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**Key psychosocial challenges in vascularized composite allotransplantation**

KumnigM *et al.* Psychological challenges in VCA

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**Abstract**

Psychosocial factors are important elements in the assessment and follow-up care for vascularized composite allotransplantation (VCA) and require multidisciplinary evaluation protocols. This review will highlight differences between VCA with solid organ transplantation (SOT), provide information on the psychosocial selection of VCA candidates, ethical issues, psychological outcomes, and on the need for multicenter research. VCA is primarily a life-enhancing procedure to improve recipients’ quality of life and psychological well-being and it represents a potential option to provide reproduction in case of penile or uterine transplantation. The risk benefit ratio is distinctly different than SOT with candidates desiring life enhancing outcomes including improved body image, return to occupations, restored touch, and for uterine transplant, pregnancy. The Chauvet Workgroup has been convened with membership from a number of transplant centers to address these issues and to call for. A multicenter research network would share similar evaluation approaches so that meaningful research on psychosocial variables could inform the transplant community and patients about factors that increase risk of non-adherence and other adverse psychosocial and medical outcomes.

**Key words**: Vascularized composite allotransplantation; Psychological evaluation; Motivation; Psychosocial outcomes; Quality of life

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**Core tip:** A psychosocial evaluation for vascularized composite allotransplantation (VCA) is unique and should be informed by many characteristics that are described in this review article including the importance of multidisciplinary care and the need for careful selection of candidates for VCA. Important areas to consider in the evaluation include: history of ability to comply with medical care, body image, adaptation to previous trauma and preparedness for transplantation, reasonable expectations, and presence of adaptive coping skills of the candidate. Multicenter research will support better understanding of psychosocial variables that predict outcome. Optimally, developing a common evaluation strategy to enhance comparison of candidates with good outcomes to those with less optimal outcomes will help in future selection of candidates.

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**The history of vascularized composite tissue allotransplantation**

The rapidly expanding vascularized composite allotransplantation (VCA) field combines the technical challenges of surgery and microsurgery with the multidisciplinary care that characterizes solid organ transplantation (SOT)[[1](#_ENREF_1),[2](#_ENREF_2)]. The technical demands of VCA and complex psychosocial issues pertaining to the recipients significantly accounts for the discrepancy between these two related fields[[3](#_ENREF_3)]. Although VCA and SOT share a common history, VCA has not yet been performed on a scale approaching that of SOT[[1](#_ENREF_1),[4](#_ENREF_4)]. Currently, the following four main domains for VCA exist: hand, face, uterus, penis transplantation although other areas are emerging.

In the history of medicine there are several well documented cases that demonstrate the developing concept of reconstructive transplantation medicine[[2](#_ENREF_2),[5](#_ENREF_5),[6](#_ENREF_6)]. One such account is “The Legend of the Black Leg (Leggenda Aurea)”, about twins Cosmos and Damian, who transplanted the leg of a man with that of an Ethiopian in 348 AD[[7](#_ENREF_7)]. In the 16th century, in Italy, Gaspare Tagliacozzi transplanted a nose from a slave to his master[[8](#_ENREF_8)]. Reports of tissue transplants occasionally were reported[[6](#_ENREF_6)]. Bunger[[9](#_ENREF_9)] performed a transplant involving a sheepskin. Carrel[[10](#_ENREF_10)] attached an artery from the arm of a father to the leg of his infant son who suffered from intestinal bleeding[[11](#_ENREF_11)]. Guthrie[[12](#_ENREF_12)] transplanted dog heads onto the neck of other-dogs. Although surgical techniques were created, the immunological challenges made transplant unfeasible[[13](#_ENREF_13)]. Until the discoveries of Medawar and colleagues[[14](#_ENREF_14)], who described rejection which allowed advances leading to modern transplant immunology[[5](#_ENREF_5),[15](#_ENREF_15)]. In 1957 Earle E Peacock[[16](#_ENREF_16),[17](#_ENREF_17)], coined the term composite tissue allograft and in 1964, Robert Gilbert[[18](#_ENREF_18)], performed the first hand transplantation (HTx) in Ecuador. A single hand was transplanted to a bilateral hand amputee, but the graft was amputated three weeks later as a result of acute rejection. This early unsuccessful experience contributed to a 30-year period of stagnation in the field. Significant developments in immunosuppressive drug therapy facilitated the growth of SOT[[2](#_ENREF_2),[5](#_ENREF_5)]. The next two HTx were performed in 1998 by pioneers Jean-Michel Dubernard[[19-21](#_ENREF_19)] in Lyon and in 1999 Warren Breidenbach[[22](#_ENREF_22)] in Louisville, thus starting the modern era of reconstructive HTx[[6](#_ENREF_6)]. Since 1998 73 HTx, 23 unilateral and 25 bilateral transplant, for a total of 48 patients have been reported[[23](#_ENREF_23)].

The encouraging outcomes in human hand transplants led to the development of human face transplant (FTx) programs[[6](#_ENREF_6)]. In 2003, surgeons in Nanjing, China transplanted a skin flap including an extensive part of the scalp and both ears[[24](#_ENREF_24)]. In 2005, by transplanting a triangular graft from the nose to the chin including the lips, Bernhard Devauchelle and Jean-Michel Dubernard from Lyon performed a partial face transplant on a woman disfigured by a dog bite[[13](#_ENREF_13),[25](#_ENREF_25)]. In April 2006, a 30-year man suffering from trauma from a bear, received the second face transplant[[26](#_ENREF_26)].

Face transplantation has garnered wide interest with the public and in the media due to the importance to identity that the face represents. Therefore, psychosocial issues in FTx are as important as in HTx or more so and the multidisciplinary evaluation and treatment has to ensure that these are addressed adequately. Since the first FTx in 2005, almost 32 face transplant have been performed worldwide with promising outcomes including reasonable functional improvements and reports of patients satisfaction[[23](#_ENREF_23),[27](#_ENREF_27)].

Recently, penile (PTx) and uterine transplantation (UTx) are the focus of VCA research. In 1992, a conceptual framework for human PTx was developed by Eberli *et al*[[28](#_ENREF_28)] in 2008 who transplanted bioengineered penises onto rabbits. Already in 2006, a Chinese man received the first donor penis, but the transplant had to be removed by surgeons because at the request of both the patient and his partner. This first case emphasizes the psychological impact that transplants can have, especially with an organ as significant to sexual function and identity as the penis. The first successful PTx was performed on a 21-year-old man in December 2014 by André van der Merwe and Frank Graewe at the University of Sellenbosch in South Africa[[29](#_ENREF_29)]. Meanwhile, the recipient has been reported to have recovered function in the organ (including urination, erection, orgasm, and ejaculation), and has, remarkably, since successfully conceived a child[[30](#_ENREF_30)].

The earliest UTx was performed in 1931 on a transgender woman in Denmark who died from rejection three months after transplantation[[31](#_ENREF_31)]. The development of [in vitro fertilization](https://en.wikipedia.org/wiki/In_vitro_fertilization) in late 70s resulted in decreased interest in this area[[32](#_ENREF_32)]. Two UTx attempts by teams with no preceding research records in this field followed. In Saudi Arabia in 2000 an UTx was performed from an older hysterectomy patient into a 26-year-old. The graft failed due to vascular occlusion[[33](#_ENREF_33),[34](#_ENREF_34)]. In 2011, the second transplant involved a uterine graft from a deceased female multiorgan donor[[35](#_ENREF_35)]. This case resulted in two pregnancies but with early miscarriage[[36](#_ENREF_36)]. The first mother-to-daughter uterine transplant was performed in 2012 in Sweden[[37](#_ENREF_37)]. Following extensive preliminary research that UTx is a treatment for absolute uterine factor infertility (AUFI) and that also this AUFI treatment, which combines in vitro fertilization and UTx, is already a viable option for selected infertile patients[[38](#_ENREF_38)]. The UTx project encompasses a total of 9 recipients and the first live birth after UTx was reported[[39](#_ENREF_39)]. Because of the risks of an invasive organ transplant procedure and to avoid the need for lifetime immunosuppression, this is considered a temporary transplant with the expectation of hysterectomy after couple of successful pregnancies[[38](#_ENREF_38)].

As already determined from SOT, transplant outcomes depend on the selection of an optimal combination of immunological, surgical, and psychosocial factors. The history of VCA underscores the importance of interdisciplinary assessment before surgery. A patient’s psychosocial suitability for VCA is as important as the surgeon’s technical ability and the effectiveness of postoperative immunosuppression[[3](#_ENREF_3)]. Several cases of noncompliance with immunosuppression and physical therapy have reveal how allograft survival needs to be supported by psychosocial stability and an ability to comply with complex medical care[[3](#_ENREF_3)]. This is especially critical when the graft is involved in tasks related to a part of the body that senses, supports instruments tasks of daily living, and is visible to others[[2](#_ENREF_2),[3](#_ENREF_3)]. Additionally, what all kinds of VCA have in common is the fact that there are still ethical concerns regarding the entire procedures, especially because the VCA is a life-enhancing not life-saving procedure, with psychosocial issues like quality of life (QOL), body image, psychological well-being, *etc*. weighing significantly in the risk benefit ratio of candidates considering VCA[[3](#_ENREF_3),[40](#_ENREF_40)].

At present the number of successful VCAs is increasing and several transplant centers worldwide have developed specific VCA programs[[40](#_ENREF_40)]. Although research provides some understanding of functional and sensory outcomes, psychosocial outcomes have been minimally reported[[3](#_ENREF_3)]. We will discuss in this paper aspects of VCA transplantation that have been reported in the literature and extrapolate from literature in SOT to anticipate key areas of interest to enhance psychosocial outcomes in VCA and discuss the key psychosocial challenges we face in VCA today.

**Psychosocial implications of VCA**

As already discussed, certain characteristics of VCA are uniquely different from SOT, particularly because VCA is primarily a procedure to improve the recipients’ QOL and psychological well-being or represents a potential option to provide reproduction in case of PTx and UTx. Since candidates considering VCA present no life-threatening illness, their motivation related to improved functional outcomes, occupational attainment, improved body image, resorted touch, and in uterine transplantation, pregnancy[[3](#_ENREF_3)]. Therefore, scientific consensus exits that the assessment of the candidates’ desire for VCA is a psychologically complex and warrants a customized psychosocial evaluation protocol that fully addresses the issues noted above[[3](#_ENREF_3)].

Again, comparing the psychosocial characteristic of VCA with SOT, visible nature of the allograft strikingly changes the experience of transplantation for VCA recipients[[40](#_ENREF_40),[41](#_ENREF_41)] (other than UTx). Visible grafts could adversely effects the recipients’ sense of themselves as an integrated whole, leading to rejection of the grafts as undesirable[[42](#_ENREF_42)]. Several cases demonstrated the importance of the successful psychological integration of the allograft for post-transplant outcomes, *e.g*., amputation of the first successfully transplanted penis because of the recipient’s and his partner’s coping inability. Notably, patients must accept a new graft while adapting their loss of a part of their body that was unique to them[[43](#_ENREF_43)]. This requires alterations in their sense of who they are, how the graft fits in with their body, and ultimately acceptance of the allograft as part of themselves[[44](#_ENREF_44)].

When considering factors that could impair candidates’ adherence with medications and physical therapy[[45-47](#_ENREF_45)], relevant information will be obtained by examining their psychiatric history, coping abilities, and social support[[48](#_ENREF_48)]. In paCoping styles, support from family and friends, financial, and logistical factors emerge as important predictors of successful outcomes[[48](#_ENREF_48)]. Therefore, the evaluation protocol should additionally provide an assessment of family relationships and anticipate stress that might come from media attention which has occurred in a number of VCA cases[[49](#_ENREF_49)]. Patients will experience an initial decrease in function and caregivers will need to prepare for increased recipients needs for instrumental tasks of daily living potentially while also carrying a heavier burden of caring for children and maintaining employment[[3](#_ENREF_3)].

***Ethical considerations***

Aside from considerations of technical demands regarding modern transplant programs and costs, the field of VCA involves a number of ethical issues[[50](#_ENREF_50)]. The principle of patient autonomy is necessary these procedures balanced by nonmaleficence support limited risk to patients. It would appear that beneficence and justice are equivocal in this population[[51](#_ENREF_51)].

No instruments exist to fully measure the impact of hand(s) loss, facial distortion, the loss of penis, and reproduction inability[[3](#_ENREF_3)]. This makes the assessment process in VCA especially challenging[[51](#_ENREF_51)]. Prospective research and qualitative studies should focus on the unique qualities of this experience including the highly individual nature of the VCA including, spiritual and cultural factors that also may be important[[52](#_ENREF_52)]. Ethical issues are myriad and collaborating with biomedical ethics experts would do justice to the complex issues that may arise for this patient population[[3](#_ENREF_3)].

Three important ethical considerations are patient selection, patient advocacy, and informed consent[[53](#_ENREF_53)]. When assessing for decision-making capacity and the candidates’ overall ethical suitability to receive a VCA, the ethical guidance process should be based on this rubric of questions[[54](#_ENREF_54),[55](#_ENREF_55)]. Similar to living donation, the Lyon team viewed the first HTx decision as being one in which the candidate had to weigh the pros and cons from themselves[[56](#_ENREF_56)]. Informed consent for VCA recipients is a detailed process focusing on risks in surgery and anaesthesia post-surgical complications (*e.g*., immunosuppressive effects, psychiatric disorders, *etc*.)[[53](#_ENREF_53),[54](#_ENREF_54),[56](#_ENREF_56)]. Consent related to the donor, also on area of interested with some countries having an “opt-out” system with implications for how families may experience the donor related experience[[56](#_ENREF_56)].

Ethical considerations were noted in the “Montreal Criteria for the Ethical Feasibility of Uterine Transplantation”[[57](#_ENREF_57)] that describe a set of criteria for the ethical practice of UTx in humans and we refer interested reader the original paper on this. Key points include that the candidate has failed other therapy and is not eligible for other options such as adoption. An assessment of the candidates’ ability to manage the tasks of motherhood is noted. The donor must have decided that their reproductive years are concluded and be able to consent to donate and be free of coercion. Finally, the institution must have all the needed staff and facilities to provide the care and ensure informed consent for donor and recipients as well as protection of anonymity in the process.

In addition, another important and challenging question is a Philosophical one related to allograft represents personal identity including implications for how one communicates with others[[56](#_ENREF_56)]. In case of PTx we have to consider the function of physical intimacy. The intimate nature of the grafts may have implications for others with whom the donors has been intimate and for future partners of the recipient[[6](#_ENREF_6),[50](#_ENREF_50),[56](#_ENREF_56),[58](#_ENREF_58)].

In summary, the ethical issues in VCA are quite complex and are unique to this population and effect the recipients very sense of being[[50](#_ENREF_50)], which may impact post-transplant motivation[[59](#_ENREF_59),[60](#_ENREF_60)]. Utilizing biomedical ethics consultation on a case basis may be especially helpful for this population[[51](#_ENREF_51)].

***Risk-benefit considerations***

As noted in the international literature, VCA is life enhancing rather than life saving such as in the case in SOT[[1](#_ENREF_1),[56](#_ENREF_56)]. VCA candidates may overestimate the benefits of the procedure while minimizing the recovery period and not fully acknowledging the surgical risk, demanding post-transplant medication regimen, and rehabilitation requirements[[3](#_ENREF_3),[61](#_ENREF_61)]. The risk benefit ratio is quite different than SOT in which the risks are offset by the lifesaving nature of the procedure[[3](#_ENREF_3),[40](#_ENREF_40),[51](#_ENREF_51)]. VCA candidates have to face potential episodes of acute rejection[[62](#_ENREF_62)] and immunosuppression-related complications are typically but can be reversed with proper medical treatment[[63](#_ENREF_63),[64](#_ENREF_64)]. Chronic allograft rejection that is predicted by the frequency and timing of rejection episodes has become a primary cause of long-term allograft failure[[62](#_ENREF_62)]. Particularly, the risks of nonspecific immunosuppression[[50](#_ENREF_50),[65](#_ENREF_65)] and the lengthy rehabilitation are the most important critical aspects that may lead to demoralization and non-adherence in rehabilitation[[52](#_ENREF_52),[66](#_ENREF_66)]. Rejection episodes and delayed function, difficulty with the rehabilitation, and long-term side effects of immunosuppressive treatment (*e.g.*, malignancy, metabolic infections/disorders, diabetes, renal failure, *etc.*)[[50](#_ENREF_50),[65](#_ENREF_65)] may cause mood changes, anxiety as well as depressive reactions that substantially impact patients’ adherence and require supportive treatment.

Although immunoregulatory protocols continue to be developed with decreased toxicity[[67](#_ENREF_67)] immunosuppressive medications are still required[[3](#_ENREF_3)], necessitating careful patient selection given the problematic nature of the risks of these therapies[[68](#_ENREF_68)] including infection, metabolic derangements[[46](#_ENREF_46),[47](#_ENREF_47),[69](#_ENREF_69),[70](#_ENREF_70)], toxicity[[70-73](#_ENREF_70)], and cancer[[69-74](#_ENREF_69)]. This potential improved function must be balanced against this significant risks[[63](#_ENREF_63),[67](#_ENREF_67)]. Patients have different risk thresholds which contribute to their decision making about how much risk they are willing to accept for improved function[[55](#_ENREF_55),[66](#_ENREF_66),[75-77](#_ENREF_75)], especially taking the psychosocial aspects of VCA into account (*e.g.*, QOL factors, sense of identity, understanding of the treatment and its limitations, *etc*.)[[50](#_ENREF_50)]. In summary, the risk versus benefit decisions has to be judged on wider criteria that must include all relevant psychosocial aspects of VCA[[78](#_ENREF_78)].

Despite the encouraging results regarding the aesthetic and functional outcomes that have been achieved in patients who have undergone HTx in the last 15 years risks persist[[50](#_ENREF_50),[66](#_ENREF_66),[75](#_ENREF_75),[76](#_ENREF_76)]. The International Registry on Hand and Composite Tissue Transplantation (IRHCTT)[[23](#_ENREF_23),[64](#_ENREF_64)] represents the world’s largest database and research initiative to collect information from each case of VCA or composite tissue allotransplantation (CTA), as it provides a comprehensive overview about what is happening in this new field of transplantation medicine. Currently, the IRHCTT includes cases of upper extremity and face allotransplantation performed all over the world[[23](#_ENREF_23)] with rejection rates of 85% of the hand and face patients in the first year and three recipients have died[[23](#_ENREF_23),[64](#_ENREF_64)]. 7hands grafts were lost due to rejection in China[[23](#_ENREF_23),[63](#_ENREF_63)] and a similar number have been lost to rejection and other complications in European and American experience[[23](#_ENREF_23),[63](#_ENREF_63),[64](#_ENREF_64),[79](#_ENREF_79),[80](#_ENREF_80)]. Fortunately rejection was often detected and treated without loss of graft[[23](#_ENREF_23),[63](#_ENREF_63),[64](#_ENREF_64)].

This literature highlights the need for careful patient selection to ensure that proper adherence to medication regimens occurs[[3](#_ENREF_3),[68](#_ENREF_68)]. Unilateral amputees appear to be more risk adverse due to the less compelling need for the graft while bilateral hand patients may be willing to accept the risk of rejection which is offset by the potential for significantly enhanced independence[[3](#_ENREF_3),77].

Similar to the risk-benefit profile of HTx candidates, those who consider FTx also have to face specific risks and make their decision on the expected benefits[[81](#_ENREF_81)]. Beside the documented benefits of FTx, like the improved functionality (*e.g.*, ability to breathe, speak, swallow, smile, *etc*.), the restoration of a near-normal facial appearance, and the reduction of pain and discomfort (FTx is one large procedure, whereas conventional face reconstruction involves many surgeries), there are certain risks that tend to be peculiar to FTx: For example, the donor’s appearance is not transferred to the recipient and the recipient is not typically recognizable immediately following surgery, so that the patient potentially may feel upset about having a new (changed) face[[81-84](#_ENREF_81)]. The IRHCTT[[64](#_ENREF_64)] data document episodes of acute rejection in 60% during the first year after FTx (on average two episodes per year). One FTx team declared a case of “chronic” rejection whereas other teams described chronic rejection to the IRHCTT. When looking at the patients’ survival: One patient (simultaneous face and bilateral hand transplantation) died for cerebral anoxia on day 65; one patient died for lung failure 11 mo after transplantation; one patient died for pharyngo-laryngeal neoplasia 3 years after transplantation. Only one graft has been removed for unknown causes. In addition, the following complications/side effects have been reported: Opportunistic infections (*e.g*., herpes virus, bacterial infection, *etc.*), metabolic complications (*e.g*., hypertension, increased creatinine values, *etc*.), malignancies (*e.g.*, basal cell carcinoma, pharyngo-laryngeal neoplasia), and other side effects (*e.g.*, neurofibromatosis of the transplanted face, trauma of grafted face, *etc*.)[[27](#_ENREF_27)].

Candidates who consider PTx or UTx share the same burdens and risks that are characteristic of VCA. The candidates have to face the risks of the surgical procedure, of ischemic injury, of graft loss, psychosocial complications (*e.g.*, inability to accept the allograft, interpersonal conflicts, non-adherence, *etc*.)[[85](#_ENREF_85)]. In case of UTx, additionally, the risks of living donors (in most cases the mother of the female recipient became the donor who provided the uterus) need to be considered since they have to bear the particular burden of hysterectomy. Notably, the examination of mental conditions and QOL after hysterectomy is important, because a donor may have decreased QOL due to complications (*e.g.*, affected sexuality). Donors after hysterectomy may have unstable mental conditions including anxiety and depression, and may have additional burden from severe stress due to postoperative pain[[85](#_ENREF_85)]. Because the uterus is a symbol of femininity, childbearing, sexuality, vitality, youth, attractiveness[[86-88](#_ENREF_86)], the hysterectomy can lead to postoperative regression[[89-92](#_ENREF_89)], distortion of body image[[87](#_ENREF_87),[93](#_ENREF_93)], and loss of feminine self-image[[94](#_ENREF_94)].

**Psychosocial research in hand transplantation**

While it is universally accepted that a psychosocial evaluation is needed in SOT[[95](#_ENREF_95),[96](#_ENREF_96)], the literature is still evolving and no single evaluation strategy has emerged[[3](#_ENREF_3)]. Although no standard approach has been published[[20](#_ENREF_20),[22](#_ENREF_22),[41](#_ENREF_41),[49](#_ENREF_49),[51](#_ENREF_51),[97-113](#_ENREF_97)], several domains have emerged as important and predictive on increased risk[[3](#_ENREF_3),[114-121](#_ENREF_114)]. Recent efforts in research are occurring to attempt to address this deficiency in the literature[[40](#_ENREF_40)].

Generic instruments have been developed to identify areas relevant to transplant populations (*e.g*., psychiatric disorders, adherence, transplant health literacy, *etc*.)[[3](#_ENREF_3),[122-124](#_ENREF_122)], but are not designed areas specific for HTx such as satisfaction with prostheses, body image, physical limitations, and phantom limb pain[[40](#_ENREF_40)]. Creating a screening instrument customized for these patients is a goal for the field[[40](#_ENREF_40),[125](#_ENREF_125)].

A review of psychosocial evaluation strategies has been previously reported[[40](#_ENREF_40)] which includes semi-structured psychiatrist or psychologic evaluations and/or psychometric and projective testing[[20](#_ENREF_20),[22](#_ENREF_22),[41](#_ENREF_41),[49](#_ENREF_49),[51](#_ENREF_51),[97-113](#_ENREF_97)]. Case studies focusing on patients QOL, satisfactions with outcomes, and body image improvements have been a large part of the research reported[[40](#_ENREF_40),[101](#_ENREF_101)]. Overall, the majority of recipients reported having psychologically integrated the hand, and reported improved confidence in appearance and in social situations[[102](#_ENREF_102),[105](#_ENREF_105)]. The recipients assimilated the transplanted hand(s) into their body-/self-image and were able to develop a sense of “ownership”. Another important outcome was the observed improvements in QOL and ADLs[[3](#_ENREF_3)].

Unmet expectations and either new or recurring psychiatric conditions have been reported[[126](#_ENREF_126)]: Including suicide attempts following hand transplant[[105](#_ENREF_105)]; request for amputation because the recipient could not integrate the grafted hand into his sense of self[[111](#_ENREF_111)]. The inability to psychologically incorporate the transplanted hand(s) may result in non-adherence with medications[[40](#_ENREF_40),[45-47](#_ENREF_45)], which in turn will lead to rejection and may necessitate amputation[[45](#_ENREF_45)]. Additionally, recipients may be frustrated with the lengthy process of recovery including loss of ability to do tasks while rehabilitating leading to decreases physical QOL at least initially[[3](#_ENREF_3),[63](#_ENREF_63)].

Optimally candidates will have a strong motivation for transplant and have demonstrated good compliance with medical care in the past, have strong family support, utilize acceptance, flexibility and problem solving in adapting to the loss of function from the injury/deficit and for future rehabilitation following transplant[[3](#_ENREF_3),[127-129](#_ENREF_127)]. Having appropriate expectations regarding immunosuppressive risks, surgical complications, and realistic understanding of functional gains after transplant is the best scenario for a psychologically prepared candidate[[55](#_ENREF_55),[61](#_ENREF_61)].

The optimal assessment includes: Health literacy regarding transplantation, assessment of pain related to amputation and phantom limb pain, family support, adaptation to prosthesis, financial and family stressors, assessed through multiple interactions with a variety of assessors including psychiatrists, psychologists, social workers, hand therapists, and all team members[[3](#_ENREF_3),[48](#_ENREF_48),[130](#_ENREF_130)]. Future research efforts directed at sharing similar evaluation strategies across centers in research protocols to determine best practices and predictive factors for optimal outcomes are needed[[3](#_ENREF_3)]. Another important component of interdisciplinary screening should be the identification of at-risk candidates. Intervention strategies to assist these candidates might then lead them to be eligible for this treatment and might especially be beneficial in supporting their ability to succeed with medication adherence and overall QOL post transplantation[[3](#_ENREF_3),[49](#_ENREF_49),[131](#_ENREF_131)].

**Psychosocial research in face transplantation**

FTx results in a visible change that affects social interactions and self-esteem in a profound way[[81](#_ENREF_81),[132](#_ENREF_132)], because the face is closely linked with a person’s identity[[83](#_ENREF_83)] and can be conceptualized as an allotransplant with various functions (including communication, expression of emotion, perfection, *etc*.)[[133](#_ENREF_133)]. For the reason, FTx is never performed for cosmetic reasons alone[[134](#_ENREF_134)]. In case of facial disfigurement several difficulties, such as depression, anxiety, low self-esteem and QOL, poor marital and social relationships, and changes in body image have frequently been reported[[135](#_ENREF_135)]. What all types of VCA have in common, including FTx, is the fact that increased emphasis is placed on informed consent for a life-enhancing surgical procedure. Speech therapy and reintegrating into social settings are important[[134](#_ENREF_134)] as are tracheotomy care and strategies for maintaining nutrition[[81](#_ENREF_81),[136](#_ENREF_136)]. Plans for managing graft failure with a skin graft or flap are also described in the literature[[134](#_ENREF_134)].

When selecting candidates for FTx, the idea that the ideal candidate should not manifest some degree of anxiety and depression may be unrealistic, because patients with facial disfigurement suffer from painful dentition, chronic pain disorders related to damaged orofacial structures, and may have residual symptoms of PTSD. The candidate’s adaptation to disfigurement using adaptive strategies rather than avoidance has been described[[81](#_ENREF_81)]. Similar to other types of VCA, there are specific psychosocial domains that need to be considered in FTx evaluation protocols, including perception of appearance, mood disorders, presence of chronic pain, social ostracism, QOL, confidence, and social connectedness and integration[[81](#_ENREF_81)]. In addition to the semi-structured psychological interviews that are used to assess potential candidates for FTx, specific rating instruments (predominantly self-report measurements) have been developed for the purpose of prioritizing candidates for FTx: (1) the Perception of Teasing-FACES[[137](#_ENREF_137)]; (2) Facial Anxiety Scale-State[[138](#_ENREF_138)]; and (3) the Cleveland Clinic FACES score[[134](#_ENREF_134),[136](#_ENREF_136)], analogous to the MELD score. Usually, the pre-transplant psychosocial evaluation protocol used to identify the suitability of candidates for FTx, served as basis for the comparison in the post-transplant period[[83](#_ENREF_83)]. To improve the candidates’ pre-transplant assessed suitability and to give them an adequate support during the course of FTx, psychiatric and psychological consulting/treatment were performed[[84](#_ENREF_84)].

Concern about depersonalization towards the transplanted face and identity confusion with the donors face have not been reported[[27](#_ENREF_27)], and psychological outcomes for recipients of FTx have been generally favorable[[139](#_ENREF_139),[140](#_ENREF_140)]. The review of international literature about the assessment of psychological outcomes after FTx shows lower rates of depression and verbal abuse and significantly improved body image and social integration[[81](#_ENREF_81),[82](#_ENREF_82),[134](#_ENREF_134),[141-145](#_ENREF_141)]. Some studies report an initial decrease of psychological functioning and QOL immediately after FTx[[81](#_ENREF_81),[83](#_ENREF_83),[134](#_ENREF_134)]. In such cases the recipients have often adjusted to their deficits before transplantation and the extensive rehabilitation may lead to a temporary decrease of thee psychosocial factors. In addition, psychological findings point to less psychological distress and depression, less verbal abuse, improved affective responsiveness, and social integration[[84](#_ENREF_84)]. Patients acceptance of the transplant and reports of improved QOL is encouraging[[27](#_ENREF_27)], with additional psychosocial improvements after FTx (*e.g.*, return to work, *etc*.)[[82](#_ENREF_82),[84](#_ENREF_84),[141](#_ENREF_141),[143](#_ENREF_143),[144](#_ENREF_144),[146-148](#_ENREF_146)]. Two adaptive coping styles were common to almost all recipients, namely use of active coping and emotional support, and recipients reported normal to high self-esteem[[83](#_ENREF_83)]. Particularly, the rigorous preoperative psychosocial evaluation and follow-up of well selected candidates has led to an overwhelmingly positive psychological outcome[[27](#_ENREF_27),[149](#_ENREF_149)]. One exception is the non-adherent patient who used traditional medicinal approaches leading to multiple episodes of rejection and ultimately death[[27](#_ENREF_27),[142](#_ENREF_142)]. This highlights the need for careful patient selection, transplant health literacy, and careful ongoing monitoring for non-adherence following transplant[[27](#_ENREF_27)].

**Psychosocial research in penile and uterine transplantation**

At present, the existing literature on psychosocial evaluation and outcomes in PTx and UTx is limited and these still experimental surgical procedures have been performed in small numbers of patients. But also in the field of PTx and UTx there exists the scientific consensus that psychosocial factors are important and the psychosocial evaluation is crucial for all candidates considering transplantation. By considering the already developed psychosocial evaluation and follow-up protocols for other VCA populations, *e.g*., of hand(s) as wells as face, almost the identical psychosocial aspects are of great importance. Nevertheless there are specific psychosocial aspects that are characteristic for PTx and UTx. Particularly, the function of physical intimacy of the allograft makes one great difference and the motivation for PTx or UTx can emerge from the desire to restore bodily integrity, body image concerns, and even the hope to get pregnant/to beget a child, *etc*.[[150](#_ENREF_150),[151](#_ENREF_151)]. In case of UTx, moreover, the graft will not be for lifelong use and will be removed after the patient has had a limited number of children[[38](#_ENREF_38),[39](#_ENREF_39)], which may results in the recipient having limited time to partly adapt to the post-transplant regimen[[150](#_ENREF_150)].

Currently, the Swedish uterus transplant experience presents the most established VCA program for female candidates considering UTx[[38](#_ENREF_38)], and this was derived from a previously created face transplant protocol[[152](#_ENREF_152)]. The colleagues from the Sahlgrenska University of Gothenburg have developed a standardized evaluation protocol that uses a comprehensive pre-transplantation selection process that determines the suitability of the candidates and donors (*e.g*., including psychological questionnaires regarding QOL and mood as well as semi-structured interviews with partners) and identifies potential vulnerabilities that need additional supportive treatment. Both the candidates and donors are assessed for psychiatric disorders, chemical dependency, social support, interpersonal conflicts, unrealistic expectations, and other factors related to lifestyle[[150](#_ENREF_150)].

Nine UTx have been performed, with two grafts removed in the first few months[[39](#_ENREF_39),[150](#_ENREF_150)]. The other seven women adapted well and following the initiation of menses expressed relief in organ function and happiness about having a return to possible reproductivity. According to the follow-up outcomes 6 mo after UTx, the couples reported readjustment to baseline QOL and satisfactory sexual experience (no difference in sexual function or satisfaction). Despite the couples feeling well prepared and well informed about complications, couples with graft failure and subsequent removal had worse physical and psychological outcomes. Recipient-donor relationships returned to their pre-transplant state, which occurred more quickly with mothers/daughter pairs. However, the recipients who received a graft from someone other than their mother felt guilt related to an increased sense of responsibility to the donor[[150](#_ENREF_150)]. Finally, the Swedish UTx program highlights the importance of a multifaceted evaluation strategy and that the evaluation should include identifying adaptive coping strategies and a strong alliance characterized by assertive and fluid communication with the transplant team[[38](#_ENREF_38)].

Penile defect is rare and only two cases of PTx are documented in the international literature[[151](#_ENREF_151),[153](#_ENREF_153)]. Although, the currently existing data of psychosocial aspects in PTx is limited, we can hypothesize that the psychosocial evaluation and follow-up are equal crucial as for any other life-enhancing types of VCA. The first case of PTx occurred in a 44-year-old male with previous trauma of the penis. Following transplant, the penis had to be removed because of psychological problems between the patients and his spouse at day 14 postoperatively[[151](#_ENREF_151)]. The psychological consequences of PTx showed that it is not easy to use and permanently see the allograft that was derived from a dead person. Nevertheless, in December 2014 a successful PTx was performed on a 21-year-old man following an unsuccessful circumcision procedure at age 18. Currently, the results of the psychological evaluation and follow-up were not reported, but the recipient previously had threatened to commit suicide if not considered for PTx[[153](#_ENREF_153)]. According to latest media reports the recipient has in the meantime successfully conceived a child[[30](#_ENREF_30)].

**Role of multicenter research**

Because there is still this lack of quantifiable data in the field of VCA[[40](#_ENREF_40)] and the inhomogeneous psychosocial protocols that have been developed from the transplant centers worldwide[[3](#_ENREF_3),[40](#_ENREF_40)], we feel strongly that our understanding of psychosocial predictors of outcomes will only be identified when sufficient numbers of patients are studied in multicenter research protocols[[3](#_ENREF_3),[154](#_ENREF_154)]. Because VCA is still uncommon, candidates who agree to undergo the surgery may be atypical in ways that are difficult to appreciate. Hence, it is recommended that transplant centers consider selecting several assessment and follow-up protocols to be administered collaboratively and consistently to all VCA recipients to strengthen and deepen our knowledge about psychosocial issues in VCA[[83](#_ENREF_83),[132](#_ENREF_132)], including prospective measurements across the continuum of time points from pre to post transplant[[3](#_ENREF_3)]. Therefore, it will be important that all transplant teams adhere to well-defined psychosocial guidelines and provide necessary multidisciplinary expertise[[6](#_ENREF_6)]. In addition, quality improvement strategies and qualitative research as well as demonstrable improvements in efficacy and financial cost offsets should take place[[3](#_ENREF_3),[67](#_ENREF_67)]. Once this occurs, VCA will become increasingly attractive to patients, insurance providers, and the medical community[[6](#_ENREF_6)].

**Conclusion**

In modern multidisciplinary transplantation medicine the four areas of VCA (to date hands and faces have been transplanted in larger numbers, but also penile and uterine transplantations have occurred) represent an evolving field[[155](#_ENREF_155)] where psychosocial factors are important in successful outcomes[[3](#_ENREF_3),[40](#_ENREF_40),[48](#_ENREF_48),[49](#_ENREF_49)]. This review contrasted VCA with SOT, provided information to guide psychosocial selection and risk-benefit assessment of VCA candidates[[1](#_ENREF_1),[4](#_ENREF_4)]. VCA is primarily a life-enhancing procedure to improve the recipients’ QOL and psychological well-being. The candidates’ motivation for VCA is multifaceted and fundamentally different from SOT[[3](#_ENREF_3),[48](#_ENREF_48)].

Although it is clear that successful outcome requires a multi-staged multi-disciplinary psychosocial process to select candidates best equipped for VCA[[3](#_ENREF_3)], standardized evaluations have not been determined[[40](#_ENREF_40),[48](#_ENREF_48)]. Collaborative research on psychosocial predictors of outcome is needed[[3](#_ENREF_3)]. Additionally interventions to enhance the coping strategies of candidates and support their innate resilience are needed for them to best adapt to post transplant life[[3](#_ENREF_3),[49](#_ENREF_49),[156-158](#_ENREF_156)]. Thoughtful consideration of ethical challenges related to informed consent and the balance of autonomy and nonmaleficence is needed and future collaboration with experts in biomedical ethics is welcomed. We support and are involved in the development of multidisciplinary/-multicenter VCA research to identify psychosocial factors that can impact outcomes following VCA and will lead to further improvements for this patient population[[3](#_ENREF_3),[40](#_ENREF_40),[49](#_ENREF_49)].

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