PAMELA | WP3 - Evidence based recommendations and teaching material for surgical techniques for preventing the development of PLP

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At a glance

Recommendation 1.1
Surgical techniques addressing symptomatic neuroma can effectively reduce phantom limb pain.

Recommendation 1.2
If PLP and concomitant NP occur, surgical interventions should be applied as soon as possible to avoid chronification of pain.

Recommendation 2.1
Early consideration of TMR and RPNI as preventive measures help to minimize the risk of phantom limb pain in individuals undergoing amputation.

Recommendation 3.1
Adhere to the basic principles of peripheral nerve surgery when carrying out Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI) procedures in order to achieve successful outcomes.

Recommendation 3.2
Phantom limb pain and residual limb pain interact with each other. During residual limb revision surgery address other relevant conditions contributing to residual limb pain as bone spurs, ischemia, and scars etc. to improve the chances of achieving pain relief.

Recommendation 3.3
To successfully perform TMR, it is recommended to possess a comprehensive set of surgical skills and microsurgical equipment. These skills are essential for carrying out the procedure with precision and expertise.

Recommendation 3.4
RPNI is an appropriate alternative for the treatment and prevention of PLP. It does not require microsurgical equipment and requires less operative time than TMR. Currently, it does not allow for myoelectric prosthesis control.

Recommendation 4.1
Nerve sutures should be protected from pressure, forced bending, and any movements that put excessive stress on the micro-suture for a period of three weeks.

Recommendation 4.2
Long-term follow-up of amputees and revision surgery for persistently symptomatic limbs can dramatically improve prosthesis use, function, and quality of life.

Recommendation 4.3
A skilled multidisciplinary team approach for long-term follow-up of amputees is imperative to maximize outcomes.

Recommendation 4.4
The patient should be fitted with a functional prosthesis as soon as possible after the operation.

Recommendation 5.1
Amputations after trauma should be managed in an open, length-preserving fashion; guillotine amputations sacrifice residual limb length and viable tissue. Subsequent revision and closure may require the use of atypical flaps of opportunity to salvage valuable residual limb length, functional joint levels and innovations within primary amputation to improve the overall outcome and decrease the incidence of PLP.

Recommendation 5.2
TMR, in conjunction with advancements in prosthetic technology enables improved outcomes, prosthetic acceptance and helps to achieve the goals of active-duty service members.

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Scope and Purpose

Objectives

Regardless of the cause of the amputation, amputation-associated pain can occur. This pain can be divided into two types: Phantom limb pain (PLP) and Residual limb pain (RLP). Residual limb pain is localised in the residual limb and is felt as pain via nociceptors. Neuroma pain (NP) is neuropathic pain and can originate from severed nerves in the residual limb; it is categorised as RLP. PLP is caused by peripheral, spinal and central pathomechanisms leading to maladaptive cortical reorganisation and leading to the perception of pain or discomfort in a limb that is no longer there. Non-painful perceptions of the amputated body part are called phantom sensations.[1] Phantom sensation, unlike phantom limb pain, does not typically require specific treatment interventions. However, it is important to provide patient education in addressing phantom sensation to promote understanding and address potential concerns related to this experience.

Recently, there had been a lack of evidence supporting the efficacy of surgical techniques in treating phantom limb pain (PLP).[2–4] Both central pain and peripheral pain have distinct underlying mechanisms that are rooted in nervous tissue, potentially explaining their interactions. It has been observed that residual limb pain (RLP) can accompany PLP, and each type of pain has the capability to trigger or worsen the other.[5] In 2018, literature reviews by Poppler[2] and Eberlin[3] indicated that reconstructive techniques are more effective than ablative techniques in addressing neuropathic pain (NP).

A recent randomized controlled trial (RCT)[6] compared the standard procedure of burying the nerve in a muscle, which was considered the gold standard treatment for painful neuroma, with targeted muscle reinnervation (TMR) as a reconstructive approach. The findings of the study revealed that TMR effectively addressed both PLP and RLP, including NP, suggesting its potential superiority over the standard nerve burial technique[7]. Subsequent reports and reviews have consistently supported these findings for both TMR and the regenerative peripheral nerve interface (RPNI), a second reconstructive technique that facilitates the regeneration of mixed nerves into their original targets.[8,9] These emerging results indicate the potential effectiveness of reconstructive surgical techniques, particularly TMR and RPNI, in addressing PLP, and NP.

Given that evidence, we would like to highlight herein the following:

- Diagnostic Criteria: Neuroma Pain vs. Phantom Limb Pain
- Basic Principles of Peripheral Nerve Surgery
- Surgical Steps for the Reconstructive Techniques Targeted Muscle Reinnervation (TMR), Targeted Sensory Reinnervation (TSR), Regenerative Peripheral Nerve Interface (RPNI), and the
- Post-Operative Care
- Further remarks:
    - Special Considerations in Combat Surgery

Area of treatment/care

Surgical techniques for preventing the development of phantom limb pain in primary amputation:

- TMR
- TSR
- RPNI

Surgical techniques for a therapeutical treatment of phantom limb pain in revision surgery:

- TMR
- TSR
- RPNI

Target group

Complex combat injuries with an high risk for amputation and combat related amputation.[10]

Chapter 1: Brief introduction to Phantom Limb Pain and Neuroma Pain after Amputation

Background

Phantom limb pain presents as a distressing sensation in the amputated extremity whereas residual limb pain is located at the residual limb.[1] Pain after major limb amputation is a common occurrence, with up to 79.9% of the patients reporting PLP, 67.7% reporting RLP including NP and 62.3% of the patients reporting back pain.[11] Neuroma pain originates in the nerve tissue of the residual limb, while phantom pain manifests peripherally, spinally, and cortically.[1]

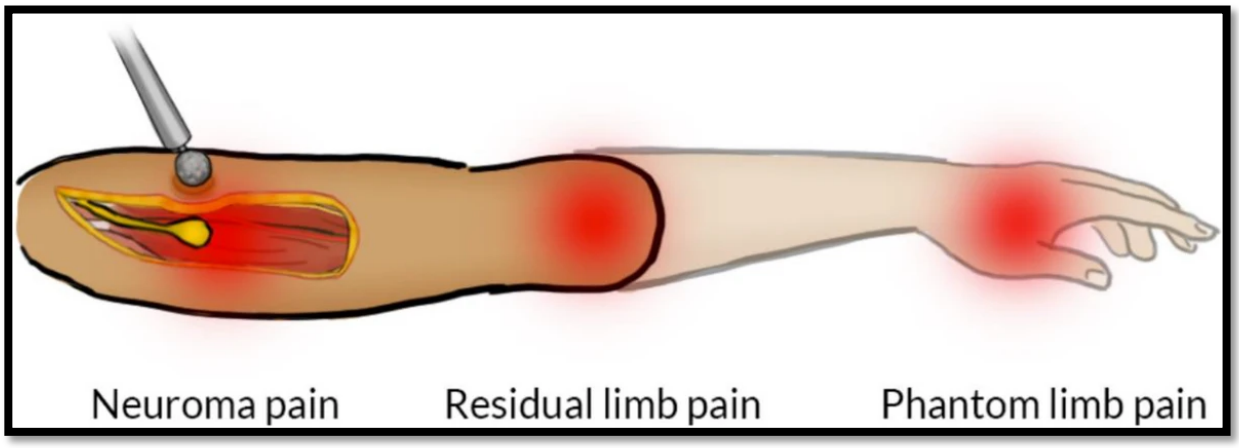


Figure 1: Illustration of the three different pain types: neuroma pain, residual limb pain, and phantom limb pain (Copyright Pettersen et al., 2023 [12])

The impact of phantom pain and neuroma pain on individuals with amputations is complex and multidimensional, significantly influencing their quality of life. Distinguishing between the two types of pain can be challenging, as both present with distinct characteristics. In the context of neuropathic pain, these sensations bear resemblances manifested in the form of stabbing, throbbing, electrical shooting, and burning.[1,5]

Neuroma Pain

Peripheral nerves lose contact with their target organs when a limb is lost. Following a traumatic nerve amputation, a complicated process that triggers the nerve cell's capacity for regeneration is started close to the site of the amputation.[13] While Waller degeneration causes the distal axon to break down and degrade due to loss of contact with the nerve cell, proximal degeneration typically only occurs to a very limited degree, typically up to the next Ranvier's cord.[14] Throughout the process, each individual axon starts to spread out proximally once more in an attempt to find a matching target organ. The so-called "growth cone," a specialized, mobile structure from which multiple finger-like projections emerge, is located at the tip of the regenerating axon. The regeneration should ideally occur in the direction of the distal nerve stump, and this is determined by the growth cone. Nevertheless, in the event of an amputation, the distal nerve stump is lost, so the regenerating axons typically do not find a corresponding "target." This causes the

nerve fibers to grow in an uncontrolled manner, which ultimately results in the development of neuromas. The neuropathic pain that results from a neuroma can be explained by the fact that the nerve fibers inside of it are demonstrably highly sensitive and have the ability to fire on their own.[15–17]

Possible symptoms of a neuroma pain can be allodynia (a pain sensation triggered by stimuli that do not normally cause pain), hyperalgesia (an increased pain sensation in response to painful stimuli), and a positive Hoffmann-Tinel sign (discomfort triggered by tapping on the nerve radiating into the area supplied by the nerve).[1]

The diagnostic criteria are as follows:

All three of the following criteria must be met:
1. Pain exhibiting at least three of the following characteristics: burning, cutting, shooting, electrifying, paraesthesia, numbness, or cold intolerance.
2. Symptoms confined to a specific neuroanatomical region.
3. A history of an actual or suspected nerve injury.

Additionally, at least one of the following criteria must be met:
1. Positive Tinel's sign (for cutaneous nerves).
2. Response to infiltration with a local anesthetic.
3. Confirmation of a neuroma through imaging (neurosonography, MRI).

Figure 2: Diagnostic criteria for symptomatic neuroma (German S3 guideline on the treatment of peripheral nerve injuries[18], outlined in Chapter 9)

In the second step visualization of the neuroma by ultrasound, diagnostic ultrasound-guided infiltration with a local anesthetic should follow. A positive result is a temporary reduction or elimination of pain.[1]

Phantom limb pain

The precise underlying mechanism driving the development of phantom limb pain remains under current investigation and has not yet been definitively established[5]. Research suggests that alterations in the peripheral and central nervous systems may contribute to phantom pain, with psychosocial factors also exerting a significant influence on its onset and persistence.[5,19] The pain experienced in a phantom limb involves both peripheral and central components of the nervous system (CNS), including the residual limb, dorsal root ganglion, spinal cord, supraspinal centers such as the brainstem, thalamus, cortex, and limbic system.[20]

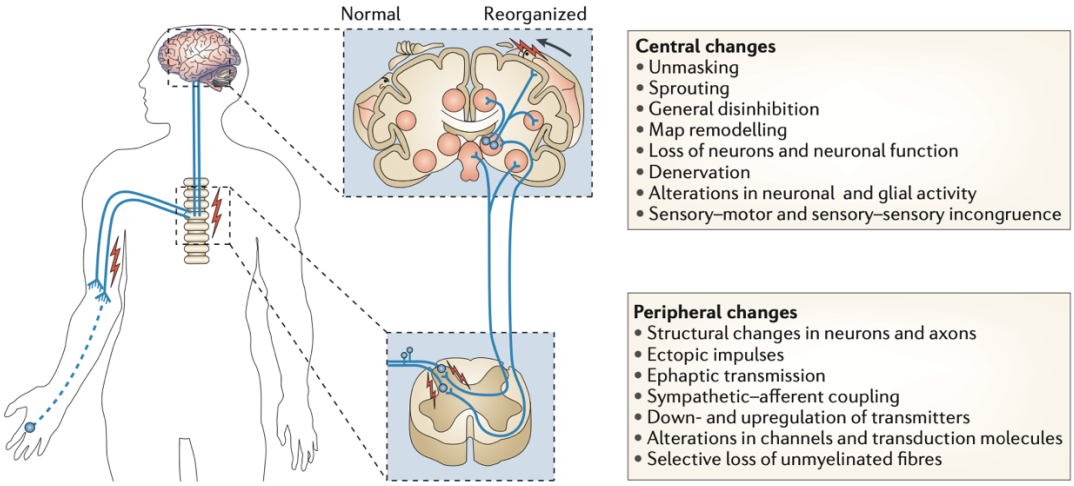


Figure 3: A schematic diagram of the areas involved in the generation of phantom limb pain and the main peripheral and central mechanisms from the paper "Phantom limb pain: a case of maladaptive CNS plasticity?" by Herta Flor (2006)[20] (Copyright Nature Publishing Group, 2006)

In light of recent evidence, it is important to distinguish RLP from PLP, as there has been a potential shift in the treatment approach for amputation-associated pain. While surgical interventions were once deemed ineffective in treating PLP, recent research suggests otherwise, thus highlighting the need for further investigation and clinical consideration of the relationship between RLP and PLP.[2–4]

For decades, surgical interventions for phantom limb pain (PLP) and neuroma pain have shown limited efficacy. However, in recent years, targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI) have emerged as promising techniques for enhancing prosthetic control and reducing pain associated with amputation, including PLP.[8,21] This has been corroborated by several case series and case-control studies. Despite the increasing interest in these techniques, comparative studies and randomized controlled trials (RCTs) are currently lacking to determine the relative effectiveness of each approach.

Literature Review

A review of the existing literature on surgical interventions for phantom limb pain reveals the paucity of randomized controlled trials, with only one such trial published in 2019 by Dumanian[6]. This trial compared the effects of burying the nerve into a muscle[7], the standard approach, with the innovative TMR[22] approach. Given that the TMR approach requires additional skills and operating time, careful evaluation of its indication and potential benefits is essential. Furthermore, the limited comparative evidence underscores the need for RCTs to enhance the level of certainty in the evidence.[23]

Recent Studies and Future Directions

A recent literature search focusing on published research after November 2021 identified a range of studies, including systematic literature reviews, prospective cohort studies, ret-

rospective cohort studies, chart reviews, observational cost-benefit studies, and case-control studies. The observational data suggest that TMR and RPNI reduce phantom limb pain and the incidence of painful neuromas. However, to further elucidate the comparative effectiveness of these techniques, conducting randomized trials is imperative.

Ongoing Research

In response to the need for evidence, a double-blind RCT[12] (NCT05009394) has been initiated to compare the effectiveness of TMR, RPNI, and an active control (neuroma excision and muscle burying) in alleviating residual limb pain, neuroma pain, and phantom limb pain. The trial, spanning multiple countries, aims to follow patients for a period of 4 years. This aligns with the imperative to address phantom limb pain, which affects a significant proportion of major limb amputees, profoundly impacting their quality of life. Distinguishing between phantom pain and neuroma pain is crucial, as both types of pain have unique characteristics and require tailored interventions.

Chapter 2: Surgical Techniques for the Prevention and Treatment of Phantom Limb Pain

Background

The brief background of the pathophysiological mechanisms might explain the potential of reconstructive nerve techniques as TMR and RPNI in the prevention and treatment of NP and PLP. Unlike other methods, they give a specific purpose to the severed nerve endings, providing a clear direction for their growth and potentially preventing their disorganization. Both strategy seem to actively manage the transected nerve by restoring its function, offering a promising approach for addressing NP and might decrease deafferentation and -efferentiation.[9,24,25] The findings from functional MRI studies comparing amputees who have undergone TMR and TSR interventions on the residual limb to those who have not, indicate a similarity in the activity of the primary motor and sensory cortex areas to that of healthy individuals. This suggests that reafferent interventions can potentially prevent or mitigate pathological cortical adaptations following amputation. These insights underscore the potential of such interventions in facilitating functional recovery and enhancing the neuroplasticity of the remaining neural pathways.[17,26]

Principles of Targeted Muscle Reinnervation (TMR)

TMR was initially introduced by Kuiken et al.[27] as a control strategy to enhance the functionality of myoelectric prostheses for amputees. The principle of Targeted Muscle Reinnervation (TMR) involves redirecting affected proximal nerve stumps to a smaller motor nerve branch that leads to an intact muscle. This denervated muscle is then reinnervated through primary end-to-end coaptation at the nerve entry point, allowing the sprouting axons to enter the motor nerve branch and subsequently reinnervate the denervated muscle tissue or motor end plates. This facilitates highly selective reinnervation of individual muscle areas.[18,22,28]

Initially developed for bionic prosthetics, this technique entailed coapting blind-ending nerves to selected muscle branches to increase the number of individually motorized signals used for prosthetic control. An incidental benefit observed was a very low rate of painful neuroma formation and a reduction in PLP. Subsequent studies have shown excellent results for both pain qualities.[6,29,30] The efficacy of the technique has been demonstrated for both secondary targeted muscle reinnervation (TMR) in the treatment of existing neuromas and primary prophylactic TMR for recent amputations, which is increasingly becoming a standard practice in clinical settings.[28,31]

The targeted muscle reinnervation (TMR) method is not exclusively intended for macrostump treatment; it can also be utilized for addressing painful finger neuromas. TMR represents an improved therapeutic approach compared to surgical resection alone or simple nerve burial within the muscle.[8]

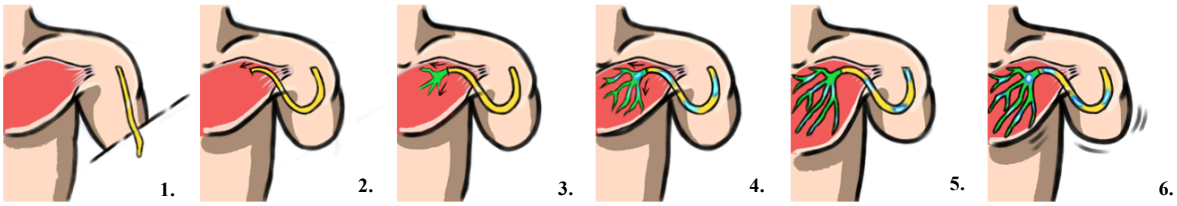


Figure 4: Targeted muscle reinnervation in major limb amputation: 1. Identify the donor nerve under blunt dissection and gently isolate the donor nerve under loupe magnification using microsurgical instruments as needed. Mobilize the donor nerve for as long as necessary to reach the recipient site. 2. Identify all motor nerve branches to the target muscle by blunt dissection. Transfer the donor nerve to the target muscle and coapt the distal nerve end of a transected motor nerve by end-to-end neurorrhaphy. 3.-6. This provides the nerve with a guide structure via which it grows into the muscle and reinnervates it. (Copyright: Katharina Kasprzak, MHH)

Surgical Roadmap

A standardized surgical protocol has been published recently and is summarized below.[32]

Terms:

Donor nerve: a nerve with a painful neuroma to be transferred to a recipient residual or "target" nerve.

Recipient residual nerve: the transected segment of a nerve (freshly prepared nerve stump) natively innervating a target muscle.

Target muscle: a viable muscle supplied by the recipient residual or "target" motor nerve in or near the residual limb.

1. Presurgical preparations

1. Diagnose the painful neuroma(s): For neuroma pain, physical stimulation in the form of digital pressure (e.g. Tinel's sign test) will be used to elicit pain where the neuroma is suspected. No physical stimulation will be used to elicit residual limb pain or PLP; rather, participants will be asked to close their eyes and localize the pain in order to distinguish between the two types. In cases where gentle skin indentation results in RLP, the area can be locally anaesthetized to reduce it and uncover neuroma pain during the physical stimulation. Neuroma pain can also be distinguished by the distally referred painful sensations it elicits in the phantom limb during physical stimulation. At least one of the following methods should be applied to document the presence of neuroma pain: compatible symptomatology, Tinel's sign test, imaging (ultrasound or MRI), or nerve block.[12]
2. Conduct a thorough physical assessment to detect potential muscle targets and evaluate the flexibility of the soft tissue surrounding the nerve. Perform an EMG evaluation of those target muscles in case muscle contraction is hardly assessable.
3. Plan the skin incisions depending on the results from steps 1.1 and 1.2

2. Preparation of the donor nerve

1. Perform either regional or general anesthesia without the use of muscle relaxants to allow for effective nerve stimulation. NOTE: The type of anesthesia depends on the site of the procedure.

2. Depending on the planned amputation or site of the painful neuroma, place the patient in a supine or prone position. For the upper extremity, use a surgical arm board to place the arm.
3. Carry out the skin incision using a scalpel. The length and shape of the skin incision depend on the available soft tissue or location of the painful neuroma.
4. Identify the donor nerve or the painful neuroma under blunt dissection.
5. Gently isolate the donor nerve or the neuroma under loupe magnification using microsurgical instruments as needed. NOTE: Isolation of the neuroma is optional.
6. Mobilize the donor nerve for as long as necessary to reach the recipient site, considering that the following nerve sutures are free of tension in all range of motions in the proximal joints. Transect the neuroma or transect the nerve using a commercial nerve cutting/preparation set. NOTE: Resection of the neuroma is optional when challenging.
7. Repeat steps 2.4-2.6 for each nerve with an identified painful neuroma in the current exposed area.

3. Motor point identification

1. Identify all motor nerve branches to the target muscle by blunt dissection.
    1. Set a hand-held-nerve stimulator at 0.5-1.0 mA, put it in contact with the nerve branches, and stimulate each of them. During stimulation, the nerve that provides the largest muscle contraction is the one that will be used as the recipient nerve. In *Table 1,* target muscles are suggested for each nerve at a specific amputation level.
    2. Use the known most proximal innervation points when possible.
    3. Denervate the target muscle completely when possible.
2. Once active contraction is confirmed, transect the nerve using straight microscissors without tension as close as possible to its entry point. Aim for less than 1 cm.
3. Transpose the proximal nerve end of the transected recipient nerve proximally away from the coaptation site without any specific management.

Amputation level	Donor nerve		Suggested target muscle(s)
Shoulder disarticulation	Musculocutaneous	→	Pectoralis Major – Clavicular Head
	Median	→	Pectoralis Major – Sternal Head
	Ulnar	→	Pectoralis Major – Split Sternal Head Pectoralis Minor Latissimus Dorsi Serratus Anterior
	Radial	→	Latissimus Dorsi Pectoralis Major -Split Sternal Head Serratus Anterior
Transhumeral	Musculocutaneous	→	Biceps Brachii – Long Head
	Median	→	Biceps Brachii – Short Head
	Ulnar	→	Brachialis Biceps Brachii – Short Head
	Radial – Distal branch	→	Triceps Brachii – Lateral Head

	Radial – Proximal branch	→	Triceps Brachii – Long Head
Transradial	Median	→	Flexor Digitorum Superficialis Flexor Digitorum Profundus
	Ulnar	→	Flexor Carpi Ulnaris Flexor Pollicis Longus
	Radial – Superficial branch	→	Extensor Carpi Radialis Flexor Digitorum Profundus Brachioradialis
Hip disarticulation	Sciatic	→	*If posterior thigh flap is preserved:* Semi-membranosus Semitendinosus Biceps femoris *If medial thigh flap is preserved:* Gracilis Adductor longus Adductor magnus Adductor brevis
	Femoral nerve	→	Sartorius (if present) or obturator nerve transfer Rectus femoris Vastus lateralis
	Saphenous	→	Sartorius (if present) or obturator nerve transfer
	Obturator	→	Preserved into the flap
	Lateral Femoral Cutaneous	→	Semimembranosus Semitendinosus Biceps femoris Sartorius
	Posterior Femoral Cutane-ous	→	Semimembranosus Gracilis Adductor Longus Adductor Magnus Adductor Brevis
Transfemoral	Sciatic - Peroneal Compo-nent	→	Biceps Femoris
	Sciatic - Posterior Tibial Component	→	Semitendinosus Semimembranosus
	Saphenous	→	Vastus Medialis
	Posterior femoral cutane-ous	→	Biceps Femoris - Distal motor branch
Transtibial	Posterior tibial	→	Soleus Medial Gastrocnemius Flexor Digitorum Longus
	Common peroneal	→	Lateral Gastrocnemius Medial Gastrocnemius
	Deep peroneal	→	Tibialis Anterior

	Superficial peroneal	→	Extensor Digitorum Longus Peroneus Longus
	Medial sural	→	Flexor Hallucis Longus Medial Gastrocnemius
	Lateral sural	→	Lateral Gastrocnemius

Table 1: Target muscles are suggested for each nerve at a specific amputation level.[32] Adaptation determine by the individual patient case are always possible.

4. Nerve-to-nerve coaptation

1. Suture the donor nerve to the recipient residual or "target" motor nerve with an 8-0 non-resorbable monofilament suture, placing the stitch in the center of the donor nerve.
   NOTE: Each donor nerve is larger in caliber with more fascicles than the recipient motor nerve. Significant mismatch is usually encountered.
2. Reinforce with two or three 8-0 non-resorbable monofilament sutures that secure the donor nerve epineurium to the fascia and epimysium that surround the recipient nerve. Ensure that the coaptation is performed with neither tension nor excessive redundancy.
3. Close the surgical wounds in layers.

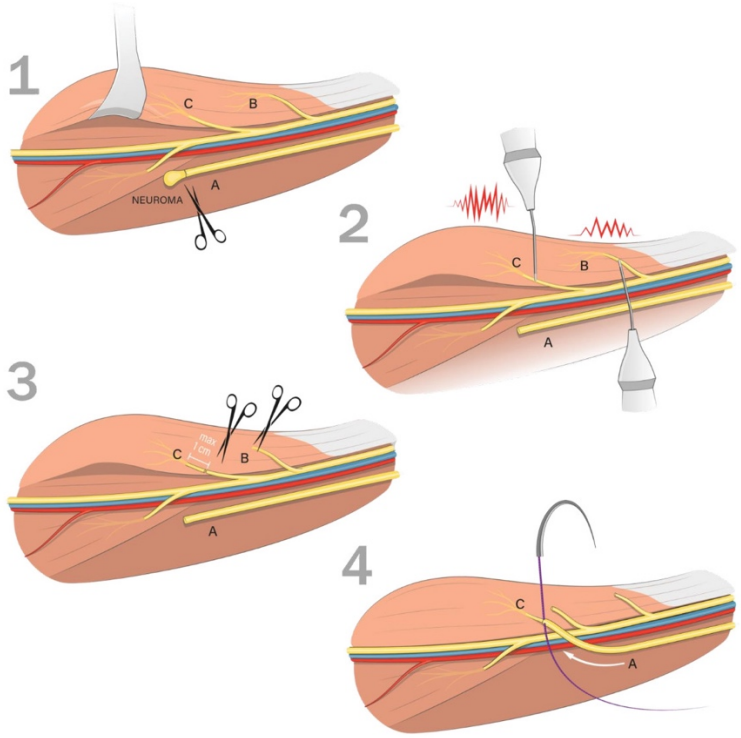


Figure 5: Figures explaining the single steps for TMR: 1) Identify and isolate the donor nerve with the painful neuroma (A). Mobilize the donor nerve and transect the neuroma up to healthy neural fascicles. 2) Identify motor nerve(s) to the target muscle and confirm muscle contraction using a hand-held nerve stimulator. 3) If several motor branches are identified, choose the motor branch that results in the largest contraction (C). Transect the nerve without tension as close as possible to its entry point (maximum 1 cm). Dennervate other identified motor branches to the same muscle when possible (B). 4) Suture the prepared donor nerve to the recipient residual or "target" nerve with the stitch placed in the center of the donor nerve. Reinforce with two or three microsutures that secure the donor nerve epineurium to the fascia and epimysium that surrounds the recipient nerve. (Copyright Pettersen et al., 2024 [32])

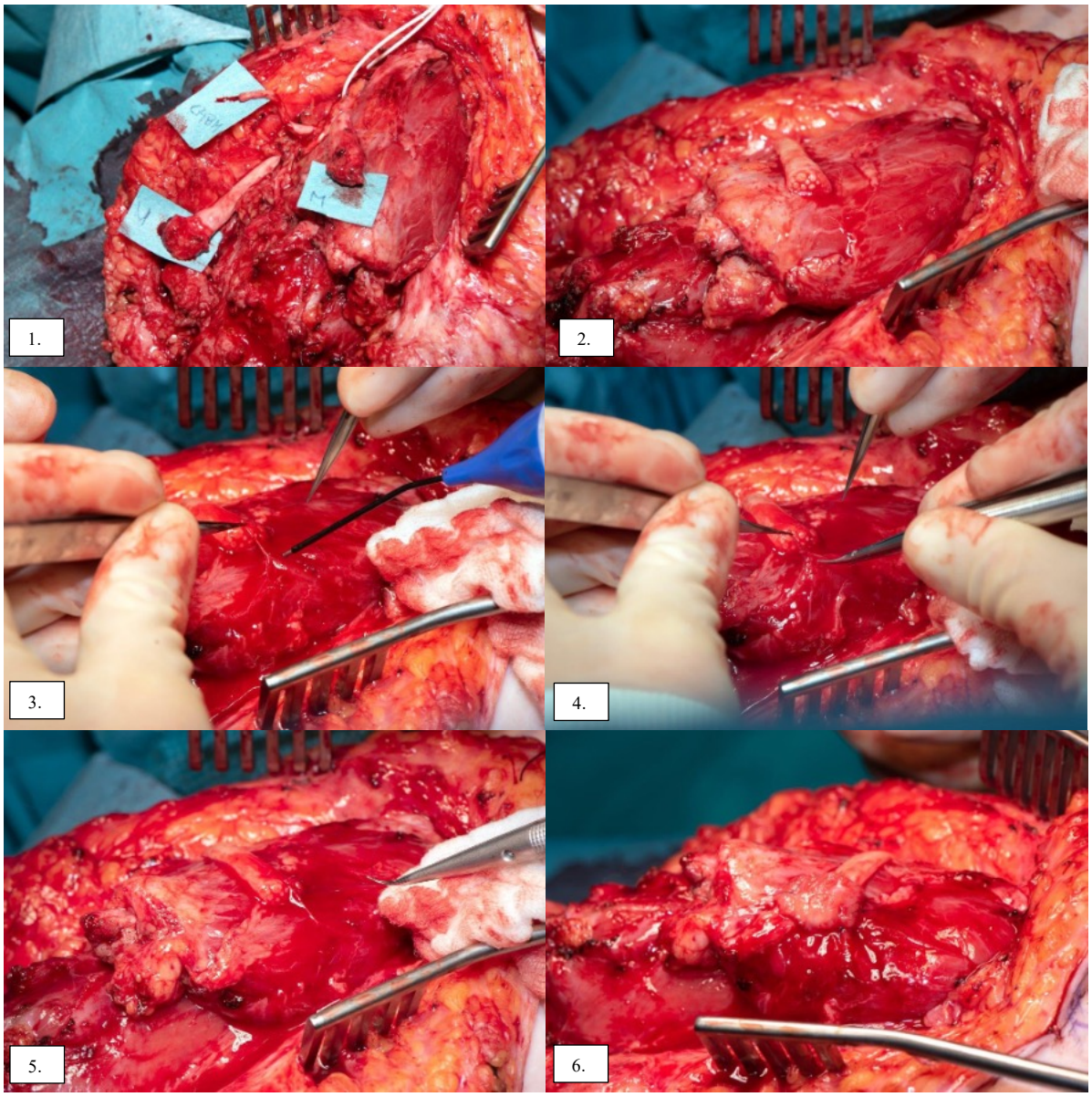


Figure 6: Surgery pictures explaining the single steps for TMR: **1.** Identify the donor nerve or the painful neuroma under blunt dissection. Gently isolate the donor nerve or the neuroma under loupe magnification using microsurgical instruments as needed. Mobilize the donor nerve for as long as necessary to reach the recipient site, considering that the following nerve sutures are free of tension in all range of motions in the proximal joints. **2.** Transect the neuroma or transect the nerve using a commercial nerve cutting/preparation set **3.** Identify all motor nerve branches to the target muscle by blunt dissection. Set a hand-held-nerve stimulator at 0.5-1.0 mA, put it in contact with the nerve branches, and stimulate each of them. During stimulation, the nerve that provides the largest muscle contraction is the one that will be used as the recipient nerve. **4.** Once active contraction is confirmed, transect the nerve using straight microscissors without tension as close as possible to its entry point. Aim for less than 1 cm. Transpose the proximal nerve end of the transected recipient nerve proximally away from the coaptation site without any specific management. **5.** Suture the donor nerve to the recipient residual or "target" motor nerve with an 8-0 non-resorbable monofilament suture, placing the stitch in the center of the donor nerve. NOTE: Each donor nerve is larger in caliber with more fascicles than the recipient motor nerve. Significant mismatch is usually encountered. Reinforce with two or three 8-0 non-resorbable monofilament sutures that secure the donor nerve epineurium to the fascia and epimysium that surrounds the recipient nerve. **6.** Ensure that the coaptation is performed with neither tension nor excessive redundancy. To avoid axonal sprouting outside the epineural nerve suture a standard RPNI is wrapped around the coaptation side, please see chapter RPNI. Close the surgical wounds in layers. (Copyright: Almuth Siefke, MHH)

Troubleshooting and Considerations

Felder et al. reported experiences of technical challenges, such as nerve redundancy, size mismatch, neuroma formation, the positioning of coaptation sites, full muscle denervation at the target site, and the selection of the optimal target for prosthetic functionality.[33]

Principles of Targeted Sensory Reinnervation (TSR)

The impact of sensory feedback on the control of prostheses, along with the associated enhancements in embodiment and alleviation of phantom pain, has been substantiated by a multitude of research studies.[34–36] For more authentic sensory feedback, a purely sensory nerve can be selectively transposed in analogy to a TMR procedure. This is the principle of targeted sensory reinnervation surgery (TSR).[37] The process described involves selectively reinnervating a specific area of skin by connecting a sensory donor nerve from the amputation to a defined sensory skin branch. This allows for the stimulation of the skin area in synchronization with the prosthesis function using a sensory feedback system that can be integrated into the socket system. This technique can provide sensory feedback, and it has been shown to improve functionality and embodiment of the prosthesis.[1,38]

Note: During the TMR procedure, the overlying skin is reinnervated by redirecting mixed donor nerves carrying sensor and motor nerve fibers to nearby muscle targets. This facilitates the restoration of sensation and motor control in a non-directed way.[39–41]

Following protocols for TSR have been described:

Donor Nerve	Recipient Nerve (TSR)	Reinnervated skin area and sensation	Source
Median Nerve	A fascicle of the median nerve was coapted to the intercostobrachial cutaneous (T2)	It innervates the skin covering the medial side of the upper arm	Herbert (2014)
Ulnar Nerve	A fascicle of the ulnar nerve was connected to the cutaneous branch of the axillary nerve	It innervates the skin covering the inferior region of the deltoid muscle (the regimental badge area)	Herbert (2014)
Sural Nerve	Transtibial (TT): Transposition of the ipsilateral sural nerve to the cutaneous territory of the saphenous nerve	It innervates the skin area on the front and medial side of the lower leg	Gardetto (2021)
Sural Nerve	Transfemoral (TF): Transplantation of the contralateral sural nerve as an autologous graft from the distal stump of the sciatic nerve to the cutaneous territory of the lateral femoral cutaneous nerve	It innervates the skin covering the lateral thigh	Gardetto (2021)

Table 2: Protocols for Targeted Sensory Reinnervation (TSR)

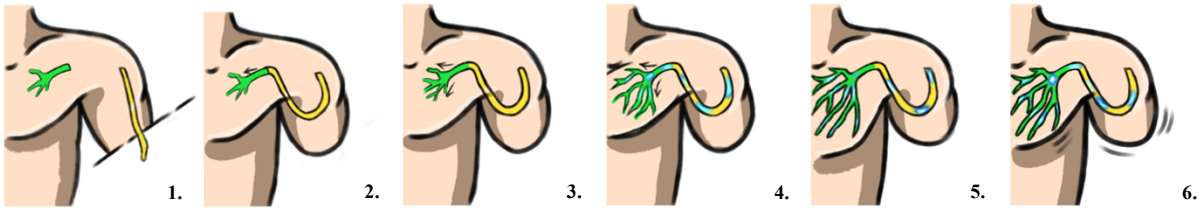


Figure 7: Targeted sensory reinnervation in major limb amputation: 1. Identify the donor nerve under blunt dissection and gently isolate the donor nerve under loupe magnification using microsurgical instruments as needed. Mobilize the donor nerve for as long as necessary to reach the recipient site. 2. Identify all sensory nerve branches to the target muscle by blunt dissection. Transfer the donor nerve to the defined sensitive skin branch and coapt the distal nerve end of the transected sensory nerve by end-to-end neurorrhaphy. 3.-6. This provides the nerve with a guide structure growing into the skin, finding skin receptor and reinnervating the according skin area. (Copyright: Katharina Kasprzak, MHH)

Surgical Roadmap

It is important to provide patients with comprehensive information about available options and limitations of current available technology and course of skin incisions. Currently there is one commercially available solution for lower limb stimulation reinnervating skin with vibrotactile feedback, and it is not yet available for upper limb application. However, it is also worth noting that such innovations may pave the way for potential use as a man-machine interface in the future.

1. Preparation of the donor and recipient nerve

1. Perform either regional or general anesthesia without the use of muscle relaxants to allow for effective nerve stimulation. NOTE: The type of anesthesia depends on the site of the procedure.
2. Place the patient appropriate to reach the surgical field, depending on the planned amputation or the site of the painful neuroma.
3. Carry out the skin incision using a scalpel. The length and shape of the skin incision depend on the available soft tissue or location of the painful neuroma.
4. Identify the donor nerve or the painful neuroma under blunt dissection.
5. Identify the recipient nerve under blunt dissection.
6. Gently isolate the donor and recipient nerve or the neuroma under loupe magnification using microsurgical instruments as needed.
7. Mobilize the donor nerve for as long as necessary to reach the recipient site, considering that the following nerve sutures are free of tension in all range of motions in the proximal joints. Transect the recipient nerve or transect the painful neuroma using a commercial nerve cutting/preparation set.
8. Transpose the donor nerve end to the distal transected recipient nerve.
9. Bury the proximal end of the transected nerve away from the coaptation site and surface. RPNI can be applied to the proximal end of the transected nerve.

2. Nerve-to-nerve coaptation

1. Suture the donor nerve to the recipient residual or "target" motor nerve with an 8-0 non-resorbable monofilament suture or smaller, placing the stitch in the center of the donor nerve. NOTE: Each donor nerve is larger in caliber with more fascicles than the recipient motor nerve. Significant mismatch is usually encountered.

2. Reinforce with two or three 8-0 non-resorbable monofilament sutures that secure the donor nerve epineurium to the surrounding tissue of the recipient nerve. Ensure that the coaptation is performed with neither tension nor excessive redundancy.
3. Close the surgical wounds in layers.

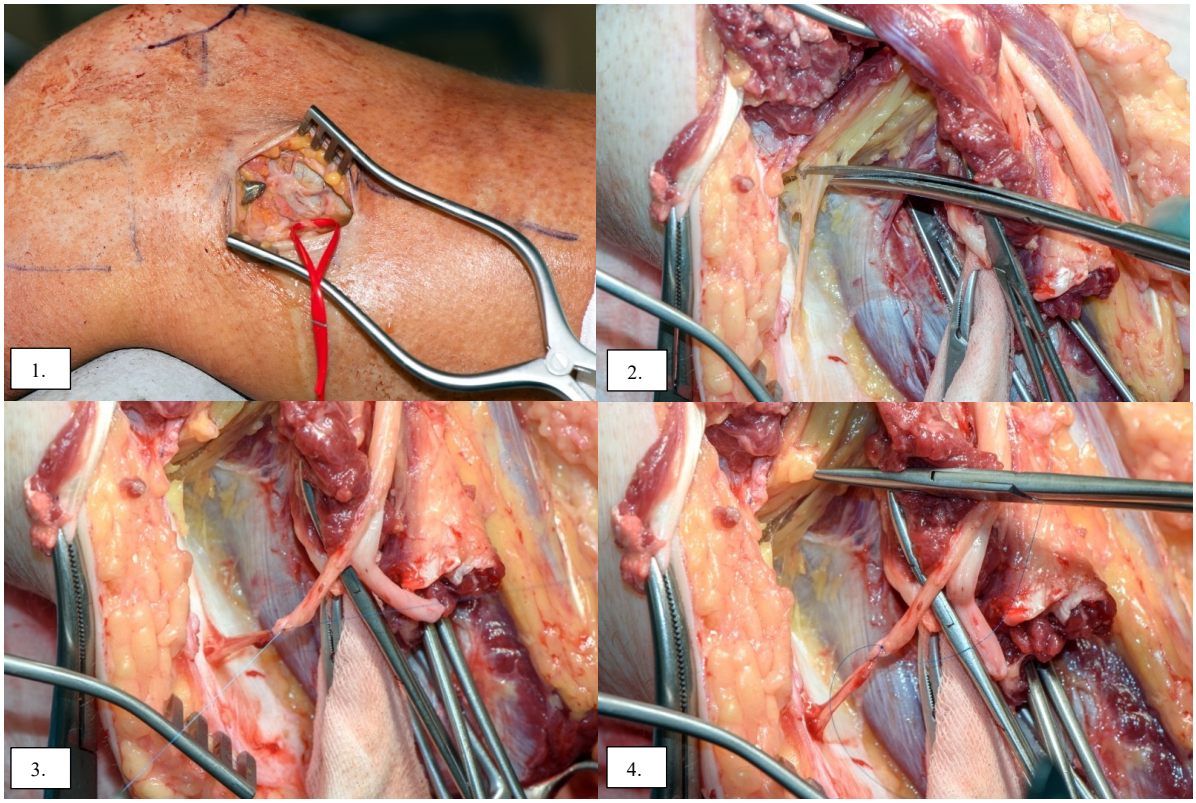


Figure 8: **1.** Identify all sensory nerve branches to the target skin by blunt dissection **2.** Transect the nerve using straight microscissors that cut the nerve at a length allowing for the nerve coaptation without tension. Transpose the proximal nerve end of the transected recipient nerve proximally away from the coaptation site. Bury it in a muscle away from the surface to avoid exposure to pressure or wrap RPNI around it. **3.** Suture the donor nerve to the recipient residual or "target" sensory nerve with an 8-0 non-resorbable monofilament suture, placing the stitch in the center of the donor nerve. NOTE: Each donor nerve is larger in caliber with more fascicles than the recipient sensory nerve. Significant mismatch is usually encountered. If needed a standard RPNI can be wrapped around the coaptation. **4.** Reinforce with two or three 8-0 non-resorbable monofilament sutures that secure the donor nerve epineurium to the fascia and epimysium that surrounds the recipient nerve. Ensure that the coaptation is performed with neither tension nor excessive redundancy. Close the surgical wounds in layers. (Copyright: Almuth Siefke, MHH)

Troubleshooting and considerations

The reported experiences of technical challenges include nerve redundancy, donor and recipient nerve distances, size mismatch, neuroma formation, the positioning of coaptation sites, temporary or full skin denervation at the target site with possible dysesthesia, and the selection of the optimal target for prosthetic and feedback system functionality.[33]

Currently, there is only one commercially available feedback system (Suralis, Saphenus Medical Technology, 3500 Krems, Austria) for lower limb amputees outside of laboratory prototypes. This system involves the reinnervation of the medial site of the lower leg by transplanting the sural nerve, which is then coapted to the saphenous nerve at the lower thigh for below-knee amputees or the sural nerve to the lateral cutaneous nerve at the thigh level for above-knee amputees.[37] By integrating pressure sensors into a sock worn

over the prosthetic foot and hindfoot, this system is able to encode pressure into a vibrotactile feedback paradigm. As a result, it provides a man-machine interface that delivers sensory information to the reinnervated area on the thigh or lower leg. This innovation has the potential to significantly enhance proprioceptive feedback for individuals with prosthetic limbs, which could ultimately lead to improved gait and overall functionality.[1,37]

Principles of Regenerative Peripheral Nerve Interface (RPNI)

Regenerative Peripheral Nerve Interface (RPNI) also describes a selective nerve transfer. In comparison to TMR, this procedure requires significantly less time and can be performed by non-microsurgeons. In this procedure, a small free avascular denervated muscle graft is utilized.[42] Subsequently, neovascularization of the muscle graft is followed by reinnervation through regeneration of the nerve. Originally, the method was demonstrated in combination with implanted electrodes in animal models to identify muscle signals that might be utilized for prosthesis control.[43] It was proven that the transplanted muscle tissue is reinnervated and has the potential to function as a signal transmitter in the future. It is crucial to ensure the viability of the free muscle graft by limiting its dimensions to a maximum of 30-40 mm in length, 15-20 mm in width, and 5-6 mm in thickness.[42,44] The avascular, denervated muscle graft serves as a target for the regenerating axons of the nerve stump. The individual nerves are split interfascicularly to form multiple distinct nerve endings, either to facilitate the passage of more signals or to supply the axons with additional muscle tissue for reinnervation.[44] This process allows the formation of new neuromuscular connections that effectively prevent the formation of new symptoms of neuropathy. The use of RPNIs has been shown to reduce phantom limb pain by up to 53 percent and neuroma pain by 71 percent.[1,8,42]

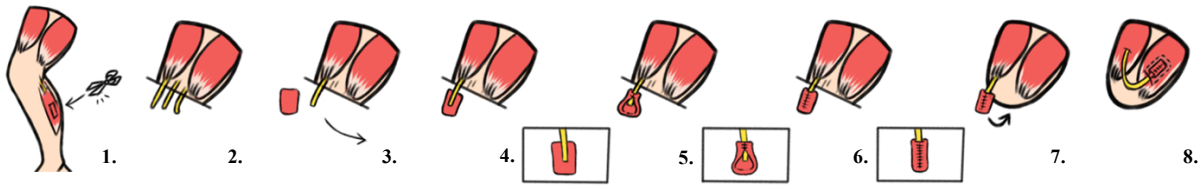


Figure 9: Regenerative peripheral nerve interface in major limb amputation: 1. Identify a healthy donor muscle and harvest a muscle graft (dimensions 3 cm (length) x 1.5 cm (width) x 0.5 cm (thickness). 2. Identify and isolate the nerve. Transect possible painful neuroma. 3.-4. Place the fascicle in the muscle graft and secure the nerve with sutures. 5.-6. Fold the muscle graft around the fascicle and secure with sutures. 7.-8. Perform blunt dissection in the residual limb to provide a protected area where each RPNI can lie comfortably and out of weight-bearing surfaces of the limb (Copyright: Katharina Kasprzak, MHH)

Surgical Roadmap

A standardized surgical protocol has been published recently and is summarized below.[45]

1. Presurgical preparations

1. Diagnose the painful neuroma(s) if present

2. Plan the skin incisions depending on the results from step 1.1 and depending on the location of each painful neuroma. NOTE: In principle, any healthy skeletal muscle can be used; however, the muscle graft was originally recommended to be harvested from the vastus lateralis muscle in the thigh.[46]

2. Preparation of the recipient site

1. Perform either regional or general anesthesia. NOTE: The type of anesthesia varies depending on the site of the procedure.
2. Place the patient in a supine or prone position, depending on the planned amputation or site of the painful neuroma. For upper extremity, place the arm on a surgical arm board.
3. Carry out the length and shape of the skin incision depending on the available soft tissue or location of the painful neuroma.
4. Identify the nerve or the painful neuroma under blunt dissection.
5. Gently isolate the nerve or neuroma with fine instruments. Use loupe magnification if needed. NOTE: Isolation of the neuroma is optional when challenging.
6. Mobilize the nerve and transect or transect the neuroma up to healthy neural fascicles using a commercial nerve cutting/preparation set. NOTE: Resection of the neuroma is optional when challenging.
7. Make longitudinal intraneural dissections from the distal end of the nerve for about **2-3 cm with straight microscissors. The number of fascicles will depend on the amputation level and the size of the nerve. Ensure that the diameter of each fascicle is a maximum of 4-6 mm**. For each nerve, a number of neural fascicles that should be prepared are suggested in *Table 2*.

Amputation level	Nerve	Suggested number of neural fascicles
Shoulder disarticulation	Axillary	2
	Musculocutaneous	2
	Median	3
	Ulnar	2
	Radial	2
Transhumeral	Axillary	2
	Musculocutaneous	2
	Median	3
	Ulnar	3
	Radial	2
Transradial	Median	3
	Ulnar	2
	Radial	1*
Hip disarticulation	Sciatic	4
	Femoral	3
	Lateral Cutaneous Femoral	1*

	Obturator	1*
	Posterior Cutaneous Thigh	2
Transfemoral	Sciatic	3
	Tibial	2
	Deep peroneal	1*
	Superficial peroneal	1*
	Sural	1*
	Saphenous	1*
Transtibial	Tibial	2
	Deep peroneal	2
	Superficial peroneal	1*
	Sural	1*
	Saphenous	1*
* Use the nerve entirely		

Table 3: Suggested number of neural fascicles specified for each nerve at a specific amputation level.[45] Adaptation determine by the individual patient case are always possible.

3. Preparation of the donor site

1. Identify a healthy native donor muscle as a source for obtaining a free muscle graft. Harvest the muscle graft as follows:
    1. Ensure that each graft has the dimensions 3 cm (length) x 1.5 cm (width) x 0.5 cm (thickness). NOTE: The main axis should be parallel to the muscle fibers.
    2. Dissect the muscle graft using delicate dissecting scissors following the main axis of the muscle fibers. Use magnifying loupes as needed.
    3. Gently excise adipose tissue and the muscle fascia from the muscle graft using dissecting scissors.
2. Keep the harvested muscle in a moist gauze with 0.9% NaCl sterile until utilization in section 4.
3. Repeat steps 3.1-3.2 for each muscle graft, based on the number of nerves and corresponding nerve fascicles to be wrapped with a prepared free muscle graft for an RPNI construct.

4. RPNI construct fabrication

1. Expose the nerve, already isolated and divided in fascicles.
2. Place the fascicle on the muscle graft so that the distal stump **falls in the central or proximal third of the muscle graft while having its orientation parallel to the muscle fibers.** NOTE: A parallel orientation is preferred to optimize successful axonal reinnervation.
3. Secure the nerve stump in the center of the longitudinal axis of the muscle graft using 6-0 non-resorbable monofilament sutures. Add one more stitch to secure the nerve at the proximal edge of the muscle graft. NOTE: Do not suture the nerve end into the muscle graft; the transected portion of the nerve remains free.

4. Fold the muscle graft around the fascicle and secure it with a 6-0 interrupted or continuous non-resorbable monofilament suture.
5. Repeat steps 4.1-4.4 for each fascicle.
6. Perform blunt dissection in the residual limb to provide a protected area where each RPNI can lie comfortably and out of weight-bearing surfaces of the limb. Where possible, offset the location of each RPNI in series.
7. Close the surgical wounds in layers.

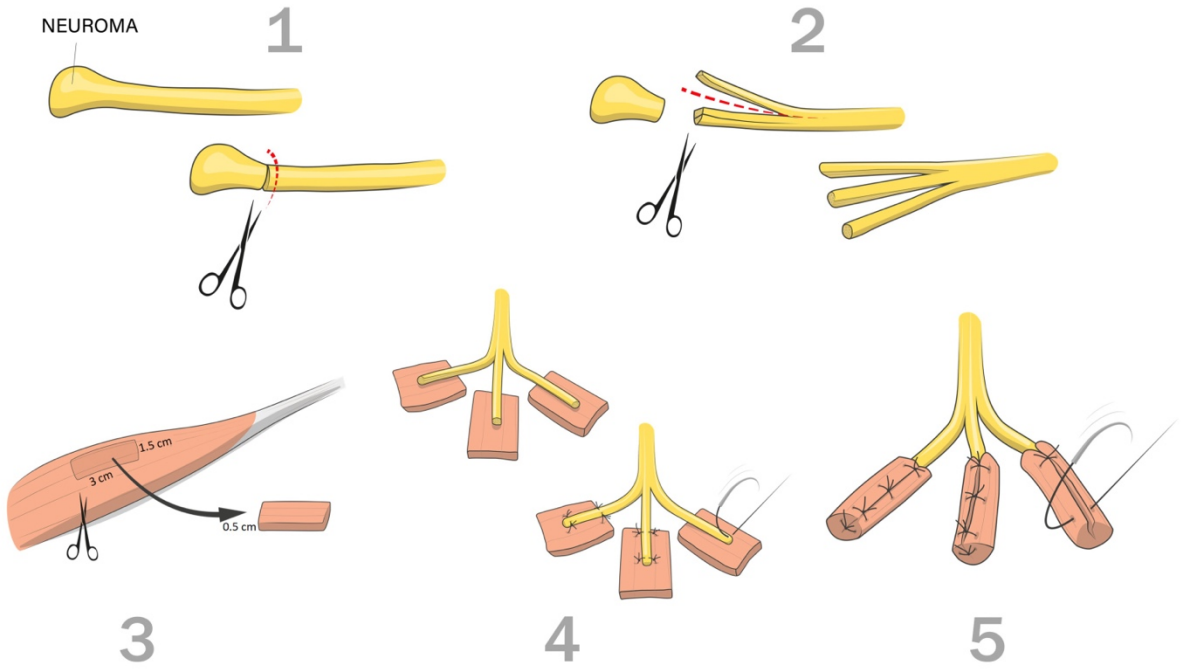
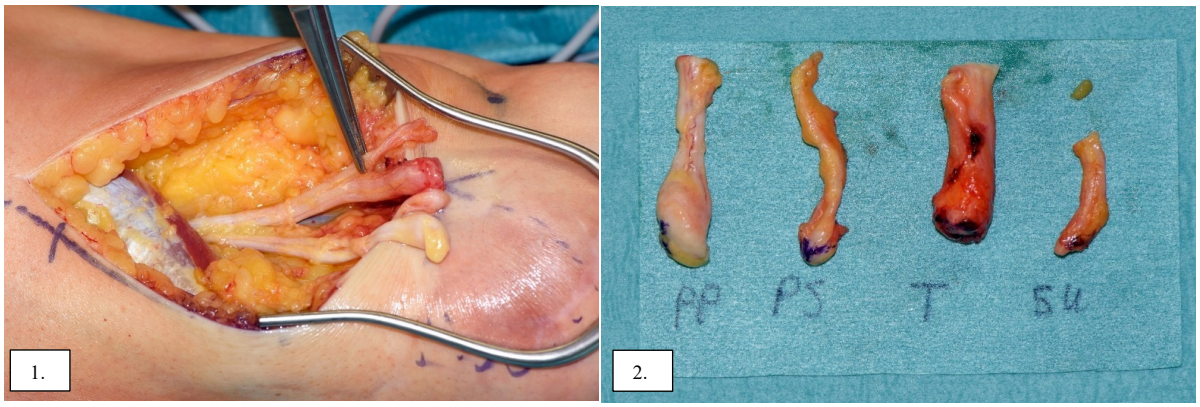


Figure 10: Figures explaining the single steps for RPNI: 1) Identify and isolate the nerve with the painful neuroma. Mobilize the nerve and transect the neuroma up to healthy neural fascicles. 2) Perform longitudinal intraneural dissections from the distal end of the nerve. The number of neural fascicles depends on amputation level and the size of the nerve. 3) Identify a healthy native donor muscle and harvest a muscle graft with the dimensions: 3 cm (length) x 1.5 cm (width) x 0.5 cm (thickness). 4) Place the fascicle in the muscle graft so the stump falls in the center of the muscle graft while having its orientation parallel to the muscle fibers. Secure the nerve within the muscle graft with sutures proximally and distally of the nerve stump. 5) Fold the muscle graft around the fascicle and secure. (Copyright Pettersen et al., 2024 [45])



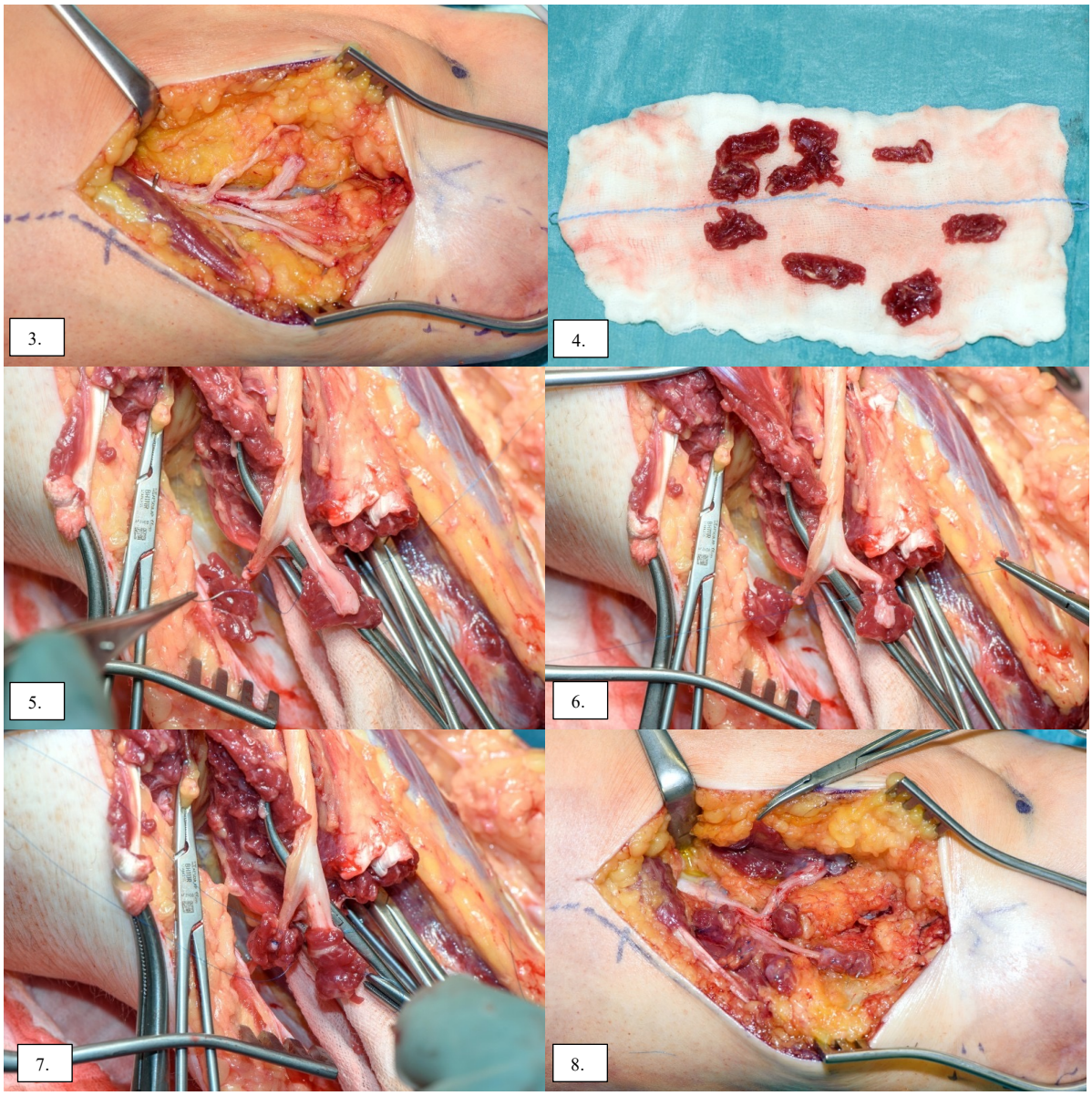


Figure 11: Surgery pictures explaining the single steps for RPNI: **1.** Identify the nerve or the painful neuroma under blunt dissection. Gently isolate the nerve or neuroma with fine instruments. Use loupe magnification if needed. **2.** Mobilize the nerve and transect or transect the neuroma up to healthy neural fascicles using a commercial nerve cutting/preparation set. **3.** Make longitudinal intraneural dissections from the distal end of the nerve for about 2-3 cm with straight microscissors. The number of fascicles will depend on the amputation level and the size of the nerve. Ensure that the diameter of each fascicle is a maximum of 4-6 mm. **4.** Identify a healthy native donor muscle as a source for obtaining a free muscle graft. Harvest the muscle graft as follows: a) Ensure that each graft has the dimensions 3 cm (length) x 1.5 cm (width) x 0.5 cm (thickness). b) Dissect the muscle graft using delicate dissecting scissors following the main axis of the muscle fibers. c) Gently excise adipose tissue and the muscle fascia from the muscle graft using dissecting scissors. **5.-6.** Expose the nerve, already isolated and divided in fascicles. Place the fascicle on the muscle graft so that the distal stump falls in the central or proximal third of the muscle graft while having its orientation parallel to the muscle fibers. Secure the nerve stump in the center of the longitudinal axis of the muscle graft using 6-0 non-resorbable monofilament sutures. Add one more stitch to secure the nerve at the proximal edge of the muscle graft. **7.** Fold the muscle graft around the fascicle and secure it with a 6-0 interrupted or continuous non-resorbable monofilament suture. Repeat steps for each fascicle. **8.** Perform blunt dissection in the residual limb to provide a protected area where each RPNI can lie comfortably and out of weight-bearing surfaces of the limb. Where possible, offset the location of each RPNI in series. Close the surgical wounds in layers. (Copyright: Almuth Siefke, MHH)

Refresher: Basic principles of peripheral nerve surgery

The basic principles of peripheral nerve surgery include meticulous dissection using appropriate magnification, careful handling, and protection of the nerve. For coaptation, please reinforce a suture with two or three 8-0 non-resorbable monofilament sutures (or

equivalent) that secure the donor nerve epineurium to the fascia and epimysium surrounding the recipient nerve. Ensure that the coaptation is performed with neither tension nor excessive redundancy.[7,47–49]
The nervous tissue should lie comfortably and away from the weight-bearing surfaces of the limb. It also entails managing associated soft tissue and bony components to optimize the outcome. Additionally, postoperative protection of the nerve suture for three weeks, rehabilitation, and monitoring are essential components of successful surgery.[7,47–49]

Literature Review

Our literature research conducted on April 18, 2024, targeted research published on this subject after November 2021, building upon previous reviews[8,9] examining the impact of TMR and RPNI on PLP and RLP. The search yielded 16 systematic literature reviews, 3 prospective cohort studies, 10 retrospective cohort studies, 2 retrospective chart reviews, 1 observational cost-benefit study, and 2 case control studies, categorized with Levels of Evidence (LoE) of 1, 2, or 3. Following we summarized the result we grouped into therapeutical approach, preventive approach, surgical considerations, post-operative care, and combat-related surgical considerations.

I Therapeutical approach

1.1	**Recommendation**	**adapted/new**
Grade of recommendation (GoR): **GoR A**	**Surgical techniques addressing symptomatic neuroma can effectively reduce phantom limb pain.** *Sources:* De Lange et al. (2022) LoE II Dumanian et al. (2019) LoE Ib	
Level of evidence: **II**	Consensus strength:	

1.1

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

1.2	**Recommendation**	**adapted/new**
Grade of recommendation: **GoR B**	**If PLP and concomitant NP occur, surgical interventions should be applied as soon as possible to avoid chronification of pain.** *Sources:* Goodyear et al. (2024) LoE III Yuan et al. (2024) LoE IIa	
Level of evidence: **II-III**	Consensus strength:	

1.2

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

II Preventive approach

2.1	Recommendation	adapted/new
Grade of recommendation: **GoR A**	**Early consideration of TMR and RPNI as preventive measures help to minimize the risk of phantom limb pain in individuals undergoing amputation.** *Sources:* De Lange et al. (2022) LoE II Yuan et al. (2022) LoE IIa	
Level of evidence: **II**	Consensus strength:	

2.1

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

III Surgical considerations

3.1	Recommendation	adapted/new
Grade of recommendation: **GoR B**	**Adhere to the basic principles of peripheral nerve surgery when carrying out Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI) procedures in order to achieve successful outcomes.** *Sources:* Pettersen et al. (2024) LoE V De Lange et al. (2022) LoE II	
Level of evidence: **III**	Consensus strength:	

3.1

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

3.2	Recommendation	adapted/new
Grade of recommendation: **GoR B**	**Phantom limb pain and residual limb pain interact with each other. During residual limb revision surgery address other relevant conditions contributing to residual limb pain as bone spurs, ischemia, and scars etc. to improve the chances of achieving pain relief.** *Sources:* Liu et al. (2015) LoE III Erlenwein et al. (2021) LoE V	
Level of evidence: **IV**	Consensus strength:	

3.2

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

3.3	**Recommendation**	**adapted/new**
Grade of recommendation: **GoR B**	**To successfully perform TMR, it is recommended to possess a comprehensive set of surgical skills and microsurgical equipment. These skills are essential for carrying out the procedure with precision and expertise.** *Sources:* Pettersen et al. (2024) LoE V De Lange et al. (2022) LoE II	
Level of evidence: **III**	Consensus strength:	

3.3

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

3.4	**Recommendation**	**adapted/new**
Grade of recommendation: **GoR B**	**RPNI is a suitable alternative for the treatment and prevention of PLP. It does not require microsurgical equipment and requires less operative time than TMR. Currently, it does not allow for myoelectric prosthesis control.** *Sources:* Pettersen et al. (2024) LoE V De Lange et al. (2022) LoE II	
Level of evidence: **III**	Consensus strength:	

3.4

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Chapter 3: Post-operative care

Surgical post-operative care

The postoperative protection of the nerve suture for a period of three weeks, rehabilitation, and monitoring are essential components of successful surgery.[7,47–49]

Prosthetic Rehabilitation

The use of a prosthesis can ease the reduction of sensorimotor incongruence following an amputation by providing tactile and visual stimuli that are reinforced through the prosthesis itself. Wearing and using a prosthesis has a similar pain-relieving effect to mirror therapy's reorganization of the sensorimotor cortex and phantom pain. Furthermore, wearing the prosthesis helps the body's "embodiment" process and restores its integrity, both of which can lessen phantom pain.[50] Somatosensory feedback enhances embodiment, lessens phantom pain, and improves prosthesis functionality.[51–53] This beneficial effect, for example, can be achieved by myoelectric prostheses with or without feedback systems integrated into the prosthesis socket.[38] In addition to the previously mentioned advantages, these feedback systems provides sensory feedback to the skin, which has been shown to improve function, safety, mobility, and the skin's sense of agency and ownership.[1,34,38,53,54]

General Rehabilitation

Close long-term follow-up in a multidisciplinary team is crucial for addressing and treating persistently symptomatic limbs, ultimately leading to increased prosthetic use and overall improved outcomes for patients.[10]

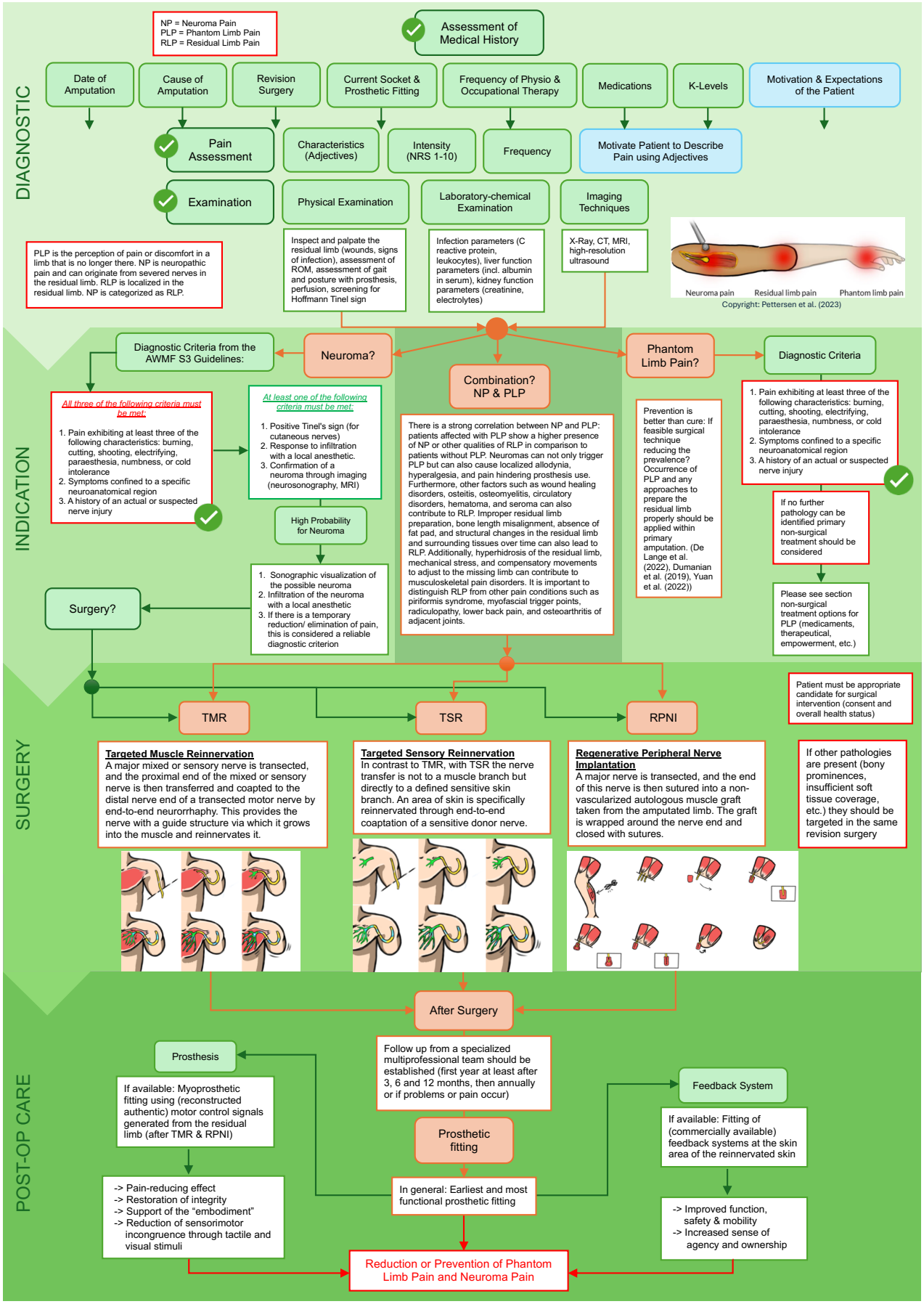


Figure 12: Algorithm for the diagnosis and treatment of phantom limb pain (Copyright: Jennifer Ernst, Marlene Arlt, MHH)

IV Post-operative care

4.1	Recommendation	adapted/new
Grade of recommendation: **GoR B**	**Nerve sutures should be protected from pressure, forced bending, and any movements that put excessive stress on the micro-suture for a period of three weeks.** *Sources:* Dellon und Mackinnon (1986) LoE IV Krishnan et al. (2005) LoE IV Mackinnon et al. (1985) LoE III	
Level of evidence: **IV**	Consensus strength:	

4.1

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

4.2	Recommendation	adapted/new
Grade of recommendation: **GoR 0**	**Long-term follow-up of amputees and revision surgery for persistently symptomatic limbs can dramatically improve prosthesis use, function, and quality of life.** *Sources:* Tintle et al. (2016) LoE V	
Level of evidence: **V**	Consensus strength:	

4.2

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

4.3	Recommendation	adapted/new
Grade of recommendation: **GoR A**	**A skilled multidisciplinary team approach for long-term follow-up of amputees is imperative to maximize outcomes.** *Sources:* World Health Organization. (2017). WHO standards for prosthetics and orthotics LoE I American Academy of Orthopaedic Surgeons. (2019). Management of limb amputations LoE I	
Level of evidence: **I**	Consensus strength:	

4.3

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

4.4	Recommendation	adapted/new
Grade of recommendation: **GoR A**	**The patient should be fitted with a functional prosthesis as soon as possible after the operation.**	

	Sources: World Health Organization. (2017). WHO standards for prosthetics and orthotics LoE I American Academy of Orthopaedic Surgeons. (2019). Management of limb amputations LoE I
Level of evidence: **I**	Consensus strength:

4.4

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Chapter 4: Considerations Combat-related Amputations

Special Considerations in Combat Surgery

Combat polytrauma presents unique challenges, particularly in the context of injuries sustained from improvised explosive device blasts. These injuries, often compounded by penetrating trauma from small arms fire, manifest as a distinct pattern of wounds characterized by extensive tissue damage and limb loss.[58] The anatomical disruption caused by blast or penetrating injuries can lead to nervous system trauma and subsequent neuropathic pain in various parts of the body.[59,60]

In the realm of combat surgery, time and special considerations are pivotal in striving for optimal outcomes for the affected individuals. Time sensitivity is paramount in the battlefield, where prompt medical attention can be the defining factor between life and death. Further, the constraints of limited resources, challenging working conditions, and the necessity of prioritizing critical cases underscore the criticality of swift and effective decision-making in combat surgical procedures. Medical personnel must be well-prepared, adaptable, and capable of making rapid, sound decisions in order to maximize the prospects of survival and recovery for the injured.[58–60]

On the battlefield:

In the context of combat scenarios, tourniquet education is critical in preventing short amputations. A tourniquet can be used to apply pressure to a limb to control severe bleeding, thereby preventing further damage and reducing the risk of amputation. Proper training in tourniquet application and awareness of the proper timing and techniques for its use can significantly impact the outcome of combat injuries. It is essential for individuals involved in combat situations to be well versed in tourniquet education as part of their medical training to effectively respond to life-threatening situations and minimize the risk of short amputations.[61–63]

The management of post-trauma amputations should prioritize open, length-preserving techniques to preserve residual limb length and viable tissue. The use of atypical flaps is recommended to salvage valuable residual limb length and functional joint levels. Keep viable structures and nerves as long as possible to implement surgical advancements (TMR, RPNI) to primary amputation. Guillotine amputations result in the sacrifice of residual limb length and viable tissue.[10]

Long-term follow-up and potential revision surgery for persistently symptomatic limbs can significantly enhance prosthesis use, function, and quality of life. Additionally, addressing accompanying PTSD and psychological disorders through a multidisciplinary approach is essential for maximizing outcomes. Further advancements, such as osseointegration, has shown to be a viable option for patients who have rejected prosthetic wear due to the high incidence of short residual limbs in war-related amputations. TMR has

proven effective in improving the intuitive function of upper extremity prostheses, and TMR and RPNI are beneficial in preventing or treating symptomatic neuromata.[10,64]

The energy associated with traumatic injuries often leads to significant soft tissue defects, higher amputation levels, and increased post-amputation pain. Targeted Muscle Reinnervation (TMR), in conjunction with advancements in prosthetic technology and ongoing military research, offers improved outcomes to aid active-duty service members and further war-related (young) amputees in achieving their goals. The capabilities and applications of TMR and other advancements are rapidly expanding due to its high surgical success rate, technological innovations in prosthetic care, and favorable patient outcomes. As technology continues to evolve to include osseointegration techniques and bidirectional neuroprosthetic devices, the future of amputation surgery holds immense promise, presenting innovative solutions to optimize patient outcomes.[10,64]

V Combat related Surgical Considerations

5.1	Recommendation	adapted/new
Grade of recommendation: **GoR 0**	**Amputations after trauma should be managed in an open, length-preserving fashion; guillotine amputations sacrifice residual limb length and viable tissue. Subsequent revision and closure may require the use of atypical flaps of opportunity to salvage valuable residual limb length, functional joint levels and innovations within primary amputation to improve the overall outcome and decrease the incidence of PLP.** *Sources:* Tintle et al. (2016) LoE V	
Level of evidence: **V**	Consensus strength:	

5.1

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

5.2	Recommendation	adapted/new
Grade of recommendation: **GoR B**	**TMR, in conjunction with advancements in prosthetic technology enables improved outcomes, prosthetic acceptance and helps to achieve the goals of active-duty service members.** *Sources:* Rask et al. (2023) LoE III	
Level of evidence: **III**	Consensus strength:	

5.2

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Military Rehabilitation

The majority of the military cohort at the time of injury are young, healthy, fit men who work in a specific psychosocial environment.[55] Veterans of the armed forces are a unique population with unique health needs and a distinct culture that includes particular values, ethos, codes of conduct, and obedience to authority.[56] Additionally, compared to the general population, they have been found to use opioid medications more frequently and to be at a higher risk of overdosing.

Supplementary data

I Methods

A systematic literature search was conducted on April 18, 2024, across the following databases: PubMed, MEDLINE (via PubMed), Cochrane Library, and Google Scholar, using the following search terms:

PubMed and MEDLINE (via PubMed):

(((Neuroma/ OR Neuralgia/ OR Phantom Limb/ OR neuroma*) OR ((neuropathic*[Title/Abstract] OR phantom*[Title/Abstract] OR stump*[Title/Abstract] OR nerve[Title/Abstract]) ADJ3 (pain*))) AND ((exp Amputation/ OR Amputation Stumps/ OR Amputees/)) OR (amputat*[Title/Abstract] OR disarticulat*[Title/Abstract] OR amputee*[Title/Abstract])) AND (Neuroma* Surgery* OR Neuroma* Treatment* OR Surgery* Phantom Limb Pain*) Filters: MEDLINE, from 2021/11/6 - 2024/4/18

"Regenerative Peripheral Nerve Interface" OR "Regenerative Peripheral Nerve Interfaces" OR "Targeted muscle reinnervation" Filters: MEDLINE, from 2021/11/6 - 2024/4/18

("Targeted muscle reinnervation") OR ("Regenerative Peripheral Nerve Interface" OR "Regenerative Peripheral Nerve Interfaces") Filters: Randomized Controlled Trial (only PubMed)

Cochrane Library:

((neuroma* OR ((neuropathic* OR phantom* OR stump* OR nerve) NEAR/3 (pain*)))):ti,ab,kw AND ((amputat* OR disarticulat* OR amputee*)):ti,ab,kw (with Cochrane Library publication date from Nov 2021 to Apr 2024, (Word variations have been searched))

Google Scholar:

neuroma OR "neuropathic OR phantom OR stump OR nerve pain" AND amputation OR amputated OR disarticulation OR amputee

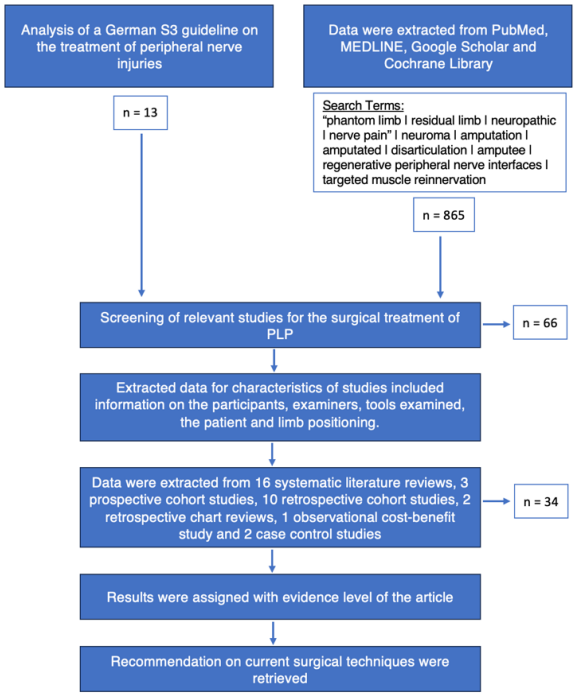


Figure 13: The graphic illustrates the process of conducting the literature search

The systematic literature search of the databases identified a total of 865 results. The specific search terms were documented above. The literature search included studies in English that were published between November 6, 2021, and April 18, 2024. The topic is surgical techniques for neuroma therapy and phantom limb pain reduction or prevention. A literature search on MEDLINE via PubMed yielded 222 results, a search on PubMed yielded 386 result, a search on Google Scholar yielded 200 results, and a search on Cochrane Library yielded 75 results. After screening the titles and abstracts of the studies, 799 results were excluded from the search. 66 studies were screened for eligibility using full-text screening. The studies were excluded if the following criteria were not met: Only studies with patients, no animal or cadaver studies. Focus on trauma patients, no studies solely with cancer patients, diabetes patients, or patients with other diseases. Only studies with a level of evidence (LOE) 1-3 will be considered. This screening allowed 32 studies to be excluded from the search. A total of 34 studies were included in this study. The table can be found in the appendix.

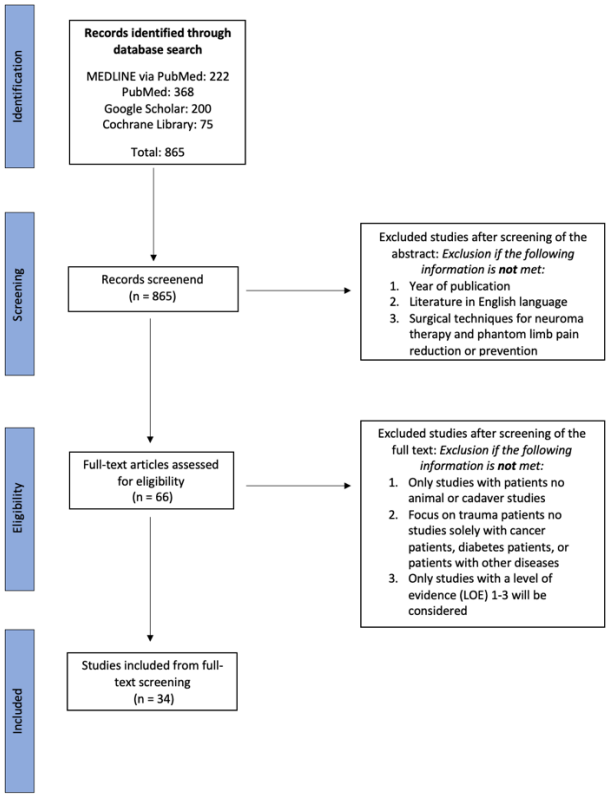


Figure 14: PRISMAR flow chart of study selection, own illustration based on Moher et al. (2009)[65]

II Funding

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III Abbreviations

CNS	Central Nervous System
GoR	Grade of Recommendation
LoE	Level of Evidence
NP	Neuroma Pain
PLP	Phantom Limb pain
RLP	Residual Limb Pain
RPNI	Regenerative Peripheral Nerve Interfaces
TMR	Targeted Muscle Reinnervation
TSR	Targeted Sensory Reinnervation

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V Conflict of Interests

	Consultancy and expert activities	Participation in a scientific advisory board	Paid lecture or training activity	Paid authorship or co-authorship	Research projects/ Conducting clinical studies	Ownership interests (patent, copyright, share ownership)	Indirect interests (membership in a specialist society)
Name: Dr. Jennifer Ernst	☒ yes ☐ no	☒ yes Specify: ERC Project (Advisory Board) ☐ no	☒ yes ☐ no	☐ yes ☒ no	☒ yes Specify: Research Project IITs Ottobock SE & Co. KGaA ☐ no	☒ yes ☐ no	☐ yes Specify: ☒ no
Name: Marlene Arlt	☐ yes ☒ no	☐ yes Specify: ☒ no	☐ yes ☒ no	☐ yes ☒ no	☐ yes Specify: ☒ no	☐ yes ☒ no	☐ yes Specify: ☒ no
Name	☐ yes ☐ no	☐ yes Specify: ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes Specify: ☐ no	☐ yes ☐ no	☐ yes Specify: ☐ no
Name	☐ yes ☐ no	☐ yes Specify: ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes Specify: ☐ no	☐ yes ☐ no	☐ yes Specify: ☐ no

VI Appendix

Author	Titel	APA-Style Citation	Statement	Study Design	Cohort Size	Amputation Level	Duration of the Study	Reported Outcome	Primary (Preventive) or Secondary (Therapeutic) Amputation	RLP/NP Reduction	PLP Reduction	Level of Evidence (LOE)
Tham, J., Sood, A., Saffari, T. M. & Khajuria, A.	The effect of targeted muscle reinnervation on post-amputation pain and functional outcomes: a systematic review and meta-analysis	Tham, J., Sood, A., Saffari, T. M. & Khajuria, A. (2023). The effect of targeted muscle reinnervation on post-amputation pain and functional outcomes: a systematic review and meta-analysis. European Journal Of Plastic Surgery, 46(4), 475–497. https://doi.org/10.1007/s00238-022-02021-5	Despite varying study quality, pooled analysis shows a significant reduction in RLP and PLP across all PROMIS domains and significant reduction in NRS scores in the TMR group. Additionally, TMR demonstrated improved functional outcomes for amputees.	Systematic review and meta-analysis	10 studies; 943 patients	n.a.	Mean: 17,9 M. Range: 9,6 - 24,0 M.	Pain scores (PROMIS scores & NRS), improvement in limb function, complication rates, pain medication & resubmission rates	Secondary	RLP: Mean difference was − 2.68 ($p < 0.0001$) in favor of the TMR group	PLP: Mean difference: − 2.17 ($p < 0.0001$) in favor of the TMR group	Ia bzw. IIa
Hagiga, A., Aly, M., Gumaa, M., Rehan Youssef, A., & Cubison, T.	Targeted muscle reinnervation in managing post-amputation related pain: A systematic review and meta-analysis	Hagiga, A., Aly, M., Gumaa, M., Rehan Youssef, A., & Cubison, T. (2023). Targeted muscle reinnervation in managing post-amputation related pain: A systematic review and meta-analysis. Pain practice : the official journal of World Institute of Pain, 23(8), 922–932. https://doi.org/10.1111/papr.13262	There is limited evidence of good quality favoring TMR in reducing postamputation PLP and RLP pain compared with standard care. Randomized clinical trials are encouraged to compare the efficacy of different surgical techniques	Systematic review and meta-analysis	5 studies; 127 patients	n.a.	12 M. Follow-up	Pre- and postoperative pain outcomes (NRS & PROMIS)	Secondary	RLP assessed using PROMIS showed significantly lower pain intensity in the TMR group p-value was considered to be less than or equal to 0.05.	TMR Group: Significantly better PLP assessed by the NRS & PLP assessed using PROMIS significantly lower pain intensity p-value was considered to be less than or equal to 0.05.	IIa

Berger, L. E., Shin, S., Haffner, Z. K., Huffman, S. S., Spoer, D. L., Sayyed, A. A., Franzoni, G., Bekeny, J. C., Attinger, C. E., & Kleiber, G. M.	The application of targeted muscle reinnervation in lower extremity amputations: A systematic review	Berger, L. E., Shin, S., Haffner, Z. K., Huffman, S. S., Spoer, D. L., Sayyed, A. A., Franzoni, G., Bekeny, J. C., Attinger, C. E., & Kleiber, G. M. (2023). The application of targeted muscle reinnervation in lower extremity amputations: A systematic review. Microsurgery, 43(7), 736–747. https://doi.org/10.1002/micr.31030	The application of TMR to LE amputations is effective in reducing PLP and RLP with limited complications. Continued investigations are warranted to better understand patient outcomes specific to anatomic location using validated patient-reported outcome measures (PROM).	Systematic literature review	11 studies; 318 patients	Lower Extremity	n.a.	Patient-reported outcomes (NRS & questionaires), functional outcome & complications	n.a.	NP: Postoperative neuroma development in 7.2% of the cases Effective in reducing RLP	Effective in reducing PLP	IIa
ElAbd, R., Dow, T., Jabori, S., Alhalabi, B., Lin, S. J., & Dowlatshahi, S.	Pain and Functional Outcomes following Targeted Muscle Reinnervation: A Systematic Review	ElAbd, R., Dow, T., Jabori, S., Alhalabi, B., Lin, S. J., & Dowlatshahi, S. (2024). Pain and Functional Outcomes following Targeted Muscle Reinnervation: A Systematic Review. Plastic and reconstructive surgery, 153(2), 494–508. https://doi.org/10.1097/PRS.0000000000010598	The literature evidence suggests that TMR is a promising therapy for improving pain, prosthesis use, and functional outcomes after limb amputation.	Systematic literature review	39 studies; 449 TMR patients, 716 control group patients	TMR group: 309 lower-limb & 159 upper-limb amputations Control group: 557 lower-limb & 108 upper-limb amputations	Mean: 25 M.	Pain, prosthesis control, life quality, limb function, and disability	n.a.	RLP: Measures were lower for cases for intensity, behavior, and interference, but they failed to reach significance	PLP scores were lower by 10.2 points for intensity (p = 0.01), 4.67 points for behavior (p = 0.01), and 8.9 points for interference (p = 0.09)	IIa
Chou, J., Liston, J. M., & DeGeorge, B. R.	Traditional Neuroma Management Strategies: A Systematic Review	Chou, J., Liston, J. M., & DeGeorge, B. R. (2023). Traditional Neuroma Management Strategies: A Systematic Review. Annals of plastic surgery, 90(6S Suppl 4), S350–S355. https://doi.org/10.1097/SAP.0000000000003342	Passive treatment modalities can offer reliable pain relief in appropriately selected patients but do not allow for nerve regeneration. As such active, reconstructive modalities should be used when possible.	Systematic Review and Meta-Analysis	22 studies	n.a.	n.a.	Pain and functional outcomes	n.a.	NP: Passive treatment modalities can offer reliable pain relief in appropriately selected patients but do not allow for nerve regeneration	n.a.	IIa

Fulton, Z. W., Boothby, B. C., & Phillips, S. A.	Targeted Muscle Reinnervation for Trauma-Related Amputees: A Systematic Review	Fulton, Z. W., Boothby, B. C., & Phillips, S. A. (2022). Targeted Muscle Reinnervation for Trauma-Related Amputees: A Systematic Review. Cureus, 14(8), e28474. https://doi.org/10.7759/cureus.28474	TMR is a technique used for amputees that can benefit neuroma pain, phantom limb pain, residual limb pain, and potentially narcotic use and prosthetic wear. TMR performed in the acute or delayed setting in this population appears to have equally improved outcomes related to pain and function. Limited high-quality TMR studies have been performed on the trauma population. This area would significantly benefit from further investigation.	Systematic literature review	6 studies	n.a.	Mean: 14,55 M.	Prosthesis use, post-TMR opioid use, PROMIS & NRS scores for phantom limb pain and residual limb pain & overall pain resolution/reduction	Primary & Secondary	NP: Neuroma pain resolution in 88.2% of the patients. Mean: 86.2%, primary TMR 91.7%, secondary TMR 84.2% Overall pain reduction/resolution in 92.9% of the patients: Mean: 90.7, primary TMR 91.4%, secondary TMR 90.1%	n.a.	IIa
Yuan, M., Gallo, M., Gallo, L., Huynh, M., McRae, M., McRae, M., Thoma, A., Coroneos, C. J. & Voineskos, S. H.	Targeted Muscle Reinnervation and Regenerative Peripheral Nerve Interfaces Versus Standard Management in the Treatment of Limb Amputation: A Systematic Review and Meta-Analysis	Yuan, M., Gallo, M., Gallo, L., Huynh, M., McRae, M., McRae, M., Thoma, A., Coroneos, C. J. & Voineskos, S. H. (2022). Targeted Muscle Reinnervation and Regenerative Peripheral Nerve Interfaces Versus Standard Management in the Treatment of Limb Amputation: A Systematic Review and Meta-Analysis. Plastic Surgery, 229255032211074. https://doi.org/10.1177/22925503221107462	The observational data suggests that primary TMR/RPNI reduces incidence, pain scores and PROMIS scores of PLP and RLP.The data also suggests that primary TMR/RPNI may reduce incidence of neuromas, but this did not achieve statistical significance. Surgeons should weigh the uncertainty of evidence with potential harms and benefits when considering the use of primary TMR/RPNI in the surgical management of major limb amputations. Going forward, randomized trials are warranted to evaluate this research question, particularly to improve the certainty of evidence.	Systematic review and meta-analysis	11 studies	n.a.	n.an (search on June 1, 2021, studies from 1946 to June 2021)	Incidence of neuroma, phantom limb pain and residual limb pain. Severity of Pain, Pain intensity, behavior, and interference for PLP and RLP (PROMIS)	Primary	NP: The study evidence suggests that TMR/RPNI may result in a large reduction in incidence of neuroma formation, but is limited in this study due to evidence from only one study RLP: The evidence suggests that primary TMR may result in a large reduction in the incidence of RLP	The evidence suggests that primary TMR likely results and RPNI may result in a large reduction in the incidence of PLP	IIa

Ryan, C., Bhanja, D., McNutt, S., Daggubati, L. & Rizk, E.	Evaluating the Evidence: A Systematic Review of Targeted Muscle Reinnervation for Post-Amputation Phantom and Residual Limb Pain	Ryan, C., Bhanja, D., McNutt, S., Daggubati, L. & Rizk, E. (2022). 139 Evaluating the Evidence: A Systematic Review of Targeted Muscle Reinnervation for Post-Amputation Phantom and Residual Limb Pain. Neurosurgery/Neurosurgery Online, 68(Supplement_1), 41. https://doi.org/10.1227/neu.0000000000001880_139	There is insufficient and poor evidence to recommend TMR over standard neuroma excision for the reduction of PAP. The literature remains inconsistent due to the lack of validated pain scale data and variable results based on the amputation/ TMR site. This highlights the importance for a national registry to compare outcomes across surgical techniques.	Systematic literature review	23 studies: 1 study LOE 1 (RCT), 3 studies LOE 2 & 19 studies LOE 4	n.a.	n.a. (Search until March 2021)	Pain resolution, level of amputation, time from amputation to TMR, time from TMR to follow-up and reported pain scales (NRS & PROMIS)	Secondary	There is insufficient and poor evidence to recommend TMR over standard neuroma excision for the reduction of Post-Amputation Phantom and Residual Limb Pain	There is insufficient and poor evidence to recommend TMR over standard neuroma excision for the reduction of Post-Amputation Phantom and Residual Limb Pain	IIa
Le, E., Greyson, M. A., Constantine, R. S. & Iorio, M. L.	A review of pain outcomes following targeted muscle reinnervation in lower extremity limb pain	Le, E., Greyson, M. A., Constantine, R. S. & Iorio, M. L. (2022). A review of pain outcomes following targeted muscle reinnervation in lower extremity limb pain. Pastic And Aesthetic Research, 9(9), 55. https://doi.org/10.20517/2347-9264.2022.47	Primary and Secondary TMR does prevent and improve PLP, RLP, and GLP; however, a minority of studies report quantifiable pain outcomes. All future TMR studies should include validated pain outcomes to better quantify the expected pain and quality of life improvements after lower extremity TMR	Systematic literature review	10 studies, 414 patients	341 lower extremities 90 upper extremities	n.a. (search between January 1997 to April 2022)	Pain outcome (NRS & PROMIS)	Primary & Secondary	Average primary TMR PROMIS scores for PLP and RLP were lower than amputees without primary TMR. Average NRS scores and PROMIS Pain scores in secondary TMR demonstrated improvements in PLP, RLP, and GLP (General limb pain). Primary and Secondary TMR does prevent and improve PLP, RLP, and GLP; however, a minority of studies report quantifiable pain outcomes.	Average primary TMR PROMIS scores for PLP and RLP were lower than amputees without primary TMR. Average NRS scores and PROMIS Pain scores in secondary TMR demonstrated improvements in PLP, RLP, and GLP (General limb pain). Primary and Secondary TMR does prevent and improve PLP, RLP, and GLP; however, a minority of studies report quantifiable pain outcomes.	IIa

Power, D., Curtin, C., Bellemère, P., Nyman, E., Pajardi, G., Isaacs, J., & Levin, L. S.	Surgical Treatment of Symptomatic End-Neuroma With a New Bioresorbable Copolyester Nerve Capping Device: A Multicenter Prospective Cohort Study	Power, D., Curtin, C., Bellemère, P., Nyman, E., Pajardi, G., Isaacs, J., & Levin, L. S. (2023). Surgical Treatment of Symptomatic End-Neuroma With a New Bioresorbable Copolyester Nerve Capping Device: A Multicenter Prospective Cohort Study. Annals of plastic surgery, 91(1), 109–116. https://doi.org/10.1097/SAP.0000000000003596	End-neuroma treatment with excision and capping resulted in long-term significant reduction in reported pain, disability, and analgesic medication use. Adverse event rate was low	Prospective Cohort Study	73 patients (46 patients completed 24 m. follow-up)	50 upper-extremity 23 lower-extremity	24 M. Follow-up	Pain (VAS-Pain score), function, recurrence of symptomatic neuroma, use of analgesics & adverse events	Secondary	NP: Mean VAS-Pain score at baseline was 70.2 ± 17.8 (scale 0-100) and decreased significantly to 31 ± 32.5 ($p < 0.001$)	n.a.	IIb
de Lange, J. W. D., Duraku, L. S., Power, D. M., Rajaratnam, V., van der Oest, M. J. W., Selles, R. W., Huygen, F. J. P. M., Hundepool, C. A., & Zuidam, J. M.	Prevalence of post-traumatic neuropathic pain after digital nerve repair and finger amputation	de Lange, J. W. D., Duraku, L. S., Power, D. M., Rajaratnam, V., van der Oest, M. J. W., Selles, R. W., Huygen, F. J. P. M., Hundepool, C. A., & Zuidam, J. M. (2022). Prevalence of post-traumatic neuropathic pain after digital nerve repair and finger amputation. Journal of plastic, reconstructive & aesthetic surgery : JPRAS, 75(9), 3242–3249. https://doi.org/10.1016/j.bjps.2022.06.033	This study shows that persistent pain and neuropathic pain are common after finger trauma with nerve damage. One of the significant prognostic factors in developing neuropathic pain is treatment delay between trauma and time of digital nerve repair, which is of major clinical relevance for surgical planning of these injuries. Treatment delay of longer than three weeks has a significant higher chance in developing neuropathic pain, which may modify current clinical practice; however, a prospective randomized trial should be conducted to verify this conclusion.	Prospective Cohort Study	120 patients	50 patients with 91 digital amputations & 70 patients with 87 fingers with digital nerve repair	min. 12 M. Follow-up, Amputation Group: Mean 44 M. (Range 22–97 M.) & Nerve Repair Group: Mean 55 M. (Range 18–109 M.)	Short Form DN4 (S-DN4) to assess neuropathic pain, age, BMI, diabetes, tobacco dependence, treatment side, hand dominance and type of trauma; sharp or crush, time between trauma and treatment, and additional pain treatment during follow-up, such as a visit to a pain physician or further operation	Secondary	Amputation group: 32% of the patients had pain (18% neuropathic pain & 14% non-neuropatic) Digital nerve group: 38% of patients reported pain (14% neuropathic pain & 24% non-neuropathic)	n.a.	IIb

Reid, R. T., Johnson, C. C., Gaston, R. G., & Loeffler, B. J.	Impact of Timing of Targeted Muscle Reinnervation on Pain and Opioid Intake Following Major Limb Amputation	Reid, R. T., Johnson, C. C., Gaston, R. G., & Loeffler, B. J. (2024). Impact of Timing of Targeted Muscle Reinnervation on Pain and Opioid Intake Following Major Limb Amputation. Hand (New York, N.Y.), 19(2), 200–205. https://doi.org/10.1177/15589447221107696	TMR is an effective procedure to reduce pain following major limb amputation. Patients with TMR performed acutely had significantly lower VAS pain scores at both intermediate and final follow-up than patients with TMR performed in a delayed setting.	Prospective Cohort Study	43 patients, 25 patients in acute TMR group & 18 patients in delayed TMR group	n.a.	Two Follow-ups: 1. 4.-8. M. post OP 2. ?	VAS pain scores and patient-reported opioid consumption	Secondary	VAS: Delayed TMR group: 5.2 (intermediate) & 6.2 (final) Acute TMR group: 1.9 (intermediate) & 1.9 (final) Intermediate p = .01 Final p = .002	n.a.	IIb
Lin, Z., Yu, P., Chen, Z., & Li, G.	Regenerative peripheral nerve interface reduces the incidence of neuroma in the lower limbs after amputation: a retrospective study based on ultrasound	Lin, Z., Yu, P., Chen, Z., & Li, G. (2023). Regenerative peripheral nerve interface reduces the incidence of neuroma in the lower limbs after amputation: a retrospective study based on ultrasound. Journal of orthopaedic surgery and research, 18(1), 619. https://doi.org/10.1186/s13018-023-04116-6	This study suggested that RPNI can effectively prevent the formation of symptomatic neuroma after amputation using ultrasound.	Retrospective cohort study	14 patients, 7 RPNI & 7 traditional amputation (TA)	14 lower extremity	3. M & 6. M & 12 M. Follow-up	General information, pathology of primary disease, history of limb-salvage treatment, amputation level of nerve & pain scales (NRS and MFPDI)	Primary	NRS 3 M.: TA 6.4 ± 1.1 RPNI 4.3 ± 1.0 (p=0.002) NRS 6 M.: TA 6.9 ± 1.3 RPNI 3.1 ± 0.7 (p< 0.001) MFPDI 3 M.: TA 37.9 ± 2.3 RPNI 34.7 ± 2.7 (p=0.036) MFPDI 6 M.: TA 39.4 ± 1.1 RPNI 28.4 ± 1.8 (p< 0.001)	n.a.	III
Maslow, J. I., LeMone, A., Scarola, G. T., Loeffler, B. J., & Gaston, R. G	Digital Nerve Management and Neuroma Prevention in Hand Amputations	Maslow, J. I., LeMone, A., Scarola, G. T., Loeffler, B. J., & Gaston, R. G. (2023). Digital Nerve Management and Neuroma Prevention in Hand Amputations. Hand (New York, N.Y.), 18(5), 838–844. https://doi.org/10.1177/15589447211065074	Digital nerve end-to-end neurorrhaphy is a method for neuroma prevention in partial hand amputations that results in decreased residual hand pain without increase complications. Depression and worker's compensations status were significantly associated with symptomatic neuroma formation.	Retrospective cohort study	54 patients	54 upper extremity (hand or digital amputation)	n.a. (2010 to 2020)	Development of a neuroma, revision surgery, complications & visual analog pain scores	Primary	NP: Significantly fewer patients reported persistent pain if an end-to-end coaptation was performed (0% vs. 11.8%, p < .01)	n.a.	III

Goodyear, E. G., O'Brien, A. L., West, J. M., Huayllani, M. T., Huffman, A. C., Souza, J. M., Schulz, S. A., & Moore, A. M.	Targeted Muscle Reinnervation at the Time of Amputation Decreases Recurrent Symptomatic Neuroma Formation	Goodyear, E. G., O'Brien, A. L., West, J. M., Huayllani, M. T., Huffman, A. C., Souza, J. M., Schulz, S. A., & Moore, A. M. (2024). Targeted Muscle Reinnervation at the Time of Amputation Decreases Recurrent Symptomatic Neuroma Formation. Plastic and reconstructive surgery, 153(1), 154–163. https://doi.org/10.1097/PRS.0000000000010692	Patients who underwent acute TMR reported improved pain scores and a decreased rate of neuroma formation compared with TMR performed in a delayed fashion. These results highlight the promising role of TMR in the prevention of neuropathic pain and neuroma formation at the time of amputation.	Cross-sectional, retrospective chart review	103 patients (73 acute TMR limbs and 32 delayed TMR limb)	n.a.	min. 6 M. Follow-up, acute TMR mean Follow-up: 34,5 M. delayed TMR mean Follow-up: 40 M.	Symptomatic neuroma recurrence, surgical complications, PROMIS pain intensity, interference, and behavior scales and an 11-point numeric rating scale (NRS) form	Primary & Secondary	Symptomatic neuromas recur: Acute 1%, Delayed 19% (p< 0.05). Acute TMR patients reported significantly lower RLP PROMIS pain intensity (P < 0.05), and RLP PROMIS pain interference (P < 0.05) scores in comparison to the delayed group.	Acute TMR patients reported significantly lower PLP PROMIS pain interference (P < 0.05) in comparison to the delayed group.	III
Lu, V., Zhou, A., & Krkovic, M.	Variation on a technique for the intra-muscular insertion of nerve endings to minimise neuropathic and residual pain in lower limb amputees: a retrospective cohort study	Lu, V., Zhou, A., & Krkovic, M. (2023). Variation on a technique for the intra-muscular insertion of nerve endings to minimise neuropathic and residual pain in lower limb amputees: a retrospective cohort study. European journal of orthopaedic surgery & traumatology : orthopedie traumatologie, 33(4), 1299–1306. https://doi.org/10.1007/s00590-022-03281-4	Surgical insertion of nerve endings into adjacent muscle bellies during lower limb amputation is a simple yet effective way of minimising PLP and RLP, improving patients' subsequent quality of life. Additional comparisons with targeted muscle reinnervation should be performed to determine the optimal treatment option.	Retrospective cohort study	44 patients (8 nerve insertion patients (NI) & 36 standard treatment patients (Control))	Lower Extremity	min. 12 M. Follow-up, Mean Follow-up NI 18,5 M. & Mean Follow-up Standard 26,75 M.	NRS pain severity & PROMIS pain intensity, interference, and behavior scales & Neuro-QoL Lower Extremity Function assessing mobility	Primary	RLP: NRS worst Pain NI 2.6 Control 4.44 (P=0.035). Mean 'best pain' and 'current pain' scores were also superior in the NI cohort for RLP (p = 0.018, p = 0.134). Mean PROMIS t scores (NI vs. Control): 40.1 vs 49.4 for pain intensity; p = 0.014, 44.4 vs 48.2 for pain interference; p = 0.085, 42.5 vs 49.9 for pain behaviour; p = 0.025.	PLP: NRS worst Pain NI 3.5 Control 4.89 (P=0.298). Mean 'best pain' and 'current pain' scores were also superior in the NI cohort for PLP (p = 0.003, p = 0.022). Mean PROMIS t scores (NI vs. Control): 42.5 vs 52.7 for pain intensity; p = 0.018; 45.0 vs 51.5 for pain interference; p = 0.015, 46.3 vs 51.1 for pain behaviour; p = 0.569	III

Denton, S. R., McBride, C., Hammond, A. P. & LoGiudice, A.	Early Outcomes in Targeted Muscle Reinnervation for Traumatic Amputations	Denton, S. R., McBride, C., Hammond, A. P. & LoGiudice, A. (2023). Early Outcomes in Targeted Muscle Reinnervation for Traumatic Amputations. Journal Of Reconstructive Microsurgery Open, 08(01), e54–e59. https://doi.org/10.1055/a-2086-5446	These findings support the use of TMR for reducing RLP in traumatic amputees. Relative to a similar group treated without TMR in the comparison study, this cohort's RLP was significantly improved. Future studies should aim to recruit more amputees to allow for analysis of functional outcomes, especially in upper limb amputees.	Retrospective cohort study	17 patients with TMR, other RCT study as control group with standard care	n.a.	min. 12 M. Follow-up	NRS & PROMIS	n.a.	RLP: With TMR significant reduction worst pain scores compared with the group without TMR	PLP: Worst pain was significantly higher in this cohort relative to the comparison study's TMR group.	III
Toyoda, Y., McGraw, J. R., Mah'moud, M., Sulkar, R., Saikali, L., Lopez, S. & Kovach, S. J.	Development of Neuropathic Pain after Primary TMR and RPNI in Lower Extremity Amputation: A 4-Year Retrospective Analysis of Prognostic Factors	Toyoda, Y., McGraw, J. R., Mah'moud, M., Sulkar, R., Saikali, L., Lopez, S. & Kovach, S. J. (2024). Development of Neuropathic Pain after Primary TMR and RPNI in Lower Extremity Amputation: A 4-Year Retrospective Analysis of Prognostic Factors. Plastic And Reconstructive Surgery – Global Open, 12(1S1), 18. https://doi.org/10.1097/01.gox.0001005932.81450.aa	Development of neuropathic pain after primary TMR/RPNI in lower extremity amputation is not insignificant. Preoperative comorbidities and level of amputation did not significantly affect risk of pain development in our cohort. Limitations of our study include small sample size, heterogeneity of the treated nerve, and minimum follow up of one year. Further investigation with larger patient samples and longer follow up could help identify patients at risk of recalcitrant neuropathies to strategize for optimal outcomes.	Retrospective cohort study	68 patients by a single surgeon (TMR 36, RPNI 53)	Lower Extremity	min. 12 M. Follow-up	Patient demographics, comorbidities, operative details & neuropathic pain	Primary	NP: 17 patients (25%) developed new-onset neuropathic pain following the procedure (median: 110d; range: 0-979d) Of the patients who developed these symptoms: TMR: n=2; RPNI n=10; TMR & RPNI n=5	n.a.	III

Smith, T. P., Cognetti, D. J., Cook, A., Lynch, T. B., Alderete, J. F., Lybeck, D. O., & Dowd, T. C.	Similar rates of re-operation for neuroma after transtibial amputations with and without targeted muscle reinnervation	Smith, T. P., Cognetti, D. J., Cook, A., Lynch, T. B., Alderete, J. F., Lybeck, D. O., & Dowd, T. C. (2024). Similar rates of reoperation for neuroma after transtibial amputations with and without targeted muscle reinnervation. OTA international : the open access journal of orthopaedic trauma, 7(1), e297. https://doi.org/10.1097/OI9.0000000000000297	Symptomatic neuroma is one of the most common reasons for revision amputation; however, this study was unable to demonstrate a difference in revision surgery rates for neuroma for patients undergoing primary transtibial amputation with or without targeted muscle reinnervation.	Retrospective cohort study	112 patients; 29 with TMR & 83 without TMR	Lower Extremity (TT)	Median: 14,4 M.	Demographics, indications for amputation, amputation technique, including TMR or RPNI , if performed, revision surgery & VAS pain score	Primary	VAS: 2 weeks Post-Op TMR: 3.26 ± 2.44 (n = 27), no TMR: 3.33 ± 2.58 (n = 64) with no significant difference in VAS scores between TMR and no TMR at 2 weeks (p=0.91). 6 weeks Post-Op TMR: 2.21 ± 2.20 (n = 28), no TMR: 1.83 ± 2.17 (n = 64) with no significant difference between TMR and no TMR at 6 weeks (p=0.43). NP: Reoperation rates for neuroma TMR: 3.6%, n = 1/28, no TMR: 4.0%, n = 3/75 (p=0.97).	n.a.	III

Suresh, V., Schaefer, E. J., Calotta, N. A., Giladi, A. M., & Tuffaha, S. H.	Use of Vascularized, Denervated Muscle Targets for Prevention and Treatment of Upper-Extremity Neuromas	Suresh, V., Schaefer, E. J., Calotta, N. A., Giladi, A. M., & Tuffaha, S. H. (2022). Use of Vascularized, Denervated Muscle Targets for Prevention and Treatment of Upper-Extremity Neuromas. Journal of hand surgery global online, 5(1), 92–96. https://doi.org/10.1016/j.jhsg.2022.06.001	This study demonstrated favorable short-term outcomes in a small cohort of patients treated with VDMTs in the upper extremity. Larger, prospective, and comparative studies with validated patient-reported and objective outcome measures and longer-term follow-ups are needed to further evaluate the benefits of VDMTs in upper-extremity neuroma management and prevention.	Retrospective chart review	9 patients (2 pediatric and 7 adult)	Upper Extremity (5 transradial, 1 transhumeral)	Follow-up 5.6 ± 4.1 M., Range: 0.5-13.2 M.	VAS pain score	Primary & Secondary	Postoperative pain score: 1.1 (n=7) range, 0-8; (n=6) Pain score: 0, (n=1) Pain score: 8	(n=2) experienced some degree of PLP	III
Zamore, Z., Yesantharao, P., Aravind, P., & Dellon, A. L.	Economic Cost-Benefit Analysis of "Nerve Implanted into Muscle" versus "Targeted Muscle Reinnervation" versus "Regenerative Peripheral Nerve Interface", for Treatment of the Painful Neuroma	Zamore, Z., Yesantharao, P., Aravind, P., & Dellon, A. L. (2024). Economic Cost-Benefit Analysis of "Nerve Implanted into Muscle" versus "Targeted Muscle Reinnervation" versus "Regenerative Peripheral Nerve Interface", for Treatment of the Painful Neuroma. Journal of reconstructive microsurgery, 10.1055/a-2273-3940. Advance online publication. https://doi.org/10.1055/a-2273-3940	Evaluation of costs and utilities associated with the various surgical options for management of painful neuromas suggest that nerve implantation into muscle is the least expensive option with the best improvement in QALY, while demonstrating comparable outcomes to TMR and RPNI with regards to pain symptoms.	Observational Cost-Benefit Study	n.a.	n.a.	n.a. (data from 2020)	PROMIS, NRS & quality-adjusted life years (QALYs)	n.a.	n.a.	n.a.	III

Chang, B. L., Mondshine, J., Attinger, C. E. & Kleiber, G. M.	Targeted Muscle Reinnervation Improves Pain and Ambulation Outcomes in Highly Comorbid Amputees	Chang, B. L., Mondshine, J., Attinger, C. E. & Kleiber, G. M. (2021). Targeted Muscle Reinnervation Improves Pain and Ambulation Outcomes in Highly Comorbid Amputees. Plastic And Reconstructive Surgery, 148(2), 376–386. https://doi.org/10.1097/prs.0000000000008153	Targeted muscle reinnervation reduces pain and improves ambulation in patients undergoing below-knee amputation, which may be critical in improving morbidity and mortality rates in this comorbid patient population.	Retrospective cohort study	200 patients, 100 TMR & control group 100	TMR group Lower limb = 100 General group Lower limb = 10	TMR: 9,6 ± 5.7 M. Follow-up, Control: 18,5 ± 14.5 M. Follow-up	Presence of residual and phantom limb pain, pain severity, opioid use, ambulation ability, and mortality rates	Primary	TMR group 14% General group 57% p < 0.01	TMR group 19% General group 47% p < 0.01	III
Kang, N. V., Woollard, A., Michno, D. A., Al-Ajam, Y., Tan, J., & Hansen, E.	A consecutive series of targeted muscle reinnervation (TMR) cases for relief of neuroma and phantom limb pain: UK perspective	Kang, N. V., Woollard, A., Michno, D. A., Al-Ajam, Y., Tan, J., & Hansen, E. (2022). A consecutive series of targeted muscle reinnervation (TMR) cases for relief of neuroma and phantom limb pain: UK perspective. Journal of plastic, reconstructive & aesthetic surgery : JPRAS, 75(3), 960–969. https://doi.org/10.1016/j.bjps.2021.09.068	TMR surgery appeared to relieve both NP and PLP although the retrospective nature of this study limits the strength of this conclusion. However, complication rates were high, and it is crucial for surgeons and patients to fully understand the course and outcomes of this novel surgery prior to undertaking treatment.	Retrospective cohort study	36 patients	Upper limb = 11 Lower limb = 29	Baseline, 3, 6- and 12-months	Changes in NP and PLP levels, surgical techniques, complications, and satisfaction with TMR	Secondary	Upper limb 53%, p = 0.006 Lower limb 43.5%, p < 0.0001	Upper limb 44%, p = 0.007 Lower limb 26%, p = 0.009	III

Chang, B. L., Hill, A. L., Mondshine, J., Harbour, P. W., Episalla, N. C., Attinger, C. E., & Kleiber, G. M.	Primary Targeted Muscle Reinnervation in Above-Knee Amputations in Patients with Unsalvageable Limbs from Limb-Threatening Ischemia or Infection	Chang, B. L., Hill, A. L., Mondshine, J., Harbour, P. W., Episalla, N. C., Attinger, C. E., & Kleiber, G. M. (2024). Primary Targeted Muscle Reinnervation in Above-Knee Amputations in Patients with Unsalvageable Limbs from Limb-Threatening Ischemia or Infection. Journal of reconstructive microsurgery, 40(2), 109–117. https://doi.org/10.1055/a-2086-0395	TMR can safely and effectively be performed at time of a through- and above-knee level amputation and improves pain outcomes.	Retrospective cohort study	41 patients with TMR & 58 patients control group	Through or above-knee amputation	TMR: January 2018 to June 2021, Control: January 2014 to December 2017	Comorbidities (Charlson Comorbidity Index), presence and absence of RLP and PLP, overall pain severity, chronic narcotic use, ambulatory status, and complications	Primary	RLP: TMR 26.8%, no TMR 44.8% (p=0.04) Overall pain: TMR 41.5%, no TMR 67.2% (p=0.01)	PLP: TMR 19.5%, no TMR 43.1% (p=0.02)	III
Shammas, R. L., Azoury, S. C., Sergesketter, A. R., Lee, H. J., Poehlein, E., Othman, S. E., Cason, R. W., Levinson, H., Kovach, S. J., & Mithani, S. K.	Primary Targeted Muscle Reinnervation after Below-Knee Amputation Is Not Associated with an Increased Risk of Major or Minor Surgical Complications: A Multi-Institutional, Propensity Score-Matched Analysis	Shammas, R. L., Azoury, S. C., Sergesketter, A. R., Lee, H. J., Poehlein, E., Othman, S. E., Cason, R. W., Levinson, H., Kovach, S. J., & Mithani, S. K. (2022). Primary Targeted Muscle Reinnervation after Below-Knee Amputation Is Not Associated with an Increased Risk of Major or Minor Surgical Complications: A Multi-Institutional, Propensity Score-Matched Analysis. Plastic and reconstructive surgery, 150(3), 589–598. https://doi.org/10.1097/PRS.0000000000009441	Despite an increased incidence of postoperative complications, undergoing below-knee amputation with targeted muscle reinnervation does not confer a statistically significant increased risk of major or minor complications. Future studies are needed to delineate patient selection criteria when assessing the suitability of targeted muscle reinnervation at the time of major limb amputation.	Retrospective cohort study	96 patients, 31 with TMR & 65 without	Below-knee amputation	n.a.	Incidence of major or minor complications within 60 days	Primary	n.a.	n.a.	III

Langeveld, M., Bosman, R., Hundepool, C. A., Duraku, L. S., McGhee, C., Zuidam, J. M., Barker, T., Juszczak, M., & Power, D. M.	Phantom Limb Pain and Painful Neuroma After Dysvascular Lower-Extremity Amputation: A Systematic Review and Meta-Analysis	Langeveld, M., Bosman, R., Hundepool, C. A., Duraku, L. S., McGhee, C., Zuidam, J. M., Barker, T., Juszczak, M., & Power, D. M. (2024). Phantom Limb Pain and Painful Neuroma After Dysvascular Lower-Extremity Amputation: A Systematic Review and Meta-Analysis. Vascular and endovascular surgery, 58(2), 142–150. https://doi.org/10.1177/15385744231197097	This meta-analysis demonstrates the high prevalence of phantom limb pain after dysvascular LLA. Given the often prolonged and disabling nature of neuropathic pain and the difficulties managing it, more consideration needs to be given to strategies to prevent it at the time of amputation.	Systematic Review and Meta-Analysis	12 studies; 1924 patients	Lower Extremity	n.a. (Search: October 5th, 2022)	Presence of PLP and symptomatic neuroma with Pain scores (VAS & NRS), Kooijman Phantom Pain Questionnaire, Groningen Questionnaire of Problems after Leg Amputation, Dysvascular Conditions Scale Questionnaire, Phantom phenomena questionnaire and Haber's Phantom Limb Questionnair	Secondary	69% of patients experience phantom limb pain (95% CI 53-86%) NP: 5% in 1 study	PLP: (0-10) ranged between 2.3 ± 1.4 and 5.5 ± .7	IIIa
Walsh, A. R., Lu, J., Rodriguez, E., Diamond, S., & Sultan, S. M.	The Current State of Targeted Muscle Reinnervation: A Systematic Review.	Walsh, A. R., Lu, J., Rodriguez, E., Diamond, S., & Sultan, S. M. (2023). The Current State of Targeted Muscle Reinnervation: A Systematic Review. Journal of reconstructive microsurgery, 39(3), 238–244. https://doi.org/10.1055/s-0042-1755262	While there is evidence that TMR reduces neuroma-related pain and improves the quality of life for amputees, further outcomes studies are needed to study the patient experience with TMR on a larger scale. Establishing standardized, validated patient-reported outcomes assessment tools is critical to future investigation in this field.	Systematic Literature Review	13 studies; 338 patients	Lower Extremity & Upper Extremity	22,3 M. Follow-up	Geographic location, patient demographics, TMR indication, amputation level, number of nerve transfers performed, length of follow-up & reported outcomes (PROMIS & NRS)	Primary & Secondary	3 studies found that patients undergoing immediate TMR had lower pain scores compared with non-TMR controls.	In 3 studies with delayed TMR: Significant or trending toward significant reduction in PLP (NRS & PROMIS). One study with delayed TMR: 9/10 patients with improved or complete resolution of PLP.	IIIa

Rask, D. M. G., Adams, M. H., Liverneaux, P., Plucknette, B. F., Wilson, D. J., Alderete, J. F., & Sabbag, C. M.	Targeted muscle reinnervation in upper extremity amputation in military hand surgery: A systematic review	Rask, D. M. G., Adams, M. H., Liverneaux, P., Plucknette, B. F., Wilson, D. J., Alderete, J. F., & Sabbag, C. M. (2023). Targeted muscle reinnervation in upper extremity amputation in military hand surgery: A systematic review. Hand surgery & rehabilitation, 42(5), 392–399. https://doi.org/10.1016/j.hansur.2023.07.006	The reviewed literature revealed multiple motor targets described for upper extremity TMR out of our included 51 studies. However, the selection of motor targets is influenced by the availability of viable options based on injury patterns and amputation levels. Conventional transfer patterns provide useful guidance for determining appropriate motor targets in transradial and transhumeral amputations.	Systematic Literature Review	51 studies	Upper Extremity	n.a.	n.a. (identify the prevailing motor targets, while considering injury patterns and amputation levels)	Secondary	n.a.	n.a.	IIIa
Carter, J., Richardson, P., Stark, H. & Henton, J.	Regenerative peripheral nerve interface in the prevention and treatment of post-amputation pain: a systematic review	Carter, J., Richardson, P., Stark, H. & Henton, J. (2024). Regenerative peripheral nerve interface in the prevention and treatment of post-amputation pain: a systematic review. European Journal of Plastic Surgery 47, 25. https://doi.org/10.1007/s00238-024-02167-4	Results of this systematic review suggest that regenerative peripheral nerve interface should be implemented as a minimum gold standard at the time of amputation and as a treatment for intractable post-amputation pain.	Systematic literature review	7 studies	n.a.	n.a.	Effectiveness of regenerative peripheral nerve interface in preventing and treating post-amputation residual and phantom limb pain, as well as any effects on analgesia and prosthetic use	Primary & Secondary	RLP: Improvement in residual limb pain in the respective prophylactic and treatment groups. NP: Studies demonstrate the effectiveness of RPNI in prophylactic prevention or treatment of post-amputation pain by reduction of neuroma formation.	PLP: Improvement in phantom limb pain in the respective prophylactic and treatment groups	IIIa

Bishay, J., Yeap, I., & Wang, T.	The effectiveness of targeted muscle reinnervation in reducing pain and improving quality of life for patients following lower limb amputation	Bishay, J., Yeap, I., & Wang, T. (2024). The effectiveness of targeted muscle reinnervation in reducing pain and improving quality of life for patients following lower limb amputation. Journal of plastic, reconstructive & aesthetic surgery : JPRAS, 92, 288–298. Advance online publication. https://doi.org/10.1016/j.bjps.2024.03.013	The systematic review underscores TMR's potential benefits in alleviating pain, fostering post-amputation rehabilitation and enhancing overall well-being for lower limb amputees.	Systematic literature review	20 studies	Lower Extremity = 584 Upper Extremity = 194	n.a. (Search 2010-2023)	Pain reduction, functional outcomes and patient-reported quality of life measures (PROMIS & NRS)	Primary & Secondary	RLP: Primary TMR exhibited lower average PROMIS score. Secondary TMR led to improvements in RLP and general limb pain indicated by NRS & PROMIS.	PLP: Primary TMR exhibited lower average PROMIS score. Secondary TMR led to improvements in PLP indicated by NRS & PROMIS	IIIa
Di Valerio, E., Lautenslager, L., Vonu, P., Mustafa, C., Chim, H. & Satteson, E.	Efficacy of targeted muscle reinnervation for treating and preventing postamputation pain - a systematic review	Di Valerio, E., Lautenslager, L., Vonu, P., Mustafa, C., Chim, H. & Satteson, E. (2022). Efficacy of targeted muscle reinnervation for treating and preventing postamputation pain - a systematic review. Pastic And Aesthetic Research, 9, 62. https://doi.org/10.20517/2347-9264.2022.50	Included studies demonstrated TMR had lower maximal pain and pain intensity, behavior and interference compared to the standard of care. Secondary TMR used to treat patients with established painful neuromas also reported improvement in pain compared to baseline.	Systematic literature review	9 studies including 101 upper extremity and 252 lower extremity nerve transfers	Upper extremity = 101 Lower extremity = 252	n.a. (Search May 2021)	Prosthetic use and functionality, improvement or persistence of pain (PROMIS), indications, complications, donor nerves, technical aspects of TMR	Primary & Secondary	RLP: 3 out of 4 studies reporting significant improvements in PROMIS scores in TMR subjects compared to controls. Five additional studies did not analyze PROMIS scores but reported subjective improvements in pain outcomes.	PLP: 3 out of 4 studies reporting significant improvements in PROMIS scores in TMR subjects compared to controls. Five additional studies did not analyze PROMIS scores but reported subjective improvements in pain outcomes.	IIIa

Langeveld, M., Hundepool, C. A., Duraku, L. S., Power, D. M., Rajaratnam, V., & Zuidam, J. M.	Surgical Treatment of Peripheral Nerve Neuromas: A Systematic Review and Meta-Analysis	Langeveld, M., Hundepool, C. A., Duraku, L. S., Power, D. M., Rajaratnam, V., & Zuidam, J. M. (2022). Surgical Treatment of Peripheral Nerve Neuromas: A Systematic Review and Meta-Analysis. Plastic and reconstructive surgery, 150(4), 823e–834e. https://doi.org/10.1097/PRS.0000000000009545	The choice of surgical management in treating symptomatic peripheral neuroma is challenging, yet surgical intervention achieves significant pain relief in the majority of cases. Targeted muscle reinnervation is promising for the management of painful neuromas.	Systematic review and meta-analysis	30 studies	n.a.	n.a.	Numerical (VAS/NRS) or nonnumeric postoperative pain scores after surgical treatment of peripheral neuroma	Secondary	n.a.	n.a.	IIIb
Wee, C., Boas, S., Coquillard, C., Cai, Y., Kurlander, D., Maasarani, S., Leavitt, T., Long, T., Lineberry, K., & Khouri, J.	Combined Targeted Muscle Reinnervation With Regenerative Peripheral Nerve Interfaces Decreases Long-Term Narcotic Use in Amputees: A Case Control Study	Wee, C., Boas, S., Coquillard, C., Cai, Y., Kurlander, D., Maasarani, S., Leavitt, T., Long, T., Lineberry, K., & Khouri, J. (2024). Combined Targeted Muscle Reinnervation With Regenerative Peripheral Nerve Interfaces Decreases Long-Term Narcotic Use in Amputees: A Case Control Study. Annals of plastic surgery, 92(4), 432–436. https://doi.org/10.1097/SAP.0000000000003836	This study demonstrates that TMRpni may translate to decreased rates of chronic opiate use. Continued study is indicated to optimize TMRpni techniques and patient selection and to determine its long-term efficacy.	Case Control Study	62 patients, 31 with TMRpni & 31 without TMRpni (control gorup)	n.a.	n.a. (Patients who underwent surgical procedures between 2019 and 2021)	Opioid use	Primary	n.a.	n.a.	IIIb

Valentine, L., Weidman, A. A., Foppiani, J., Hernandez Alvarez, A., Kim, E., Hassell, N. E., Elmer, N., Engmann, T. F., Lin, S. J., & Dowlatshahi, S.	A National Analysis of Targeted Muscle Reinnervation Following Major Upper Extremity Amputation	Valentine, L., Weidman, A. A., Foppiani, J., Hernandez Alvarez, A., Kim, E., Hassell, N. E., Elmer, N., Engmann, T. F., Lin, S. J., & Dowlatshahi, S. (2024). A National Analysis of Targeted Muscle Reinnervation Following Major Upper Extremity Amputation. Plastic and reconstructive surgery, 10.1097/PRS.0000000000011439. Advance online publication. https://doi.org/10.1097/PRS.0000000000011439	TMR has purported benefits of pain reduction, neuroma prevention, and increased prosthetic control. Access to this beneficial procedure following UE amputation varies by demographics and geographic region. Given that TMR has not been shown to increase cost while simultaneously decreasing patient length of stay, increased efforts to incorporate this procedure into training and practice will help to ensure equitable care for amputation patients	Case Control Study	8.945 patients of those 310 with TMR (8.635 without TMR)	Upper Extremity	n.a. (Patients from the database 2016-2019)	Demographics, geographic region, total cost of hospitalization , length of the hospital stay, pain reduction, neuroma prevention & increased prosthetic control	Primary	n.a.	n.a.	IIIb