Name of Policy:  
Composite Tissue Allotransplantation (CTA) of the Hand and Face

Policy #: 521      Latest Review Date: August 2018
Category: Surgery       Policy Grade: D

Background/Definitions:  
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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 that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Composite tissue allotransplantation (CTA) is defined as transplantation of histologically different tissues. CTA 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.

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 CTA have been hand and face (partial and full) transplantations, although there are also reported cases of several other CTAs, including transplantation 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. The first complete facial transplant was performed in Spain in 2010. In the United States, the first facial transplant was done in 2008; 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 1999.

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 and 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.

CTA 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 eight and 12 hours. In all hand transplants, bone fixation occurred 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, CTA 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 may be better following CTA than with alternative interventions e.g., grasping and lifting after hand transplants and basic functions such as blinking and mouth closure after facial transplants. In addition, 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**

CTA is associated with potential challenges and risks as well as potential 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 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 patients. 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 to 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.

**Policy:**

*Composite tissue allotransplantation (CTA) of the hand and/or face does not meet* Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered *investigational.*

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

The policy was created in February 2013, with a current literature search of the MEDLINE database through June 7, 2018.

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 the 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 PICOTS were used to select literature to inform this review.

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

**Interventions**
The therapy being considered is composite tissue allotransplantation.

**Comparators**
The following practice is currently being used to make decisions about grafting 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).

**Timing**
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.
Setting
Composite tissue allotransplantation is administered at a specialized surgical center with experts qualified to perform the procedure and postsurgical follow-up.

Systematic Reviews
As of December 2015, a total of 37 face allotransplantation operations have been conducted, 20 partial face and 17 full face. The most systematic review 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 one face transplant in humans. A total of 36 articles reported on 27 worldwide face transplantations. 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 of the face transplant recipients with at least one year postsurgical follow-up were reported to experience at least one episode of acute rejection days or months 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 a mean of 4.1 months after surgery when nerve repair was performed, and a mean of 7.3 months otherwise. Temperature sensitivity recovered a mean of 4.3 months with nerve repair and 12.5 months without nerve repair. Motor recovery began a mean of 7.8 months after surgery. Recovery of motor function has started with contractions of single muscles, and complex movements have 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
Also in 2015, Fischer et al identified a total of 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 who previously had 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 (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 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 PICOTS 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.

Comparators
The following practice is currently being used to make decisions about grafting a hand or arm after amputation: 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).

Timing
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.
Setting
Composite tissue allotransplantation is administered at a specialized surgical center with experts qualified to perform the procedure and postsurgical follow-up.

Case Series
The most comprehensive reporting of the worldwide experience with hand/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: one occurred after a bilateral hand transplant, and the other 3 followed multi-type 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; 8 of these were also associated with multiple CTA procedures and another seven 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 eight were bilateral (limb or digit) procedures. There was one immediate graft loss of the bilateral transplanted limb/digit.

An additional 3 patients experienced hand loss at approximately 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.

The International Registry on Hand and Composite Tissue Allotransplantation published an article describing registry data (2011). At the time data were extracted, hand transplants had been reported to the registry for 39 patients. The article stated that 85% of transplant recipients experienced at least one episode of acute rejection in the first year after transplant. Acute rejection episodes were reversible in all patients who were compliant with treatment. The most commonly reported complications were metabolic complications (35 of 39, 90%) and opportunistic infections (30 of 39, 77%). Transient hyperglycemia occurred in 17 patients (44%) and cytomegalovirus reactivation in ten patients (26%). Ten patients required surgery for complications (n=2 arterial thrombosis, n=1 venous thrombosis, n=6 small area of skin necrosis and n=1 venous fistula). Five cases of graft loss were reported between day 5 and 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. Hand function was reported in figures included in the article, but specific numbers, e.g. mean function scores, were not included in the text.

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,
Principles of facial transplantation were developed by the American Society of Plastic Surgeons (ASPS) and the American Society for Reconstructive Microsurgery (ASRM) in 2006. These guidelines include:

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.
5. To facilitate informed consent:
   - The physician must provide the patient with the latest and complete information on the risks associated with facial transplant.
   - The preoperative evaluation of potential donors may involve additional considerations as more experience is gained. At this time the results of facial transplantation are unknown. If early results are less than optimal, potential patients should be informed of any newly identified limitation of the procedure.
   - Patients must demonstrate a thorough understanding of all the known risks and benefits.
   - The physician should regard the facial transplantation procedure as experimental and it should be subjected to the evaluation of an independent research ethics committee.
   - The informed consent should include an alternative and acceptable solution for management of the recipients’ face in the event of transplant failure… “
U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Composite tissue allotransplantation (CTA), Vascularized composite tissue allotransplantation (VCA), Reconstructive transplantation (RT), Facial allograft transplantation, Hand allotransplantation

Approved by Governing Bodies:
Hand and face allotransplantation is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT Codes: No comparable CPT code exists for this procedure, so an unlisted procedure code is reported

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>21499</td>
<td>Unlisted musculoskeletal procedure, head</td>
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<tr>
<td>26989</td>
<td>Unlisted procedure, hands or fingers</td>
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References:
**Policy History:**

Medical Policy Panel, February 2013  
Medical Policy Group, February 2013 (3): New Policy adopted; investigational per policy statement  
Medical Policy Administration Committee, March 2013  
Available for comment March 12 through April 25, 2013  
Medical Policy Panel, February 2014  
Medical Policy Group, February 2014 (3): 2014 Updates to Key Points & References; no change in policy statement  
Medical Policy Panel, February 2015  
Medical Policy Group, February 2015 (2): 2015 Updates to Key Points, Practice Guidelines and Position Statements, and References, no change to policy statement.  
Medical Policy Panel, February 2016  
Medical Policy Group, February (2): 2016 Updates to Key Points, Approved by Governing Bodies, and References; no change to policy statement.  
Medical Policy Panel, August 2017  
Medical Policy Group, August 2017 (7): Updates to Key Points and References. No change in Policy Statement.  
Medical Policy Panel, August 2018  
Medical Policy Group, August 2018 (3): Updates to Description and Key Points. No change in Policy Statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.