Human Facial Transplantation: 15 Year Update

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Citation

P Clark, K Massada, J Stout, B McNierney, J Treacy, T Webster, T McCarthy, I Kondrat. *Human Facial Transplantation: 15 Year Update*. The Internet Journal of Surgery. 2022 Volume 38 Number 1.

DOI: 10.5580/IJS.56265

Abstract

Ever since composite tissue allotransplantation of the face was first introduced as a viable option for individuals with severe facial disfigurement in 2005, several advancements have been made to improve the procedure preoperatively, perioperatively, and post-operatively. Improvement in surgical technique has allowed physicians to include a greater number of facial structures thus providing increased functionality. Despite these improvements, there is still a great deal of research to be done regarding the long-term effects of being placed on immunosuppressants and the quality of life the patient will enjoy post-transplant. Furthermore, both quality and quantity of life must be examined from both a pharmacoeconomic and psychosocial standpoint. At this time, it has been determined that from a pharmacoeconomic standpoint the procedure should not be performed but from the psychosocial perspective it should.

I. INTRODUCTION- 15-YEAR UPDATE

In 1954, the inception of transplants began with the first human kidney transplant. Advancements in transplant procedures proliferated as physicians attempted to perfect the art and by the 1990s, transplant procedures were being performed ubiquitously. Furthermore, the rejection rates of transplants decreased significantly as the procedure was refined over time. In September of 1998, a team of French surgeons pioneered the field of transplantation by completing the first successful hand transplant [4]. This elective procedure challenged the view that transplants are exclusively reserved for essential organs. This paradigm shift instigated both medical and ethical controversy.

In 2004, researchers at the University of Louisville Medical Center produced a detailed outline for face transplantations. This contentious outline received criticism from both the Royal College of Surgeons in England and France's Comité Consultatif National d'Ethique, which claimed that the risks of such a procedure outweighed the benefits, making it unethical [23].

Despite these early criticisms, the first documented face transplant was performed on Isabelle Dinoire in Amiens, France in 2005. Isabelle had reportedly overdosed on sleeping pills, and her dog mutilated her face while reportedly trying to wake her from her unconscious state. Isabelle underwent a partial facial allograft transplant, receiving portions of the nose, mouth, and shin in a triangular format. Unfortunately, in 2016, Isabelle succumbed to cancer which she presumably acquired due to her immunosuppressive regimen.

Since Isabelle's transplant, there have been great strides in the field of facial reconstruction. Prior to the first full face transplant that occurred in Spain in 2010, all face transplants were partial. Now there have been 45 partial or full-face transplants reported worldwide in 2021. The exponential growth of facial transplants performed in the instances of trauma, head and neck cancer, genetic defects such as from neurofibromatosis, and burns suggests facial allograft transplants are a feasible procedure. Nevertheless, the question remains whether this procedure is a viable option considering persistent risks. In this paper we seek to answer this question by analyzing the medical, financial, psychosocial, and ethical aspects of face transplants.

II. MEDICAL OVERVIEW OF FACE TRANSPLANT PROCEDURE

In its early stages, face transplantations consisted only of soft tissue components, the layers of tissue that form the skin, and subcutaneous tissue. However, physicians quickly

noticed that implanting just the soft tissue components led to sagging of the face overtime, as there was no scaffolding to hold the tissue in place; thus, the practice of also transplanting bony and cartilaginous structures began [15], [31], [41], [29].

The goal of plastic and reconstructive surgery is not merely to achieve aesthetics, but also to help the patient regain functionality of the reconstructed anatomical component. In a 2018 review article about the advancements made in the field of face transplants, Rifkin et al. discussed several aspects of the discoveries that led to the improvement of facial transplants [31]. The field of facial transplantation has greatly improved especially with the adoption of Vascularized Composite Tissue Allotransplantation (VCA), which involves the transplantation of the scaffolding nasal cartilage, bones, facial muscles, and nerves, in addition to skin containing the structures of the forehead, cheeks, nose, and lips [29]. The transfer of the aforementioned components has allowed surgeons to create better structurally composed faces [31]. Despite surgeons now harvesting more tissue from the donor face, the recipient of a facial transplant will not look identical to his or her donor due to individual differences in the bony structure of the skull. These differences in the relationship between the dental components and bony structures of the human skull is its own field of study known as Cephalometry. Thus, awareness of cephalometric differences is essential for the creation of a human face [31].

To reconstruct damaged structures on the recipient skull, it is crucial that vascularized donor structures including bone, and in certain cases intraoral components such as teeth and tongue, are harvested in the preoperative planning stage. This stage also involves obtaining an angiographic map of the recipient's face to evaluate patent blood vessels that will be used as recipients of the pedicles that accompany the tissues to be transplanted [31], [41], [29]. In addition, functionality of the transplanted facial components is dependent upon motor and sensory innervation to achieve facial expressions, to acquire sensation of the new face, and to perform other functionalities such as speech and swallowing [31], [41], [29]. The development of computer software that enables the juxtaposition of the layers involved in the reconstructive aspect plays a key role in creating predictive models of the postoperative outcomes [31]. Additionally, part of the preoperative planning is dedicated to finding a donor of similar age with similar skin color and texture [38].

In a 2012 article, Dr. Bohdan et al. discussed in detail the surgical technique of facial allograft harvest and implantation [29]. Patient inclusion criteria for receiving face transplant has been established by the American Society of Plastic Surgeons (ASPS) and the American Society of Reconstructive Microsurgery (ASRM) to be persons who have lost at least a quarter of their face, with significant facial deformity present, such as victims of severe trauma or devastating illness [41]. Per Dr. Bohdan's description, the facial transplant procedure begins with acquisition of the graft which is accomplished by first making an arched incision from ear to ear, across the head and scalp. The skin and its layers are then lifted from the skull and shaved downward until a few centimeters above the eye at which point the dissection is deepened to include the muscles that help to open and close the eye and to isolate the nerves that innervate those muscles. The nose and the bony triangle that gives it shape are then removed. The dissection is also undertaken from the area just before the ears and moving inward toward the middle of the face. This dissection is crucial as it preserves the nerves of facial expression and jaw movement, the latter of which in turn helps with speech and keeping the mouth closed while eating. The layers of tissue that line the inside of the lips and mouth are occasionally included in the dissection of the maxilla, which is the bone that supports the upper lip area. Furthermore, the facial artery, which is the major blood supply to both sides of the face, are taken with extra length so that they can be sewn to the receiving patient's vessels. The dissection is then continued toward the lower part of the face and down to the neck, including the thin muscle under the neck known as the platysma. [29]

Dr. Bohdan et al. proceeded to describe the transplantation of the harvested graft onto the recipient's face. The recipient and procurement operations are usually coordinated to reduce the cold ischemia time, the time during which tissues risk getting compromised. During this time, the tissues are detached from the donor, but not yet implanted into the recipient; during this time, the tissues are no longer being perfused with blood and instead are being preserved by the infusion of nutrient-rich special solutions. These solutions replace the physiological action of blood while the tissues are being transported from the procurement site to the transplantation site. In the operating room of the transplant recipient, facial dissection is conducted, the blood vessels that were pre-identified are dissected, and exposed. The nerves, both motor and sensory, are exposed and the skin is denuded, which usually consists of removing previous skin

grafts. Vascular anastomoses are conducted based on the patient's needs. The specific vessels that were identified in the pre-operative studies and were exposed during the recipient facial preparation are anastomosed with the donor's blood vessels under a magnifying microscope. Both arteries and veins are anastomosed. In the same manner, the nerves are also sewn together, and sometimes, a nerve graft is used to connect two nerves that are far from each other. Bone fusions also occur during this phase utilizing plates and screws to facilitate its proper placement and attachment. Subsequently, the skin is adjusted for proper covering of all the areas needing grafting and is sutured in place. [29]

Following the transplant, patients are placed on immunosuppressive medication to prevent the recipient's immune system from attacking the donor face or vice versa. Immunosuppression induction is typically done with either anti-thymocyte globulin, IL-2 antibody, or other monoclonal antibodies. Long term maintenance is then achieved with tacrolimus, mycophenolate mofetil, and steroids [41]. The patients will remain on these medications indefinitely as there will always be the threat of rejection. In 2017, all the facial transplant recipients were reported to have experienced at least one episode of rejection, which is treated in the acute setting with high dose steroids [36]. However, these immunosuppressive medications are not without harm as they put patients at risk of kidney failure, infections, cancer, hypertension, and metabolic derangements such as diabetes and hyperlipidemia [21]. Additionally, facial transplant patients are at a 10 times increased risk of lymphoproliferative disorder compared to patients who receive solid organ transplants [10].

III. PHARMACOECONOMIC ANALYSIS

Accurately determining the cost of healthcare expenditures is a complicated but necessary component of a sustainable healthcare system. The rising costs of pharmaceuticals and medical procedures have compelled patients, hospital systems, and governing bodies to view the price tag of a treatment as a key component of its viability. Therefore, pharmacoeconomics, the description and analysis of the costs of drug therapy to health care systems and society, is utilized to assess the true cost of a medical treatment [43].

By utilizing pharmacoeconomic methodologies, it is possible to determine the value and costs associated with a procedure, thereby providing both patients and their treatment team with an objective metric to determine the best treatment option for all stakeholders. The two pharmacoeconomic methodologies we will utilize to determine the feasibility of face CTA are a cost-minimization analysis and a cost-utility analysis.

A cost-minimization analysis is a tool utilized to compare two or more treatment options that possess similar patient outcomes [3]. We will be analyzing the costs associated with traditional reconstruction methods and comparing those with the costs of face CTA. Typically, the outcome units of this methodology are expressed in dollars.

A study comparing the associated costs of face CTA and facial reconstruction found that the former modality is typically costlier. The study states that the average first year costs associated with a face CTA are $337,360, whereas average costs associated with reconstruction are $70,230 [24]. The primary cost driver of both treatment options are hospital expenses, rather than physician costs. Furthermore, it is important to note that face CTA procedures are still in their infancy and as the practice progresses, the associated costs should decrease. The cost breakdown analysis is described in more detail in table A.

Table A

First Year Cost Comparison of Face Transplantation vs Conventional Reconstruction

First Year Cost Comparison of Face Transplantation vs Conventional Reconstruction						
	Conventional Reconstruction			Facial Transplantation		
	Mean	Median	SD	Mean	Median	SD
Total physician costs	$2,817	$3,005	$1,436	$27,727	$18,998	$23,096
Total hospital costs	$68,349	$62,218	$41,027	$291,565	$303,569	$115,925
Physician plus hospital	$70,230	$64,451	$41,949	$312,360	$313,068	$128,306
Procurement costs	NA	NA	NA	$25,000	$25,000	$0
Physician plus hospital plus Procurement	$70,230	$64,451	$41,949	$337,360	$338,068	$128,306

Once adjusted for severity, the associated costs for each modality become more similar. This study utilized data from four separate patients that received face CTAs and compared its costs with the hypothetical costs if the aforementioned patients received analogous facial reconstruction surgeries. The study found that the average cost of the face CTA was $307,125, whereas the facial reconstruction cost was $155,475 in the same cohort. Although the cost of the facial allograft transplantation is still relatively higher than the more traditional procedure, the cost profiles per patient are drastically more similar when evaluated on a cost-per-facial

subunit basis. Another expense associated with face transplants is the perpetual cost of immunosuppressants. Although there is not sufficient data to accurately determine the yearly cost of immunosuppressants, the costs of immunosuppressant for kidney transplantations have an approximate cost of $12,000 a year [19] [16]. The cost breakdown analysis is described in more detail in table B.

Table B

First Year Cost Comparison of Actual Face Transplantation vs Predicted Cost of Analogous Conventional Reconstruction

First Year Cost Comparison of Actual Face Transplantation vs Predicted Cost of Analogous Conventional Reconstruction			
Face CTA Patient	**Estimate Procurement**	**Actual Cost of Face CTA**	**Predicted Cost of Face CTA**
1	$25,000	$373,586	$97,053
2	$25,000	$157,222	$170,392
3	$25,000	$233,552	$170,392
4	$25,000	$380,961	$184,061
Mean	$25,000	$307,125	$155,475

In conclusion, a cost-minimization approach would lead a treatment team to choose a conventional facial reconstruction procedure in lieu of a face CTA if the patient were to experience similar outcomes. A cost-utility analysis is a tool that analyzes the costs and benefits of a treatment in terms of quantity and quality of life gained from a treatment [3]. The uniqueness of this methodology is that it prioritizes the perspective of the patient when determining the value of a treatment option. Typically, the outcome units of this methodology are expressed as cost per quality-adjusted life-year gained (QALY).

In the case of face CTA, the QALYs gained or lost are highly dependent on the degree to which the life expectancy of the patient decreases as a result of the transplant. If there is no notable decrease in life expectancy, the average QALYs gained are 8.77 [9]. However, if the decrease in life expectancy is like that experienced by renal transplant patients, there is an average loss of 6.68 QALYs [9].

The total lifetime cost of a face CTA will vary depending on the post-procedural life expectancy of the patient. Since the procedure is only approximately 15 years old and without long term data, both cases (that of no decrease in life expectancy and that of decrease in life expectancy like that seen in renal transplants) will be examined. The lifetime costs were calculated based on a patient that received the transplant when they were 30 years old.

Table C

Lifetime Costs of Face CTA for Patients who Received the Transplant at Age 30 ([1] Cost of immunosuppressive therapy based on costs of immunosuppression for kidney transplants.)

Lifetime Costs of Face CTA for Patients who Received the Transplant at Age 30		
Outcome	**No Decreased Life Expectancy (80.7 years)** [9]	**Decreased Life Expectancy (58.5 years)** [9]
Pre-operative, perioperative, and post-operative costs	$349,959 [35]	$349,959 [35]
Cost of immunosuppressive therapy (from age 30 to death)[1]	$608,400 [19]	$342,000 [19]
Total Cost	$958,359	$691,959

Table D

Cost per QALY for Face CTA Performed at Age 30 ([2]Cost per QALY= lifetime cost/ QALYs gained (lost))

Cost per QALY for Face CTA Performed at Age 30		
Outcome	**No Decreased Life Expectancy (80.7 years)** [9]	**Decreased Life Expectancy (58.5 years)** [9]
QALYs gained (lost)	8.77 [9]	(6.68) [9]
Lifetime Cost	$958,359	$691,959
Cost per QALY[2]	$109,277	n/a
Cost Saved per QALY lost	n/a	$103,587

In conclusion, a cursory pharmacoeconomic analysis of face CTA suggests that it is not a feasible treatment option. The cost-minimization analysis provides data that suggests a total conventional facial reconstruction procedure potentially provides a comparable outcome to a face CTA for less costs. Therefore, hospital administrators and insurers would argue that this treatment plan is the most effective use of resources, especially since health outcomes are reasonable. Additionally, the cost-utility analysis methodology supports that face CTA is not a feasible option. In the United States, there is a cost-effectiveness threshold of $104,000 [27]. Therefore, with a best-case scenario cost per QALY gained of $109,277, face CTA is not a cost-effective procedure. In the worst-case scenario where the patient would have a decreased life-expectancy, there is a loss of QALYs. Therefore, in not doing the procedure there would be a cost-savings of $103,587 per QALY lost.

IV. PSYCHOSOCIAL ISSUES

When deciding to undergo any surgical procedure, patients are often tasked with weighing the potential risks, benefits, and alternatives as they pertain to their physical health. The prospect of a face transplant; however, goes a step further as

it also requires individuals to weigh psychologically demanding variables pertaining to their identity, their lifestyle, and their interpretation of quality vs quantity.

The face is unique in that it serves as a functional unit of the body while also being intimately tied with a person's individual self-concept. Specifically, the "individual's belief about himself or herself, including the person's attributes and who and what the self is" [2]. This internal sense of self essentially defines a person's identity and the way they engage with those around them. For this reason, severe facial disfigurement can be debilitating both physically and psychologically.

From a purely psychological perspective, face transplants are very different from organ transplants because the recipient is obtaining part of someone else's identity and losing a part of their own. After completion of the procedure, the recipient's new face appears as a hybrid face resembling both the donor and the recipient, which will essentially serve as a new identity. It is possible that the process of coping with this new identity could be difficult for the individual and may even lead to further psychological distress. Conversely, the increased facial expressivity offered by an allograft transplant allows the recipient to regain a sense of identity as their capacity to partake in social interactions is enhanced. Either way, the recipient's emotional acceptance of the transplanted face is a key concern both pre and post operatively, as successful integration of their new appearance with their existing self-concept is vital to avoiding potential psychological issues [40].

The medical literature shows that the extent of psychological distress from a visible difference is not well predicted by the extent or severity of the disfiguration. Some cope well with an extensive and very visible disfigurement while others struggle with a relatively minor difference. In the case of face transplantation, a patient's preoperative dispositions appear to play a key role in eventual acceptance of the transplanted face. Those who demonstrate a strong preoperative self-concept seem better equipped to adapt to changes in physical appearance and suffer fewer negative psychosocial consequences than transplant patients lacking a strong preoperative self-concept [39]. Given the complexity of outcomes, it would benefit the patient to administer preoperative psychological tests assessing patient self-concepts as well as in depth informed consent procedures highlighting role of identity in face CTA.

Proponents argue that a face CTA gives severely disfigured persons a new and improved quality of life. Without facial movement, normal talking and eating are impossible, and simple yet important tasks, such as closing the eyes, are hindered [18]. These difficulties, along with stigma associated with such facial disfigurement, can lead individuals to become isolated and reclusive. Research shows that facial disfigurement results in lower self-confidence and a negative self-image. It is also common for these individuals to exhibit social anxiety, fear of negative social evaluation, and social avoidance [32].

The conventional reconstructive autograft surgery consists of numerous operations over an extended period of time to try and reconstruct the person's face using his or her own skin. The problem with this type of surgery is that the resultant skin lacks animation and normalcy of texture and color. Often what is created is a mask-like effect that can act as a barrier to social interaction. By contrast, a face transplant consists of one surgery, and because the underlying arteries and veins are included, the tissue remains supplied with blood, the texture and color are much better, and there is sensitivity and animation. The resulting increase in function allows for the individual to regain a level of nonverbal communication via facial expressions. This form of communication would aid the transplant recipient in expression of emotions, conveyance of attitudes and personality traits, and easier facilitation of verbal communication. Increased functionality in turn can allow for easier social interaction and may lessen the occurrence of social isolation in such individuals.

There is also the issue of quality versus quantity of life. Unlike a typical organ transplant, this procedure does not prolong a patient's survival, instead it does quite the opposite. The aim of this surgery is to improve function, appearance, and quality of living, as opposed to quantity of living. The recipient will be aware that they will potentially sacrifice years of life due to the complications of immunosuppressant drugs in exchange for a particular quality of life. Psychologically, the recipient will have to come to terms with their own death and its effects. "The psychological impact of knowing from what and how one will die should not be trivialized; in other circumstances this is used as a means of torture" [26]. Much of this will depend on the individual person's self-esteem as well as the extent of their social support.

When considering the mental and emotional impact of the procedure, it is important to acknowledge the psychological state of the patient prior to surgical intervention. A single

center study published by Lantieri et al. in 2016 that followed 20 face transplant recipients over an average of 6 years found that social support and pre-existing psychiatric conditions played a significant role in the patient's long-term quality of life. Patients who lacked social support or had pre-existing mental conditions were more likely to experience episodes of rejection, had lower quality of life, and difficult follow up. Additionally, patients who received face transplants following self-inflicted injury had lower rates of social reintegration and higher rates of rejection than those who received the transplant following unintentional injury or circumstance [21]. While there are no universal contraindications to facial transplant, typically patients will be excluded if they have active psychological disease, active bulimia nervosa, active substance use, poor social support, repeated suicide attempts, severe ambivalence about the procedure, and a traumatic brain injury that limits capacity [10].

ETHICAL ANALYSIS

The issue of face transplantation has raised serious interdisciplinary concerns. Many have called for a continued public debate on the issue of face transplantation that would examine all aspects of it including the crucial ethical and moral implications. However, some have warned that "the agenda of the debate, especially the moral debate, should not be wholly framed within the aspirations of the practitioners. This is in effect an issue of the equality of stakeholders. The surgeons involved are still talking in terms of 'how should we' proceed rather than 'should we'" [26]. If this is going to be an open debate with all parties participating, then all options must be placed on the table, including the option that we should not proceed with face transplantations. To determine if this procedure is ethical, the principles of respect for persons, beneficence, nonmaleficence and justice will be applied to this procedure and its consequences.

Respect for persons refers to the right of a person to exercise self-determination and to be treated with dignity and respect. Proponents argue that a face transplant would give severely disfigured individuals the chance to become active members of society. Many of these individuals live behind masks, or worse, behind closed doors. Because their appearance is so disfigured and their self-esteem so badly damaged, many retreat from the world and live within the confines of a limited existence. What this surgery would do is give them back an identity and a quality of life. Opponents argue that this is a non-life saving surgery and that the risks of rejection and the effects of the immunosuppressant drugs negate the quality of life argument. As the CCNE states, "This is in fact surgical experimentation and research, which must not be confused with a routine surgical procedure" [44]. The opponent's argument centers on the fact that there is the viable option of conventional reconstructive surgery that would utilize their own skin and relieve them from the effects of immunosuppressant drugs. Proponents argue that respect for persons is protected because any participant in this experimental surgery would give their informed consent and be made well aware of the animal trials and human face transplants that have preceded this surgery and the potential risks and benefits. In addition, they would know that the surgery has met the conditions of being ethically justified research by the local Institutional Review Boards (IRB). The problem is that in the United States and many European countries a new surgical technique requires no formal regulatory approach and is controlled primarily through surgeons' self-regulation that is sometimes, but not always supplemented by local control over research including peer review and IRB approval of a formal protocol [34]. The conditions for approval by an IRB are: 1) a reasonable prospect that the research will generate the knowledge that is sought; 2) the necessity of using human subjects; 3) a favorable balance of potential benefits over risks to the subject; and 4) a fair selection of subjects [13]. Proponents argue that the duty of the IRB is to check that researchers have not overestimated the potential success and underestimated the possible risks. Their duty is also to ensure that the risk-benefit ratio of undergoing this surgery is reasonable [34]. Approval by the IRB would be an added assurance to potential recipients.

To give valid informed consent to be a subject in an experimental surgery, two conditions must be met: the consent must be freely obtained from a competent person and the individual must be adequately informed regarding all aspects of the experimental surgery [1], [13], [42]. First, from the recipient's perspective, the options open to patients with severe facial disfigurement have been limited to the patchwork restoration done with tissue grafts and reconstructive surgery. The most common procedure for rebuilding a shattered face is known as a "lateral arm flap," a process that involves taking part of the patient's arm – the bone, muscle, nerves and skin – and molding it into what's left of the ruined face. This procedure requires 10 to 16 hours of preliminary surgery, followed by dozens of subsequent operations to make the face resemble a somewhat normal face, aesthetically and functionally [5]. A major problem with conventional reconstructive surgery is

that it is difficult for surgeons to reconstruct a patient's face because it needs to be able to move so that the person can convey expressions and feelings, particularly the lips, eyes and cheeks. Skin grafts taken from other parts of the body do not allow movement or sensitivity, creating a mask-like effect [17]. Besides the loss of normalcy of texture there is also the loss of color. By contrast, surgeons believe a face transplant would produce better results. Instead of as many as fifty conventional skin-graft surgeries, the face transplant would be one surgery. The benefits of this would be that it would allow for more animation, flexibility and skin color tone. The problem is that besides the risk of rejection, which would mean removal of the face, the patient would also have to be on immunosuppressant drugs for the remainder of his or her life, which are expensive and have serious side-effects.

This is still an experimental procedure that is non-lifesaving. Yet, by comparison to the conventional skin grafts, it is being touted as a revolutionary advancement for those with severe disfigurement. Realistically, even though it is experimental with serious risks, it consists of fewer surgeries and may give these individuals a far better quality of life. Under these circumstances, it is questionable whether the recipient is really free to give consent for such a procedure. Research has shown that whenever a new form of surgery is proposed that patients tend to dwell more on the benefits than the risks [20]. "If potential patients are desperate for a procedure, the question arises whether it is feasible for them to assess if possible, improvements in quality of life outweigh the potential morbidity and mortality caused by long-term immunosuppression" [20]. It is very difficult to determine if informed consent can be freely obtained with the way the media has sensationalized this surgery and the hype by various surgeons about its potential benefits. The consent may appear to be free but unfortunately, it may be based upon unrealistic expectations. At the present time, what this procedure realistically offers these patients is a shortening in the duration of their life for a possibility of improvement in the quality of their life.

Second, for a patient to give informed consent, he or she must have the necessary information to make such a decision. The basic elements of informed consent are:

1) A fair explanation of the procedures to be followed, including an identification of those which are experimental;

2) A description of the attendant discomforts and risks;

3) A description of the benefits to be expected;

4) A disclosure of appropriate alternative procedures that would be advantageous for the subjects;

5) An offer to answer any inquiries concerning the procedures;

6) An instruction that the subject is free to discontinue participation in the project or activity at any time [42], [5], [17], [20], [11]

In a specific sense, the surgeons who want to perform face transplants have an ethical obligation to give an objective, unbiased assessment of all materially relevant information pertaining to the animal studies and the cadaver trials as well as the 45 partial/full previous face transplants so that the patient can give informed consent. In addition, the rates of rejection, the costs and side-effects of the immunosuppressant drugs, the hope of about 50% return of nerve function, the psycho-social issues, the value of quality over quantity, and other risks must be clearly stated and explained to the patient. The surgeons are also responsible to verify, to the best of their ability, that the patient can comprehend and has comprehended the information and has not engaged in "selective hearing." Under the circumstances, it is not uncommon for patients to engage in "selective hearing," that is, taking in all information about potential benefits and filtering out all information about potential risks. In addition to this, surgeons must be vigilant against their influence over subjects, who may unwarily treat the surgeon with the same deference as they treat their primary care physicians. Dr. Robert Levine, professor of Medicine at Yale University, describes the surgeon/researcher's obligation as one of "forthright disclosure." This includes preliminary evidence and data from animal studies and previous human clinical trials that indicate the risks and benefits as well as the safety and efficacy of these controlled studies [22]. Patients need to have information that reasonable people would require to make well-reasoned decisions that will protect their personal interest.

The problem is determining what sort of knowledge translates to what degree of risk to patients. This is a value judgment that must be made by the surgeons. The concern is that the judgment of some surgeons may be biased by considerations of career self-interest and even financial gains [33]. "The potential for coercion can be difficult for surgeons. On the one hand, most accept that the final choice for surgery should be left to the patient. On the other hand,

surgeons want what they believe to be best for their patients. Therefore, there is ample room for unintentional coercion through selecting information for disclosure that overtly reinforces the surgeon's beliefs" [45]. There is also the problem of forming an "innovative alliance." Patients may encourage their surgeons to try any new and promising technique to improve their quality of life or prospects for survival and surgeons also may be eager to apply a promising new technique for the same reasons. It is the duty of the surgeons to decide whether responsible behavior lies in attempting an innovative technique or in concluding that the background research is not sufficient to warrant its use, even when the patient consents [34]. The surgeon has the responsibility to act in the best interest of the patient. The belief that this experimental surgical procedure will not cause too much harm to too many people or that society will benefit at the possible expense of particular individuals violates the duty of the surgeon/researcher to act in the best interest of the patient. To determine whether that duty has been breached, a surgeon/researcher's actions should be measured against the accepted practice as set by professional norms. Those researchers whose treatments fall below the professional standards and cause harm to patients may be held civilly liable for that failure [26]. Various ways have been proposed that ensure individuals going into research protocols are giving informed consent, these include: written and oral forms of consent so that the patient has time to read and reflect on the risks and benefits; someone other than a member of the surgical team obtains the informed consent; obtaining second opinions from other knowledgeable physicians regarding the feasibility of such a procedure; and appointing an objective advocate who would accompany the patient during the decision-making process. These advocates would ensure that the patient is capable of understanding the information and comprehends all the information, that researchers do not overestimate potential benefits and underestimate potential risks, and that all viable options are given, even the option of no transplant. These are not only excellent ideas; they should be implemented with every research protocol.

The complexity of this experimental surgery and its multileveled physical, psychological and social dimensions, make informed consent very complex. Since this surgery has been performed on a limited basis, it would be hard for surgeons to evaluate the long-term potential risks and then adequately inform the patient of them to satisfy informed consent. Therefore, information that is necessary for informed consent is limited at the present time. In fact, the obstacles to informed consent in this situation seem almost insurmountable. In addition to weighing the risks and benefits, we are also asking individuals considering a face transplant to weigh just as many psychologically demanding variables as those involving their identity, their lifestyle and the premises of research-therapy, let alone choosing between quality and quantity. These issues only highlight the complexity and the impossibility of giving informed consent under the circumstances.

Beneficence involves the obligation to prevent and remove harm and to promote the good of the person by minimizing the possible harms or risks and maximizing the potential benefits. Beneficence includes *nonmaleficence*, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim *Primum non nocere*: "Above all do no harm."

Proponents argue that a face transplant will give those individuals who are severely disfigured a new quality of life, if not a "new life." The present conventional reconstructive surgery consists of numerous operations over the course of years to try and reconstruct the person's face using his or her own skin. The problem is that with this type of surgery the skin lacks animation and normalcy of texture and color. Often what is created is a mask-like effect. By contrast, a face transplant would consist of one surgery and because the underlying arteries and veins are included, the tissue would remain supplied with blood, the texture and color would be much better and there would be sensitivity and animation. Proponents also argue that the psychological criticism that the recipient will have the same identity as the donor is untrue. Between the grafts that have been done on corpses by Barker's team and some virtual replications, and the limited number of face transplants to date, it appears that once the skin is draped over the bone and muscle structure of the recipient, what is created is a hybrid face. It would look somewhat like the recipient and somewhat like the donor. Proponents agree that the recipient would have to undergo a regimen of immunosuppressant drugs for the remainder of his or her life and that these drugs do have side-effects, but with the advances that have occurred since the time of the first-hand transplant, the new drug cocktail would sufficiently suppress the immune system while ensuring a tolerable level of toxicity for the patient. There is the chance of rejection and with rejection would come the removal of the face and either a second transplant or reconstructive surgery. However, according to Barker and his team, they

believe the chances of success are high and the quality of the end result will offset the possible risks. In research terms, they believe the equipoise consideration has been satisfied. (Equipoise describes a situation of uncertainty in which the clinical investigator regards the potential outcome of an experiment or clinical trial as truly balanced between its potential for benefiting the patient or for causing unintended harms. The equipoise condition is a fundamental ethical requirement for proceeding with a clinical trial) [34]. Proponents like Barker contend that the risks are present as they are with any form of transplantation, but that if a patient comprehends the risks and benefits and consents freely and knowingly to the surgery, then that individual should be given the right to make that informed decision. To delay the inevitable when the knowledge, technology and skills are available and when patients believe this surgery is in their best interest, is not only standing in the way of scientific advancement but is failing to promote the good of the patient.

Opponents, including the panel of experts at the Royal College of Surgeons in England and the CCNE in France, are not averse to the surgery and recognize it as a possible future treatment, but at the moment, they believe the risks outweigh the potential benefits. The three major risks are: failure of the transplant, side-effects of the immunosuppressant drugs, and the psycho-social effects of the transplant. First, rejection of the face transplant is a real possibility. Surgical teams are confident of potential success because of the successes they have seen with limb transplants and the previous 45 partial/full face transplants. The problem is that these previous limb transplants have taken place in the last ten years so we do not know how long they will last. The question arises: how many years does the limb graft have to last for it to be considered successful? [26]. The Royal College of Surgeons panel estimates that there might be a "graft loss of around ten per cent from acute rejection within the first year and significant loss of graft function from chronic rejection in around 30–50 per cent of patients over the first 2–5 years might be a reasonable estimate [45]. Opponents argue that even with the latest immunosuppressant drugs, transplanted kidneys survive less than 10 years on average, and they doubt that hand or face transplants will last much longer. Rejection could occur within hours due to clotting of the arteries or veins. If it were rapidly diagnosed the anastomosis might be salvageable by re-exploration and re-anastomosis of the vessels. If this failed the transplant would have to be removed. Acute rejection of the transplant would be apparent generally within days or weeks and unless reversed by medications would lead to necrosis of the transplant tissue. In the event of either a technical failure or acute rejection the transplant would have to be removed. Because previous skin grafts would have been removed prior to the transplantation, the patient would have to have further skin grafts of their own tissue to replace the failed rejected tissue, assuming that there were sufficient healthy donor skin sites. In this event there is the possibility of even more scarring than there was originally. The risk of free tissue transfer failure for technical reasons in experienced units is considered to be less than 5%. The risk of failure of an allografted free tissue transfer from acute rejection is unknown but might be 10% with current immunosuppression [45]. The medical and psychological trauma this would cause the patient is incalculable. It is possible that the patient would be in worse shape after rejection than before the face transplant. The patient would be converted "from a stable, non-evolving situation of physician and functional disability with psychological repercussions, to an unstable extensive wound with possible serious physical and psychological consequences" [28]. This possibility alone would convince most that more time is needed until better techniques are developed to prevent rejection.

Second, after a face transplant, the recipient would have to take a regimen of immunosuppressant drugs for the remainder of his or her life. The skin is likely the main target of rejection. "The skin is particularly susceptible to rejection and this is one of the major obstacles to the success of human composite tissue transplantation" [45]. Barker and his team have developed a three-drug mixture (FK506, MMF and Prednisone) that "maximizes immunosuppression and minimizes systemic toxic side effects" [5]. This successful combination has allowed for the 20 or so limb transplants worldwide. However, with any type of transplant – organ or limb – there are serious side-effects to these immunosuppressant drugs including conditions that may shorten life. "Long-term side effects of the immunosuppressants fall into three categories: opportunistic infections (cutaneous fungal, and tinea infections, and cytomegalovirus and herpes virus recurrences), metabolic disorders (diabetes, Cushing's syndrome), and malignancies (basal cell and squamous cell carcinomas and Epstein-Barr virus B-cell lymphoproliferative disorders)" [28]. Since higher doses would be needed following a face transplant because of the large quantity of skin in the graft, this will provoke a stronger immune reaction than in other organs [30]. These serious side effects overshadow the benefits of

correcting physical or functional disabilities. In addition, some wonder if recipients would follow the strict regimen of antirejection drugs, and some associated lifestyle changes such as sun exposure and changes in diet [37]. The issue of non-compliance with immunosuppressive medications is a major concern in all organ transplants. “An estimated 15–18% of organ transplant recipients become non-compliant. The problem is highest in the young and from those in lower socio-economic groups. Non-compliance invariably leads to graft failure and is difficult to manage because this behavior is usually unpredictable and may not have a clearly identifiable cause” [45]. What this procedure would do, if successful, is improve the person’s quality of life at the same time intentionally making the person sick due to the harmful side-effects. For a nonlife saving procedure that has a viable option, the risks clearly outweigh the benefits.

Third, from a psychological perspective, face transplants are very different from organ transplants because you are taking a part of someone’s identity and losing a part of your identity. A face is such a part of one’s identity that the problems of coping with a new face and the psychological difficulties that will ensue would be highly problematic. Barker and his team are confident that the recipient’s new face will be a hybrid face resembling both the donor and the recipient. But in any case, it will be a new face and thus a new identity. The medical literature shows that the extent of psychological distress from a visible difference is not well predicated by the extent or severity of the disfiguration. Some cope well with an extensive and very visible disfigurement while others struggle with a relatively minor difference. Coping well can be attributed to a high self-esteem that is derived from other factors than physical appearance. Those who cope poorly derive self-esteem from their appearance, and believe others evaluate them largely based on their physical appearance. These individuals are more prone to unrealistic expectations of change following surgical interventions. Therefore, the more vulnerable will be less equipped to deal with the aftermath of complex transplant surgery, uncertain outcomes and ongoing treatment regimens [45], [12]. It should be noted that the first-hand transplant patient was ill-prepared psychologically, did not comply with the immunosuppressant therapy, and finally, got to the point where he could not stand the sight of his hand. The hand was then removed [44]. The removal of a face transplant would have disastrous consequences both medically and psychologically for the recipient.

Another issue psychologically is the issue of quality versus quantity of life. The recipient will know that he or she will sacrifice years of life because of the immunosuppressant drugs and complications for a particular quality of life. Psychologically, one will have to face one’s own death and its effect. “The psychological impact of knowing from what and how one will die should not be trivialized; in other circumstances this is used as a means of torture” [26]. Much of this will depend on the individual person and his or her self-esteem. However, it seems almost too much for any one person to have to handle psychologically because there are so many variables and unknowns. There is also the psychological impact on the donor’s family. Such families may have feelings of guilt if they allow for the transplant and as a result, bury their faceless loved one. The American death ritual of an open casket and public viewing of the body would be impossible in such cases. “Carving up a body is already seen as a form of violence which is only acceptable because it can save other lives. To remove a face only to give hope to one whose face has been destroyed is unlikely to be accepted as lifesaving” [44]. Many families may believe that since the donor was a living person, then their corpse should be treated with the proper respect. There is also the issue of seeing the face of a deceased loved one on another person. In most organ donations the donor remains anonymous. However, because of the external nature of the face, which involves a persons’ identity and because of the large amount of publicity that will surround this surgery, it will be difficult to conceal the donor’s identity from relatives and friends [6]. It will also be difficult to protect the anonymity and confidentiality of the donor, recipient, and their respective families from the public and the press. Some fear the large amount of publicity will place unrealistic expectations on the recipient thus creating additional psychological stress and pressure for him or her and reinforce the notion that a good quality of life can never be achieved by individuals with disfiguring conditions [45]. To imagine or even calculate the psychological impact on the recipient, his or her family and the family of the donor seems almost impossible.

No one will dispute that balancing the benefits and risks is difficult. Some will say that it is the severely disfigured person who should be given this opportunity because for some people, quality of life is far more important than quantity of life. However, after reviewing the facts concerning the state of our knowledge regarding the rate of rejection, the effects of immunosuppressant drugs and the inevitable psychological impact on the recipient and the

donor's family, it is clear that this surgery does not minimize the risks incurred by these patients but exposes them to unnecessary risks that have the potential for injury, harm, and even death. This is still an experimental, non-lifesaving surgery with serious and even deadly unknowns. Arguably, this surgery not only fails the test of beneficence, but also fails the test of nonmaleficence.

Finally, *justice* recognizes that each person should be treated fairly and equitably, and be given his or her due. The principle of justice can be applied to this situation in two ways. First, questions of justice have been raised about whether those patients who are severely facially disfigured might be classified as vulnerable individuals and whether this type of experimental surgery is a form of exploitation. No one seems to dispute that surgeons have the skills and techniques needed to perform this microsurgery. However, there also seems to be a competition present among the 5 surgical teams worldwide to be the first to perform this type of surgery. This debate cannot and must not be framed within the aspirations of the surgeons. There must be equality between the surgeons and the possible recipients. To allow these charismatic surgeons to present this form of transplantation in the media in such a way that seems to trivialize the side-effects and downplays the possibility of rejection and even death, is to exploit these recipients and use them as a means to an end. At the present time the debate among the transplant surgeons is on how they should proceed. Barker himself states clearly that he sees no need for a delay in increasing the surgery because there is nothing to be learned during this time of delay [30]. With this attitude, how objective and unbiased will the information about the surgery and its possible benefits and risks be that will be disclosed to potential recipients? Are these potential recipients not in some cases desperate to regain their quality of life? How will surgeons know when the potential vulnerability of some patients is unduly influencing their willingness to consent? These transplant surgeons have suggested ways they believe will ensure informed consent however, because this is a non-lifesaving transplant and there are other viable options, one could say it is unjust to place these vulnerable individuals in this position now when more time might give them a better chance at survival.

Second, the issue of justice pertains to face transplantation specifically in regard to distributive justice, which concerns the fair and equitable allocation of medical resources. As we have shown above, face transplantations are not cost-effective and place an undue financial burden on the healthcare system as a whole. Another issue here is research priorities. Should funds be used to support face transplantation surgery now when the risks seem unreasonable and even deadly? The amount of money spent on these surgeries could certainly be invested in new ways to tolerate immunosuppressant drugs and primate experimentation to lessen the rejection rate. This would help to minimize the risks and maximize the benefits not only for recipients of face transplants but for all transplant patients. Also, immunosuppressant drugs cost tens of thousands of dollars a year. Will this not limit the individuals who would qualify for this surgery? If so, this now becomes a social justice issue, because those who would have access to this technique would logically be those who are privileged. The poor, the uninsured, the underinsured, and many middle-class individuals would never be viable candidates for this surgery, because they could not afford the cost of a life-time supply of immunosuppressant drugs. As a matter of social justice, who this surgery would benefit and whether it is a fair and equitable allocation of medical resources is an important ethical issue. Medical professionals have an ethical obligation to use available resources fairly and to distribute them equitably.

Ethically, if there is a standardization of outcomes and comprehensive inclusion/exclusion criteria for face transplants and guidelines for informed consent, then and only then would this surgery be ethically permissible.

V. CONCLUSION

Utilizing an interdisciplinary approach to analyze the quandary that is face CTA has revealed that the benefits of the procedure do not outweigh its drawbacks, thus making it a nonviable treatment option. Although there have been significant medical advancements since its inception in 2005, the face CTA procedure still lacks long term data needed to generate standardized outcomes. Furthermore, the procedure is not cost-effective and places an undue financial burden on the healthcare system as a whole. Granted, face CTA does provide an avenue for improved psychological outcomes in patients with severe facial disfigurement. However, these benefits may be compromised based on various patient specific factors. As seen from the medical perspective, there is not enough data to generate standardized psychosocial outcomes as a result of undergoing face CTA.

While research shows that facial disfigurements result in psychological trauma and decreased willingness to interact

socially, at this point in time the potential harms associated with facial transplants outweigh the benefits. Although recipients of these transplants agree that undergoing such an experimental procedure is worth the increased quality of life, one must consider the unethical medical risks associated with such an art and the complexity of obtaining truly informed consent in these cases. Facial transplantations fail to adhere to the principles of beneficence and nonmaleficence. Rejection, side-effects of life-long reliance on immunosuppressants, and psycho-social effects are simply a few of the most prominent risks. Regarding justice, facial transplants may be taking valuable funds away from more beneficial and ethical research that does not approach the exploitation of vulnerable patients. Although the facial transplantation realm is prospering, from an ethical perspective, standards must be enacted if the field wishes to continue to progress.

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