Composite tissue allotransplantation of the hand and/or face is considered investigational.

There are no specific CPT codes for this procedure; however, should the procedure receive a code, it is likely that a combination of existing codes or the unlisted code for the anatomic area would be used:
- **26989**: Unlisted procedure, hands or fingers

Composite tissue allotransplantation is offered at specialized centers. Locations offering this procedure include:
- Brigham and Women’s Hospital
- Cleveland Clinic
- Duke University
- Jewish Hospital Hand Care Center (in partnership with Kleinert Kutz & Associates and the University of Louisville), Louisville, Kentucky
- Johns Hopkins School of Medicine
- MD Anderson Cancer Center’s Department of Plastic Surgery
- University Medical Center at the University of Arizona
- University of California at Los Angeles (UCLA)
- University of Pittsburgh McGowan Institute for Regenerative Medicine

Composite tissue allotransplantation (also referred to as vascularized composite allotransplantation) is defined as transplantation of histologically different tissues. This type of transplantation is being proposed for facial transplants in patients with severely disfigured faces, and for hand transplants in patients dissatisfied with prosthetic hands. The treatment has potential benefits in terms of improving functional status and psychosocial well-being. It also has potential risks, most notably those associated with a lifelong regimen of immunosuppressive drugs.

Related Policies
- N/A

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Hand and face allotransplantations are surgical procedures and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

Rationale

Background

Composite Tissue Allotransplantation

Composite tissue allotransplantation refers to the transplantation of histologically different tissue that may include skin, connective tissue, blood vessels, muscle, bone, and nerve tissue. The procedure is also known as reconstructive transplantation. To date, primary applications of this type of transplantation have been of the hand and face (partial and full), although there are also reported cases of several other composite tissue allotransplantations, including that of the larynx, knee, and abdominal wall.

The first successful partial face transplant was performed in France in 2005, and the first complete facial transplant was performed in Spain in 2010. In the United States, the first facial transplant was done in 2008 at the Cleveland Clinic; this was a near-total face transplant and included the midface, nose, and bone. The first hand transplant with short-term success occurred in 1998 in France. However, the patient failed to follow the immunosuppressive regimen, which led to graft failure and removal of the hand 29 months after transplantation. The first hand transplantation in the United States took place in Louisville, Kentucky, in 1999.

Hand and face transplants have been shown to be technically feasible. The most commonly performed face transplant procedure has been to restore the lower two-thirds of facial structure, especially the perioral area (i.e., lips, cheeks, chin) and in some cases the forehead, eyelids, and scalp. Facial transplantation has been performed on patients whose faces have been disfigured by trauma, burns, disease, or birth defects and who are unable to benefit from traditional surgical reconstruction. Hand transplantations have been done in patients who lost a hand due to trauma or life-saving interventions that caused permanent injury to the hand. To date, hand transplants have not been performed for congenital anomalies or loss of a limb due to cancer.

Composite tissue allotransplantation procedures are complex and involve a series of operations using a rotating team of specialists. For face transplantation, the surgery may last 8 to 15 hours. Hand transplant surgery typically lasts between 8 and 12 hours. Bone fixation occurs first, and this is generally followed by artery and venous repair and then by suture of nerves and/or tendons. In all surgeries performed to date, the median and ulnar nerves were repaired. The radial nerve was reconstructed in about half of the procedures.

Unlike most solid organ transplantations (e.g., kidney and heart transplants), composite tissue allotransplantation is not life-saving, and its primary aim rests mainly in a patient’s cosmetic satisfaction and quality of life. In the case of facial transplantations in particular, there is immense potential for the psychosocial benefits when a surgery is successful. Moreover, the goal of composite tissue transplantation is to improve function (e.g., grasping and lifting after hand transplants, blinking and mouth closure after face transplants) without alternative interventions such as prosthetics. Additionally, in the case of face transplantation, the procedure may be less traumatic than “traditional” facial reconstructive surgery using the patient’s own tissue. For example, traditional procedures often involve dozens of operations, whereas facial transplantation only involves a few operations.

Adverse Events

Composite tissue allotransplantation is associated with potential risks and benefits, and patients who undergo face or hand transplantation must adhere to a lifelong regimen of immunosuppressive drugs. Risks of immunosuppression include acute and chronic rejection,
opportunistic infection that may be life-threatening, and metabolic disorders such as diabetes, kidney damage, and lymphoma. Other challenges include the need to participate actively in intensive physical therapy to restore functionality and the potential for frustration and disappointment if functional improvement does not meet expectations. Moreover, there is the potential for allograft loss, which would lead to additional procedures in hand transplant patients, and there are limited reconstructive options for facial transplantation. Furthermore, in the case of hand transplants, there is a risk that functional ability (e.g., grasping and lifting objects) may be lower than that with a prosthetic hand, especially compared with newer electronic prosthetic devices. Due to the importance of selecting candidates who can withstand these physical and mental challenges, potential hand and face transplant recipients undergo extensive screening for both medical and psychosocial suitability.

**Literature Review**

**Face Allotransplantation**

As of December 2015, a total of 37 face allotransplantation operations have been conducted, 20 partial face and 17 full face. A systematic analysis of outcomes was published in 2014 by Smeets et al. Reviewers included English-language articles, published through September 2013, that provided data on at least 1 face transplant in humans. Thirty-six articles reported on 27 worldwide face transplantsations. University Hospital Henri Mondor in Creteil, France, and Brigham and Women’s Hospital in Boston, Massachusetts, were the centers with the most experience. Of the 27 cases, 10 were full face transplants (the first successful full face transplant was in 2010) and the remainder were partial face transplants. The literature does not report any case of graft loss, hyperacute (within the first 48 hours) or chronic rejection, or graft-versus-host disease. However, all transplant recipients who were at least 1-year postsurgical follow-up reported experiencing at least 1 episode of acute rejection after the procedure. Other common complications were related to drug toxicity from immunosuppressive therapy, leading to opportunistic infections, metabolic disorders, and increased incidence of malignancy. There have been 3 reported cases of malignancy to date. Three deaths occurred in transplant recipients. One patient died 27 months after surgery due to lack of compliance with immunosuppressive therapy. A second death occurred in a French recipient who had multidrug-resistant infection and graft necrosis (an early transplant in France). The third patient died of recurrent cancer.

In terms of function, tactile sensitivity recovered at a mean of 4.1 months postsurgery when nerve repair was performed or at a mean of 7.3 months otherwise. Temperature sensitivity recovered at a mean of 4.3 months with nerve repair and at 12.5 months without nerve repair. Motor recovery began at a mean of 7.8 months after surgery. Trialists indicated that recovery of motor function started with contractions of single muscles, and complex movements appeared within the first year in a number of patients. Long-term results are still pending in most cases. After 5 years of follow-up, the first face transplant recipient was able to fully open her mouth, smile, speak, chew, and swallow.

Also in 2015, Fischer et al identified 29 face transplants performed through December 2013 and reported functional outcomes in 5 patients treated at their center. The investigators compared each patient’s pre- and postsurgical functioning on various dimensions. Before surgery, all 5 patients had compromised respiration, breathing, sensation, and facial expression. After surgery, they had substantial recovery in all of these areas. In terms of breathing, the 5 patients were able to breathe through their noses postsurgery, and the 2 patients with tracheostomy tubes had them removed. Speech became understandable to an unfamiliar listener 3 to 9 months after surgery and that at time most allografts were responsive to light touch, and patients could distinguish between heat and cold. Facial expression, including the ability to smile, recovered after transplantation in all patients. Three of 5 patients were unable to chew solid food before surgery; and 2 patients had liquid leakage. All patients were capable of oral food intake 3 to 29 days after surgery, and 3 to 12 months after surgery, all had unrestricted or nearly unrestricted eating and drinking. The 2 patients with compromised ability to smell both reported a substantial
improvement in smelling, comparable with their functioning before facial trauma. All 5 patients
developed opportunistic infections (viral or bacterial) after facial transplantation.

Section Summary: Face Allotransplantation
Thirty-seven face transplants had been conducted worldwide as of December 2015 and data
are reported in several case series. The available studies on composite tissue allotransplantation
of the face have suggested that the surgery is technically feasible. To date, however, given the
limited number of patients worldwide who have undergone the procedure, there is not sufficient
evidence to determine whether the potential benefits to patients outweigh the potential risks
(e.g., of surgical complications, immunosuppression, opportunistic infections).

Hand and Upper-Extremity Allotransplantation
The most comprehensive reporting of the worldwide experience with hand and upper-limb
transplants was published by Shores et al in 2015. They identified 72 patients: 35 received
bilateral transplants and 37 unilateral, for a total of 107 transplanted hand/upper extremities.
There are four known mortalities: one occurred after a bilateral hand transplant; the other three
followed multitype composite tissue allotransplantations (CTAs; i.e., combined upper- and lower-
limb or combined upper-limb and face transplants). Twenty-four graft losses have been
reported; eight of these were also associated with multiple composite tissue allotransplantation
procedures and another seven occurred in China during early efforts with hand transplantation.
In the United States, 21 known patients have undergone isolated upper-limb transplantation; 13
were unilateral and 8 were bilateral (limb or digit) procedures. There was 1 immediate graft loss
of the bilateral transplanted limb/digit. An additional 3 patients experienced hand loss at 9
months, 2 years, and 4 years posttransplant, respectively. Few data on functional outcomes after
hand transplantation have been reported. The authors noted that there is a lack of agreement
on appropriate outcome measures, and the level of transplantation varies greatly among
patients, making it difficult to compare functional improvement.

An article describing data from the International Registry on Hand and Composite Tissue
Allotransplantation was published in 2011. At the time data were extracted, hand transplants
had been reported to the registry for 39 patients. The authors stated that 85% of transplant
recipients experienced at least 1 episode of acute rejection in the first year after transplant.
Acute rejection episodes were reversible in all patients compliant with treatment. The most
commonly reported complications were metabolic complications (35/39 [90%]) and
opportunistic infections (30/39 [77%]). Transient hyperglycemia occurred in 17 (44%) patients and
cytomegalovirus reactivation in 10 (26%) patients. Ten patients required surgery for
complications (2 arterial thromboses, 1 venous thrombosis, 6 small area of skin necrosis, 1 venous
fistula). Five cases of graft loss were reported between day 5 and day 275 after transplant. The
early (day 5) graft loss occurred in a patient who underwent face and bilateral hand transplant,
and this patient died at day 65 from cerebral anoxia. This was the only reported death in this
series of patients. Specific hand function data (e.g., mean function scores) were not reported.

One study identified had compared health outcomes in patients undergoing hand
transplantation with those receiving hand/upper-limb prostheses. The study, published in 2016 by
Salminger et al, compared outcomes for 5 patients who had below-elbow hand transplantation
with 7 patients who had prosthetic hands. There were 3 unilateral and 2 bilateral hand
transplants, for a total of 7 transplanted hands. The prosthetic patients received myoelectric
prostheses that were controlled by simple direct control. Functional assessments were
undertaken a mean of 9.0 years (standard deviation [SD], 3.9 years) after transplantation. The
following standardized instruments were used to evaluate function: the Action Research Arm
Test, the Southampton Hand Assessment Procedure (SHAP), and the Disabilities of the Arm,
Shoulder and Hand (DASH) measures. In addition, quality of life was assessed using the 36-Item
Short-Form Health Survey (SF-36). There were no statistically significant differences between
groups in functional scores on the standardized measures. For example, the mean SHAP score
was 75.0 in the transplanted group and 75.4 in the prosthetic group. For the quality of life scores,
transplant patients had significantly higher scores on the SF-36 role-emotional and mental health
subscales and there were no significant differences on the SF-36 physical functioning, bodily pain, general health, or social functioning subscales. The authors did not report total SF-36 scores.

Section Summary: Hand and Upper-Extremity Allotransplantation
A total of 107 hand and upper-extremity transplants had been conducted worldwide as of 2015 and data are reported in a number of case series. The available studies on composite tissue allotransplantation of the hand have suggested that the surgery is technically feasible. A single study (N=12) has compared outcomes for patients who had hand transplants with those receiving prostheses. It found no statistically significant differences in functional outcomes between groups, and no differences in 4 of 7 SF-36 subscales. Given the limited number of patients worldwide have undergone the procedure and the limited amount of data comparing outcomes with the best available prosthetics, the evidence is insufficient to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections).

Summary of Evidence
For individual who have a severely disfigured face (e.g., burns, trauma) who receive composite tissue allotransplantation, the evidence includes a small case series and several systematic reviews of case series. Relevant outcomes are functional outcomes, quality of life, resource utilization, and treatment-related mortality and morbidity. The available studies on composite tissue allotransplantation of the face have suggested that the surgery is technically feasible; however, to date, only a limited number of patients worldwide have undergone the procedure, and the data are not sufficient to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individual who have hand and upper-extremity amputation(s) who receive composite tissue allotransplantation, the evidence includes a small case series, several systematic reviews of case series, and a nonrandomized comparative study. Relevant outcomes are functional outcomes, quality of life, resource utilization, and treatment-related mortality and morbidity. The available studies on composite tissue allotransplantation of the hand have suggested that the surgery is technically feasible. The only study comparing outcomes in patients who had hand transplants with those who received prostheses included 12 patients. It found no differences between groups in functional outcomes and little difference in quality of life. Given the limited number of patients worldwide have undergone the procedure and the limited amount of data comparing outcomes with the best available prosthetics, evidence is insufficient to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections). The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American Society for Surgery of the Hand
In 2013, the American Society for Surgery of the Hand published a position statement on hand transplantation. The Society recognized that hand transplantation is an alternative to prostheses and rehabilitation in appropriately selected patients, yet the guidelines still considered hand transplantation an “innovative intervention.” The statement emphasized the need for further advances in the areas of patient selection, surgical technique, and immunosuppression and recommended that, at this time, the procedure be carried out only in centers with extensive experience in both hand surgery and solid organ transplantation.
National Institute for Health and Care Excellence
In 2011, the National Institute for Health and Care Excellence published guidance on hand allotransplantation. The guidance stated that the quantity of current evidence on the efficacy and safety of hand allotransplantation is inadequate.

American Society for Reconstructive Microsurgery and American Society of Plastic Surgeons
In 2006, the American Society for Reconstructive Microsurgery and the American Society of Plastic Surgeons published guiding principles on facial transplantation for plastic surgeons. Selected principles follow:

1. Facial transplantation should only be utilized for patients with severe facial deformities who cannot be helped through traditional reconstructive surgical measures.
2. Facial transplantation should only be undertaken in institutions with appropriate Institutional Review Boards familiar with the many intricacies for approval and application of new clinical procedures and protocols.
3. Facial transplantation should be conducted in the context of a transplant team having appropriate institutional resources and commitment to the project....
4. Appropriate patient selection criteria should be established and a complete risk/benefit ratio must be considered for each patient on a case-by-case basis.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>Face Transplantation for Treatment of Severe Facial Deformity</td>
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<td>NCT01281267</td>
<td>Human Upper Extremity (hand and forearm) Allotransplantation</td>
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<td>NCT01459107</td>
<td>Human Upper Extremity Allotransplantation</td>
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<td>Jun 2026</td>
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NCT: National Clinical Trial.

References

**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>Unlisted procedure, hands or fingers</td>
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<tr>
<td>HCPCS</td>
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<tr>
<td>ICD-10 Procedure</td>
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<td>Transplantation of Face, Allogeneic, Open Approach</td>
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<td>0XYJ0Z0</td>
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<td>0XYK0Z0</td>
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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<td>05/29/2015</td>
<td>BC BSA Medical Policy adoption</td>
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<td>05/01/2016</td>
<td>Policy revision without position change</td>
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<tr>
<td>10/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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</table>

**Definitions of Decision Determinations**

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.
Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.