



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

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

Policy # 00493

Original Effective Date: 02/17/2016

Current Effective Date: 02/17/2016

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of adipose-derived stem cells in autologous fat grafting to the breast to be **investigational**.\*

### Background/Overview

#### **Autologous Fat Grafting to the Breast**

Autologous fat grafting to the breast has been proposed for indications that include breast augmentation and following oncologic surgery. Proposed indications after oncologic surgery include as an adjunct to reconstruction post mastectomy or lumpectomy for contour deformities and improved shape and volume of the breast, for post mastectomy pain syndrome (neuropathic pain), and for irradiated skin to soften the skin and restore it to nonirradiated appearance and consistency which may reduce complication and failure rates of implant reconstruction. Variability in long-term results and oncologic concerns have limited its application in the breast.

Note: This evidence review does not address the use of autologous fat tissue in aesthetic breast augmentation (ie, cosmesis).

#### **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. 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. 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.

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Current methods for isolating ADSCs can involve various processes, which may include centrifugation and enzymatic techniques that rely on collagenase digestion 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, and newly developed culture conditions provide an environment within which the study of ADSCs can be done without the interference of animal serum. They also allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

Yoshimura et al, in an effort to address the problems of unpredictability and low rates of fat graft survival, developed a technique known as cell-assisted lipotransfer (CAL), which produces autogenous fat rich in ADSCs. In CAL, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs, while 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 (Cytori Therapeutics) is designed to transfer a patient's own adipose tissue from 1 part of the body to another in the same surgical procedure.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In September 2006, Celution Cell Concentration System (Cytori Therapeutics) was cleared for marketing by the U.S. Food and Drug Administration's (FDA) Center for Devices and Radiological Health 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 own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urologic surgeries and procedures. FDA product code: CAC.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

This evidence review was created with the most recent literature search performed through September 13, 2015.

The literature on the use of fat grafting to the breast with the use of adipose-derived stem cells (ADSCs) consists of retrospective cohort studies, case series, and case reports. Following is a summary of the key literature to date, including systematic reviews of the studies using fat grafting to the breast and all identified case series using fat grafting to the breast with the supportive use of ADSCs.

Several review articles summarize autologous fat grafting and ADSCs.



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Pérez-Cano et al 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 150 mL or less (the RESTORE-2 trial). Trial end points included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months after procedure. Female patients (age range, 18-75 years) presenting with partial mastectomy defects and without breast prosthesis were eligible. 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 radiotherapy 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 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 postradiation signs and symptoms. (LENT-SOMA is one of the most common systems to assess the late effects of radiotherapy.) The investigators found the LENT-SOMA insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA grade 3 and 4 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 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 ADRC-enriched fat grafting compared with traditional fat grafting in various clinical circumstances. The follow-up of the study was inadequate to draw conclusions on long-term risk of cancer recurrence.

In 2008, Yoshimura et al reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection. From 2003 to 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 suggested CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection, but that additional study was necessary to further evaluate the efficacy of this technique.

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In 2007, Rigotti et al reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (LENT-SOMA scale grades 3 and 4). Mean patient age was 51 years (range, 37-71 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 such as 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 2 to 3 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 1 in 5 patients, 2 in 8, 3 in 6, and 6 in 1 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. 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 4, 5 and 1 cases, respectively. In 1 case, no improvements were observed. In the 4 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 5 and 4 cases, respectively.

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

### Summary of Evidence

The evidence for the use of ADSCs in patients who have breast cancer and are undergoing autologous fat grafting to the breast includes small single-arm studies, some of which are prospective. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease severity, morbid events, functional outcomes, quality of life, resource utilization, and treatment-related morbidity. Studies have mainly reported patient and investigator satisfaction and functional and cosmetic results. Limitations of the data are small numbers of patients, short-term follow-up, and lack of understanding of the possible oncologic influence ADSC may have on the fat grafting procedure. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

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### Policy History

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02/04/2016 Medical Policy Committee review

02/17/2016 Medical Policy Implementation Committee approval. New Policy.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 02/2017

### Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Code Type	Code
CPT	19366, 19499, 20926
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

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