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# Complex upper extremity injuries: targeted muscle reinnervation, free functional muscle transfer, and vascularized composite allotransplantation

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## Abstract

Restoration of upper extremity function poses a unique surgical challenge. With considerations ranging from ensuring appropriate skeletal support and musculotendinous and ligamentous anatomy, restoring adequate vascularity and innervation, and providing sufficient soft tissue coverage, upper extremity injuries present a diverse range of reconstructive problems. Recent history has been marked by an expansion of novel techniques for addressing these complex issues. Sophisticated modalities, such as targeted muscle reinnervation, free functional muscle transfer, and vascularized composite allotransplantation, have become some of the most powerful tools in the armamentarium of the reconstructive surgeon. This review article aims to define the distinguishing features of each of these modalities and reviews some of their unique advantages and limitations.

**Keywords:** Targeted muscle reinnervation, free functional muscle transfer, vascularized composite allotransplantation



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## INTRODUCTION

Disabling upper extremity injuries encompass a broad spectrum of clinical conditions. These injuries have devastating functional consequences for the patients who sustain them and present complex reconstructive and rehabilitative challenges to the clinicians who treat them. Whether of a traumatic, congenital, ischemic, or oncologic nature, the partial or complete loss of hand and upper extremity function brings with it physical, psychological, and emotional barriers for patients and their providers to work through together.

Algorithmic approaches have been proposed for the initial management of serious traumatic upper extremity injuries<sup>[1-4]</sup>. However, the long-term restorative and rehabilitative management of each patient represents a unique clinical situation and must be handled as such. Patients' needs, desires, and abilities will differ dramatically based on a host of patient-specific variables, as will the reconstructive options available for a given injury and degree of functional loss.

Historically, the choices available to patients who sustained truly devastating hand and upper extremity injuries were limited. Before the 1970s, problems such as amputations, devascularizing or denervating trauma, or mangled bony and soft tissue injuries were either managed by formalized amputation and body-powered or early electric prostheses<sup>[5]</sup> or by limb salvage to heal wounds and fractures followed by rehabilitation to attain the most meaningful possible use of the injured extremity. The 1960s saw the first replantation of an upper extremity at the level of the shoulder by Ronald Malt in 1962<sup>[6]</sup> and the first successful digital reattachment by Komatsu and Tamai in 1965<sup>[7]</sup>. The first successful microsurgical transplant of a segment of omentum in a human by Harry Buncke and Donald McLean in 1969 opened the door to an entirely new array of techniques involving free tissue transfer<sup>[8,9]</sup>. Within the past few years, there has been a considerable increase in the options within the armamentarium of the reconstructive upper extremity surgeon. Improvements in prosthetic technology brought about with the advent of myoelectric prostheses<sup>[5]</sup> combined with progress in peripheral nerve surgery, such as regenerative peripheral nerve interfaces<sup>[10-12]</sup> and targeted muscle reinnervation (TMR)<sup>[13-17]</sup>, have markedly improved the functional outcomes following amputation<sup>[18]</sup>. At the same time, widespread refinement of microsurgical techniques has made possible the transfer of vascularized and neurotized muscle, termed free functional muscle transfer (FFMT), with the aim of restoring specific upper extremity functions<sup>[19-23]</sup>. Furthermore, in the two decades since the first successful hand transplant by Jean-Michel Dubernard in 1998 ushered in the era of vascularized composite allotransplantation (VCA)<sup>[24]</sup>, there have been significant advances in the availability and feasibility of hand and upper extremity transplantation.

With the many novel and highly sophisticated reconstructive options now available as well as the rapid pace at which technology is evolving and adapting, it can be challenging for surgeons, therapists, and prosthetists alike to remain abreast of the most recent developments. This article explores three methods for reconstruction and restoration of upper extremity function, namely, TMR and a myoelectric prosthesis following traumatic or elective amputation, FFMT, and VCA. In reviewing them, the goals are to define each modality and explore their benefits as well as current limitations.

## TARGETED MUSCLE REINNERVATION

TMR refers to the surgical transfer of nerves, often following amputation of an extremity, to a new "target" in the form of a remaining muscle. While the fundamental technique was successfully described as early as 1917<sup>[25]</sup>, the ability to harness its full potential has only recently started to be realized. TMR is now widely performed in both the upper and lower extremities, given its proposed two-fold benefits of reducing post-amputation neuroma pain and phantom limb pain and of facilitating improved control of a myoelectric prosthesis<sup>[26]</sup>. The mechanistic underpinnings of reduced residual limb pain result directly from guiding the

process of axonogenesis in severed nerves to a specified target, described by Cheesborough *et al.* as giving "... the nerves somewhere to go and something to do"<sup>[14]</sup>. With regard to facilitating enhanced control of the prosthesis, harnessing the power of TMR allows redirection of neural signals intended for a missing limb into input fed to a predefined target muscle that has been surgically stripped of all additional motor input. This in turn reliably and predictably generates electromyographic signals that can be detected by the prosthetic device. It is through this creation of "control sites" that electrodes from a myoelectric prosthesis can translate neural input into meaningful movements and functions. These include transfer of a distal branch of the radial nerve to the lateral head of triceps with the intention of facilitating hand opening and transfer of the median nerve to the short head of biceps to drive hand closure<sup>[27]</sup>. It is worth noting that, at present, the limited sophistication of the lower extremity prosthetics available in comparison with those for the upper extremity has constrained the extent to which the promise of TMR can be realized in below-knee and above-knee amputations.

In the upper extremity, TMR is most frequently performed in patients who have sustained an injury that has left them with no or significantly limited function proximal to the wrist<sup>[28]</sup>. These patients can be divided into three groups: those who have undergone an amputation in whom TMR is performed in anticipation of eventual use of a myoelectric prosthesis; those who already use a prosthesis and desire improved control of their artificial limb; and those opting for an elective amputation because of dissatisfaction with their current level of upper extremity function post-injury. Amputations can be at the transradial, transhumeral, or shoulder disarticulation level, and each TMR procedure differs with respect to the anatomy, technical aspects, and number of control sites that can be created.

The success of TMR, and even the ability to offer it to a given patient, remains dependent on several potentially limiting factors. Post-injury anatomy must be such that the residual nerves that will be coapted to target muscles have not sustained damage that would preclude meaningful reinnervation, as could be present in those with multilevel injuries or amputations involving an avulsion mechanism. Furthermore, the patient's residual limb must be able to tolerate a prosthetic device, which can be challenging in patients with systemic conditions such as diabetes mellitus and peripheral vascular disease or burn injuries<sup>[27]</sup> in whom the soft tissue is compromised. Finally, a variety of socioeconomic factors warrant consideration before pursuing TMR with a myoelectric prosthesis. Despite evidence that these devices can have a cost-benefit over the lifetime<sup>[29]</sup>, they are associated with a significant upfront cost burden, particularly for those without adequate health insurance coverage<sup>[30]</sup>. They also require a substantial time investment to learn how to attain maximum functionality and are associated with high rates of abandonment<sup>[31,32]</sup>. However, regardless of an individual's ability to attain or operate a myoelectric prosthesis, TMR still offers the benefit of less neuropathic pain following amputation and should be considered whenever feasible.

## FREE FUNCTIONAL MUSCLE TRANSFER

FFMT entails the transposition of viable innervated tissue intended to restore some of the function that has been lost. In upper extremity reconstruction, a typical candidate for FFMT is an individual with an avulsive brachial plexus injury, loss or aberrant development of upper extremity musculature, or a time course of injury and characteristics that preclude use of nerve or tendon transfers<sup>[22]</sup>. The muscles used and the specific techniques employed vary according to the individual's reconstructive goals. However, common aims include the restoration of shoulder abduction, elbow flexion/extension, and flexion/extension of the digits.

There are several well-established workhorse flaps for each of the above aims. Shoulder abduction is often addressed by transfer of the latissimus dorsi muscle or a combination of adductor longus and gracilis<sup>[33]</sup>.

Restoring elbow flexion is the most common indication for functional muscle transfer in the upper extremity<sup>[34]</sup>. While the free gracilis flap and free or pedicled latissimus dorsi flap are overwhelmingly the most popular options<sup>[35,36]</sup>, use of rectus femoris and vastus lateralis has also been described. Loss of elbow extension, although a less common indication for FFMT, has also been addressed with the gracilis muscle flap<sup>[37]</sup>. Purposeful movement of the hand and fingers can be addressed via free gracilis muscle transfer, which is facilitated by attaching the distal tendinous portion of gracilis to the tendons of the digital flexors or extensors<sup>[38,39]</sup>.

With FFMT, the reconstructive surgeon must also carefully select which donor nerve will be used to power the transferred muscle (a consideration that does not necessarily apply in pedicled functional muscle transfer). The choice of nerve will depend on the goals of a particular procedure and the options available in that setting, considering that the donor nerves available will differ substantially between a patient with a total brachial plexus avulsion and a patient with loss of elbow flexion following an oncologic extirpation. As described by Mackinnon and Novak in their 1999 seminal paper on nerve transfers, the ideal donor nerve should be expendable, located in close proximity to its intended target, contain the specific fiber types desired, and in the case of motor nerves, derive from a donor muscle that is synergistic with its destination<sup>[40]</sup>. There are several popular options for upper extremity FFMT, including but not limited to intercostal nerves, the spinal accessory nerve, the contralateral C7 root, or spared roots of the ipsilateral brachial plexus<sup>[37,38,41]</sup>.

However, while a number of donor nerves have demonstrated success in FFMT, the evidence suggests that they are not universally interchangeable. Among the factors that are critical to consider when selecting a donor are whether the nerve originates within the brachial plexus (intra-plexal) or outside of it (extra-plexal) and the axon count ratio of the donor to recipient nerves. Intra-plexal donors include the ipsilateral brachial plexus roots as well as the medial pectoral, thoracodorsal, and ulnar nerves, while common extra-plexal nerves chosen are the contralateral C7 root along with the spinal accessory and intercostal nerves<sup>[42-44]</sup>. A 2016 paper by Nicoson *et al.* that reviewed outcomes using several different donor nerves in free functional gracilis muscle transfer to restore elbow flexion following brachial plexus injury described intra-plexal donors as the best choice for achieving better motor strength<sup>[45]</sup>. Regarding the proposed advantages of intra-plexal donors, the authors cited the quality and quantity of axons in these nerves as well as their proximity to the transferred muscle, which can subvert the need for a nerve graft. However, despite these theoretical benefits, extra-plexal nerves have also shown promise in FFMT, with a paper by Cho *et al.* showing no differences in outcomes pertaining to motor strength across 38 patients undergoing FFMT for brachial plexus injuries according to whether the spinal accessory or ulnar nerves were used as donors<sup>[46]</sup>. With respect to axon counts in donor and recipient nerves, the 2015 paper by Schreiber *et al.* has provided much of the evidence pairing axon count ratios with functional outcomes<sup>[44]</sup>. In reviewing average axon counts for the donor nerves frequently used in upper extremity FFMT, they observed that the axon counts are generally higher for intra-plexal donors than for extra-plexal donors. They found that increased donor nerve axon counts tended to increase the likelihood of a meaningful functional outcome, and ultimately advised a donor-to-recipient ratio of at least 0.7:1 for the best chance of regaining useful muscle strength<sup>[44]</sup>.

The complexity of functional muscle transfer derives largely from the numerous variables that must be carefully considered and addressed to achieve a meaningful functional outcome. Preoperatively, this begins with obtaining a thorough understanding of a patient's history of injury and meticulous evaluation of their anatomy and examination, with attention paid to abilities and deficits. Observation of the patient performing occupational tasks or other activities of daily living can be informative, and coordination with a hand and occupational therapy team is essential. Surgical planning must aim to anticipate potential

challenges that may necessitate deviations or conversions to secondary options, such as tendon grafting or use of alternative donor nerves. Intraoperatively, success is contingent not simply upon meticulous microsurgical dissection and anastomosis of the vessels and nerves but upon correct positioning of the muscle and tensioning of tendons to enable their excursion and provide the desired movement. In the early postoperative period, careful monitoring of the transferred muscle is critical to ensure its survival and successful healing of the recipient and donor sites. If all the above are accomplished, the final and most important component will involve the rehabilitation and retraining process, which will demand intimate and coordinated collaboration with hand and occupational therapy colleagues to achieve a meaningful functional outcome.

## VASCULARIZED COMPOSITE ALLOTRANSPLANTATION

In keeping with the oft-cited surgical principle of replacing “tissue losses in kind”<sup>[47]</sup>, VCA of the hand and upper extremity seeks to restore form and function following limb loss in a manner that is not possible with other reconstructive modalities. Although fewer than 25 years have passed since the first successful hand transplant, the procedure has now been performed in at least a dozen countries and on more than 100 patients. High mortality and devastating graft loss rates have been reported for combination VCA procedures that involve upper extremity transplantation in conjunction with a craniofacial or lower extremity transplant; however, isolated unilateral or bilateral upper extremity VCA has proven to be a more reliably attainable goal. The patient survival rate has been reported to be 99%, while overall long-term graft survival is approximately 85% across all recipients and more than 95% with stringent adherence to an immunosuppressive medication regimen<sup>[48,49]</sup>.

However, it is that same regimen of immunosuppressive agents that underpins the shortcomings and drawbacks of VCA. Since its inception, the field of transplantation has been plagued by the need for lifelong use of these medications. Their well-described toxicities leading to both graft and organ damage as well as increased susceptibility to infection and malignancy are certainties that all transplant recipients accept. While much progress has been made towards inducing chimerism and tolerance<sup>[50,51]</sup>, at present, these remain theoretical goals, the promise of which has yet to be fully realized. Until the ability to minimize or eliminate immune responses to transplanted tissue in the absence of pharmacologic intervention becomes a reality, constant diligence will remain necessary to balance the harmful effects of immunosuppressants against the risk of graft rejection.

With respect to VCA specifically, discussions of its ethics and risk-benefit profile often cite that, unlike transplantation of a solid organ, such as a liver or kidney, VCA involving the face or an upper extremity is life-changing but not life-saving. Nonetheless, the psychosocial benefits of VCA demonstrate the substantial impact that transplantation can have on an individual’s life, in many circumstances easing the burdens of isolation, loneliness, and loss of personhood that may accompany the “social death” experienced following a disfiguring injury<sup>[52,53]</sup>. In 2016, Breidenbach *et al.* performed a statistical analysis of hand transplantation with the aim of discerning whether the procedure met the necessary threshold to be deemed the standard of care<sup>[54]</sup>. The group concluded that when considered against solid organ transplants, hand transplantation demonstrates a superior ability to attain adequate immunosuppression and has a lower risk of chronic graft rejection and a decreased incidence of renal failure. This finding, in combination with a functional ability that was superior to that of the prosthetic devices available at the time, suggested that hand and upper extremity VCA had merits.

Despite the wealth of literature published on the subject and the growing number of centers globally that are offering the procedure, assessment of functional outcomes following hand transplantation has proven

challenging. Multiple authors cite inconsistencies in the metrics used, variations in the anatomic level at which transplantation is performed, and the proposed theory that a recipient will only attain maximum function after years of post-transplant therapy and rehabilitation<sup>[48,49,55]</sup>. Furthermore, the standards that define an acceptable functional outcome inevitably differ between unilateral and bilateral transplant recipients. The concept of bilateral hand transplantation is fairly widely accepted as an indication, given the disabling nature of bilateral hand/arm loss. However, the morbidity of immunosuppression, substantial economic burden associated with VCA, and ever-improving prosthetic technology raise questions about the practice of unilateral hand transplants<sup>[56]</sup>. Nonetheless, the evidence suggests that following unilateral or bilateral hand transplantation, most patients attain a reasonable degree of sensation and strength, have DASH (Disabilities of the Arm, Shoulder and Hand) scores indicating an ability to perform most activities of daily living, and demonstrate continued improvement with increasing time since transplant<sup>[49,57]</sup>.

## CONCLUSION

Despite the ever-evolving sophistication of the methods used for hand and upper extremity reconstruction, the devastating sequelae of mutilating injuries and amputations continue to pose substantial challenges. The past few decades have seen remarkable refinements in the ways surgeons are able to restore form and function using techniques such as FFMT and VCA. At the same time, advances in prosthetic technology paired with the leveraging of peripheral nerves through TMR offer the promise of meaningful functional outcomes for those in whom limb salvage or transplantation is not a viable option. In summary, these techniques represent the pillars of the new era of upper extremity reconstructive surgery.

## DECLARATIONS

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Both authors declared that there are no conflicts of interest.

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