Healthy Blue

Medical Policy

Subject:	Adipose-derived Regenerative Cell Therapy and Soft Tissue Augmentation Procedures		
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Description/Scope

This document addresses the following soft tissue augmentation procedures:

- Autologous adipose-derived regenerative cell therapy (for example, Lipogems);
- Autologous fat grafting* (autologous fat transfer); and
- Injectable soft tissue fillers.

*Note: For procedures done as part of breast reconstruction, see SURG.00023 Breast Procedures; including Reconstructive Surgery, Implants and Other Breast Procedures.

Autologous adipose-derived regenerative cell therapy, (also referred to as autologous cellular implant derived from adipose tissue), involves the removal of a heterogenous mixture of cells derived from adipose tissue (including but not limited to adult stem cells, vascular endothelial cells, vascular smooth muscle cells, fibroblasts, T-regulatory cells, and macrophages) from one part of the body and injecting it into another part of the same body with the intent to modify, treat, reverse, or cure a disease or condition by contributing, inducing or promoting tissue healing. The use of stem cells that have been isolated in order to be used as a treatment or therapy for some condition, including adipose-derived stem cell therapy, is addressed in TRANS.00035 Other Stem Cell Therapy.

Autologous fat grafting is a soft tissue augmentation technique used to correct volume loss due to various causes including but not limited to trauma, congenital defects, surgical resection, radiation, or the natural process of aging.

Injectable soft tissue fillers are volume-producing agents that are injected or implanted into the dermal layers of the skin to correct reduce contour defects in the face, neck, and body through the replacement of tissue volume lost due to aging, trauma, or other events. Soft tissue fillers are used for multiple cosmetic and therapeutic indications. A variety of injectable filling agents are available, including temporary fillers that are composed of biodegradable ingredients, such as hyaluronic acid, collagen, calcium hydroxylapatite, and poly-L-lactic acid, and fillers that persist indefinitely in tissue (for example, those containing polymethylmethacrylate microspheres, silicone, or hydrogel polymers).

For related documents see:

- ANC.00007 - Cosmetic and Reconstructive Services: Skin Related
- ANC.00008 - Cosmetic and Reconstructive Services of the Head and Neck
- ANC.00009 - Cosmetic and Reconstructive Services of the Trunk and Groin
- MED.00110 - Silver-based Products for Wound and Soft Tissue Applications
- SURG.00023 - Breast Procedures; including Reconstructive Surgery, Implants and Other Breast Procedures
- TRANS.00035 - Therapeutic use of Stem Cells, Blood and Bone Marrow Products

Medically Necessary: In this document, procedures are considered medically necessary if there is a significant functional impairment AND the procedure can be reasonably expected to improve the functional impairment.

Reconstructive: In this document, procedures are considered reconstructive when intended to address a significant variation from normal related to accidental injury, disease, trauma, treatment of a disease or a congenital defect.

Note: Not all benefit contracts/certificates include benefits for reconstructive services as defined by this document. Benefit language supersedes this document.

Cosmetic: In this document, procedures are considered cosmetic when intended to change a physical appearance that would be considered within normal human anatomic variation. Cosmetic services are often described as those that are primarily intended to preserve or improve appearance.

Position Statement

I. **Autologous Adipose-derived Regenerative Cell Therapy:**

A. Autologous adipose-derived regenerative cell therapy (for example, Lipogems) is considered **investigational and not medically necessary** for all indications.

II. **Autologous Fat Grafting:**

A. Autologous fat grafting is considered **medically necessary** when there is documented evidence of significant functional impairment and the procedure can be reasonably expected to improve the functional impairment.

B. Autologous fat grafting is considered **reconstructive** when there is a significant variation from normal related to accidental injury, disease, trauma, or treatment of a disease or congenital defect (for example, for breast contouring following breast reconstruction procedures).

C. Autologous fat grafting is considered **cosmetic and not medically necessary** when performed in the absence of a significant functional impairment, is not reconstructive, and is intended to change a physical appearance that would be considered within normal human anatomic variation.

III. **Injectable Soft Tissue Fillers** (for example: poly-L-lactic acid [PLLA], synthetic calcium hydroxylapatite, hyaluronic acid, or collagen)

A. Use of injectable soft tissue fillers is considered **medically necessary** when there is documented evidence of significant functional impairment and the procedure can be reasonably expected to improve the functional impairment.

B. Use of injectable soft tissue fillers is considered **reconstructive** when there is a significant variation from normal related to accidental injury, disease, trauma, or treatment of a disease or congenital defect.

C. Use of injectable soft tissue fillers is considered **cosmetic and not medically necessary** when performed in the absence of a significant functional impairment, are not reconstructive, and are intended to change a physical appearance that would be considered within normal human anatomic variation. An example includes, but is not limited to, lip enhancement procedures.

Rationale

Autologous Adipose-derived Regenerative Cell Therapy

Autologous adipose-derived regenerative cell therapy, (also referred to as autologous cellular implant derived from adipose tissue), involves the removal of a heterogenous mixture of fat-derived cells, (including but not limited to adult stem cells, vascular endothelial cells, vascular smooth muscle cells, fibroblasts, T-regulatory cells, and macrophages), from one part of the body and injecting it into another part of the same body. Although autologous adipose-derived regenerative cells are of mesodermal origin, they have the potential, under the proper conditions, to differentiate into multiple lineages of adipogenic, chondrogenic, osteogenic, myogenic, cardiomyogenic, and neurogenic cells (Tabit, 2012). Autologous adipose-derived regenerative cells have been investigated as a potential source of regenerative medicine for a wide range of indications including but not limited to erectile dysfunction, urinary incontinence, soft tissue therapy for scarred or irradiated tissue or chronic wounds (Tabit, 2012). However, there are only a small number of published peer-reviewed studies describing the safety and efficacy of this treatment in the clinical setting.

Haahr (2018) reported the results of a case series study involving 21 subjects with post-prostatectomy erectile dysfunction who received a single intracavernous injection of autologous adipose-derived regenerative cells. Pre-operative continence was reported in 15 subjects and the remaining 6 were incontinent at baseline. At 12 months, 8 of the 15 continent subjects reported erectile function sufficient for intercourse. No benefits were reported in the incontinent group. Another study by Gotoh (2019) reported the results of a case series study involving 13 subjects with persistent stress urinary incontinence after prostate surgery who underwent periurethral injection of adipose-derived regenerative cells. Urinary incontinence progressively improved up to 12 months after treatment in 10 of the 13 participants, and 1 participant with moderate incontinence achieved total continence at 14 weeks after injection. In the 10 participants who showed improvement at the final assessment, the mean daily leakage volume improved from 281.5 g to 119.0 g (reduction rate 57.7%)**.** These results persisted 4-5 years of follow-up.

Several small studies have described the use of "microfragmented" or "microfractured" adipose tissue therapy, marketed under the name Lipogems. Panchal (2018) reported the results of a case series study involving 17 subjects with refractory knee osteoarthritis. A total of 26 knees were treated with Lipogems-created microfractured autologous adipose tissue and followed for 12 months post-treatment. Knee Society Score (KSS) measures improved from 79.6 at baseline to 81.6 at 12 months (p=0.014). Similar findings were reported for the KSS subscale for function, but not for the subscale for activity (p=0.014 and p=0.087, respectively). No significant adverse events were reported. In an RCT involving 20 participants, Sembronio and colleagues (2021) compared the use of Lipogems technology injected after arthrocentesis to standard treatment with hyaluronic acid in individuals with degenerative temporomandibular joint disease. In both groups, pain reduction and mouth opening significantly

improved compared with the preoperative condition (p=0.001). At 6-month follow-up, there was only a statistically significant improvement of mouth opening (p=0.327). Overall, statistical analyses showed that the intervention group had more procedures that met success criteria than the control group (p=0.018). A small RCT is underway to investigate the use of Lipogems-produced microfractured autologous adipose tissue for osteoarthritis of the knee (Jones, 2018). The results of this study will provide additional insight into the value of this proposed therapeutic option.

The use of Lipogems-produced microfractured autologous adipose tissue has also been investigated for gastrointestinal conditions, including for refractory complex fistulizing perianal Crohn's disease (Laureti, 2019). This small case series study involved 15 subjects who were all treated with microfractured autologous adipose tissue. All subjects were followed for 24 weeks, at which time 10 were reported to have both clinical and radiographic remission, 4 demonstrated improvements, and 1 failed treatment. These results were confirmed in all subjects by pelvic MRI. The authors reported no relevant postoperative complications or adverse events. They concluded that this therapy is a promising potential rescue therapy for individuals with refractory complex fistulizing perianal Crohn's disease. Naldini (2018) reported on a similar population of 19 subjects, 12 of whom received treatment with Lipogems-produced microfractured autologous adipose tissue as a first line therapy and 7 who had prior sphincter-saving procedures. Reported adverse events included 3 cases of minor abdominal wall hematoma that did not require any treatment and 1 case of perianal abscess. Mean follow-up was 9 ± 3.1 months (range 3-12 months), with the overall healing rate reported to be 73.7%. The first-line therapy group's healing rate was reported to be 83.3%, and the group with prior treatment had a 57.1% healing rate.

Autologous Adipose-derived Regenerative Cell Therapy for Scleroderma

Scleroderma, (crest syndrome, systemic sclerosis), is a chronic connective tissue disease generally classified as one of the autoimmune rheumatic diseases. Scleroderma may lead to changes in the skin, blood vessels, muscles, and internal organs. The underlying cause of scleroderma is not known; however, it is suspected that the disease may be related to a buildup of collagen in the skin and other organs due to an abnormal immune system response. There are two principal types of scleroderma: localized scleroderma, which only affects the skin; and systemic scleroderma, which affects the skin, internal organs, blood vessels and internal organs. There is no cure for scleroderma. Treatment varies depending on the individual's symptoms (National Center for Advancing Translational Sciences, 2016).

Autologous adipose-derived regenerative cell therapy has been investigated as a modality to treat scleroderma-related hand dysfunction. Granel and colleagues (2015) reported the results of a randomized-controlled trial that investigated the safety, tolerability and efficacy of autologous adipose-derived stromal vascular fraction injections in the fingers of individuals with scleroderma. The study was an open-label, single arm study, at one study site. The 12 female participants were followed for 6 months. A total of four minor adverse events were reported and resolved spontaneously. The authors reported a significant improvement in hand pain and disability. Raynaud's phenomenon, finger edema and quality of life was also observed. The authors concluded that the potential efficacy needs confirmation in additional studies, more specifically, randomized placebo-controlled trials with more robust populations.

In another study, Daumas and colleagues (2017) described the longer follow-up observations at 22 and 30 months after initial treatment for the same 12 participants reported on by Granel and colleagues (2017) above. Multiple

subject-reported outcomes showed persistent improvement, in comparison with the assessment performed just before surgery. In addition to a decrease in the number of digital ulcers reported, mobility, strength and fibrosis of the hand also demonstrated improvement. None of the 8 participants who had previously received the subcutaneous injection of autologous adipose-derived stromal vascular fraction required new infusion. All of the enrolled participants had surgery, and there were no dropouts or participants lost to follow-up. No severe adverse events occurred during the procedure and follow-up. The authors were in favor of a review of the results of the two ongoing studies before final determination of "the place of this innovative therapy" for individuals with scleroderma.

Wang and colleagues (2021) conducted a randomized pilot trial comparing the feasibility and efficacy of improving fat retention using adipose-derived stem cell (ADSC)-assisted, stromal vascular fraction (SVF)-assisted, and conventional autologous fat grafting methods in individuals with facial localized scleroderma. The study involved 18 participants followed for 6 months. Volume retention was measured by MRI and clinical photographs. At 6-month follow-up, fat retention in the ADSC-assisted group was significantly higher than the SVF-assisted group ($p=0.0004$) and conventional autologous fat grafting group ($p<0.0001$). There was also a significant difference in observed fat retention in the SVF-assisted group compared to the conventional group ($p=0.0346$). However, the findings in this study are limited by the sample size and short-duration of follow-up. The clinical significance of the findings are also uncertain.

The available evidence addressing the safety and efficacy of autologous adipose-derived regenerative cell therapy is promising but weak. Additional trials with rigorous methodology are needed.

Autologous Fat Grafting

Autologous fat grafting (also referred to as autologous fat transfer, autologous adipose-derived tissue grafting) is a soft tissue augmentation procedure that uses liposuction to remove unprocessed or minimally processed fat tissue from one part of a person to another part of the same person. Autologous fat grafting is being explored as a treatment for individuals with volume loss due to various causes including but not limited to, disease, trauma, congenital defects, surgical resection, radiation, or the natural process of aging (Tabit, 2012). A disadvantage of autologous fat grafting is the variable rate and degree of resorption, which limits the predictability of long-term outcomes. Due to this unpredictable characteristic, repeat injections are often required.

Autologous Fat Grafting As a Reconstructive Breast Surgery Procedure

Autologous fat grafting has also been explored as a reconstructive breast surgery option for individuals following a unilateral or bilateral mastectomy, or after breast conservation therapy that has had a less-than-ideal cosmetic result. Weichman and colleagues (2013) conducted a retrospective review of all subjects undergoing autologous breast reconstruction with microvascular free flaps at a single institution. The researchers divided the participants into 2 groups: those requiring postoperative fat grafting and those that did not require fat grafting. Participant demographics, indications for surgery, body mass index, history of radiation therapy, mastectomy specimen weight, need for rib resection, flap weight, and complications were analyzed in the comparison. A total of 228 participants underwent 374 microvascular free flaps for breast reconstruction and 100 (26.7%) reconstructed breasts underwent postoperative fat grafting, with an average of 1.12 operative sessions. Fat was most commonly injected in the superior and medial poles of the breast and the average volume injected was 147.8 mL per breast (22-564 ml. The

researchers found that the participants undergoing fat grafting were more likely to have had deep inferior epigastric perforator and profunda artery perforator flaps as compared to muscle-sparing transverse rectus abdominis myocutaneous. The autologous fat graft cohort was more likely to have a prophylactic indication 58% (n=58) versus 42% (n=117) (p=0.0087), rib resection 68% (n=68) versus 54% (n=148) (p<0.0153), and acute postoperative complications requiring operative intervention 7% (n=7) versus 2.1% (n=8) (p<0.0480). Additionally, participants undergoing autologous fat grafting had slighter body mass index, mastectomy weight, and flap weight.

Sollie and colleagues (2022) conducted a single-center, double-blind, randomized clinical trial comparing the effects of fat grafting compared to a sham operation for treating postmastectomy pain syndrome. The study involved 35 participants who were randomized to receive scar-releasing rigotomy and either fat grafting to the area of pain in the intervention group (n=18) or a placebo of saline solution (n=17). The primary outcome was the degree of pain measured using the Numerical Rating Scale. The results revealed no statistically significant changes in average and maximum pain or neuropathic pain.

In 2015, the American Society of Plastic Surgeons published insurance coverage criteria for autologous fat grafting to the breast. The ASPS concluded that:

> Autologous fat grafting should no longer be considered experimental but should be regarded as part of reconstructive surgery when it is performed to approximate a normal appearance of the breasts following mastectomy or lumpectomy or in patients with asymmetry or hypoplasia of other origins.

The ASPS provided the following rationale for their conclusion:

> An evaluation of available literature on autologous fat grafting following mastectomy with no remaining native breast tissue indicates that the body of evidence is comprised mostly of case series, and when combined, the studies provide consistent evidence, thus resulting in grade B recommendations. A grade B recommendation encourages clinicians to employ the available information while remaining cognizant of newer, evidence-based findings. The existing evidence suggests autologous fat grafting is an effective adjunct to breast reconstruction following mastectomy demonstrating moderate to significant aesthetic improvement. In addition, the available evidence also cites autologous fat grafting as a useful modality for alleviating post mastectomy pain syndrome. Furthermore, the evidence suggests autologous fat grafting as a viable option for improving the quality of irradiated skin present in the setting of breast reconstruction.

The Women's Health and Cancer Rights Act of 1998 (WHCRA) mandated that reconstructive breast surgery for women and men who have undergone mastectomy be covered by their benefits for those who have opted to have breast reconstruction. In individuals who have undergone a medically necessary lumpectomy, surgery to create a more normal anatomy is considered reconstructive.

Autologous Fat Grafting for Other Indications

Phulpin, and colleagues (2009) reported on their experience using autologous fat grafting to correct aesthetic defects following radiation therapy for head and neck cancer. A total of 11 individuals underwent autologous fat transfer. Researchers were able to follow 9 of the participants for more than 2 years. Aesthetic and functional

improvements were documented. The histological exam carried out in 6 of the participants demonstrated an improvement in the vascular network density, reduced fibrosis and absence of necrotic areas. However, 6 subjects required fat reinjection 3 months subsequent to the first treatment, due to fat resorption, which led to a volume loss of 20-40%.

Klinger and colleagues (2013) reported the results of a case control study that investigated the use of autologous fat grafting as a treatment of painful and retractile scars that compromised the normal daily activity/mobility of the joint involved. A total of 694 participants were enrolled in the study and autologous fat grafting was performed on 20 of them. Keloids were excluded and although hypertrophic scars were described, the exact number was not specified. Each scar was divided into two parts: one part was infiltrated with normal saline and one part was treated with autologous fat grafting. Outcomes were evaluated using Patient and Observer Scar Assessment Scale (POSAS) and Durometer measurements. Study participants s were followed-up at 5 and 14 days and 1, 3, 6 and 12 months. A statistically significant improvement was observed in skin hardness (Durometer measurements) and all POSAS parameters except itching.

In another study, Fredman and colleagues (2016) conducted a retrospective case review of 7 individuals who underwent autologous fat grafting as a treatment of chronic, refractory neuropathic pain secondary to burn injury. Each participant had failed conventional therapy, which included medical, pharmacologic and laser treatment of the burn scars. Each subject underwent a total of two fat grafting sessions, spaced 2 months apart. The Patient-Reported Outcomes Measurement Information System (PROMIS) was used to assess the perception of pain perception, with participants answering the questionnaire before and after fat grafting. Six of the 7 participants reported improvement in neuropathic pain following fat grafting, which resulted in a reduction in their neuropharmacologic regimen. At 1-year follow-up, 3 of the 5 participants who completed PROMIS questionnaires had PROMIS scores signifying improvement in pain. One participant had similar preoperative and postoperative PROMIS scores, and another had an increase in pain at follow-up; however, he had experienced an additional burn to the same extremity. Donor-site seroma was reported in 1 participant, however no other complications were reported.

Shuck and colleagues (2013) conducted a systematic review to compare the safety, efficacy, and long-term treatment outcomes of autologous fat grafting and injectable dermal fillers for human immunodeficiency virus (HIV)-associated facial lipodystrophy. Based on U.S. Food and Drug Administration approval in HIV lipoatrophy, studies included in the review were limited to the use of hyaluronic acid and/or poly-L-lactic acid. The researchers documented facial volume, subjective participant satisfaction, standardized outcome scales, reinjection rates, and complication rates. A total of 19 studies were included in the analysis, representing 724 participants; hyaluronic acid/poly-L-lactic acid cohort, n=549 and 175 in the autologous fat transfer cohort. Improvements in facial volume and durability of treatment were comparable between dermal fillers and fat transfer, as measured by both subjective participant outcomes and objective means. However, the poly-L-lactic acid cohort was reinjected at a rate three times that of autologous fat, and was associated with a relatively high rate of subcutaneous papule formation at 22% (range, 3 to 44 %t). The authors concluded that both, dermal fillers and autologous fat transfer are effective treatments for HIV-associated facial lipoatrophy, with high rates of facial volume restoration and participant satisfaction. However, autologous fat transfer may provide superior long-term durability but with less of a financial burden compared with injectable fillers. The authors acknowledged that limitations in data and heterogeneity in reporting modalities negated any statistically significant comparison.

Bourne and colleagues (2021) conducted a prospective cohort study evaluating the outcomes for surgical autologous fat transfer applied for traumatic and postsurgical craniofacial deformities. The study involved 20 participants who underwent autologous fat transfer. Volume retention over time was determined using high-resolution computed tomography. Flow cytometry was used to assess cellular subpopulation and viability in the stromal vascular fraction. After completion of the 9-month follow-up, 5 participants were enrolled for a second treatment. Volume retention average was 63 ± 17% at 9 months. The 3-month retention strongly predicted 9-month retention ($r=0.996$, $p<0.0001$). There was no correlation between the total volume injected and retention. Participants that underwent a second procedure had similar volume retention as in their first procedure ($p=0.05$). There were no serious adverse events. The authors note that a limitation of fat grafting is the unpredictability of volume retention.

Common complications and side effects that may be associated with autologous fat grafting include but are not limited to loss of volume, swelling, redness, tingling, and bruising. Less common complications may include cellulitis, hematoma, fibrosis, oil cysts, and calcification. A disadvantage of autologous fat transfer is the unpredictable degree and rate of resorption, which limits the predictability of long-term outcomes. It is not unusual that repeat injections may be required.

Most of the peer-reviewed published literature on autologous fat grafting has explored its use as a reconstructive or cosmetic procedure in individuals who have undergone reconstructive breast procedures. Researchers continue to explore the use of autologous fat grafting additional indications.

Injectable Soft Tissue Fillers

Injectable soft tissue fillers are volume-producing agents that are injected or implanted into the dermal layers to restore the loss of tissue volume due to factors such as lipoatrophy, injury, trauma or aging. A number of injectable fillers including autologous fat may be used for medical purposes in non-facial areas such as the chest (to improve chest wall defects following mastectomy) and the breast (nipple contouring and breast reconstruction) post breast surgery or radiation therapy for the treatment of breast cancer.

Injectable soft tissue fillers may be made from a variety of biologic products, synthetic materials, and from absorbable or nonabsorbable compounds and are generally divided into the following categories: calcium hydroxylapatite (CaHa), collagen, hyaluronic acid and poly-L-lactic acid (PLLA) (U. S. FDA, 2018). Some injectable soft tissue fillers, such as injectable collagen and hyaluronic acids, perform primarily through a volume-filling effect. Others, including poly-L-lactic acid and calcium hydroxylapatite fillers, act as platforms for endogenous collagen formation.

Collagen Injections and Implants

Collagen is a type of dermal (soft tissue) filler that may be used to make the skin appear fuller. Collagen fillers are made from a variety of materials including biologic or synthetic materials, and from absorbable or nonabsorbable compounds. Collagen injections and implants involve either the injection of raw collagen or the surgical implantation of a pre-formed collagen implant under the surface of the skin. This procedure may be used to restore the appearance or function after accidental injury. It may also be used to enhance appearance.

Hyaluronic acid

Hyaluronic acid is a naturally occurring glycosaminoglycan polysaccharide that is present in body tissues, such as in skin and cartilage. When combined with water, hyaluronic acid can expand into a gel form, causing a smoothing/filling effect. The injection of exogenous hyaluronic acid into the skin diminishes visible signs of volume loss. Sources of hyaluronic acid used in dermal fillers can be from bacteria or rooster combs (avian). In some cases, hyaluronic acid used in dermal fillers is chemically modified (crosslinked) to make it last longer in the body. The effects of this material last approximately 6-12 months. Examples of hyaluronic acid fillers that are available in the United States includes, but is not necessarily limited to Juvéderm and Restylane.

Poly-L-Lactic Acid as a Treatment of Human Immunodeficiency Virus (HIV)-associated Lipoatrophy

Some medical conditions may result in a condition called lipoatrophy, characterized by facial wasting of fat under the skin of the face and other parts of the body, resulting in a gaunt or wasted appearance. Reconstructive treatments available to HIV-associated lipoatrophy involve the injection of U.S. Food and Drug Administration (FDA) approved dermal fillers such as poly-L-lactic acid implant (Sculptra®, Dermik laboratories: Sanofi, U.S. LLC., Bridgewater, NJ) or synthetic calcium hydroxylapatite (Radiesse®, Merz North America, Inc., Franksville, WI). Poly-L-lactic acid is a biodegradable synthetic substance used in the manufacture of absorbable stitches and implantable medical devices. Sculptra is an injectable form of this material injected under the skin of an Individual with lipoatrophy to restore a more normal facial or body contour. Radiesse, a semi-solid, cohesive implant whose principal component is a synthetic calcium hydroxylapatite suspended in a gel carrier, is also injected subdermally for restoration, correction, or both for individuals with HIV-associated lipoatrophy.

As mentioned above, Shuck and colleagues (2013) compared the safety, efficacy, and long-term treatment outcomes of dermal fillers in HIV-associated facial lipoatrophy to other treatment modalities, reporting high rates of facial volume restoration and participant satisfaction with the procedure.

Synthetic Calcium Hydroxylapatite (Radiesse®) as a Treatment of Glottic Insufficiency

Although Radiesse® was originally granted FDA approval as a wrinkle filler, in 2007, the FDA granted additional clearance for the product (Radiesse Laryngeal Implant) to be used as a treatment of vocal cord insufficiency (2007). The Radiesse Laryngeal Implant is a sterile, non-pyrogenic injectable material comprised of calcium hydroxylapatite (CaHA) suspended in an aqueous formulation sterile water, glycerin, and sodium carboxymethylcellulose, stabilized with a phosphate buffer. According to the FDA approval letter (K070090): BioForm's Radiesse Laryngeal Implant is indicated for vocal fold medialization and vocal fold insufficiency that may be improved by injection of a soft tissue hulking agent. Radiesse Laryngeal Implant injection augments the size of the displaced or deformed vocal fold so that it may meet the opposing fold at the midline for improved phonation. Vocal fold insufficiency associated with serious aspiration difficulties may be an urgent indication. In February 2010, BioForm Medical Inc. was acquired by Merz Aesthetics Inc. which now manufactures Radiesse Laryngeal Implant under the names Radiesse Voice and Radiesse Voice Injectable Implant. Merz Aesthetics Inc. (Sturtevant, WI) has also been granted an FDA clearance for Prolaryn® Plus, a CaHA compound intended as an injectable, space-occupying implant for vocal fold medialization and augmentation.

Rees and colleagues (2008) reviewed the clinical results of the thyrohyoid approach for in-office vocal fold augmentation using calcium hydroxylapatite (CaHA/Radiesse). The researchers conducted a chart review of all individuals who underwent in-office thyrohyoid vocal fold augmentation between June 1, 2005 and June 1, 2007. Information with respect to participant demographics, indications, complications, and clinical outcome was summarized. A total of 51 thyrohyoid vocal fold augmentations were performed in 33 participants (26 men; mean age of 66 years). Six (13%) procedures were aborted due to an inability to achieve an appropriate injection angle. Two (6%) self-limited complications reported included a vasovagal episode and a small ulcer identified near the petiole of the epiglottis. Pre- and post-procedure data were available for 62.5% of participants. The mean 10-item Voice Handicap Index (VHI) reflected an improvement from 27.9 (± 8.40) pre-procedure to 13.5 (± 10.52) post-procedure ($p<0.001$). The authors concluded that in-office vocal fold augmentation with the use of the thyrohyoid approach produces excellent clinical results.

Rosen and colleagues (2009) evaluated the long-term effectiveness of CaHA vocal fold injection for individuals with glottic insufficiency. Each participant served as his/her own control. Voice-related outcome measures were assessed for pre-injection, 1, 3, 6, and 12 months. A total of 63 subjects were available for evaluation; 53% of the injection procedures were performed in the office and 57 % of participants were diagnosed with unilateral paralysis and 43% with glottal incompetence with mobile vocal folds. Participant satisfaction 12 months after injection demonstrated 67% reporting a significant improvement in voice and 81 % reporting at least a moderate improvement in voice. Utilizing the VHI-10, visual analog scale (vocal effort), Consensus Assessment Perceptual Evaluation V (judgments of voice severity), and objective voice measures of glottal closure (maximum phonation time and S:Z ratio), paired-t tests demonstrated significant improvements after treatment. A 22% further treatment rate was observed at the 12-month time point. The authors concluded that 1-year results of this group of subjects with glottal incompetence treated with CaHA vocal fold injection demonstrate that excellent clinical results were achieved.

Carroll and colleagues (2011) investigated the long-term effectiveness of CaHA/Radiesse as a vocal fold injectable by assessing data from a cohort of subjects who underwent injection for glottal insufficiency (also known as vocal fold insufficiency). Participants who underwent CaHA injection for glottal insufficiency due to any cause were considered for inclusion in the study. The change in VHI-10 scores between pre-injection scores and best post-injection scores as well as between the pre-injection and the most recent VHI-10 scores were employed as primary outcome measures to determine the persistence of benefit or the time to loss of benefit. Complications among the participants were ascertained. A total of 90 individuals who underwent 108 vocal fold injections with CaHA were evaluated for inclusion. A total of 20 individuals with 22 injections met the criteria for inclusion. Fourteen of 22 (64%) participants demonstrated loss of benefit of the CaHA material. The average length of benefit was 18.6 months, (ranging from 8 to 36 months). Complications were identified in three of the original cohort of 108 injections. The authors concluded that CaHA is an effective and safe long-term vocal fold injectable with an average length of benefit of 18.6 months.

In a prospective study, Mohammed and colleagues (2016) assessed the voice outcomes in individuals with unilateral vocal cord palsy undergoing vocal fold injection augmentation laryngoplasty with Radiesse in a clinic-based setting. Outcomes were assessed using a 10-item voice handicap index (VHI-10) administered as a postal survey before and after intervention. The study involved 43 participants. However, 15 participants died of malignant disease. Only 21 participants responded to the survey. The results of the survey suggest a sustained improvement at 3 months ($p<0.01$) and 6 months ($p<0.033$) post-injection.

Other studies have evaluated the role of injection laryngoplasty using CaHA or alternative agents, such as hyaluronic acid, in individuals with unilateral vocal fold paralysis. In a meta-analysis involving 4 cohort studies, Vila and colleagues (2018) found that individuals who received injection laryngoplasty within 6 months following onset of vocal fold paralysis had a relative risk of 0.25 (95% CI, 0.14 to 0.45) compared to conservative management (late or no injection). In another meta-analysis involving 14 studies, Wang and colleagues (2020) found that hyaluronic acid injection laryngoplasty could improve glottal closure insufficiency, maximal phonation time could be prolonged, and perceptual evaluations of the voice could improve. Although the duration of treatment varied across studies, injection laryngoplasty showed promise as an alternative to permanent medialization thyroplasty in appropriately identified individuals.

Background/Overview

Autologous Adipose-derived Regenerative Cell Therapy

Autologous adipose-derived regenerative cell therapy involves the injection of a heterogenous mixture of fat-derived cells, either unprocessed or minimally processed, from one part of a person to another part of the same person. This treatment method has been proposed as a regenerative treatment of a wide variety of indications, including orthopedic injuries. One commercially available device used to produce this type of therapeutic product is named Lipogems (Lipogems International, Norcross, GA), which is used to produce "microfractionated minimally manipulated adipose tissue."

This device was cleared in 2016 by the U.S. FDA with these indications:

> The Lipogems System is a sterile medical device intended for the closed-loop processing of lipoaspirate tissue in medical procedures involving the harvesting, concentrating and transferring of autologous adipose tissue harvested with a legally marketed lipoplasty system. The device is intended for use in the following surgical specialties when the transfer of harvested adipose tissue is desired: orthopedic surgery, arthroscopic surgery, neurosurgery, gastrointestinal and affiliated organ surgery, urological surgery, general surgery, gynecological surgery, thoracic surgery, laparoscopic surgery, and plastic and reconstructive surgery when aesthetic body contouring is desired. Only legally marketed accessory items, such as syringes, should be used with the system. If harvested fat is to be transferred, the harvested fat is only to be used without any additional manipulation.

Scleroderma

Scleroderma (also known as crest syndrome) is a chronic (long-lasting) connective tissue disease generally classified as one of the autoimmune rheumatic diseases. Symptoms of scleroderma may include tightening of the skin, joint pain, an exaggerated response to cold and heartburn. There are two principal types of scleroderma: localized, which affects only the skin; and systemic which affects the skin as well as the blood vessels and internal organs,. The seriousness of scleroderma will vary depending upon the area(s) of the body that are affected.

Autologous Fat Grafting

Autologous fat grafting involves the use of liposuction to remove unprocessed or minimally processed fat tissue from one part of a person to another part of the same person. Autologous fat grafting has been used for the correction of various contour defects involving the face or body. The main advantage of autologous fat grafting in comparison to other soft tissue fillers is the decreased risk for hypersensitivity or foreign body reactions. While the risk for hypersensitivity reactions is small, autologous fat grafting procedures may be complicated by factors such as morbidity in the donor site, infections, contour irregularities, prolonged edema and necrosis or calcification of the injected fat.

Injectable Soft Tissue Fillers

Injectable soft tissue fillers may be made from a variety of biologic products, synthetic materials, and from absorbable or nonabsorbable compounds. According to information provided on the U.S. FDA website, soft tissue fillers (dermal fillers) are generally divided into the following categories:

- Calcium Hydroxylapatite:
  Synthetic calcium hydroxylapatite (CaHA) (for example, Radiesse™) is formed from calcium and phosphorus ions. The CaHA microspheres used in Radiesse have the same chemical arrangement as the inorganic constituent of human teeth and bone. Because CaHA is native to the body, the product does not create antigenic or inflammatory responses (Jacovella, 2008). For wrinkle filling in the hand or face, calcium hydroxylapatite particles are suspended in a gel-like solution and then injected into the wrinkle in the face or under the skin in the dorsum of the hand. While in the body, CaHA will be visible in x-rays and may conceal underlying features.
- Collagen:
  Collagen is a type of protein that is a major component of skin and other tissues in the body. Sources of purified collagen used in soft tissue fillers can be from human or bovine cells.
- Hyaluronic acid:
  Hyaluronic acid is a type of polysaccharide that is present in body tissues, such as in cartilage and skin. It is able to combine with water and swell when in gel form, causing a filling/smoothing effect. The hyaluronic acid used in dermal may be derived from bacteria or rooster combs (avian). In some instances, hyaluronic acid used in soft tissue fillers is crosslinked (chemically modified) to make it last longer in the body.
- Poly-L-lactic acid (PLLA):
  PLLA is a biocompatible, biodegradable, man-made polymer. This material has wide uses in bone screws and absorbable stitches. PLLA is a long lasting filler material that is administered in a series of injections over a period of several months.

Several other injectable soft tissue fillers have received approval from the FDA, including but not limited to Belotero Balance, Prevelle Silk, Restlyne Lyft, and Revanesse Versa. For additional information on FDA approved dermal fillers, see: https://www.fda.gov/medical-devices/aesthetic-cosmetic-devices/fda-approved-dermal-fillers.

Definitions

Autologous adipose-derived regenerative cell therapy: A medical therapy proposed to treat a wide array of conditions using fat cells from an individual which are extracted from one part of the body and then injected into another. In some cases, the fat cells are processed in some fashion prior to reinjection.

Collagen injection or implants: The injection of raw collagen, a naturally occurring substance that gives skin its elasticity, or the implantation of an implant made of collagen, to create a fuller appearance to the skin.

Facial lipodystrophy syndrome (LDS): A condition characterized by the localized loss of fat from the face, resulting in extremely sunken cheeks.

Glottic insufficiency: A condition that occurs when the vocal cords cannot close completely. Also known as vocal cord insufficiency.

Larynx: The tube for the passage of air between the pharynx above and the trachea below. During sound production, the vocal cords close together and vibrate as air forced from the lungs passes between them. The larynx is also known as the glottis or voice box.

Reconstructive: A service or procedure that is intended to address a significant variation from normal related to accidental injury, disease, trauma, treatment of a disease or a congenital defect.

Regenerative therapy: A cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products that intends to modify, treat, reverse, or cure a disease or condition by contributing, inducing or promoting tissue healing. Regenerative therapies may purport to promote the growth and division of repair cells or mediate the inflammatory process associated with an injury or disease, or produce a regenerative effect via their direct incorporation into injured tissue and adjacent tissue.

Scleroderma: A chronic connective and autoimmune rheumatic tissue disease that involves the tightening and hardening of the skin and connective tissues. Scleroderma is also referred to as systemic sclerosis and crest syndrome.

Soft tissue fillers: Biocompatible materials used for soft-tissue augmentation, also referred to as dermal fillers.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Autologous Adipose-derived Regenerative Cell Therapy

When services are Investigational and Not Medically Necessary:
For the following procedure codes or when the code describes a procedure or product indicated in the Position Statement section as investigational and not medically necessary.

CPT	
46999	Unlisted procedure, anus [when specified as perianal injection of autologous adipose-derived regenerative cells, e.g., for fistulizing Crohn's disease]

55899	Unlisted procedure, male genital system [when specified as intracavernous injection of autologous adipose-derived regenerative cells, e.g., for erectile dysfunction]
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands
0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
0566T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; injection of cellular implant into knee joint including ultrasound guidance, unilateral
0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral

ICD-10 Diagnosis

All diagnoses

Autologous Fat Grafting

When Services may be Medically Necessary or Reconstructive when criteria are met:

CPT	
15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof
15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate
15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof

ICD-10 Diagnosis

All diagnoses

When services are Cosmetic and Not Medically Necessary:

For the procedure codes listed above when criteria are not met for medically necessary or reconstructive services; or when the code describes a procedure indicated in the Position Statement section as cosmetic and not medically necessary.

Injectable Soft Tissue Fillers

When Services may be Medically Necessary or Reconstructive when criteria are met:

CPT	
11950-11954	Subcutaneous injection of filling material (eg, collagen) [includes codes 11950, 11951, 11952, 11954]
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when specified as injection of a dermal soft tissue filler]
31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral
HCPCS	
C1878	Material for vocal cord medialization, synthetic (implantable) [e.g., RenuVoice, RenuGel]
G0429	Dermal filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)
L8607	Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies
L8699	Prosthetic implant, not otherwise specified [when specified as a hyaluronic acid gel agent such as Juvederm or Restylane]
Q2026	Injection, Radiesse, 0.1 ml
Q2028	Injection, Sculptra, 0.5 mg
ICD-10 Diagnosis	
	All diagnoses

When services are Cosmetic and Not Medically Necessary:
For the procedure codes listed above when medically necessary or reconstructive criteria are not met, or when the code describes a procedure indicated in the Position Statement section as cosmetic and not medically necessary.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	05/12/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated the Rationale, Background/Overview, References and Index sections. Updated Coding section with 07/01/2022 CPT changes, added 0717T, 0718T.
Revised	05/13/2021	MPTAC review. Removed the word "physical" from the term "physical functional impairment" throughout the document. In the reconstructive position statement for autologous fat grafting, added the phrase "(for example, for breast contouring following breast reconstruction procedures)". Updated the Rationale, Background/Overview, Definitions and References sections.
	04/07/2021	In Description section, added more prominent note referring reader to SURG.00023. Revised medically necessary definition text in the Description section. Updated Coding section, added L8699 NOC replacing J3490 NOC.
New	05/14/2020	MPTAC review. Initial document development. Information on dermal fillers, collagen injections and hyaluronic acid gel products removed from ANC.0007 Cosmetic and Reconstructive Services: Skin Related and now addressed in this document. Includes medically necessary criteria for injectable soft tissue fillers. Information on adipose-derived regenerative cell therapy removed from MED.00110 Silver-based Products and Autologous Skin-, Blood- or Bone Marrow-derived Products for Wound and Soft Tissue Applications and now addressed in this document.