

## **Medical Policy Manual**

**Topic:** Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells

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**Section:** Surgery

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### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Recent advances and innovations in surgical techniques and radiology and the discovery that multipotent adult stem cells are present in human adipose tissue have contributed to renewed interest in performing autologous fat grafting to the breast for aesthetic and reconstructive purposes.

#### **Adipose Tissue Thysiology in Fat Grafting**

Harvesting of adipose tissue by liposuction is technically easy, minimally invasive, and associated with little patient discomfort and morbidity. Small amounts (100-200 mL) can be obtained under local anesthesia.

Adipose tissue is a highly vascularized tissue, and adipocytes are in direct contact with adjacent capillary vessels. In free fat grafting, direct diffusion of nutrients from plasma in the surrounding bed and subsequent revascularization usually occurs within 48 hours and are essential for graft survival. If the local environment does not undergo revascularization, the grafted fat tissue eventually undergoes necrosis, one complication after fat grafting. There is general unpredictability and a low rate of graft survival due to partial necrosis. Other complications include oil cyst formation, indurations in either the subcutis or breast parenchyma, calcification, and severe breast deformity.<sup>[1]</sup>

#### **Adipose-derived Stem Cells**

Stem cell biology, and the related field of regenerative medicine, involves multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. Studies have shown that 1 gram of adipose tissue yields approximately  $5 \times 10^3$  stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow.<sup>[1]</sup> Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. Adipose tissue in particular represents an abundant and easily accessible source of adipose-derived stem cells (ADSCs), which can differentiate along multiple mesodermal lineages.<sup>[1]</sup> ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site.

This identification of several potentially beneficial therapeutic properties of ADSC has led to proposed novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting, including the differentiation of ADSC into adipocytes as a reservoir for adipose tissue turnover, the differentiation of ADSC into endothelial cells and the subsequent increase in blood supply to the grafted fat tissue, thereby decreasing the rate of graft resorption, the release of angiogenic growth factors by ADSC and the induction of angiogenesis, protection of the graft from ischemic reperfusion injury by ADSC, and acceleration of wound healing at the recipient site.<sup>[1]</sup>

### **Regulatory Status**

A point-of care system is available for concentrating ADSC from mature fat. The Celution™ system (Cytori Therapeutics, Inc.) is designed to transfer a patient's own adipose tissue from one part of the body to another in the same surgical procedure. The system received 510(k) marketing clearance from the U.S. Food and Drug Administration as a cell saver device. The system is cleared for the collection, concentration, washing and re-infusion of a patient's own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urological surgeries and procedures.

**Note:** This policy does not address free flap autologous fat grafting with micro vascularization.

### **MEDICAL POLICY CRITERIA**

The use of autologous fat grafting and adipose-derived stem cells for augmentation or reconstruction of the breast is considered **investigational**.

### **SCIENTIFIC EVIDENCE**

#### **Literature Review**

In order to understand the impact on health outcomes of fat grafting to the breast, with or without adipose-derived stem cells, prospective clinical trials are needed, comparing fat grafting to standard reconstructive procedures. These comparisons are necessary in order to understand the safety and efficacy of the procedures and to determine whether fat grafting offers advantages over conventional surgical procedures with respect to complications, durability, post-procedure ability to detect cancer, and cosmesis.

The published literature on fat grafting to the breast, with or without adipose-derived stem cells, is limited to case series and case reports.

### Autologous Fat Grafting in Breast Augmentation and Reconstruction

#### *Randomized Controlled Trials*

There are no prospective, randomized controlled trials comparing autologous fat grafting to other breast augmentation or reconstructive procedures.

#### *Systematic Reviews*

- In a 2013 critical review, authors critically assessed the current body of literature in fat grafting to provide a framework to guide application and comparison.<sup>[2]</sup> Authors included 103 articles in their review; headings included donor site, effect of infiltration solution, harvest method, effect of centrifugation, reinjection method, supplementation, the role of adipose-derived stem cells, and scaffolding. Authors concluded that there is no consensus on the optimum technique of autologous fat grafting in both reconstructive and cosmetic surgery due to the array of research methods and short follow-up durations.
- A 2012 literature review by Saint-Cyr and colleagues on the role of fat grafting in reconstructive and cosmetic breast surgery included articles published between 2001 and 2011.<sup>[3]</sup> Due to the heterogeneity of the studies, a formal meta-analysis was not done. Out of 19 chosen studies, 11 had patients receiving autologous fat transplantation as an adjunct to breast reconstruction, 5 studies enrolled patients receiving the procedure for strictly cosmetic purposes, and three studies used fat grafting for both reconstructive and cosmetic purposes. In the studies included in the review, follow-up intervals ranged from 2 weeks to 19.1 years. The number of sessions employed per patient ranged from 1 to 7, with the intervals of time between sessions, when reported, ranging from 21 to 263 days. The review found it difficult to correlate patient or surgeon satisfaction with volume stability or complication rate as there was not a standardized method of documenting clinical success, postoperative volume stability, or follow-up intervals used to report complications; however, the majority of studies yielded results that were satisfactory or better. For fat grafting used in the setting of radiation (four studies), two studies reported a significant decrease in the LENT-SOMA scores in 95 to 100% of patients. Postoperative volume analysis was only performed in three studies. Postoperative infections, all managed with antibiotics, were reported in four of the studies. Among the 19 selected studies in the literature review, the methods used in the harvesting, processing, and injection of the adipose tissue varied widely. The authors of this review concluded that large prospective studies with well-defined follow-up measures are needed to more clearly demonstrate specific risks and answer questions concerning the amount of adipose resorption and long-term stability of the fat grafts used for reconstructive and cosmetic purposes.

#### *Nonrandomized Studies*

Following is a summary detailing the largest case series using fat grafting to the breast. In these reports, the indications for fat grafting included augmentation, congenital breast defects, postlumpectomy or postmastectomy deformity, or damaged tissue resulting from radiotherapy.

- Ho Quoc and others in 2013 evaluated the efficacy of percutaneous fasciotomies in association with fat grafting in breast surgery in a retrospective chart review of 1000 patients treated with concurrent fasciotomies and fat grafting.<sup>[4]</sup> The primary indication of patients reviewed included breast-conserving surgery after cancer, latissimus dorsi flap breast reconstruction, breast implant reconstruction, tuberous breast, Poland syndrome, and funnel chest. The following complications were recorded: 0.8% local infections (8/1000), 0.1% delayed wound healing that required medical care (1/1000), and 3% fat necrosis (31/1000). Authors concluded that in this heterogenous retrospective chart review was a safe and reliable technique.
- In a recent 2013 study authors determined which risk factors were associated with readmission after breast reconstruction.<sup>[5]</sup> Patients undergoing breast reconstruction in 2011 were identified in the National Surgical Quality Improvement Program database and grouped as purely immediate implant/tissue-expander reconstructions or purely autologous reconstruction for analysis. Of 5012 patients meeting inclusion criteria, 3960 and 1052 underwent implant/expander and autologous reconstructions, respectively. Implant/expander and autologous cohorts experienced similar readmission rates (4.34% vs 5.32%, respectively;  $P = 0.18$ ). Autologous reconstructions experienced a higher rate of overall complications compared to implant/expander reconstructions (19.96% vs 5.86%, respectively;  $P < 0.05$ ), as well as higher rates of reoperation (9.7% vs 6.5%, respectively;  $P < 0.05$ ). Authors concluded that knowledge of specific risk factors for readmission may improve patient outcomes, optimize reconstructive outcomes, and minimize readmissions.
- Caviggioli and colleagues reported on the use of autologous fat grafting for the treatment of pain in 72 women with severe scar retractions and postmastectomy pain syndrome;<sup>[6]</sup> 41 patients with post-mastectomy pain syndrome who were not treated surgically were included in the study as a control group for statistical analysis. Average difference in pain outcomes, as measured on a visual acuity scale (VAS; range 1-10) a year after intervention or enrollment in the study were compared between the 72 patients who received an autologous fat grafting procedure versus the 41 patients who did not receive any additional surgical intervention. Use of analgesics, an important factor in pain management, was not standardized between or within the treatment groups.
- In 2011, Losken and colleagues reported their experience in patients with a history of breast cancer and autologous fat grafting in secondary breast reconstruction for acquired breast deformities.<sup>[7]</sup> A retrospective review was performed for 107 patients between 1996 and 2010. The indications for fat grafting were for improvement in contour, shape, and volume of the breast following a variety of procedures. The average volume of injection was 40 mL (range, 5-150 mL). Eighty of the 107 patients had fat injection performed only once. Patients with a history of radiation therapy had a significantly increased need for repeat fat injections. The average follow-up was 8 months (range 1 month-2.5 years). Complications occurred in 11% of patients and included fat necrosis, erythema, keloid scarring, and pain.
- In 2009, Illouz and colleagues reported on their experience over 25 years with 820 patients using autologous fat transplantation to the breast.<sup>[8]</sup> Patients included in the study were candidates for either breast reconstruction after tumor resection or breast augmentation and were divided into 3 groups: patients with asymmetry after mastectomy and breast reconstruction ( $n=381$ ), patients with congenital breast asymmetry ( $n=54$ ), and patients requesting bilateral breast augmentation ( $n=385$ ). A total of 820 consecutive female patients were operated on between 1983 and 2007. Twenty-five to 180 mL of fat was grafted into each breast in each session (mean 145 mL). The number of sessions needed to achieve the desired result ranged from 1 to 5 (mean 3 sessions). The total amount of fat transplanted in each breast ranged from 25 to 900 mL (mean 540 mL). Complications included ecchymosis ( $n=76$ ), striae ( $n=36$ ), hematomas ( $n=12$ ), and infections ( $n=5$ ). Long-term breast asymmetry was seen in 34 cases.

- In 2009, Delay and colleagues reported the results of fat transplantation to the breast in 880 procedures over 10 years.<sup>[9]</sup> The lipomodeling procedures were performed for breast reconstruction (n=734), correction of congenital deformities (n=106), aesthetic breast surgery (n=30), and correction of a previous surgical defect (n=10). To compensate for fat resorption, 140 mL of fat was injected for a desired final volume of 100 mL. Clinical follow-up suggested that the morphologic results with regard to the volume obtained were stable 3-4 months postoperatively if the patient's weight remained constant. The authors stated that the postoperative radiologic appearance was that of normal breasts, sometimes showing images of fat necrosis that would not confuse the differential diagnosis of cancer for radiologists experienced in breast imaging. Oncologic follow-up at 10 years postoperatively, for the first patients treated, suggested no increased risk of local recurrence of cancer or development of a new cancer. The complications included one case of infection at the harvest site, 6 cases of infection at the injection site, and 1 case of intraoperative pneumothorax that was successfully treated in the recovery room with no further consequences. The incidence of fat necrosis was 3%.
- Panettiére and colleagues reported on outcomes of 61 consecutive women with irradiated prosthetic reconstructed breasts following mastectomy for breast cancer who underwent a comparative case series trial (20 patients were enrolled in the treatment arm of the trial and 41 patients were considered controls and not given any additional treatment).<sup>[10]</sup> Three months after surgical intervention, LENT-SOMA scores and cosmetic outcomes were compared between groups, and the authors reported significant improvements in the LENT-SOMA scores in the group receiving free fat transfers.

In general, these studies contribute to the body of knowledge concerning autologous fat grafting and may be used to provide direction for future research. However, valid and reliable conclusions about the impact of autologous fat grafting on health outcomes cannot be reached from these studies due to methodological limitations such as lack of adequate control groups. Without adequate control groups it is not possible to account for the many types of bias that can affect study outcomes.

### Autologous Fat Grafting and the Use of Adipose-derived Stem Cells (ADSC)

#### *Randomized Controlled Trials*

There are no prospective, randomized controlled trials comparing autologous fat grafting with adipose-derived stem cells to other breast augmentation or reconstructive procedures.

#### *Nonrandomized Studies*

The following summarizes all identified case series using fat grafting to the breast with the supportive use of adipose-derived stem cells. In these reports, the indications for fat grafting varied.

- Authors used a triple-blind, placebo-controlled trial to compare the survival of fat grafts enriched with autologous adipose-derived stem cells (ASCs) versus non-enriched fat grafts in 10 participants.<sup>[11]</sup> Participants underwent two liposuctions taken 14 days apart: one for ASC isolation and ex-vivo expansion, and another for the preparation of fat grafts. In this small study of healthy participants, the authors concluded the ASC-enriched fat grafts had significantly higher residual volumes compared to the control grafts.
- Pérez-Cano conducted a single-arm, prospective, multicenter clinical trial of 71 women who underwent breast conserving surgery for breast cancer and autologous adipose-derived

regenerative cell (ADRC)-enriched fat grafting for reconstruction of defects  $\leq 150$  mL (the RESTORE-2 trial).<sup>[12]</sup> Trial endpoints included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months post-procedure. Female patients (18-75 years of age) presenting with partial mastectomy defects and without breast prosthesis were eligible. The RESTORE-2 protocol allowed for up to two treatment sessions and 24 patients elected to undergo a second procedure following the six-month follow-up visit. Of the 67 patients treated, 50 reported satisfaction with treatment results through 12 months. Sixty-one patients underwent radiation therapy as part of their treatment; two patients did not receive radiation and the status of radiation treatment was not known for the other 4 patients. Using the same metric, investigators reported satisfaction with 57 out of 67 patients. There were no serious adverse events associated with the ADRC-enriched fat graft injection procedure. There were no reported local cancer recurrences. The LENT-SOMA scale included investigator and patient assessment of post-radiation signs and symptoms. The investigators of the trial found that LENT-SOMA was insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA III and IV scores (most severe symptoms) were excluded during screening, which may have contributed to the subtle LENT-SOMA score changes observed in the trial. The investigators reported improvement from baseline through 12 months in the degree of retraction or atrophy in 29 out of 67 patients, while 34 patients had no change and 4 patients reported worse symptoms. Post-radiation fibrosis at 12 months was reported as improved in 29 patients, while 35 patients had no change and 3 patients had worse symptoms. Management of atrophy was reported as improved in 17 patients, with 48 patients having no change and 2 patients reporting worse symptoms. Improvement in these measures reached statistical significance. The authors concluded that future comparative studies are needed to determine the incremental benefit of ADRC-enriched fat grafting as compared to traditional fat grafting in various clinical circumstances.

- In 2011, Kamakura and Ito reported on the use of ADSC enriched fat grafting for breast augmentation in a prospective, nonrandomized open-label study of 20 Japanese women.<sup>[13]</sup> After the adipose tissue was harvested by liposuction, it was processed in the Celution 800 System® to wash and isolate the adipose-derived regenerative cells and produce a fat graft enriched with the regenerative cells. Clinical outcomes measured included improvement in circumferential breast measurement from baseline state. There was improvement in circumferential breast measurement in all patients, and breast measurements were stable by 3 months after grafting. At 9 months, the mean breast measurement had increased 3.3 cm from preoperative measurements. The procedure was well-tolerated without any serious adverse events. Postoperative cyst formation was seen in 2 patients.
- In 2008, Yoshimura and colleagues reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection.<sup>[14]</sup> From 2003-2007, the group performed CAL in 70 patients: in the breast in 60 patients (including 8 who had breast reconstruction after mastectomy). They reported outcomes for 40 patients with healthy thoraxes and breasts who underwent CAL for purely cosmetic breast augmentation; patients undergoing breast reconstruction for an inborn anomaly or after mastectomy were not included. Nineteen of the 40 patients had been followed for more than 6 months, with a maximum follow-up of 42 months. The authors observed that the transplanted adipose tissue was gradually absorbed during the first 2 postoperative months, and the breast volume showed a minimal change thereafter. Final breast volume showed augmentation by 100 to 200 mL after a mean fat amount of 270 mL was injected. The difference in breast circumference (defined as the chest circumference at the nipple minus the chest circumference at the inframammary fold) had increased in all cases by 4 to 8 cm at 6 months. Cyst formation or microcalcification was detected in 4 patients. The authors concluded that their preliminary

results suggest that CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection but that additional study is necessary to further evaluate the efficacy of this technique.

- In 2007, Rigotti and colleagues reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for side effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage.<sup>[15]</sup> The rationale behind the study was that the ADSCs, which have been shown to secrete angiogenic and antiapoptotic factors and to differentiate into endothelial cells, could promote neovascularization in ischemic tissue such as irradiated tissue.

The number of procedures was 1 in five patients, 2 in eight, 3 in six, and 6 in one patient. Clinical follow-up varied between 18 and 33 months (mean 30 months). Clinical results after treatment with lipoaspirates were assessed by LENT-SOMA scoring, one of the most common systems to assess the late effects of radiation therapy. The 11 patients initially classified as LENT-SOMA grade 4 (irreversible functional damage) progressed to grade 0 (no symptoms), grade 1 and grade 2 in four, five and one cases, respectively. In one case, no improvements were observed. In the four patients who had undergone mastectomy and had breast prostheses and areas of skin necrosis, the necrosis showed complete remission. In the group of 9 patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and 1 in five and four cases, respectively.

As with the literature for autologous fat grafting without ADSC, valid and reliable conclusions cannot be reached from the studies described above.

### *Clinical Practice Guidelines*

- In 2012, the American Society of Plastic Surgeons (ASPS) published results of their non-peer reviewed systematic review of the current evidence.<sup>[16]</sup> The 2012 Post-Mastectomy Fat Graft/Fat Transfer ASPS Guiding Principles developed by the Patient Safety Committee, and is described by ASPS as an update and supplement to the 2009 Fat Transfer/Fat Graft and Fat Injection ASPS Guiding Principles. The ASPS concluded the following from their review:

“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 as an effective option in breast reconstruction following mastectomy while 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 main outcome of the review: “The safety, efficacy and final outcome of any given case is dependent on the technique used. Although there is no standardization for technique, detailed descriptions of fat graft harvest, preparation, storage and injection have been described in the literature. Overall, autologous fat grafting to the post mastectomy breast with no remaining native tissue yields aesthetic improvement and significant patient satisfaction.”

- In 2009, the American Society of Plastic Surgeons Fat Graft Task Force published results of their systematic review of the current evidence.<sup>[17]</sup> The task force concluded the following:

“Based on a review of the current literature and a lack of strong data, the task force cannot make specific recommendations for the clinical use of fat grafts. Although fat grafts may be considered for use in breast and other sites, the specific techniques of graft harvesting, preparation, and injection are not standardized...Although there are few data to provide evidence for long-term safety and efficacy of fat grafting, the reported complications suggest that there are associated risks.”

The task force further defined areas for future research, stating, “The current fat grafting literature is limited primarily to case studies, leaving a tremendous need for high-quality clinical studies.” Randomized controlled trials were recommended to assess safety and efficacy of fat grafting and specific fat grafting techniques. Further study was also recommended to assess the effect of fat grafting on breast cancer detection and treatment, identify risk factors and improve patient selection, and investigate cell/tissue viability and graft survival.

- The American Society of Plastic Surgeons report on autologous fat grafting did not address the use of ADSC.

## Summary

Fat grafting to the breast for reconstructive and aesthetic purposes has been gaining popularity over the past several years; however, the published literature is limited to case series data. A number of research questions remain unanswered, including: safety and efficacy, ideal grafting techniques, appropriate patient selection criteria, durability of treatment effects, graft survival, and influence on breast cancer detection and treatment. Because the impact on net health outcomes is unknown, fat grafting in augmentation or reconstruction of the breast is considered investigational.

The use of adipose-derived stem cells in conjunction with fat grafting to the breast represents a potential new advance in the field of regenerative medicine. Although there is a possible role that these stem cells could play in graft survival through both adipogenesis and angiogenesis, a complete understanding of the mechanisms of interactions among adipose stem cells and growth factors is lacking, as is the understanding of any possible role they may have in tumorigenesis. The mechanism of injected fat survival, the way to control adipose-derived stem cell differentiation and the fate of the stem cells also remains unknown. Therefore, the use of adipose-derived stem cells in conjunction with fat grafting is considered investigational.

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## CROSS REFERENCES

[Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

[Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants](#), Surgery, Policy No. 40

[Reduction Mammoplasty](#), Surgery, Policy No. 60

CODES	NUMBER	DESCRIPTION
There is no specific CPT code for this procedure. One of the following CPT codes might be used:		
CPT	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	19366	Breast reconstruction with other technique
	19499	Unlisted procedure, breast
HCPCS	None	