Prior Authorization Review Panel
MCO Policy Submission

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*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0819 Face Transplantation**

Clinical content was never revised. Additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

**Update History since the last PARP Submission:**

02/07/2019-This CPB has been updated with an additional reference.

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<th>Name of Authorized Individual (Please type or print):</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
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Face Transplantation

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers face transplantation (including cross-gender facial transplantation) experimental and investigational because of insufficient evidence of safety and effectiveness in the peer-reviewed published medical literature.

Background

Face transplantation entails partial or full replacement of a patient's face with a donor's face. The patient's face is removed and replaced, including the underlying fat, nerves and blood vessels, but no musculature. Thus, face transplantation does not give the patient's face the appearance of the deceased donor's face because the underlying musculature and bones are different. Individuals with faces disfigured by burns, cancer extirpation, trauma, or congenital birth defects might benefit from the procedure, which consists of a series of operations with issues of age, sex, skin color, and tissue type. In some cases, face transplantation may improve patients' basic functions (e.g., breathing, eating, speaking, and swallowing). The surgery may take 8 to 24 hours, followed by a 10 to 14 days hospital stay. Following the transplantation, a lifetime regimen of immunosuppressants is needed to prevent rejection. Long-term immunosuppression increases the risk of the development of life-threatening infections, kidney damage, and cancer. The surgery may result in complications such as infections that would require a second transplant or reconstruction with skin grafts. Psychological effects of the procedure may include disappointment, remorse, or grief/guilt toward the donor.
Dubernard and colleagues (2007) performed the first human partial face allograft on November 27, 2005 and reported outcomes up to 18 months after transplantation. The post-surgical induction immunosuppression protocol included thymoglobulins combined with mycophenolate mofetil, prednisone, and tacrolimus. Donor hematopoietic stem cells were infused on post-operative days 4 and 11. Sequential biopsy specimens were taken from a sentinel skin graft, the facial skin, and the oral mucosa. Functional progress was assessed by tests of sensory and motor function performed monthly. Psychological support was provided before and after transplantation. Sensitivity to light touch, as assessed with the use of static monofilaments, as well as sensitivity to heat and cold had returned to normal at 6 months after transplantation. Motor recovery was slower, and labial contact allowing complete mouth closure was achieved at 10 months. Psychological acceptance of the graft progressed as function improved. Rejection episodes occurred on days 18 and 214 after transplantation and were reversed. A decrease in inulin clearance led to a change in immunosuppressive regimen from tacrolimus to sirolimus at 14 months. Extracorporeal photochemotherapy (ECP) was introduced at 10 months to prevent recurrence of rejection. There have been no subsequent rejection episodes. At 18 months, the patient was satisfied with the esthetic result. The authors concluded that in this patient who underwent the first partial face transplantation, the functional and esthetic results 18 months after transplantation were satisfactory.

Lantieri and associates (2008) reported a 1-year follow-up of a patient who underwent face transplantation with a composite tissue allograft (CTA). On January 21, 2007, a 29-year old man with neurofibromatosis type 1 underwent resection of a massive plexiform neurofibroma that infiltrated diffusely the middle and lower part of his face. The main goal was to restore both the cutaneous appearance and functions of the face, including, in particular, control of orbicularis oculi and oris muscle contraction. The issues of immunosuppressive therapy, psychological outcome, and social re-integration were addressed, together with the monitoring of graft rejection by biopsies of the skin and mucosa. The initial post-operative course was uncomplicated; 2 episodes of clinical rejection occurred on days 28 and 64. The second episode was associated with cytomegalovirus (CMV) infection. Both episodes resolved favorably, with no further clinical signs of rejection, making the reduction of immunosuppressive treatment possible. A year after surgery, the functional outcome was very good, with successful sensory and motor re-innervation in the transplanted territory. Psychological recovery was excellent, with complete social re-integration. The authors concluded that this case demonstrated the feasibility of surgically removing a large part of the face and replacing it with a CTA. This facial repair procedure, which seems to have a satisfactory risk-to-benefit ratio, could be offered in rare and selected cases.

Guo and associates (2008) performed a partial facial transplant in 2006, and reported the 2-year follow-up of the patient. The patient was mauled by a bear in October 2004. Allograft composite tissue transplantation was done in April 2006 after careful systemic preparation. The surgery
included anastomosis of the right mandibular artery and anterior facial vein, whole repair of total nose, upper lip, parotid gland, front wall of the maxillary sinus, part of the infra-orbital wall, and zygomatic bone. Facial nerve anastomosis was done during the operation. Quadruple immunomodulatory therapy was used, including corticosteroids, mycophenolate mofetil, tacrolimus, and humanized IL-2 receptor monoclonal antibody. Follow-up included T lymphocyte subgroups in peripheral blood, pathological and immunohistochemical examinations, functional progress, and psychological support. Composite tissue flap survived well. There were 3 acute rejection episodes at 3, 5, and 17 months post-transplantation, but these were controlled by adjustment of the tacrolimus dose or the use of methylprednisolone pulse therapy. Hepatic and renal functions were normal, and there was no infection. The patient developed hyperglycemia on day 3 after transplantation, which was controlled by medication. The authors concluded that facial transplantation could be successful in the short-term, but the procedure was not without complications. However, promising results could mean that this procedure might be an option for long-term restoration of severe facial disfigurement.

Siemionow and co-workers (2009) described an innovative approach entailing a single surgical procedure of face allograft transplantation that is a viable alternative of multiple reconstructive procedures. In December 2008, a 45-year old woman with severe mid-face trauma underwent near-total face transplantation in which 80% of her face was replaced with a tailored CTA. After the operation, the patient did well physically and psychologically, and tolerated immunosuppression without any major complication. Routine biopsy on day 47 after transplantation showed rejection of graft mucosa; however, a single bolus of corticosteroids reversed rejection. During the first 3 weeks after transplantation, the patient accepted her new face; 6 months after surgery, the functional outcome has been excellent. In contrast to her status before transplantation, the patient can now breathe through her nose, smell, taste, speak intelligibly, eat solid foods, and drink from a cup. These researchers showed the feasibility of reconstruction of severely disfigured patients in a single surgical procedure using composite face allotransplantation. Thus, this approach should be taken in consideration as an early option for severely disfigured patients.

Siemionow and colleagues (2010) noted that a total of 9 face transplants have been performed since 2005. Multiple esthetic subunits (i.e., eyelids, lips, nose) with or without underlying craniofacial skeletal defects (i.e., mandible, maxilla) have been successfully restored, thereby providing restoration of vital facial functions (e.g., smiling). As of today, face transplantation carries an estimated 2-year mortality of 20%. Concomitant CTA, which involves a variable combination of allograft subtypes, has been performed in 2 of the 9 face transplant patients. These have included simultaneous bilateral hand transplants and tongue with mandible. The authors concluded that more studies are needed to examine the potential advantages and disadvantages of using this approach versus a staged approach for reconstruction.
Lantieri et al (2011) reported the reproducibility, difficulties, serious adverse events and outcomes of their patients who had undergone face transplantation. Five patients were included in a registered clinical research protocol after thorough screenings assessed by an independent expert committee that discussed systematically the alternative options. One patient suffered from plexiform neurofibromas, 2 from third-degree burns and 2 from gunshot injuries. They were included on a national waiting list with a dedicated face procurement procedure. Transplants were harvested from heart beating brain-dead donors before other tissues and organs. Induction immunosuppressive therapy included anti-thymocyte globulins, steroids, mycophenolate mofetil and tacrolimus. Maintenance therapy included steroids, mycophenolate mofetil, tacrolimus, and ECP. Four patients were transplanted with 7- to 38-month follow-up. One could not undergo facial transplantation due to multiple panel reactive antibodies after 18 months on the waiting list. Acute cellular rejections were controlled by conventional treatment. Opportunistic infections affected all patients and resulted in the death of a patient 2 months after the transplantation. Voluntary facial activity appeared at 3 to 5 months following transplant. The authors concluded that face transplantation has been reproducible under conventional immunosuppression. Major improvements in facial esthetic and function allowed patients to recover social relations and improved their quality of life.

Pomahac and colleagues (2011) reported the functional and anatomical restoration 1 year after face transplantation. A 59-year old man with severe disfigurement from electrical burn injury was treated with a facial allograft composed of bone and soft tissues to restore mid-facial form and function. An initial potent anti-rejection treatment was tapered to minimal dose of immunosuppression. There were no surgical complications. The patient showed facial redness during the initial post-operative months. One acute rejection episode was reversed with a brief methylprednisolone bolus treatment. Pathological analysis and the donor's medical history suggested that rosacea transferred from the donor caused the erythema, successfully treated with topical metronidazol. Significant restoration of nasal breathing, speech, feeding, sensation and animation was achieved. The patient was highly satisfied with the esthetic result, and regained much of his capacity for normal social life.

Petruzzo et al (2011) evaluated all allograft structures by histology, magnetic resonance imaging, ultrasonography and high resolution peripheral quantitative computed tomography scan in 4 bilateral hand-grafted patients (10, 7, 3 and 2 years of follow-up, respectively) and in 1 facial allotransplantation (5 years of follow-up). All the recipients presented normal skin structure without dermal fibrosis. Vessels were patent, without thrombosis, stenosis or intimal hyperplasia. Tendons and nerves were also normal; muscles showed some changes, such as a variable degree of muscular hypotrophy, particularly of intrinsic muscles, accompanied by fatty degeneration that might be related to denervation. In the majority of hand-grafted patients graft radius and recipient tibia showed a decrease in trabecular density, although in the graft radius
the alterations also involved the cortices. No deterioration of graft function was noted. In these cases of CTA no signs of chronic graft rejection have been detected. However, the possibility that chronic rejection may develop in CTA exists, highlighting the necessity of close continuous follow-up of the patients.

Vasilic and Kon (2011) noted that CTA is a new development in reconstructive surgery that makes it possible to use identical tissue to repair large mutilating deformities (e.g., the face). Until now, a total of 13 face transplants have been performed worldwide. The functional and esthetic results are encouraging. However, the lifelong immunosuppressive therapy necessary to prevent rejection has considerable side effects.

Gordon et al (2011) stated that CTA is fraught with complexities similar to those of solid organ transplantation, including donor-related CMV transmission. With this in mind, the authors' objective was to (i) report their team's experience with infections and donor-related CMV transmission in relation to face transplantation, and (ii) review the facial CTA literature as it pertains to CMV and other various infections. A Medline literature search and article review was performed in July 2010 on all published articles specific to face transplantation, CMV disease, and all related infections and/or complications. In addition, the authors retrospectively reviewed their own institution's experience with face transplantation. Two of the world's first 4 face transplant recipients acquired CMV viral infection by means of their donated facial organs. Also, the French experience, and the authors' own, has been challenged by CMV re-activation and graft rejection, therefore necessitating a critical evaluation. These researchers have also learned from their own experience that facial CTA containing mucosa and para-nasal sinuses present a distinct challenge with regard to their accompanying flora. The authors concluded that although the risk of donor-derived CMV is acceptable in life-saving solid organ transplantation, for face transplantation patients, the scenario is different. When the authors' team performed the first nearly total face/maxilla transplantation (December 2008), there was little known regarding the consequences of CMV-related donor transmission in face transplantation. Therefore, the authors now recommend that all candidates be fully informed as to the risks of CMV/infectious transmission and that aggressive viral, bacterial, and fungal prophylaxis be instituted.

Morris et al (2007) noted that 3 years ago, the Working Party of the Royal College of Surgeons of England on Facial Transplantation concluded that until there was more information available about risks any potential patient would be exposed to, it would be unwise to proceed with transplantation of the human face. Over the last 3 years, there has been a deepening understanding of the potential psychological problems of facial transplantation as well as a very considerable debate on the ethical aspects of the procedure. Further data on experimental work in animal models of facial transplantation as well as medium-term follow-up data from 24 hand
and forearm transplants in 18 patients has now become available. Furthermore, a partial facial transplantation has been performed in France and a second one in China. In this second edition of the report, the technical, immunological, psychological, and ethical issues were discussed again in light of this developing knowledge. In particular, there has been a major expansion of the sections on the psychological and societal issues, as well as the ethical and legal problems of facial transplantation. The report cited the many psychological issues that face transplant recipients must confront, including unrealistic expectations, the risk of devastating transplant failure, and the reactions of others to their altered appearance. Face transplantation also entails “invasive press interest and publicity”. While updated experience with hand transplants as well as the French face transplant recipient suggested that close monitoring and treatment adjustments can head off problems with acute rejection, the risks of chronic rejection remains unknown. The Working Party still has considerable reservations about facial transplantation. Although it accepts that on balance the risks can not be precisely quantified, they remain substantial. Thus, if patients are allowed to make an informed choice to proceed, they must be very carefully selected and protected in the process, along with the families of both the donors and the recipients. To achieve this, the Working Party insists that 15 minimum requirements must be fulfilled before it would be appropriate for a research ethics committee/institutional review board to approve of a proposal to undertake facial transplantation.

Chenggang and colleagues (2008) reviewed some issues associated with facial transplantation, especially focusing on the individual who underwent the transplant in the authors’ department. These investigators discussed surgical indications, techniques, risks versus benefits, informed consent and psychosocial, societal and financial issues of facial transplantation. In their opinion, with the progresses in CTA, partial or full facial transplantation is becoming a timely and effective remedy for the significantly disfigured patients. However, there are a lot of unsolved problems, and as these researchers have performed the transplant on only 3 patients, no long-term outcome data are available. The authors stated that facial transplantation needs further research.

Mathes et al (2009) examined the current attitudes about the emerging field of CTA from those who treat complex facial injuries. In 2007, a Web-based blinded survey was sent to both burn and plastic surgeons involved in facial reconstruction. These researchers examined the practice profile with regard to complex facial injuries and asked respondents to assess the level of risk in CTA and indications for facial transplantation. Surgeons were asked to evaluate 3 clinical cases (2 closely mirroring clinical face transplantations) for suitability for treatment with CTA. A total of 164 surgeons responded (54 % response rate) and averaged 17.3 years in practice. They saw 12.1 severe facial-injury patients per year. A total of 78.7 % agreed that current techniques do not provide adequate reconstruction for severe facial injuries, and 26.2 % were in favor of performing CTA on immunosuppression. Acceptable indications for CTA were multiple failed
reconstructions (70 %), total facial burn (59 %), and absence of remote tissue (55 %). Ten percent saw no acceptable indication for CTA. The scenarios that mimicked recent transplantations had moderate support in favor of CTA (20.7 % for the Chinese patient and 29.3 % for the French patient). The authors concluded that this survey demonstrated support for use of CTA to reconstruct complex facial deformities. Surgeons continue to be wary of immunosuppression and chronic rejection, and many want to wait for better immunologic treatment options.

Siemionow and Gordon (2010) stated that it must be emphasized that face transplantation is still experimental and its therapeutic value remains to be validated. All surgical teams pursuing this endeavor must dedicate an attention to detail and should accept a responsibility to publish their outcomes in a transparent manner in order to contribute to the international field. However, due to its inherent complexity, facial transplantation should only be performed by university-affiliated medical institutions capable of orchestrating a specialized multi-disciplinary team with a long-term commitment to its success.

Unlike other organ transplantations, much is unknown about the long-term side effects of face transplants. The known risks are similar to other organ transplantation procedures such as a need for lifelong immunosuppressive medications, diabetes, lymphoma, risk of infection, and risk of rejection. While many other organ transplantations (e.g., heart or liver transplantation) are life-saving, face transplantation is a non-life saving reconstructive procedure. Moreover, face transplant recipients need to take immunosuppressive drugs for the remainder of their lives and, despite dramatic improvements in the safety of modern immunosuppressive protocols, they continue to suffer from adverse effects, a fact which raises ethical doubts regarding the legitimacy of face transplantation given its non-life saving nature. Furthermore, the effectiveness of immunosuppressive treatment in preventing chronic rejection remains unclear.

The CTA Working Group of the European Society for Organ Transplantation (Schneeberger et al, 2011) stated that more than 60 hand/forearm/arm transplantations as well as 16 face transplantations have been performed in the past 12 years. In the European experience, 3 grafts have been lost in response to a vascular thrombosis (n = 1), rejection and incompliance with immunosuppression (n = 1) and death (n = 1). The overall functional and esthetic outcome is very satisfactory, but serious side effects and complications related to immunosuppression are challenges hindering progress in this field. The high levels of immunosuppression, skin rejection, nerve regeneration, donor legislation and the acceptance level need to be addressed to promote growth of this promising new field in transplantation and reconstructive surgery.
Pomahac and colleagues (2011) stated that face transplantation has the unique potential to restore facial form and function in patients with severe facial defects. Current indications for face transplantation remain limited by unknown long-term outcomes and the requirements for life-long immunosuppression and substantial plans for reconstruction in case of failure. These investigators initially obtained Institutional Review Board approval for partial face transplantation in patients with defects comprising 25% of the face and/or loss of 1 or more major facial features. They launched an outcome-oriented face transplantation study and screened 13 potential patients between February 2008 and January 2011. Experience gained during screening motivated the expansion of indications to include full facial defects and the consideration of patient-specific complex issues on a case-by-case basis. Although the authors’ program focuses on restoring absent or severely compromised motor and sensory functions, they recognize aesthetic appearance as a crucial facial function. Patients are extensively educated on the risks and benefits of facial transplantation and then allowed to play the main role in the decision-making process, as long as no absolute exclusion criteria are present. As more data about the long-term outcomes of face transplantation and safe reduction of immunosuppression are gathered, face-transplant indications may expand from major unreconstructable defects towards potentially minor defects.

Siemionow and Ozturk (2012) stated that since 2005, 17 facial allo-transplantations have been performed worldwide. These investigators presented a brief summary of current cases with ongoing concerns. A total of 15 publications were reported for 10 facial allo-transplantations. For the remaining 7 transplantations, information was gathered from scientific meeting presentations and media releases. The summary of current cases in terms of etiology, indications, results, complications, and outcomes were based on these data. The discussion of ongoing concerns, controversies, and overview of future implications was accomplished by reviewing the literature of ethical debates, experimental studies, clinical studies, and personal opinion. Two of the 17 face transplant recipients died. Overall survival rate was 88%. No early graft loss due to technical failure was reported. All reported cases that have more than 1-year follow-up had at least 1 acute rejection episode, which was reversible with treatment. Opportunistic infections and metabolic complications were observed as adverse effects. Motor recoveries were slower than the sensorial recoveries, as expected. Functional and aesthetic outcomes were satisfactory. Concerns and controversies about concomitant face and hand transplantation, recipient blindness, recipient age, primary reconstruction option in facial trauma cases, funding, graft failure risks, and future treatment options were discussed. The authors concluded that because of uncertainty about long-term outcomes, immunosuppression-related concerns and ethical debates limit world-wide application of facial allo-transplantation. However, in selected group of patients, it is an unique reconstruction method with promising outcomes. They stated that further research and investigation in transplant immunology and treatment hold the key to advance this treatment option.
Baccarani et al (2013) stated that total face transplantation is now a clinical reconstructive option in the treatment of patients with acquired facial deformity. These investigators reviewed the status of total face transplantation based on their clinical experience in dealing with traditional microsurgical head and neck reconstructions and on the basis of their published pre-clinical research investigating technical aspects of the facial allo-transplantation procedure in cadaveric models. The authors first discussed the harvesting options and proposed 2 facial flaps, which addressed different reconstructive needs. Next, the concept of donor-recipient anatomical compatibility was introduced, and the possible outcome of the chimeric face was studied, following the insetting of a fascio-cutaneous facial allograft. Finally, the authors addressed the major technical challenges associated with transplanting the most complex osteomyocutaneous allograft. Significant improvement has been made in the field of vascularized composite tissue allo-transplantation over the last 5 to 6 years. They stated that the results of the 13 face transplants performed worldwide are encouraging both functionally and aesthetically, when compared with traditional reconstructive procedures.

Sedaghati-Nia et al (2013) stated that the face-grafting techniques are innovative and highly complex, requiring well-defined organization of all the teams involved. Subsequent to the first report in France in 2005, there have been 17 facial transplantations performed worldwide. These investigators described anesthesia and post-operative management, and the problems encountered, during the course of 7 facial composite tissue grafts performed between 2007 and 2011 in their hospital. The reasons for transplantation were ballistic trauma (n = 4), extensive neurofibromatosis (n = 2), and severe burns (n = 1). Anesthesia for this long procedure involves advanced planning for airway management, vascular access, technique of anesthesia, and fluid management. Preparation and grafting phases were highly hemorrhagic (greater than 1 blood volume), requiring massive transfusion. Median (range) volumes given for packed red cell (PRC) and fresh-frozen plasma (FFP) were 64.2 ml/kg (35.5 to 227.5) and 46.2 ml/kg (6.3 to 173.7), respectively. Blood loss quantification was difficult because of diffuse bleeding to the drapes. The management of patients with neurofibromatosis or burns involving the whole face was more difficult and hemorrhagic than the patients with lower face transplantation. Average surgical duration was 19.1 hrs (15 to 28). Post-operative severe graft edema was present in most patients. Most patients encountered complications in the intensive care unit, such as renal insufficiency, acute respiratory distress syndrome, and jugular thrombosis. Opportunistic bacterial infections were a feature during the post-operative period in these highly immunosuppressed patients.

Gordan et al (2013) noted that sex-specific anthropometrics, skin texture/adnexae mismatch, and social apprehension have prevented cross-gender facial transplantation from evolving. However, the scarce donor pool and extreme wait-list times are currently sub-optimal. These
researchers (i) performed and assessed cadaveric facial transplantation for each sex-mismatched scenario using virtual planning with cutting guide fabrication, and (ii) reviewed the advantages/disadvantages of cross-gender facial transplantation. Cross-gender facial transplantation feasibility was evaluated through 2 mock, double-jaw, Le Fort-based cadaveric allotransplants, including female donor-to-male recipient and male donor-to-female recipient. Hybrid facial-skeletal relationships were investigated using cephalometric measurements, including sellion-nasion-A point and sellion-nasion-B point angles, and lower-anterior-facial-height to total-anterior-facial-height ratio. Donor and recipient cutting guides were designed with virtual planning based on the team's experience in swine dissections and used to optimize the results. Skeletal proportions and facial-aesthetic harmony of the transplants \( (n = 2) \) were found to be equivalent to all reported experimental/clinical sex-matched cases by using custom guides and Mimics technology. Cephalometric measurements relative to Eastman Normal Values are shown. The authors concluded that on the basis of these findings, they believe that cross-gender facial transplantation can offer equivalent, anatomical skeletal outcomes to those of sex-matched pairs using pre-operative planning and custom guides for execution. Lack of literature discussion of cross-gender facial transplantation highlighted the general stigmata encompassing the subject. The authors hypothesized that concerns over sex-specific anthropometrics, skin texture/adnexae disparity, and increased immunological resistance have prevented full acceptance thus far. Advantages of cross-gender facial transplantation include an increased donor pool with expedited reconstruction, as well as size-matched donors.

Bergfeld et al (2013) noted that in December of 2008, their institution performed a near total face transplant. The patient was monitored for signs of rejection assessed by paired skin and mucosa biopsies. The results of histological review of 120 biopsies collected during the first 4 years post-transplant were discussed. All biopsies were stained with hematoxylin and eosin, periodic acid-Schiff, immunohistochemical and TUNEL assays and graded using the Banff 2007 classification. Grade III rejection was diagnosed clinically at weeks 45 and 66, post-transplant; week 45 was determined as folliculitis while the erythema episode at week 66 confirmed an acute rejection (AR) that required hospitalization. The mucosa frequently showed inter-face inflammation without clinical signs of rejection and was not present in skin biopsies. In all, 34 of the 45 mucosal biopsies (75 %) showed these inter-face changes. Clinical symptoms concurred with skin pathology in 2 grade III rejections. The mucosa showed histologic signs of rejection more frequently, which may indicate: increased mucosal sensitivity to rejection, a different type or subtype of AR that is specific to the mucosa, or a non-specific process such as a drug effect. The authors stated that with more data and world experience, the diagnosis of face transplant rejection will be better defined and the Banff classification enhanced.
The need for lifelong immunosuppression and unpredictable functional outcomes preclude face transplantation from routine acceptance in clinical practice. There is currently a clinical trial at the Brigham and Women's Hospital (Boston, MA) that aims to develop the best practices for facial transplantation, which will improve the outcomes of future face transplant recipients. The estimated number of enrollment is 5; and the estimated study completion date is February 2012. The inclusion as well as exclusion criteria of this clinical trial are as follows:

**Inclusion Criteria**

- Age between 18 and 60 years
- Loss of a major part of the face (e.g., the nose or the lips, or at least 25 % of the facial tissue)
- Signed written informed consent
- The facial defect can not be restored with traditional reconstruction techniques
- Willing to complete psychological and social evaluations
- Willing to take immunosuppressants for life
- Willing to return for follow-up visits as determined by the treating physician and to comply with extensive post-transplant rehabilitation therapy
- Willing to receive standard vaccinations prior to the transplant (e.g., influenza and hepatitis B)

**Exclusion Criteria**

- Absence of adequate donor sites for skin grafting in the event of transplant failure
- Active malignancy
- Any diagnosis that puts the subject at risk during the face transplant surgery
- Findings of psychological evaluation that indicate inability to comply with physician's orders or mental instability
- High risk of return of malignancy
- History of persistent non-compliance

Murphy et al (2013) noted that in vascularized composite allotransplantation (VCA), multiple types of tissue are transferred from donor to recipient as a single functional unit. This technique has been performed for upper extremity, face, and abdominal wall transplants, among many others. These investigators reviewed the existing cases of face and upper extremity VCA performed to-date and described the functional outcomes and challenges associated with this new procedure. They also reviewed the immune suppression protocols required for these procedures. A literature review was performed using PubMed and online registries where available to identify patients who have undergone upper extremity and face transplant
procedures. These were compiled and cross-referenced to abstracts, conference presentations, and press releases in the media to create a list of procedures performed to date. More than 70 patients have undergone upper extremity transplantation with very good functional outcomes routinely achieved; 25 face transplants were identified that have been completed to-date and details regarding patient outcome were included. One cases of human face allotransplantation with pre- and post-operative images was included as an example of what can be achieved with this technique. The authors concluded that VCA is an emerging field that provides an exciting new avenue for reconstructive procedures and achieves functional and cosmetic outcomes not previously possible with existing techniques. However, these investigators stated that VCA is not without its challenges and considerable work is still needed before widespread adoption of these new reconstructive techniques.

Diaz-Siso and colleagues (2013) stated that VCA is a viable treatment option for injuries and defects that involve multiple layers of functional tissue. In the past 15 years, more than 150 VCA surgeries have been reported for various anatomic locations including, but not limited to, trachea, larynx, abdominal wall, face, and upper and lower extremities. Vascularized composite allotransplantation can achieve a level of esthetic and functional restoration that is currently unattainable using conventional reconstructive techniques. Although the risks of lifelong immunosuppression continue to be an important factor when evaluating the benefits of VCA, reported short- and long-term outcomes have been excellent, thus far. Acute rejections are common in the early post-operative period, and immunosuppression-related side effects have been manageable. A multi-disciplinary approach to the management of VCA has proven successful. Reports of long-term graft losses have been rare, while several factors may play a role in the pathophysiology of chronic graft deterioration in VCA. Alternative approaches to immunosuppression such as cellular therapies and immunomodulation hold promise, although their role is so far not defined. The authors concluded that experimental protocols for VCA are currently being explored.

Infante-Cossio and associates (2013) provided an update on clinical results obtained by the first world-wide facial transplantation teams and reviewed the literature concerning the main surgical, immunological, ethical, and follow-up aspects described on facial transplanted patients. A total of 18 clinical cases were studied. The mean patient age was 37.5 years, with a higher prevalence of men. Main surgical indication was gunshot injuries (6 patients). All patients had previously undergone multiple conventional surgical reconstructive procedures that had failed. Altogether 9 transplant teams belonging to 4 countries participated; 13 partial face transplantations and 5 full face transplantations had been performed. Allografts were varied according to face anatomical components and the amount of skin, muscle, bone, and other tissues included, though all were grafted successfully and remained viable without significant post-operative surgical complications. The patient with the longest follow-up was 5 years; 2
patients died 2 and 27 months, respectively, after transplantation. The authors concluded that clinical experience had demonstrated the feasibility of facial transplantation as a valuable reconstructive option, but it still remains considered as an experimental procedure with unresolved issues to settle down.

Pomahac et al (2014) stated that VCA is a novel therapeutic option for treatment of patients suffering from limb loss or severe facial disfigurement. To-date, 72 hand and 19 facial transplantations have been performed worldwide. Vascularized composite allotransplantation in hand and facial transplantation is a complex procedure requiring a multi-disciplinary team approach and extensive surgical planning. Despite good functional outcome, courses after hand and facial transplantation have been complicated by skin rejection. The authors concluded that long-term immunosuppression remains a necessity in VCA for allograft survival. To widen the scope of these quality-of-life-improving procedures, minimization of immunosuppression to limit risks and side effects is needed.

Kueckelhaus and colleagues (2014) stated that VCA is utilized for restoration of complex defects. In this context, restoration describes the replacement of destroyed tissue by identical anatomic structures. To-date, over 150 VCAs including 31 face transplantations have been performed world-wide. Face transplantation is a life-giving, rather than life-saving procedure that is intended to significantly improve the patient's quality of life. Safe re-vascularization as well as aesthetic and functional re-integrations are the ultimate goals of face transplantation. The necessary lifelong immunosuppression with potentially life-threatening side effects imposes the need for a very strict risk-benefit ratio assessment and currently limits the indications of face transplantation. Different transplant centers use different protocols for induction and maintenance immunosuppression. Skin is the most immunogenic part of the vascularized composite allograft and has been the focus of intensive research efforts in order to replicate the success of immunosuppressive regimens for solid organ transplantation. Organ preservation during transfer from donor to recipient is another important field of research within VCA. The general public's originally rejecting attitude towards non-lifesaving VCA procedures has changed towards a general acceptance following the publication of promising results after the first cases of face transplantation. The authors concluded that further improvements of surgical techniques and immunosuppressive strategies will be important to drive these young and exciting procedures forward in the future.

Smeets et al (2014) noted that face transplantation (FT) is an innovative achievement of modern reconstructive surgery and is on the verge of becoming a common surgical opportunity. These researchers provided an update on this surgical field, especially regarding clinical outcomes, benefits, and complications implied. They performed an extensive research on all English-language Medline articles, case reports, and reviews published online until September 15, 2013.
Used search terms were "face transplantation", "face transplant", "facial transplantation", "facial transplant", "face allograft", and "facial allograft". To-date, a total of 27 FTs had been performed world-wide; 19 of these cases have been published in the Medline database. Long-term follow-up reports of FT cases are rare; 3 deaths associated with the procedure have occurred to-date. The clinical outcomes of FT are satisfying. Re-innervation of sensation has been faster than motor recovery. Extensive functional improvements had been observed. Due to strict immunosuppression protocols, no case of hyper-acute or chronic rejection and no graft-versus-host disease (GVHD) have occurred to-date. The authors concluded that as studies on long-term outcomes are missing, particularly regarding immunosuppression-related complications, FT will stay experimental for the next years.

Mohan and associates (2014) in the last 10 years, facial vascularized composite allo-transplantation has earned its place at the top of the reconstructive ladder. However, as in free tissue transfer, post-operative revisions are necessary to achieve optimal functional and aesthetic results. Although revising a facial vascularized composite allo-transplantation may potentially risk the integrity of the graft, the authors believed that the advantages of appropriately chosen revisions may provide great benefit. Following the most extensive FT performed to date, revisions were performed in 2 surgical procedures: (i) The first included a Le Fort III osteotomy for malocclusion correction, mid-face tissue re-suspension and coronal eyebrow lift to correct soft-tissue ptosis, and submental lipectomy, and (ii) The second included bilateral blepharoplasty to minimize tissue excess and scar revision carried out at a subsequent operation. Cephalometric analysis and angiography were performed and blink data collected. Before FT, the patient was in class III mal-occlusion. After FT, class I occlusion was obtained; however, the patient subsequently returned to class III occlusion. After skeletal revision, class I occlusion was obtained; however, a corneal blink deficit was noted. Eight months after skeletal revision, blink had improved spontaneously. Angiography revealed collateralization providing retrograde flow from the flap to the recipient. The authors concluded that although the necessity for revisions is clear, determining which revisions to safely perform and their timing and execution have not been explored. These researchers addressed 4 distinct categories of revisions including soft-tissue revision, hard-tissue mismatch, as well as craniofacial skeleton and dental occlusion. They illustrated the success of these revisions and assessed their advantages, disadvantages, and relative risk.

Fischer and colleagues (2015) provided a compilation of functional impairments before and improvements after FT in 5 FT recipients at the authors' institution; and all FTs reported in current literature. Functional outcome included the ability to smell, breath, eat, speak, grimace and facial sensation. Before FT, all 5 patients revealed compromised ability to breath, eat, speak, grimace and experience facial sensation. The ability to smell was compromised in 2 of 5 patients; 2 patients were dependent on tracheostomy and 1 on gastrostomy tubes. After FT, all
abilities were significantly improved and all patients were independent from artificial air airways and feeding tubes. Including data given in current literature about the other 24 FT recipients in the world, the abilities to smell, eat and feel were enhanced in 100 % of cases, while the abilities of breathing, speaking and facial expressions were ameliorated in 93 %, 71 % and 76 % of cases, respectively. All patients who required gastrostomy and 91 % of patients depending on tracheostomy were decannulated following FT. The authors noted that unfortunately, outcomes remain unreported in all other cases and therefore they were unable to comment on improvements.

Coffman (2015) noted that there have now been a total of 32 FT done in the world since the first performed in France in 2005. There have been 3 published reports of prospective quantitative assessments of FT candidates related to psychological outcomes with FT recipients. Various instruments have been used in assessment, including the Beck Depression Inventory, Patient Health Questionnaire-9 (PHQ-9), and Center for Epidemiologic Studies Depression Scale for rating depressive symptoms. Quality-of-life instruments used have included the Short Form-12, the Short Form-36, the Euro-QOL-5D (EQ-5D), the WHO Quality of Life rating scale (WHO-BREF), and the Psychosocial Adjustment to Illness Scale-Self-Report. The authors concluded that there have been 3 deaths in the first 32 cases of FT (9.4 %), 2 cases of post-transplant lymphoproliferative disorder in the first 20 face transplant recipients (10 %). This rate of post-transplant lymphoproliferative disorder is about 10 times the rate seen in solid-organ transplant recipients. These investigators stated that collaborative assessment protocols are needed to examine if the improvement in quality of life with FT is justified in the face of the risk of lifelong immunosuppression.

Fryer and colleagues (2015) stated that broader clinical application of reconstructive hand and face transplantation is hindered by the need for lifelong immunosuppression for allograft maintenance. These researchers summarized various cell-based approaches to tolerance induction currently under investigation in both clinical and pre-clinical models to alleviate the need for chronic immunosuppression. These include strategies to induce mixed hematopoietic chimerism, therapy with T and B regulatory cells, regulatory macrophages, tolerogenic dendritic cells, and mesenchymal stem cells. The vascularized, intra-graft bone components inherent to reconstructive transplants serve as a continuous source of donor-derived hematopoietic cells, and make hand and face transplants uniquely well suited for cell-based approaches to tolerance that may ultimately tilt the risk-benefit balance for these life-changing, but not life-saving, procedures.

Breidenbach et al (2016) performed a rigorous statistical analysis of all hand and face transplantations to examine if hand and/or face transplantation is the standard-of-care. Data from September 1998 until March 2014 on all hand and face transplantations in the world were
obtained through publications, news articles, personal communications, and presentations. Data on solid organ transplantation (SOT) were obtained from the Scientific Registry of Transplant Recipients for comparison with the results of hand transplantation. Re-sampling and permutation statistical analysis was used to compare structured cohorts of hand, face, and SOT. Routine immunosuppression can achieve intermediate- to long-term graft survival in hand transplantation that is empirically superior to SOT. Chronic rejection (CR) in hand transplantation is statistically significantly less than in SOT. Renal failure in hand and face transplantation is empirically less than in SOT. Bone marrow transplant with hand transplantation produces both statistically superior and statistically inferior results compared with hand transplantation without bone marrow. In hand transplantation, acute rejection did not appear to increase late allograft loss. The function of hand transplantation is statistically significantly superior to prosthesis yet inferior to hand replantation. Not all hand and face transplants have good results, yet those hand transplants completed within certain parameters obtained excellent results. The authors concluded that certain hand transplants arguably can be considered the standard-of-care; face transplantation requires more time and patient numbers and a clearer definition of inclusion and exclusion criteria before standard-of-care assessment can be made. However, the parameters that resulted in excellent results in hand transplantation are not clearly delineated.

In an update on “Chronic rejection in human vascularized composite allotransplantation (hand and face recipients)”, Kanitakis et al (2016) noted that VCA have become a viable option to restore severely damaged parts of the body that cannot be repaired with conventional surgical techniques. Acute rejection develops frequently in the early post-graft period both in human and experimental VCA, but the possibility of human VCA to undergo CR remained initially unknown. The experience gained over the years showed that, similar to SOT, human VCA can also develop CR. Chronic rejection is clinically mostly apparent on the skin and targets preferentially skin and deep vessels, leading, as in SOT, to graft vasculopathy and often to graft loss. Dermal sclerosis and adnexal atrophy are additional features of CR. The pathogenetic immune mechanisms involved (cell-mediated versus humoral) remain incompletely known. The changes of CR can be detected with skin and deep tissue biopsies. Modern in-vivo imaging tools can detect vascular narrowing and have the advantage of being non-invasive. However, the diagnosis and treatment of CR remain challenging, as several important questions remain to be answered: a more accurate definition of CR in VCA is needed to establish criteria allowing an accurate and early diagnosis. The authors concluded that the pathogenetic mechanisms of CR need to be better understood to allow more effective treatment; and favoring/triggering factors of CR need to be better understood so that they can be avoided. They stated that as in SOT, there is a need for efficient tolerance-inducing protocols that will favor graft acceptance and circumvent the necessity of lifelong immunosuppression.
The U.S. Department of Health and Human Services (DHHS)’ Organ Procurement and Transplantation Network (OPTN) has formed a 18-member National Committee to develop nationwide standards and policies for hand and face transplantation (2014). While face and hand transplantation are currently the most widely known VCA procedures, other types of VCA transplantation may be developed in the future. In July 2013, the DHHS announced that VCAs will be added to the definition of transplantable organs covered by federal regulation and legislation effective July 3, 2014. Dr. Kenneth Andreoni, President of the OPTN/UNOS (United Network for Organ Sharing) noted that "The demand for VCA transplants and the potential for future forms of these transplants, is growing rapidly, and it is important to establish consistent, national standards at this point to ensure that all patients are considered fairly and that we maintain the best possible outcomes for recipients". The OPTN/UNOS Vascularized Composite Allograft Transplantation Committee will determine which organ combinations will be covered in policy and develop national standards and processes for VCA donor consent and recovery, as well as a system to prioritize VCA transplant candidates for available organs. Other tasks will include developing a national set of clinical data to be collected on VCA transplants and establishing institutional standards for hospitals that perform VCA transplants. The committee will present its recommendations to the OPTN/UNOS Board of Directors for final action.

Sosin and Rodriguez (2016) stated that 10 years after the 1st face transplantation, the available data in peer-reviewed literature, various media outlets, and recent specialty meetings and courses are conflicting and inconsistently reported. These investigators consolidated the available data by means of multiple sources to reflect an accurate and current state of facial vascularized composite allotransplantation as of December of 2015. Using applied search terms pertaining to face transplantation, a systematic PubMed search, Google search, and review of Plastic Surgery Education Network News Connection e-mailed newsletters were performed, and data presented at 3 meetings (i.e., the most recent American Society of Reconstructive Transplantation biennial meeting, the American Society of Reconstructive Microsurgery annual meeting, and the biennial AO North America State of the Art: Face Reconstruction and Transplantation course) were consolidated to capture the most contemporary and accurate data in face transplantation. A total of 37 face transplants have been performed (20 partial and 17 full face) from 2005 to December of 2015. A discrepancy between actual transplantations performed and peer-reviewed reports exists at multiple time-points, with a propensity for under-reporting; 10 cases were described through media outlets but were not reported by the surgical teams in peer-reviewed literature; 2 clinical cases were not described in peer-reviewed literature or media. There have been a total of 5 deaths, and post-transplant malignancy and revision surgery have been under-reported. The authors concluded that this update served as the most contemporary and all-inclusive face transplantation review. They stated that there is a critical need for timely reporting and outcome transparency in the reconstructive transplant community.
Russo and Genden (2016) noted that reconstruction of severe facial deformities poses a unique surgical challenge: restoring the aesthetic form and function of the face. Facial transplantation has emerged over the last 10 years as an option for reconstruction of these defects in carefully selected patients. As the world experience with facial transplantation grows, debate remains regarding whether such a highly technical, resource-intensive procedure is warranted, all to improve quality of life but not necessarily prolong it.

Park and colleagues (2016) stated that face allotransplantation represents a novel frontier in complex human facial defect reconstruction. To develop more refined surgical techniques and yield fine results, it is first imperative to make a suitable animal model. The development of a composite facial allograft model in swine is more appealing: the facial anatomy, including facial nerve and vascular anatomy, is similar to that of humans. Two operative teams performed simultaneously, one assigned to harvest the donor and the other to prepare the recipient in efforts to shorten operative time. The flap was harvested with the common carotid artery and external jugular vein, and it was transferred to the recipient. After insetting the maxilla, mandible, muscles, and skins, the anastomosis of the external jugular vein, external carotid artery, and facial nerve were performed. The total mean time of transplantation was 7 hours, and most allografts survived without vascular problems. The authors documented that this model is well qualified to be used as a standard transplantation training model and future research work, in every aspect.

Cunico and associates (2016) described the surgical technique of face transplantation in swine, investigating the reproducibility of the methods as an experimental model in transplantation. A total of 7 pigs were operated upon. After euthanasia, the left hemi-facial area was removed and implanted onto the same location on the same animal from which it was removed. The vascular pedicle was based on the facial artery, the caudal auricular artery, and the external jugular vein. The ventral buccal and dorsal buccal branches of the facial nerve and the transverse facial branch of the auricular nerve were taken into the flap. The mean time of the procedure was 4.5 hours. Differences in vascularization were found as the vessel that provided blood supply to auricular region can be the caudal auricular artery, instead of the temporal artery, as described in the literature. Operative difficulty increased if the animal was more obese; a medical student who had training in microsurgical procedures was able to perform the entire procedure. The authors concluded that this study described an experimental model of face transplantation in swine, providing a good model for training of the surgical technique. The method is reproducible in any setting that offers resources in experimental surgery and microsurgery.

Also, an UpToDate review on "Principles of burn reconstruction: Overview of surgical procedures" (Leon-Villapalos and Dziewulski, 2016) states that "Facial transplantation procedure, a controversial reconstructive technique, offers hope to patients with severe facial burns or other
deformities. Facial transplantation remains predominantly an experimental technique. Restrictions to this procedure include a limited availability of fascial tissue allografts, inherent complexity of the technique, required presence of a skilled multidisciplinary surgical team, and a lifelong requirement for immunosuppression. Postoperative sensory recovery is reported to occur between 3 and 6 months and acceptable motor recovery occurs between 9 and 12 months. In a review of 28 procedures performed worldwide, episodes of acute skin rejection have been able to be controlled with conventional immunosuppressive agents with no cases of chronic rejection reported.

Lantieri and associates (2016) stated that more than 30 FTs have been performed worldwide since 2005, but no documented long-term follow-up has been reported in the literature. These investigators studied the long-term risks and benefits of FT. In this prospective, single-center, open-label study, these researchers evaluated 20 patients presenting with facial defects; 10 patients were selected, and, after 3 were secondarily excluded, 7 were transplanted: 2 with neurofibromatosis type I, 1 with a burn, and 4 with self-inflicted facial gunshot injuries. These investigators reported the long-term outcomes of 6 FT recipients at an average of 6 years (range of 3.4 to 9 years) after the transplantation. All admissions to hospital except for planned revisions and immunosuppressive follow-up therapy were reported as adverse events (AEs; safety end-point). Pre-defined immunological, metabolic, surgical, and social integration end-points were collected prospectively. Patients underwent quantitative health-related quality of life (QOL) assessments through Short Form 36 health questionnaires; 2 of 7 patients died: 1 at 65 days due to transplant destruction with concomitant pseudomonas infection and the 2nd at 3.4 years after transplantation by suicide. The 6 patients alive at long-term follow-up presented with functional transplants. Safety end-points were related to infection in the 1st month, AR from 1 day to 7 years after transplantation, or side-effects of immunosuppressive therapy. Recurrent rejection episodes justified maintenance therapy with high-dose steroids at high levels in all patients at last follow-up, yet none of the patients developed diabetes; 3 patients were found to have hypertension with 1 requiring therapy. All patients had a noticeable reduction in glomerular filtration rate (GFR). All recipients and their families accepted their transplant. Improvements in social integration and QOL were highly variable among the patients and depended on baseline levels and psychiatric comorbidities. The authors concluded that these long-term findings showed the crucial effect of patients' social support and pre-existing psychiatric conditions on the risk-benefit ratio of FT. They stated that careful pre-operative patient selection and long-term post-operative follow-up programs under strict institutional review board controls should be used for any future grafts of this type.

Aycart and colleagues (2017) stated that critical to the advancement of the burgeoning field of reconstructive transplantation is the quality of the methods used to measure and report the impact of FT on QOL. These investigators performed a systematic search using PubMed and
Embase for all studies matching the a priori inclusion criteria from 2005 through 2015. Bibliographies of included studies were also reviewed; 2 authors independently performed screening of titles. These researchers identified 17 articles reporting on QOL outcomes among 14 FT recipients. Combinations of objective and subjective measures were used to evaluate QOL. Instruments used to assess QOL after FT included over 25 different instruments. Four centers, comprising 8 patients, have reported using prospective, systematic data with validated instruments. Overall, there is reported improvement in QOL after FT. Heterogeneity and a paucity of data between articles precluded a quantitative analysis. The authors concluded that anecdotal and subjective reports of improvements in QOL after FT constituted the majority of reported outcomes in the English peer-reviewed literature. They stated that improved efforts in methods and standardization of collection and reporting of QOL data after FT are needed to better appreciate the impact of FT on QOL and justify lifelong immunosuppression and its attendant risks and morbidity.

Siemionow (2017) stated that at the 10th year anniversary of the first FT, a total of 37 patients worldwide, were the recipients of faces coming from human donors; 5 patients died due to complications, non-compliance with immunosuppressive medications and development of cancer. Despite the initial debates and ethical concerns, FT became a clinical reality with satisfactory functional outcomes. The areas of controversy still include the impact of life-long immunosuppression on otherwise healthy patients as well as the selection process of FT candidates. Other concerns include financial support for this new generation of transplants as well as social re-integration and patients return to work after FT.

Giatsidis and colleagues (2017) noted that on November 27, 2005, Isabelle Dinoire underwent the world's first partial FT in Amiens (France) after a dog attack had left her face severely disfigured. The abrupt surgical leap found the medical community and society unprepared to deal with the scientific, ethical, and societal implications of a surgical procedure that was striving to transition from sci-fi novels to science. Today, 10 years and over 35 transplants later, public opinion has become accustomed to the concept of "face restoration" through transplantation. However, FT is far from being a safe "routine" surgery and the science behind it is still mostly unknown. Patients and multi-disciplinary teams of physicians confront daily medical challenges, life-threatening risks, and personal struggle that only in part come to light. Could (or should) this be the laborious, uncertain, and high-risk trajectory of disruptive medical innovation? Over the past 10 years, some medical discoveries and surgical advancements in the field have been closely accompanied by partial regulatory frameworks, intense ethical discussions, and meaningful changes in social beliefs across cultures and continents. Yet, a very long way is to come and the questions researchers still have today greatly outweigh the answers they can offer.

Morelon and co-workers (2017) noted that 10 years after the 1st FT, these researchers reported
the partial loss of this graft. After 2 episodes of AR occurred and completely reversed in the first post-transplantation year, at 90 months post-transplantation the patient developed de-novo class II donor-specific antibodies, without clinical signs of AR. Some months later, she developed several skin rejection episodes treated with steroid pulses. Despite rapid clinical improvement, some months later the sentinel skin graft underwent necrosis. Microscopic examination showed intimal thickening, thrombosis of the pedicle vessel, and C4d deposits on the endothelium of some dermal vessels of the facial graft. Flow magnetic resonance imaging (MRI) of the facial graft showed a decrease of the distal right facial artery flow. Three steroid pulses of 500-mg each, followed by intravenous immunoglobulins (2 g/kg), 5 sessions of plasmapheresis, and 3 cycles of bortezomib 1.3 mg/m² were administered. Despite rescue therapy with eculizumab, necrosis of the lips and the peri-oral area occurred, which led to surgical removal of the lower lip, labial commissures, and part of the right cheek in May 2015. In January 2016, the patient underwent conventional facial reconstruction because during the re-transplantation evaluation a small-cell lung carcinoma was discovered, causing the patient's death in April 2016.

Win and associates (2017) noted that rejection affects greater than 80% of FT, yet no diagnostic criteria for antibody-mediated rejection (AMR) following FT have been established. Given that different treatment strategies are needed to address AMR and T cell-mediated rejection (TCMR), there is a critical need to delineate the features that can differentiate these 2 allo-immune responses. These investigators reported the longitudinal immunological examination of what we believe to be the 1st and only highly sensitized recipient of a crossmatch-positive FT up to 4 years following transplantation. These researchers conducted gene expression profiling on allograft biopsies collected during suspected AMR and TCMR episodes as well as during 5 non-rejection time-points. The data suggested that there were distinctive molecular features in AMR, characterized by over-expression of endothelial-associated genes, including ICAM1, VCAM1, and SELE. Although these findings were limited to a single patient, these findings high-lighted the potential importance of developing and implementing molecular markers to differentiate AMR from TCMR to guide clinical management. Furthermore, this case illustrated that molecular assessment of allograft biopsies offers the potential for new insights into the mechanisms underlying rejection. The authors concluded that their medium-term outcomes demonstrated that FT in a highly sensitized patient with a positive pre-operative crossmatch was feasible and manageable. The authors noted that a drawback of the present study was that these findings were derived from a single patient. The pitfalls of single-case analyses include concerns regarding the reliability and reproducibility, and they acknowledged that the extent to which these findings are generalizable is unclear. These investigators stated that additional research with an adequate number of patient samples to ensure statistical validity are needed to test this notion. They noted that given the paucity of VCA transplants and rarity of AMR, this will require a multi-center approach with consensus diagnostic criteria to enable robust conclusions.
Two-Stage Face Transplantation

Ramirez et al (2015) noted that animal models and clinical cases of facial allo-transplantation have been performed as a single-stage procedure. A staged surgery might offer some advantages in selected cases. These researchers evaluated the feasibility and safety of a 2-stage FT in a rat model: Brown Norway rats were used as donors and Lewis rats as recipients. A total of 33 hemiface-scalp transplantations were performed. Syngeneic orthotopic transplantations were performed either in 1-stage (1 single stage surgery; n = 3), local 2-stage [heterothopic transplantation to the neck during the first stage and graft rotation as a pedicled flap to cover the facial defect on post-operative day (POD) 2; n = 3], or distant 2-stage approaches (heterothopic transplantation to the groin during the first stage and free graft transfer to the face on POD 2; n = 3). In the allo-transplantation groups using the same approaches, 12 received no treatment (n = 4 each subgroup) and 12 received the same tapering dose of cyclosporine (10 to 2 mg/kg/day; n = 4 each subgroup). Graft survival and the rejection grades were assessed clinically and pathologically. All syngeneic transplants survived for the follow-up period of 180 days. The mean rejection-free survival and total survival of the allograft in the no treatment group was 6 ± 0.3 and 14.3 ± 4.5 days in the 1-stage group, 6 ± 0.4 and 18.5 ± 1 days in the local 2-stage group and 6 ± 0.2 and 14.3 ± 5.7 in the distant 2-stage group (p > 0.05). All allografts in the treatment groups did not develop rejection during the 42 days follow-up period. The authors concluded that it is feasible, reliable, reproducible, and safe to perform a 2-stage FT in rats. This novel approach has the potential to be applied in research and eventually in selected clinical cases of facial allo-transplantation.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".

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<th>Code</th>
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<td>S09.8XX+</td>
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<td>S09.93X+</td>
<td>Unspecified injury of head and face</td>
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<tr>
<td>T20.00X+</td>
<td>Burn and corrosion of head, face, and trunk</td>
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<tr>
<td>T20.79X+</td>
<td>Burn and corrosion confined to eye and adnexa</td>
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www.aetna.com/cpb/medical/data/800_899/0819.html
The above policy is based on the following references:


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0819 Face Transplantation

There are no amendments for Medicaid.