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| 7.03.13 Composite Tissue Allotransplantation of the Hand and Face | |
| Original Policy Date: May 29, 2015 | Effective Date: October 1, 2023 |
| Section: 7.0 Surgery | Page: Page 1 of 10 |

Policy Statement

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

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Currently, there are no specific CPT codes for this procedure; however, should these procedures receive codes, it is likely that a combination of existing codes or the unlisted code for the anatomic area would be used (e.g., 26989 unlisted procedure, hands or fingers).

Description

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 Application

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.

An independent member of the Blue Shield Association

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 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. A review of 115 facial or upper extremity transplants found an overall acute rejection rate of 89% with 11% of recipients with chronic rejection.¹ 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, 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Face Allotransplantation

Clinical Context and Therapy Purpose

The purpose of composite tissue allotransplantation in individuals 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 following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is composite tissue allotransplantation.

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.² 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 therapy is currently being used to treat a face after burns or trauma: standard care without facial allotransplantation.

Outcomes

The general outcomes of interest are functional improvement, graft failure, quality of life (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.

Study Selection Criteria

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 events, 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

Systematic Reviews

As of August 2020, 47 face allotransplantation operations had been conducted.³ A systematic analysis of outcomes was published by Smeets et al (2014).⁴ 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 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 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 post surgery 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.

Case Series

Fischer et al (2015) identified 29 face transplants performed through December 2013 and reported functional outcomes in 5 patients treated at their center.⁵ 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, patients had substantial recovery in all of these areas. In terms of breathing, all were able to breathe through their noses postsurgery, and 2 with tracheostomy tubes had them removed. Speech became understandable to an unfamiliar listener 3 to 9 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 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 the facial trauma. All 5 patients developed opportunistic infections (viral or bacterial) after facial transplantation.

Section Summary: Face Allotransplantation

The available case series 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 individuals 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 following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is composite tissue allotransplantation.

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 therapy is currently being used to treat a hand or arm after amputation: standard care without hand and upper-extremity allotransplantation.

Outcomes

The general outcomes of interest are functional improvement, graft failure, quality of life (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.

Study Selection Criteria

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 events, 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

Case Series

The most comprehensive reporting of the worldwide experience with hand and upper-limb transplants was published by Shores et al (2015).⁶ They identified 72 patients who received a total of 107 transplanted hand/upper extremities (35 received bilateral transplants, 37 unilateral). There are 4 known mortalities: 1 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; 8 of them were also associated with multiple composite tissue allotransplantation procedures and another 7 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 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 by Pertuzzo and Dubernard (2011).⁷ 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 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.⁸ There were 3 unilateral and 2 bilateral hand transplants, for a total of 7 transplanted hands. The prosthetic patients received myoelectric prostheses controlled by simple direct control. Functional assessments were undertaken a mean of 9 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, 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 Southampton Hand Assessment Procedure 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 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).

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2011, the National Institute for Health and Care Excellence published guidance on hand allotransplantation.⁹ The guidance stated that the quantity of current evidence on the efficacy and safety of hand allotransplantation was inadequate.

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

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|----------------|---|--------------------|-----------------|
| <i>Ongoing</i> | | | |
| NCT01459107 | Human Upper Extremity Allotransplantation | 30 | Jun 2026 |
| NCT05699187 | Face Transplantation | 4 | Dec 2030 |

NCT: national clinical trial.

References

1. Milek D, Reed LT, Echternacht SR, et al. A Systematic Review of the Reported Complications Related to Facial and Upper Extremity Vascularized Composite Allotransplantation. *J Surg Res.* Jan 2023; 281: 164-175. PMID 36162189
2. Infante-Cossio P, Barrera-Pulido F, Gomez-Cia T, et al. Facial transplantation: a concise update. *Med Oral Patol Oral Cir Bucal.* Mar 01 2013; 18(2): e263-71. PMID 23229268

3. Alberti FB, Hoyle V. Face Transplants: An International History. J Hist Med Allied Sci. Sep 06 2021; 76(3): 319-345. PMID 34179990
4. Smeets R, Rendenbach C, Birkelbach M, et al. Face transplantation: on the verge of becoming clinical routine?. Biomed Res Int. 2014; 2014: 907272. PMID 25009821
5. Fischer S, Kueckelhaus M, Pauzenberger R, et al. Functional outcomes of face transplantation. Am J Transplant. Jan 2015; 15(1): 220-33. PMID 25359281
6. Shores JT, Brandacher G, Lee WPA. Hand and upper extremity transplantation: an update of outcomes in the worldwide experience. Plast Reconstr Surg. Feb 2015; 135(2): 351e-360e. PMID 25401735
7. Petruzzo P, Dubernard JM. The International Registry on Hand and Composite Tissue allotransplantation. Clin Transpl. 2011: 247-53. PMID 22755418
8. Salminger S, Sturma A, Roche AD, et al. Functional and Psychosocial Outcomes of Hand Transplantation Compared with Prosthetic Fitting in Below-Elbow Amputees: A Multicenter Cohort Study. PLoS One. 2016; 11(9): e0162507. PMID 27589057
9. National Institute for Health and Care Excellence (NICE). Hand allotransplantation [IPG383]. 2011; <https://www.nice.org.uk/guidance/ipg383>. Accessed June 12, 2023.

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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|------------------|-------|--------------------------------------|
| CPT [®] | 26989 | Unlisted procedure, hands or fingers |
| HCPCS | None | |

Policy History

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

| Effective Date | Action |
|----------------|--|
| 05/29/2015 | BCBSA Medical Policy adoption |
| 05/01/2016 | Policy revision without position change |
| 10/01/2017 | Policy revision without position change |
| 10/01/2018 | Policy revision without position change |
| 11/01/2019 | Policy revision without position change |
| 10/01/2023 | Policy reactivated. Previously archived from 08/01/2020 to 09/30/2023. |

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

| POLICY STATEMENT | |
|--|---|
| BEFORE | AFTER <i>Blue font: Verbiage Changes/Additions</i> |
| Reactivated Policy Policy Statement: N/A | <i>Composite Tissue Allotransplantation of the Hand and Face 7.03.13</i> Policy Statement: I. Composite tissue allotransplantation of the hand and/or face is considered investigational . |