Hand Transplantation

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» Upper extremity limb loss is catastrophic. It affects nearly every activity of daily living, leaving patients with substantial disability.

» Despite high rates of rejection of upper extremity prostheses, hand transplantation remains controversial.

» The indications for hand transplantation remain relatively ill defined.

» The American Society for Reconstructive Transplantation (ASRT) and the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) have been founded to advance the science, to educate, to report outcomes, and to define the indications for vascularized composite allotransplantation.

Upper extremity loss represents a life-changing, often devastating event, affecting nearly every activity of daily living and subsequently leaving a patient with substantial disability[1,2]. The potential immediate dependency and despair resulting from the loss of one or both hands cannot be overstated. Promising technological advances in upper extremity prostheses include improved neural-control interfaces, multiple-degrees-of-freedom terminal devices, and prototype haptic feedback mechanisms[3,4]. However, the available literature still demonstrates high prosthesis rejection rates for upper extremity amputees[5-12], suggesting that prostheses continue to inadequately replicate the complex, prehensile functions of the native hand and arm. The most commonly cited reasons for upper extremity prosthesis rejection remain limited usefulness, weight, and residual limb discomfort[5,13].

Pioneers of hand transplantation recognized that prosthetic devices probably would never completely satisfy the upper extremity amputee for these very reasons. Even if the prehensile function and dexterity of the human hand could be restored, these would do little to restore patient body image or hand sensibility, both traits coveted by amputees. Rather, they postulated that these could only be replaced with "like" human tissue[14]. The field of vascularized composite allotransplantation has grown from this basic desire to fully restore both the functional and emotional aspects of the human hand, building on the foundations developed by solid organ transplantation, hand surgery, and reconstructive microsurgery.

The concept of using composite tissue allograft was first suggested in 1960 by Peacock, when he utilized cadaveric flexor tendons along with their synovial sheaths in order to reconstruct end-stage tendon incarcerations that otherwise would have

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required amputation[15-18]. Shortly after this early success with composite tissue allografts, and likely inspired by the rapid growth of the solid organ transplantation community, the world's first hand transplantation was performed in South America in 1964[1,19,20]. Unfortunately, probably because of the relatively primitive immunosuppression as well as a lack of basic-science preparation, acute rejection predictably occurred and the transplanted limb was amputated about three weeks later[15,21]. Perhaps reflecting the scientific hazards of reaching too far, too fast, the next attempt at hand transplantation did not occur until thirty-four years later in Lyon, France, in 1998[15,22,23]. Technically, this second procedure succeeded; however, this success was not functionally realized and sustained because the patient did not adapt psychologically to the new hand and discontinued the use of immunosuppressive medications. The transplanted limb was eventually amputated[1]. The first hand transplantation in the United States was performed the following year in Louisville, Kentucky. At the time of writing, this third patient still had the transplanted hand, nearly fourteen years later[15,24].

The early success of hand transplantation in the late 1990s was made possible by advances in solid organ transplantation. Specifically, the development of new medications such as cyclosporine, tacrolimus, and mycophenolate mofetil made the avoidance of rejection possible. In addition, animal models of vascularized composite allotransplantation provided the basic and translational science evidence that successful composite tissue allotransplantation without rejection was possible with use of these medications[15,25-27]. Since that time, the field of vascularized composite allotransplantation has grown dramatically. Eighty-nine hand transplantations have been performed worldwide to date, and there are at least seven centers in the United States at which hand transplantation has been performed.

Indications for Transplantation and Ethical Considerations

"Primum non nocere"—"first do no harm" —remains a paramount principle as the field of vascularized composite allotransplantation progresses. In the 2002 position statement of the American Society for Surgery of the Hand, Cooney and Hentz echoed this sentiment when they recommended "great caution and a measured approach to the patient requesting a limb transplant."[28] This caution, along with appropriate ethical considerations, have tempered the growth of vascularized composite allotransplantation as compared with solid organ transplantation. Hand transplantation is very different from most solid organ transplantations in that the candidate for hand transplantation is not faced with a life-or-death decision[29]. For this reason, developing widely accepted indications for subjecting a physiologically healthy person to the risks of life-long immunosuppression remains a challenge for the allotransplantation community[30].

In 2009, Hollenbeck et al. indicated that there were no current, well-defined indications for vascularized composite allotransplantation of the hand or face[14]. Unfortunately, this remains the case today[31,32]—the indications remain open to interpretation by individual vascularized composite allotransplantation centers. While this autonomy to develop indications to accompany slightly different approaches is ostensibly important in a developing field, the vascularized composite allotransplantation community is attempting to develop universally accepted indications for hand transplantation based on the evidence available. Having recognized the need for defined and accepted indications for hand transplantation, the allotransplantation community founded the American Society for Reconstructive Transplantation (ASRT) in 2008. The goal of the ASRT is to provide a platform for the advancement of education, science, and the practice of composite tissue allotransplantation as relevant to reconstructive and transplant surgery. Last year, the ASRT published guidelines for medical necessity determination for transplantation of the hand and/or upper extremity (Fig. 1).

Psychological Screening

The majority of amputee patients are afflicted by a psychological disorder[33]. This consideration complicates hand transplantation in that the outcome of a hand transplantation is very much dependent on the participation, cooperation, and compliance of a patient with hand therapy, medications, and follow-up screening appointments. A kidney, liver, or heart transplant depends only on compliance with medications, and even still there are relatively high rates of medication noncompliance in this population[34,35]. In a combined heart and heart/lung transplant population, it was found that the only risk factor for graft loss between six and twelve months was being unmarried or not living in a stable relationship[34,35]. It is therefore imperative that all patients who are to be considered for hand transplantation undergo extensive psychological and psychiatric screening prior to selection for hand transplantation. In addition, the social support for an individual candidate must be identified, and a transplantation should not occur if the surgeon is not comfortable with the patient's support system.

Immunosuppression

Conventional Immunosuppression

Aside from the ethical issues surrounding hand transplantation, perhaps the most critical reason that vascularized composite allotransplantation has lagged behind solid organ transplantation is the skin. Skin is the most antigenic tissue of the composite tissues that constitute a hand transplant, and preventing the immune system from rejecting the skin was necessary prior to successful hand transplantation[1,36-38]. In the 1990s, the aforementioned pharmacologic discoveries and subsequent animal testing provided evidence

GUIDELINES FOR MEDICAL NECESSITY DETERMINATION FOR TRANSPLANTATION OF THE HAND AND/OR UPPER EXTREMITY

These proposed Guidelines for Medical Necessity Determination (Guidelines) identify the clinical information the American Society of Transplantation (AST) Vascular Composite Allotransplantation (VCA) Advisory Council believes is needed to determine medical necessity for hand transplantation. These Guidelines are based on generally accepted standards of practice, review of the medical literature, and federal laws applicable to Medicare or Medicaid programs (See also Medicare National Coverage Determinations; Part 1, 2 and 3 (Rev. 129, 12-08-10).)

SECTION I. GENERAL INFORMATION

Allotransplantation of one (unilateral), or both (bilateral) hands and/or hands and arms has become a clinical reality. The indications are amputation or irreversible traumatic functional loss. At this time, patients should have attempted use of prosthetic devices unless medically contraindicated. Additionally, until research demonstrating plasticity of neural networks in congenital patients has been performed, patients seeking hand and upper arm transplantation to correct congenital defects should seek opportunities in clinical trials.

SECTION II. CLINICAL CRITERIA

The basis of determination of medical necessity for hand transplantation is a combination of clinical data and the presence of indicators that would affect the relative risks and benefits of the procedure, including post-operative recovery. These include, but are not limited to, the following.

A. A comprehensive medical history and physical exam has been conducted by a hand surgeon to evaluate the need for transplantation.
B. A surgical treatment plan that outlines the surgical approach and the prognosis for improvement of clinical signs/symptoms pertinent to the diagnosis has been developed.
C. A comprehensive medical history and physical exam has been conducted by a transplant physician or surgeon to evaluate the medical ability of the patient to undergo transplantation
D. A comprehensive social and psychological exam has been performed to evaluate the motivation and ability of the patient to successful manage a VCA allograft
E. The patient is generally over 18 years of age and has had inadequate functional recovery with conventional reconstructive surgical treatment and/or non-surgical rehabilitation.
F. The amputation or loss of function is accompanied by medical or functional complications, demonstrable loss of quality of life as determined by psychological evaluation, and may or may not include tissue necrosis or ulcerations of the extremity unresponsive to nonsurgical treatments.
G. Comorbid etiologies of the symptoms have been considered and ruled out.
Section IV. Contraindication of CMS coverage of hand transplantation

At this time because of unknowns with respect to plasticity of neural networks to congenitally missing appendages and long term complications from conventional immunosuppression, the following patients would not currently be eligible for CMS coverage of hand transplantation

1. Unilateral amputees with no evidence of significant functional, social or financial impairment as a result of their amputation
2. Congenital amputees
3. Pediatric traumatic amputees

Patients in these populations who are seeking a hand transplant could participate in clinical trials with funding for transplant using novel therapies or techniques in hand transplantation that would not be classified as standard of care treatment.

Fig. 1
ASRT Guidelines for Medical Necessity Determination for Transplantation of the Hand and/or Upper Extremity. (Reproduced with permission from the American Society for Reconstructive Transplantation.)

that skin rejection could be overcome with acceptable, often minimal, side effects[25,39].

The International Registry on Hand and Composite Tissue Transplantation (IRHCTT)[40] indicates that the majority of hand transplant recipients undergo induction therapy at the time of hand transplantation with use of either polyclonal antibody preparations (antithymocyte globulins [ATG]) or monoclonal antibody preparations (e.g., alemtuzumab, basiliximab) targeted against the recipient's lymphocytes in order to minimize the initial host immune response to the newly transplanted hand. Following induction therapy, the most frequently utilized conventional immunosuppressive regimen is triple-drug therapy similar to the medications that renal

TABLE I Immunosuppression Complications

Complication	No. of Patients
Serum sickness	1
Opportunistic infections	29
Post-transplant lymphoproliferative disorder	1
Basal cell carcinoma of the nose	1
Metabolic complications	23
Hyperglycemia	9 (not reversible in 3 patients, who needed hypoglycemic medications)
Elevated creatinine	5
End-stage renal disease	1 (8 years after transplantation)
Arterial hypertension	5
Cushing syndrome	1
Osteonecrosis of the hip	1
Hyperparathyroidism	1

transplantation patients receive, generally consisting of tacrolimus, mycophenolate mofetil, and prednisone[30,41].

While conventional, this immunotherapy has been extremely effective in the field of hand transplantation: no hand transplant has been lost because of acute rejection when conventional triple-drug immunosuppression has been used[30]. This 100% rate of graft survival at one year after transplantation has not been achieved to date in any other field of transplantation[30]. Despite this impressive statistic, however, 85% to 90% of these twenty-four transplanted extremities were associated at least one episode of acute rejection within the first year following transplantation[30,40,41].

The side effects of these medications are well documented in the solid organ transplantation literature and have been further reported by the IRHCTT following vascularized composite allotransplantation[40,42]. The most common side effects reported by the IRHCTT include both opportunistic infections and metabolic abnormalities. Infections have included cytomegalovirus, clostridium difficile enteritis, herpes simplex, cutaneous mucosis, and osteomyelitis. The metabolic complications include hyperglycemia, diabetes, hyperlipidemia, hyperparathyroidism, Cushing syndrome, osteonecrosis, and impaired renal function[30,40]. Two low-grade malignant lesions also have been reported as a result of immunosuppression in patients managed with vascularized composite allotransplantation, but both were treated successfully (Table I). Finally, one confirmed case of lymphoproliferative disorder leading to a central nervous system lymphoma was recently diagnosed in a patient who was managed with bilateral lower extremity transplantation[43]. This patient had removal of the transplanted extremities, with immediate cessation of immunosuppression.

Immunomodulation

Despite the fact that few life-threatening complications have developed in patients managed with conventional therapy, standard immunosuppression may not represent an acceptable risk for patients managed with vascularized composite allotransplantation given the evolving indications and the pre-transplantation health of appropriate candidates[44]. That is, because the absence of one or both hands does not lead to death, many have argued that the acceptable risks of surgery and immunosuppression ostensibly should be lower than those of solid organ transplantation[45]. This point is clearly controversial; however, less-toxic, minimal immunosuppressive regimens that could produce equivalent long-term functional outcomes after transplantation could lead to both a more widely accepted risk-benefit ratio and expanded indications for vascularized composite allotransplantation.

This ambition is the impetus for the development of novel protocols that aspire to shift the paradigm from one of immunosuppression to one of immunoregulation and graft tolerance[45]. Some unique features of vascularized composite allotransplantation make this field particularly amenable to the potential for decreased immunosuppression. The highly antigenic skin is visible and represents a distinct advantage for vascularized composite allotransplantation monitoring. Acute rejection is easily and quickly detected because of the maculopapular skin changes that rapidly develop. Immediate medication changes can be made, and serum markers of rejection are therefore generally not necessary to detect rejection. In addition, topical medications sometimes can be utilized to treat acute cutaneous rejection, reversing or preventing rejection episodes with minimal systemic effects[40,45,46]. This benefit in terms of both monitoring and treatment

represents an advantage that cannot currently be exploited in the field of solid organ transplantation.

Attempts to minimize immunosuppression following solid-organ transplantation by infusing bone marrow from donors into recipients have successfully led to decreased immunosuppressive medication requirements[47-51]. The goal of such an infusion is to create chimerism, in which the host does not attack the graft and, vice versa, there is no graft-versus-host disease[52-54]. Studies have demonstrated that as little as 1% "microchimerism" has been sufficient to allow for the development of tolerance[55,56]. The resulting chimerism, as well as the use of cell-based therapies, may lead to host tolerance for the grafted hand, resulting in potentially lower immunosuppressive requirements and subsequently fewer treatment-related morbidities and sequelae.

Since 2009, one group in the United States has been utilizing a bone-marrow-cell-based treatment protocol (the so-called Pittsburgh protocol) in efforts to minimize maintenance immunosuppression[47]. This protocol includes standard induction followed by tacrolimus monotherapy. On the fourteenth day after transplantation, the patients receive an infusion of donor bone-marrow cells isolated from nine vertebral bodies of the donor patient[47]. The authors had performed a successful trial of a similar regimen in a swine model prior to implementing this method in humans[44,47]. In this miniature swine model of hindlimb allotransplantation across a major histocompatibility complex barrier, the authors were able to induce tolerance to the musculoskeletal elements of the transplanted hindlimb in two of three swine treated with bone marrow cells along with enteral cyclosporine for monotherapy immunosuppression. The third animal died early (on the forty-second day after transplantation) as a result of an upper gastrointestinal bleed[44]. The authors did not demonstrate chimerism in the animal recipients and, unfortunately, tolerance to skin was not achieved.

Schneeberger et al.[47] reported on their cell-based protocol to minimize immunosuppression in human trials involving five patients. All patients had successful hand/arm transplantation with use of tacrolimus monotherapy for maintenance immunosuppression. Two patients had three episodes of rejection each, whereas the other three patients had one episode each. All episodes were treated with steroid bolus therapy and/or topical tacrolimus and clobetasol. These episodes of rejection are consistent with the world experience with hand transplantation[40]. Donor-specific alloantibodies were detected in four of the five patients and were associated with skin rejection in most instances. However, the authors demonstrated that their protocol involving tacrolimus monotherapy following bone-marrow-cell infusion was successful for maintaining viability of a hand/arm transplant. They concluded that larger and/or randomized controlled trials with long-term follow-up were needed to confirm their early findings[47].

Outcomes

The IRHCTT was founded in May 2002[40], with the aim of the registry being to combine international clinical experiences so that state-of-the-art knowledge can be shared among those already working in or approaching the field of composite tissue allotransplantation. According to the IRHCTT itself, one of the main limitations that currently exists with the registry is that some international and even some United States vascularized composite allotransplantation programs had not submitted their patients' data at the time of the last publication from the IRHCTT[40].

The IRHCTT reported on thirty-three patients who had undergone upper extremity transplantation in 2010[40]. One death has been reported among the patients from the registry who were managed with vascularized composite allotransplantation of the hand. The patient was managed in France and underwent bilateral hand transplantation as well as face transplantation. This patient sustained cerebral anoxia as a result of an obstructed airway and died on the sixty-fifth postoperative day. Two additional deaths have now been reported in Turkey[57-59]. These two deaths represent substantial concern in that they occurred following triple and quadruple limb transplantations. These questionably indicated lower extremity transplantations are reminiscent of the first hand transplantation that was performed in 1964 with poor indications and little or no basic-science preparation.

In China, at least seven grafts have been removed. The indications for graft removal in these patients included noncompliance with medications, a lack of appropriate immunosuppressive therapy, the long distance from the patient homes to the transplant centers, and/or unreported episodes of rejection that were discovered on eventual follow-up. In Western countries, there have been three published reports of graft losses. One patient with bilateral involvement lost one hand transplant forty-five days postoperatively as a result of infection, one patient lost a graft 275 days postoperatively because of intimal hyperplasia (potentially representing chronic rejection), and one patient lost the transplanted limb twenty-nine months postoperatively as a result of noncompliance with immunosuppressive medications and poor function.

To date, 85% of the thirty-three patients in the registry have experienced at least one episode of acute rejection, and many have had multiple episodes (Table II). These rejection events frequently correlated with short-term noncompliance with medications and/or a decrease in immunosuppression as ordered by the vascularized composite allotransplantation team for various reasons. However, all episodes of rejection were reversed with short-term increases in medication dosing, the use of topical agents, and/or intravenous steroid boluses.

While no definite chronic rejection has been reported to our knowledge, the

TABLE II Acute Rejection Episodes in Registry Patients	
No. of Patients	No. of Acute Rejection Episodes
15	1
7	2
3	3
2	4
1	5

patient who required graft removal at 275 days postoperatively for myointimal proliferation had experienced four untreated episodes of acute rejection. In addition, all patients from the Louisville program now have evidence of graft vasculopathy, a concern that is being closely followed and potentially will become the focus of frequent monitoring in vascularized composite allotransplantation programs worldwide[60]. Importantly, no evidence of graft-versus-host disease has been reported from any program, to our knowledge.

Functional Results

Thirty-one of the thirty-three recipients from the registry were included in the functional assessment as they had more than one year of follow-up at the time of data analysis. Despite concerns regarding relatively high rates of immunosuppression-related side effects, acute rejection, and composite graft loss, the motor and sensory recovery following composite tissue allotransplantation has been better than expected. Importantly, registry data demonstrate that motor and sensory improvements may continue for as long as five years following transplantation[40]. All patients developed protective sensation, thirty developed tactile sensibility, and twenty-eight developed discriminative sensibility[40].

Motor recovery following upper extremity transplantation has been better than what would be expected following similar-level nerve repairs, with the return of extrinsic muscle function first allowing pinch and grip activities. This has been followed by unusual intrinsic muscle function at nine to fifteen months after the time of transplantation in a majority of the patients despite often high-level nerve coaptation. In several hands, recovery of intrinsic function has been confirmed with use of electromyography. The composite recovery of extrinsic and intrinsic motor function as well as functional sensibility has allowed recipients to independently perform most activities of daily living, including eating, driving, grasping objects, riding a motorcycle or bicycle, using the telephone, and writing[40]. As expected, the more distal transplants have demonstrated relatively greater motor and sensory function as the nerves have to regenerate over shorter distances; however, good results have been obtained even with proximal-level amputations as high as the deltoid[61,62]. Despite these overall good results, detailed functional assessments involving comparisons with highly trained prosthetic users as well as comparisons based on the levels transplanted are necessary in order to truly narrow and refine the indications for hand transplantation.

Quality of Life

The quality-of-life assessment of patients managed with transplantation is one of the most important parameters of success of vascularized composite allotransplantation, but such assessments have not been adequately reported or captured by the literature to date. The IRHCTT has utilized the Hand Transplantation Score System (HTSS) and the Disabilities of the Arm, Shoulder and Hand (DASH) score to evaluate outcomes following transplantation. The HTSS score evaluates both the cosmetic and functional results of transplantation, including the psychological outcome, social behavior, work status, subjective satisfaction, body image, and well-being of the patient. The registry indicates that quality of life improved in >75% of patients, and a return to work has been a consistent feature for a majority. While pre-transplantation HTSS scores were not reported, the average score was 52 at one year following transplantation and was 88 at ten years (maximum score, 100). Similarly, the mean DASH score was 38 at one year and 16 at ten years (best score, 0)[40]. Moving forward, it will be imperative to gather these same data on upper extremity amputees successfully utilizing modern prostheses in order to make valid comparisons.

Economics of Hand Transplantation

The economics of vascularized composite allotransplantation have become an important issue and may even begin to dictate the future of many vascularized composite allotransplantation programs, especially in light of both their experimental, generally funded nature as well as the changing healthcare economic environment in the United States[31,63,64]. Fifteen years ago, prior to the first successful hand transplantation, McCabe et al.[64] performed a decision analysis in order to attempt to guide decision-making with regard to the cost effectiveness of hand transplantation. Understanding decision analysis is important in order to interpret both this initial study as well as a subsequent study by Chung et al.[31] on the economics of hand transplantation.

In the study by McCabe et al., twenty-two young adult volunteers were interviewed about limb loss. The patients were allowed to choose to remain in a defined state of poor health or to trade future years of life for an improved health state. The volunteers' willingness to trade corresponded with the value placed on the various states of health[64]. McCabe et al. found, on the basis of the decision analysis, that unilateral hand transplantation was not economically recommended.

In the similar study recently performed by Chung et al.[31], 100 medical student volunteers were utilized to assign utilities. The investigators found that, in the setting of unilateral hand amputation, prosthesis use was favored over hand transplantation. They found that bilateral hand transplantation was favored over prosthesis use in the setting of bilateral limb loss; however, the incremental cost-utility ratio of bilateral transplantation was $381,961 per quality-adjusted life year (QALY), which greatly exceeds the traditionally accepted cost-effectiveness threshold of $50,000 per QALY[31]. Nonetheless, the authors concluded that prosthesis adoption was the dominant strategy for unilateral hand amputation and that bilateral hand transplantation exceeds the societal acceptable threshold for general adoption.

Despite the importance of viewing the success and feasibility of an intervention financially, there are inherent flaws in decision analysis, which both McCabe et al.[64] and Chung et al.[31] brought to light in their discussions. Perhaps the biggest problem with such decision analysis lies in the fact that the assigning of utilities will vary among different populations of people and critically affects the outcome of the analysis[64]. While assessing the general public is important to determine the societal perspective, surrogate patients from the general public and even medical students may not be able to truly assess the benefit of a transplanted hand or to comprehend the complications associated with long-term immunosuppression[29,31].

Future of Hand Transplantation

Reconstructive surgeons have made considerable progress over the last fifteen years and can now offer functional restorative surgery to patients with upper extremity limb loss that cannot be treated with conventional techniques. The lingering question at this point is whether this trend can and will continue. Recent reports have described limb loss after transplantation due to progressive vasculopathy, patient noncompliance with immunosuppression, failure of functional recovery despite a living transplant, and substantial psychiatric pathology adversely affecting functional outcomes[40]. In addition, two cases of perioperative failure resulting in reamputation have occurred in the United States. Even more concerning, however, are the reports of perioperative mortality that have occurred following questionably indicated and undoubtedly aggressive triple and quadruple limb allotransplantations performed outside of the United States[57]. Similarly, potentially premature implementation of lower extremity vascularized composite allotransplantation has led some to conclude that "just because you can, does not mean that you should."[65] Rather than accelerating the advancement and acceptance of composite tissue allotransplantation, ill-advised and potentially reckless utilization of the technique threatens to endanger the field.

The risk-benefit ratio guides us as surgeons and influences our decision to offer various procedures. This is no different in the case of hand transplantation, except that the risks and benefits of the procedure have yet to be clearly defined[29]. However, the intermediate risks of hand transplantation are relatively well defined in the literature[40], and the long-term risks of immunosuppression can be extrapolated from the data on solid-organ transplantation. We now have evidence that a patient who has had a leg transplantation will likely die of an immunosuppression-related central nervous system tumor in the near future. It is critical to the future of this field that appropriate indications for transplantation are established and that our patients are counseled about the complications of immunosuppression, including potential death.

Moving forward, it is imperative that the physical and mental benefits of hand transplantation are carefully reported and evaluated[66]. In this regard, attempts to better understand the social and psychological impact of upper extremity limb loss and then to document the change in these factors after transplantation will need to be closely scrutinized in order for the risk-benefit ratio to be defined accurately. In addition, objective sensory and motor testing with breakdown by the level of transplantation as well as the use of accepted functional assessments (e.g., the Carroll test) need to be embraced and widely utilized. Last, rapid and transparent reporting of complications to the IRHCTT is necessary in order to both quantify and qualify both failures and successes. Only then can an accurate assessment of the risk-benefit ratio be performed, indications be refined, immunosuppression and immunomodulation regimens be adjusted, and candidate patients be appropriately screened and counseled. As physicians and surgeons, we can accept nothing less for our patients, and doing so ostensibly may jeopardize the entire field of composite tissue allotransplantation.

While the field remains in its infancy, hand transplantation has demonstrated many successes, and the future appears promising for this restorative treatment. We believe that it is now time to step back and reevaluate what has and has not worked and to reassess the current public and medical field acceptance of allotransplantation. Many obstacles remain, among them continued funding, immunology, candidate selection, and long-term assessment of outcomes, in addition to the continued refinement of indications. We should approach the future with cautious optimism and continue to evaluate all that we do with bench science, peer review of both favorable and unfavorable clinical outcomes, and ethical treatment of our patients. Video 1 demonstrates hand function following bilateral proximal forearm transplantation with complete flexor-pronator and extensor muscle transfers with coaptation of the radial, median, and ulnar nerves at the elbow.

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