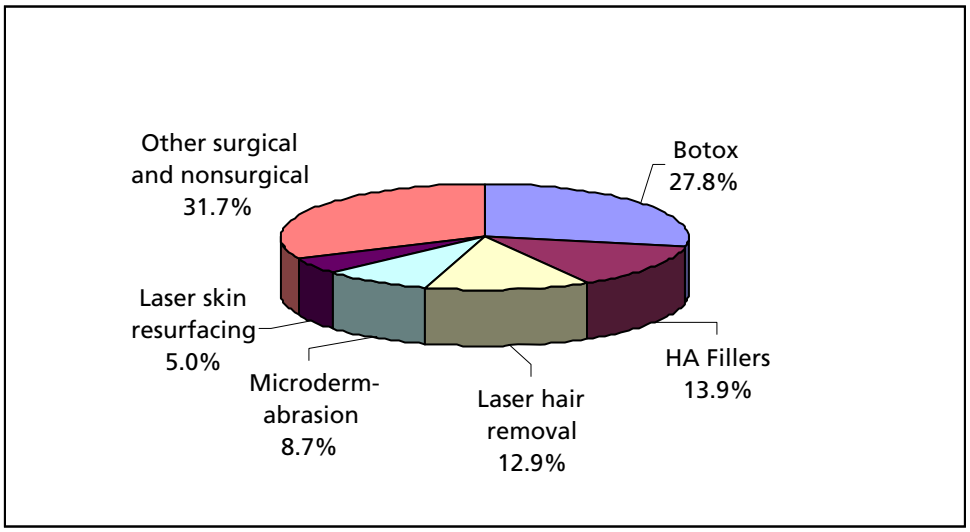
Figure 1. Total Surgical and Nonsurgical Aesthetics Procedures.



Source: ASAPS

Until about a decade ago, facial plastic surgery and chemical peels were the main options for patients seeking facial rejuvenation treatment. Thereafter, Botox, improved dermal fillers, and laser and radio frequency energy systems produced non-invasive, more elegant alternatives to address aging skin issues. In the U.S., the top five nonsurgical aesthetics procedures include Botox injections, hyaluronic acid (HA) dermal fillers, laser hair removal, microdermabrasion, and laser skin resurfacing (Figure 2).

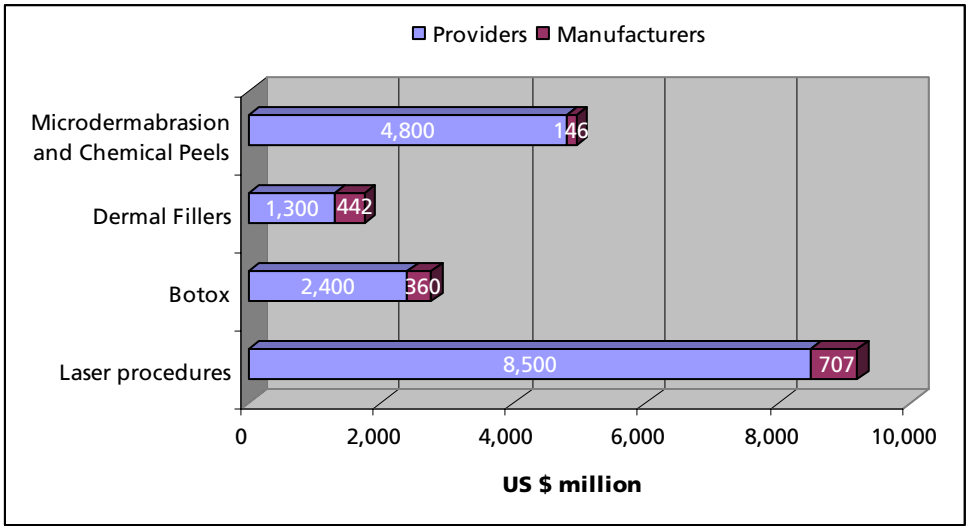
Figure 2. Top Five Nonsurgical Aesthetics Procedures and Their Overall Market Share (procedure-based).



Source: ASAPS

According to ASAPS, in 2006, HA fillers and laser skin resurfacing procedures grew by 33% and 21%, respectively. Allergan, manufacturer of Botox, reported that the worldwide use of Botox for aesthetics indications grew 32% in 2006 versus 2005. ASAPS reports that in 2006, Americans spent $12.2 billion on cosmetic procedures (Figure 3).

Figure 3. Manufacturer vs. Provider Revenues for Selected Nonsurgical Aesthetics Procedures (global 2006 data).

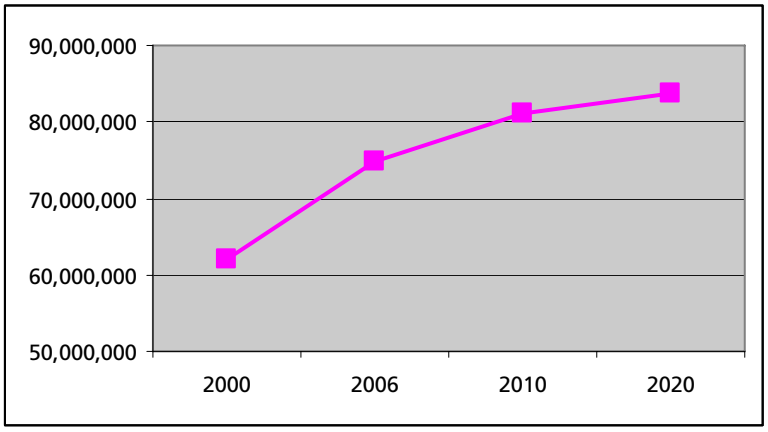


Source: Medical Insight, company information

Over the next 5-10 years the aesthetics market is expected to continue to expand driven by:

- A growing segment of the population with adequate disposable income and willing to undergo aesthetic procedures (Figure 4)
- Improved and innovative technologies with better efficacy and patient tolerability
- Lack of third-party reimbursement impediments
- A growing segment of the clinician workforce pressured by payers and seeking to enhance profitability in their practices through provision of aesthetic procedures

Figure 4. Projected Change in the U.S. Population Group of 45-64 between 2000 and 2020.



Sources: U.S. Census Bureau

We believe that the greatest consumer demand is going to be for aesthetics products and procedures that deliver long-lasting results and minimal downtime. Innovative technologies to provide less invasive and more effective means for body contouring and to enhance skin rejuvenation procedures are showing the greatest promise. For the purposes of this report, we are focusing on private companies that are addressing these highly attractive markets.

BODY CONTOURING

Lipoplasty (liposuction) is the number one cosmetics surgical procedure performed in the U.S. According to the ASAPS in 2006, there were approximately 400,000 liposuction and 170,000 abdominoplasty surgeries performed, collectively resulting in over $2 billion in consumer spending ($1.16 billion and $907 million, respectively).

While effective, liposuction is an invasive procedure that requires general anesthesia. The recovery period is painful, and patients experience significant bruising and swelling and have to take painkillers and wear compression garments for 2-10 weeks post-surgery. Clearly, noninvasive methods of fat removal would be highly attractive to consumers. Furthermore, as the population becomes increasingly overweight, the overall number of patients seeking treatment for fat reduction is expected to rise. The opportunity for aesthetic devices in this area is tremendous.

However, it should be pointed out that the market opportunity is greater than just fat removal. Cellulite is another particularly attractive target for which there are no truly satisfactory treatments available. An estimated 80% of adult women have cellulite, men are rarely affected. Reportedly, consumers spend $3 billion annually on various cellulite treatments that range from creams and mesotherapy (injections of plant extracts, vitamins, or homeopathic compounds into problem areas) to endermological devices (thermal and mechanical stimulation devices to smooth out cellulite; e.g., LPG's Endermologie, Syneron Medical's VelaSmooth, and Cynosure's TriActive). However, none of the approaches provide more than partial short-lived improvements. Thus, cellulite treatment represents another vast market opportunity for aesthetics companies.

Similar to skin rejuvenation, multiple energy sources are being explored for noninvasive body contouring.

Ultrasound

UltraShape's (Yoqneam, Israel) CONTOUR I system is a non-invasive body contouring technology based on focused therapeutic ultrasound that selectively targets and destroys adipocytes (fat cells) without damaging neighboring structures, such as blood vessels, nerves or connective tissue. The ultrasound energy is delivered in bursts of pressure to control temperature elevation of the tissue resulting in safe, non-thermal effects. Adipocyte cell membranes are lysed by mechanical stresses created by ultrasonic pressure waves. The proprietary real-time tracking and guidance system ensures complete and uniform energy delivery within the marked treatment area.

Adipocytes consist predominantly of a triglyceride-rich lipid globule, which comprises 80-90% of the cell volume. Cholesterol represents only 2-3% of the adipocyte content, and the remainder is water and small amounts of protein and nucleic acids. Upon lysis of the adipocytes, cellular debris is cleared by phagocytosis, while released triglycerides are transported to the liver where they are metabolized by endogenous enzymes. It is important to note that the amount of triglycerides released after an UltraShape treatment is very small relative to the body's capacity to handle lipids, and that no changes in serum lipids were observed in published clinical studies.

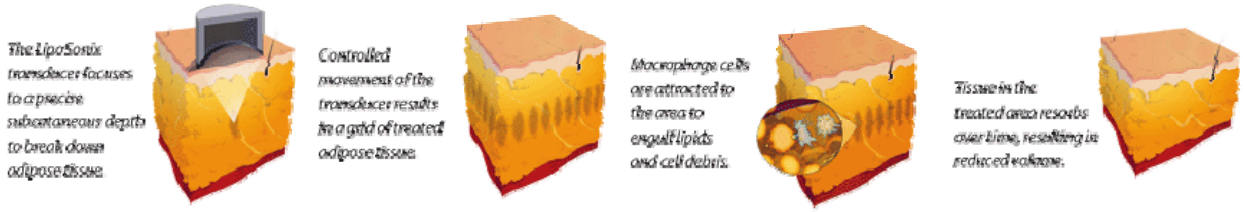
In a multi-center controlled clinical trial, an average reduction of 2 cm in body circumference was observed following a single treatment with the CONTOUR I system. Published results of an independent multiple treatment trial showed an average reduction in body circumference of 4 cm after three treatments. The procedure requires no anesthesia or sedation. The majority of patients report no pain or discomfort during or after treatment and can immediately resume their daily routines. No fibrosis, hematomas or scaring have been reported post treatment.

MEDACorp consultants express a positive opinion about the UltraShape Contour I system and UltraShape procedure. They comment that, for optimal results, three sessions, spaced 3-4 weeks apart, are recommended. The major drawback is that this procedure is relatively slow, as each treatment lasts between one and two hours. Overall, they view UltraShape as an attractive and effective "walk-in, walk out" outpatient procedure.

According to the company, more than 30,000 UltraShape treatment procedures have been performed in over 46 countries worldwide. The UltraShape CONTOUR I system is not yet cleared by the FDA for marketing in the U.S.

LipoSonix (Bothell, WA) is another company developing a noninvasive body sculpting device based on ultrasonic energy. Unlike UltraShape's pressure wave approach, LipoSonix' high-intensity focused ultrasound (HIFU) technology produces disruption of adipose tissue via thermocoagulation. Thermocoagulation of fat cells is achieved through (1) temperature rise due to direct absorption of ultrasonic energy; and (2) thermo-mechanical effects such as cavitation, streaming, and shear forces generated from high-pressure levels within the treated tissue. However, the net result appears to be similar to that of UltraShape: selective lysis of adipocytes without damage to the surrounding tissue (Figure 5). Both UltraShape and LipoSonix treatments are supposed to produce long-lasting/semi-permanent effects, provided that a patient maintains a healthy diet and exercise regimen, thereafter.

Figure 5. Schematic Diagram of LipoSonix Technology.



Source: LipoSonix

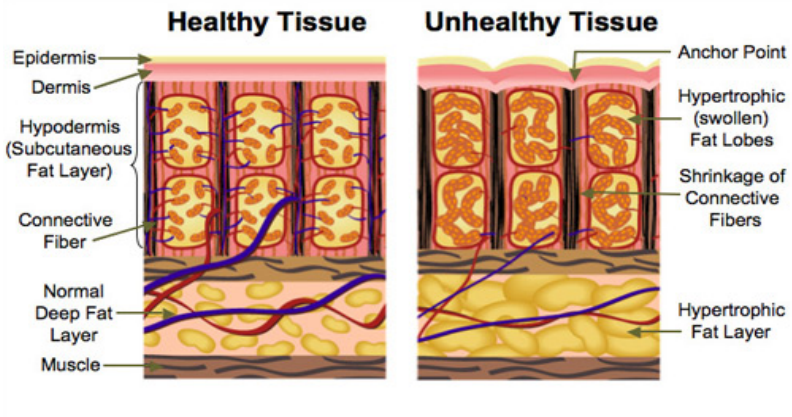
HIFU provides a controlled and safe method for performing noninvasive body sculpting. The temperature at the treatment zone and the volume of tissue treated can be precisely controlled depending on the energy setting (dosage) used. Available clinical results demonstrate excellent patient safety for the procedure. No evidence of any adverse local or systemic effects, including changes in lipids levels, was observed. Treatment was well tolerated, typically requiring little or no pain control during or after the procedure and was associated with no downtime. Some patients have achieved waist size reductions of up to two inches after single treatments.

MEDACorp consultants are attracted by the ability to control energy levels and, thus, the extent of treatment with the LipoSonix system. LipoSonix indicated that a pivotal trial for its device is planned for 2007, and potential U.S. regulatory approval might come in 2008. Approvals outside the U.S. could come as early as the second half of 2007.

Photomology

SmoothShapes (Merrimack, NH) is focused on treating cellulite using Photomology™ which is a process that combines dynamic light and laser energy with vacuum massage to modify cell activity and achieve tighter, smoother looking skin.

Figure 6. Schematic Diagram of Cellulite Anatomy.



Source: celluliterx.biz

Cellulite is formed in the subcutaneous level of tissue below the epidermis and dermis layers. In this region, fat cells are arranged in chambers surrounded by bands of connective fibers (septae) (Figure 6). Fluid retention and adipocyte expansion from weight gain stretch the septae and surrounding connective tissue. Eventually this connective tissue contracts, while the chambers between the septae continue to expand. This results in areas of the skin being held down while other sections bulge outward, resulting in the lumpy "cottage-cheese" appearance on the skin surface characteristic of cellulite.

The FDA-approved SmoothShapes 100 device works by gradually reducing the subcutaneous fat layer while firming up the skin, creating a smoother appearance. SmoothShapes 100 consists of an array of diodes emitting light at two different frequencies - 900 ± 20 nm and 650 nm, and a massage component. Longer wavelength light 900 nm penetrates into the fat, thermally heats the cells, turning them from semi-solid to a liquid state. The shorter frequency light 650 nm makes the fat cell membrane more permeable to allow lipids to be released from the cell. Suction and rollers lift and roll the skin to improve circulation and elasticity. Pressure from the rollers evacuates lipids from the fat cells. Dual-band wavelengths also stimulate collagen production in the dermis, thus making the skin firmer.

In a randomized, single-blinded, multi-center clinical study to evaluate the safety and efficacy of SmoothShapes 100, patients (n=74) were assigned to have one thigh treated with laser plus massage, the contra-lateral control thigh received massage treatment only. Patients received 12 treatments over the course of 12 weeks. The procedure was found to be safe, and most patients reported it as being "relaxing". Notably, 81% of patients experienced significant volumetric reduction of subcutaneous fat (as measured by MRI).

SmoothShapes plans a worldwide launch of this device in 2H:07. In addition to being approved for reducing appearance of cellulite, SmoothShapes 100 is also approved for the relief of minor muscle aches and pains, as well as for temporary improvement of local blood circulation.

Additional Approaches

According to MEDACorp consultants, early stage companies developing innovative solutions to noninvasive fat removal and cellulite treatment include **Cabochon Aesthetics** (Menlo Park, CA), **Juniper Medical** (Pleasanton, CA), and **Kythera Biopharmaceuticals** (Calabasas, CA). Cabochon is developing a low acoustic pressure ultrasound (i.e., low energy) system for disruption of subcutaneous tissue, such as fat, using an enhancing agent to produce a highly targeted effect. According to a recently cleared 510(k), the Juniper Cooling Device XTRA uses various temperature and massage modalities for dermatologic treatments, including reduction of the appearance of cellulite.

Kythera Biopharmaceuticals is developing a portfolio of products for the aesthetics field. ATX-101 is an injectable adipolytic agent based on a naturally occurring bile acid designed to reduce small volumes of localized fat, such as submental (under the chin) fat. Other programs under development include a novel dermal filler and prevention and treatment of photoaging.

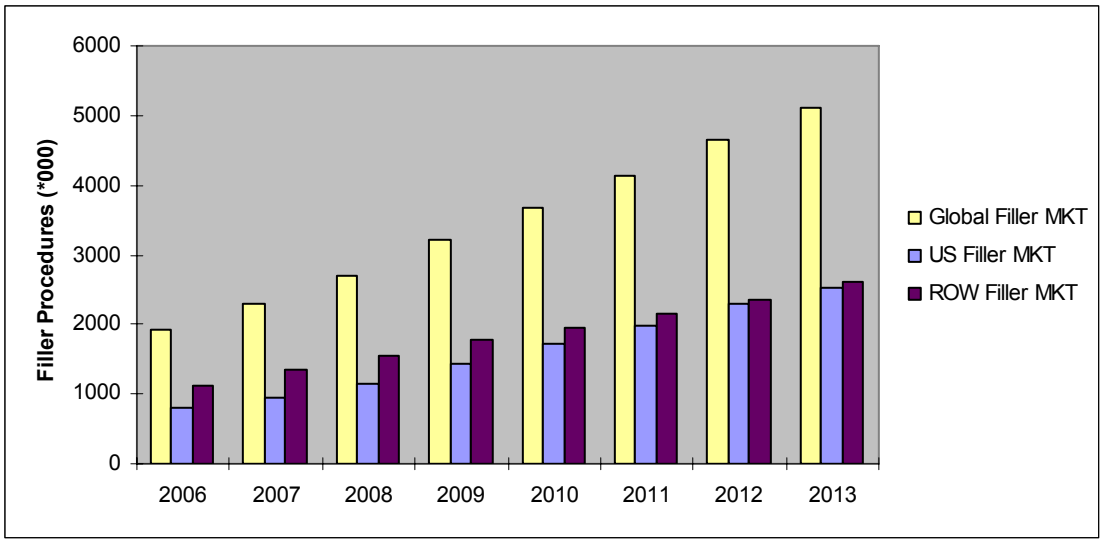
Clearly, the market opportunity for non-invasive fat removal and cellulite reduction is tremendous. Due to the currently limited number of effective options in both areas, approaches that demonstrate clinically meaningful results are poised for broad uptake.

LIQUID LIFT—LONGER ACTING DERMAL FILLERS

Facial aging is accompanied by dermal volume depletion (laxity of collagen and elastin) and overuse of some muscles for facial expression leading to wrinkles. Dermal fillers are injected to diminish appearance of wrinkles, raise scar depressions, enhance lips, and replace soft-tissue volume loss. Correcting soft-tissue contour defects and wrinkles using dermal fillers can give a more natural look than a surgical face lift.

In 2006, the worldwide market for dermal fillers grew 19% versus 2005 to $480 million, of which the U.S. market was over $200 million. In the U.S., accelerated market growth (20-25%) over the next 3 years is expected due to product rollouts of longer-lasting dermal fillers, such as Evolence (Johnson & Johnson/ColBar), Perlane (Medicis), and Radiesse (BioForm) (Figure 7).

Figure 7. Dermal Filler Market Growth.



Sources: Company information, Leerink Swann

A variety of dermal fillers are currently marketed in the U.S. (Table 1). While no perfect filler exists yet, according to MEDACorp consultants, one with the following characteristics would constitute an ideal filler:

- Biocompatible, non-animal, non-immunogenic
- Stable after injection, non-migratory
- Non-toxic, non-pyrogenic, non-inflammatory
- Natural looking
- Good clinical data and experience
- Long-lasting, but removable/resorbable

Table 1. Selected Examples of Marketed Dermal Fillers.

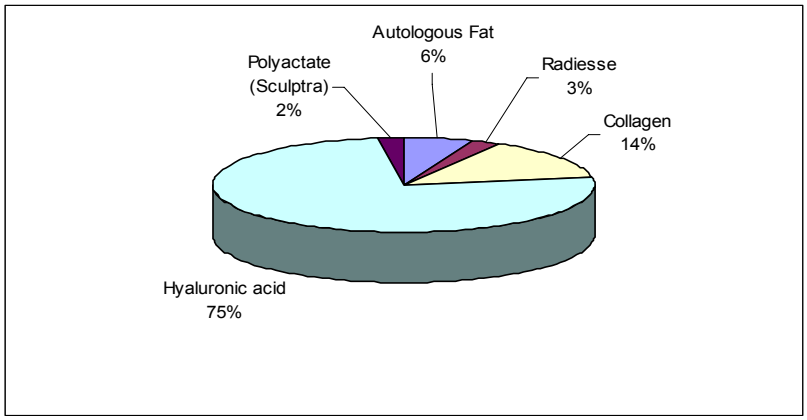
Filler/Company	Key Component	Source	Skin testing requirement	Effect Duration
Temporary				
Zyderm, Zyplast (Allergan)	Bovine collagen	Animal	Yes	3 months
CosmoDerm, CosmoPlast (Allergan)	Human collagen	Human	No	3 months
Longer lasting				
Restylane (Medicis)	Hyaluronic acid (HA)	Bacterial	No	6 months
Juvederm (Allergan)	HA	Bacterial	No	6 months
Juvederm Ultra, Juvederm Ultra Plus (Allergan)	HA	Bacterial	No	12 months
Perlane (Medicis)	HA	Bacterial	No	6-9 months
Radiesse (BioForm)	Calcium hydroxylapatite	Synthetic	No	12+ months
Evolence (ColBar/Johnson&Johnson)	Porcine collagen	Animal	No	12-18 months
Permanent				
Sculptra (sanofi aventis/ Dermik)	Poly-L-Lactic acid	Synthetic	No	Up to 2 years
Artefill (Artes Medical)	20% polymethyl-methacrylate, 80% bovine collagen	Synthetic/animal	Yes	5 years, possibly longer

Sources: Company information, MEDACorp

In terms of duration of effect, dermal fillers could be divided into these categories: temporary, lasting for 3-6 months (e.g., CosmoDerm, CosmoPlast, Restylane, Juvederm), longer-lasting, providing effect for 9-18 months (e.g., Evolence, Perlane, Radiesse), and permanent (e.g., Artefill, silicone) (Table 1).

The dermal filler market started with bovine collagen, which was a 3-month filler and required skin sensitivity testing prior to injection. The launch of HA fillers, which last about 6-9 months and eliminate the need for skin testing, tripled the number of filler procedures. Currently, the U.S. market is dominated by HA fillers, Restylane (Medicis) and Juvederm (Allergan) (Figure 8). The market share of traditional collagen fillers declined from ~90% in 2000 to ~43% in 2004, and further to ~14% in 2006 (as per ASAPS).

Figure 8. 2006 U.S. Dermal Filler Market.



Source: The American Society for Aesthetic Plastic Surgery

Over the next 3-5 years, U.S. market share is expected to shift to products that can deliver longer-lasting and satisfactory results with fewer adverse reactions (e.g., redness, swelling, pain on injection) than many of the currently available agents. Fillers that last for 9-12 months reduce patient cost and enhance per-procedure profitability for physicians (Table 2). MEDACorp consultants indicate that longer-lasting fillers should increase patient satisfaction and should translate into broader use of these fillers around the face, in particular for facial contouring applications, such as cheeks, chin, nose and jaw sculpting.

Table 2. Dermal Filler Comparison - Nasolabial Folds Rx/Year (Average Case).

Product	Average amount injected per year	Manufacturer's Revenue	Charge to Patient*	Physician Profit
Restylane	3 cc	$720	$1100-1500	$380-780
Juvederm	2.4 cc	$720	$1100-1500	$380-780
Perlane	1.95 cc	$490	$1100-1350	$610-860
Evolence	1.5 cc	$340	$1000-1300	$660-960
Radiesse	1.3 cc	$250	$850-1100	$600-850

**- typically per volume injected* *Sources: Aesthetics Buyers Guide, Company information, MEDACorp*

The first long-lasting filler on the market in the U.S. is Radiesse from **BioForm Medical** (San Mateo, CA). It was initially approved for the correction of oral/maxillofacial defects, vocal fold insufficiency, and for radiographic tissue marking in 2001 and has received FDA approval as a dermal filler for the long-lasting correction of moderate to severe facial wrinkles and folds such as nasolabial folds in December 2006. Radiesse is also approved for the long-lasting correction of facial fat loss (lipoatrophy) in people with HIV.

Radiesse consists of small, smooth calcium hydroxylapatite (CaHA) microspheres, which are suspended in a water-based gel carrier. Radiesse not only provides immediate aesthetic improvement through tissue support, but also stimulates endogenous collagen production as the patient's own soft tissue replaces the gel carrier, thus providing longer-lasting effect than other dermal fillers. The average duration of the effect for Radiesse has been reported to be 12 months or longer. Radiesse is safe and well tolerated. Some patients might experience swelling, redness, and bruising at the injection site for a few days.

MEDACorp consultants find Radiesse particularly useful for deep nasolabial fold correction, enlargement of chins, and for cheek contouring. They also comment that it works especially well for older patients whose aging faces need more volume. Consultants find Radiesse's unique feature of stimulating new collagen production very attractive. However, physicians suggest that Radiesse is more difficult to inject compared to HA and collagen fillers and that it is less amenable to "molding" after an injection. According to a recent

MEDACorp survey, in the first quarter of 2007, Radiesse attained a 9% share of the U.S. dermal filler market ("All Systems Are Go; Adding AGN to the Focus List", Leerink Swann, March 15, 2007).

FzioMed's (San Luis Obispo, CA) synthetic dermal filler Laresse is a combination of two well-known medical polymers - carboxymethylcellulose (CMC) and polyethylene oxide (PEO). It has been on the market in the EU since August 2006 and is scheduled to begin pivotal trials in the U.S. Laresse production is totally synthetic, i.e., it is 100% free of animal and bacterial proteins, thus reducing its immunogenic potential. Compared to HA fillers, Laresse has a smoother texture, thus making it easer to inject and provide better looking results for superficial wrinkle correction and lip contouring. Furthermore, according to MEDACorp consultants, a disadvantage of HA fillers, when injected into areas with very thin skin, is an appearance of a bluish hue under certain light. This is not an issue when Laresse is used. Consultants also note that Laresse injections are less painful and result in less bruising and swelling compared to HA fillers. Overall, consultants agree that "smoother is better" for a filler.

Duration of improvement with the present version of Laresse is comparable to the leading HA products – approximately 6 months. FzioMed has developed a second generation filler, Laresse II, that is expected to have longevity of 9-12 months. Longer duration is achieved by changing the viscosity of the polymer through adjusting the ratios of CMC and PEO in the Laresse II formulation. The company expects to get a CE mark for Laresse II in Europe in mid 2007.

Kythera's ATX-104 is a novel dermal contouring agent which is photo-polymerized post-injection. This offers the promise of longer persistence and physician ability to control the shape of aesthetic corrections.

Until Restylane came onto the market, collagen-based fillers were the most widely used products for soft tissue augmentation. In recent years, their use declined dramatically, in part due to short duration post injection (~3 months) and skin sensitivity testing required for bovine products. Nevertheless, collagen fillers have a number of attractive features: they are easy to inject, have a shorter patient "downtime" (less bruising and swelling than HA products), hold shape better than HA and other synthetic fillers, are softer to the touch, and overall provide a more natural look. Therefore, MEDACorp consultants suggest that a long-lasting collagen filler would be very attractive and could be used in up to 50% of all procedures. Furthermore, a long-lasting collagen filler potentially expands the market, thus attracting new patients and increasing the number of return visits of satisfied customers.

FibroGen's (South San Francisco, CA) FG-5017 and FG-5030 dermal fillers are comprised of crosslinked formulations of recombinant human collagen type III (produced in yeast). FG-5017 and FG-5030 are designed to have the positive attributes of the classical collagen filler, such as ease of administration and naturally looking effects, and to have persistence in line with other long-lasting, non-permanent fillers on the market. Neither product is expected to be immunogenic and, thus, would not require skin testing.

Collagen is a triple-helical protein; triple helix provides stability to the molecule. The formation of this helical structure requires hydroxylation of individual collagen molecules by an enzyme prolyl hydroxylase. FibroGen developed a manufacturing system that allows for co-expression of collagen together with prolyl hydroxylase, thus resulting in production of thermally stable collagen. Further crosslinking of the molecules results in an even more stable product, thereby improving its longevity as a dermal filler. FG-5017 is crosslinked with glutaraldehyde, while FG-5030 uses a novel crosslinker. In preclinical studies, formulations based on type III collagen were shown to persist longer than those based on type I, which is the main type of collagen in products currently on the market. Fibrogen plans to initiate clinical testing of FG-5017 in 2007 and FG-5030 in 2008.

SKIN REJUVENATION

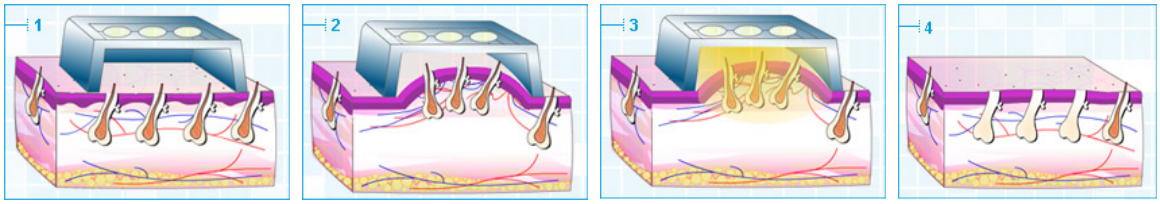
Skin rejuvenating procedures are designed to treat fine lines, wrinkles, and other signs of sun damage and aging, such as rough skin texture and irregular pigmentation. In addition to achieving a smoother skin surface, skin rejuvenation procedures can also tighten the skin by stimulating remodeling of the collagen-rich dermis. Traditional, skin rejuvenation techniques include chemical peels, microdermabrasion and ablative laser surgery. More recently, patient demand for better tolerated procedures has been driving innovation in this area. Several new modalities have ether come to market or are being investigated.

Photopneumatic Therapy

Photopneumatic Therapy (PPx), developed by **Aesthera** (Pleasanton, CA), uses a combination of pneumatic energy and broadband light to deliver energy in a more efficient manner than traditional light-based devices. PPx is supposed to achieve aesthetic results, including hair removal and treatment of veins and pigmented lesions, comparable to laser systems while using only one-fifth the power. Consequently, treatment is supposed to be much safer and involve less discomfort for the patient. PPx is approved for both dermal and epidermal aesthetic applications (hair removal, skin rejuvenation, treatment of pigment and vascular lesions, and acne).

During a PPx treatment, a handpiece is placed on the skin (Figure 9.1); then, a vacuum is applied, thus drawing skin into the treatment tip (Figure 9.2). As a result, the skin is stretched, reducing the concentration of the absorptive chromophores, hemoglobin and melanin. Also, the targets, such as hair follicles, are brought closer to the skin's surface (Figure 9.2). When light is applied (Figure 9.3), elevated targets, reduced melanin and blanched dermal vessels allow 4-5-times light penetration to impact the target. This permits significantly reduced energy levels to achieve the desired treatment results, thus, providing a safer and virtually painless procedure (PPx does not require use of local anesthetics or surface cooling). In addition, PPx treatment is 4-7 times faster than traditional light-based approaches: full leg and whole back treatments could be completed in less than 20 minutes, thus ensuring efficient use of physician time, and potentially creating opportunity for additional revenue.

Figure 9. Schematic Representation of Photopneumatic Therapy.



Source: Aesthera

MEDACorp consultants expressed a positive opinion about Aesthera's photopneumatic therapy. They comment that this system is particularly useful for the treatment of scars and acne. Consultants suggest that the applied vacuum, acting in synergy with light therapy, probably helps to unclog the pores that can lead to acne. The system is also being viewed as excellent for hair removal, especially over large areas – fast and pain free. For a typical busy practice the amortization of the device costs approximately $8/patient – one of the lowest cost devices on the market.

Lasers

Many ablative and non-ablative lasers are available for skin resurfacing (e.g., Alma Lasers, Candela, Cutera, Cynosure, Lasercope, Lumenis, Palomar Medical, Syneron Medical, Radiancy, and Sciton).

Both ablative and non-ablative lasers are designed to heat target tissues by selective photothermolysis (SP). Choosing an appropriate laser type (wavelength) is essential for selective targeting of structures in the skin (chromophores). In SP, only wavelengths of light that are more strongly absorbed by the target chromophore than by the surrounding tissue are used. Laser energy, absorbed by a chromophore, is converted into heat that destroys the target. Delivering energy in concentrated pulses ensures that it destroys the target before it has time to diffuse and damage surrounding tissue.

At present, ablative CO_2 and Erbium:YAG lasers both target water in the superficial skin and remain the gold standards. While effective, these lasers have significant drawbacks: long downtime and potential complications, such as scaring, infections, and dyspigmentation. This approach is not recommended for darker skin types due to risk of pigment changes.

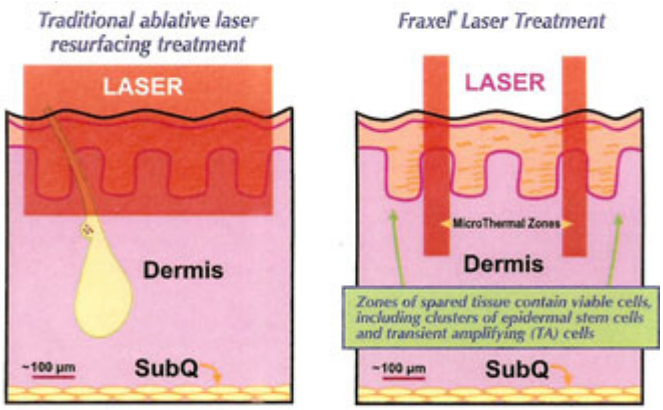
Non-ablative lasers (e.g., 1320 nm Nd:YAG laser and 1450 nm semiconductor diode laser) target the deeper layers of collagen in the skin without damaging the protective epidermal layer. Thus, they reduce downtime and the complications associated with CO_2 and Er:YAG resurfacing. However, the degree of clinical improvement is modest and much less predictable than with ablative resurfacing. Non-ablative resurfacing

typically requires more than one treatment and a delay of several months before the clinical effect becomes apparent.

Fractional Laser Skin Resurfacing

Increasing demands for improved efficacy, shorter downtime, greater patient comfort, and availability of treatment for darker skin types have led to the development of fractional laser resurfacing. Unlike ablative CO2 resurfacing that destroys the entire epidermal protective layers of skin, fractional resurfacing employs a spot welding-like approach that preserves the protective epidermal layer between "spot welds". These preserved areas of skin reduce complications and accelerate healing.

Figure 10. Fractional versus Ablative Laser Resurfacing.



A fractional laser delivers light in an array of microbeams in a process called fractional photothermolysis. The microbeams create narrow, but deep columns of dermal tissue coagulation (microthermal zones) (Figure 10). During treatment, a pixel-like pattern of micro wounds is created. The uninjured tissue promotes natural and rapid healing of these areas (Figure 10).

Coagulated collagen and cellular debris are expelled as skin is resurfaced. Zones of collagen denaturation in the dermis cause upregulation of the inflammatory cascade inducing collagen remodeling and new collagen formation, resulting in skin tightening.

Source: www.facialplasticsurgery.com

Fractional lasers combine the efficacy of ablative procedures with the safety and minimal downtime of non-ablative techniques (Table 3). Most patients can resume their normal activities within 1-3 days after the procedure. However, optimal treatment requires 3-5 sessions spaced several weeks apart (typically 1-4 weeks, depending on patient's skin response and healing time). In contrast to ablative resurfacing, fractional laser treatment could be used on darker skin types.

According to MEDACorp consultants, fractional resurfacing is replacing ablative procedures in popularity driven in part by patient demand for less aggressive procedures and high patient satisfaction with the results.

Table 3. Comparison of Ablative, Non-Ablative, and Fractional Resurfacing.

	Ablative	Non-ablative	Fractional
Efficacy	High	Modest	High
Number of treatments	1	2+	3-5
Downtime	2-6 weeks	3-5 days	1-3 days
Side effects	Medium/High	Low	Low

Source: MEDACorp

Reliant Technologies' (Mountain View, CA) Fraxel SR1500 was the first nonablative fractional resurfacing device introduced to market. The Fraxel system employs a 1550 nm fiber laser coupled with an Intelligent Optical Tracking System to deliver an optimized pattern of microthermal injury (proprietary software determines ideal spot density). The Fraxel laser optical spot size is adjusted at each pulse energy level to optimize the depth of thermal damage depending on an indication, ensuring maximal efficacy and safety—capability not available with traditional laser systems. In addition, the ability to precisely control the amount of thermal damage minimizes patient discomfort.

An additional differentiating feature of Fraxel SR1500 is that it allows resurfacing up to a depth of 1400 microns and poses a minimal risk of scaring. Ablative lasers cannot be used for deep resurfacing (300-400 microns maximum) due to the risk of scaring. Melasma, a pigment disorder that typically is refractory to laser treatment, is amenable to Fraxel treatment.

The only other mid infra-red nonablative fractional device on the market is **Palomar**'s Lux1540 laser. The Palomar Lux1540 laser employs a stamped (fixed) pattern of injury and uses two "easy-change" heads for different treatment applications. For deeper corrections, such as wrinkles and resurfacing, the MB100 head is deployed. The MB100 has a 10 mm spot size and delivers energy up to 100 mJ per microbeam, thus creating deep columns of thermal coagulation. The MB320 head, used for moderate corrections, such as melasma and photodamage, has a 15 mm spot size, delivers energy of up to 15 mJ per microbeam, and creates narrower and shallower columns of thermal damage.

Palomar has recently submitted a 510(k) for skin resurfacing for a next generation Lux1540-Z Fractional Laser Handpiece. Lux1540-Z will allow the user to control manually micro-beam density and focal depth, as well as spot size, which should allow for a more efficient energy use compared to a fixed spot system.

Table 4. Reliant and Palomar Fractional Laser Systems.

	Reliant Fraxel SR1500	Palomar Lux1540
Wavelength	1550 nm	1540 nm
Energy output	Up to 70 mJ/cm^2	Up to 70 mJ/cm^2
Depth of penetration	1.4 mm	1.0 mm
Price	$110,000	$85,000

Source: Company information, Aesthetic Buyers Guide

Plasma Skin Regeneration

Rhytec (Waltham, MA) has developed the Portrait Plasma Skin Regeneration (PSR) system for non-invasive skin rejuvenation. PSR technology uses energy delivered from plasma (ionized gas) to heat the skin and induce a natural regenerative process. The Portrait PSR device generates plasma by passing radio-frequency energy through nitrogen gas. The plasma is emitted in brief pulses from the hand piece of the Portrait PSR device and delivers energy to target tissue upon contact. By using variable energy settings, the depth of thermal damage can be adjusted from superficial epidermal effects similar to microdermabrasion (low energy ~ 1-2 J) to deeper dermal heating similar to CO_2 resurfacing (high energy up to 4 J). Neither setting ablates the epidermal barrier. The drawback of high energy treatment is a longer recovery time for the patient; however, equivalent results with less downtime could be achieved with multiple treatments at low energy. Healing time has been reported to be between 4-9 days after each low energy treatment. While the PSR procedure is generally well tolerated, it does require use of local anesthesia. A whole face can be treated in 15-25 minutes. PSR treatment results have been shown to last, and even improve over time. Evidence of new collagen formation 9-12 months post treatment has been documented (histological studies).

Rhytec's Portrait PSR device is approved by the FDA for the treatment of superficial skin lesions, as well as of both facial and non-facial wrinkles. MEDACorp consultants comment that PSR offers a middle ground between ablative and non-ablative skin resurfacing – it offers improved safety and downtime compared to the former and is more efficacious than the latter. Physicians suggest that PSR is effective at treating moderate to severe sun damage. They also point out that PSR could be used in combination with fractional lasers to achieve optimal results of treating deep wrinkles while still keeping downtime to a minimum.

Ultrasound

Ulthera (Mesa, AZ) is developing the Ulthera System, an ultrasound-based device for non-invasive skin rejuvenation. The device uses high frequency ultrasound technology to both visualize various skin layers (epidermis, dermis, subdermis, and muscle) and to create minute thermal impact zones in targeted tissues. The ultrasound energy produces tissue coagulation in a precise fashion at prescribed depths below the surface of the skin while inflicting no damage to the epidermis. Initial skin tightening results from collagen shrinkage, and longer-lasting effects are due to new collagen formation.

The Ulthera System consists of a control unit with a touch-screen user interface. The display screen contains all controls for setting treatment parameters. It also provides a visualization of skin tissue to plan and monitor the treatment process. A handpiece incorporates various multi-patient disposable transducers that image the tissue and deposit energy at specific depths. This technology can be customized for specific patient requirements by adjusting depth, frequency, exposure time, density of treatment lines, and spacing of lesions. Full face

procedures take 30-45 minutes, require no topical anesthetic or cooling device and result in minimal, if any, downtime. Some patients might experience minor facial redness, which resolves rapidly.

In three clinical trials conducted to date, the procedure was shown to be safe and well tolerated. The optimal number of treatments and duration of the effect have not been established yet. Clinical trials to refine treatment protocols are ongoing. MEDACorp consultants suggest that Ulthera's approach is ideal for treating skin laxity of the jaw line, neck, and under the eyes.

Ulthera is seeking a U.S. FDA 510(k) clearance in 2007 and is also pursuing international registration opportunities. The company was granted a CE Mark in January 2007.

An additional company focused on the use of ultrasound for skin resurfacing is Massachusetts-based **Julia Therapeutics**. Julia Therapeutics is a very early stage company, which has several significant patents for the use of ultrasound for skin resurfacing.

In summary, MEDACorp consultants suggest that no single skin rejuvenation technique is going to be capable of addressing the diverse needs that various patients might have. Therefore, there is significant room in this market for multiple approaches and technologies.

HOME-USE DEVICES

An emerging trend to monitor is the development of home-use devices for aesthetic treatments. At the end of 2006, Palomar received FDA 510(k) over-the-counter (OTC) clearance for a home-use light-based hair removal device. **Palomar** has also announced agreements with consumer product heavyweights Gillette and Johnson & Johnson for the development of OTC aesthetics devices. The Gillette agreement involves the development of a light-based hair removal device for women, while the Johnson & Johnson collaboration focuses on devices for use in applications including reduction of the appearance of skin aging, reduction or prevention of acne, as well as on devices for reshaping of body fat, including cellulite.

Also focusing on the OTC opportunity is **Xthentix** (Phoenix, AZ). Xthetix technology originated from Arizona-based Guided Therapy Systems, the same incubator that spun out Ulthera. Xthetix is developing a handheld, high-frequency ultrasound device for treatment and prevention of acne, which it plans to sell directly to consumers. The device is supposed to heat up deeper skin structures—the sebaceous glands and hair follicles—thereby inhibiting the formation of sebum and, thus, preventing mild to moderate acne from erupting. Xthetix expects to receive FDA 510(k) clearance for OTC use in 2007. MEDACorp consultants comment that a home device for acne would be attractive to patients; however, given that there are multiple acne treatment options available, it would have to be moderately effective for wide adoption.

Overall, consultants suggest that, to ensure safety, OTC devices may use sub-therapeutic energy levels and, thus, are unlikely to displace physician-supervised treatment paradigms.

SUMMARY

A $12 billion aesthetics market is expected to continue its rapid expansion driven by a large, aging population that wants to live gracefully until the end and is willing to pay out-of-pocket for it. In addition to the traditional providers of aesthetics procedures — dermatologists and plastic surgeons — other medical professionals feeling the pinch of managed care and seeking to enhance profitability of their practices are now offering cosmetic procedures, thereby driving further market expansion. Aesthetics technologies that are less invasive, better tolerated, and produce meaningful clinical results are expected to be in great demand by patients. The role of direct-to-consumer advertising should not be underestimated.

We believe that the major value creation opportunities in the aesthetics space for both companies and investors lie in the areas of body contouring, dermal augmentation, and skin rejuvenation. A future of wrinkle-free faces and attractively contoured bodies lies before us.

Important Disclosures

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