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The 2020 Facial Transplantation Update: A 15-Year Compendium

Gustave K. Diep, MD
Zoe P. Berman, MD
Allyson R. Alfonso, BS, BA
Elie P. Ramly, MD
Daniel Boczar, MD
Jorge Trilles, BS
Ricardo Rodriguez Colon, BS
Bachar F. Chaya, MD
Eduardo D. Rodriguez, MD, DDS

Summary: Over the past 15 years, landmark achievements have established facial transplantation (FT) as a feasible reconstructive option for otherwise irreparable craniofacial defects. However, as the field matures and long-term outcomes begin to emerge, FT teams around the world are now facing new challenges. Data for this review were identified by searches of the PubMed/MEDLINE database from inception through August 2020. All English-language articles pertaining to FT were included. Significant advances in candidate selection, technology, operative technique, posttransplant care, and immunosuppressive management have contributed to the tremendous expansion of the field, culminating in the execution in the past 3 years of 2 facial re-transplantations, and most recently the world's first successful combined face and double hand transplant in August 2020. Despite these achievements, the allograft donor pool remains limited, with long wait times, requiring surgical experimentation with cross-sex FT. Immunosuppressive management has improved, but significant adverse events continue to be reported. Most recently, the COVID-19 pandemic has placed an unprecedented strain on the healthcare system, with various implications for the practice of reconstructive transplantation. In this article, we provide the most comprehensive and up-to-date FT review, highlighting fundamental lessons learned and recent advancements, while looking toward the challenges ahead. Over the past 15 years, extensive multidisciplinary efforts have been instrumental to the establishment of FT as a feasible reconstructive option. As novel challenges are beginning to emerge, continued collaborative and multispecialty research efforts are needed to further this field.
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INTRODUCTION

The field of facial transplantation (FT) has significantly evolved since the first patient was operated on in 2005.[1] Important advancements include improvements in preoperative evaluation, surgical preparation, operative techniques, and postoperative management, allowing for refinement of outcomes. With 48 FTs described to date, the field has expanded tremendously. However, as new milestones are reached, new obstacles are emerging that FT teams must now overcome. Additionally, the COVID-19 pandemic is reshaping the healthcare system as a whole, requiring adaptations for the delivery of care to FT candidates and recipients. We herein aim to provide the most comprehensive and up-to-date FT review as of August 2020, reflecting on the key lessons learned through 15 years of worldwide experience, discussing the field's most recent advances, and examining future directions and challenges.

METHODS

Data for this review were identified by searches of the PubMed/MEDLINE database from inception through August 2020. The search included the keywords and subject headings listed in Table 1. Title and abstract screening was performed independently by 2 reviewers, followed by full-text review. All articles pertaining to FT were included. Additionally, because the most recent FT cases performed over the past 3 years have not yet been described in the peer-reviewed literature, a separate search via Google was conducted using the same search terms, as indicated in Table 1. Studies in languages other than English, conference abstracts, and animal studies were excluded.

From the Hansjörg Wyss Department of Plastic Surgery, NYU Langone Health, New York, N.Y.

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Table 1. PubMed/MEDLINE Comprehensive Search Strategy for Articles on Facial Transplantation[2]

	PubMed/MEDLINE
Search Terms	"facial transplantation" [MeSH:no exp] "face transplant*" [tw] "facial transplant*" [tw] "face transplantation" [tw] "facial transplantation" [tw] "face allotransplantation" [tw] "facial allotransplantation" [tw] "facial vascularized composite allotransplantation" [tw] "face vascularized composite allotransplantation" [tw] "face vascularized composite allograft" [tw] "facial vascularized composite allograft" "face allograft" [tw] "facial allograft" [tw] "face composite tissue allotranspalntation" [tw] "facial composite tissue allotransplatnation" [tw] "face composite tissue allograft" [tw] "facial composite tissue allograft" [tw]

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PRE-TRANSPLANTATION CONSIDERATIONS

Candidate Selection and Work-up

Compatibility between donor and recipient is paramount for success in FT. Traditional considerations in solid organ transplantation (SOT) involve immunologic cross reactivity and viral serology. With FT, additional factors include matching of skin tone, hair color, and facial structure. Histocompatibility is generally more difficult to attain, as most FT candidates are typically profoundly immunosensitized secondary to initial resuscitation with blood products and skin grafting.[3] Although crossmatching is traditionally performed with peripheral blood using flow cytometry, a disproportionate rate of false negatives may be observed in highly sensitized patients. As a result, many vascularized composite allotransplantation (VCA) centers have now adopted the use of donor lymph nodes for tissue typing.[4] Viral serology mismatch poses additional challenges, as seen with 1 patient who developed monoclonal B-cell lymphoma following FT with Epstein-Barr virus mismatch.[5]

Context of the initial injury and baseline functional status must also be considered. To date, 3 patients with acquired bilateral blindness have undergone successful FT.[6–9] Criticism against FT for blind individuals has focused on the recipients' inability to appreciate the extent of their pre-transplantation injury and aesthetic improvements following FT, as well as inability to fully assess others' perceptions of their pre- and post- FT appearance. Furthermore, blindness can compromise adequate self-monitoring for rejection. Still, as seen with aesthetic surgery, blind patients may benefit from FT, as it allows for significant improvement in motor and sensory function, improved self-image and successful social reintegration.[10,11] Thus, blindness on its own should not warrant exclusion from consideration for FT, and an extensive caretaker consent process should be implemented to assess FT candidates' support system.[6]

Of the 48 documented FTs, 21 have been performed for high-energy ballistic facial trauma, with several index injuries explicitly described as self-inflicted.[12–15] To date, only 1 of these patients has died by suicide, in the context of longstanding suicidal behavior, lack of social support, and significant financial encumbrance.[16] Nonetheless, numerous reports have demonstrated a decrease in depressive symptoms, improvement in quality of life, sense of self, and social reintegration following FT. Ethical analyses have suggested that self-inflicted injury alone should not be an absolute contraindication for FT.[17,18] Regardless of documented psychiatric history, comprehensive and longitudinal psychiatric evaluation is an imperative component of FT candidate work-up and ongoing care. Mental health should be reassessed at all visits to support patient compliance, and ultimately reduce the risk of allograft failure.

Donor Pool Expansion

The VCA donor pool is limited. Despite 40% of brain-dead donors meeting initial screening criteria for VCA donation, wait times for FT may exceed 2 years, reflecting the potential to expand the VCA donor pool.[19] Furthermore, authorization for VCA donation is often difficult to navigate with families, although educational intervention has been proved to significantly increase willingness to donate.[20]

Currently available patient-oriented educational material on VCA is well above both the National Institutes of Health and American Medical Association's recommended reading level.[21] Recent efforts to expand the donor pool include optimization of the readability of and access to VCA educational materials, conceptualization of a multimodal VCA donation campaign strategy, research investigating donor-recipient sex-mismatched FT, and nationwide partnership to expand the donor search radius.[22–24] Additional investigations have also shown that, although organ procurement coordinators play a critical role in discussions surrounding VCA, there are significant disparities in distribution practices of educational materials. Future collaboration with organ procurement organizations (OPO) will be paramount to mitigate these disparities.[25]

SURGICAL CONSIDERATIONS

The Current State of Facial Transplantation

Since the first partial myocutaneous FT in 2005, efforts to push the boundaries of facial reconstruction have been documented worldwide, including the execution of full FT, immediate FT bypassing autologous reconstruction, re-transplantation for allograft failure and combined face, and double hand transplant (FT-DHT). To date, 48 FTs have been performed on 46 recipients (Table 2).[12,14,15,26–31] The most common indications for FT are craniofacial defects from ballistic trauma (43.7%), followed by thermal, chemical, or electrical burn injuries (25.0%). In 1 instance, FT was successfully executed following the acute phase of injury, before any autologous reconstructive procedures, with encouraging outcomes.[27] The first described case in an African American recipient was executed as a *full* rather than the initially planned *partial* FT, because

Table 2. Facial Transplantation Worldwide as of August 2020

Patient	Surgical Team	Location, Date of Transplant	Recipient (Age, Gender)	Indication	Extent of Defect	Allograft Type	Allograft Vascular Pedicle	Status (COD, TFT)	Acute Rejection	Chronic Rejection
1	Devauchelle, Dubernard	Amiens, France, 11/2005	38, woman	Animal attack	Cheek, nose, lips, chin	Partial	Facial artery	Deceased (malignancy, 11 years)	Yes	Yes
2	Guo	Xi'an, China, 04/2006	30, woman	Animal attack	Cheek, nose, upper lip, maxilla, orbital wall, zygoma	Partial	Maxillary artery	Deceased (non-compliance, 27 months)	Yes	No
3	Lantieri	Paris, France, 01/2007	29, woman	NF	Forehead, brows, eyelids, nose, lips, cheeks	Partial	ECA	Alive	Yes	No
4	Siemionow	Cleveland, Ohio, 12/2008	45, woman	Ballistic trauma	Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla	Partial	Facial artery	Deceased ("infection," 11 y and 7 mo)	Yes	No
5	Lantieri	Paris, France, 03/2009	27, man	Ballistic trauma	Nose, lips, maxilla, mandible	Partial	ECA	Alive	Yes	No
6	Lantieri	Paris, France 04/2009	37, man	Third degree burn	Forehead, nose, eyelids, ears, cheek	Partial	ECA	Deceased (sepsis, 2 mo)	No	No
7	Pomahac	Boston, Mass. 04/2009	59, man	Electrical burn	Lower eyelid, cheek, nose, lips, maxilla, zygoma	Partial	ECA + facial artery	Deceased (HCC, 10 y)	Yes	Yes
8	Lantieri	Paris, France, 08/2009	33, man	Ballistic trauma	Cheek, nose, lips, maxilla, mandible	Partial	ECA	Alive	Yes	No
9	Cavadas	Valencia, Spain, 08/2009	42, man	ORN after malignancy	Lower lip, tongue, floor of mouth, mandible	Partial	CCA	Deceased (malignancy)	Yes	No
10	Devauchelle, Dubernard	Amiens, France, 11/2009	27, man	Ballistic trauma	Mandible, upper and lower lips, chin, perioral area	Partial	—	Alive	Yes	Yes
11	Gomez-Cia	Seville, Spain, 01/2010	35, man	NF	Cheek, lips, chin, mandible	Partial	CCA	Alive	Yes	No
12	Barret	Barcelona, Spain, 03/2010	30, man	Ballistic trauma	Eyelids, nose, lips, lacrimal apparatus, zygoma, maxilla, mandible	Full	ECA	Alive	Yes	No
13	Lantieri	Paris, France, 06/2010	35, man	NF	Eyelids, ears, nose, lips, oral mucosa	Full	ECA	Alive	Yes	Yes
14	Pomahac	Boston, Mass., 03/2011	25, man	Electrical burn	Forehead, eyelids, left eye, nasal bone, cheek, lips	Full	Linguofacial trunk	Alive	Yes	Yes
15	Lantieri	Paris, France, 04/2011	45, man	Ballistic trauma	Nose, mandible, maxilla	Partial	ECA	Alive	Yes	No
16	Lantieri	Paris, France, 04/2011	41, man	Ballistic trauma	Nose, mandible, maxilla	Partial	ECA	Deceased (suicide, 36 mo)	Yes	No
17	Pomahac	Boston, Mass., 04/2011	30, man	Electrical burn	Forehead, eyelids, nasal bone, cheek, lips	Full	Facial artery + ECA	Alive	Yes	No
18	Pomahac	Boston, Mass., 05/2011	57, woman	Animal attack	Forehead, eyelids, eyes, nasal bone, lips, maxilla, mandible	Full	Facial artery + ECA	Alive	Yes	No
19	Blondeel	Ghent, Belgium, 12/2011	54, man	Ballistic trauma	Eyes, eyelid, cheek, nose, maxilla, mandible, lips	Partial	Facial artery	Alive	Yes	No
20	Ozkan	Ankara, Turkey, 01/2012	19, man	Burn	Forehead, nose, cheeks, lips	Full	ECA	Alive	Yes	No
21	Nasir	Ankara, Turkey, 02/2012	25, man	Burn	—	Full	—	Alive	—	—
22	Ozmen	Ankara, Turkey, 03/2012	20, woman	Ballistic trauma	Nose, upper lip, teeth, maxilla, mandible	Partial	—	Alive	—	—
23	Rodriguez	Baltimore, Md., 03/2012	37, man	Ballistic trauma	Forehead, eyelids, nose, cheek, lips, zygoma, maxilla, mandible	Full	ECA	Alive	Yes	No
24	Ozkan	Ankara, Turkey, 05/2012	35, man	Thermal burn	Forehead, eyelids, nose, cheeks, lips	Full	ECA	Alive	Yes	No

(Continued)

Table 2. (*Continued*)

Patient	Surgical Team	Location, Date of Transplant	Recipient (Age, Gender)	Indication	Extent of Defect	Allograft Type	Allograft Vascular Pedicle	Status (COD, TFT)	Acute Rejection	Chronic Rejection
25	Devauchelle, Dubernard	Amiens, France, 09/2012	–, woman	Vascular tumor	Lower eyelid, mandible, maxilla, tongue	Partial	—	Alive	Yes	No
26	Pomahac	Boston, Mass., 02/2013	44, woman	Chemical burn	Nose, lips, eyelids, forehead, cheek, ears, eyes, neck	Full	—	Alive	Yes	Yes
27	Maciejewski	Gliwice, Poland, 05/2013	32, man	Blunt trauma	Nose, lips, eyelid, cheek, maxilla	Partial	ECA	Alive	Yes	No
28	Ozkan	Ankara, Turkey, 07/2013	26, man	Ballistic trauma	Forehead, eyelids, left eye, nose, cheek, mandible	Full	ECA	Alive	Yes	No
29	Ozkan	Ankara, Turkey, 08/2013	54, man	Ballistic trauma	Scalp, forehead, eyelids, nose, left eye, maxilla, mandible, tongue	Full	ECA	Deceased (respiratory failure, 11 months)	Yes	No
30	Maciejewski	Gliwice, Poland 12/2013	28, woman	NF	Forehead, eyelids, nose, maxilla, lips, mandible	Full	ECA	Alive	Yes	No
31	Ozkan	Ankara, Turkey, 12/2013	22, man	Ballistic trauma	Forehead, lips, nose, maxilla, mandible	Partial	ECA + Facial artery	Alive	Yes	No
32	Pomahac	Boston, Mass., 03/2014	39, man	Ballistic trauma	Forehead, nose, lips, lower face	Full	—	Alive	Yes	No
33	Papay	Cleveland, Ohio, 09/2014	44, man	TINI	Scalp, forehead, eyelids, nose, eye, maxilla, cheeks	Partial	ECA	Alive	Yes	No
34	Pomahac	Boston, Mass., 10/2014	31, man	Ballistic trauma	Forehead, mandible, maxilla, lips and nose	Full	Facial artery	Alive	Yes	No
35	Barret	Barcelona, Spain, 02/2015	45, man	AVM	Lower face, neck, lips, tongue, pharynx	Full	—	Alive	—	—
36	Volokh	Saint-Petersburg, Russia, 05/2015	22, man	Electrical burn	Forehead, nose, lips	Partial	ECA	Alive	Yes	No
37	Rodriguez	New York, N.Y., 08/2015	41, man	Thermal burn	Scalp, forehead, eyelids, nose, cheeks, lower face, ear, lips, neck	Full	ECA	Alive	Yes	No
38	Tornwall	Helsinki, Finland, 02/2016	34, man	Ballistic trauma	Nose, maxilla, central mandible	Partial	ECA + facial artery	Alive	No	No
39	Mardini	Rochester, Minn., 06/2016	32, man	Ballistic trauma	Nose, maxilla, mandible, cheeks, salivary glands, lower face	Partial	—	Alive	Yes	No
40	Papay	Cleveland, Ohio, 05/2017	21, woman	Ballistic trauma	Scalp, forehead, eyelids, orbit, nose, cheeks, maxilla, mandible	Full	—	Alive	—	No
41	Rodriguez	New York, N.Y., 01/2018	25, man	Ballistic trauma	Eyelids, nose, cheek, lips, maxilla, mandible, zygoma, right orbital floor	Partial	ECA	Alive	Yes	No
42	Lantieri	Paris, France, 01/2018	43, man	CR of previous FT	—	Full	—	Alive	—	—
43	Lassus	Helsinki, Finland, 03/2018	58, man	Ballistic trauma	Maxilla, mandible, full face soft tissue	Full	—	Alive	No	No
44	Borsuk	Montreal, Canada, 05/2018	64, man	Ballistic trauma	Maxilla, mandible, nose, lower 2/3 of face	Partial	—	Alive	—	—
45	Santanelli, Longo	Rome, Italy, 09/2018	49, woman	NF	—	—	—	—	—	—
46	Pomahac	Boston, Mass., 07/2019	68, man	Thermal burn	Lips, nose, facial skin	Full	—	Alive	—	—
47	Pomahac	Boston, Mass., 07/2020	52, woman	CR of previous FT	—	Full	—	Alive	—	—
48	Rodriguez	New York, N.Y., 08/2020	21, man	Thermal burn	Forehead, eyelids, ears, nose, lips	Full	ECA	Alive	No	No

AVM, Arteriovenous malformation; CCA, Common carotid artery; COD, Cause of Death; CR, Chronic rejection; ECA, External carotid artery; FT, Face transplant; HCC, Hepatocellular carcinoma; NF, neurofibromatosis; ORN, osteoradionecrosis; TFT, Time from transplantation; TINI, Trauma-induced necrotizing inflammation.

achieving an acceptable donor–recipient color match proved difficult.[29] This case underscores the well-established ethnic and racial disparity observed in willingness to donate both solid organ and VCA, and further echoes the limited availability of skin-containing allografts for people of color.[32] Despite the paucity of long-term outcome reports, the data available indicate that most FT recipients remain alive to this day (81.2%), while 8 (16.7%) have died (Table 3).

Computerized Surgical Planning

The feasibility of FT is now widely established and the focus of the field has shifted to optimizing safety and outcomes, with the integration of new surgical technologies into cadaveric and clinical procedures.[14,33] The application of computerized surgical planning (CSP) and computer-aided design and manufacturing (CAD/CAM) of patient-specific devices has been instrumental to allow FT teams to adopt a customized approach to various clinical scenarios and achieve superior functional and aesthetic outcomes, including optimized operative flow and cephalometric and occlusal relationships after transplantation.[34] At least 8 other FT teams have relied on various forms of three-dimensional (3D) imaging and CAD/CAM for preparation and execution of their FTs.[1,13,15,28,35,36] Nonetheless, CSP should serve as a guide for FT surgeons, rather than dictate intraoperative decision-making; deviating from the computerized plan may be necessary in real time.

Intraoperative surgical navigation (ISN) provides real-time 3D guidance with 1- to 2-mm precision, and its use in craniomaxillofacial surgery has been extensively documented.[37] To date, 2 clinical FTs have utilized ISN as an adjunct to CSP, allowing intraoperative guidance of LeFort III osteotomies in the first patient and image-guided allograft inset and fixation in the second patient.[34] Mixed reality (MR) technology has recently been proposed as a complementary option for use in FT planning and intraoperative visualization.[38] In addition to the perceived benefits of MR, including enhanced visualization and easier maintenance of sterility, costs and surgical planning time have been cited as advantages of the holographic model over CSP and CAD/CAM. Further clinical comparative studies between the 2 modalities should be conducted to evaluate the role of MR in future FTs.

Table 3. Summary of the 48 Face Transplants Performed to Date

Face Transplant Recipient Characteristics (n = 48)	n (%)
Demographics	
Men	38 (79.1)
Women	10 (20.8)
Mean Age ± SD	37.2 ± 12.4
Indications	
Ballistic injury	21 (43.7)
Burn	12 (25)
Neurofibromatosis	5 (10.4)
Animal attack	3 (6.25)
Tumor	2 (4.2)
Blunt trauma	1 (2.1)
Trauma-induced necrotizing inflammation	1 (2.1)
Arteriovenous malformation	1 (2.1)
Re-transplantation for chronic rejection	2 (4.2)
Allograft type	
Partial	24 (50.0)
Full	23 (47.9)
Unknown	1 (2.1)
Status	
Alive	39 (81.2)
Deceased	8 (16.7)
Unknown	1 (2.1)

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POST-TRANSPLANTATION CONSIDERATIONS

Immunosuppression and Management of Allograft Rejection

Lifelong immunosuppression, allograft surveillance, and management of rejection ultimately dictate allograft survival. To date, 6 cases of CR have been reported, and nearly all FT recipients have had at least 1 incidence of acute rejection (AR) (Table 2). Immunosuppression induction regimens generally consist of anti-thymocyte globulin (ATG) or anti-IL-2 receptor antibody in combination with tacrolimus, mycophenolate mofetil (MMF), and steroids. Other reported induction protocols include a combination of steroids with either ATG, ATG with anti-CD20, ATG with MMF, or anti-CD52.[10,12,39] Maintenance therapy traditionally consists of triple therapy with corticosteroids, MMF, and tacrolimus, although some groups have used dual therapy with MMF and tacrolimus.[40] Appropriate antimicrobial prophylaxis is necessary because immunosuppression increases susceptibility to opportunistic infections, particularly given the unique craniomaxillofacial flora (Table 4).[41]

Given the composite nature of tissue transplanted in FT, different methods of allograft surveillance have been proposed, with skin biopsy remaining the gold standard.[42] Although the use of oral mucosal biopsy has been frequently described, its clinical utility remains unclear, as high rates of discordance with skin biopsy have been noted. Additionally, compared with the oral mucosa, skin histology is more likely to confirm clinical suspicion of rejection.[43,44] Some groups have advocated additional use of sentinel flaps for clinical monitoring, although the benefits of this approach are unclear.[1,44] Noninvasive methods to detect rejection have also been reported, including ultrasound biomicroscopy, epidermal skin-stripping, and circulating donor-derived cell-free DNA; however, clinical application of these methods remains under investigation.[45–47] Ultimately, we recommend close clinical follow-up and visual inspection of the allograft to detect clinical signs of AR followed by histologic confirmation with skin biopsy depending on clinical suspicion, as opposed to routine surveillance biopsy.[44,48]

Management protocols for AR in FT remain nonstandardized and underreported.[40] Most groups have reported successful use of pulse-dose corticosteroids, with or without topical agents and/or increased maintenance doses of immunosuppression.[12] Other therapies described include a combination of plasmapheresis, intravenous immunoglobulins, extracorporeal photopheresis, ATGs, eculizumab, and bortezomib.[36,40,49] Successful management of AR has been proposed as a rationale for the relatively low incidence of CR in FT. Although reports are beginning

Table 4. Common Pathogens and Antimicrobial Prophylaxis/Treatment in Facial Transplantation

	Pathogen	Origin	Prophylaxis/Treatment
Virus	HSV-1	Oral cavity, oropharynx	Acyclovir for the first 4 weeks after transplant
	VZV	Skin	Varicella vaccine* more than 4 weeks before transplantation/induction of immunosuppression
	Influenza	Paranasal sinus	Yearly influenza vaccine
	CMV	—	Prophylaxis/treatment: valgancyclovir or gancyclovir
	EBV	—	Treatment: reduction of immunosuppression, chemotherapy, and anti-B-cell therapies, such as rituximab.
Bacteria	MRSA	Skin, oral cavity, oropharynx	Empiric treatment: vancomycin
	Anaerobes	Oral cavity	Ampicillin-sulbactam perioperatively**
	Streptococcus pneumoniae	Paranasal sinus	Updated pneumococcal vaccinations Ampicillin-sulbactam perioperatively**
	Streptococcus pyogenes	Skin, oral cavity, oropharynx	Ampicillin-sulbactam perioperatively**
	Atypical bacterial	Oral mucosa infection	Empiric treatment: doxycycline or azithromycin
Fungus	*Candida*	Skin, oral cavity, oropharynx	Prophylaxis/treatment: nystatin or clotrimazole
	Coccidioides	Paranasal sinus	Avoid gardening, farming, construction, home remodeling, and landscaping
	Pneumocystis carinii	—	Prophylaxis: trimethoprim-sulfamethoxazole*** for at least 3 months posttransplant
Others	*Toxoplasma gondii, Isospora belli, Cyclospora cayetanensis*	—	Prophylaxis: trimethoprim-sulfamethoxazole*** for at least 3 months posttransplant

*Zoster vaccine if transplant candidate is above 50 years old.
**If no penicillin allergy.
***If allergy to trimethoprim-sulfamethoxazole: dapsone, atovaquone, or pentamidine.
CMV, Cytomegalovirus; EBV, Epstein-Barr Virus; HSV, Herpes Simplex Virus; MRSA, Methicillin-Resistant *Staphylococcus Aureus*; VZV, Varicella Zoster Virus.
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to emerge, the timeframe for CR remains unknown and expert consensus on CR management and allograft failure has not been established.[5,50] Clinical findings range from early fibrotic changes such as facial skin thinning and/or accelerated wrinkling, telangiectasia, dyschromia and skin sclerosis with allograft dysfunction, to frank necrosis.[5,51,52] In the event of allograft loss, surgical salvage strategies are necessary and both autologous reconstruction and re-transplantation have been reported.[26,30,51,53]

Allograft Revisions

Due to the en bloc nature of FT, restoration of multiple facial subunits can be achieved in a single surgery. Aesthetic and functional outcomes can be further refined with allograft revisions. Despite the inherent risks of additional surgeries related to immunosuppression, potential vascular compromise, and triggering of AR, secondary allograft procedures are nearly ubiquitous and can be successfully performed at various timepoints in the post-transplant course.[2,14,51] The range of indications is wide, including emergent return to the operating room, elective aesthetic surgery, unplanned functional corrections, and end-stage salvage procedures.[2] Overall, facial allograft revisions allow optimization of functional and aesthetic outcomes after FT (Table 5).

Quality of Life

Quality of life (QoL) of FT recipients' remains the ultimate measure of FT success. Currently, there is a lack of consistent reporting using validated measures for QoL, with most FT centers only offering subjective assessments. Among the teams that report using objective assessments, more than 25 unique instruments have been employed, and none have been validated for use in FT.[54] This underscores the need for standardized, FT-specific patient-reported outcomes measures (PROMs). Although robust quantitative analyses are currently limited by the relatively small number of FTs, further qualitative studies may continue to inform the development of standardized PROMs. Open collaboration between teams and consensus on outcomes reporting will be critical to advance the field.

Data on functional outcomes remain largely underreported, and have included assessments of olfaction, breathing, facial motor and sensory functions, speech, and eating.[55] Comparison of postoperative functional outcomes across the FT recipient cohort is further nuanced by patient-specific variations in preoperative functional status, mechanism of injury, and allograft composition.[55] Facial tracking technology, video analysis software, and facial surface electromyography have been used to non-invasively track recovery of speech, eyelid function, and facial expression, with results showing at least partial restoration of function after FT and the potential for personalized rehabilitation.[56–58] Additionally, objective measures such as timing to tracheostomy decannulation, gastrostomy tube removal and resumption of regular oral diet are important parameters to report for QoL assessment.

FUTURE OF FACIAL TRANSPLANTATION

Advances in Facial Transplantation

Two unsuccessful attempts at combined FT-DHT have been reported in the past.[8] Ongoing postoperative infectious complications ultimately resulted in death of the first recipient on postoperative day (POD) 65, and vascular complications necessitated removal of the second recipient's upper extremities on POD 5.[8] In August 2020, the world's first successful combined FT-DHT was performed amidst the COVID-19 pandemic in a 21-year-old man who

Table 5. Categorization of the Most Commonly Performed Secondary Revisions after Facial Transplantation

Secondary Allograft Revisions									
Soft Tissue		Craniofacial Skeleton, Dental		Oro-nasal Cavity, Salivary Glands, Facial Nerve		Ocular		Additional	
Indication	**Example**	**Indication**	**Example**	**Indication**	**Example**	**Indication**	**Example**	**Indication**	**Example**
Allograft augmentation	Fat grafting Alloplastic implant placement	Malocclusion	LeFort III osteotomy Midface advancement Hardware removal	Intraoral wound dehiscence, necrosis or fistula	Palatal fistula repair Tissue rearrangement of floor-of-mouth Hyoid and genioglossus advancement Wound debridement	Fistula	Orbital floor fistula repair Medial canthal fistula repair	Vascular revisions	Venous thrombectomy Arterial repair (iatrogenic injury) Anastomotic revision
Facial contouring	Fat grafting or lipectomy Tissue removal Scar revision Local tissue rearrangement	TMJ-related complications	Coronoidectomy Condylectomy	Sialocele	BT injection Drainage Stenting of Stensen ducts	Eyelid revisions	Ectropion repair Blepharoplasty Canthopexy V-Y AF of medial canthus Levator muscle plication	Fluid collection, necrotic tissue	Hematoma evacuation Abscess drainage Debridement and washout
Tissue resuspension	Allograft resuspension and advancement Rhytidectomy with SMAS plication	Dental	Tooth extraction Osseointegrated dental implant placement	Facial nerve revisions	Revision of nerve coaptation Nerve transfer with interposition graft	Eyebrow ptosis	Coronal lift Direct lift	Chronic rejection	Allograft removal Free flap reconstruction Facial re-transplantation

AF, advancement flap; BT, Botulinum Toxin; SMAS, Superficial Muscular Aponeurotic System; TMJ, Temporomandibular joint.
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had sustained an 80% total body surface area burn injury. Advances in technology, surgical technique, transplant immunology, and expertise gained through 15 years of clinical FT experience, coupled with meticulous preparation and strict adherence to COVID testing and guidelines culminated in the safe execution of this procedure, the most comprehensive VCA to date.[31]

In concert with the field's expansion, cross-sex facial transplantation (CSFT) has been proposed as a method of expanding the restricted VCA donor pool. Successful outcomes have been observed in clinical extremity transplantation, including 4 upper extremity transplants and 1 lower extremity transplant.[59,60] Although it has yet to be performed in the clinical setting, CSFT has shown promising results in cadaveric simulations, and survey data show acceptance of the practice among members of the general public as well as by the ethics community.[22,61,62]

Despite a trend toward increasingly complex reconstructive undertakings, the inclusion of certain anatomic structures within the facial allograft has yet to be described. To date, only 1 clinical FT involved a unilateral condyle.[63] As trauma to the craniofacial skeleton and subsequent reconstructive attempts can lead to temporomandibular joint (TMJ) ankylosis, FT candidates can experience TMJ-related complications after FT, even with normal TMJ anatomy on pretransplant imaging.[64] For FT candidates with TMJ pathology, either preexisting or as a result of their injury, inclusion of bilateral condyles in the allograft could in theory represent a potential option to restore TMJ function. Three methods of TMJ harvest have been explored in cadaveric simulations, with full passive mandibular range of motion obtained posttransplant.[65,66] However, important clinical considerations for TMJ-containing FT remain largely unaddressed, including TMJ dynamics after FT, occlusion, and long-term development of TMJ-related complications.

New Ethical Considerations

With FT recipients now living longer posttransplant, we must prepare for an increasing number of CR and allograft failure. Thus far, re-transplantation appears technically feasible; however, acceptance of the practice may depend on patient-specific determinations of its impact on QoL, as in primary FT. Among FT experts, a majority believe re-transplantation should be considered in cases of graft loss.[50] In theory, re-transplantation may carry increased immunological risks due to recipient sensitization to the primary allograft, which could lead to earlier rejection of a new allograft. Altered recipient vessel architecture from previous anastomoses might contribute to technical complexity. Careful monitoring will inform the long-term implications of this surgical intervention.

To date, no pediatric FT has been documented, although 62% of survey respondents at an international ethics conference were in favor, given appropriate indications.[61] Ethical concerns surrounding consent, immunological risks, and ongoing development of children and adolescents weigh against enhanced QoL, psychosocial well-being, social integration, and restoration of function.[67] Nonetheless, discussions addressing donor availability, a dynamic consent process, treatment adherence, and procedural considerations are underway.[68,69]

Facial Transplantation in the Post-COVID-19 World

The COVID-19 pandemic and associated global economic crisis have placed an unprecedented strain on healthcare systems throughout the world. Financing schemes for FT differ significantly across countries and healthcare systems. In European countries, FTs have typically been financed by the national health care system or public research programs.[15,70] Most FTs in the United States continue to be performed using a combination of institutional resources and research grants from agencies such as the Department of Defense. In 2018, the first FT to be partially supported by an employer-mediated third-party private insurer was performed.[14] Financial, regulatory, and access-related considerations have pushed some patients to seek VCA care in countries other than their own, but this may become less feasible as travel restrictions, infection-control practices, and resource allocation measures tighten in the aftermath of the COVID-19 pandemic.[71] Select teams have already engaged in long-distance follow-up care of FT recipients living in areas far from their VCA centers.[72] This approach may gain traction in the post-COVID-19 era, as the challenges imposed by the pandemic meet an accelerated integration of telemedicine throughout the field of plastic and reconstructive surgery.[73,74] Standardization of monitoring practices with quality control measures are necessary to maximize the benefit of remote patient interactions. Clinical evaluation using photography, serial documentation of signs and symptoms of rejection, and monitoring for medication-related adverse events must all be incorporated.[75]

CONCLUSIONS

Over the past 15 years, landmark achievements have shaped the field of FT as a feasible, sometimes preferable reconstructive option for otherwise irreparable craniofacial defects. The field is expanding, and outcomes are encouraging. With some facial allografts beginning to succumb to CR, FT teams were challenged to innovate with re-transplantation to overcome new hurdles. Most recently, the world's first successful combined FT-DHT established the feasibility of simultaneous VCA, marking the entry of FT into a new phase in caring for patients with extensive composite defects. In this new decade, amidst a global pandemic, we are now presented with a novel set of challenges as we strive to further the field. Continued research efforts will be necessary to validate the feasibility of CSFT. Community outreach, education, and connectedness with local OPOs will set the stage for expansion of the donor pool. Finally, transparency and standardization of clinical protocols and outcomes reporting will be fundamental to the maturation of the field.

Eduardo D. Rodriguez, MD, DDS
Hansjörg Wyss Department of Plastic Surgery
NYU Langone Health
222 E 41st Street, 6th Floor
New York, NY 10017
E-mail: eduardo.rodriguez@nyulangone.org

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