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

There are no specific CPT codes for this procedure; 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.

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 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.

Hand and face transplants have been shown to be technically feasible. 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 U.S., the first facial transplant was done in 2008; it 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 U.S. took place in 1999.

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 the 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, there is immense potential for the psychosocial benefits when 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, an 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 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**
Evidence reviews 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 (QOL), 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 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.

**Face Allotransplantation**

**Clinical Context and Therapy Purpose**
The purpose of composite tissue allotransplantation in patients who have a severely disfigured face due to burns or trauma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does composite tissue allotransplantation improve the net health outcome in those with a severely disfigured face due to burns or trauma?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals who have a severely disfigured face due to burns or trauma.

**Interventions**
The therapy being considered is composite tissue allotransplantation. Composite tissue allotransplantation is administered at a specialized surgical center with experts qualified to perform the procedure and postsurgical follow-up.

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.

**Comparators**
The following practice is currently being used to make decisions about grafting a face after burns or trauma: standard care without facial allotransplantation. Comparator is performed by a physician in a hospital or outpatient setting.
Outcomes
The general outcomes of interest are functional improvement, graft failure, QOL (e.g., psychosocial well-being), and treatment-related adverse events (e.g., surgical complications, immunosuppression, infections).

Due to the complex nature of this lengthy surgical procedure, immediate postsurgical follow-up is needed, and lifelong follow-up will be necessary due to the immunosuppressive drugs required to prevent graft failure.

Systematic Reviews
As of December 2015, 37 face allotransplantation operations had been conducted, 20 partial faces and 17 full faces. A systematic analysis of outcomes was published by Smeets et al (2014). 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 transplantations. 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 one-year postsurgical follow-up reported experiencing at least one 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 three 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 a multidrug-resistant infection and graft necrosis (an early transplant). 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 five years of follow-up, the first face transplant recipient was able to fully open her mouth, smile, speak, chew, and swallow.

Case Series
Also, Fischer et al (2015) 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 five patients had compromised respiration, breathing, sensation, and facial expression. After surgery, patients had substantial recovery in all of these areas. In terms of breathing, all were able to breathe through their noses postsurgery, and two with tracheostomy tubes had them removed. Speech became understandable to an unfamiliar listener three to nine months after surgery and at that time most allografts were responsive to light touch, and patients could distinguish between heat and cold. Facial expressions, including the ability to smile, recovered after transplantation in all patients. Three of five patients were unable to chew solid food before surgery, and two 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 two patients with compromised ability to smell both reported a substantial improvement in smelling, comparable with their functioning before the facial trauma. All five 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 have been 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, the evidence is not sufficiently robust 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
Clinical Context and Therapy Purpose
The purpose of composite tissue allotransplantation in patients who have had a hand or upper-extremity amputation is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does composite tissue allotransplantation improve the net health outcome in those who have lost a hand or arm due to amputation?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals who have had a hand or upper-extremity amputation.

Interventions
The therapy being considered is composite tissue allotransplantation. Composite tissue allotransplantation is administered at a specialized surgical center with experts qualified to perform the procedure and postsurgical follow-up.

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.

Comparators
The following practice is currently being used to make decisions about grafting a hand or arm after amputation: standard care without hand and upper-extremity allotransplantation. Comparator is performed by a physician in a hospital or outpatient setting.

Outcomes
The general outcomes of interest are functional improvement, graft failure, QOL (e.g., psychosocial well-being), and treatment-related adverse events (e.g., surgical complications, immunosuppression, infections).

Due to the complex nature of this lengthy surgical procedure, immediate postsurgical follow-up is needed, and lifelong follow-up will be necessary due to the immunosuppressive drugs required to prevent graft failure.

Case Series
The most comprehensive reporting of the worldwide experience with hand and upper-limb transplants was published by Shores et al (2015). They identified 72 patients who received a total of 107 transplanted hand/upper extremities (35 received bilateral transplants, 37 unilateral). There are four known mortalities: one occurred after a bilateral hand transplant; the others followed multitype composite tissue allotransplantations (i.e., combined upper- and lower-limb or combined upper-limb and face transplants). Twenty-four graft losses have been reported; eight of them were also associated with multiple composite tissue allotransplantation procedures and another seven occurred in China during early efforts with hand transplantation. In the U.S., 21
known patients have undergone isolated upper-limb transplantation; 13 were unilateral and 8 were bilateral (limb or digit) procedures. There was one immediate graft loss of the bilateral transplanted limb/digit. An additional three patients experienced hand loss at nine months, two years, and four 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 by Pertuzzo and Dubemard (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 (two arterial thromboses, one venous thrombosis, six small areas of skin necrosis, one 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 a 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. This study, by Salminger et al (2016), compared outcomes for 5 patients who had below-elbow hand transplantation with 7 patients who had prosthetic hands. There were three unilateral and two bilateral hand transplants, for a total of seven transplanted hands. The prosthetic patients received myoelectric prostheses controlled by simple direct control. Functional assessments were undertaken a mean of nine years (standard deviation, 3.9 years) after transplantation. The following standardized instruments were used to evaluate function: the Action Research Arm Test, the Southampton Hand Assessment Procedure, and the Disabilities of the Arm, Shoulder and Hand measures. In addition, QOL 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 Southampton Hand Assessment Procedure score was 75.0 in the transplanted group and 75.4 in the prosthetic group. For the QOL scores, transplant patients had significantly higher scores on the SF-36 role-emotional and mental health subscales and there were no significant differences in 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 who have undergone the procedure and the limited amount of data comparing outcomes with the best available prosthetics, the evidence is not sufficiently robust to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections).

**Summary of Evidence**

For individuals who have a severely disfigured face due to burns or trauma who receive composite tissue allotransplantation, the evidence includes a small case series and several systematic reviews of case series. The relevant outcomes are functional outcomes, QOL.
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 sufficiently robust 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 individuals 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. The relevant outcomes are functional outcomes, QOL, 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 the QOL. Given the limited number of patients worldwide who have undergone the procedure and the limited amount of data comparing outcomes with the best available prosthetics, the evidence is not sufficiently robust 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
The American Society for Surgery of the Hand (2013) 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
The National Institute for Health and Care Excellence (2011) published guidance on hand allotransplantation. The guidance stated that the quantity of current evidence on the efficacy and safety of hand allotransplantation was inadequate.

American Society for Reconstructive Microsurgery and American Society of Plastic Surgeons
The American Society for Reconstructive Microsurgery and the American Society of Plastic Surgeons (2006) 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 ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<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>NCT01459107</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 codes 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>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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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 be directed to the Prior Authorization Department. Please call (800) 541-6652 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.