

Emerging Ethical Challenges Raised by the Evolution of Vascularized Composite Allotransplantation

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Abbreviations:

VCA: Vascularized Composite Allotransplantation

UNOS: United Network of Organ Sharing

UAGA: Uniform Anatomical Gift Act

OPTN: Organ Procurement and Transplantation Network

IRHCTT: International Registry on Hand and Composite Tissue Transplantation

Abstract

Background. Despite early skepticism, the field of vascularized composite allotransplantation (VCA) has demonstrated feasibility. The ethics of VCA have moved past doubts about the morality of attempting such transplant to how to conduct them ethically. **Methods.** Leaders of each program performing and/or evaluating VCA in the United States were invited to participate in a working group to assess the state and future of VCA ethics and policy. Four meetings were held over the course of 1 year to describe key challenges and potential solutions. **Results.** Working group participants concluded that VCA holds great promise as treatment for patients with particular injuries or deficits, but the field faces unique challenges to adoption as standard of care, which can only be overcome by data sharing and standardization of evaluation and outcome metrics. **Conclusions.** Adequate attention must be given to concerns including managing the uniquely intense physician-patient relationship, ethical patient selection, ensuring patients have adequate representation, informing and earning the trust of the public for donation, standardizing metrics for success, and fostering an environment of data sharing. These steps are critical to transitioning VCA from research to standard of care, and to its insurance coverage inclusion.

Introduction

Vascularized composite allotransplantation (VCA) is defined as “the transplant of intact vascularized body parts, such as hands and faces.”¹ Twenty years after the first successful hand transplant was performed, in France in 1998, the field has expanded to include faces, abdominal walls,² arms,³ legs,⁴ penises,⁵ and uteri.⁶ VCA is offered as innovative treatment for certain cases in which current standard of care treatment – such as skin and bone grafts for face, and prosthetics for limbs – has not been satisfactory. Despite early skepticism, the field has demonstrated feasibility and success.^{3,5,6,7} The benefits for patients indicate that the ethics of VCA have moved past doubts about the morality of even attempting such transplants to *how* to conduct them within an appropriate ethical framework.

Prompted by the first VCA attempts and subsequent milestones in the field, bioethicists and transplant professionals have raised significant ethical and regulatory issues over the past 2 decades, including: 1) Are the psychological, functional, and quality of life benefits of these non-life-saving procedures sufficient to justify their risks including immunosuppression, transplant rejection, graft failure, reduced life expectancy, and, for some VCA transplants, physical identity changes?⁸ 2) Should interventions that help individuals achieve “normal” form and function be developed, or should efforts focus on creating a society more accepting of physical differences and capabilities?⁹ 3) In an era of increasingly constrained healthcare resources, are these expensive new procedures justifiable?¹⁰ In part due to the restricted number of VCA surgeries performed to date, early research has focused on feasibility, with limited attention paid to these ethical questions. Fewer than 200 VCAs have been performed worldwide as of 2015, utilizing a variety of techniques.^{3,5,6,7}

Early data suggests that these transplants have the ability to provide aesthetic and functional outcomes beyond what is feasible with current alternative treatments, and patients have demonstrated enhanced independent living and societal reintegration.^{3,5,6,7} Early success in VCA has brought legitimacy to the field. To advance and flourish, public support and trust must be further established, without which community members will be unwilling to supply needed organs and tissues. Department of Defense funding has supported the majority of clinical trials in hand and face transplantation in the USA. These trials have been open to inclusion of both military and civilian candidates. However, clinical trial research funding is episodic and transient. Stable funding sources need to be identified, without which we only have proofs of concept for a practice that will remain financially inaccessible to many patients who might benefit. Simultaneously, a clear ethical framework needs to be developed, adopted in practice, and maintained.

The majority of existing data on VCAs come from face, hand, and uterus transplants. These demonstrate generally successful outcomes in terms of form, function, and patient satisfaction, although outcome metrics have yet to be standardized. Penile transplant appears promising, with 3 of 4 procedures declared successful.¹¹ Lower limb transplantation has proved more challenging with only 1 technical success.¹² VCA for other organs, including the larynx and chest wall, remain in the proof of concept phase. Expanding VCA access to the pediatric population (already underway for pediatric hand transplant), or as part of gender affirmation therapy, raises new ethical challenges. These include informed consent/assent, weighing risks

and benefits, and addressing equitable participation in research for vulnerable or marginalized populations.^{13,14,15}

The core ethical principles of autonomy, justice, nonmaleficence, and beneficence must be woven into evolving policy and governance frameworks that address: Informed consent of recipients, donors (or surrogates), and perhaps families and partners; fair access to procedures; transparency of outcomes; minimizing provider conflicts of interest; and maximizing patient benefit through appropriate selection, support, and uniform metrics of success. Without public and patient trust, secured by a core set of values, the field's future is at risk.

Methods

To begin developing an ethical framework for the future of VCA, the leadership of VCA and ethics programs at New York University and Johns Hopkins formed a working group. Leadership from these programs performed a literature review to identify individuals publishing clinical and ethical research in VCA. Colleagues in the field and at the United Network for Organ Sharing (UNOS) were asked to review the list of individuals and suggest additions for invitation. The working group leaders identified and agreed upon invitations to members with the intent of mixing bioethicists with physician experts from VCA programs across the United States. Participating members were asked to provide expert opinion and react to drafts of a proposed ethical framework crafted by NYU and Hopkins leadership. Members met for 4 sessions, one 1-day meeting in New York City at NYU, two 2-day meetings in New York City at NYU, and one 2-day meeting in Baltimore at Johns Hopkins. Members were informed from the outset that they would not be asked to provide primary authorship of the intended manuscript,

but that their contributions in raising issues, critiquing drafts and suggesting changes would be acknowledged as a function of their membership in the NYU/Hopkins working group.

The first 2 working group meetings consisted of structured discussion, with the initial session designed to identify broad themes which were then explored and refined during the second session. Prior to the third session, several working group members were asked, based on their particular expertise, to generate discussion points and to lead portions of the discussion during the third meeting. Following the third session, discussion points and comprehensive meeting notes from all sessions were compiled and synthesized by the NYU/Hopkins leadership team to serve as the starting point for drafting a manuscript. NYU Division of Medical Ethics staff reviewed the literature to frame and contextualize the issues raised by the working group, and their review was incorporated by the NYU/Hopkins leadership team in the draft manuscript. The draft was circulated to working group members for comment multiple times prior to and following the fourth meeting and revised accordingly by NYU/Hopkins authors. Key issues, represented by the following section headings, were identified, discussed, and incorporated into a final draft for publication.

Protecting and Empowering the VCA Patient

Provider-Patient Relationship

Better relationships between patients and providers predict better outcomes,^{16,17} but too much personal attachment might bias the eligibility determination process. In VCA, controlling for the bias introduced by this close relationship is critical to fair patient selection and adequate consideration of factors that influence postoperative outcomes. Surgeons and teams should

exercise heightened awareness of these interpersonal dynamics. Currently there is no standardized criteria for patient selection or how much authority each member of the selection team holds.^{18,19}

While views vary as to whether the intensity of the physician-patient relationship in VCA is unique compared to other procedures requiring long-term follow up, patient-provider relationship challenges are evident throughout the full lifecycle of a VCA. Surgeons and teams spend extensive time with VCA recipients in part due to the complexity and long-term risks. This may result in unhealthy attention, priority, or favoritism of the patient, or a patient having unrealistic expectations of the provider. As a result, the surgeon and medical teams should remain conscious of a previous recipient's feelings when focus shifts to a new recipient. This is reinforced by the temporary celebrity status that many VCA patients acquire from media coverage,²⁰ which can leave them disappointed and angry with their medical team when the media loses interest. Careful attention to relationship management—maintaining clear boundaries and promoting realistic expectations about long-term media visibility—is critical to the integrity of the VCA patient-provider interactions. Also, if a surgeon or recipient relocates, obstacles to necessary long-term care in light of the limited number of qualified VCA providers may arise.²¹ As VCA becomes more common, these issues will need to be thoughtfully managed.

Patient Selection

The complexities of care and medical risks in VCA mandate that transplantation should proceed only when a patient's needs cannot adequately be met by existing therapies. Candidacy for transplantation must weigh the patient's objective physical condition and medical comorbidities,

with subjective determination of ability to attend medical appointments and comply with a complex medical regimen, ability to participate in prolonged rehabilitation, and the existence of stable psychosocial support.

While VCA procedures tend to be considered life-enhancing and thus ethically different from solid organ transplants which are typically life-saving, there is growing recognition that, for some, the social costs of severe disfigurement are so profound as to amount to a state of 'social death.'²² In this case, VCA might actually allow recipients to reengage socially in a manner that could be considered life-saving. VCA requires providers to judge the extent of a potential candidate's distress and consequent need. This is perhaps the greatest ethical challenge in the clinical selection process. A graft or prosthesis might provide a satisfactory outcome for one patient but not for another with similar injury and functional outcome. Because VCA recovery is psychologically taxing and requires consistent adherence to monitoring and treatment protocols, some patients might be better psychosocially suited to VCA than others, based on variables including anxiety, stress-related, somatic, psychotic, and substance misuse disorders, maladaptive coping strategies, good treatment adherence and connection with social supports.

During interviews, patients and their loved ones have reported to working group members that they see VCA transplant as key to their personal identity, largely because VCA transplants are typically visible, unlike solid organ transplants. Issues of body image, sense of identity, bodily integrity, cognitive preparedness, and perception of quality of life arise, along with the possibility of psychological regression, negative response from family and friends, and acute distress.^{20,21,23,24} Various mental health clinicians, including psychiatrists, psychologists,

and social workers, are often involved in assessing this array of variables. Significant diversity in scope of practice among mental health clinicians involved in VCA evaluation, disparity in assessment tools utilized, and variation in inclusion/exclusion criteria for VCA across programs currently exist.¹⁸ Not every program shares its practices, making assessment difficult.

Disparity in evaluation criteria also raises concerns about fair access. Some patients might be denied VCA even when this might be the optimal treatment because the institution fears reputational and financial consequences of negative outcomes. Choosing the “easier” patient, who might have better social support or less significant psychological complications, allows for more confidence in successful outcomes and better press coverage, which contribute to mainstream acceptance of the field. It is possible that institutions have forgone less ideal candidates for this reason, but there do not appear to be public data regarding candidate refusals and related reasons. When considering the available treatment options, less psychosocially ideal patients – those who have self-harmed, or those with comorbidities or disabilities – might receive the greatest benefit from VCA among their treatment options if they are provided with additional support to reduce contraindications and improve long term care compliance. Determining eligibility is further complicated by the fact that some mechanisms of injury leading to candidacy for VCA, such as self-inflicted gunshot wounds, are considered by some institutions to be absolute contraindications to VCA.^{25,26}

Discrimination in the service of optimizing outcome cannot become simple discrimination based on disability, criminal history, suicidal behavior, or economic status. Patient eligibility should not be founded strictly on comparing the likelihood of successful

outcomes among patients, but comparing the likelihood of VCA success with requisite support versus likely alternative treatment success for each individual patient. Institutions performing VCA should work together to identify thresholds for providing patient support that consider resource limitations facing patients and prevent unjustifiable patient discrimination.

Initial efforts have been taken to address concerns about psychosocial evaluation. The Chauvet workgroup, an international workgroup of VCA providers, was created in Chauvet, France in 2012 to examine the psychosocial assessment process for VCA. It has published a report of its findings for upper extremity VCA procedures from its initial 2014 meeting.²⁷ While the initial report was specific to upper extremity, the Chauvet workgroup is taking crucial steps to identify challenges and strategies related to the psychosocial assessment process across VCA types. VCA programs must continue to collaborate openly to establish and disseminate best practices for other VCA procedures, each of which carries a unique set of psychosocial considerations.

Patient Advocacy

A patient advocate or similar support group may provide additional protection for persons considering VCA who are made vulnerable by the psychosocial sequelae of trauma and/or disfigurement and by the inevitable burdens associated with even the most successful transplant outcomes. Patient advocates for living donation in renal and liver transplantation typically work within a well-known field, with risks and benefits proven over decades. However, those patient advocates working in the VCA field must have particular expertise in the risks and potential benefits of innovative therapies, and must be comfortable supporting a patient's decision to

weigh longevity against quality of life. Appropriately trained VCA advocates can ensure a sound consent by independently assessing voluntariness, motivation, understanding of the treatment and its risks (including but not limited to long-term immunosuppression and chronic rejection graft failure), and factors that might influence adherence to immunosuppressive and physiotherapy regimens.²⁸ The use of patient advocates might also improve patient selection by providing balance against a transplant team biased toward proceeding with the operation and could empower the vulnerable patient.^{18,29,30} Ideally, such advocates would also provide ongoing postsurgical advocacy, particularly, as commonly happens, when patients return home far from the medical center where selection, surgery, and intensive initial support occurred.

Depending on the composition of the transplant team, the advocate role might be filled by an external psychiatrist, social worker, ethicist, chaplain or nurse, or a team composed of such persons. As with all patient advocates who are employees of the treating institution, conflict of interest must be addressed by ensuring independence from the transplant team. Metrics for patient satisfaction specific to advocacy support should be developed to refine advocacy standards.

Collaboration, Standardization, and Funding

VCA is evolving. With over 100 hand and approximately 40 face transplants to date, these VCA procedures are the most well established.^{3,7} In the United States (where VCA growth is strong), the transition to standard of care treatment requires an intensified drive to create an established reimbursement model. The transition from experimental research to standard of care requires standardized protocols and patient outcome data; a key requisite for medical insurance coverage

for most payers. The majority of VCA programs in the U.S have been funded by research grants, most commonly from the U.S. Department of Defense, philanthropy, and institutional support.¹⁹ Based on the experience of working group members and their colleagues, insurance support has been limited to coverage of immunosuppression and routine long-term postoperative care.

Now that the surgical techniques and transplant aftercare for VCA have transitioned from experimental to more established modalities, stable funding for innovative therapy represents an essential unmet need. Without implementation of alternate funding models, the field risks stagnation and potential collapse. Maintaining comprehensive data in standardized, transparent formats will be key to long-term viability of the field. VCA has to date been characterized by competition among pioneering centers across the globe. The future will be guaranteed by collaboration and cooperation in sharing protocols, outcomes and evidence.

Metrics Necessary for Funding to Continue

More than in solid organ transplantation, each VCA procedure addresses a constellation of functional and aesthetic deficits unique to each individual. As a result, quantifiable “indication” and “success” metrics are more difficult to establish. Additionally, the heterogeneity of tissue loss and concomitant factors make it hard for VCA centers to agree on indications and contraindications for operative and immunosuppression strategies. As a result, VCA parallels treatment of rare ‘orphan’ diseases such as acromegaly or job syndrome, which affect smaller numbers and do not have obvious best-choice treatments, more than typical high-volume solid organ transplants.

As with solid organ transplantation, VCA graft and patient survival must be objectively measured if access is to be granted to patients in the future. Numerous measures exist, such as objective hand function tests and quality of life surveys,³¹ though there is no currently agreed upon standard tool for various VCA grafts.

The psychological impact of VCA, regarding an individual's sense of self-worth, dignity, and potential for reintegration into society, is crucial to outcomes assessment. The VCA environment today relies on a single-center, surgeon-specific model with inherent conflicts of self-interest. At worst, the surgeon's goals of attempting a VCA might run counter to the patient's wishes or best interests. This environment sometimes rewards self-promotion in data reporting. The VCA field must show that: (1) VCA is both safe and effective in the short- and long-term; (2) VCA is better than available alternatives (eg, prosthetics, reconstruction, surrogacy, etc.); and (3) there is consensus on the indications for various VCA procedures.

Standardized collection of metrics is required to justify payment coverage. Maturing fields must share protocols and outcomes to secure support from government programs. Measurements must take into account variability in presurgical function and the expected time for recovery. Notably, measures of success according to the medical field, eg, survival, comorbidity, function, psychological outcomes, are likely to be somewhat discordant with measures of success as judged by the general population, most notably aesthetic outcome, novelty, and biased media depictions of transformation. Furthermore, comparison studies to alternative treatments (such as prostheses, no intervention, or reconstruction) and negative outcomes data must be shared to advance the field and to demonstrate efficacy to regulators and

fundere. Cooperation across centers is critical to gaining payer acceptance and patient access. Collaborators in this effort can help define standards for success rather than having third parties do so, as discussed during the 2017 Johns Hopkins University symposium on “Evolving Issues of Vascularized Composite Allotransplantation.”

The first cooperative step has already occurred: recognition and data collection through the United Network of Organ Sharing (UNOS).³² To register with UNOS, a VCA program must demonstrate that it has necessary expertise including psychiatry, social work, rehabilitation, and transplant experience. Programs must also commit to submitting data to UNOS. While UNOS has worked with VCA programs to define outcome data points that must be collected for hand and face transplant, greater consistency in outcome metrics across all types of VCA procedures is needed. The International Registry on Hand and Composite Tissue Transplantation (IRHCTT) was developed in 2002 to facilitate collaboration and data sharing.³³ However, participation is voluntary. It is unclear what percent of active VCA programs are participating in the IRHCTT and whether all data including negative outcomes is being submitted.

Public Trust

Among medical procedures, organ transplantation is unique in that it relies on the public’s willingness to donate organs. Decades ago, fears and misgivings about solid organ transplantation – ie, that the sick would be used as guinea pigs, that a recipient would assume the donor’s identity, or that a person might be killed for his organs – were assuaged as the technology developed and outcomes improved. Public education campaigns played an important role in this progress. Although faced with initial resistance from many in the medical

community, heart, kidney, and liver transplants eventually proved efficacious enough to warrant support through donation. This led to national organ donation promotion efforts³⁴ and to transparent distribution systems that potential donors could see were fair.³⁵

Earning trust from the general public for VCA will require: (1) further assessment of public awareness of VCA and identification of reasons why people say they would not donate organs for VCA; (2) the development of objective education materials explaining the medical indications for VCA and its benefits, costs, and limitations; (3) refinement of existing donor laws, and (4) development of education delivery opportunities about VCA.

Gauging Public Awareness and Beliefs

A few small studies examining public awareness and willingness to donate VCA organs have found greater hesitancy compared to solid organ donation, but also indicate that education can increase willingness. One survey administered to more than 1000 people in an inner-city New Jersey hospital emergency department found that respondents were more willing to donate solid organs (kidney 77.5%, liver 77.1%, and heart 76.4%) than VCA (hand 54.6% and face 44.0%). Similarly, respondents said they were more willing to receive a kidney (85.2%) than a hand (60.0%) or face (49.4%).³⁶ A 2016 study of almost 1500 respondents across the US showed over 65% willingness to donate hands and legs, 48% willingness to donate faces, and 75% willingness among women to donate uteri.³⁷ Three hundred survey participants from New York City found a similar disparity in willingness to donate solid organs (69%) versus face (51%). This study also showed that the use of a brief educational video on the purpose and outcomes of face VCA

increased willingness to donate from 51% to 69%, thereby bringing face VCA willingness in line with solid organ willingness.³⁸

Education about Need

Some of the barriers to VCA donation willingness stem from myths about its purpose and realistic outcomes. Common myths ascertained during authors' lectures on VCA with medical students and the general public include: (1) VCA is used for cosmetic purposes, (2) the recipient will look like the donor, and (3) the recipient might assume the donor's identity. Education must clarify that VCA is considered only in cases of extreme trauma, limb loss, and serious medical need. To dispel unfounded fears and enable informed donation decisions, the content should touch on at least 3 general areas: 1) separating VCA myths from facts to "demystify" procedures for the general public; 2) the physical, psychosocial, and public burden of disfigurement or loss of organ function with specific focus on persons for whom and conditions for which VCA is an option; and 3) the relationship of VCA to solid organ transplantation.

Revising Existing Law

Education efforts must be mirrored by policy that reflects and protects the existing values framework associated with the altruistic, voluntary gift of organ donation. The Uniform Anatomical Gift Act (UAGA) exists to ensure that donor organs are procured ethically by codifying the rights and duties of potential donors, as well as the rights and duties of organ transplant research and education professionals. The UAGA creates the option to register as a donor while applying for a driver's license and sets standards that states must adhere to if they choose to establish donor registries,³⁹ now the main method by which donors make their wishes

known. As such, the UAGA is the most appropriate means to ensure donor consent with regard to the evolving world of VCAs. Currently, there is no mention of VCA in the UAGA standards, any state donor registry, or the new national DonateLife National Registry.

In 2006 the UAGA was amended to protect donor decisions from family refusals and to allow donors to specify their intentions by enrolling in a registry. The amendment has been widely adopted: all states now have donor registries, and more than 117 million U.S. citizens are registered donors, and 43 percent of recovered organs are authorized through these registries.^{40, 41}

The UAGA does not require registries to provide specific organ and tissue options or information about organ transplants. States may, and many do, provide more nuanced registration options, but none provides explicit information or options regarding donation pertaining to face, limb, uterus, or other VCAs.^{42,43}

In contrast to other organs and tissues, current Organ Procurement and Transplantation Network (OPTN) policy now requires explicit consent to VCA donation prior to procurement for transplant.⁴⁴ As long as lack of public awareness about VCA exists, faces, hands, uteri, penises, legs, and other VCAs will continue to be procured by surrogate family consent. Although surrogate consent is morally preferable to no consent, laws like the UAGA exist to protect donors' rights, not the rights of a possible donors' family members. The eventual benchmark should be the same as applies to all other organ donation -- first person consent.

There is a risk that as requests for VCA tissues become more common, public fears based on myths and lack of transparency will not only make people unwilling to donate VCAs but also solid organs. If existing donors or those interested in becoming donors discover the existence of VCA without receiving more information, they might change their overall donation intentions. As the number of successful VCA transplantations increases, conversations about VCA will certainly change over time from a 2-step process — first person consent plus family consent — to one conversation about organ donation, including VCA.

VCA practice is at a critical juncture, shifting from proof of concept to innovative therapy that requires proponents to recognize the importance of patient and public trust in obtaining organs. The actions (or inactions) of a single VCA program could have profound consequences for the entire field. Strategies should be developed for funeral preparation, procurement, and follow up with donor families. Potential donors must be able to make informed decisions according to the benefits that VCAs confer on recipients.

Conclusion

VCA is at an inflection point, maturing past an era when it was characterized by providers competing against one another to achieve transplant “firsts.” Today more programs, as represented by working group participants, believe initial outcomes justify describing VCA as innovative therapy. A complementary ethical framework, rooted in transparency, uniformity, sharing, and cooperation is required to secure both public trust and financial support. While the field has made preliminary steps toward aggregating data, much work remains to ensure fairness by developing transparent eligibility criteria, uniform sharing of protocols and outcomes data,

establishing patient centered advocacy programs, and updating current laws to reflect the emergence of VCA donation.

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