Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Composite Tissue Allotransplantation

Description/Background

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

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

Hand and face transplants have been shown to be technically feasible. The most commonly performed face transplant procedure has been to restore the lower two-thirds of facial structure, especially the perioral area (i.e., lips, cheeks, chin) and in some cases the forehead, eyelids, and scalp.[1] Facial transplantation has been performed on patients whose faces have been disfigured by trauma, burns, disease, or birth defects and who are unable to benefit from traditional surgical reconstruction. Hand transplantations have been done in patients who lost a hand due to trauma or life-saving interventions that caused permanent injury to the hand. To date, hand transplants have not been performed for congenital anomalies or loss of a limb due to cancer.

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

Unlike most solid organ transplantations (e.g., kidney and heart transplants), composite tissue allotransplantation is not life-saving, and its primary aim 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 the immunosuppression regimen. Other challenges include the need to actively participate in intensive physical therapy to restore functionality and the potential for frustration and disappointment if 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 allotransplantation is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Medical Policy Statement

Composite tissue allotransplantation of the hand and/or face is experimental/investigational. There is insufficient evidence in the published peer-reviewed medical literature to demonstrate the safety and effectiveness of these procedures.

Other composite tissue allotransplantation that is experimental/investigational **includes but is not limited to**:

- Auricular
- Nasal
- Human eye(s)
- Larynx/Pharynx
- Trachea
- Penile
- Uterus
- Abdominal wall
- Lower limb(s)/upper limb(s)

Note: Post-surgery immunosuppressant therapy is non-covered.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

21499	26989	22999	30999	31599	31899
42999	55899	67599	69399	0667T	0668T

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 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 **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.[1] 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.

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).

Systematic Reviews

As of December 2015, a total of 37 face allotransplantation operations have been conducted, 20 partial face and 17 full face.[2] The most systematic analysis of outcomes was published in 2014 by Smeets et al[3]. 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 postsurgery when nerve repair was performed or at a mean of 7.3 months otherwise. Temperature sensitivity recovered at a mean of 4.3 months with nerve repair and at 12.5 months without nerve repair. Motor recovery began at a mean of 7.8 months after surgery. Trialists indicated that recovery of motor function started with contractions of single muscles, and complex movements appeared within the first year in a number of patients. Long-term results are still pending in most cases. After 5 years of follow-up, the first face transplant recipient was able to fully open her mouth, smile, speak, chew, and swallow.

Case Series

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.[4] 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 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/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 **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.

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).

Case Series

The most comprehensive reporting of the worldwide experience with hand and upper-limb transplant was published by Shores et al in 2015.[5] 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; 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 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.[6] 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; 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 in the article, but specific numbers (e.g., mean function scores) were not included in the text.

One study was identified that compared health outcomes in patients undergoing hand transplantation vs. receiving hand/upper-limb prostheses. The study, published in 2016 by Salminger et al, compared outcomes for five patients who had below-elbow hand transplantation with seven patients who had prosthetic hands.[7] There were three unilateral and two bilateral hand transplants, for a total of seven 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 Tests (ARAT), the South Hampton Hand Assessment Procedure (SHAP) and the Disabilities of the Arm, Shoulder and Hand measures (DASH). 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-46 physical functioning, bodily pain, general health, or social functioning subscales. The authors did not report total SF-36 scores.

Section Summary: Hand/Upper Extremity Allotransplantation
A total of 107 hand/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 suggest that the surgery is technically feasible. A single study (n=12) has compared outcomes in 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, evidence is insufficient to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections).

AURICULAR ALLOTRANSPLANTATION

In the field of experimental facial vascularized composite tissue allotransplantation (VCA), a human auricular subunit model, pedicled on both superficial temporal (STA) and posterior auricular (PAA) arteries was described.[8] Clinical cases of extensive auricular replantation however, suggested that a single artery could perfuse the entire flap. In a report by Duisit et al

(2017), variants of this single pedicle approach have been studied, aiming to develop a more versatile replantation technique, in which the question of venous drainage has also been addressed. For arterial perfusion study, we harvested 11 auricular grafts, either on a single STA pedicle (n=3) or a double STA-PAA pedicle (n=8). We then proceeded to selective barium injections, in STA, PAA or both PAA-STA. Arteriograms were acquired with a Micro-CT scan and analyzed on 3D-reconstructed images. Venous drainage was investigated in eight hemi-faces, carefully dissected after latex injection.

Observations showed a homogenous perfusion of the whole auricle in all arterial graft variants. Venous drainage was highly variable, with either a dominant superficial temporal vein (37.5%), dominant posterior auricular vein (12.5%) or codominant trunks (50%). The authors concluded that auricular subunit VCA can be performed on a single artery, relying on the dynamic intra-auricular anastomoses between STA and PAA branches. Potentially, this vascular versatility is prone to simplify the subunit harvest and allows various strategies for pedicle selection. Venous drainage, however, remains inconstant and thus the major issue when considering auricular transplantation.

NASAL ALLOTRANSPLANTATION

The science and technical acumen in the field of vascularized composite allotransplantation has progressed rapidly over the past 15 years, and transplantation of specialized units of the face, such as the nose, appears possible. No study to date has evaluated the technical feasibility of isolated nasal unit transplantation (NUT).

In one study, Dorafshar et al (2017) explored the anatomy and technical specifics of NUT.[9] In this study, four fresh cadaver heads were studied. Bilateral vascular pedicle dissections were performed in each cadaver. The facial artery was cannulated and injected with food dye under physiologic pressure in two cadavers, and with lead oxide mixture in two cadavers to evaluate perfusion territories supplied by each vascular pedicle. The facial artery and vein were found to be adequate pedicles for NUT. Divergent courses of the vein and artery were consistently identified, which made for a bulky pedicle with necessary inclusion of large amounts of subcutaneous tissue. In all cases, the artery remained superficial, while the vein coursed in a deeper plane, and demonstrated consistent anastomoses with the superior transverse orbital arcade. While zinc oxide injection of the facial artery demonstrated filling of the nasal vasculature across the midline, dye perfusion studies suggested that unilateral arterial inflow may be insufficient to perfuse contralateral NUT components. Discrepancies in these two studies underscore the limitations of nondynamic assessment of nutritive perfusion. The authors concluded that NUT based on the facial artery and facial vein is technically feasible. Angiosome evaluation suggests that bilateral pedicle anastomoses may be required to ensure optimal perfusion.

HUMAN EYE ALLOTRANSPLANTATION

Vascularized composite allotransplantation of the eye is an appealing, novel method for reconstruction of the nonfunctioning eye. Davidson et al (2016) has established the first orthotopic model for eye transplantation in the rat.[10] With advancements in immunomodulation strategies together with new therapies in neuroregeneration, parallel development of human surgical protocols is vital for ensuring momentum toward eye transplantation in actual patients. Cadaveric donor tissue harvest (n = 8) was performed with orbital exenteration, combined open craniotomy, and endonasal approach to ligate the ophthalmic artery with a cuff of paraclival internal carotid artery, for transection of the optic nerve at the optic chiasm and

transection of cranial nerves III to VI and the superior ophthalmic vein at the cavernous sinus. Candidate recipient vessels (superficial temporal/internal maxillary/facial artery and superficial temporal/facial vein) were exposed. Vein grafts were required for all anastomoses. Donor tissue was secured in recipient orbits followed by sequential venous and arterial anastomoses and nerve coaptation. Pedicle lengths and calibers were measured. All steps were timed, photographed, video recorded, and critically analyzed after each operative session.

The technical feasibility of cadaveric donor procurement and transplantation to cadaveric recipient was established. Mean measurements included optic nerve length (39 mm) and caliber (5 mm), donor artery length (33 mm) and caliber (3 mm), and superior ophthalmic vein length (15 mm) and caliber (0.5 mm). Recipient superficial temporal, internal maxillary artery and facial artery calibers were 0.8, 2, and 2 mm, respectively; and superior temporal and facial vein calibers were 0.8 and 2.5 mm, respectively. According to the authors, this surgical protocol serves as a benchmark for optimization of technique, large-animal model development, and ultimately potentiating the possibility of vision restoration transplantation surgery.

LARYNX, PHARYNX AND TRACHEA ALLOTRANSPLANTATION

Laryngeal transplantation offers the potential for patients without a larynx to recover their voice, which is critical in our communication age. Widespread adoption of this surgery has been slowed due to the ethical concerns of life-long immunosuppression after a nonvital organ transplant. In a case report, Farwell and colleagues (2013), reports on a laryngotracheal transplantation was performed in a 51-year-old prior kidney pancreas transplant recipient presenting with complete laryngotracheal stenosis.[11] Surgical modifications were made in the previously described technique related to retrieval, vascular supply, and reinnervation. This resulted in a robustly vascularized organ with well-perfused long-segment tracheal transplant and early return of motor reinnervation. A multidisciplinary approach resulted in a successful transplant without evidence of rejection to date. Postoperatively, the patient continues to rely on a tracheotomy but has had the return of an oral and nasal airway, vocalization, smell, and taste, all experienced for the first time in 11 years. The authors concluded that their methods may result in a successful laryngotracheal transplant.

Krishnan et al (2017) reviewed all human laryngeal allotransplants that have been undertaken and reported in the English literature in order to evaluating the success of the procedure.[12] Inclusion criteria were case reports of patients who had undergone human laryngeal allotransplantation. Information regarding indications, operative techniques, complications, graft viability, and functional outcomes were extracted. A total of 5,961 articles, following removal of duplicates, matched the search criteria and were screened, with five case reports relating to two patients, ultimately fulfilling the entry criteria. Two laryngeal transplants have been reported in the medical literature. Although both patients report improved quality of life relating to their ability to communicate with voice, further research is necessary to shape our understanding of this complicated operation, its indications, and its functional outcomes.

Grajeck and colleagues (2017) evaluated the possibility of performing a complex vascular allotransplant of all neck organs including skin.[13] There are 2 previous attempts described in the literature. The first one is nonfunctional due to chronic rejection, the second one is viable yet considerably limited in complexity (no parathyroids, no skin). The allotransplantation was performed simultaneously on 2 adjacent operating rooms, using microsurgical techniques. The patient's voice, breathing through mouth, swallowing, and endocrinal functions have been fully

restored. Achieved results show that such operations performed in selected patients can nearly fully restore functional and aesthetic effects in 1 single procedure.

PENILE ALLOTRANSPLANTATION

Penile transplantation is a novel approach to management of penile loss in the developing field of composite tissue allotransplantation (CTA). Prior management for significant penile loss has been free flap phalloplasty with issues related to function, cosmesis, and functional loss from the location of flap harvest. Transplantation has been an evolving field with advancement in CTA over the past several decades leading to the option of penile transplant. Management of penile injury with replantation provided some preliminary groundwork on the technical aspects for penile transplantation. Additionally, penile transplantation raises many ethical, emotional, and psychological considerations with need for patience amidst ongoing advancement within the field.[13]

Sopko et al (2017) performed a comprehensive literature review for the years 1970-2016 penile allotransplantation.[14] Three human allogeneic penile transplantations have been performed to date of which 1 was removed 14 days after transplantation. The second recipient reports natural spontaneous erections and impregnating his partner. All three patients were able to void spontaneously through the graft's urethra. The complexity of the transplant is determined by how proximally the penile shaft anastomosis is performed and additional pelvic tissue may be transplanted en bloc if needed. The authors concluded that penile transplantation is a technically demanding procedure with significant ethical and psychosocial implications that can provide tissue and functional replacement, including urinary diversion and natural erections. It remains unclear how rejection and immunosuppression may affect graft function. Better models and more preclinical research re needed to better understand and optimize penile transplantation.

UTERINE ALLOTRANSPLANTATION

Uterus transplantation is a vascularized composite allograft transplantation. It allows women who do not have a uterus to become pregnant and deliver a baby. Testa et al (2017) analyzed the first five cases of living donor uterus transplantation performed in the United States.[15] The first three recipients lost their uterus grafts at days 14, 12, and 6, respectively, after transplant. Vascular complications, related to both inflow and outflow problems, were identified as the primary reason for the graft losses. Two recipients, at 6 and 3 mo, respectively, after transplant, have functioning grafts with regular menstrual cycles. Ultimate success will be claimed only after a live birth. The lessons learned were instrumental in allowing the authors to evolve from failure to technical and functional success.

According to Petrini et al (2017), since 2000, 13 uterine transplantations (UTxs) have been performed in women with absolute uterine infertility factor (AUIF), from both living and deceased donors, in different transplantation centers worldwide.[16] At present the birth of 4 children following UTx is documented by the literature, and a woman was having a second pregnancy in October 2015. Following these successes it is likely that the procedure will become part of healthcare practice, even though at the moment it is still experimental and, as such, requires careful attention. Because the emotional aspects that are tied to UTx may foster the "therapeutic misconception" of participants, which consists in an overestimation of the benefits and an underestimation of the risks, careful attention should be paid also to informed consent (IC), which must include the following: describing techniques, pointing out risks and possibility of failure, and informing about the treatments required after the intervention.

Because the final aim of UTx is the birth of a healthy child, the IC document must include details not only of the transplantation itself, but also of the very particular pregnancy deriving from it, and the need to remove the uterus following delivery(ies) to avoid these risks. Here we suggest that the IC process includes counseling techniques, possibly involving the psychologist that is part of the transplantation team, to target the information and decision-making process to the specific situation of each couple.

ABDOMINAL WALL ALLOTRANSPLANTATION

Candidates for multivisceral transplantation present with complex defects often beyond traditional reconstructive options. Light et al (2017) describe a dissection technique for a total abdominal wall vascularized composite flap.[17] In addition, the authors suggest a classification system for complex abdominal wall defects. Forty fresh, cadaveric hemiabdomens were dissected, with care taken to preserve the iliofemoral, deep circumflex iliac, superficial circumflex iliac, deep inferior epigastric, and superficial inferior epigastric arteries and corresponding veins. Perfusion patterns of the flaps were then studied using computed tomographic angiography. The deep circumflex iliac, superficial circumflex iliac, deep inferior epigastric, and superficial inferior epigastric arteries were identified along a 5-cm cuff of the iliofemoral artery centered on the inguinal ligament. Perfusion with an intact deep circumflex iliac artery yielded improvement in lateral perfusion based on CTA. The authors propose an algorithm for abdominal wall reconstruction based on defect size and abdominal wall perfusion, and their technique for harvesting a total vascularized composite abdominal wall flap for allotransplantation. Total abdominal wall transplantation should be considered in the subset of patients already receiving visceral organ transplants who also have concomitant abdominal wall defects.

LOWER LIMB(S) ALLOTRANSPLANTATION

Fattah et al (2011) describes the only one successful complete lower limb transplantation to date, in which a functioning limb from one ischiopagus twin with a lethal cardiac anomaly was transplanted to the other.[18] Six years later, the patient is mobilizing well and engaging in sporting activities with her peers in a mainstream school. Clinical evaluation of motor and sensory modalities demonstrated a good functional result. Quality of life was assessed using the short form-36 health survey and lower extremity functional scale disclosing a high level of social and physical capacity. Functional magnetic resonance imaging was performed and showed cortical integration of the limb; the implications of cortical plasticity and vascularized composite allotransplantation for the correction of congenital limb anomalies were presented.

SUMMARY OF EVIDENCE

Composite tissue allotransplantation in individuals who have a severely disfigured face (e.g., burns, trauma) 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. To date, however, 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.

Composite tissue allotransplantation in individuals who have hand amputation(s) includes small case series and 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 and found no differences between groups in functional outcomes and little difference in quality of life. Given the limited number of patients worldwide have undergone the procedure and the limited amount of data comparing outcomes with the best available prosthetics, evidence is insufficient to determine whether the potential benefits to patients outweigh the potential risks (e.g., of surgical complications, immunosuppression, opportunistic infections).The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for composite tissue allotransplantation in individuals with auricular, nasal, eye, larynx/pharynx/trachea, penile, uterus, abdominal wall or lower limb amputations is extremely limited. Some studies suggest that the surgeries are technically feasible. To date, however, the data is not sufficient to determine whether there are potential benefits to patients that outweighs the potential risks. Therefore, these procedures are considered experimental/investigational.

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01889381	Human craniomaxillofacial allotransplantation	15	Aug 2026
NCT01140087	Face transplantation	5	Dec 2025
NCT03240822	Human penile tissue allotransplantation for devastating penile and concomitant genital trauma	5	Dec 2025
NCT03307356	Penn uterine transplantation for uterine factor infertility trial (UNTIL)	5	Jul 2029
NCT01459107	Human upper extremity allotransplantation	30	Jun 2026
Unpublished			
NCT00722280	Human upper extremity (hand and forearm) allotransplantation	300	Jan 2018 (terminated)

NCT: national clinical trial

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.[8] 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 U.K. published guidance on hand allotransplantation.[9] 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.[10]

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.
5. To facilitate informed consent:
   a. The physician must provide the patient with the latest and complete information on the risks associated with facial transplant.
   b. 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.
   c. Patients must demonstrate a thorough understanding of all the known risks and benefits.
   d. The physician should regard the facial transplantation procedure as experimental and it should be subjected to the evaluation of an independent research ethics committee.
   e. 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.

Government Regulations
National:
There is no national coverage determination on this topic.

Local:
There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/18	2/20/18	2/20/18	Joint policy established
5/1/19	2/19/19		Routine policy maintenance, no change in policy status.
5/1/20	2/18/20		Routine policy maintenance, no change in policy status.
5/1/21	2/16/21		Routine policy maintenance, no change in policy status.
5/1/22	2/15/22		Added codes 0667T and 0668T to policy as E/I. No change in policy status.

Next Review Date: 1st Qtr. 2023

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: COMPOSITE TISSUE ALLOTRANSPLANTATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.