Policy Number	**SUR716.021**
Policy Effective Date	**04/01/2025**

Adipose-Derived Stem Cells in Autologous Fat Grafting to the Breast

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

The use of adipose-derived stem cells in autologous fat grafting to the breast **is considered experimental, investigational and/or unproven.**

Policy Guidelines

This policy does not address the use of autologous fat tissue in aesthetic breast augmentation (i.e., cosmesis).

Description

Fat Grafting to the Breast
Autologous fat grafting to the breast has been proposed for indications that include breast augmentation following oncologic surgery. Grafting would be performed as an adjunct to reconstruction after mastectomy or lumpectomy, and it would be of benefit in the following

areas: for contouring purposes, improving breast shape and volume; and for alleviating post-mastectomy pain syndrome (neuropathic pain), and irradiated skin (thereby reducing complication and failure rates of implant reconstruction). Variability in long-term results and oncologic concerns has limited application of autologous fat grafting in the breast.

Adipose-Derived Stem Cells (ADSCs)

Stem cell biology and the related field of regenerative medicine involve multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. A single gram of adipose tissue yields approximately 5000 stem cells; this is 100 to 500 times the number of mesenchymal stem cells in an equivalent amount of bone marrow. (1) Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. In particular, adipose tissue represents an abundant and easily accessible source of ADSCs, which can differentiate along multiple mesodermal lineages. ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site. (1, 2)

The potentially therapeutic properties of ADSC have led to novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting. Differentiation of ADSC into adipocytes may provide a reservoir for adipose tissue turnover. Differentiation of ADSC into endothelial cells, with the release of angiogenic growth factors by ADSC, may decrease the rate of graft resorption by increasing blood supply to the grafted fat tissue. Further, ADSC may serve to accelerate wound healing and protect the graft from ischemic reperfusion injury. (1) Current methods for isolating ADSCs can involve various processes, which may include centrifugation and enzymatic techniques that rely on collagenase digestion which, in turn, is followed by centrifugal separation to isolate the stem cells from primary adipocytes. Isolated ADSCs can be expanded in monolayer on standard tissue culture plastic with a basal medium containing 10% fetal bovine serum. (3) Newly developed culture conditions provide an environment in which the study of ADSCs can be done without the interference of animal serum and may also allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

To address the problems of unpredictability and low rates of fat graft survival, Yoshimura et al. (2008) developed a technique known as cell-assisted lipotransfer, which produces autogenous fat rich in ADSCs. (4) In cell-assisted lipotransfer, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs; meanwhile the other half is washed, enzymatically digested, filtered and spun down to an ADSC-rich pellet. The latter is then mixed with the former, converting a relatively ADSC-poor aspirated fat to ADSC-rich fat.

A point-of-care system is available for concentrating ADSC from mature fat. The Celution® System is designed to transfer a patient's adipose tissue from one part of the body to another in the same surgical procedure.

Regulatory Status

In September 2006, Celution® Cell Concentration System (Cytori Therapeutics; San Diego, CA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process as a cell saver device. The system is cleared for the collection, concentration, washing, and reinfusion of a patient's cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urologic surgeries and procedures. In 2007, Cytori Therapeutics received the FDA 510(k) clearance to market the Autologous Fat Transfer system, which transfers a patient's own adipose tissue from one part of the patient's body to another. FDA product code: CAC.

In 2017, the Revolve Envi 600 Advanced Adipose System (LifeCell Corporation, Branchburg, NJ) was cleared for marketing by the FDA through the 510(k) process. The system harvests, filters, and transfers autologous adipose tissue for fat grafting. Uses include reconstructive surgery. In May of 2020, the Revolve Envi 600 System underwent various design modifications (K163647). FDA product code: MUU.

This is not an "all inclusive" list of autologous fat grafting systems. Refer to the FDA web site at <https://www.fda.gov> for the most current listing of autologous fat grafting systems.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Adipose-Derived Stem Cell Enrichment of Autologous Fat Grafts
Clinical Context and Therapy Purpose

The purpose of autologous fat grafting with adipose-derived stem cell (ADSC) enrichment in individuals with breast cancer who have undergone reconstructive surgery is to improve graft survival.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with breast cancer who have undergone reconstructive surgery and have received autologous fat grafting.

Interventions
The therapy being considered is ADSC enrichment of autologous fat grafting to the breast. Growth factors within the ADSC may promote neovascularization thereby increasing blood supply to the grafted fat tissue, which would decrease the rate of graft resorption, accelerate wound healing, and protect the graft from reperfusion injury.

Comparators
The comparator of interest is autologous fat grafting to the breast without ADSC.

Outcomes
Absorption of the fat graft can be assessed after a few months. Long-term effects of the ADSC enhancement may not manifest for months to years following the procedure.

Due to the heterogeneity in outcome reporting in studies of autologous fat grafting to the breast, an international committee of experts in both breast and plastic surgery specialties used a Delphi consensus exercise to develop a core set of outcomes for determining safety and efficacy for this intervention. (5) Consensus was reached on 13 core outcomes within 6 domains:

- Oncologic outcomes: the rate of histologically confirmed locoregional cancer recurrence; the rate of distant cancer recurrence; and mortality rate.
- Clinical outcomes: complications; and donor site morbidity.
- Aesthetic and functional outcomes: surgeon assessment of volume, shape, symmetry, scarring, and improvements in skin quality; and ability to function and complete daily tasks (assessed by a validated instrument such as the EuroQol five-dimension scale [EQ-5D] or BREAST-Q).
- Patient-reported outcomes: patient satisfaction (preferably assessed by BREAST-Q); and impact on quality of life.
- Process outcomes: number of graft sessions needed to get optimal results; and readmission or unplanned surgery for any reason.
- Radiological outcomes: incidence of radiological abnormalities; and number of interferences with subsequent mammography scannings.

<u>Study Selection</u>

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The literature on the use of fat grafting to the breast with the use of ADSCs consists only of retrospective and small prospective cohort studies, case series, and case reports. The following is a summary of the key literature to date, of the studies using fat grafting to the breast and case series using fat grafting to the breast with the supportive use of ADSCs.

Rigotti et al. (2007) reported on the results of a pilot study assessing the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse events of radiotherapy to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (Late Effects Normal Tissues-Subjective, Objective, Management, Analytic [LENT-SOMA] scale grades 3 and 4). (6) Patients' mean age was 51 years (range, 37 to 71 years). 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 (e.g., irradiated tissue). Targeted areas included the supraclavicular region, the anterior chest wall after mastectomy (with or without breast prosthesis), and breast after quadrantectomy. A lipoaspirate purification procedure was performed by centrifugation to remove a large part of the triglyceride portion of the tissue and to disrupt the cytoplasm of the mature adipocytes to favor their rapid clearance after injection. A stromal-vascular fraction was isolated by enzymatic digestion of extracellular matrix, centrifugation, and filtration, and the fractions were cultured for two to three weeks to obtain a homogenous cell population. To assess the presence of mesenchymal stem cells, the stromal-vascular fraction derived from the adipose tissue was cultured and characterized by flow cytometry. The number of procedures was one in five patients, two in eight, three in six, and six in one. Clinical follow-up varied between 18 months and 33 months (mean, 30 months). Clinical results after treatment with lipoaspirates were assessed by the LENT-SOMA scale, which is a common system used to assess the late effects of radiotherapy. The 11 patients, who were 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 nine patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and grade 1 in five and four cases, respectively.

Yoshimura et al. (2008) reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection. (4)

From 2003 to 2007, the group performed CAL in 70 patients. Of these patients, CAL was performed in the breast for 60 patients (8 of whom had had breast reconstruction after mastectomy); for the remaining patients, CAL was performed in the face or hip. The authors reported outcomes for 40 patients with healthy thoraxes and breasts who underwent CAL for purely cosmetic breast augmentation; patients who were undergoing breast reconstruction for an inborn anomaly or following a 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 two 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 cm to 8 cm at six months. Cyst formation or microcalcification was detected in four patients. The authors concluded that their preliminary results suggested CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection, but that additional study was necessary to evaluate the efficacy of this technique further.

Pérez-Cano et al. (2012) 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-enriched fat grafting for reconstruction of defects 150 mL or less, a Clinical Evaluation Of Adipose Derived Regenerative Cells In The Treatment Of Patients With BrEast Deformities Post Segmental Breast ResecTion (Lumpectomy) With Or Without Radiation ThErapy (RESTORE-2 trial). (7) Trial endpoints included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months after procedure. Eligible female patients included women 18 to 75 years of age who presented with partial mastectomy defects and without breast prosthesis. The RESTORE-2 protocol allowed for up to 2 treatment sessions, and 24 patients elected to undergo a second procedure following the 6-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; 2 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 adipose-derived regenerative cell-enriched fat graft injection procedure. There were no reported local cancer recurrences. The investigators found the LENT-SOMA scale insufficiently sensitive to reflect the clinical improvements seen in the trial population adequately. Patients with LENT-SOMA grade 3 and 4 scores (most severe symptoms) were excluded during screening (note: this 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 of 67 patients, while 34 patients had no change and 4 patients reported worse symptoms. Postradiation 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 was statistically significant. The authors concluded that future comparative studies are needed to determine

the incremental benefit of adipose-derived regenerative cell-enriched fat grafting compared with traditional fat grafting in various clinical circumstances. The follow-up of the study is inadequate to conclude the long-term risk of cancer recurrence.

Jeon et al. (2020) evaluated the efficacy of CAL on the fat graft retention rate in patients with volume deficit after undergoing autologous breast reconstruction following total mastectomy. (8) This 12-month prospective study included 20 patients (20 breasts) between 2017 and 2019. Patients were divided into 2 groups: autologous fat graft without stromal-vascular fraction (i.e., without ADSC) or autologous fat graft with stromal-vascular fraction of ADSC. The retention rate of the fat graft was higher in the group with ADSC than in the group without at both postoperative 6 months (73.8% vs 62.2%; p=.03) and 12 months (65.4% vs 48.4%; p=.03). Based on a modified BREAST-Q questionnaire at 12 months, the group who received fat graft with ADSC reported higher patient satisfaction (49.4 points out of 55 compared to 44.2 points out of 55), although this was not statistically significant. Fat necrosis occurred in 1 patient each in both groups, however, locoregional recurrence was not observed in any patient during follow-up. The authors concluded that CAL with stromal-vascular fraction provided better outcomes in terms of volume retention compared to CAL without ADSC.

Section Summary: Autologous Fat Grafting to the Breast with ADSC Enrichment
Evidence for the use of autologous fat grafting to the breast with ADSC enrichment consists of cohort studies, case series, case reports. The studies were heterogeneous in the patient selection, methods in harvesting stem cells, number of procedures, and outcomes measured. One small, prospective study (N=20 patients) found that the use of ADSC enrichment with autologous fat grafting over autologous fat grafting alone improved the retention rate of the fat graft postoperatively at 6- and 12-months. Larger clinical trials are needed to confirm this benefit.

Summary of Evidence
For individuals who have breast cancer who receive autologous fat grafting to the breast with adipose-derived stem cell (ADSC) enrichment of the graft, the evidence includes small single-arm studies, some of which are prospective. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, resource utilization and treatment-related morbidity. The observational studies were heterogeneous in the patient selection, methods in harvesting stem cells, number of procedures, and outcomes measured. Studies have mainly reported patient and investigator satisfaction and functional and cosmetic results. One small, prospective study found that the use of ADSC enrichment with autologous fat grafting over autologous fat grafting alone improved the retention rate of the fat graft postoperatively at 6 and 12 months. Larger clinical trials are needed to confirm this benefit. Limitations of the data include sample sizes, short-term follow-up, and uncertainty about the possible oncologic influence ADSC may have on the fat grafting procedure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
American Society for Aesthetic Plastic Surgery and American Society of Plastic Surgeons

In 2011, the American Society for Aesthetic Plastic Surgery and the American Society of Plastic Surgeons released a joint position statement on the use of stem cells in aesthetic surgery. (9) Based on a systematic review of the peer-reviewed literature, the Societies concluded that while there is potential for the future use of stem cells in aesthetic surgical procedures, the scientific evidence and other data are very limited in terms of assessing the safety or efficacy of stem cell therapies in aesthetic medicine.

Ongoing and Unpublished Clinical Trials

No relevant ongoing clinical trials were identified as of November 2023.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	15769, 15771, 15772, 19380, 19499
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/01/2025	Reviewed. No changes.
09/15/2024	Document updated with literature review. Coverage unchanged. No new references added.
01/01/2024	Reviewed. No changes.
05/15/2022	Document updated with literature review. Coverage unchanged. Added/updated the following references: 8-9.
08/01/2021	Reviewed. No changes.
11/15/2020	Document updated with literature review. Coverage unchanged. No new references added.
08/15/2019	Document updated with literature review. Coverage unchanged. Reference 5 added.
06/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. Coverage unchanged. The following information was added: Refer to Medical Policy – Reconstruction and Contralateral Mammaplasty (SUR716.011) for coverage explanation of harvesting and grafting autologous fat tissue when used during breast reconstruction.
11/01/2016	Reviewed. No changes.

05/01/2016	New medical document. The use of adipose-derived stem cells in autologous fat grafting to the breast is considered experimental, investigational and/or unproven.