Composite Tissue Allotransplantation of the Hand and Face

Policy Number: MM.07.028
Original Effective Date: 08/01/2014
Line(s) of Business: HMO; PPO
Current Effective Date: 10/27/2017
Section: Transplants
Place(s) of Service: Inpatient

I. Description

Composite tissue 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 unsatisfied with prosthetic hands. The treatment has potential benefits in terms of functional status and psychosocial well-being. It also has potential risks, most notably those associated with a lifelong regimen of immunosuppressive drugs.

For individuals who have a severely disfigured face (e.g., burns, trauma) who receive composite tissue allotransplantation in individuals, the evidence includes small case series and 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 suggest that the surgery is technically feasible, however, to date only a limited number of patients worldwide have undergone the procedure and 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 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. 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 suggest 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 (eg, of surgical complications, immunosuppression, opportunistic infections). The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

**COMPOSITE TISSUE ALLOTRANSPLANTATION**

Composite tissue allotransplantation refers to the transplantation of histologically different tissue which 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 U.S., 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 U.S. took place in Louisville, KY 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 causing 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 was 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 is to increase a patient’s quality of life, e.g., by having a more normal appearance and a sense of wholeness. In the case of facial transplantations in particular, there is a large potential psychosocial benefit of successful surgery. Moreover, it is hoped that function (e.g., grasping and lifting after hand transplants, blinking and mouth closure after face transplants) may be better after composite tissue transplantation than
with alternative interventions. 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 involves only a few operations.

Adverse Events
Composite tissue allotransplantation is associated with potential risks and benefits. 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. There are also potential adverse impacts on quality of life including the need to commit to a lifetime immunosuppression regimen. Other challenges include the need to actively participate in intensive physical therapy in order to obtain functionality and the potential for frustration and disappointment if the level of functionality 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.

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.

II. Policy
Composite tissue allotransplantation of the hand and/or face is not covered as it is not known to be effective in improving health outcomes.

III. Policy Guidelines
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 (e.g., 26989 unlisted procedure, hands or fingers).

IV. Scientific Background
This evidence review was created in February 2013 with a search of the MEDLINE database through January 14, 2013. This evidence review has been updated regularly; most recently, the literature was reviewed through December 14, 2015. Following is a summary of the key literature to date.
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. The authors included English language articles published through September 15, 2013, that provided data on at least 1 face transplant in humans. A total of 36 articles reported on 27 worldwide face transplantations. University Hospital Henri Mondor in Creteil, France, and Brigham and Women’s Hospital in Boston, Massachusetts, were the centers with the most experience. Ten of the 27 cases were full face transplants (the first successful full face transplant was in 2010) and the remainder were partial face transplants. The literature did 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 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.

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 post surgery, and the 2 patients with tracheostomy tubes had them removed. Speech became understandable to an unfamiliar listener 3 to 9 months after surgery. Three to 9 months post surgery, 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 (eg, of surgical complications, immunosuppression, opportunistic infections).

Hand and Upper-Extremity Allotransplantation
The most comprehensive reporting of the worldwide experience with hand and upper-limb transplant was published by Shores et al in 2015. The authors identified 72 patients: 37 received bilateral transplants and 35 unilateral, for a total of 107 transplanted hand/upper extremities. There are 4 known mortalities: 1 occurred after a bilateral hand transplant; the other 3 followed multitype composite tissue allotransplantations (CTAs; ie, combined upper- and lower-limb or combined upper-limb and face transplants). Twenty-four graft losses have been reported; 8 of these were also associated with multiple CTA procedures and another 7 occurred in China during their early experience 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 post-transplant, 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 prepared for the article, hand transplants had been reported to the registry for 39 patients. The article 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 thrombosis, 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 (eg, of surgical complications, immunosuppression, opportunistic infections).

SUMMARY OF EVIDENCE
For individual who have a severely disfigured face (eg, 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 (eg, of surgical complications, immunosuppression, opportunistic infections). The evidence is insufficient to determine the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society for Surgery of the Hand
In November 2013, the American Society for Surgery of the Hand (ASSH) published a position statement on hand transplantation. ASSH 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 Clinical Excellence
In March 2011, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom published guidance on hand allotransplantation. The guidance stated that the quantity of current evidence on the efficacy and safety of hand allotransplantation is inadequate. NICE recommended that the procedure only be available under special arrangements (e.g., in a research setting).

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 are listed below:

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>Trial Name</th>
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NCT: National Clinical Trial

V. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References