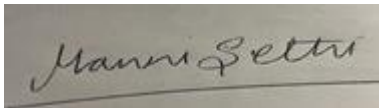


Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First	Submission Date: 1/2/2025
Policy Number: ccp.1438	Effective Date: 1/2020 Revision Date: November 1, 2024
Policy Name: Face transplantation	
Type of Submission – Check all that apply: <div style="margin-left: 20px;"><input type="checkbox"/> New Policy <input checked="" type="checkbox"/> Revised Policy* <input type="checkbox"/> Annual Review – No Revisions <input type="checkbox"/> Statewide PDL</div>	
<p>*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document.</p> <p>Please provide any clarifying information for the policy below:</p> <p>See tracked changes below.</p>	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

Face transplantation

Clinical Policy ID: CCP.1438

Recent review date: 11/2024

Next review date: 3/2026

Policy contains: Face transplantation.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

Face transplantation is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Plastic reconstruction surgery.

Background

Plastic surgery is a surgical specialty dedicated to correcting functional impairments of the face and body caused by congenital defects, developmental abnormalities, trauma, burns, infection, tumors, and disease (American Board of Cosmetic Surgery, 2023; American Society of Plastic Surgeons, 2023). A functional impairment is a direct and measurable reduction in physical performance of an organ or body part. Surgery is generally performed to improve function but may also be done to approximate a normal appearance. While many plastic surgeons choose to complete additional training and perform cosmetic surgery, the basis of their surgical training remains reconstructive in nature (American Board of Cosmetic Surgery, 2023; American Society of Plastic Surgeons, 2023).

Face transplantation is a procedure to replace part or all of a person's facial components by using deceased donor tissue and/or allografted tissue. It was developed as an alternative to standard surgical procedures of the face for severe cases. Transplantation procedures conducted to date have largely been patients whose face had become badly deformed due to animal attacks, burns, trauma or shotgun blasts (Smeets, 2014).

A considerable amount of preparation is needed prior to the procedure. Identifying a suitable donor may be the most critical aspect of preparation. After the procedure, patients must take immunosuppressants for the remainder of their lives, to prevent rejection of the implantation (Mayo Clinic, 2022).

Face transplant recipients undergo exhaustive physical and psychologic screening by the facial transplant team to determine muscle and nerve health as well as size, and the status of nerve regrowth and function essential for facial movement. Candidates and their support systems are interviewed to evaluate their ability to adhere to the recovery requirements such as taking rejection medications, attending physical therapy and follow up office visits, lab visits and subsequent surgeries.

The procedure is fraught with risks. Short-term risks include the length and complexity of the procedure; clotting of blood vessels; infection; wound healing problems; pain; bleeding; and development of other medical issues. Long-term risks include rejection of a new face, and limits to bone healing. Finally, immunosuppression-related risks include infection; cancer; diabetes; kidney damage; and heart disease (Johns Hopkins Medicine, 2023).

During the period prior to the first (partial) transplant in 2005, much of the literature focused on ethical issues (Toure, 2006).

As of mid-2013, a total of 27 procedures had been performed worldwide, led by France (9) and the U.S. (7), along with Belgium, China, Poland, Turkey, and Spain. Only 5 of 27 patients were females, and only 4 of 27 patients were not between the ages of 25 and 45 (Smeets, 2014).

The latest worldwide total of procedures, performed by August 2020, is 47 (Alberti, 2021), including 15 in the U.S. (Advisory Board, 2019). Only a small number of institutions with the appropriate personnel, equipment, and support are able to perform this surgery. The number of procedures had risen to nearly 90 by May, 2023 (Barrow, 2023).

Of the first 32 procedures performed, all were adults. Face transplantation in the pediatric population presents special risks but affected children could benefit from the procedure in the future, according to a team of specialists who view any decision to treat children based on ethical barriers (Marchac, 2016).

The International Registry on Hand and Composite Tissue Transplantation, founded in 2002, collects data on each case of composite tissue allotransplantation or vascularized composite allotransplantation, including face transplantation. It provides a reference for clinicians publishing articles (International Registry on Hand and Composite Tissue Transplantation, 2023).

Findings

The Working Party on Facial Transplantation issued the first (albeit crude) set of guidelines after the first two face transplantation procedures, stating considerable reservations about the risks of the procedure, and listing 15 requirements to be fulfilled before submitting a request to an institutional review board (Morris, 2007). The Cleveland Clinic, the pioneering American facility in face transplant, stated that the only facilities to perform the procedure had to be a university-based institution that included a multidisciplinary team dedicated to publishing results and with a long-term commitment to achieve success (Siemionow, 2010).

In summary, the professional medical literature on medical necessity of facial transplantation is lacking in several aspects. Only a small, insignificant number of procedures have been performed. Reviews are limited to mostly

case studies and are not randomized or controlled. Because the first procedure was performed relatively recently (2005), no data on long-term outcomes currently exist.

Staff members from Hopital Edouard Herriot in Lyon, France, who performed the first transplant, described the condition of the patient. Sensitivity to light touch, and to heat and cold was normal at six months; labial contact allowing complete mouth closure was reached at 10 months. Rejection episodes occurred on days 18 and 214 but were reversed. At 18 months the patient was satisfied psychologically and aesthetically (Dubernard, 2007).

The first U.S. face transplantation was conducted at the Cleveland Clinic in December 2008, on a 45-year-old woman injured in a shotgun blast who had 80% of her face replaced. Aside from a rejection of graft mucosa (reversed by corticosteroids), the patient responded well physically and psychologically; six months after surgery, she could breathe through the nose, smell, taste, speak intelligibly, eat solid foods, and drink from a cup (Siemionow, 2009). In 2020, the patient, who was the longest-living face transplant recipient, died of an infection unrelated to the procedure (Pietsch, 2020).

In July 2020, a 52-year-old New Hampshire woman whose face transplant was failing after ten years received a second transplant, the second re-transplant worldwide and the first in the U.S. Physicians expressed optimism that the second transplant would last as long as the first (Associated Press, 2020).

Carefully selecting patients for the procedure, which has considerable risks, surfaced after two of the first eight partial procedures ended in death within five years (Coffman, 2010). The Cleveland Clinic reported that from 2004 to 2016, over 200 persons were referred to the institution for face transplant. Of these, 60 were eligible for further evaluation, 13 were invited for in-person evaluation and physical examination, and five underwent face transplant (Knackstedt, 2020).

A review of 110 articles by staff at Brigham and Women's Hospital in Boston, the 2nd U.S. facility to offer face transplantations documented physician attitudes towards the procedure as evolving from an outlandish and morally objectionable procedure to greater acceptance as a feasible and necessary treatment option for the most significant facial defects (Kiwanuka, 2013).

Brigham and Women's medical staff members published several articles in the New England Journal of Medicine. A four-month follow-up of three patients found each survived; all had post-operative infections; and two had single rejection episodes that were successfully managed (Pomahac, 2012). A five-year follow up of six patients showed all survived; all but one reported improved quality of life; achievement of an average of 60% of maximal motor function; between 2-7 acute rejection episodes; and no new onset of diabetes, lipid disorders, cancers, or hypertension, excepting one who developed hypertension (Tasigiorgos, 2019).

After an analysis of the first 27 face transplantations, authors concluded that the procedure will remain experimental until studies on long-term outcomes, especially on immunosuppression-related complications, are conducted on larger patient populations (Smeets, 2014).

A 2010-2011 study showed one-year median costs for facial transplantation were far higher than for conventional reconstruction (\$313,068 versus \$64,451) (Nguyen, 2015).

For the first 44 face transplantation cases, the proportion in which institutional protocols existed were 61% (antimicrobial prophylaxis), 75% (immunosuppressive induction), 73% (maintenance immunosuppression), 70%

(graft surveillance), 70% (medical management of rejection), and 43% (surgical salvage strategies to manage graft failure (Daneshgaran, 2019).

The youngest recipient of a face transplant ever performed in the U.S. was to (then) 21-year-old Katie Stubblefield at the Cleveland Clinic in May 2017. After surviving a self-inflicted gunshot wound when she was 18, Stubblefield underwent 22 surgical procedures to rebuild parts of her nose, mouth, and forehead. After the 31-hour face transplant, she became the subject of a cover story in National Geographic magazine in 2018 (Pitofsky, 2018).

A systematic review of 24 programs concluded there was little consensus on criteria for selecting candidates for face transplant, and that selection remains heavily dependent on physicians or programs (Parker, 2022). Another systematic review of 19 studies concludes that computer assisted technologies were helpful in the planning and intraoperative phases of face transplant (Shpigel, 2022).

In 2024, we found three systematic reviews and a scoping literature review on face transplantation. However, no policy changes were warranted. Each article highlighted significant complications associated with facial transplantation procedures. One review analyzed 65 studies involving (n = 115) patients who underwent facial or upper extremity vascularized composite allotransplantation between 1998 and 2021. The study found that 23% of patients experienced surgical complications, with vascular anastomosis thrombosis occurring in 14% of cases. Acute rejection episodes were reported in 89% of patients, and chronic rejection occurred in 11%, leading to partial or complete allograft loss in 19% of patients. Opportunistic infections were noted in 58% of cases, and immunosuppression-related complications such as impaired glucose metabolism, renal insufficiency, hypertension, and hyperlipidemia were common (Milek, 2022).

Similarly, another review analyzed 28 studies involving (n = 46) patients who underwent a total of 48 face transplantation procedures since 2005. Adverse outcomes were reported in 14 cases (29%), including allograft loss in seven patients (14.6%) and death in ten patients (21.7%). Chronic rejection was the leading cause of allograft loss, with a median time to irreversible rejection of 90 months (interquartile range 88.5–102 months). The primary causes of death were infectious complications, malignancies, non-compliance with immunosuppression, and suicide, with a median time to death of 48.5 months (Longo, 2023).

A systematic review by Huelsboemer (2024) analyzed immunosuppressive strategies in face and hand transplantation, including (n = 45) face transplant patients, (n = 91) hand transplant patients, and (n = 3) patients who received both face and hand transplants. The study found that the standard triple maintenance therapy (tacrolimus, mycophenolate mofetil, and steroids) often required adjustments due to nephrotoxicity or high incidence of rejection. Alternative treatments such as sirolimus or everolimus were utilized in hand transplantation, while photophoresis, sirolimus, or belatacept were used in face transplantation. Rejection episodes were reported in 73% of face transplant patients and 65.9% of hand transplant patients. Graft loss occurred in 8.9% of face transplants and 13.2% of hand transplants. Clinical cytomegalovirus (CMV) infection was observed in 15.5% of face transplant recipients and 6.6% of hand transplant recipients. The study concluded that facial grafts exhibited a higher incidence of rejection episodes and clinical cytomegalovirus infections, possibly due to the inclusion of facial mucosa, highlighting the need for individualized immunosuppressive regimens and further research (Huelsboemer, 2024).

Additionally, a scoping review of 19 articles focusing on face transplantation emphasized long-term outcomes and ethical considerations. While the total number of patients reviewed was not specified, it was highlighted that over the past two decades, 48 face transplantation procedures have been performed in 46 patients, with two

documented retransplantations. The review noted that nearly all face transplant recipients experienced at least one episode of acute rejection, and six cases of chronic rejection were reported. At least eight patients (17.4%) have died following face transplantation, with causes including chronic rejection, infection, malignancy, and complications related to immunosuppression (La Padula, 2022).

Collectively, these studies underscore a high incidence of significant complications associated with facial transplantation procedures, including high rates of rejection, infection, immunosuppression-related complications, and mortality. This suggests that the risks may outweigh the benefits for some patients considering this procedure (Huelsboemer, 2024; Milek, 2022; Longo, 2023; La Padula, 2022).

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On August 22, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “face transplant.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

11/2019: initial review date and clinical policy effective date: 1/2020

11/2020: Policy references updated.

11/2021: Policy references updated.

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11/2023: Policy references updated.

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