

# The Development and Future of Reconstructive and Microvascular Surgery of the Hand

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**Abstract:** The hand is often thought of as a key discriminator in what makes humans human. The hand is both intricate and fascinating in its design and function, allowing humans to interact with their surroundings, and each other. Due to its use in manipulation of the person's environment, injury to the hand is common.

Devastating hand injuries have a profound, physical, psychological, financial and socially crippling effect on patients.

Advances in operative techniques and improvements in microscopes and instruments allowed Malt &McKhann to perform the first successful arm replantation in 1962 [1].

This was followed by a myriad of autologous free flaps of varying composition, that were discovered after the mapping of the cutaneous blood circulation by Taylor and Palmer [2] and Mathes & Nahai's classification of muscle flaps [3] providing us with countless options to harvest and transfer healthy, well vascularised tissues into areas of injury.

Since the late sixties, with the emerging subspecialty of microvascular reconstruction, surgeons have had the technical ability to salvage many amputated parts, even entire limbs.

The measure of functional outcomemust incorporate the evaluation and severity ofthe initial injury and the subsequent reconstructive surgeries [4].

**Keywords:** Free tissue transfer, hand injuries, microsurgery, upper limb reconstruction.

## INTRODUCTION

The hand is often described as the key discriminator in what makes humans human. The hand is both intricate and fascinating in its design and function, allowing humans to interact with their surroundings, and each other. Due to its use, humans have the ability to manipulate their environment and consequently injury to the hand is common.

Hand injuries pose a significant threat to an individual's work and social lives, as well as basic functioning. This paper aims to highlight the main concerns to both the patient and treating practitioner when a soft tissue injury to the hand occurs. Related to this, management and key points will be discussed, as early and appropriate management is key to a good outcome for the patient.

## EPIDEMIOLOGY

Hand injuries account for between 10 and 20% of the patients attending the emergency department [5].

Studies have shown that the majority of these are related to lacerations to the hand [6-8]. Other causes include soft tissue injury (including bruising and amputations), fractures (including dislocations), burns and infection.

Although a hand injury is very rarely life threatening, the high proportion of profound functional disablement means that they take on significant economical importance to the patient, as well as impacting greatly on their quality of life. Related to this they also have an impact on cost to society due to related time off from work [9].

Hand trauma, in general, often affects the younger population, is greater in the male sex and in the majority of cases is related to occupational, or assault injuries [6, 7, 10].

In terms of site of injury, the distal phalanges of the long and ring fingers are more commonly injured [6, 10].

The British Society for Surgery of the Hand [11] revealed data in 2007 stating 20% of patients attending Accident and Emergency Departments have hand injuries, equating to more than 1.36 million attendances for hand injuries in theUK each year. One in five of these injuries (271,000) require specialist care, and 71,000 patients require surgery [12, 13].

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In the UK, the Health and Safety Executive is responsible for enforcing health and safety in the workplace. Their latest data, from the twelve month period during 2009 and 2010, reveals an increased proportion of injuries in skilled trade occupations, process, plant and machine operatives as well as elementary occupations as compared with office workers [14]. Upper limb trauma, is amongst the highest incidence anatomically speaking.

The hand, wrist and fingers are top scoring as a region, followed by the back, the arm and lower limb [15].

Lacerations are highly reported, and when combined with fractures accounted for over 30,000 incidents over this twelve month period [16].

It is not only the patient who can be affected by hand trauma; several studies highlight the importance of appropriate and timely management of these injuries with up to 65% of malpractice claims aimed at emergency department management [17]. High figures are also seen with claims attributed to errors at surgery and outpatient visits [18]. The importance of the first examination and the 'fate of the hand' have been documented many times, including textbooks such Rockwood and Green [19].

### THE HAND: AN ANATOMICAL OVERVIEW [20]

The hand is complex. This paper aims to deal with soft tissue injuries to the hand, but it is important to remember that soft tissue injuries can be complicated by bony injury. The hand has 27 bones, which act as a framework for the

soft tissues to function. The hand is best described in terms of the palmar, or volar surface and the dorsal surface, or back of the hand. The back of the hand consists of little soft tissue incorporating thin skin (compared to anywhere else in the body and allowing a greater range of movement), multiple lymphatic vessels and veins and the very superficial extensor tendons. The palmar aspect of the hand consists of a thicker skin, with much reduced pliability protecting the main nerves and arteries of the hand as well as the extrinsic flexor tendons, and deeper intrinsic muscles. The palm is also highly sensitive with a high ratio of sensory nerve output.

Regarding the muscles of the hand, these are easily divided into extrinsic and intrinsic muscles. The extrinsic muscles of the hand are named due to the fact that their muscle belly is almost always found outside the hand unit, with their insertion within. They include the flexors and extensors of the digits. The extrinsic muscles of the hand are not discussed in this paper. The intrinsic muscles of the hand, with both their origin and insertion found in the hand, consist of four main groups; the thenar and hypothenar groups, the interossei and the lumbricals. These groups have their key points summarised in Table 1.

The thenar muscles are related to the thumb, originating from the flexor retinaculum and carpal bones and inserting into the proximal phalanx of the thumb. These muscles enable the great versatility of the thumb movement, allowing grip, pincer and grasping movements. Hence why the thumb accounts for almost 40% of the whole hand function [21, 22].

**Table 1. Recreated from Moore KL, Dalley AF. Clinically Orientated Anatomy (Fourth edition) 1999 (Upper Limb pp766-771).**

Group and Muscle		Proximal Attachment	Distal Attachment	Innervation	Main Action	
Thenar Muscles (compartment)	Abductor Pollicis Brevis	Flexor Retinaculum and tubercles of scaphoid and trapezium	Lateral side of base of proximal phalanx of thumb	Recurrent branch of median nerve	Abduction of thumb (+ Opposition)	
	Flexor Pollicis Brevis				Flexion of thumb	
	Opponens Pollicis		Lateral side of 1 <sup>st</sup> metacarpal		Opposition of thumb	
Adductor compartment	Adductor Pollicis	2 heads; Oblique-2 <sup>nd</sup> /3 <sup>rd</sup> metacarpal bases, capitate and carpals Transverse- 3 <sup>rd</sup> metacarpal body	Medial side of proximal thumb phalanx		Adduction of thumb	
Hypothenar Muscles (compartment)	Abductor Digiti Minimi	Pisiform	Medial side of base of proximal phalanx 5 <sup>th</sup> digit	Deep Branch of Ulnar nerve	Abduction of 5 <sup>th</sup> digit	
	Flexor Digiti Minimi	Hook of hamate and flexor retinaculum				Flexes proximal phalanx of 5 <sup>th</sup> digit
	Opponens Digiti Minimi				Medial border of 5 <sup>th</sup> metacarpal	Opposition of 5 <sup>th</sup> digit
Lumbricals	Lumbricals 1 and 2 (Radial)	Lateral two tendons of flexor digitorum profundus	Lateral sides of extensor expansions of digits 2-5	Median Nerve	Flexion of digits at MCPJ and extension of interphalangeal joints	
	Lumbricals 3 and 4 (Ulnar)	Medial three tendons of flexor digitorum profundus				
Interossei	Dorsal Interossei (1-4)	Adjacent sides of two metacarpals	Extensor expansions and bases of proximal phalanges 2-4	Deep Branch of Ulnar nerve	Abduction of digits (also assistance to Lumbricals)	
	Palmar Interossei (1-3)	Palmar aspect of 2 <sup>nd</sup> , 4 <sup>th</sup> and 5 <sup>th</sup> metacarpals	Extensor expansions of digits and proximal phalanges of digits 2, 4 and 5		Adduction of digits (Also assistance to Lumbricals)	

The hypothenar muscles lie on the ulnar aspect of the hand, and are all innervated by the ulnar nerve. These, like the thenar muscles originate from the proximal carpal region and insert towards the proximal digits of the little finger.

The interossei group of muscles involves three volar and four dorsal muscles, arising from the metacarpals. The former are involved in adduction of the fingers, the latter abduction, and are again innervated by the ulnar nerve.

The lumbricals of the hand, of which there are eight, help to flex the metacarpophalangeal joints, putting the hand in the ‘writing position’, as well as extending the interphalangeal joints. They are the only muscles of the human body without a bony attachment.

These muscle groups and their surrounding fascia form several compartments. The thenar compartment, and the hypothenar compartments can be made up of several smaller compartments, and the individual interossei form their own [23]. Added to this there are two potential spaces, the thenar and midpalmar spaces. The thenar space underlies the thenar compartment and is related distally to the index finger synovial tendon sheath and the common flexor sheath in the carpal tunnel proximally.

The midpalmar space lies between the middle, ring and small finger flexor tendons and the volar interossei muscles. This extends from the radial midpalmar septum to the ulnar lying hypothenar muscles. Between these two potential spaces lies the strong lateral fibrous septum and its attachment to the 3<sup>rd</sup> metacarpal.

Regarding the digits there are potential spaces within the individual finger pulps. Potential spaces can also be found within the sheaths protecting, the flexors of the digits, which begin at the level of the metacarpal-phalangeal joint. These often communicate with the radial and ulnar flexor sheaths of the thumb and little finger, which can extend into the forearm.

**CLASSIFICATION OF HAND INJURIES**

Apart from anatomically describing the injured areas of a hand and communicating the clinical findings to colleagues, or documenting the injuries in a descriptive fashion, there are several other ways of classifying hand injuries.

These aim to be accurate, standardised, user friendly and should facilitate communication between clinicians [24]:

The primary author’s preferred classification system is ‘The Tic-Tac-Toe’ classification. It was developed and first described by Jeffrey and Norman Weinzweig in 1997, and aims to offer a comprehensive classification system that enables an accurate description (and predicted outcome) for hand injuries [24].

The *hand* itself is subdivided into nine zones of injury. (See Table 2).

The *hand injuries* are categorized then into seven types, as shown in Table 3.

The *hand injury subcategories* include three subtypes: (A) soft-tissue loss, (B) bony loss, and (C) combined tissue

loss, with or without loss of vascular integrity, which is recorded as: (0) vascularity intact or (1) devascularised.

**Table 2. Nine zones of the hand (‘Tic-Tac-Toe’ classification).**

<b>1</b> Thumb Phalanges	<b>2</b> Index & Middle Phalanges	<b>3</b> Ring & Little Phalanges
<b>4</b> Thumb Metacarpal	<b>5</b> Index & Middle Metacarpal	<b>6</b> Ring & Little Metacarpal
<b>7</b> Scaphoid, Trapezium, Trapezoid.	<b>8</b> Capitate, Lunate.	<b>9</b> Hamate, Triquetrum, Pisiform.

**Table 3. Hand injury types (‘Tic-Tac-Toe’ classification).**

I	Dorsal mutilation
II	Palmer mutilation
III	Ulnar mutilation
IV	Radial mutilation
V	Transverse amputations
VI	Degloving injuries
VII	Combination injuries

Therefore, as an example, the injury code: Type I, C1, Zone 2, would correspond to a dorsal injury with both bone and soft tissue loss to both index and middle fingers with vascular compromise.

It becomes obvious that this method will allow the surgeon who first assesses an injured, mutilated hand, to convey a fairly accurate and informative picture about the extent of the clinical findings.

Reid classified mutilating hand injuries in 1984 and subdivided them into six categories, including dorsal and palmar amputations, radial and ulnar hemi amputations, distal amputations and degloving injuries [25].

A preceding system is the Modified Pulvertaft classification devised in 1971. This is based purely on an anatomical, descriptive approach when it divides mutilating hand injuries. It comprises five subtypes: Ulnar, radial, central, transverse and other [26].

Wei’s classification [27] has a more specific function, as it only focuses on describing the ‘metacarpal hand’ [28] and aims to offer surgeons a guide, when aiming at reconstructing a functional ‘tripod pinch’ for their patients, to enable them to make use of their mutilated stump. It divides the injured hand into two categories:

Type I: thumb is intact; all fingers are amputated from the proximal interphalangeal joint.

Type II: Thumb is amputated, proximal to the interphalangeal joint; at least three fingers amputated, proximal to proximal interphalangeal joint.

## HISTORY OF MICROVASCULAR HAND RECONSTRUCTION

Wound closure with the patient's own, healthy, well perfused tissue remains the 'gold standard' of treatment [29], that every reconstructive surgeon should aim for, when dealing with the mutilated hand and considering the various steps of the reconstructive ladder.

Equally important however, is the thorough debridement of wounds prior to definitive repair of damaged tissues. Inadequate removal of devitalised or foreign material may lead to deep seated chronic infections that will ultimately result in failure of the reconstructive procedure.

Advances in operative techniques alongside improvements in microscopes and instruments allowed Malt & McKhann to perform the first successful arm replantation in 1962 [1], heralding the dawn of a new era for reconstructive surgery, namely the 'microvascular' subspecialty. 1964 saw the first free transfer of vascularised intestine to reconstruct the cervical esophagus, by Nakayama [30].

This was followed by Komatsu and Tamai, who in 1968 performed the first successful digit replantation [1].

A year later Cobbett reconstructed a lost thumb with the first successful toe-to-thumb transfer [30]. However, the history of successful free tissue transfer started in the early 1970's when Rollin Daniel performed the first autologous free groin flap, using it to cover a soft tissue defect.

This was followed by a myriad of autologous free flaps of varying composition, that were discovered after the mapping of the cutaneous blood circulation by Taylor and Palmer [2] and Mathes & Nahai's classification of muscle flaps [3] providing us with countless options to harvest and transfer healthy, well vascularised tissues into areas of injury.

The ideal reconstruction of a damaged hand occurs when the amputated component is available, having been salvaged from the scene of the accident and deemed suitable for replantation. Depending on the anatomical part involved, both cold and warm ischaemia times may vary greatly.

Muscle is the tissue most susceptible to ischemia and undergoes irreversible changes after 6 hours at room temperature. As digits do not contain muscle, they have a much longer ischemic tolerance [1].

Successful replantations after 33 hours of warm and 94 hours of cold ischemia have been reported. A hand amputation has been successfully replanted after 54 hours of cold ischemia [1].

The first step in replantation and hand trauma has to be adequate bony fixation with repair of periosteum. This will offer the surgeon a more robust structure to work with and is then followed by the repair of the extensor, and then flexor, tendons.

Only after the tendon repairs are complete, is the arterial repair performed; attempting a reconnection of the artery sooner, would jeopardise the anastomoses. Subsequently the neuroorrhaphy is to be undertaken, before repairing the veins.

Finally the skin closure completes the steps of replantation [1, 31].

Both absolute and relative contraindications, as described by Neil F. Jones [1] can be found in Table 4.

**Table 4. Absolute and relative contraindications.**

<b>Absolute Contraindication:</b>
Significant associated injuries
Multiple injuries within the amputated part
Systemic illness
<b>Relative Contraindications:</b>
Patient's advanced age
Patient's psychological problems
Single-digit amputation
Avulsion injuries
Massive contamination
Prolonged warm ischemia time

## TOE AUTOTRANSPLANT TO CREATE 'PINCER'

The question of limb salvage versus primary amputation, most commonly for injuries involving vascular compromise and crush injuries, poses a difficult choice for both the surgeon and the patient. The decision to amputate may have significant psychological, socioeconomic, and last but not least medico legal repercussions [32].

When amputation is inevitable, performing early surgery enhances patient survival reduces pain, disability and shortens hospitalization [33].

Since the late sixties, with the emerging subspecialty of microvascular reconstruction, surgeons have had the technical ability to salvage many amputated parts, even entire limbs. However, this sometimes represents "technique over reason" and may have a physically, psychologically, financially and socially crippled patient-with a useless, salvaged limb-as the end result [34].

Michon and Dolich coined the term metacarpal hand in 1974, and defined the metacarpal hand as either a complete loss of all the digits or a hand with an intact thumb (entirely or partially), 'thumb without fingers' [35].

As previously mentioned, Wei *et al.* proposed a classification and guidelines for the treatment of metacarpal hand [36]. The main idea was to reconstruct a tripod pinch for the injured hand.

With bilateral metacarpal hands, a maximum of five toes may be used in the reconstructive transfer to reduce donor site complications. The dominant hand should be reconstructed as the first operation where the thenar function was considered adequate [36].

## DISCUSSION

H.C. Brown stated in his paper, published as early as 1968: "Any salvage of workable or sensory parts in a hand is worthwhile and infinitely better than a prosthesis" [37]. Several other studies [38, 39] came to the same conclusion

after comparing the functional results of replantation as opposed to prosthesis in the upper extremity following amputation.

Very often hopelessly infected, complex wounds would have resulted in loss of limb or even life, if it were not for the constantly expanding fields of science and medicine. Numerous biomedical and mechanical adjuncts have been recently added to the armamentarium of non surgical aids available to us, when dealing with complex injuries.

One of these adjuncts is Negative Pressure Wound Therapy (NPWT):

Research into this field started in 1989 by Dr. Louis Argenta and Prof. Michael Morykwas of Wake Forest University School of Medicine in North Carolina, of the USA.

In 1997, Morykwas and Argenta approved that NPWT both enhanced granulation tissue formation and simultaneously helped bacterial clearance, through the application of negative pressure [40, 41].

This was confirmed in 2005, when Armstrong and Lavery concluded that NPWT was assisting in the development of granulation tissue in complicated wounds [42].

It was also shown to clear excess exudates [43] leaving behind a moist wound bed; advantages of this include reduced pain and reduced exposure to infection [44]. In addition it prevents eschar formation that would delay epithelial migration, thus allowing wound healing to occur more effectively than in wounds with a dry surface [45].

NPWT has been shown to effectively treat osteomyelitis and soft tissue infections after adequate surgical debridement of necrotic, nonviable tissue and appropriate antibiotics [46-54].

Oedema, that can occur as a direct response to tissue injury results in an increase in interstitial pressure. This in turn causes occlusion of the microvasculature and lymphatics resulting in a lack of nutrient and oxygen delivery to the tissues. Secondary to this, there is an accumulation of metabolic waste and increased bacterial count, which results in the release of protein degrading enzymes, causing capillary damage and hypoxia. This ultimately increases inflammation and creates a proteolytic environment [55].

The negative suction facilitates the removal of excess interstitial fluid thus may improve some of those parameters.

As mentioned previously, NPWT is useful in aiding granulation tissue formation. This was shown in a porcine study model involving 25 pigs where laser Doppler probes were placed inside surgically created wounds and the blood flow was studied [40].

The authors found that when negative pressure was applied, in 25 mmHg increments up to 400 mmHg (lasting 15 minute intervals) the optimal maximal improvement of blood flow is 125 mmHg, which results in an increase in blood supply by 400%.

This increase is only sustainable for approximately 5 minutes before it declines. The pressure has to be paused for at least 2 minutes between each application. It is therefore advisable to choose the 'intermittent' therapy option when applying NPWT to a wound.

In a similar study Morykwas *et al.* [40] inoculated surgical wounds in five pigs, with 108 infecting organisms. They then applied 125mmHg negative suction to some of these wounds and harvested full thickness biopsies from each of these sites every 24 hours. Between day four and five, wounds treated with NPWT had a decrease in bacterial load by 10<sup>5</sup>.

Contraindications to the use of NPWT are highlighted in Table 5.

**Table 5. Contraindication to NPWT.**

1	Malignancy in the wound
2	Untreated osteomyelitis
3	Unexplored fistulae
4	Necrotic tissue with eschar present
5	Exposed organs and blood vessels

Dermal Substitutes form another facet in the ever broadening spectrum of advances to science. These products have provided soft tissue coverage, when there is lack of soft tissue, to close wounds:

**CULTURED AUTOLOGOUS KERATINOCYTES**

It has been possible to prepare sheets of keratinocytes in a laboratory for over 20 years [56, 57]. These cultured sheets can be applied to acute wounds, burns [58, 59] and also chronic leg ulcers [60].

They are expensive to produce with a 2cm<sup>2</sup> biopsy producing a 1.8m<sup>2</sup> sheet of tissue, in a process that takes approximately four weeks to complete. Cultured keratinocytes may be preserved frozen; however, the colony forming efficiency of these cells decreases by almost 50% [61].

Similar to split-skin grafts, the take of these fragile cultured epithelial cells depends on the wound bed. Healthy granulation tissue and muscle fascia, give the best result [61].

The resulting epithelial wound cover is unstable and remains susceptible to infection and contractures for the first few months after reconstruction [62].

Histologically, this fragility and increased susceptibility of the grafted sheets may be related to the immaturity of the dermo-epidermal junction, which results in inadequate anchoring that improves with maturation of the autograft, seen after the first 6-12 months [63].

ALLODERM is a human dermal graft that is a cellular, and is used for soft-tissue reconstruction in the trauma patient. It originates from human cadaveric skin, being denuded of epithelium and decellularized in such a way that the extracellular dermal matrix and basement membrane

architecture are preserved. It is freeze-dried, with a shelf life of up to two years.

Once the product is used to cover a soft tissue defect, it becomes fully incorporated as part of the recipient's body. This happens through a process of revascularisation followed by cellular repopulation with the recipient's own cells [64].

*BIOBRANE* is a bilaminar membrane composed of a nylon mesh stuck to a thin layer of silicone [65].

The nylon is covered with peptides originating from type I collagen, derived from pigs and promotes fibrovascular ingrowth. The silicone carrier is semi-permeable, thus preventing the collection of exudate under the film.

Biobrane separates as the wound heals and is easily peeled away from the surface of the healing injury. It is best used on superficial partial-thickness burns sites within the first 6h of injury, as it works best on uncontaminated wounds. Burns can be fully healed within approximately two weeks. Hospital stay may be reduced by 46% [66].

*INTEGRA* is currently the most widely accepted synthetic skin substitute and was first described by Yannas *et al.* in 1980 [67, 68].

Integra has a bilaminar structure, formed of bovine collagen and glycosaminoglycan, coated on one side with a porous silicone membrane that provides epidermal function. The pore size is between 70-200µm, which allows migration of the patient's own endothelial cells and fibroblasts. Smaller pores may interfere with optimal biointegration and larger pores don't provide sufficient attachment area for the migrating host cells.

Once a wound is debrided thoroughly and the Integra is used to cover the clean wound bed, the collagen layer is biointegrated through a process of cellular invasion by the host cells. From the resulting angiogenesis, concludes in the formation of a vascular 'neodermis'; this process takes approximately 3-6 weeks. Once the biointegration stage has reached maturity at three weeks, the silicone layer will peel off quite readily and an ultra-thin split skin graft can be applied, as a second stage of the reconstructive process. One of Integra's main advantages is that it provides immediate wound cover. Initial problems with this product included haematoma and seroma formation and premature silicone separation, as highlighted by a study in 1981 [69].

Numerous subsequent studies of patients treated with Integra showed the areas grafted with artificial skin to be cosmetically superior when compared to those where autograft was utilised on its own. It has also been demonstrated that the areas grafted with the artificial skin grew with the child, without any problems [70]. Further reports by Stem *et al.* showed that there was no evidence of an immune reaction or scarring [71].

Current research is focusing on modifying the collagen-glycosaminoglycan matrix through the incorporation of peptides [72] and antibiotics; [73] cultured autologous keratinocytes have also been shown to produce a surface epithelium when seeded as a suspension onto Integra, in animal trials [74].

The most daring advancement in recent years, which may well represent the final frontier of microvascular free tissue transfer, is undoubtedly cadaveric allografting of the hand:

During the years of 1998 and 2009, 42 hand and 3 arm allotransplants were performed in 33 patients worldwide. These patients were followed up between 17 to 120 months and so far 25 of these transplants have survived [75].

Patients are usually treated with monoclonal antibodies, corticosteroids, Azathioprine, Methotrexate, and non-steroidal drugs [76-79] to permit graft survival, by suppressing the recipient's immune response.

At present the cocktail of immunosuppressant medication and steroids may lead to cardiac and hepatic failure, cataracts and numerous cutaneous malignancies for example Basal and Squamous Cell Carcinomata [80].

It is the author's opinion, that scientific advancement will eventually provide us with medication that will keep both acute and chronic graft rejection at bay, with fewer side effects, causing less morbidity to the recipient.

Cadaveric allografting of entire limbs is bound to become more readily available; routinely performed 'spare-part' surgery, which will then solve the daunting socio-economic challenges these trauma patients were faced with, after losing a limb.

## CONCLUSION

Severe hand trauma may be a devastating and life-altering experience, which has a huge psychosocial and economic impact on both the patient's and their families. The sustained injuries and prolonged path to recovery have far reaching effects on the patient's ability to work, perform activities of daily living and to lead an independent life, ultimately affecting their psychological well being.

When dealing with devastating hand injuries, it is vital to remember that the road to reconstruction is complex, lengthy and emotionally charged.

In their study of 2003 Bueno and Neumeister summed the journey of the mangled hand up, by stating that: 'the measure of functional outcome must incorporate the evaluation and severity of the initial injury and the subsequent reconstructive surgeries' [4]. It is imperative all surgeons dealing with hand injuries consider this statement when executing management.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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