Université de Montréal

Treatments of Proximal Upper Extremity Amputations

Utility of Hand Allotransplantation Versus Myoelectric Prostheses

par

Ionut Efanov, MD CM, FRCSC

Faculté de Médecine

Thèse présentée à la Faculté de Médecine

en vue de l'obtention du grade de PhD en

Sciences Biomédicales, option Médecine Expérimentale

Date de dépôt initial

20 septembre 2021

Université de Montréal

Faculté de Médecine

Cette thèse intitulée

Treatments of Proximal Upper Extremity Amputations

Utility of Hand Allotransplantation Versus Myoelectric Prostheses

Présentée par

Ionut Efanov

A été évaluée par un jury composé des personnes suivantes

Dre Manon Choinière
Président-rapporteur

Dr Alain Danino
Directeur de recherche

Dr Ali Mojallal
Examinateur externe

Dr Joshua Vorstenbosch
Membre du jury

Dr Sami Moubayed
Représentant du doyen

Résumé

Les amputations d'un membre supérieur sont non seulement dévastatrices pour le bien-être physique, psychologique et social des patients, mais elles comportent également des répercussions financières importantes pour l'individu et le système de santé. Les allotransplantations de tissus composites vascularisés ont été proposées en tant que solution permettant de rétablir la forme et la fonction au détriment d'une immunosuppression à vie et d'un taux élevé de rejet chronique. Les prothèses myoélectriques combinent l'expertise chirurgicale avec les avancées technologiques pour réhabiliter les fonctions motrices d'un moignon amputé, mais elles demeurent limitées par un taux élevé d'abandon et des coûts importants.

Dans les systèmes de santé avec des ressources limitées, les dirigeants ont la tâche complexe de partager équitablement l'allocation de ressources entre plusieurs maladies et interventions. Dans le domaine de l'économie de la santé, les analyses de type coût-bénéfice ont été développées pour répondre à ces questions. Les mesures d'utilité doivent incorporer l'impact que le traitement suscite sur l'espérance de vie et la qualité de vie. Ces utilités sont ensuite rapportées en fonction du coût, ce qui permet aux dirigeants de la santé de déterminer dans quels traitements il serait préférable d'investir les ressources.

Dans cette thèse, nous proposons un modèle pour étudier les coûts-utilité des allotransplantations de la main et des prothèses myoélectriques. Pour commencer, une étude pilote a été effectuée sur les amputations du pouce traitées avec des lambeaux libres de l'orteil, ce qui nous a permis de confirmer la faisabilité des questionnaires d'utilité conçus. Par la suite, les utilités ont été mesurées dans une population d'amputés du membre supérieur, de patients réimplantés proximalement et de contrôles en santé. Les résultats démontrent que 1) les patients réimplantés rapportent la meilleure utilité avec les prothèses myoélectriques, 2) les amputés unilatéraux préfèrent significativement les prothèses myoélectriques également, et 3) aucune différence n'a été recelée entre les deux traitements chez les amputés bilatéraux. Au final, une analyse des coûts-bénéfices a été effectuée dans le contexte du système de santé

canadien, démontrant que le traitement des patients amputés unilatéralement avec des prothèses myoélectriques permettrait de sauver davantage de coûts, alors que l'écart en épargnes monétaires se rétrécit pour les amputés bilatéraux traités avec une allotransplantation ou une prothèse.

Avec les résultats rapportés dans cette thèse, nous pouvons proposer une mise à jour des indications de traitements pour les patients avec une amputation du membre supérieur. Basé sur l'analyse de type coût-utilité, nous concluons que les amputés unilatéraux sont de meilleurs candidats pour des prothèses myoélectriques, alors que les deux traitements sont encore adéquats pour les amputations bilatérales.

Mots-clés: amputation du membre supérieur, allotransplantation de tissus composites vascularisés, prothèses myoélectriques, utilité, analyse coût-bénéfice

Abstract

Amputations of the upper extremity are not only devastating for the patient’s physical, psychological and social well-being, but they also yield significant financial repercussions to the individual and the healthcare system. Vascularized composite allotransplantations of the upper extremity were proposed as a solution to restore form and function, albeit to the detriment of lifelong immunosuppression and high rates of chronic rejection. New-generation myoelectric prostheses combine surgical prowess with technological refinements to rehabilitate motor functions of the amputated stump, but remain plagued by high rates of abandonment and significant costs.

In healthcare systems wherein resources are limited, financial regulators have the difficult task of proposing an equitable divide of resource allocations between a multitude of diseases and interventions. In the field of health economics, cost-benefit analyses were developed to assist in this decision-making process. Utility outcome measures need to encompass the impact that a treatment elicits on life expectancy and quality of life. Comparison of utilities of different interventions as a function of cost further indicates which route healthcare regulators should partake.

In this thesis, we propose a model to study cost-utilities of hand allotransplantation and myoelectric prostheses. To begin, a pilot study was performed on thumb amputations treated with free toe flaps, which allowed to confirm the feasibility of the utility questionnaires that we developed. Afterwards, utilities and quality adjusted life years were measured in a population of upper extremity amputees, proximally replanted patients and healthy controls. Findings demonstrated that 1) replanted patients reported the highest utility outcomes for myoelectric prostheses, 2) unilateral amputees significantly preferred myoelectric prostheses as well, and 3) no significant preference between both interventions was obtained in patients with bilateral amputations. Finally, a cost-benefit analysis was performed in the context of the Canadian healthcare system, demonstrating that significant savings can be achieved with treatment of

unilateral amputations with myoelectric prostheses, whereas the gap in cost savings between both treatment groups becomes less significant in bilateral amputees.

With the findings reported in this thesis, we can propose an update of the indications for treatment in patients with upper extremity amputations. From the perspective of cost-utility analyses, we conclude that unilateral amputees are better candidates for myoelectric prostheses, and that both treatments can still be offered in cases of bilateral amputations.

Keywords: upper extremity amputation, vascularized composite allotransplantation,
myoelectric prostheses, utility outcomes, cost-benefit analysis

Table des matières

Introduction 17

0.1 The personal and societal costs of upper extremity amputations 17

0.2 The field of vascularized composite allotransplantation (VCA) 20

0.2.1 History of VCA 20

0.2.2 Outcomes of hand allotransplantation 23

0.2.2.1 Benefits and functional outcomes of hand VCA 23

0.2.2.2 Safety and complications of hand VCA 25

0.2.3 Bioethics of hand VCA 26

0.2.3.1 Autonomy 27

0.2.3.2 Beneficence 29

0.2.3.3 Non-maleficence 30

0.2.3.4 Justice 32

0.3 The advent of myoelectric prostheses 35

0.3.1 History and engineering developments 35

0.3.2 Distal (forearm/hand) myoelectric prostheses 38

0.3.3 Proximal (shoulder/humerus) myoelectric prostheses 40

0.4 Utility health outcomes in medicine 43

0.4.1 Purpose, definitions, and methods 43

0.4.2 Direct methods for measuring utility 44

0.4.3 Indirect methods for measuring utility 49

0.4.4 Quality-adjusted life years (QALYs) 50

0.5 Study objectives 51

0.6 Thesis overview 52

Chapter 1: Model simulation with utility of free toe flaps 53

1.1 Investigating Patients' Perception of Microvascular Free Toe Flap for Reconstruction of Amputated Thumbs: A Guide for Surgeons During Informed Consent 53

1.1.1 Introduction 54
1.1.2 Methods 55
1.1.2.1 Study design 55
1.1.2.2 Inclusion and exclusion criteria 55
1.1.2.3 Patient characteristics questionnaire 56
1.1.2.4 Brief Michigan Hand Questionnaire (bMHQ) 56
1.1.2.5 Patient attitudes questionnaire 56
1.1.2.6 Utility outcomes questionnaire 57
1.1.2.7 Statistical analysis 57
1.1.3 Results 58
1.1.3.1 Patient characteristics 58
1.1.3.2 Patient-reported hand function 60
1.1.3.3 Factors Influencing Decision-Making 62
1.1.3.4 Utility outcome measures 65
1.1.4 Discussion 67
1.1.5 Conclusion 70
Chapter 2: Utility of hand transplantation and myoelectric prostheses 71
2.1 Applying Health Utility Outcome Measures and Quality-Adjusted Life Years to Compare Hand Allotransplantation and Myoelectric Prostheses for Upper Extremity Amputations 71
2.1.1 Introduction 72
2.1.2 Methods 73
2.1.2.1 Study Design 73
2.1.2.2 Data Collection 73
2.1.2.3 Statistical Analysis 74
2.1.3 Results 75
2.1.3.1 Patient Characteristics 75
2.1.3.2 Functional patient-reported outcomes on bMHQ 77
2.1.3.3 Utility Measures 78
2.1.3.4 Quality-adjusted life years 80
2.1.3.5 Patient preferences 82
2.1.4 Discussion 84
2.1.5 Conclusion 87

Chapter 3: Costs of upper extremity allotransplantation and myoelectric prostheses 89
3.1 A Review of Utilities and Costs of Treating Upper Extremity Amputations with Vascularized Composite Allotransplantation Versus Myoelectric Prostheses in Canada 89
3.1.1 Introduction 90
3.1.2 Methods 91
3.1.3 Results 92
3.1.3.1 Prevalence of upper extremity amputations 92
3.1.3.2 Personal and societal costs of upper extremity amputations 92
3.1.3.3 Utility studies in hand allotransplantation 94
3.1.3.4 Previous studies on actual costs of hand allotransplantation 95
3.1.3.5 Costs of performing hand VCA in Canada 96
3.1.3.6 Utility studies with myoelectric prostheses 97
3.1.3.7 Previous studies on actual costs of myoelectric prostheses 98
3.1.3.8 Costs of implementing myoelectric prostheses in Canada 99
3.1.3.9 Gains from potential return to work 99
3.1.3.10 Cost comparisons between hand VCA and myoelectric prostheses 101
3.1.4 Discussion 102
3.1.5 Conclusion 104
Chapter 4: Discussion and conclusions 105
4.1 Feasibility of utility outcome models in upper extremity amputations 105
4.2 Utility outcomes and QALYs for VCA and myoelectric prostheses 106
4.3 Indications for unilateral versus bilateral amputations 109
4.4 Implementation of both interventions in the Canadian healthcare system 110
4.5 Future directions 113
Bibliography 116

Liste des tableaux

Table 1. Advantages and disadvantages of passive prostheses

Table 2. Advantages and disadvantages of body-powered prostheses

Table 3. Advantages and disadvantages of externally-powered prostheses

Table 4. Systematic review of the literature on functional outcomes of prostheses in upper limb amputees

Table 5. Step-by-step approach to the technique of "targeted muscle reinnervation"

Table 6. Example of health state dimensions for a unilateral or bilateral upper extremity amputation, based on results reported in the literature (with references)

Table 7. Demographic/patient characteristics, mechanism of injury and type of treatment

Table 8. Brief Michigan Hand Questionnaire (bMHQ)

Table 9. Percentage of participants who consider these factors to influence the decision of undergoing a free-toe-transfer according to the type of treatment previously received

Table 10. Utility of free toe transfers according to the type of treatment received after a thumb amputation

Table 11. Patient demographics and injury characteristics according to the group of patients

Table 12. Health utility outcomes measures based on the group of patients and treatments scenarios

Table 13. Quality-adjusted life years based on the group of patients and the treatment scenario…61

Table 14 – Comparison of cost utility studies for upper extremity VCA

Table 15 – Head-to-head comparison of costs for VCA and myoelectric prostheses

Liste des figures

Figure 1. Visual analog scale used to measure utility values

Figure 2. Example and formula to measure utility values with the TTO technique in a scenario of binocular blindness

Figure 3. Example and formula to measure utility values with the SG technique in a scenario of binocular blindness

Figure 4. Distribution of baseline hand function as reported on the brief Michigan Hand Questionnaire (bMHQ)

Figure 5. Bar chart demonstrating the influence of several factors on the decision-making process of undergoing a free toe transfer

Figure 6. Average score of utility for free toe transfers as determined by the "time trade-off" technique

Figure 7. Average score of utility for free toe transfer as determined by the "standard gamble" technique

Figure 8. Flow-chart depicting exclusion and inclusion of participants in each group of the study

Figure 9. Functional patient-reported outcomes based on the bMHQ in each group of patients

Figure 10. Self-reported quality of life as per the SF-12 questionnaire in each group of patients

Figure 11. Impact of unilateral versus bilateral amputation and patient preference for treatment with hand transplantation versus myoelectric prosthesis in each group of patients

Figure 12 – Potential total cost savings in the Canadian population if upper limb amputees underwent VCA or myoelectric prostheses over a 30-year lifespan

Figure 13 – Total costs of implementing VCAs or myoelectric prostheses in all Canadian patients with *unilateral* upper limb amputations subtracted from expected savings from return to work over a 30-year lifespan

Figure 14 – Total costs of implementing VCAs or myoelectric prostheses in all Canadian patients with *bilateral* upper limb amputations subtracted from expected savings from return to work over a 30-year lifespan

Figure 15 – Pros and cons of VCA and myoelectric prostheses according to the level of amputation

Liste des sigles

ADLs: activities of daily living

ASSH: American Society for Surgery of the Hand

bMHQ: Brief Michigan Hand Questionnaire

CADTH: Canadian Agency for Drugs and Technologies in Health

CBA: cost-benefit analysis

CEA: cost-effectiveness analysis

CIHR: Canadian Institute of Health Research

CUA: cost-utility analysis

DASH: Disabilities of the Arm, Shoulder and Hand

ECog: electrocortograms

EEG: electroencephalograms

EQ-5D: EuroQol-5D

EMG: electromyographic

HRQoL: health-related quality of life

HTA: health technology assessment

HTSS: Hand Transplant Score System

HUI: Health Utilities Index

ICER: incremental cost-effectiveness ratio

ICUR: incremental cost-utility ratio

IRHCTT: International Registry on Hand and Composite Allotransplantation

MHQ: Michigan Hand Questionnaire

PROs: patient reported outcomes

PTSD: post-traumatic stress disorder

QALYs: quality-adjusted life years

SF-12: Short Form Health Survey

SF-36: Short Form-36 Health Survey Scores

SF-6D: Short-Form six dimension

SG: standard gamble

TMR: targeted muscle reinnervation

TTO: time trade-off

VAS: visual analog scale

VCA : vascularized composite allotransplantation

Liste des abréviations

Dr. : Doctor

Prof. : Professor

Remerciements

To innovate: I will be forever grateful for crossing paths with Prof. Alain Danino, who has shaped my career in the most positive ways an apprentice could wish for. His passion for plastic surgery research and his drive to constantly *innovate* in our field are qualities that he has demonstrated as my research director and chief of service, and that I wish to emanate in return.

To lead: A *leader* is one who knows the way, goes the way, and shows the way. Prof. Patrick Harris is all of that and more, and I thank him for allowing plastic surgeons like myself to flourish into indispensable members of the healthcare corps, as both clinicians and investigators.

To collaborate: First as teachers, now as colleagues, I constantly thrive to learn from my fellow plastic surgeons and friends. Thank you in particular to Dr. Izadpanah, Dr. Bou-Merhi, Dr. Paek, Dr. Borsuk and Dr. Odobescu with whom I've *collaborated* on several publications.

To mentor: A career as a clinician-investigator would have never occurred to me if it wasn't for Prof. Jacques Lacroix and his valuable *mentorship* as program director of the CIP program at Université de Montréal.

To learn: If I delve into any academic milestones I have ever achieved, it will always originate from the immeasurable impact that my elder sister, Dr. Simona Efanov, has made on my education. She has taught me the pleasures of *learning* and helped me to develop an inquisitive mind, for which I will always be grateful.

To give: My parents, Radu and Monica Efanov, have given me more tools to succeed in life than I could ever thank them for. The sacrifices they made for their children, from immigrating to Canada to investing in our education and much more, will never be forgotten. I cherish every family memory I hold, and I aim to live by the same values of *generosity*, kindness, and love that you have inculcated in our household.

To love: Most of all, I am thankful for sharing a life with the most wonderful partner one could wish for, my wife Dr. Catherine Besner Morin. Your unconditional *love* and support have lifted me through difficult times and given me strength to pursue my dreams, including the difficult but rewarding endeavour of writing this thesis. You motivate me to become a better doctor and a better person every day. You are my role model, and I feel blessed for having you in my life.

Introduction

"Remember, if you ever need a helping hand, it's at the end of your arm.
As you get older, remember you have another hand:
The first is to help yourself, the second is to help others."
Sam Levenson

0.1 The personal and societal costs of upper extremity amputations

The hand, one of the most intricate structures of the human body, has invariably been a source of wonder through the ages. At the core of our day-to-day living, the hand feeds, the hand makes, the hand feels, the hand protects, the hand communicates. It is omnipresent and powerful, yet discreet and, at times, fragile.

The loss of any body part unquestionably alters a person's self-sense of wholeness. And if one were to use Dr Penfield's distorted representation of the human body within the cortical homunculus (1), only the loss of the face would be more devastating than the loss of the hand. Indeed, grief at the loss of an upper extremity has been compared to grief from widowhood after death of a loved one (2). Because it is easily drawn to the stranger's eye, concealment of this undesirable "difference" after limb loss is seldom possible.

Epidemiological studies that quantify the problem are few. Global prevalence of traumatic upper limb amputations is estimated at 11.3 million patients for unilateral and 11.0 million patients for bilateral (3), keeping in mind that these numbers represent only traumatic causes and emanate from databases of high-income countries solely. In the United States, a total of 41,000 individuals were living with an upper extremity amputation in 2005, a number which is projected to double by 2050 (4). The current rate of hand amputation proximal to the wrist due to trauma was calculated at 0.02 per 100,000 people, which is significantly lower than the 2.8 per 100,000 rate seen in finger amputations (5). Amongst overall trauma admissions, major upper extremity amputations amount to 46 to 62 cases per 100,000 (6).

To the best of our knowledge, there are no scientific nor governmental data that depict the prevalence of upper extremity amputations in Canada. What is known is that over 227,000 individuals in Canada have had either a lower or upper extremity amputation (including toes and fingers) as of 2013 (7). Extrapolating from other studies whereby only 3% of limb amputees involve the proximal upper extremity (4), a ballpark number of patients would be around 6800 Canadians amputated proximal to the wrist.

Acknowledging that hand amputations remain a rare entity, one can comprehend why healthcare resource allocations and research funding aimed at treating these patients has been historically scarce, especially when compared with common healthcare problems such as cancer research or cardiovascular diseases for instance. However, prevalence numbers in medicine don't always reflect the burden of disease, and this is particularly true for upper extremity amputations. Indeed, beyond the impact on one's self-identity, hand amputations can afflict several other spheres of life as well: functional, psychological, emotional, spiritual, cultural, societal, and economical.

When considering the functional impact of limb loss, previous studies have demonstrated significant obstacles in activities of daily living (ADLs), including simple tasks such as tying shoelaces (63.7%), opening and drinking from a bottle (46.5%), using scissors (42.9%), and buttoning shirts (42.1%) (8). Only 23.5% of upper limb amputees reported satisfaction with completion of their ADLs, despite use of cosmetic or mechanical prostheses (8). Additionally, phantom limb pain torments more than 50% to 80% of patients (9), with unestablished efficacy of pharmacological agents and nonpharmacological therapy. Symptomatic painful neuromas of the stump further worsen functional recovery and is thought to occur in up to 25% of patients (10).

Psychological consequences of hand amputations have been extensively studied as well (11,12,13). Drastic changes occur in the patient's life, often with very little time and preparation to cope with the limb loss. Upper extremity amputees are significantly more at risk of developing post-traumatic stress disorder (PTSD) than the general amputee population (14), with rates as high as 77% (15). Other reported psychiatric conditions following this life-changing event include major depressive disorder (30%), adjustment disorder (24%), anxiety disorder (13%) and panic disorder (4%) (16). Loss of autonomy, guilt/punishment and potency are other sentiments that have been described as well (17).

On the economical and societal standpoints, upper extremity amputations provoke multifaceted repercussions. First, there are healthcare costs associated with acute and long-term care of these patients. In a pediatric population, the average length of hospital stay was 11,3 days, with a mean of 2,3 surgeries and average charges of 22 015 $, a cost calculated in the year 1996 (18). Considering that healthcare spending has grown by an average of 6% per year from 1993 to 2013 (19), it can be estimated that current charges for hospitalisation of amputated patients is around 94 485 $ in 2021. These costs do not take into consideration any rehabilitative treatments such as prostheses and long-term care. Indeed, a previous study estimated that veterans with upper extremity amputation spend between 31 890 $ and 117 440 $ on average on prosthetics-related expenses over 5 years, depending on injury severity (20).

Finally, there are individual costs, albeit more difficult to calculate, yet undoubtedly more significant from the financial standpoint. For the manual laborer who makes a living with his/her hands, disabilities from these devastating traumas have lifetime consequences, whereby pursuit of one's passions and talents is not only nullified by this affliction, but lifetime incomes and socioeconomic status also experience hardships. Considering that limb loss to the upper extremity occurs at an average age of 42 years (21), a Canadian amputee will live almost half of his remaining life in this state (Canadian life expectancy at birth is 81.1 years, Statistics Canada 2017 (22)). He/she will also be unable to contribute to the workforce for more than 22.5 years (average age at retirement in Canada is 64.5 years, Statistics Canada in 2020 (23)) at a median yearly after-tax income of 62 900 $ (Statistics Canada in 2019 (24)).

By demonstrating these functional, psychological and socioeconomic consequences, it is permitted to hope that increasing healthcare resource allocations towards development of innovative treatments for these patients may diminish these afflictions.

0.2 The field of vascularized composite allotransplantation (VCA)

0.2.1 History of VCA

The pursuit of replacing amputated limbs and restoring severe facial deformities has been imprinted in human minds for millennia. Historians relate the story of Saints Cosmas and Damian from the 3rd century, who had allegedly and miraculously transplanted the black leg of an Ethiopian man onto the white body of a verger with cancerous leg, the tale of the "Black Leg" (25). Although immediate transplant success is possible even without immunosuppression, the truth remains that all historical attempts were failures in the end.

Although skin allotransplantation had been described in ancient Egypt and Hindu in 3000 BC (26), the birth of the modern field of transplantation only occurred after World War II with the seminal work of biologist Peter Medawar and plastic surgeon Thomas Gibson, who reconstructed severe burn deformities of British Allies and pioneered allograft immunology at the Plastic Surgery Unit in Glasgow, Scotland (27).

The first successful solid organ transplantation is attributed to Joseph E. Murray and colleagues from Boston in 1954, who performed a kidney graft between identical twins (28). For this ground-breaking intervention, Murray earned a Nobel Prize in Medicine, becoming the only plastic surgeon to receive this greatest recognition (29).

Still, the aforementioned isograft (a transplant performed between identical twins) does not qualify as the first successful human allotransplantation. It is in fact attributed to a visionary plastic surgeon, Erle E. Peacock Jr., who described the first successful allotransplantation with an an-bloc digital flexor tendon mechanism (30). To differentiate its terminology from solid organ grafts, Peacock coined these structurally complex grafts with multiple layers of tissue as "composite tissue allografts". Revascularized through inosculation, tendon allografts produced adequate outcomes with over 70% salvage rate (31) and were only abandoned with the introduction of silicone rods, which allowed pseudosheath formation without the need for complicated logistics of cadaveric tendon procurement.

Following successful outcomes with renal allografts owing to the advent of pharmacological immunosuppression in the 1960s, Ecuadorian surgeon Robert Gilbert attempted the first hand vascularized composite allotransplantation (VCA) in 1964 (32). After a successful technical and vascular outcome in the acute phase, the patient suffered from acute rejection at 3 weeks despite immunosuppressive therapy with azathioprine and prednisone (33). This failure, along with unsuccessful attempts on animal models, hindered further developments in the field of VCA for the subsequent three decades. A great majority of scientists abandoned the idea of composite allografts that included skin, arguing that the epithelium's antigenicity was insurmountable with current immunosuppressive drugs (34).

The field of VCA was subjected to a renaissance in the 1990s, in large parts due to the emergence of cyclosporine, tacrolimus and mycophenolic acid in the immunosuppressive armamentarium. Animal studies produced encouraging results, whereby transplanted limbs in rat models survived through the acute and subacute phases of graft rejection (35,36). Several VCA teams were founded across North America and Europe, and when researchers and surgeons met at the first symposium on composite tissue allotransplantation in 1997 to discuss about taking the leap from animal VCAs to human VCAs, they came to the conclusion: "*Just do it*" (37). The race to the first vascularized hand transplantation was underway.

In September 1998, Dubernard and colleagues from Lyon, France became the first group to successfully transplant an arm from a cadaver (38). The procedure was performed on a 48-year-old man who had an amputation of the distal third of his forearm. In their Lancet paper reporting on outcomes at 6 months, the authors stated that no surgical complications were seen, immunosuppression was well tolerated, mild cutaneous rejections resolved with increased doses of prednisone, satisfactory progress of motor function was obtained, and sensory recovery reached the palm for deep pressure but not light touch (38). Unfortunately, three years later, the patient requested to be re-amputated, evoking reasons such as poor hand function and undesirable side-effects of his immunosuppressive regimen (39).

Shortly thereafter in 1999, Breidenbach and colleagues from the Louisville Hand Transplant Team performed the second successful hand transplantation on the dominant hand of a 37-year-old man who had lost his limb 13 years prior (40). Postoperative complications included three episodes of moderate cellular rejection, all resolving with intravenous methylprednisolone and topical tacrolimus. The patient recuperated temperature, pain and pressure sensation after one year, and was able to perform functional activities that were previously impossible with his prosthesis, such as throwing a baseball, writing and tying shoelaces (41). Twenty years later, the patient had not rejected the allograft and continued to benefit from a functional hand, the longest ever reported thus far (42).

The following year in 2000, the first bilateral hand VCA was performed by Dubernard and colleagues (43), and here again, the patient continues to live to this day with their allografts, reporting high satisfaction and adequate long-term outcomes (44). Over the following ten years, more than 45 hand VCAs were performed in multiple countries across Europe, China and the United States (45). As of May 2019, the *International Registry on Hand and Composite Tissue Transplantation* reported 73 unilateral and 43 bilateral hand transplantations one worldwide (46).

Upper extremity allotransplantation has been the solace for research in other fields of VCAs. Most notably, facial transplantation became promoted after successful outcomes were reported for hand VCAs in the early 2000s. However, ethical discussions on the acceptability of face allografts ensued (47,48,49), until Devauchelle and Dubernard performed the first case in 2005 in Amiens, France (50). Although face transplantation continues to be debated even nowadays, other applications of VCAs continue to expand, such as larynx (51), knee/femur (52), abdominal wall (53), peripheral nerve (54), tongue (55), scalp (56), uterus (57), and penis (58). The remaining history in the field of VCAs continues to be written.

0.2.2 Outcomes of hand allotransplantation

0.2.2.1 Benefits and functional outcomes of hand VCA

Benefits of upper extremity allotransplantations can be reported in terms of functional outcomes, both motor and sensory, patient-reported outcomes (PROs) and quality of life outcomes.

A systematic review of the literature revealed several publications focusing on functional outcomes of hand allotransplantations. Clinical evaluation of recipients demonstrated that patients were able to use their allograft for activities of daily living as early as 1 year after surgery, including eating, driving, grasping objects, riding a bicycle, shaving and writing (59). The French group from Lyon reported, on four bilateral recipients with 4 to 13 years of follow-up, that the average Carroll scores (60) were 69% for dominant hands and 55% for non-dominant hands in comparison to normal function (61). The grip strength however was only 4-28% of normal function. Furthermore, the Louisville team described similar functional improvements, namely Carroll scores ranging from 57-59 and autonomy on ADLs in five out of six recipients 62. Other groups presented similar favorable functional motor outcomes (63,64,65,66,67,68).

In terms of sensation, of the first 31 hand vascularized composite allotransplantations reported in the international registry in 2010, 100% of recipients acquired important protective sensitivity, 97% presented signs of tactile sensitivity and 90% benefitted from discriminative sensitivity (45). The same group from Lyon also demonstrated recovery of sensation of at least S3 on the modified Highet scale (69). Impressively, the first American patient with a hand transplantation from 1999 acquired near-normal two-point discrimination (5-9 mm) and grade 4/5 intrinsic thumb function (62). Recovery of sensation is arguably one of the main advantages of upper extremity allotransplantations in comparison to prosthetics.

Patient-reported outcomes persist to occupy an important role in evaluation of clinical progression and in research protocols when comparing functional outcomes of patients prior and post hand allotransplantation. In the same registry by Petruzzo et al. in 2010, mean DASH score

("*Disabilities of the Arm, Shoulder and Hand"*) in 31 transplant recipients was 37,9 after 1 year (45). Another study by Landin et al. demonstrated that pre- and post-transplantation DASH scores in 10 patients improved from 71,01 to 43,39 (higher scores indicate more disability and vice versa) (70). This mean difference in DASH score was found to be statistically significant (p=.005) and exceeded the minimum clinically important difference of 13 points. Other studies have also reported DASH scores on upper extremity VCAs with comparable results (61,63,64,67,68).

In four studies including 17 upper extremity transplantations reporting on the Chen functional grades (used mainly in proximal replantation surgery) (71), all but one patient (5.8%) improved from grade IV to grade III (41,2%), grade II (47,1%) or grade I (5,9%) (45,72,73,74). In the same four studies, the Hand Transplant Score System (HTSS) (75) was reported in 14 patients, with a mean score of 74,21 and 71,85 for the right and left allografts respectively, which is rated as good.

Very few studies report quality of life outcome measures in recipients of hand transplantation. Singh et al. reported Short Form-36 Health Survey Scores (SF-36) on a patient with bilateral upper extremity transplantation, which failed to show significant changes over a 3,5 follow-up period (76). In another study comparing hand allografts with prosthetics, the SF-36 revealed better scores on aspects of "mental health" for the allograft group but higher scores for the "general health" and "social functioning" in the prosthetic group (77).

In summary, the benefits of upper extremity vascularized composite allotransplantation, as measured by motor and sensory recovery, patient-reported outcomes and quality of life measures, has demonstrated to be superior to the current standard of care, which is no transplantation. Furthermore, recipients of hand transplantation performed, at best, as well as patients with mechanical prosthetics on functional outcome measures. At the moment, the principal superiority measure of hand VCAs over prosthetics relates to sensory recovery, which is non-negligible. On the other hand, there is very little scientific evidence that compares the effectiveness of hand allotransplantations with new-generation myoelectric prostheses.

0.2.2.2 Safety and complications of hand VCA

The latest review on upper extremity VCA accounts for 159 transplants in 116 patients reported in the literature and in the International Registry on Hand and Composite Allotransplantation (IRHCTT) (46). The more accurate estimation of hand allotransplants performed worldwide should be around 200, considering that this review dates from early 2019 and that not all hand VCAs have been published in the literature.

Nonetheless, based on the latest review (78), isolated upper extremity transplantations (without concomitant face or lower extremity allografts) presented an overall patient survival rate exceeding 98.5%, with only one patient death occurring in Mexico in a bilateral arm transplantation complicated by pulmonary edema and congestive heart failure on the first postoperative day (79). Three other fatalities have been reported, including two patients with hand and leg transplants and one patient with hand and face VCA (80). Overall, a total of 24 hand transplants have been lost due to patient death (4 patients, 8 limbs), acute rejection (3 patients, 5 limbs), and chronic rejection (11 patients, 11 limbs), which results in a graft survival rate of 77.6% (78). However, the Chinese groups have had difficulties with patient noncompliance and lack of access to immunosuppressive drugs, skewing the graft survival rate for their cohort at 58%. When excluding the Chinese recipients and those with multi-anatomic transplants, the overall transplant survival rate is 90.5%.

Acute and chronic rejection constitute the major concern for postoperative surveillance of transplant patients. According to Petruzzo et al., more than 76% of hand VCAs will experience acute rejection in the first year after the procedure (81). Patients had an average of 1,8 episodes, ranging from a single episode to five episodes. Although common, acute rejection is manageable in most cases with adjustments in immunosuppressive therapy. On the other hand, chronic rejection occurs at a rate of 10,6%, of which 80% ultimately required revision amputation of their allograft (81). These events occurred between 265 days after transplantation to 13 years. This data reflects the necessity of compliance with postoperative immunosuppression and a thorough follow-up to assess and rapidly treat these episodes. Such an endeavour necessarily requires a significant cost to be absorbed by the patient and the healthcare system.

Several other early or late complications of upper extremity VCAs have been reported. Based on the latest data from the IRHCTT (81), the most common complications include cytomegalovirus infection, bacterial infection and metabolic disorders such as hyperglycemia, which are mostly adverse effects of immunosuppressive therapy. Other complications that are rarer but significant include deep vein thrombosis, arterial thrombosis, pulmonary edema and congestive heart failure, which occurred in only 8.5% of patients and within the first 3 months post-transplant.

Finally, there is also a theoretical risk for development of malignancy as extrapolated from solid organ transplantation literature, although there has only been one report of basal cell carcinoma in a patient with unilateral upper extremity allotransplantation to date (82). The cost of management of all these complications needs to be taken into consideration when performing a cost-benefit analysis, which is influenced by the incidence of each event. This represents a strong argument in favor of the necessity to continue to report these pitfalls in the literature.

0.2.3 Bioethics of hand VCA

With modern surgical advancements, a fundamental questioning is required with each innovative technique: when is it technically and ethically appropriate to seek a novel approach to improve patient ailments? The well-known dictum, "*Where there's a will, there's a way*", has often been employed to justify medical breakthroughs aimed at healing patients. However, this ideology can clash with multiple bioethical principles.

In an editorial published by Rohrich in 2017, the author proposes 15 codes of conduct for plastic surgeons to excel, be safe, and achieve great outcomes (83), amongst which one can read: "*Just because you can, does not mean you should*". This important lesson is particularly relevant in the field of upper extremity VCAs.

Even if feasibility of the technique is now part of reality, attitudes and perceptions of hand allografts continue to cause turmoil. In 2009, Mathes et al. surveyed 474 hand surgeons on their opinion about hand VCAs (84). More than 45% of participants were opposed to allotransplantations, 31% were undecided, and only 24% were favorable. When certain conditions were met, such as adequate selection of patients, 71% considered that the procedure was favorable with respect to ethical principles. Indications that were judged favorably included bilateral amputations in 78% of participants and dominant hand in only 32%.

A simplistic approach to determination of acceptability of hand transplantation can be to perform an analysis of risks and benefits. On the one hand, advocates for VCAs will favor the capacity to reconstruct “like-with-like”, while permeating the need for donor site morbidity and allowing for restoration of function and quality of life to the same extent that replantation has been previously described to produce in the literature (85,86,87). On the other hand, critics of vascular composite allotransplantation will argue that the long-term risks associated with immunosuppression in the context of a procedure that is not life-saving, the challenges of rigorous patient selection, and the medico-economical considerations represent strong arguments to oppose VCA as the gold standard treatment for upper extremity amputees.

A more complex approach, and perhaps necessary one, would be to approach the debate with a thorough analysis of bioethical principles. As such, the topic of upper extremity VCAs can be decorticated according to the four principles of bioethics: autonomy, beneficence, non-maleficence, and justice (88).

0.2.3.1 Autonomy

In bioethical sciences, autonomy refers to the doctor’s obligation to respect the patient’s decisions with respect to medical care, when presented with all the information required to make an informed consent (89). In 1998 before the first hand transplant was performed, a bioethicist was mandated during the first symposium on allotransplantations to comment on the ethical acceptability of performing these procedures in humans (90). The discussion principally revolved around the necessity to offer a thorough informed consent to amputated candidates, while underlying the fact that very little knowledge was available at that time, and that all possible risks, common and rare, simple and complex, be explained.

Even so, can a patient *really* provide a valid informed consent when knowledge about the procedure is at its infancy? Some VCA programs have incorporated informed consent as an essential part of preoperative evaluation, whereby the process of consent occurs over two clinical visits that are recorded on camera and where all potential risks associated with the procedure are carefully and thoroughly discussed (91). Some have also suggested to include previous patients (amputees, replanted patients, transplant patients) as part of the initial evaluations with the VCA candidates (92).

With over twenty years of hindsight since the first hand allograft and more than 150 subsequent cases, surgeons possess more data and knowledge to present to patients during informed consent. Nonetheless, long-term outcomes of immunosuppression, chronic rejections, success rates, death rates, and long-term motor and sensory outcomes are yet to be definitive, which limits the capacity of performing a truly voluntary, capable and informed consent (93).

Arguably, upper extremity composite allotransplantation has a long road ahead before being considered as a gold standard treatment, and as such remains an experimental surgery. Some are favorable to the idea of requiring a comprehension test from future candidates, in order to ensure that all aspects involved in decision-making are well-understood by the patient (94). Every interaction that the surgeon has with the upper limb amputee should be as objective as possible, in order to avoid any undue influence or pressure which would favor VCA in the eye of the patient. If all these elements are respected, patient’s autonomy of choosing to proceed with a hand allograft remains a fundamental right insured by this pillar of bioethics (93).

0.2.3.2 Beneficence

The obligation to act in the patient's best interest constitutes the second pillar of bioethics (88). Before modern medicine, the quest for beneficence was enough justification to perform novel techniques on human patients and allowed for rapid progress in several specialties, including the field of vascular composite tissue allotransplantations (90). However, beneficence alone is not above the three other principles of bioethics (95). It is part of the explanation why modern medicine has seen a shift in accepted experiments on patients, focusing more on patient autonomy and justice rather than beneficence (96,97).

In spite of that, the premise of acting for the beneficence of upper extremity amputees remains paramount in the elaboration of VCA programs across the world. The goal is to restore the physical, esthetic, and functional integrity of the human hand. Slatman et al. argued that bodily integrity did not only refer to the physical character or the deficiency of a limb, but also to the degree of re-identification that the patient might perceive with respect to a mutilated part of the body (98). According to the authors, hand VCA would be acceptable only if "*the intervention enables the person to be the body he or she has*". Indeed, the concepts of bodily image and self-identity are fundamental to a successful upper extremity transplant, because the hand is constantly subjected to the recipient's and the public's eyes, thus the benefit of undergoing this procedure as opposed to living with an amputated stump or prosthesis (87).

Apart from restoration of physical integrity and esthetics, the quest for beneficence is driven by the potential gains in function (motor and sensory) and quality of life, as described in the previous section. Previous studies have even demonstrated comparable, if not superior, functional outcomes when compared with replanted proximal upper extremities (99). Quality of life was also reported to be improved in over 75% of patients with hand VCAs (45). When compared with conventional prosthetics, transplant recipients scored higher on SF-36 questionnaires of quality of life for the "mental health" subsection, but less than prosthetics patients for "general health" and "social functioning" subsections (77).

Improving quality of life with hand VCAs has often been compared to improving quality of life with renal transplants. The analogy is valid, because patients with chronic renal failure can survive on long-term hemodialysis. Thus, even if renal transplantation is not a life-saving procedure per se, it does improve quality of life significantly (100). The same can be said about hand transplantation, yet more debate around bioethical acceptability surrounds the field of VCA than the field of renal transplantation (101).

Finally, beneficence with hand VCA also refers to the objective of social and professional re-integration. There are quantifiable benefits, both psychosocial and economic, for the amputee and for the society to help with re-insertion onto the workforce (102). Indeed, Petruzzo et al. reported that more than two thirds of transplant recipients returned to work within two years of follow-up (103).

Based on the positive outcomes and data described above, one could affirm that hand VCAs are in line with the bioethical principle of beneficence. However, a caveat needs to be issued in this regard, because it is possible that publication bias could over-estimate the benefits on functional recuperation, quality of life improvements and social re-integration. For example, a patient with bilateral hand transplantations stated recently that he is seeking a re-amputation because his hand is completely non-functional and suffers from a worsened quality of life (104). These findings are unfortunately under-reported in the scientific literature, but are rather published in magazines, newspaper and broadcasts. The question becomes: how many of the reported "successful" 159 hand transplants are truly adhering to the principle of beneficence?

0.2.3.3 Non-maleficence

"*Primum non nocere*", the ancient dictum of medical ethics from the Hippocratic oath, continues to be relevant in modern medicine, especially when referencing experimental surgeries such as vascular composite allotransplantation. All efforts should be aimed at minimizing risks and complications when a technical innovation arises.

For hand VCAs, the main obstacle to the principle of non-maleficence relates to the long-term risks of immunosuppression. A great majority of research articles in the field of VCA bioethics touch upon this subject (72,105,106). This also explains why research on VCA came to a standstill for more than 30 years after the first failure of a hand transplant in 1964 (33). To fail at ensuring patient safety and preventing harm with experimental surgery is to halt medical progress for years to come.

Although immunosuppressive drugs had improved in 1990s and allowed for the renaissance of human VCAs, history somewhat repeated itself with the first successful hand transplant recipient. Indeed, the patient from Lyon was noncompliant with the immunosuppression, which inevitably led to re-amputation (107). Following this event, a spike in scientific articles were questioning the bioethics of proceeding with hand VCAs (108), and the American Society for Surgery of the Hand (ASSH) emitted a statement that called for precaution and return to fundamental research rather than human (109). Further refinements with immunologic protocols allowed future cases to proceed, with an estimated success rate at preventing acute and chronic rejections of 90.5% in the past decade (78).

Despite lessons learned from initial failures, it cannot be forgotten that immunosuppressive therapies yield undesirable side effects which go against the concept of non-maleficence. Cardiovascular (hypertension, pulmonary oedema, cardiac failure) and metabolic (diabetes, hyperlipidemia) diseases worsen with some of these protocols (110). Risks of infection are also a source of concern, most notably for cytomegalovirus, herpes and cutaneous mycoses (111). Endocrinopathy and renal diseases constitute other complications that have been reported in the literature on hand VCAs (81). There was even a reported case of avascular necrosis of the hip which required a total arthroplasty (41).

Besides reported complications to this day, immunosuppression in recipients of upper extremity VCA are also theoretically at risk of developing malignant tumors. Only one case has been described thus far with allografts, which is a patient that developed a basal cell carcinoma on the transplanted hand (82). Considering that these tumors can arise after several years and that long-term data is still lacking, it becomes foreseeable that the incidence of this serious complication will increase in the next decades, such as it has been demonstrated in the literature on renal transplants whereby the relative risk is 3 to 5 times greater than normal (112). In cases such as the risk of malignancy associated with VCA where data is lacking, it is primordial that informed consent emphasizes the higher risk of developing a cancer, and consequently of decreasing life expectancy. This represents the most substantial hurdle to bioethical acceptability of upper extremity allotransplantation.

The other facet falling under the principle of non-maleficence is related to the primordial process of patient selection whereby VCA teams need to ensure that potential harms of the procedure do not worsen an already afflicted amputee (85). The outcomes from the Chinese groups who performed hand VCAs are perfect examples, because their success rates are 58% in main part due to non-compliance with postoperative immunosuppression (78). Factors for non-adherence with postoperative immunosuppression include non-adherence with pre-operative medications, lack of social support, level of education, and degree of "conscientiousness" (113).

In summary, most publications in the field of hand allografts focus on the risks rather than the benefits. This reflects the actual state of debate, which is that there's no consensus yet on the acceptability of this procedure. Most decisions pertaining to VCAs need to be made on a case-by-base basis and depend on several patient factors such as whether a unilateral or bilateral hand is amputated, or whether adequate access to prostheses allow for completion of ADLs. In any case, there are still many unknowns, and future studies on risks and complications of the procedure are greatly needed.

0.2.3.4 Justice

The definition of justice in bioethics correlates with the obligation to respect the laws pertaining to patients' rights and to promote equitable distribution of resources in the healthcare system (88). The field of VCAs faces many challenges in relation with bioethical justice.

First of all, VCA programs have the obligation to provide this treatment to those that would benefit the most (109). Social justice indicates that it would be unfair for amputees from distant geographical regions to have less access than others. Even though most programs cover for initial travel expanses, the main problem remains when postoperative rehabilitation begins, whereby resources are often deficient outside of urban centers and frequent postoperative visits are required. The other aspect of social justice is the tenet of universal healthcare, where great care should be taken to avoid that wealthy patients get preferential treatment over underprivileged individuals who would not be able to pay out of pocket. Although not applicable to our situation in Canada, this is a major challenge in healthcare systems similar to the one in the United States.

Second of all, some debate is still ongoing on the difference between solid organ donors and composite tissue allograft donors. Legally speaking, are VCAs considered organs or tissues? In the United States, all VCAs of the hand performed before 2014 were considered tissues, and as such were not regulated by the "Organ Procurement and Transplantation Network" of the "U.S. Department of Health and Human Services" (114). After becoming incorporated as an organ rather than a tissue in the governmental organisational structure, VCAs became more regulated and a better redistribution of potential donors became possible. In Canada, there is currently no distinction between organs and tissues, but they rather all fall within the jurisdiction of the "Safety of Human Cells, Tissues and Organs for Transplantation Regulations" (115).

Third of all, consent from potential donors is also a debated topic falling under the pillar of justice. The main reason why certain individuals sign their donor cards is to save lives with donation of solid organs, but they might not be informed that this consent opens the possibility for donation of composite allografts as well (116). This is why consent for procurement of composite allografts is, to this day, exclusively done by family members of deceased individuals. Many ethical dilemmas can ensue, because perception of an upper extremity is individual, personified, intimate, and as a consequence an extension of the personality of the loved ones that were lost (117). Furthermore, physical integrity of the donor's deceased body is compromised to a greater extent than organ donors, whereby it is there to see for all who attend an open-casket funeral. Replacing the donor's upper extremity with a prosthesis of similar dimension and texture can alleviate this deficit. And finally, when family members are encountered for consent to procure VCAs, the discussion should not discourage them to proceed with solid organ donation for which lives of several other patients depend (118).

Fourth of all, preservation of anonymity of the donors is a complex task for VCAs. In the United States, identity of the donors and recipients can be revealed if both parties are consenting, whereas in Canada and Quebec, the law prohibits any disclosure of confidential information for both donor and recipient (119). Considering that hand allotransplantation is visible and unique to each person, the Canadian laws will have to adapt to this new reality that preservation of anonymity might not always be possible with VCAs.

Finally, the principle of justice in bioethics inevitably refers to the reality that there are a finite number of resources in the healthcare system. Allocating these resources requires fair et equitable distribution across different stakeholders, and is determined by precepts of healthcare economics (120). Vascularized composite allotransplantation of the hand is one of the most expensive procedures in medicine, which requires not only large budgets, but also utilizes a significant portion of human and material resources. Previous studies based on fictional models have estimated that the total cost of a hand transplantation over 30 years is between 665 709 $ and 1 224 459 $ (121,122). Another study calculated that increasing the quality-adjusted life years (QALYs) by 1 year in this patient population would cost 3,8 million $, which is beyond the acceptable threshold of 66 516 $ commonly citated in the literature (7,123,124). However, these numbers, although astronomic, do not take into consideration the value of patients' return to the workforce. They are also limited by their simulation models and don't reflect the real costs of procedures that have been performed worldwide. In fact, there is no data in the literature which divulges the total cost that VCA teams billed for these procedures. The other missing information in the literature is a comparison with the current "gold standard" treatment, which is conventional prostheses, and furthermore with newer-generation myoelectric prostheses that will be described in the upcoming section.

0.3 The advent of myoelectric prostheses

0.3.1 History and engineering developments

Surprisingly enough, the earliest record of a prosthesis for replacement of a human part was not an arm, a leg nor any facial structure, but rather a great toe. An archeological discovery from a burial chamber in Egypt uncovered a wooden toe prosthesis on the foot of a mummy (125). Particularly important in Ancient Egypt, the toe was necessary to wear the traditional sandals which corresponded to a specific status in society. The history of prosthetics, as depicted with this fortuitous finding, is as much about function as it is about identity.

The Roman general, Marcus Sergius, is attributed with the earliest example of a hand prosthesis, an iron hand, in 218-201 BC when the artificial limb enabled him to successfully return to battle in the siege of Cremona (126). Afterwards, the history of warfare in medieval times goes hand in hand with the history of prosthetics, whereby iron hands were fashioned for injured knights to go to battle. The most famous belonged to German knight Götz von Berlichingen (circa 1505), who wore an iron hand with digits that could be flexed/extended passively enabling him to hold reins, yield weapons and return to battle by attaching the device to its armour (127). Significant advances were made by French doctor Ambroise Paré in the 16th century, both in amputation surgery and development of prosthetic limbs, by developing the first detailed designs of a spring-loaded prosthetic hand and a prosthetic leg with a locking knee joint (128). Several other artificial limbs were developed afterwards, most of them considered “*passive*” prosthetics, in that they cannot provide prehension functions but rather aim to recreate the physical appearance of a missing limb, to act as a crutch for unidimensional pull/push force and to attach tools or external devices for specific functions. Very few passive prosthetics are manufactured nowadays, except for cosmetic purposes. Table 1 lists advantages and disadvantages of these devices.

Table 1. Advantages and disadvantages of passive prostheses

Advantages	Disadvantages
Potential for cosmesis	Unidimensional, only one function
Light weight	No prehension abilities
Low maintenance, no straps/cables	Cannot perform bimanual tasks
Acts as a crutch/extension of the missing limb for lifting, pushing, pulling	
Can attach external devices or specific tools	
Minimal harnessing	
Low cost	

The idea of "*body-powered*" prosthetics only came in the early 19th century when dentist Peter Baliff from Germany used transmission of tension through leather straps to enable intact muscles of the trunk and shoulder girdle to elicit motion in the prosthesis (129). The American Civil War and both World Wars were responsible for a considerable increase in number of limb casualties, which required technological advancements in development of prosthetics. The "Association of Limb Manufacturers of America" (nowadays "American Orthotic & Prosthetic Association") and the Canadian "Amputations Association of the Great War" (nowadays "War Amps") were born out of necessity in the 1910s-1920s. In 1948, the Bowden cable body-powered prosthesis was invented, which used a system of tension cables instead of traditional bulky straps (130). Today's body-powered prostheses are essentially variations of the original Bowden cable device. Table 2 lists different advantages and disadvantages of body-powered devices.

Table 2. Advantages and disadvantages of body-powered prostheses

Advantages	Disadvantages
Durable, portable, heavy-duty construction	Uncomfortable
Impressive range of motion, speed and force	Limited complex motor tasks
Ability to use both hands simultaneously	Mostly non-cosmetic appearance
Able to predict the position of the device without visual feedback by sensing cable tension (proprioception)	
Relatively affordable	

An "*externally-powered*" prosthesis, although described conceptually in books as early as 1919 (131), was published for the time in 1948 by Reinhold Reiter, who developed a prosthesis that transformed surface electromyographic (EMG) current to power body parts, but it unfortunately did not gain commercial acceptance (132). However, in 1960, Russian scientist Kobrinski unveiled the first clinically significant myoelectric prosthesis (133). The "Russian Hand" was plagued by numerous problems and fell out of favor. Over the subsequent two decades, most rehabilitation centers across the world incorporated myoelectric prosthesis as the gold standard for reconstruction of amputated upper limbs (134). Table 3 summarizes the pros and cons of externally-powered prostheses.

Table 3. Advantages and disadvantages of externally-powered prostheses

Advantages	Disadvantages
Capacity to perform complex functions with more than two degrees of liberty	Battery maintenance
Increased grip force	Increased weight
Better comfort, less bulky	Susceptible to damage
Potential for cosmesis	Increased costs
Interchangeable components, customizable	

0.3.2 Distal (forearm/hand) myoelectric prostheses

Distal myoelectric prostheses of the forearm work by generating an electromyographic current recorded by surface electrodes overlying specific forearm muscles (135). Motor impulses from these devices are intercepted only if muscular groups of flexors and extensors of the forearm are intact. The first prototypes were limited in their conventional control of commands, namely by intermittence ("*on/off*"). In other terms, the grip of a myoelectric prosthesis could only open or close, without being able to stop the command mid-way through the function.

Through decades of technological refinements, recording motor nerve firings through electromyographic electrodes and analyzing signals in real-time allowed engineers to manufacture prostheses that were more efficient with elaborate functions (136,137). For example, the concept of "*simultaneous and proportional kinematic control*" refers to voltage transmitted to the prosthesis being proportional in intensity to the electromyographic influx recorded at the surface of muscles in the forearm (138). The main advantage of these prototypes lies in the capacity to perform different functions simultaneously and with proportional kinetics. Functions with two degrees of liberty become feasible, such as flexing the *fingers with extension of the wrist (tenodesis effect). The principal disadvantage however is depicted by the term "cross-talk", meaning that if the electrode records activation of a muscle in the vicinity that* was not targeted to receive the electromyographic feedback, the prosthesis will produce an undesired function. To palliate to the issue of electromyographic cross-talk, prostheses with direct control were invented (139). These devices require implantation of invasive captors within the muscles of the forearm. It constitutes the most effective technique to control specific functions of the hand with a prosthesis, but remains limited due to its invasive nature and maintenance.

The new-generation myoelectric prostheses employ algorithms of “pattern recognition control” to classify activation of different muscle in real-time and to respond simultaneously with production of different pre-determined movements (140). These myoelectric configurations are extremely precise and allow movements such as supination or pronation of the forearm, flexion or extension of the wrist, ulnar or radial deviation of the wrist, and even individual control of single digits with more than four degrees of liberty simultaneously and proportionally (141,142).

For partial amputations of the hand, the “Starfish procedure” was developed to restore individual functioning of the fingers. Gaston et al. described a surgical technique where intact interossei muscles (while preserving vascular pedicles) were transferred onto the dorsum of metacarpal bones. By diminishing the distance from muscle to surface electrodes, the myoelectric prosthesis was capable of discerning myoelectric signals with more precision allowing for independent movement of three fingers at the time (143). Outcomes from their study demonstrated complete range of motion of all fingers, capacity to lift weights of 9kg and a pain score of 1.3 out of 10 on the “Visual Analog Scale” (VAS).

Several studies have reported on functional outcomes of myoelectric prostheses of the forearm, demonstrating encouraging but imperfect results (144,145). In the most recent systematic review of the literature (146), the main findings are summarized in Table 4. Comparing functional outcomes of myoelectric prostheses is a difficult task, considering the multitude of products on the market, the different levels of amputations, the heterogeneity of instruments to measure function and the lack of comparative studies. Nonetheless, functional benefits continue to improve with newer technologies. Despite this technological advancement, the data demonstrates that lack of comfort on the stump and daily maintenance of the apparatus are the principal reasons why 20% of patients with a distal forearm myoelectric prosthesis will abandon it long-term (147).

Table 4. Systematic review of the literature on functional outcomes of prostheses in upper limb amputees

Wright V. Prosthetic outcome measures for use with upper limb amputees: a systematic review of the peer-reviewed literature. JPO Journal of Prosthetics and Orthotics. 2009;21(9):3-63.
- Significant improvement of function in patients wearing prostheses versus patients who decline to wear them, as demonstrated on the DASH score (148)
- Inferiority of prostheses compared to forearm replantation on measures of the "*Carroll test*" (149)
- Better results on measures of social, mental and psychological functioning on the "Nottingham Health Profile" for upper extremity prostheses when compared with lower extremity prostheses (150)
- Improved quality of life as measured by the PedsQL for users of myoelectric prostheses in comparison to non-users (151)

0.3.3 Proximal (shoulder/humerus) myoelectric prostheses

In upper limb amputees who lack forearm muscles, conventional prostheses cannot control multiple joints with more than two degrees of liberty, which translates into deficient grip, ineffective completion of simple tasks and dissatisfaction with the devices leading to high abandonment rates amongst amputees (148). In order to augment functional properties of myoelectric prostheses, Kuiken and Dumanian conceived in 2002 a novel technique that they coined as "targeted muscle reinnervation" (TMR) (149). The concept behind this intervention was to perform multiple peripheral nerve transfers towards a targeted regional muscle in order to increase the number of electromyographic signals available for fitting of a multi-joint myoelectric prosthesis (150).

The step-by-step approach to the surgical technique has been thoroughly described in the literature (151,152) and is summarized in table 5. Muscular reinnervation is measurable as early as 8 to 12 weeks after the procedure, then becomes strong enough to allow for control of the myoelectric prosthesis at 4 months, and finally has been shown to be perfectly assimilated after a rehabilitation process of 8 weeks (153,153). Current indications are limited to 1) healthy patients, 2) amputated at the mid-humeral level or with disarticulated shoulders, 3) with documented failure of rehabilitation with conventional prostheses, 4) intact cortical control of brachial plexus nerves, 5) presence of thoracic cage muscles, and 6) adequate soft tissue coverage of the TMR region (154).

Table 5. Step-by-step approach to the technique of "targeted muscle reinnervation"

	Technical description
Step 1	Dissection, identification, and mobilisation of available nerves from the brachial plexus
Step 2	Denervation of the targeted regional muscle as close to the muscle fibers as possible
Step 3	Nerve transfers of the brachial plexus towards functional segments of the targeted muscle
Step 4	Interposition of an adipofascial flap between the muscular segments and thinning/defatting of excess subcutaneous adipose tissue in order to facilitate electromyographic leads capture
Step 5	Rapid return to prior use of prosthesis in order to promote cortical remodeling

Since 2002, more than 100 patients have benefited from a TMR-controlled myoelectric prosthesis worldwide (155). Muscle reinnervation was achieved in 96% of cases and functional results demonstrate considerable gains compared with preoperative motor performance. Indeed, the first recipient of this technique is now capable of maneuvering complex tasks such as throwing a baseball, opening jars, eating with utensils, and much more (153). Moreover, a series of five patients treated with TMR and myoelectric prostheses reported a 323% improvement on the "box and blocks test", a standardized and validated measure of global functioning of the hand (154). Several other studies have described encouraging outcomes after this procedure, namely an enhanced comfort with prosthesis wear, more intuitive rehabilitation, and improved quality of life (153,154,156).

However, the most significant progress attributed to development of TMR-powered prostheses is the potential for sensory recuperation, which had never been possible with prior conventional prostheses. Indeed, Kuiken et al. were the first authors to describe this idea of "targeted sensory reinnervation", a process in which a specific skin region in the vicinity of the TMR is denervated of sensory nerves (157). This happened as a fortuitous discovery when the cutaneous zone covering the side of TMR that was denervated during subcutaneous dissection (in order to place electromyographic electrodes) became reinnervated by afferent sensory nerves going from muscle to skin. By placing sensory leads on the fingertips of the myoelectric prosthesis, the authors were able to transfer the influx of information onto the reinnervated cutaneous zone which allowed the patient to feel light touch sensation (158). This corresponded to the first ever prosthesis that was capable of reproducing simultaneous motor and sensory function controlled by the central nervous system (159,160).

Another unexpected discovery occurred with the advent of TMRs. It is well-established that patients with proximal limb amputations are at higher risk of suffering from chronic pain, due to painful neuromas of the stump or the phantom limb syndrome. By re-routing sectioned nerves towards proximal muscle targets with TMR, intra-muscular growth of nerve axons responsible for reinnervation have been shown to decrease development of painful neuromas and pain associated with phantom limbs (161,162). A comparative clinical study between TMR and traditional burying of nerve endings under muscle (deemed standard of care) revealed that the number of patients with resolution of phantom pain increased from 17.6% to 47.1% at a follow-up of 18 months with TMR (154). The encouraging reports from this study has even motivated surgeons to incorporate TMR at the moment of amputation rather than months/years later, which preliminary reports seem to suggest that it would prevent neuroma formation and phantom limb syndrome (163).

0.4 Utility health outcomes in medicine

0.4.1 Purpose, definitions, and methods

In the context of any healthcare system wherein resources are limited, authorities that are in charge of decisions about resource allocation have the obligation to determine an equitable divide between a multitude of diseases and interventions (164). This complex task needs to be based on data that is objective, reproducible, and comparative. The principal difficulty with this endeavour is to compare healthcare outcomes across diseases that are distinct and heterogenous. A common denominator becomes a necessity (165).

The ideal measure of comparison needs to encompass the impact that a disease or a treatment yields on life expectancy AND quality of life. In the field of health economics, "Quality-adjusted life years" were developed with the scope of incorporating the remaining duration of life expectancy and its associated quality of life within a common denominator measure, which can be compared across several diseases and interventions (166). Studies that report outcomes as units of years-health (such as QALYs for example) are called "Cost-Utility Analyses" (CUA). In comparison, studies that are called "Cost-Effectiveness Analyses" (CEA) do not measure the quantity nor the quality of life, but rather use units of measure that are unidimensional (such as weight loss in kilograms for example). The last type of study design, coined "Cost-Benefit Analyses" (CBA), includes dimensions of quantity and quality of life as a function of a monetary value aimed at facilitating decision-making about whether the costs justify the benefits (167).

To obtain a measure for a CUA or a CBA study when analyzing a surgical intervention, one needs to determine the "utility measure" beforehand. By definition, a measure of utility is a cardinal value which reflects preferences of an individual, a group or a society with respect to different outcomes in healthcare (120). In other terms, it evaluates the desirability or the value of a particular health state.

The values obtained from these studies range from 0 (representing death) to 1 (representing perfect health/quality of life). To measure utility values, there are direct and indirect instruments that have been developed (168). Direct measures are obtained from personalized questionnaires aimed at studying a specific health state or intervention, whereas indirect measures utilize generic or disease-specific algorithms such as "patient-reported outcomes" or "health-related quality of life" (HRQoL) (172).

0.4.2 Direct methods for measuring utility

When designing a methodology for a cost-utility analysis study, there are three decisional aspects to consider beforehand: what are the healthcare impacts of the disease, which direct methods of evaluation will be employed, and the preferences of which individuals will be measured.

For upper limb amputees, the healthcare impacts of the disease comprise several dimensions and features. Amongst these healthcare impacts, one can include the dimensions on functional capacities, physical/aesthetic appearance, psychological well-being, social interactions, cognitive functioning, reported symptoms and pain.

Then, participants are informed about these dimensions as part of a real-life scenario, or as part of a fictional framework depending on the group. After acquiring this information about the disease burden, they are better equipped to analyze the health state that a patient with unilateral or bilateral limb amputations might endure. No more than 7 dimensions can be included in the scenarios, otherwise it has been shown that the capacity to retain information from a particular scenario significantly decreases (169). Furthermore, features from every dimension of health state described in the scenario need to correspond to actual knowledge of the disease or treatment outcomes. Using testimonials from amputated patients or studies published in the literature are paramount. Table 6 is an example of a table that was shown to participants from the study described later in this thesis in Chapter 2, which aims to inform patients on the health state of a unilateral or bilateral amputation prior to completing a questionnaire that will be used to measure utility.

Table 6. Example of health state dimensions for a unilateral or bilateral upper extremity amputation, based on results reported in the literature (with references)

Health state dimensions	Results reported in the literature
Functional capacities	MAJOR functional deficits for activities requiring both hands (Driving, lifting heavy weights, sports, etc.) (170)
Physical/Aesthetic appearance	COMPLETE loss of physical/aesthetic appearance of the upper extremity (171)
Psychological well-being	IMPORTANT psychological troubles (depression, adjustment disorder, anxiety, poor self-esteem, etc.) (172)
Social interactions	SIGNIFICANT difficulties with social interactions (shake hands, intimacy, marginalization, etc.) (173)
Cognitive functioning	NO cognitive deficit associated with amputations (174)
Reported symptoms	INCREASED risk of reporting chronic symptoms (phantom sensation, chronic wounds on stump, etc.) (175,176)
Pain	INCREASED rates of phantom limb pain and painful neuromas (177)

When participants have been introduced to the scenario with the real-life or fictional health states, a utility measure is obtained from one of the direct methods of evaluation that was chosen. Three direct methods have been employed in this thesis. First, the « Visual Analog Scale » (VAS), the easiest to comprehend and administer, requires that patients attribute a score from 0 (death) to 100 (perfect health) to the health state priorly described in the scenario. An electronic form is used where the participant can click with the cursor on a scale with anchors at either end, such as the example demonstrated in figure 1. The advantages of this direct method of utility measuring resides in its simplicity and empiric performance (170), but lacks an important component of decisional process when faced with an uncertain health state (as opposed to the next two methods described below).

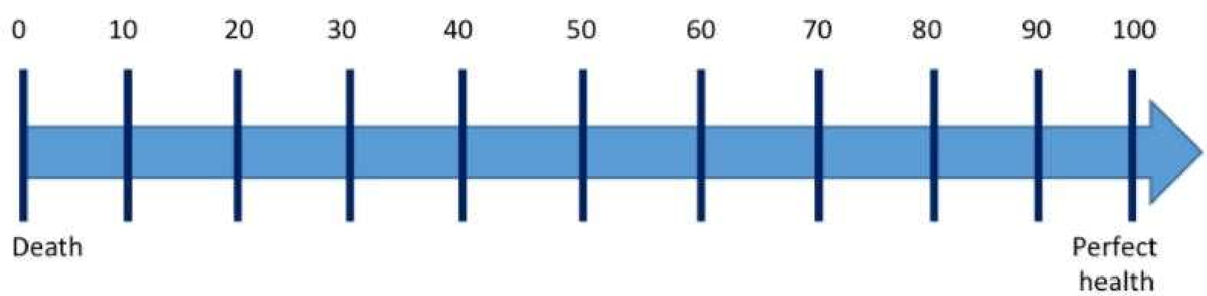


Figure 1. Visual analog scale used to measure utility values

The second direct method of utility measure, the "Time Trade-Off" (TTO), requires that participants make a decisional process about a specific number of years that they are willing to sacrifice in order to improve their quality of life in the scenario (171). The premise in the scenario stipulates that an individual with the described health state at 30 years of age will have a life expectancy of 50 more years (death at 80 years old). The therapeutic intervention proposed to the patient would improve all dimensions of health state described in Table 6, but at the cost of decreasing their life expectancy by "X" number of years. The number "X" is determined at the “point of indifference”, which represents the middle ground when the participant considers that living with the disease/burden for 50 years is equivalent to living 50 minus “X” years in perfect health. The utility value derived from the TTO technique is then determined by the formula depicted in figure 2. The main advantage of the TTO technique is reflected by the optic that the participant executes a choice between two certain outcomes (live in current health state OR die earlier with perfect health), which assumes neutrality of risk. Not all individuals behave the same with risk management, and therefore for participants with moderate to high aversion to risk, the utility values of TTO have been shown to be spared from this potential bias (172).

Scenario Example

Patient with binocular blindness is willing to “trade-off” 15 years of life to regain a perfect vision

Utility = (number of years specified in the described health state – number of years traded off at the indifference point) / number of years specified in the described health state

Utility = (50 years of life expectancy – 15 years traded off) / 50 years of life expectancy

Utility = 0.70

Figure 2. Example and formula to measure utility values with the TTO technique in a scenario of binocular blindness

The third direct method for calculating utility measures is the "Standard Gamble" (SG), where participants are required to make a choice between a certitude and a gamble, much like in real life scenarios with therapeutic interventions (173). The same premise as with the TTO technique is presented to participants with respect to living with the described health state at 30 years of age for a life expectancy of 50 more years (death at 80 years old). They are then asked to choose the point of indifference between this certainty, and the gamble of undergoing an intervention/treatment that will improve all dimensions of health state but risk "X%" chance of death. The utility value derived from the SG technique is then determined by the formula depicted in figure 3. The SG questionnaire is the classic method used in health economics for measuring utility outcomes, but it is influenced by the degree of risk aversion of the participant. Because most individuals tend to favor certainty over gamble, the utility values as measured by the SG are often more elevated than those measured by the TTO (174).

Scenario Example

Patient with binocular blindness is willing to "gamble" a risk of death of 5%

Utility = (100 – risk of death at the indifference point) / 100

Utility = (100 – 5% risk of death) / 100

Utility = 0.95

Figure 3. Example and formula to measure utility values with the SG technique in a scenario of binocular blindness

The last question remaining to be answered for the design of the methodology in utility studies is who will be chosen as participants to measure these values. This variable is important, because participants' answers with respect to the VAS, TTO and SG questionnaires will be influenced by a person's life experiences (170). In the literature on utility outcome measures, some argue that only participants of the general population should be included, because the healthcare system is sponsored by the public, and thus their beliefs and opinions regarding the utility of an intervention is the most pertinent to obtain (175). Others will counter-argument that patients truly are the ones that comprehend the best what it implies on their quality of life to live with a particular disease or undergo a specific treatment, and thus their preference are most important in utility studies (176). Because there is no consensus in the literature, this thesis aimed to measure utilities for both groups, the general population and the afflicted patients.

0.4.3 Indirect methods for measuring utility

There are also *indirect* methods of measuring utility values, which are based on general or disease-specific instruments. The most common generic methods measure a collection of non-specific health states by using data from the general population, such as the EQ-5D ("*EuroQol-5D*"), the SF-6D ("*Short-Form six dimension*") and the HUI ("*Health Utilities Index*") (172). For each instrument, an algorithm is developed by extrapolating econometrical models in order to determine the utility of a health state that was not measured directly.

For example, a study design can administer the SF-36 to participants, from which the SF-6D can be extracted to obtain a utility measure from a census of the general population with the standard gamble technique (177). The advantage of this questionnaire is rooted in its rapidity and ease of completion and its capacity to obtain utilities from different health states for comparison purposes. The main disadvantages however are related to its lack of sensitivity to the context of a specific disease, the difficulty to administer the instruments in trauma patients and the incapacity to discern small differences in utility of multiple variants of the same interventions (for example, different dosage of the same drug) (178).

In the hand surgery literature, the most common questionnaires for indirect measuring of utility are the "*Disability of the Arm, Shoulder and Hand*" (DASH) and the "*Michigan Hand Outcomes Questionnaire*" (MHQ). The DASH aims to determine the function of upper extremities as reported by the patient with a questionnaire of 30 items related to physical function and symptoms (179). On the other hand, the MHQ also calculates a measure of subjective function as reported by the patient with 37 questions, but limited only to the hand (180). Six domains are obtained, which are global hand function, activities of daily living, pain, work performance, esthetics and patient satisfaction with function.

0.4.4 Quality-adjusted life years (QALYs)

Developed in the 1970s, the concept of "Quality-adjusted life years" was designed to integrate within a same person, the improvement in health, both in quantity AND quality, and to aggregate these improvements across all individuals (181). For example, an intervention in person A that extends life by 1 year at a quality of life of 0.33 will produce a QALY gain of 0.33, whereas the same intervention in person B that improves quality of life by 0.33 for 1 year will also produce a gain of 0.33 QALYs, which means that the aggregate gain of this intervention in both individuals is 0.66 QALYs. Two basic assumptions of this model are that QALYs are independent of age (adding 0.66 QALYs in a 10-year-old is the same as adding 0.66 QALYs in a 90-year-old), but dependent on the number of people and the timeframe (gaining 0.66 QALYs for 1 year is equal to gaining 0.33 QALYs for 2 years, or gaining 0.66 QALYs in 1 person is equal to gaining 0.33 QALYs in 2 people) (182).

Assignment of weights (quality levels) to the various health states are required, but the model does not specify which weights (183). Therefore, although a number of methods have been described over the years, the most common one has been the utility-based QALY model because they reflect the preferences of the individuals in assisting in decision-making regarding appropriate treatments or interventions. When expressed as a function of cost (to the healthcare system) and utility, this constitutes the analytic model known as "cost-utility analysis" (184). The

QALY is derived from this model by multiplying the number of years expected to remain in a particular health state by the utility measured on that intervention. For example, an intervention that restores complete function of the upper extremity in an amputee yields a utility measure of 0.90, and if that individual still has 10 years of life remaining, will benefit of a QALY gain of 9 from undergoing that procedure.

Furthermore, the cost associated with an intervention that increases the QALY by 1 is referred to as "*Incremental Cost-Utility Ratios*" (ICUR). The traditional threshold of acceptability for implementing a new health technology was set at 66 226 $ per QALY gained (124). Therefore, one method to determine if governmental bodies and institutions will invest in a treatment or a procedure is to determine the utility, the QALYs and the ICURs of that intervention and whether it exceeds the accepted threshold, which corresponds to the basic definition of healthcare economics.

0.5 Study objectives

The purpose of this thesis work is to determine the utility of vascularized composite allotransplantation versus myoelectric prostheses in the treatment of upper extremity amputations. A stepwise approach was undertaken with specific objectives that required to be investigated:

1) To test the feasibility of the questionnaires by calculating utility measures in patients with amputated thumbs.
2) To measure utility outcomes and quality-adjusted life years for upper extremity allotransplantation and myoelectric prostheses.
3) To compare utility of these interventions in unilateral versus bilateral hand amputees.
4) To perform a cost-benefit analysis in the context of the socioeconomic setting of the Canadian healthcare system.

0.6 Thesis overview

This thesis is organized in four chapters. In Chapter 1, a feasibility study was performed on patients with amputated thumbs for a treatment scenario of free toe flaps. Because no patients in Quebec were ever treated with hand VCA or myoelectric prostheses, we measured utility outcomes in a population group (thumb amputees) that shared similar characteristics in terms of health burden and potential recovery of function of the upper limb. This chapter has been published in "Journal of Reconstructive Microsurgery" in March 2018.

In Chapter 2, the utility of upper extremity VCA and myoelectric prostheses was measured with three validated instruments. The results were compared between four different population groups: unilateral amputees, bilateral amputees, patients with a replanted upper extremity and healthy controls. From these utility measures, the QALYs were extrapolated for each intervention. This chapter was accepted for publication in "Plastic and Reconstructive Surgery" in May 2021.

In Chapter 3, a cost-benefit analysis of both treatments was performed based on economical models from published literature. Total costs over a lifetime of 30 years were estimated for VCA and myoelectric prostheses, and then applied to the population of upper extremity amputees in Canada. Overall cost savings were then calculated by subtracting lifetime costs of these interventions from the potential gains of return to work. This chapter was submitted for publication in "Value in Health" journal in September 2021.

In the final section, we provide our conclusions with regards to the utilities of upper extremity VCAs and myoelectric protheses, in unilateral versus bilateral amputees, as well as a discussion about whether healthcare funds should be allocated on developing VCA programs or myoelectric prostheses for the treatment of these patients in Canada.

Chapter 1: Model simulation with utility of free toe flaps

1.1 Investigating Patients' Perception of Microvascular Free Toe Flap for Reconstruction of Amputated Thumbs: A Guide for Surgeons During Informed Consent

Published in Journal of Reconstructive Microsurgery, March 2018

Authors and affiliations:

Johnny Ionut Efanov, MD[1]; Christopher Wong[2]; Clarence Guilbault[2]; Joseph Bou-Merhi, MD[1]; Patrick G. Harris, MD[1]; Ali Izadpanah MD MSc[1]; Michel Alain Danino, MD PhD[1].

[1] Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada

[2] McGill University, Montreal, Quebec, Canada

Statement of authorship:

Design of study: JIE

Conduct of the study: JIE, CW, CG

Data analysis: JIE

Writing manuscript: JIE, CW, CG

Manuscript revision: JIE, CW, CG, JBM, PGH, AI, MAD

Corresponding author:

Michel Alain Danino, MD PhD (michel.alain.danino@umontreal.ca)

1.1.1 Introduction

Traumatic amputations of the thumb elicit a significant burden for afflicted patients. In addition to the devastating loss of functional pinch and grasp, a severed thumb can cause significant distress due to aesthetic, psychological or social aspects. To avoid these consequences, a thumb amputation is an indication for single-digit replantation when they present at the time of injury. Unfortunately, not all thumb amputations are amenable to replantation, with a recent nationwide review reporting only 9.9-20.3% attempt rates and 80.5-86.2% success rates (185). Consequently, a significant portion of patients are left with amputated thumbs and seek secondary reconstructive procedures to restore function and form.

Aside from bone lengthening techniques and pollicisation, free toe-to-hand transplantation represents a workhorse flap for reconstruction of amputated thumbs. The first successful great-toe-to-thumb reconstruction performed with microvascular techniques is attributed to Cobbett in 1969 (186). In the past four decades, several modifications have been described, including second toe transfers (187), wrap-around (188), trimmed (189) and other variants of the technique (190,191,192). With an overall success rate approximating 95%, which is comparable to other free flap procedures, most patients will undergo a single procedure whereas others might require secondary corrections for bulk mismatches, pulp aesthetics or tenolyses. Furthermore, patients recover a partial range of motion, a sensory two-point discrimination of less than 10 mm and a mean subjective satisfaction score of 80% and higher (193,194,195). In light of these positive outcomes, it is safe to assume that free toe transfers will continue to be offered in the future for patients sustaining traumatic thumb amputations.

Despite encouraging results reported in the literature, the authors' experience noticed a significant proportion of patients electing not to undergo a free toe transfer for the reconstruction of thumb amputations. Previous authors described patient concerns regarding donor-site morbidity, postoperative pain and cosmetic results (196,197). Whether other reasons play a role in the decision-making process, such as cultural motives, psycho-social stigmatisation or lack of understanding of postoperative implications, has yet to be elucidated. The primary objective of this study was to investigate patient attitudes towards free toe transfers in order to improve surgeon-patient interactions when offering this reconstructive option. Concurrently, the secondary objective was to determine utility scores in thumb amputees in order to measure the quality-adjusted life years associated with this surgical procedure.

1.1.2 Methods

1.1.2.1 Study design

A survey was performed on consecutive patients treated for a thumb amputation between January 2016 to June 2017. Patient recruitment occurred within the provincial replantation referral program in our institution wherein a prospective database was implemented to collect information about demographics/epidemiology, surgical management and postoperative care of patients sustaining an upper extremity devascularization or amputation. Study enrolment was performed by telephone, email or in person during postoperative clinic visits. Participation was voluntary and the consent was obtained prior to survey completion. No patient was considering free toe transfers at the time of enrolment and they were not educated about the advantages and inconveniences of this procedure in order to prevent responder bias. The study was performed in accordance with the Declaration of Helsinki and it obtained approval from the institution's ethics review board.

1.1.2.2 Inclusion and exclusion criteria

Patients were contacted for inclusion in the study if they sustained a thumb amputation distal to the first carpo-metacarpal joint. The type of surgical management was taken into consideration but did not represent an inclusion criteria, thus patients with replantation, revision amputation and secondary reconstructive procedures were selected. Exclusion criteria were limited to patients under the age of 18, those with a pre-existing lower extremity condition or injury and those with multiple amputated fingers.

1.1.2.3 Patient characteristics questionnaire

Recruited patients were asked to complete a confidential self-reported questionnaire either online or through mail. The questionnaire was designed with an introduction to the technique of free toe flaps and four subsequent sections totaling 72 questions. The first part investigated patient demographics, including age, sex, religion/ethnicity, level of education, average income, baseline level of activity, comorbidities, trauma mechanism and type of treatment.

1.1.2.4 Brief Michigan Hand Questionnaire (bMHQ)

In the second section, the brief Michigan Hand Questionnaire (bMHQ) was administered. In this 12-item self-reported questionnaire, responses correspond to different aspects of hand function with a Likert scale of 1 to 5. These answers are normalized on a scale from 0 to 100, with higher results representing better self-reported function and patient satisfaction. The bMHQ has been validated in the literature for surgical hand procedures (192).

1.1.2.5 Patient attitudes questionnaire

The third part of the questionnaire was aimed to investigate patient attitudes with regards to the decision-making process and what might influence an individual into electing not to undergo a free toe transfer for the reconstruction of thumb amputations. To develop these questions, a survey was answered by four micro-surgeons who had performed free toe transfers in our institution and a list of 14 elements was chosen based on surgeons' experience with patients that decided not to pursue such an intervention in the past. These elements are the following: aesthetic appearance of the hand postoperatively, aesthetic appearance of the foot postoperatively, social stigmatization, religious/cultural beliefs, sacrificing a healthy body part, concerns about footwear, lack in understanding the risks and benefits, failure to choose from many reconstructive options, concerns about flap failure, complexity of rehabilitation, functional impact on walking/running, inability to take time off from work, prolonged hospital stay and concerns about revision surgeries. Patients were required to answer if these elements constituted a valid argument explaining why they would opt out of a free toe flap, with a Likert scale of 1 to 5 from "Strongly agree" to "Strongly disagree".

1.1.2.6 Utility outcomes questionnaire

In the last section of the questionnaire, measures for utility assessment of free toe transfers were obtained with the time-trade-off and standard gamble methods (185,198). With the TTO, patients have to choose between a scenario where they trade "X" number of years to live in a state of perfect health (in this case recuperating thumb function with a free toe flap) or to stay in the current health state for a given number of years. With the SG, patients have to choose between the option of "gambling" with a degree of success to attain perfect health (free toe flap) versus failure of the procedure (thumb and toe amputation) and the option of staying in their current health state. Utility values were obtained from the TTO and SG using a bisecting search routine until the indifference point was found, resulting in a value ranging from 0 (death) to 1 (perfect health). For example, if a patient answered on the TTO questionnaire that living for 50 years with a thumb amputation was equivalent to living 45 years with a functional thumb reconstructed by a free toe transfer, the calculation would be subtracting 5 years (time traded off) from 50 years (given health state) and dividing by 50 years (given health state), resulting in a utility measure of 0.9. Both TTO and SG have been used in hand surgery literature for assessment of utility measures and derivations of quality-adjusted life-years (199,200,201).

1.1.2.7 Statistical analysis

Data from the questionnaires were compiled, scored and analyzed using SPSS© Version 24 computer software (IBM™, Chicago, IL). Reported outcomes were presented with measures of central tendency, mainly mean values and inter quartile ranges. A linear regression model was used to control for independent risk factors such as demographic and injury characteristics. In order to separate the data from patients with a replantation, a revision or a delayed reconstruction, a subgroup analysis was performed according to the type of treatment received and categorical variables were evaluated with Pearson's chi-squared tests, with a level of significance set at p-value of 0.05.

1.1.3 Results

1.1.3.1 Patient characteristics

A total of 52 participants treated for a thumb amputation were contacted to be recruited in this study, but only 30 patients were able to complete the questionnaire. A vast majority of participants were male (n=26, 87%) and the population surveyed was widely Caucasian (n=23, 77%) and Christian (n=16, 53%). Educational backgrounds were equally distributed between "less than high school" (n=7, 23%) to "postgraduate university studies" (n=7, 23%). The largest proportion of participants reported incomes over 70 000 $ annually (n=12, 40%). When prompted on the context of injury, 33.33% sustained an amputation while cooking or doing housework, 30% while working (with treatment covered under the provincial's worker compensation program) and 26.67% while performing activities related to leisure. In total, 16 patients (53%) underwent a revascularization/replantation procedure, 8 patients (27%) suffered from a revision amputation and 6 patients (20%) had delayed reconstruction surgeries. None of the patients included in this study were considering free toe transfers. Amongst the 16 patients with a replantation or revascularisation, all of them had a viable thumb at hospital discharge and only 2 (12.5%) responded in the survey that the procedure was unsuccessful in terms of long-term function. The majority of participants (n=16, 53%) did not have any existing disease/comorbidity at the time of suffering their injury. Other patient and injury characteristics can be found in Table 7.

Table 7. Demographic/patient characteristics, mechanism of injury and type of treatment

Sex	N	Percentage
Male	26	86.67%
Female	4	13.33%
Religion		
Christianity	16	53.33%
Islam	3	10.00%
Judaism	2	6.67%
Atheism	6	20.00%
Other	3	10.00%

Ethnicity/Race		
Caucasian	23	76.67%
African-American	1	3.33%
Arab	3	10.00%
Other	3	10.00%
Education		
Less than high school	7	23.33%
High school diploma	4	13.33%
Vocational/technical diploma	3	10.00%
College (Cegep) diploma	8	26.67%
University undergraduate degree	5	16.67%
University graduate degree	7	23.33%
Household Income		
< 10,000 $	2	6.67%
10 000 $ - 19 999 $	0	0.00%
20 000 $ - 29 999 $	5	16.67%
30 000 $ - 39 999 $	1	3.33%
40 000 $ - 49 999 $	3	10.00%
50 000 $ - 59 999 $	4	13.33%
60 000 $ - 69 999 $	1	3.33%
70 000+ $	12	40.00%
Prefer not to answer	2	6.67%
Nature of Injury		
Occupational/work	9	30.00%
Medical/disease	1	3.33%
Sport-related	2	6.67%
Cooking/housework	10	33.33%
Leisure	8	26.67%
Tamai zone of amputation		
Zone 1	6	20.00%
Zone 2	11	36.7%
Zone 3	13	43.44%
Type of Reconstruction		
Replantation/revascularization	16	53.33%
Revision amputation	8	26.67%
Delayed reconstruction	6	20.00%

Pre-Existing Diseases/Comorbidities		
Peripheral vascular disease	4	13.33%
Diabetes mellitus	2	6.67%
Nerve lesion/pathology	1	3.33%
Active smoking	5	16.67%
Other	2	6.67%
None	16	53.33%

1.1.3.2 Patient-reported hand function

The mean normalized score for hand function reported by patients, as evaluated with the bMHQ, was 63.54 (out of 100) (Table 8). A large majority of participants (n=21, 70%) rated their hand function between scores of 60-79 (Figure 4). In the subgroup analysis according to the type of treatment administered, patients with a replantation procedure scored 68.36 on the bMHQ in comparison to 61.98 for those with a revision amputation and 72.22 for those with a delayed reconstruction. Statistical analysis between subgroups failed to demonstrate a significant difference in patient-reported hand function between the replantation group and the revision group (p=.43) or the delayed reconstruction group (p=.29). Moreover, those who perceived their replantation or delayed reconstruction to be successful (n = 16) responded more positively on the bMHQ compared to those who did not consider it a success (n = 14). The mean normalized score for the former group was 70.18 compared to 55.95 for the latter (p=.01). Linear regression models failed to find a difference in bMHQ scoring when controlling for independent patient variables (sex, level of education, race, etc.).

Table 8. Brief Michigan Hand Questionnaire (bMHQ)

Overall		Replantation/ Revascularisation		Revision amputation		Delayed reconstruction	
Score range	Number of patients (%)	Score range	Number of patients (%)	Score range	Number of patients (%)	Score range	Number of patients (%)
100	0 (0)	100	0 (0)	100	0 (0)	100	0 (0)
90-99	0 (0)	90-99	0 (0)	90-99	0 (0)	90-99	0 (0)
80-89	1 (3.33)	80-89	1 (6.25)	80-89	0 (0)	80-89	0 (0)
70-79	13 (43.33)	70-79	7 (43.75)	70-79	2 (25)	70-79	4 (66.66)
60-69	8 (26.67)	60-69	4 (25)	60-69	2 (25)	60-69	2 (33.33)
50-59	3 (10)	50-59	2 (12.5)	50-59	1 (12.5)	50-59	0 (0)
40-49	3 (10)	40-49	1 (6.25)	40-49	2 (25)	40-49	0 (0)
30-39	0 (0)	30-39	0 (0)	30-39	0 (0)	30-39	0 (0)
20-29	1 (3.33)	20-29	1 (6.25)	20-29	0 (0)	20-29	0 (0)
10-19	1 (3.33)	10-19	0 (0)	10-19	1 (12.5)	10-19	0 (0)
0-9	0 (0)	0-9	0 (0)	0-9	0 (0)	0-9	0 (0)
Raw Score Average	Normalized Score Average	Raw Score Average	Normalized Score Average	Raw Score Average	Normalized Score Average	Raw Score Average	Normalized Score Average
42.50	63.54	44.81	68.36	41.75	61.98	46.67	72.22

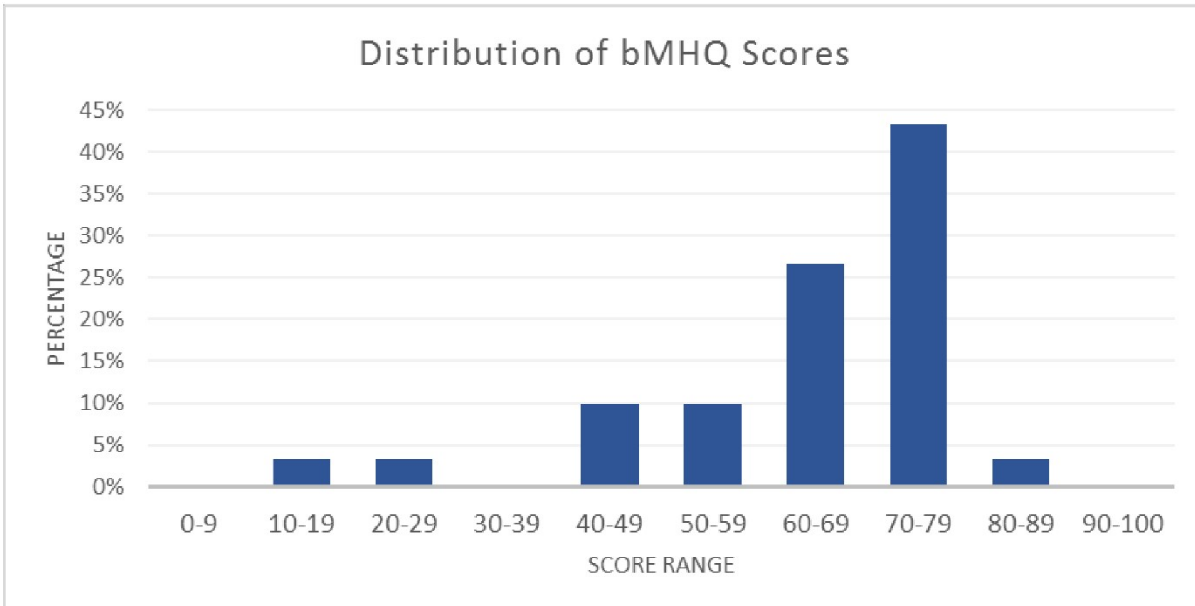


Figure 4. Distribution of baseline hand function as reported on the brief Michigan Hand Questionnaire (bMHQ).

1.1.3.3 Factors Influencing Decision-Making

Overall, more than 87% of patients strongly agreed or agreed that the consequences of a failed free toe transfer (amputated thumb and toe) constituted an important argument why some patients might opt out of this operation. The other two elements of decision-making where more than half of participants agreed had a negative impact on selecting free toe flaps were the lack of understanding of risks/benefits (80%) and the prolonged hospital stay (53%). In contrast, four elements were not estimated to be important factors by more than 50% of patients, namely religious/cultural beliefs (90%), aesthetic appearance of the foot postoperatively (80%), concerns about footwear (79%) and complexity of rehabilitation (73%%). All other elements of questioning were associated with an equal distribution of patients agreeing or disagreeing with the argument (Figure 5).

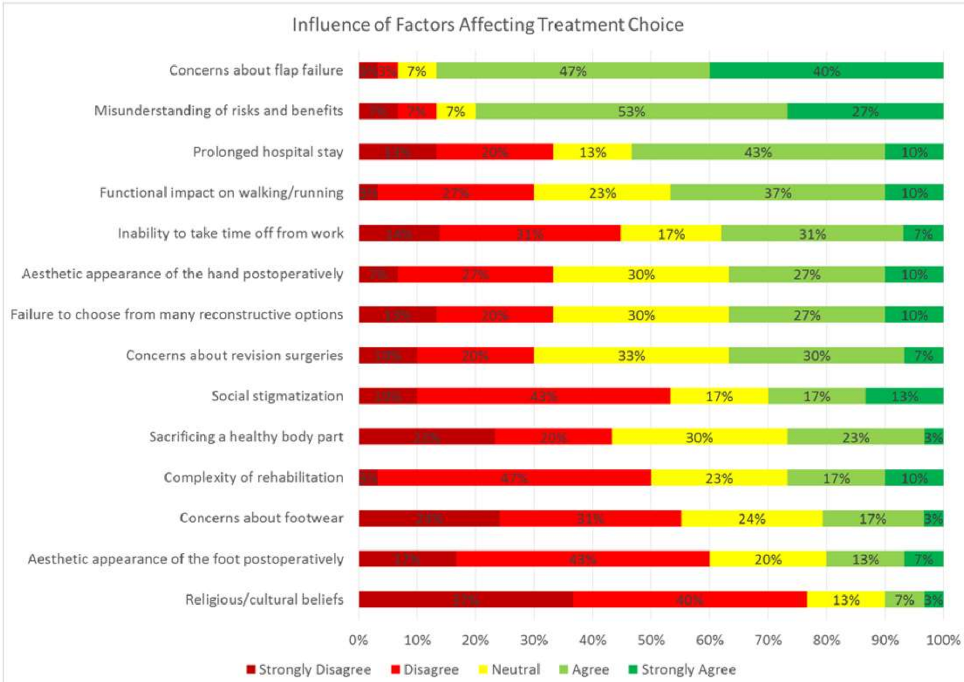


Figure 5. Bar chart demonstrating the influence of several factors on the decision-making process of undergoing a free toe transfer.

When analyzing participants according to the type of treatment received, the replantation group also believed that concerns about flap failure (87.5%), lack of understanding of risks and benefits (75%) and prolonged hospital stay (56.25%) represented important factors influencing the decision to undergo a free toe flap. In comparison, patients who had revision amputations unanimously ranked the lack of understanding in risks and benefits (100%) as the principal element of decision-making, followed by concerns about flap failure (87.5%) and functional impact on walking (75%) in that order. Finally, patients with delayed reconstruction after thumb amputation reported concerns about flap failure (83.33%) and lack of understanding of risks and benefits (66.67%) as the top two elements, following by prolonged hospital stay, failure to choose from many reconstructive options and complexity of rehabilitation in third place (50%). The breakdown of other factors influencing decision making can be found in Table 9.

Table 9. Percentage of participants who consider these factors to influence the decision of undergoing a free-toe-transfer according to the type of treatment previously received

	Replantation Revascularisation (n=16)	**Revision Amputation (n=8)**	**Delayed Reconstruction (n=6)**
Concerns about flap failure	87.5%	87.5%	83.33%
Lack of understanding of risks and benefits	75%	100%	66.67%
Prolonged hospital stay	56.25%	50%	50%
Functional impact on walking/running	37.5%	75%	33.33%
Inability to take time off from work	43.75%	50%	16.67%
Aesthetic appearance of the hand postoperatively	37.5%	50%	16.67%
Failure to choose from many reconstructive options	37.5%	25%	50%
Concerns about revision surgeries	37.5%	50%	16.67%
Social stigmatization	37.5%	37.5%	0%
Sacrificing a healthy body part	31.25%	37.5%	0%
Complexity of rehabilitation	31.25%	0%	50%
Concerns about footwear	18.75%	25%	16.67%
Aesthetic appearance of the foot postoperatively	6.25%	50%	16.67%
Religious/cultural beliefs	12.5%	12.5%	0%

1.1.3.4 Utility outcome measures

On average, patients with a history of thumb amputation were willing to accept a death occurring 7 years prematurely for a 80-year life expectancy in order to regain a functioning thumb with a free toe transfer, which translates into a time trade-off utility score of 0.8600 (Figure 6). The minimum time trade-off was 0 years in two patients and the maximum time traded for improved health was 25 years in one patient. With the standard gamble, participants tolerated a mean failure rate of 10.33% in order to have an improved function of the thumb with a free toe flap for the rest of their lives, which provides a utility score of 0.8967 (Figure 7). The minimum gamble was scored at 0% in two patients and the maximum was evaluated at 30% in three patients.

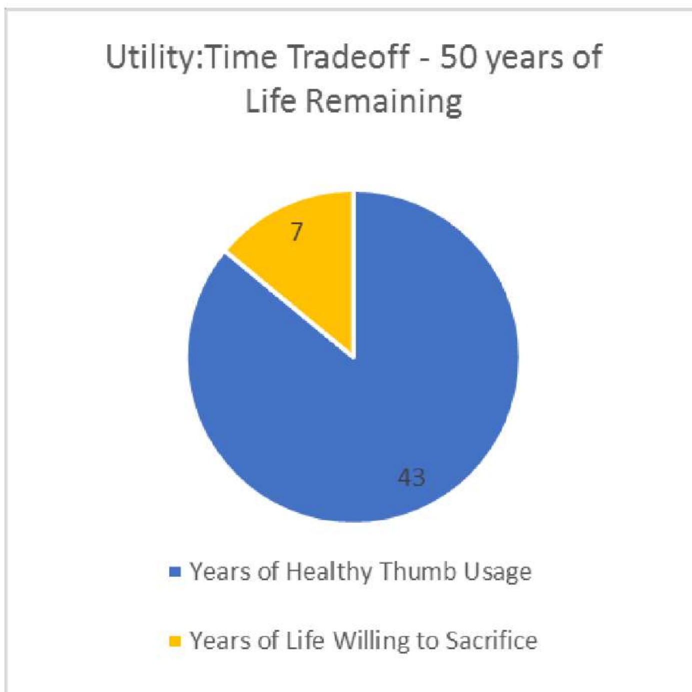


Figure 6. Average score of utility for free toe transfers as determined by the “time trade-off” technique.

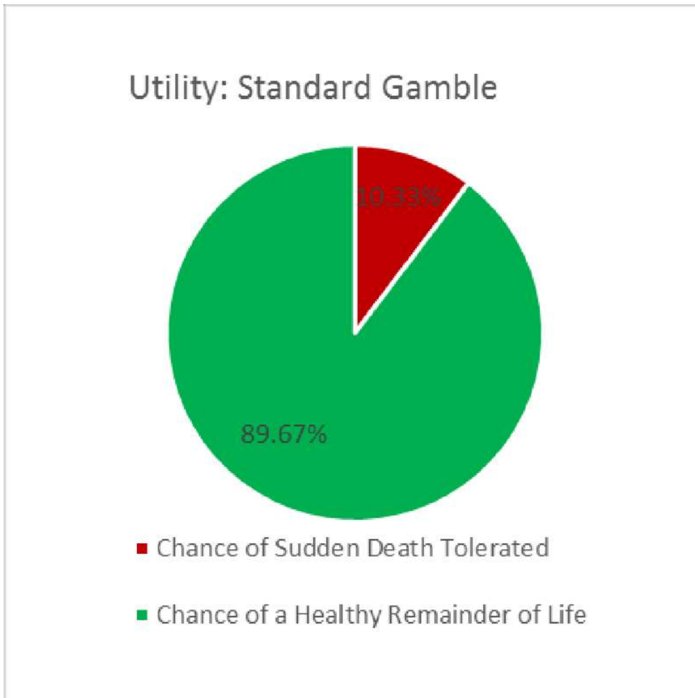


Figure 7. Average score of utility for free toe transfer as determined by the "standard gamble" technique.

When analysed according to subgroups of treatment, no statistically significant differences were found between those treated with a replantation, versus a revision amputation (p = 0.18 for time trade-off, p = 0.25 for standard gamble) or versus a delayed reconstruction (p = 0.80 for time trade-off, p = 0.71 for standard gamble) (Table 10). Other independent risk factors associated with patient characteristics (sex, race, level of education, income, etc.) were not found to be associated with a change in the utility score.

Table 10. Utility of free toe transfers according to the type of treatment received after a thumb amputation

	Time Trade-Off	P Value	Standard Gamble	P Value
Replantation/Revascularisation Group	0.8813		0.9063	
Revision Amputation Group	0.7875	0.18	0.8563	0.25
Delayed Reconstruction Group	0.9	0.80	0.925	0.71
All patients	0.86		0.8967	

1.1.4 Discussion

The great toe flap is an innervated osteo-cutaneous flap based on the first dorsal or metatarsal artery and considered by many as the gold standard for reconstruction of the thumb amputations (202). However, donor site morbidity is not insignificant, with plantar callus formation (29%), weakness in push-off (28%) and delayed wound healing (18%) being the three most common complications reported in a systematic review (207). A patient misconception is that free toe flaps might interfere with foot function and gait on walking/running, which was refuted by Lipton et al. who demonstrated that average velocity, cadence, step length, limb stance and step width did not change significantly after the operation (203). In our study, concerns about foot function upon walking/running ranked fourth amongst factors influencing patients to not undergo a free toe transfer, with 47% agreeing with this statement, 23% being neutral and 30% disagreeing. It can be hypothesized that surgeons who spend more time reassuring patients about donor site morbidity by emphasizing positive outcomes obtained in previous studies might be able to offer this procedure to a greater proportion of patients (21,204).

Another limiting factor with free toe flaps is the possibility of flap failure. With overall survival rates reported to be 97% for the great toe (93% for the second toe) (207), this procedure does not have a higher risk of failure when compared with other free flap reconstructions reported in the literature. Yet, concerns about the consequences of a failed toe flap constitutes by far the most important reason why one would elect not to undergo this type of operation, wherein 40% of patients strongly agreed and 47% agreed with this statement. It is reasonable and fundamental to patients' autonomy to opt out of a surgical procedure due to concerns about potential consequences. The surgeon's responsibility is to provide the patient with the appropriate data to make an informed consent and to discuss about the balance between the 3% risk of failure reported in the literature and the functional benefits one might gain from. Additionally, the specific causes for concerns about the risk of failure should be investigated during initial consultation and alternatives can be offered to minimize the sacrifice of a great toe, such as wraparound flaps (205) or second-toe-transfers (206).

Increased length of hospitalization (53%), prolonged time off work (38%) and concerns about future revision surgeries (37%) have been postulated as plausible reasons why one might elect not to undergo a free toe transfer in this study. Venkatramani et al. reported that patients are generally hospitalized for 10 to 14 days after the surgery (207). In their patient population, geographical distances and lack of outpatient community resources play a role in the prolonged hospitalization, whereas in our experience patients are expected to be discharged within 7 days if no complications occur. Similarly, they found that 71% of patient were able to return to the same occupation. Understanding all aspects pertaining to the length of hospitalization and postoperative rehabilitation is a crucial concept to address during the initial consultation. To the same extent, patients should be aware that revision surgeries can occur in the short and long-term. One solution to minimize these subsequent procedures has been described, which is to perform an interim groin flap to temporarily cover soft tissue defects of the thumb in order to allow for education and preoperative evaluations of a free toe transfer. Lam et al. argued that a staged reconstruction is beneficial in order to avoid shortening vital structures of the thumb, skin grafts on the hand, size of flap harvest and need for local flaps (208).

In this study, 80% of patients believed that a lack of understanding of the benefits and risks of a free toe transfer constituted a major reason for electing not to undergo this surgery. Previous studies performed on surgical patients have demonstrated that there is positive correlation between the degree of perceived benefit and the degree of perceived risk (209). Emphasizing these elements during the initial consultation might improve patients' understanding of the procedure. Also, more than a third of participants believed that failure to choose from many reconstructive options would influence their decision to undergo a free toe transfer. Once again, this underlines the idea that clarity in preoperative explanations is paramount and surgeons can improve in that regard by simplifying terminologies, providing written material to sustain 'recall memory', offering educational video tools and performing the 'repeat back' method during informed consent (210).

Interestingly, certain elements of decision-making did not constitute hurdles to proceeding with a free toe transfer. For example, the role of religious or cultural beliefs was not considered an important factor affecting treatment choice. In 2016, Shauver et al. demonstrated that Japanese surgeons were more likely to recommend replantation, rated the appearance of a hand with an amputated finger as poorer and reported more often stigmatization against finger amputees than their American colleagues (211). Considering that historically a significant portion of the literature pertaining to free toe transfers is authored from Asia and that our study population was mostly represented by patients of Caucasian descent, it would be interesting to investigate whether other races and cultures produce similar findings as those reported in this study.

Patient satisfaction with free toe flaps has been described to be greater with great toe flaps as opposed to second toe transfers for functional and aesthetic considerations, but lower for donor site (207). Chung et al. recorded MHQ scores in patients with toe transfers compared with thumb amputations, reporting significantly better hand function, activities of daily living, work performance, aesthetics and satisfaction (overall score 80.7 in toe transfer patients as opposed to 53.2 in controls) (216). The MHQ value from controls with thumb amputations compares with the results obtained in our study, where the raw score average was 42.5 and the normalized score average was 63.5. The gain in patient-reported outcomes measures with a free toe flap should be addressed with potential candidates, especially considering that 80% consider “lack of understanding of risks and benefits” as a major hurdle to this thumb reconstruction option.

Furthermore, utilities scores recorded in this study indicate that patients with thumb amputations are willing to accept a death coming 7 years early and tolerate a 10.33% risk of failure in order to have improved function of their hand with a free toe transfer. This translates into a time trade-off utility score of 0.86 and a standard gamble utility of 0.8967. In comparison, utility scores for bilateral hand amputation and transplantation were calculated at 0.63 and 0.69, respectively (122). Considering that most hand conditions have been shown to have utilities of less than 0.80 in a systematic review of hand surgery procedures (211), our study demonstrates that free toe transfers are perceived as better health states.

Certain limitations of this study need to be addressed. First of all, our in-house questionnaire about possible arguments against free toe transfers has not been standardized or validated.

Elements investigated in this study were provided by a group of surgeons performing the aforementioned procedure and produced this questionnaire based on their experience. Therefore, some elements might have been missed and others might not apply to all settings and cultures. Second of all, the group of participants was heterogeneous, with patients having benefitted from immediate replantation, others with revision amputation of the thumb and a portion with delayed secondary reconstructions. Even though the subgroup analysis demonstrated similar answers in the decision-making questionnaire, there were not enough patients to determine if these similarities were statistically significant amongst subgroups of treatment. Finally, our response rate of 58% is considered low and could reflect a selection bias. However, this rate should be analysed in the context of our regional replantation program, where some patients from distanced geographical locations might be less inclined to respond to the questionnaires by mail. Reporting point of views from 30 patients with a history of amputated thumbs is the largest study performed on this patient population and possesses nonetheless a teaching value for surgeons who wish to propose free toe transfers as a reconstructive option.

1.1.5 Conclusion

Free toe transfers constitute a workhorse flap for the reconstruction of amputated thumbs. This study shines a light on the importance of understanding factors that might influence patients' decision-making when considering this procedure. Surgeons can improve several areas of perception about free toe flaps by focusing on patients' concerns about flap failure, lack of understanding of the risks and benefits and consequences of a prolonged hospital stay .

Chapter 2: Utility of hand transplantation and myoelectric prostheses

2.1 Applying Health Utility Outcome Measures and Quality-Adjusted Life Years to Compare Hand Allotransplantation and Myoelectric Prostheses for Upper Extremity Amputations

Published in Plastic and Reconstructive Surgery, May 2021

Authors and affiliations :

Johnny Ionut Efanov, MD[1]; Ali Izapanah, MD MSC[1]; Joseph Bou-Merhi, MD[1]; Samuel J. Lin, MD MBA[2]; Michel A. Danino, MD PhD[1].

[1] Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada

[2] Beth Israel Deaconess Medical Center, Boston, MA, USA

Statement of authorship:

Design of study: JIE

Conduct of the study: JIE

Data analysis: JIE

Writing manuscript: JIE

Manuscript revision: JIE, AI, JBM, SJL, MAD

Corresponding author:

Michel Alain Danino, MD PhD (michel.alain.danino@umontreal.ca)

2.1.1 Introduction

Few will dispute the devastating consequences of suffering an upper extremity amputation, an event that can certainly be considered as life-changing. In comparison with fingers and lower extremities, the prevalence of severed proximal upper limbs only account for 0.02% of all amputations and 8% of major amputations (4). Moreover, the treatment options for hand and upper extremity amputations are more limited and complex.

Some have argued that hand transplantation constitutes the only available procedure to treat proximal amputations (122). Since the first successful vascularized composite allotransplantation (VCA) (38), roughly 150 recipients have undergone this revolutionary operation with promising results, albeit lifelong immunosuppression, graft rejection, complex rehabilitation, risk of death, and cost remain major hurdles (212). Concurrently, another treatment modality has made breakthroughs in the form of myoelectric prostheses capable of replicating precise functional movements with increased degrees of freedom and, more recently, providing even sensory feedback to the patient (213,214,215). Unfortunately, obstacles to widespread use persist in the form of financial burden, lifelong device maintenance, and high rates of abandonment (147).

Seemingly, the tug of war between VCA and myoelectric prostheses as the gold standard for hand amputations is not yet resolved. While awaiting surgical and technological advancements, regulatory bodies in charge of healthcare resource allocations will look for cost-benefit analyses comparing both treatments. Utility measures and quality-adjusted life years are well-validated components of such analyses, which are capable of capturing the impact of a treatment on a patient’s length and quality of life (170). Indeed, there is a paucity of research valuing health states of upper extremity amputation treated by VCA or by myoelectric prosthesis.

Therefore, the primary objective of this study was to compare the health utility outcome measures and QALYs of hand VCA and myoelectric prostheses. The secondary objective was to determine if there were differences between patients afflicted with a unilateral versus bilateral upper limb amputation.

2.1.2 Methods

2.1.2.1 Study Design

A survey was administered to patients who had suffered an amputation of the upper extremity from January 2004-2019. Patients were identified from a prospectively collected database and enrolled by email or in person during clinic visits. Participation in the survey was voluntary, consent was obtained prior to survey completion, and the study had approval from the institution's ethics review board in accordance with the Declaration of Helsinki.

Invitation to participate in the study was dependent on having suffered an amputation that was proximal to the level of the wrist. Only amputees with a minimum follow-up of 12 months were selected. Patients with concomitant injuries leading to upper extremity paralysis were excluded. None of the patients from this study benefitted from a vascularized composite allotransplantation or a myoelectric prosthesis (whereas most amputees included were fitted for some model of mechanical or body-powered prosthesis).

The study design separated participants into four distinct groups: bilateral amputees (Group 1), unilateral amputees (Group 2), patients with proximal replantation (Group 3), and healthy controls (Group 4). The later group was recruited from an advertisement in a university forum.

2.1.2.2 Data Collection

The survey was administered in person or by email invitation to an online SurveyMonkey form (SVMK Inc., San Mateo California). This self-reported questionnaire was comprised of five sections. In the first section, patient demographics, injury characteristics and surgical details were collected.

In the second section, the French version of the brief Michigan Hand Outcome Questionnaire (bMHQ) was administered (216). This validated tool measures hand function with a 12-item self-reported questionnaire (192). The bMHQ scores are normalized on a scale of 0 to 100, with higher numbers indicating better self-reported function and patient satisfaction.

In the third section, participants completed the Short Form Health Survey (SF-12). This questionnaire is a reduced version of the SF-36, comprised of 12 items summarized into two scales (physical and mental components) (217). It is aimed at self-reporting health-related quality of life and has been previously used in the literature for hand and wrist surgery (218,219).

In the fourth section, patients were instructed to imagine that they were 30 years-old with a life expectancy of 40 more years (death at 70 years-old). They were then asked to consider living in these four different scenarios: hand transplantation without complications, myoelectric prosthesis without complications, hand transplantation with significant complications and myoelectric prosthesis with significant complications. An image and a table with risks and benefits of each scenario was provided as previously described in the literature (220,221,222), including major complications such as vascular thrombosis, graft rejection, opportunistic infections, increased risk of malignancy and death for VCA versus prosthesis rejection (wear and use, non-compliance), maintenance/replacement of device, soft-tissue wounds/necrosis and soft-tissue/osseous infections for myoelectric prostheses. For each scenario, the utility health outcomes were measured with the visual analog scale, the time trade-off and the standard gamble techniques. Descriptions of these standardized measures are available elsewhere (223,224) and have been validated in the hand surgery literature (211,213,225). Values obtained from utility measures range from 0 (death) to 1 (perfect health), which are used to determine the quality-adjusted life years of the health state or procedure (170).

In the final section, participants were asked about the potential impact of suffering a unilateral versus bilateral amputation. They were also questioned about whether they would undergo any sort of treatment and what their preference would be between VCA and myoelectric prostheses.

2.1.2.3 Statistical Analysis

Data analysis was performed using SPSS© Version 24 (IBM™, Chicago IL). Data was presented as measures of central tendency, with means and standard deviations. A one-way ANOVA analysis was performed for each group of patients and for each scenario studied. A subgroup analysis with post-hoc tests and Bonferonni corrections was completed. Level of significance was set at a p-value of 0.05.

2.1.3 Results

2.1.3.1 Patient Characteristics

In total, there were 71 participants who completed the survey: five bilateral amputees, 12 unilateral amputees, 9 replanted patients and 45 healthy controls (Figure 8). Patient demographics and injury characteristics are presented in table 11. Only mean incomes were found to be statistically different between healthy controls and bilateral and unilateral amputees (p=.00001).

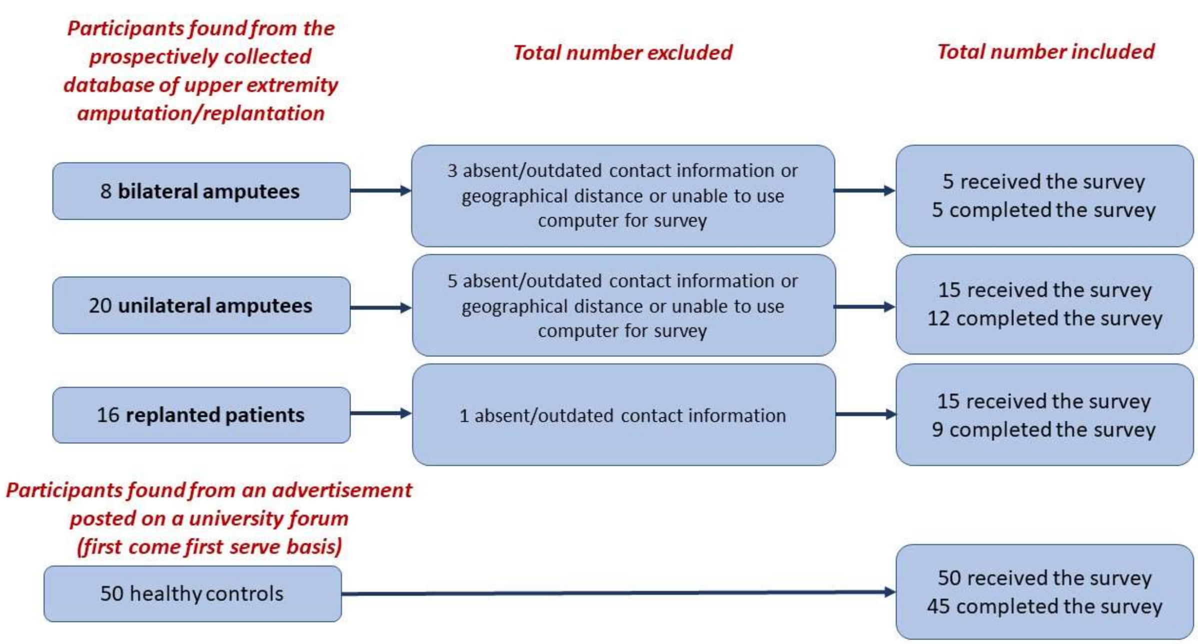


Figure 8. Flow-chart depicting exclusion and inclusion of participants in each group of the study

Table 11. Patient demographics and injury characteristics according to the group of patients

	Group 1	Group 2	Group 3	Group 4
	Bilateral amputees	Unilateral amputees	Replantation patients	Healthy controls
Patient demographics				
Mean age (+/- SD)	39.9 (+/- 10.4)	46.4 (+/- 14.4)	35.4 (+/- 11.5)	31.4 (+/- 11.0)
Male sex (%)	4 (80.0%)	11 (91.7%)	9 (100%)	25 (55.6%)
Current work (%)				
Student	0 (0%)	1 (8.3%)	1 (11.1%)	20 (44.4%)
Manual labor	0 (0%)	2 (16.7%)	0 (0%)	3 (6.7%)
Desk work	0 (0%)	7 (58.3%)	2 (22.2%)	21 (46.7%)
Unemployed/Retired	5 (100%)	2 (16.7%)	6 (66.6%)	1 (2.2%)
Mean income	14 000 $	22 500 $	51 500 $	67 500 $
Level of education				
Less than high school	1	0	2	0
High school	1	4	5	5
University	3	6	2	34
Postgraduate degree	0	2	0	6
Injury characteristics				
Level of amputation				N/A
Wrist	1	3	4	
Distal forearm	2	2	3	
Proximal forearm	0	4	2	
Elbow	1	1	0	
Proximal to elbow	1	2	0	
Mechanism of amputation				N/A
Trauma	3	9	9	
Oncologic	0	1	0	
Vascular	0	1	0	
Infectious	2	1	0	
Dominant hand amputated	5 (100%)	7 (58.3%)	4 (44.4%)	N/A

2.1.3.2 Functional patient-reported outcomes on bMHQ

Functional patient-reported outcomes yielded an average bMHQ score of 18.8, 52.1, 58.2 and 97.8 for Groups 1, 2, 3 and 4 respectively (Figure 9). Self-reported quality of life yielded scores of 31.0 (physical) and 46.1 (mental) on the SF-12 questionnaire in patients with bilateral amputations (Figure 10). In comparison, patients with unilateral amputation and those with replantation reported 40.3 (physical) with 50.9 (mental) and 41.6 (physical) with 58.1 (mental) scores respectively. These three groups scored significantly less than healthy controls on the SF-12 for the physical component (54.6, p=.0001) but not for the mental component (52.4, p=.69).

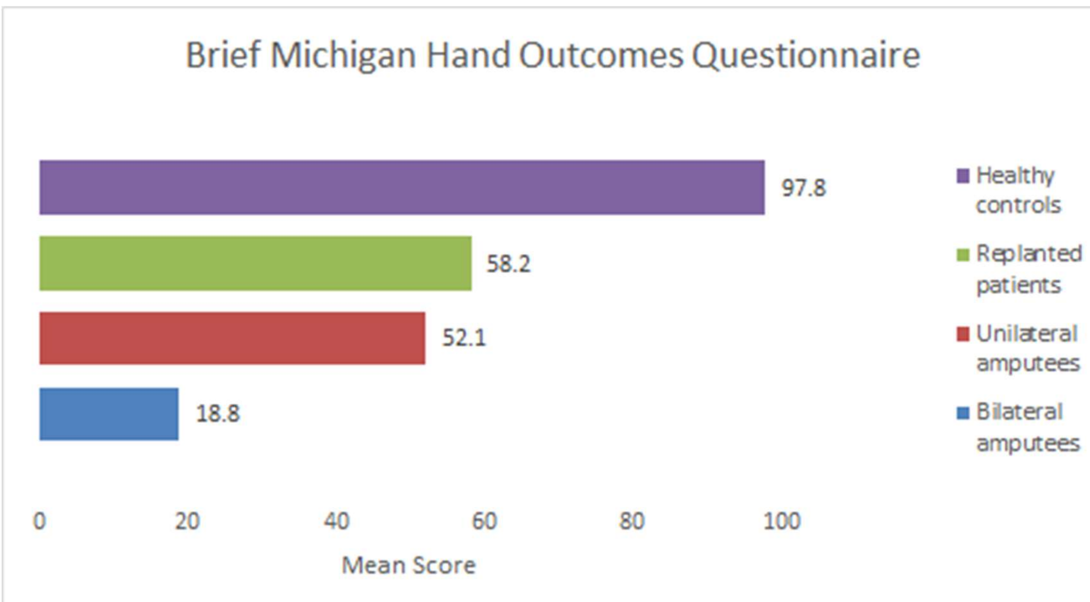


Figure 9. Functional patient-reported outcomes based on the bMHQ in each group of patients

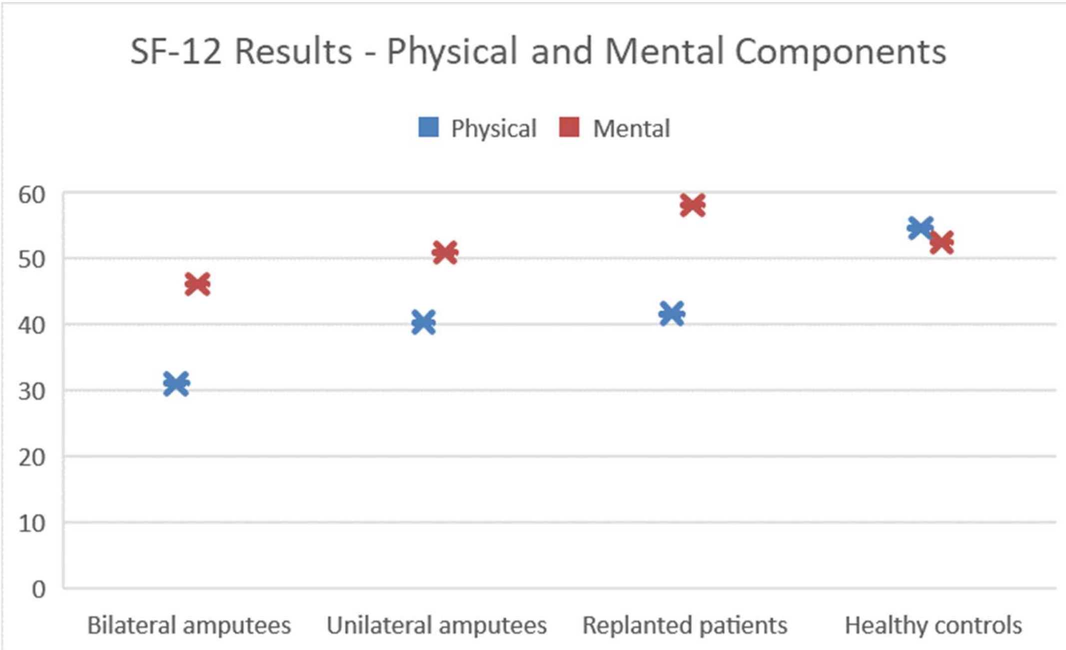


Figure 10. Self-reported quality of life as per the SF-12 questionnaire in each group of patients

2.1.3.3 Utility Measures

Utility measures of the different scenarios of treatment are depicted in Table 12. Patients with a bilateral amputation reported scores of 0.92 (VAS), 0.80 (TTO) and 0.80 (SG) for the idea of receiving a hand transplantation without complications (Scenario 1) versus 0.56 (VAS), 0.58 (TTO) and 0.51 (SG) with significant complications (Scenario 3). The difference of -0.22 between both scenarios on the time trade-off was found to be statistically significant (p=.0389). In comparison, patients with a unilateral amputation scored 0.87 (VAS), 0.83 (TTO) and 0.84 (SG) on Scenario 1 and 0.45 (VAS), 0.29 (TTO) and 0.30 (SG) on Scenario 3. Here again, the difference between both scenarios (-0.54) on the time trade-off was found to be statistically significant for patients with unilateral amputations (p<0.00001).

Table 12. Health utility outcomes measures based on the group of patients and treatments scenarios

		Group 1 Bilateral amputees	Group 2 Unilateral amputees	Group 3 Replantation patients	Group 4 Healthy controls	ANOVA
Scenario 1 Hand transplantation with no complications	VAS	0.92 +/- 0.08	0.87 +/- 0.11	0.80 +/- 0.14	0.65 +/- 0.18	P<0.00001
	TTO	0.80 +/- 0.05	0.83 +/- 0.11	0.77 +/- 0.04	0.63 +/- 0.15	
	SG	0.80 +/- 0.08	0.84 +/- 0.06	0.79 +/- 0.06	0.60 +/- 0.08	
Scenario 2 Myoelectric prosthesis with no complications	VAS	0.78 +/- 0.22	0.93 +/- 0.09	0.90 +/- 0.05	0.62 +/- 0.23	P<0.00001
	TTO	0.71 +/- 0.16	0.84 +/- 0.05	0.88 +/- 0.07	0.52 +/- 0.06	
	SG	0.68 +/- 0.11	0.81 +/- 0.05	0.83 +/- 0.05	0.51 +/- 0.07	
Scenario 3 Hand transplantation with complications	VAS	0.56 +/- 0.20	0.45 +/- 0.12	0.44 +/- 0.15	0.40 +/- 0.14	P<0.00001
	TTO	0.58 +/- 0.08	0.29 +/- 0.13	0.34 +/- 0.11	0.26 +/- 0.09	
	SG	0.51 +/- 0.04	0.30 +/- 0.11	0.32 +/- 0.10	0.24 +/- 0.04	
Scenario 4 Myoelectric prosthesis with complications	VAS	0.61 +/- 0.18	0.55 +/- 0.14	0.68 +/- 0.19	0.46 +/- 0.17	P<0.00001
	TTO	0.52 +/- 0.14	0.45 +/- 0.08	0.55 +/- 0.05	0.27 +/- 0.07	
	SG	0.50 +/- 0.13	0.42 +/- 0.06	0.53 +/- 0.08	0.24 +/- 0.05	
ANOVA		P= .0065	P<.00001	P<.00001	P<.00001	

VAS: visual analog scale, TTO: time trade-off, SG: standard gamble

Post-hoc tests based on TTO demonstrating statistically significant differences:

Group 1: Scenario 1 vs 3 (p=.0389) / Scenario 1 vs 4 (p=.0076)

Group 2: Scenario 1 vs 3 and 4 (p<.00001) / Scenario 2 vs 3 and 4 (p<.00001) / Scenario 3 vs 4 (p=.0012)

Group 3: Scenario 1 vs 2 (p=.0151) / All other scenarios head-to-head (p<.00001)

Group 4: All scenarios head-to-head (P<0.00001) except Scenario 3 vs 4

Scenario 1: Group 1 vs 4 (p=.0368) / Group 2 vs 4 (p=.0001) / Group 3 vs 4 (p=.0233)

Scenario 2: Group 1 vs 2 (p=.0046) / Group 1 vs 3 (p=.0003) / Group 4 vs all others (p<.00001)

Scenario 3: Group 1 vs 2 (p<.00001) / Group 1 vs 3 (p=.0003) / Group 1 vs 4 (p<.00001)

Scenario 4: Group 4 vs all others (p<.00001)

For the scenarios with myoelectric prostheses, patients with a bilateral amputation scored 0.78 (VAS), 0.71 (TTO) and 0.68 (SG) if there were no complications (Scenario 2) versus 0.61 (VAS), 0.52 (TTO) and 0.50 (SG) if there were significant complications (Scenario 4). However, the difference in utility measures between these two scenarios did not reach statistical significance (-0.19, p=.08). On the other hand, patients with a unilateral amputation reported utilities of 0.93 (VAS), 0.84 (TTO) and 0.81 (SG) in Scenario 2 and 0.55 (VAS), 0.45 (TTO) and 0.42 (SG) in Scenario 4, which was found to be a statistically significant difference (-0.39, p<0.00001).

When analyzing utility outcome measures of patients who have received an upper extremity replantation in the past, the values on the VAS, TTO and SG are 0.90, 0.88 and 0.83 respectively for the scenario of living with a myoelectric prosthesis without complications. These values are significantly higher than patients who have suffered from a bilateral amputation (-0.17, p=.0003) but similar to those with a unilateral amputation (-0.04, p=.14). When measuring the utility of hand transplantation with no complications in this same group of replanted patients, the outcomes were inferior to those with bilateral and unilateral amputations, with a VAS of 0.80, a TTO of 0.77 and a SG of 0.79, although not found to be statistically significant (+0.03, p=.24).

Lastly in the group with healthy controls, utility outcomes measures were lower than the other Groups in all 4 scenarios. For example, living with a hand transplantation subjected to complications yielded 0.40 (VAS), 0.26 (TTO) and 0.24 (SG) of utility and living with a myoelectric prosthesis with complications produced utilities of 0.46 (VAS), 0.27 (TTO) and 0.24 (SG). Both of these scenarios are significantly lower than the group composed of bilateral amputations (+0.32, p<0.00001 for Scenario 3 and +0.25, p<0.00001 for Scenario 4).

2.1.3.4 Quality-adjusted life years

The utility outcomes measures for each group and each treatment scenario was used to calculate quality-adjusted life years, as depicted in Table 13**.** The highest QALYs were obtained in the group with replantation patients for Scenario 2 (myoelectric prosthesis without complications), with a mean QALY of 34,8. The lowest QALYs were measured in healthy controls for Scenario 3 (hand transplantation with complications), representing a mean QALY of 12. When measured as mean QALYs for all patients/participants regardless of subgroups, there was no statistically significant difference between hand transplantation and myoelectric prosthesis (p=,36). However, when analyzed as subgroups, patients with a unilateral amputation and those who had received a replantation procedure reported higher QALYs for myoelectric prostheses rather than VCA (+6,4, p=,0015 and +8,4, p=,0001 respectively). Patients with a bilateral amputation and healthy controls did not report any significant difference in QALYs between both treatments (-2,4, p=,299 and +0,4, p=,58 respectively).

Table 13. Quality-adjusted life years based on the group of patients and the treatment scenario

		Group 1 Bilateral amputees	Group 2 Unilateral amputees	Group 3 Replantation patients	Group 4 Healthy controls	Mean
Scenario 1 Hand transplantation with no complications	VAS	36.8	34.8	32	26	32.4
	TTO	32	33.2	30.8	25.2	30.3
	SG	32	33.6	31.6	24	30.3
Scenario 2 Myoelectric prosthesis with no complications	VAS	31.2	37.2	36	24.8	32.3
	TTO	28.4	33.6	35.2	20.8	29.5
	SG	27.2	32.4	33.2	20.4	28.3
Scenario 3 Hand transplantation with complications	VAS	22.4	18	17.6	16	18.5
	TTO	23.2	11.6	13.6	10.4	14.7
	SG	20.4	12	12.8	9.6	13.7
Scenario 4 Myoelectric prosthesis with complications	VAS	24.4	22	27.2	18.4	23
	TTO	20.8	18	22	10.8	17.9
	SG	20	16.8	21.2	9.6	16.9

QALY: measured by multiplying number of years left stated treatment (40 years) by the utility measure of that procedure, VAS: visual analog scale, TTO: time trade-off, SG: standard gamble

2.1.3.5 Patient preferences

Finally, patient preference was recorded and depicted in Figure 11. If participants had to suffer a unilateral amputation, 33% would not be able to continue their current job, 92% would want treatment in the form of hand transplantation or myoelectric prosthesis and 28% consider hand transplantation to be the superior to myoelectric prosthesis. In comparison, if participants were to suffer from a bilateral amputation, 79% would need to change jobs, 100% would choose some form of treatment and 44% would consider hand transplantation to be superior. In terms of patient preferences, hand transplantation was found to be superior to myoelectric prosthesis only in the group with bilateral amputees at 60% for a unilateral amputation and at 100% for a bilateral amputation.

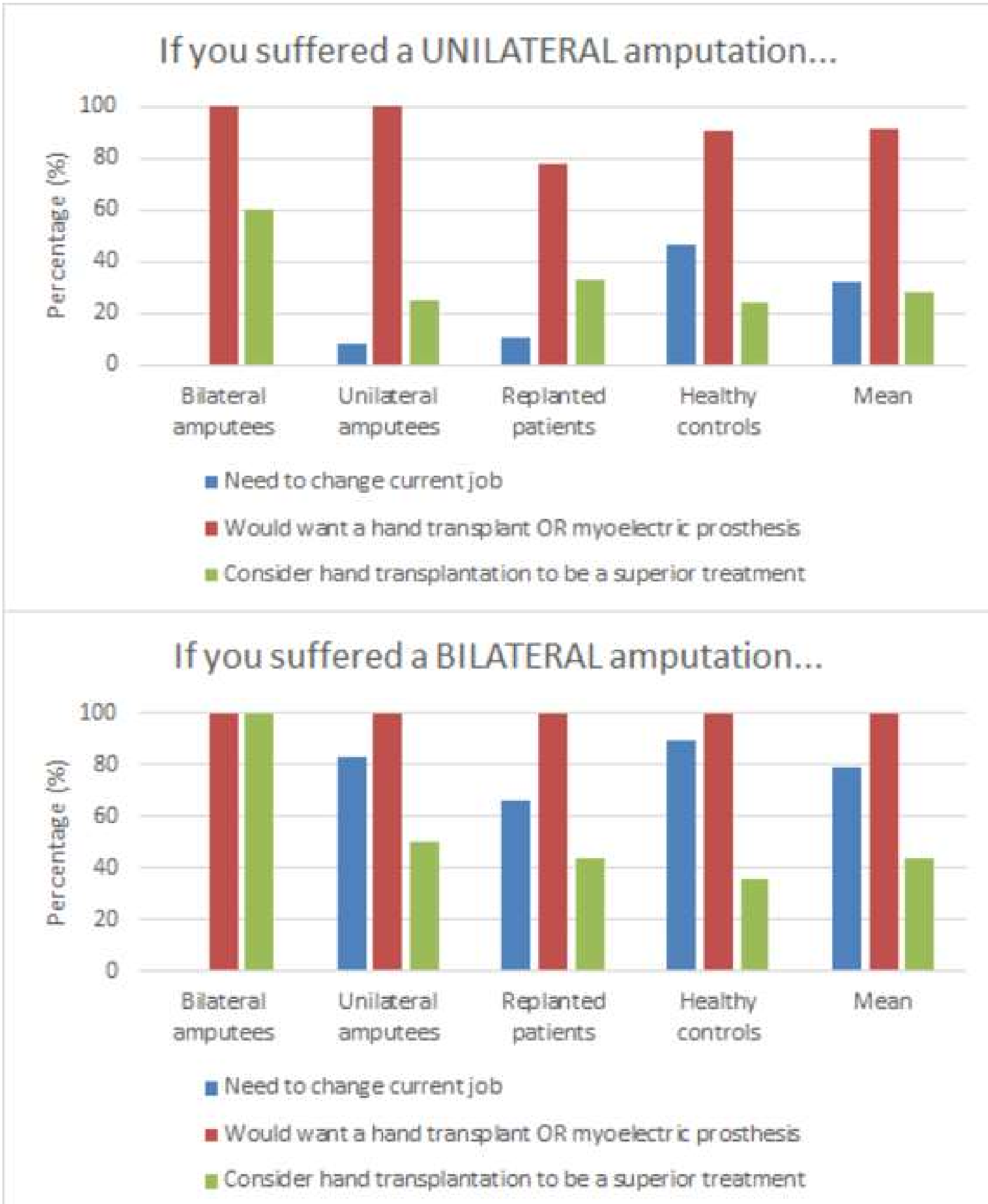


Figure 11. Impact of unilateral versus bilateral amputation and patient preference for treatment with hand transplantation versus myoelectric prosthesis in each group of patients

2.1.4 Discussion

Comparing hand transplantations with myoelectric prostheses as the gold-standard for upper extremity amputees is a difficult endeavor. Indeed, indications are constantly evolving, surgical techniques and technological advances continue to be refined, treatment outcomes aimed to be compared are numerous, and long-term results have yet to be published for large cohorts. Furthermore, some have argued that both treatments should not be viewed as competing, but rather as separate modalities with different pros and cons (226). Adding the arguments of a relatively low prevalence of upper extremity amputations, of few centers capable of offering both treatments and of limited healthcare resources, one can appreciate the reason behind the paucity of comparative studies and the lack of consensus in the literature.

To the best of our knowledge, only one other study has directly compared hand VCAs with myoelectric prostheses in 2016 (227). In this multicenter cohort study, five patients with transplanted hands were compared with seven patients with prostheses using functional patient-reported outcomes and quality of life questionnaires. The authors failed to demonstrate any significant difference in function or quality of life, except for sub-scales of the SF-36 where hand VCAs scored better for "role-physical", "vitality", "role-emotional" and "mental-health".

While waiting for comparative outcome measures for these two treatments, this pilot study is the first to compare utility and QALYs between hand transplantation and myoelectric prosthesis. Previous studies have only looked at utility of hand transplantation alone, of which none have compared results between patients with bilateral amputations, unilateral amputations, replantation and healthy controls (7,122,212,228,229) and no previous study has measured utility and QALYs for myoelectric prosthesis.

In a survey administered to one hundred medical school students, Chung et al. reported that prosthetics yielded superior QALYs for unilateral amputations (30,00 vs 28,81) whereas transplantation was favored for bilateral amputations (26,73 vs 25,20) (122). In comparison with our study, patients with unilateral amputations also favored myoelectric prostheses over transplantations (QALY +6,4, p=,0015), whereas no difference was found for patients with bilateral amputations between both treatment modalities (QALY -2,4, p=,299). Furthermore, considering that the patient population surveyed by Chung et al. (medical students) using the time trade-off technique resembles those from the group of healthy controls in our study (healthy controls), we found that hand transplantation was considered superior by this population only when minor complications occurred (QALY 25,2 vs 20,8).

In 2015, Alolabi et al. measured utility outcomes with the time trade-off and standard gamble techniques for hand transplantation versus revision amputation (without myoelectric prosthesis) (212). Surveying 30 controls and 12 amputees, they found that hand amputees did not prefer hand VCA with its inherent risks, concluding that there is no clear benefit for advocating hand transplantation. The TTO-derived utility measure that they reported for amputees (TTO=0,86) is comparable with the utility found in this current study for the scenario of hand transplantation with no complications (TTO=0,83). Interestingly in our study, the utility of hand transplantation drastically diminished when calculating the inherent serious risks associated with the procedure (TTO=0,29).

Indeed, one of the most striking findings from this article is the difference in utility and QALYs when patients are required to consider the serious side effects with each procedure, resulting in a mean decrease of 15,6 QALYs for hand VCA and 11,6 QALYs for myoelectric prostheses. Based on these findings, a majority of patients and healthy controls did not have a preference between both treatment modalities when no complications would occur, whereas the risks of major complications in hand VCA was a deterrent to choosing this option over myoelectric prostheses.

Another finding from this study that merits consideration relates to the preference of myoelectric prostheses in unilateral amputees as opposed to hand transplantation in bilateral amputees. Indeed, bilateral amputees scored significantly less on Scenario 2 than unilateral amputees (utility difference -0,13, p=,0037), but scored significantly better on Scenario 3 (utility difference +0,29, p=,0004). These results highlight a preference of living with a transplanted hand despite the risk of major complications in patients with bilateral amputation, which is not reciprocated in unilateral amputees. Previous studies have also advocated for restricting hand VCA in bilateral upper extremity amputations only (84,122,230,231,232), and the results presented hereby seem to concur with this indication.

When measuring utility outcomes for any procedure, the consensus in the literature states that both patients and the general population should be included in QALY studies, rather than experts in the field (233). This constitutes the reason why the group of healthy controls was added to this study design, which we subsequently found that they reflected slightly different utility measures when analyzed as a sub-group. In fact, for all four scenarios, healthy controls had a propensity to give less value to the utility health states of both treatment modalities when compared with amputated or replanted patients. Whether the general population might underestimate the burden of living with an amputated extremity or might overestimate the disadvantages of both treatments could be a plausible explanation for this finding.

The main objective of this study was to determine if there was any difference in utility measures between hand VCA and myoelectric prostheses. When analyzing participants' responses altogether, there was no significant difference in QALYs (p=,36). However, subgroup analysis was able to demonstrate that unilateral amputees and replanted patients reported significantly better QALYs for myoelectric prostheses with or without complications (+6,4, p=,0015 and +8,4, p=,0001 respectively). Healthy controls did not consider any treatment to be superior (p=,58). Finally, bilateral amputees valued hand transplantation with major complications significantly higher than the other 3 groups (+11,3 QALYs, p=,0001)

Finally, at the end of the survey, patients and controls were questioned about their preferences if they suffered from a unilateral or a bilateral amputation. Similar to what was found with utility measures, only 28% of participants considered hand transplantation to be the superior treatment for unilateral amputees, and 44% for bilateral amputees. On subgroup analysis, only bilateral amputees reported a preference for hand transplantation over myoelectric prostheses. These findings are comparable to previously reported data from Taiwan whereby 66% of patients with replantation procedures considered bilateral amputation to be an indication for hand transplant as opposed to 27% for unilateral nondominant hand amputation (234).

Because health utility outcome measures are dependant on certain assumptions and scenarios, some limitations of this study need to be addressed. First, none of the patients with unilateral or bilateral amputations have been offered the possibility of undergoing a hand transplantation in our province, whereas some have been exposed to some degree to upper extremity prostheses (mostly body-powered) as part of their rehabilitation program. Therefore, their understanding of each treatment modality and the associated complications might be influenced. Indeed, patients who might have tried a mechanical prosthesis and abandoned it could have a different idea of how suitable a myoelectric prosthesis really is. Second, only five patients with bilateral and 12 with unilateral amputations have been included in this study. A power calculation was not undertaken in this methodology considering that the smallest significant effect size and the estimated standard deviations were not previously described in the literature for these utility treatment outcomes. Therefore, no conclusions can be drawn from this data that would demonstrate superiority of one treatment over another in terms of clinical decision making. Nonetheless, this study contains the largest sample size of amputated patients recording utility healthcare outcomes measures for myoelectric prostheses and hand VCA, and we hope that future studies will include multiple centers with a large volume of upper extremity amputees. Finally, time elapsed from injury was not taken into consideration due to the small sample size. The patients who suffered from a hand amputation several years prior might be coping better than those with recent injuries, which could be reflected in their utility scores.

2.1.5 Conclusion

This pilot study demonstrates that utility measures and QALYs do not differ significantly between vascularized composite allotransplantation of the upper extremity and myoelectric prostheses, except when analyzed as subgroups. Indeed, unilateral amputees appear to prefer myoelectric prostheses whereas bilateral amputees reported higher QALYs for hand transplantation, albeit not significantly better than myoelectric prostheses. Utility outcome measures and QALYs are useful for health authorities to make decisions for resource allocation. Findings from this pilot study are useful for researchers planning future studies comparing hand VCA with myoelectric prostheses for unilateral and bilateral upper extremity amputees.

Chapter 3: Costs of upper extremity allotransplantation and myoelectric prostheses

3.1 A Review of Utilities and Costs of Treating Upper Extremity Amputations with Vascularized Composite Allotransplantation Versus Myoelectric Prostheses in Canada

Published in JPRAS GO, March 2022

Authors and affiliations:

Johnny Ionut Efanov, MD[1], Bianief Tchiloemba, MD MSc[2], Ali Izadpanah, MD MSc[1]; Patrick G. Harris, MD[1]; Michel A. Danino, MD PhD[1].

[1] Plastic and Reconstructive Surgery Service, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada

[2] Division of Plastic and Reconstructive Surgery, University of Calgary, Alberta, Canada

Statement of authorship:

Design of study: JIE, MAD

Conduct of the study: JIE

Data analysis: JIE, BT

Writing manuscript: JIE, BT, AI, PGH, MAD

Manuscript revision: JIE, BT, AI, PGH, MAD

Corresponding author:

Johnny Ionut Efanov, MD CM FRCSC

3.1.1 Introduction

Amputations of the upper extremity can undoubtedly be considered as one of the most devastating injuries one can suffer. Used for activities of daily living, the hand is an omnipresent and powerful tool, as well as an extension of a person's identity. The burden of living with an amputated hand can be reflected in several dimensions, such as function, psychological well-being, quality of life, cosmesis, cultural or spiritual associations, societal integration, and economic considerations.

Surgical and technological advancements have nonetheless allowed for hope in expanding the armamentarium of treatment options in the amputee population. Indeed, more than 180 vascularized composite allotransplantations (VCAs) of the hand have been performed worldwide in the past 20 years, a surgical prowess that restores like-with-like physically and functionally (46). However, complications due to lifelong immunosuppression is a major hurdle in acceptability of this experimental surgery as a gold-standard treatment.

Concurrently in the same timeframe as the advent of VCAs, engineers have refined pre-existing prosthetics to become "myoelectric-based", whereby surface electrodes attached on the patient's intact proximal muscles could send signals to the device to produce specific movements with several degrees of liberty. Despite comparable functional outcomes with VCAs, myoelectric prostheses are plagued by high costs and high abandonment rates as well (147).

Because of the low prevalence of these interventions and the lack of comparative studies, none can claim superiority of one treatment over the other at this time. Considering that both interventions require considerable costs to develop and implement, and that healthcare resources are increasingly limited, the debate between hand VCAs and myoelectric prostheses needs to include a discussion about health economics.

In this article, a review of utility outcomes and costs is performed for both interventions, with the objective to determine if hand amputees would benefit more from VCAs or myoelectric prostheses in a socioeconomic model with universal healthcare such as in Canada. A secondary objective is to compare unilateral versus bilateral amputees with respect to the cost-utility of both treatment groups.

3.1.2 Methods

A review of the literature using the PRISMA guidelines was performed. Publication databases such as Embase, PubMed and Medline were employed for selection of articles. Different keywords were used for the different outcomes to be reported:

A) Prevalence of upper extremity amputations: “Prevalence”, “Incidence”, “Rate” or “Total number” AND “Upper extremity amputation”, “Hand amputation” or “Arm amputation”.
B) Costs of upper extremity amputations: “Costs”, “Financial loss” or “Economics” AND “Upper extremity amputation”, “Hand amputation” or “Arm amputation”.
C) Utilities of both interventions: “Utility”, “Utilities”, “QALY”, “Quality-adjusted life years”, “Cost-utility”, “Time trade-off” or “Standard gamble” AND “Hand transplantation”, “Upper extremity transplantation”, “Hand vascular composite allotransplantation”, “Upper extremity vascular composite allotransplantation”, “Myoelectric prosthesis” or “Externally-powered prosthesis”.
D) Costs of both interventions: “Costs”, “Economics” or “Financial” AND “Hand transplantation”, “Upper extremity transplantation”, “Hand vascular composite allotransplantation”, “Upper extremity vascular composite allotransplantation”, “Myoelectric prosthesis” or “Externally-powered prosthesis”.

Reference lists of each article were reviewed for relevance. Publications written in a language other than English were excluded. All articles pertaining to costs of either treatment within the Canadian healthcare system were reported separately. Finally, a simulation model was performed on the total costs of implementation of hand transplantation and myoelectric prostheses as nationalized programs. This simulation included potential gains from return to work and reported interventional costs multiplied by the prevalence of cases in Canada. Financial data was obtained from the Canadian governmental institution (www.statcan.qc.ca).

3.1.3 Results

3.1.3.1 Prevalence of upper extremity amputations

Few epidemiological studies quantify the problem, making it difficult to estimate the worldwide prevalence of individuals living with upper extremity amputations that are proximal to the wrist. Nonetheless, previous studies have postulated that there are more than 11.3 million unilateral amputees and 11.0 million bilateral amputees worldwide (3). However, these numbers reflect only traumatic causes of amputation and emanate from databases of high-income countries solely.

In Canada, no studies or governmental data were published specifically for hand amputees, but it is known that over 227,000 patients had suffered either a lower or upper extremity amputation as of 2013 (7). By extrapolation from previous studies demonstrating that only 3% of limb amputees involve the upper extremity (4), a ballpark number of patients would be around 6800 Canadians amputated proximal to the wrist.

3.1.3.2 Personal and societal costs of upper extremity amputations

Aside from functional and psychological consequences of living with a missing limb, upper extremity amputations provoke multifaceted repercussions from the economical and societal standpoints. In a pediatric population with major upper extremity amputations, the average length of hospital stay was 11.3 days, with a mean of 2.3 surgeries and hospitalization costs of $22,015 in 1996 (18). Knowing that healthcare spending has grown by an average of 6% per year from 1993 to 2013 (19), estimated hospital charges after an upper limb amputation could be around $59,281 in 2013.

A more recent study in 2018 found similar results, with mean hospital charges of $28,961 and a combined total cost of $166 million in the period from 1997 to 2012 (235). These numbers are probably undervalued because the authors included finger amputations with proximal upper extremity amputations, which are significantly different in terms of costs to the healthcare system.

Furthermore, neither of these studies take into consideration any rehabilitative treatments such as prostheses and long-term care. Indeed, Blough et al. estimated that veterans with upper extremity amputation spend between $31,890 and $117,440 on average on prosthetics-related expenses over 5 years, depending on injury severity (20). Another study has postulated that direct healthcare costs over a lifetime can exceed $500,000 for an amputee (247).

Another important consideration is the loss of revenue and the economic burden of social pension plans directed at upper extremity amputees. To help these patients, the *Canadian Pension Plan Disability Benefit* program (236) offers an average monthly amount of $971,23, or $349,642 for a 30-year life expectancy.

Considering that limb loss to the upper extremity occurs at an average age of 42 years (21), an amputee in Canada will live almost half of his remaining life in this state (Canadian life expectancy at birth is 81.1 years, Statistics Canada 2017 (237)). They will also be unable to contribute to the workforce for more than 22.5 years (average age at retirement in Canada is 64.5 years, Statistics Canada in 2020 (238)) at a median yearly after-tax income of $62,900 (Statistics Canada in 2019 (239)). This represents a loss of income production and taxes to the order of $1,415,250 per amputee per lifetime if they don't return to work. Multiplied by an estimated 6800 individuals currently living with this disability in Canada, the total loss of revenue would be $9.6 billion per combined lifetimes.

3.1.3.3 Utility studies in hand allotransplantation

Chung et al. was one of the first groups to publish data on the economic analysis of hand transplantation in 2010 (122). They performed a cost-utility assessment with the "*time trade-off*" (TTO) technique on one hundred medical students. The authors reported that prosthetic use generated better cost-utility over unilateral hand VCA, but that bilateral hand transplants were favored over prosthetics. However, the "*incremental cost-utility ratio*" (ICUR) of double hand allotransplantation was $318 961/QALY, which exceeded the traditionally accepted threshold of $50,000/QALY (124) (see Table 14).

Another study investigating the utility analysis of hand transplantation was described by Alolabi et al. in 2015 (212). The authors conducted QALY measurements in 30 participants from the general population and 12 amputees using the standard gamble (SG) and (TTO) techniques. They reported that the mean health utility of a hand amputation was 0.72 (SG) and 0.80 (TTO) for the general population as opposed to 0.69 (TTO) and 0.70 (SG) for amputees. In comparison, hand allotransplantation only slightly increased the utility in the general population to 0.74 (SG) and 0.82 (TTO), whereas it increased, albeit not significantly, in hand amputees to 0.83 (SG) and 0.86 (TTO). When translated into QALYs, patients with hand amputations reported increases of 7.0 (TTO) and 7.8 (SG) QALYs, as opposed to the general population with only a gain of 0.9 QALYs (See Table 14). However, the authors also reported that a decrease in life expectancy imparted a loss of 1.7 QALYs to the participants. Therefore, they concluded that there is no clear benefit to advocate for hand transplantation based on those results.

Table 14 – Comparison of cost utility studies for upper extremity VCA

Study	Study Groups	Transplantation health outcomes (QALY)/ (Health utility SG, TTO)	Standard of care health outcomes (QALY)/ (Health utility SG, TTO)	Transplantation Costs ($)	Standard of care costs: prosthetic ($)	Incremental cost-effectiveness ratio (ICER) in $
Health Quality Ontario, 2016	Unilateral amputation	10.96	11.82	735 647	61 429	*Dominated*
	Bilateral amputation	10.10	9.93	747 837	114 057	3 765 037
Alolabi et al., 2015	Hand Amputees	43.5/0.83(SG) 41.8/0.86(TTO)	35.7/0.70(SG) 34.9/0.69(TTO)	N/A	N/A	N/A
	General population	41.6/0.74 (SG) 35.7/0.82 (TTO)	40.7/0.72 (SG) 36.6/0.80 (TTO)	N/A	N/A	N/A
Brügger et al., 2010	Unilateral amputation	N/A	N/A	1 224 459 (*Lifetime cost*)	792 084 (*Lifetime cost*)	N/A
Chung et al., 2010	Unilateral amputation	28.81	30	528 293	20 653	*Dominated*
	Bilateral amputation	26.73	25.2	529 315	41 305	318 961

3.1.3.4 Previous studies on *actual* costs of hand allotransplantation

Other studies have attempted to report *actual* costs of hand VCA. In a study by Brügger et al. from Switzerland, an economic cost-model of hand VCAs was performed (121). The study found that, for a model patient of 30 years old, with a unilateral forearm amputation, undergoing hand allotransplantation at 35 years old, with a remaining life expectancy of 46.1 years, the lifetime cost would be $1,224,459. In comparison, the authors found that the lifetime cost for the same patient treated with a conventional prosthesis would be $792,084, a difference of $432,374.

In the same study described earlier from Chung et al., the authors stipulate that the actual surgical cost for a unilateral and bilateral hand transplantation would be $18,351 and $19,432 CAD, which includes preoperative evaluation, hospitalization, and physician fees (122). These values were estimated from CPT codes of forearm replantation but failed to account for several variables. The majority of remaining costs actually originates from lifetime immunosuppressive drugs and clinic visits, estimated at $576,405.

3.1.3.5 Costs of performing hand VCA in Canada

When major decisions affecting the health of Canadians are made, the *Canadian Agency for Drugs and Technologies in Health* (CADTH) requires that investigators provide a solid foundation of evidence-based medicine on the topic. One model proposed to conduct these endeavours is a *Health Technology Assessment* (HTA)" (240).

Prior to performing this technique for the first time in Canada, the provincial advisor on the quality of health care in Ontario (*Health Quality Ontario*) completed a health technology assessment (7). In their results, they report that, for a healthy adult with a 30-year lifespan, a unilateral hand allotransplantation would cost \$735,647 as opposed to \$747,837 for bilateral transplantation, both significantly more expensive than the standard of care (defined as no transplantation) calculated at \$61,429 and \$114,057 for unilateral and bilateral hand amputation respectively. When analysing quality-adjusted life-years, single-hand transplants failed to supplant standard of care (10.96 versus 11.82), whereas double-hand transplants increased effectiveness by 0.17 QALYs only (10.10 versus 9.93).

The authors also calculated the "*incremental cost-effectiveness ratio"* (ICER), which conveys how much money it would cost to gain 1 QALY from that procedure. The value was estimated to be \$3.8 million per QALY, which far exceeds the accepted threshold of \$66,516 per additional QALY reported in the scientific literature on kidney transplants (124). The *Health Quality Ontario* group further postulated that a hand transplantation program would require a budget of \$0.9-1.2 million over 3 years to treat 3 patients per year. They concluded that due to the low quality of evidence with respect to the benefits of upper extremity VCAs, both unilateral and bilateral hand allotransplantation were not cost-effective in comparison with standard of care.

Several limitations of this study on hand transplantation HTA need to be underlined. First, the calculations of QALYs on which the incremental cost-utility ratios are calculated are derived from the study by Chung et al. in 2010 (122). Considering the absence of other comparative QALY measures on hand transplant recipients and the lack of calculation of QALYs on the population represented by Health Quality Ontario, the conclusions emanating from this study suffer from low evidence. Second, the comparative group labeled as standard of care refers to patients not receiving any sort of treatment. One could argue that the current standard of care is in fact myoelectric prosthetics. The cost-utility assessment could be different if only patients with prosthetics were included in the analysis. Third, several costs were ignored or underestimated, such as the cost of rehabilitation after 2 years, the number of personnel involved in preoperative, perioperative, and postoperative care and the management of more than two major complications or any minor complication in the early and late post-transplantation phase.

3.1.3.6 Utility studies with myoelectric prostheses

Few studies reported on the utility outcome measures, the quality-adjusted life years and the cost-utility analyses specifically associated with myoelectric prostheses.

One study looking at utilities in myoelectric prosthetics was published as a conference abstract by Baltzer et al. in 2018 (241), whereby a Markov decision analytic model was used to determine the cost-utility of VCA, myoelectric prostheses, and body-powered prostheses for transradial amputations. The authors found body-powered prosthetics to be the most cost-effective option, which increased QALYs by 14.45 at a cost of $281,795 over a lifetime (ICUR of $19,501/QALY, corresponding to the acceptability threshold of less than $50,000/QALY). In comparison, myoelectric prostheses, and upper extremity VCA produced ICURs of $75,895/QALY and $780,061/QALY, respectively. However, when myoelectric devices cost less than $31,000, they became the preferred strategy of treatment. Although interesting, these results cannot be critically appraised due to the lack of methodological details provided in the conference abstract.

Our group was the first to publish utility health outcomes and QALYs associated with myoelectric prostheses in unilateral and bilateral amputees (242). Patients with a bilateral amputation reported utility outcomes of 0.71 (TTO) and 0.68 (SG) in the scenario of receiving a myoelectric prosthesis with no complications, and 0.52 (TTO) and 0.50 (SG) with complications. On the other hand, patients with a unilateral amputation demonstrated an increase in utility measures for the scenario with no complications (0.84 TTO and 0.81 SG) but a decrease when there were associated complications (0.45 TTO and 0.42 SG). When calculated as QALYs, patients with unilateral amputations and those who had sustained a replantation procedure reported significantly higher QALYs for myoelectric prostheses than hand VCA (+6.4, p=0.0015 and +8.4, p=0.0001 respectively).

3.1.3.7 Previous studies on *actual* costs of myoelectric prostheses

The literature review on actual costs of myoelectric prostheses is difficult to interpret because of the large variety of devices available on the market, the different techniques based on the level of amputation, and the need for associated surgical procedures such as "*targeted muscle reinnervation*" (TMR).

Costs of commercially available myoelectric devices encompass a wide range, with one study suggesting that it can vary between $20,000 to $100,000 (243). In a whitepaper published at the *Bioengineering Institute Center for Neuroprosthetics*, the authors report that the typical cost varies by level of amputation, with cosmetically realistic hands at $20,000-$30,000 versus full-arm neuroprosthetics at $100,000 (244).

Another study by Resnik et al. also reports similar ranges of pricing based on the *New York region Centers for Medicare and Medicaid Services* (245). Transradial and transhumeral externally powered devices cost $25,000-$50,000 and $50,000-$75,000, respectively. This corresponds to a five-fold increase in costs when compared with body powered prosthetics in the same study.

Similarly, the *Department of Veterans Affairs* in the United States reports that a myoelectric device would cost a mean of $18,703 for partial hands, $20,329 for transradial, $59,664 for transhumeral, $61,655 for shoulder and $62,271 for forequarter disarticulation (20). Additionally, the same group demonstrated with a Markov model that the 5-year projected cost for a unilateral amputee would be $31,129 to $117,440, whereas multiple limbs would increase the cost to $130,890 to $453,696. Over a lifetime model, the mean cost was calculated at $823,239.

3.1.3.8 Costs of implementing myoelectric prostheses in Canada

Only one study has been published in Canada with respect to costs of owning an upper extremity myoelectric prosthesis (246). In their work, Chan et al. retrospectively reviewed 28 amputees who had received prosthetics, either body-powered or myoelectric. Over a five-year period, the total cumulative cost to the healthcare system was $65,520 per patient. The most substantial portion of these costs occurred during the first year which includes the cost of the device, the fitting, and the intensive rehabilitation. The average annual cost was significantly higher, as expected, in myoelectric prostheses when compared to body-powered.

They report a mean number of prosthetics repair of 1.64 per year, which is more significant in transradial amputees (1.96/year) than transhumeral amputees (1.26/year) (258). There was no significant difference in number of repairs between body-powered and myoelectric prostheses, except for transradial devices whereby myoelectric technology required twice as many repairs (1.39/year versus 0.78/year). Aside from repairs, an upper limb amputee needs to make device adjustments every two years (0.49/year average).

Rates of abandonment also need to be considered in the total cost calculation. Out of 20 patients who had a follow-up of more than 3 years, 12 have not been using their initial prosthesis, including 8 body-powered and 4 myoelectric. The authors considered that the costs of these abandoned prostheses that could have been saved amounted to $305,922.

3.1.3.9 Gains from potential return to work

When analysing the cost-benefit of these interventions, the potential gains obtained from return to work need to be included in the analysis. This information is sparse in the literature for hand

VCAs and myoelectric prostheses. Only one report demonstrated return to work in 8 out of 12 (66%) transplant recipients (103). As for myoelectric prostheses, studies report rates of return to work at 80% (247).

If we assume that 66% of hand transplant recipients would return to work, the total savings in terms of loss of income and disability pension plans for 6800 upper limb amputees in Canada would be $10.04 billion for a 30-year lifespan (Figure 12). In comparison, with the assumption of an 80% rate of return to work, myoelectric prostheses would save $12.17 billion for the same 30-year lifespan in the same population.

HAND TRANSPLANT

Total costs saved = Number of potential patients X Percentage return to work X (yearly average income + yearly governmental disability pension plan) X 30-year life expectancy

Total costs saved = 6800 X 0.66 X (62 900 $ + 11 654 $) X 30 = 10,04 billion $

MYOELECTRIC PROSTHESIS

Total costs saved = Number of potential patients X Percentage return to work X (yearly average income + yearly governmental disability pension plan) X 30-year life expectancy

Total costs saved = 6800 X 0.80 X (62 900 $ + 11 654 $) X 30 = 12,17 billion $

Figure 12 – Potential total cost savings in the Canadian population if upper limb amputees underwent VCA or myoelectric prostheses over a 30-year lifespan

3.1.3.10 Cost comparisons between hand VCA and myoelectric prostheses

Using the data reviewed in this article, Figure 13 and Figure 14 demonstrate simulation models of how much it would cost for the Canadian healthcare to treat all patients with either intervention and subtracting how much would be saved from return to work in unilateral and bilateral amputees. The total number of Canadian amputees who would benefit from either intervention (n=6800) is obtained from the calculation that 3% of all limb amputations are upper limbs and that there are an estimated 227,000 amputees in Canada (4). The total lifetime cost of a unilateral ($735,647) and a bilateral ($747,837) upper extremity VCA was obtained from the study published by *Health Quality Ontario* (7). The total lifetime cost of a myoelectric prosthesis was calculated from the study published by Chan et al., approximating $65,520 for a 5-year lifespan (258). This amount was multiplied by a factor of 6 in order to determine the cost over a lifespan of 30 years, and by an additional factor of 2 in the case of bilateral myoelectric prostheses.

HAND TRANSPLANT

Total costs = Expected savings from return to work – Number of potential patients X Lifetime cost of procedure

Total costs = 10 037 950 560 $ – 6800 X 735 647 $ = + 5 035 550 960 $

MYOELECTRIC PROSTHESIS

Total costs = Expected savings from return to work – Number of potential patients X Lifetime cost of procedure

Total costs = 12 167 212 800 $ – 6800 X (65 520 $ X 6) = + 9 493 996 800 $

Figure 13 – Total costs of implementing VCAs or myoelectric prostheses in all Canadian patients with *unilateral* upper limb amputations subtracted from expected savings from return to work over a 30-year lifespan

<u>HAND TRANSPLANT</u>

Total costs = Expected savings from return to work – Number of potential patients X Lifetime cost of procedure

Total costs = 10,037,950,560 $ – 6800 X 747,837 $ = + 4,952,658,960 $

<u>MYOELECTRIC PROSTHESIS</u>

Total costs = Expected savings from return to work – Number of potential patients X Lifetime cost of procedure

Total costs = 12,167,212,800 $ – 6800 X (65,520 $ X 2 X 6) = + 6,820,780,800 $

Figure 14 – Total costs of implementing VCAs or myoelectric prostheses in all Canadian patients with *bilateral* upper limb amputations subtracted from expected savings from return to work over a 30-year lifespan

3.1.4 Discussion

To date, this is the first study comparing lifetime costs of upper extremity VCA and myoelectric prostheses.

Several limitations of this simulation model need to be addressed. First of all, it is unrealistic to suppose that all amputees would be candidates for VCA or myoelectric prostheses. Indeed, contra-indications for allotransplantation, and to a lesser extent for myoelectric prosthetics, are very stringent, such as a lack of cognitive capacity in understanding the risks and benefits, a demonstration of lack of compliance with subsequent rehabilitation, any un-addressed psychological disorders that would impair long-term success, active infection/malignancy, congenital limb absence, and more (248). Although savings in the order of billions of dollars can be accomplished if all patients were treated with one of these interventions, even a smaller percentage of eligible candidates would produce significant benefits. For example, if as little as 5% of all 6800 Canadian amputees were *actual* candidates, the expected benefits would be $250 million for hand VCA and $474 million for myoelectric prostheses.

Second of all, extrapolation of lifetime costs from the aforementioned studies (7) is probably an under-estimation of the real costs. For allotransplantation, the values used come from analytic models that did not include all associated costs related to long-term complications of immunosuppression, because the rates of these complications are still unknown. For myoelectric prostheses, the study used to make the calculations only considered the cost of the device and its maintenance but failed to include costs of rehabilitation and costs of potential complications.

Third of all, although rates of return to work have been described in the literature, none of these studies report if patients actually return to their pre-amputation work or if they require career reorientations. The expected lifetime savings from return to work are based on average income of all Canadians, which is not necessarily the same as the expected outcomes that these patients would gain if they returned to lower-pay salaries.

Finally, the total cost savings from return to work are calculated over a lifetime of 30 years. Even though most patients suffering an amputation are in their working years (average age 42 years (21)), a significant portion would not be capable to return to the workforce because of retirement age, therefore nullifying the potential monetary gains of undergoing an allotransplantation or a myoelectric prosthesis.

3.1.5 Conclusion

Although no economical model can be perfect, this article presented a review of all studies pertaining to the measurement of utility outcomes, QALYs and cost-utility analyses of upper extremity allotransplantation and myoelectric prostheses. Based on the currently available data, no consensus can be made to affirm that one procedure is superior to the other and should therefore be considered the "gold-standard". However, most utility studies demonstrate that unilateral amputees have superior outcomes with myoelectric prostheses. On the other hand, bilateral amputees continue to be adequate candidates for both interventions.

From the socioeconomic standpoint of the Canadian healthcare system, our simulation model demonstrates that significant savings can be achieved with both treatments. Here again, treatment of unilateral amputations with myoelectric prostheses would cost significantly less to the society, whereas the gap in cost savings becomes less significant in bilateral amputees. In either case, implementing these treatment programs will not be an inexpensive endeavour to accomplish.

Chapter 4: Discussion and conclusions

4.1 Feasibility of utility outcome models in upper extremity amputations

In times when technological breakthroughs are constantly emerging in medicine and surgery, critical appraisal of all facets involved in adopting a certain type of intervention over another is paramount. Health technology assessments, or HTAs, provide a systematic evaluation of properties, effects and impacts of a particular intervention (249). The purpose of these studies is to advise payers (healthcare authorities) about coverage of these treatments and to inform clinicians about the appropriate use of an intervention for a specific patient's needs and circumstances.

There are five properties required for a comprehensive HTA: technical properties, safety, efficacy/effectiveness, economics, and social, legal, ethical or political impacts (261). There are many different avenues to investigate these factors, and cost-benefit studies constitute one type of analysis aimed at performing an HTA. Decision-makers can refer to these studies when submitting to policy decisions based on economic data and clinical outcomes.

There have been very few HTAs published in the hand surgery literature, and even less for evaluating potential treatments reserved for upper extremity amputees. Considering that most patients with an amputated arm will either choose to live with the amputated stump or adopt a cosmetic or body-powered prosthesis, novel technologies and innovative surgical procedures that aim to restore function and form should be required to yield to a thorough HTA before becoming standard of care.

Because of the paucity of cases of vascularized composite allotransplantation and state-of-the-art myoelectric prostheses performed worldwide, head-to-head comparisons of these treatments constitutes a difficult task. Indeed, one has to resolve to analytic decision models that compute data about expected outcomes (including benefits and risks) and costs before truly permitting any judgment on the preferred treatment and implementing it in their healthcare system.

Models using utility outcome measures can serve this purpose. However, feasibility of performing this type of methodology in upper extremity amputees required testing on patients who had been afflicted with these burdens in the past. Thus, we conceived a pilot study investigating utility outcome measures of a restorative procedure (free-toe-flap) in a patient population who had undergone thumb replantation, revision amputation or delayed reconstructive procedures. By measuring utilities in patients with thumb amputations, we could compare these results with prior studies reflecting utility outcomes of other hand pathologies. If the utility questionnaires (VAS, TTO and SG) yielded results within a reasonable range of what was previously published for hand injuries with loss of function, then we could use the same questionnaires on a population with proximal amputations and attempt to answer the main objective of this thesis.

What was reported in this first pilot study was that patients with thumb amputations were willing to shorten their lifespan by 7 years in order to regain complete function of their thumb with a free-toe-flap, or tolerating a 10,33% risk of failure for the same purpose. In terms of utility measures, this corresponded to a TTO of 0,86 or a SG of 0,8967. Based on a previous systematic review of utilities in the hand surgery literature (211), these values were less than a Dupuytren's fasciectomy or carpal tunnel release, but more than a total wrist arthrodesis or arthroplasty. Based on these results, we were able to confirm that the questionnaires of utility outcomes that were employed were adequate, and it was therefore feasible to utilize them for investigating utilities in proximal upper extremity amputees.

4.2 Utility outcomes and QALYs for VCA and myoelectric prostheses

Several interesting observations can be made from the study looking at utility outcomes and QALYs of VCAs or myoelectric prostheses for treatment of patients with an upper extremity amputation. Decorticating the data, the following conclusions can be drawn.

First of all, as one would expect, the scenarios where significant complications occurred after either intervention (VCA or myoelectric prostheses) produced utility scores that were significantly worse than the scenarios without complications. This was true across all groups of participants, whether they were bilateral amputees, unilateral amputees, replanted patients, or healthy controls. Although obvious at first glance, what is interesting is the degree of decreased utilities. For example, patients with a unilateral amputation demonstrated a drop of 0,54 (TTO) utilities between scenarios of hand transplantation without complications and with complications (0,83 and 0,29 respectively). In other words, patients are unwilling to trade off years of life expectancy if they are subjected to significant complications of a hand transplantation. This emphasizes the need to better refine the side effects of immunosuppression in VCA before perceiving a preference in utility for this patient population. Although utilities also decreased with myoelectric prostheses across all groups of participants, the extent was less dramatic (drop of 0,39 TTO for the group of unilateral amputees, from 0,84 TTO without complications to 0,45 TTO with complications). These results also reinforce the necessity for clinicians to fully divulge all significant complications of hand VCAs and myoelectric prostheses to potential candidates during informed consent.

Second of all, the utilities reported by participants with prior proximal replantation are probably the most similar values that one could expect to obtain from patients with upper extremity allotransplantations. Indeed, functional outcomes of replanted and transplanted patients should be similar considering that the surgical technique is identical. The only difference resides in postoperative immunosuppression. Surprisingly, this group of patients preferred, in terms of utility outcomes, the scenarios with myoelectric prostheses rather than VCAs. One hypothesis explaining this finding could be that the participants from this group suffered from functional deficits after their replantation attempts, which would make them less prone to choose a similar procedure such as allotransplantations. Indeed, the patient-reported outcomes on the bMHQ in this group was low at 58,2, which is only somewhat higher than the group with untreated unilateral amputations at 52,1. Another explanation could be that replanted patients are unwilling to trade-off or gamble years of life expectancy and the associated complications, despite having lived through the potential benefits that this procedure enlisted. Although the difference between scenarios 1 and 2 (VCA with no complication and prostheses with no complications respectively) was not statistically significant, it became evident for scenarios 3 and 4 (VCA with significant complications and prostheses with significant complications respectively) that replanted patients significantly preferred myoelectric prostheses rather than allotransplantation (SG of 0,31 for scenario 3 versus SG of 0,53 for scenario 4, p=.0001).

Third of all, participants from the general population (healthy controls) reported lower utility outcomes for hand VCA and myoelectric prostheses than participants with bilateral amputation, unilateral amputation, or replantation. For an individual that has never suffered from a debilitating injury such as a hand amputation, it is understandable that the value they attribute to the utility of upper extremity VCAs and myoelectric prostheses is less than their counterparts. This finding underlines the importance of including patients afflicted with the condition, and not only healthy controls, when measuring utility healthcare outcomes.

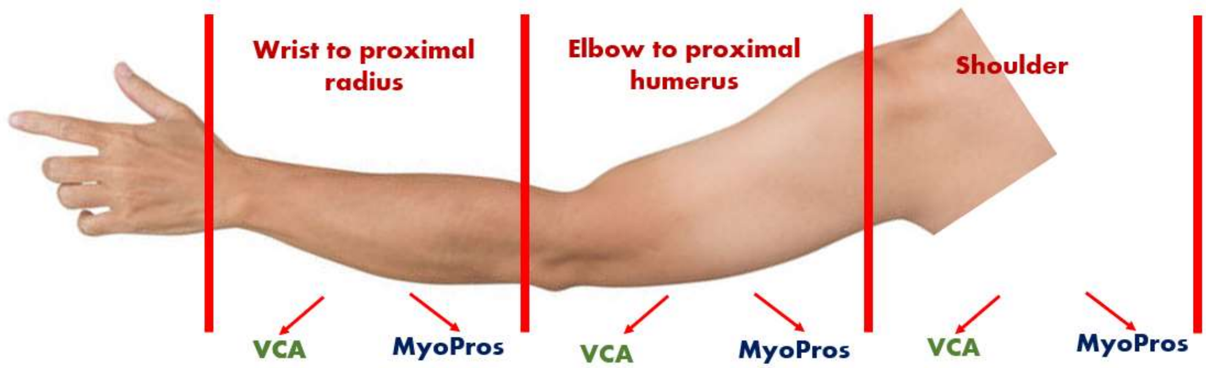
Finally, measurements of QALYs demonstrated that the highest values were obtained in replanted patients when myoelectric prostheses without complications were offered, whereas the lowest QALYs were measured in healthy controls for the scenario of hand VCA with significant complications. This study failed to demonstrate superiority of one treatment over another when all participants were analyzed as one unit (p=.36). However, subgroup analysis demonstrated interesting findings. Indeed, unilateral amputees and replanted patients reported significantly higher QALYs for myoelectric prostheses than VCAs (p=.0001). This reinforces the general opinion that unilateral amputees are not the ideal candidates for allotransplantation. On the other hand, QALYs for bilateral amputees and healthy controls did not differ significantly between VCA and prostheses (p=.58).

4.3 Indications for unilateral versus bilateral amputations

In a survey by Mathes et al., a majority of hand surgeons (78%) from the ASSH agreed that bilateral below-elbow amputations were the only indication for upper extremity VCA (84). In contrast, only 32% of surveyed surgeons agreed that a unilateral dominant hand amputation constituted an indication and close to half (45%) were altogether against any indication for allotransplantation. Initially performed on unilateral amputees, the relationship between unilateral versus bilateral cases shifted in 2008 in favor of bilateral amputees as the main indication for VCA (242).

Outcomes reported in this thesis are concordant with these trends in indications. Indeed, bilateral amputees demonstrated a slight preference in utility outcomes for hand transplantation, whether complications would occur or not. However, the higher utilities found with VCA did not reach statistical significance, thus precluding any conclusion with regards to superiority of one treatment over the other in bilateral amputees. On the other hand, patients with unilateral amputations reported significantly higher utilities and QALYs (p=.0001) for myoelectric prostheses, with or without significant complications. Based on these results, we come to the conclusion that utilities of myoelectric prostheses are superior for treatment of unilateral amputations, whereas upper extremity VCAs and myoelectric prostheses are equal for bilateral amputations.

Another consideration for indications of unilateral versus bilateral reconstruction of limbs with VCA or myoelectric prostheses is the level of amputation. From the perspective of potential functional outcomes, there are three zones of interest: below-elbow amputations (wrist and trans-radial), above-elbow amputations (elbow and trans-humerus) and shoulder amputations. Figure 15 illustrates the pros and cons of indications for upper extremity VCA and myoelectric prostheses by level of amputation.



	VCA	MyoPros	VCA	MyoPros	VCA	MyoPros
Pros	- Functional extrinsic flexors/extensors from Day 1 - Potential for intrinsic function and sensation with nerve regeneration - Best outcomes reported	- Need only two intact muscle groups for "open" and "close" hand function - Intuitive rehabilitation	- Potential forearm pronation/supination and wrist flexion/extension - "Helping hand" function only	- Potential for targeted muscle reinnervation - Better functional results	- None	- Potential for targeted muscle reinnervation - Potential for sensory nerve transfers
Cons	- Needs good shoulder and elbow function	- Needs minimum 5cm of intact ulna - Stump friction/wounds - No sensation	- More muscles to reinnervate - Longer rehabilitation - No recovery of intrinsic muscles	- Not intuitive and slow rehabilitation - Requires more electrodes and muscles groups to control 2+ joints	- No cases done - Distance for nerve regeneration too long	- Limited functional recovery - Expensive
Indications	YES	YES	MAYBE	YES	NO	MAYBE

Figure 15 – Pros and cons of VCA and myoelectric prostheses according to the level of amputation

4.4 Implementation of both interventions in the Canadian healthcare system

For both techniques to be permanently implemented in Canada and its universal healthcare system, there are several hurdles that need to be surpassed. The principal obstacle relates to the need for more research on cost-utility assessments of hand VCAs performed worldwide. With the current level of evidence in the literature, unilateral hand allotransplantations are not warranted, whereas no consensus is yet reached for bilateral hand VCAs. The second obstacle refers to agreeing on a better definition of standard of care for upper extremity amputees. Indeed, most studies compare hand VCA to mechanical prosthetics (cosmetic or body-powered) or even to no treatment at all. The advent of new generation myoelectric prosthetics mandates that comparisons of "gold standard" treatments include this technique, and as such, it will surely impact the decision model for resource allocation in this patient population.

Ultimately, the implementation of hand VCA programs and myoelectric prosthetics in Canada will depend on two factors: increased funding from third-party organizations and the population's perception of the health burden of amputees in the society. In the United States, the "Reconstructive Transplant Research" program funded by the "Department of Defense" allocated more than 81 million $ over 6 years to VCA programs across the country (250). In Canada, contributions from the "Armed Forces" could help to procure this type of treatment to hand amputees, albeit to a lesser amount than Americans. The other avenue for integration of these techniques in Canada is through research funding. Developing research programs with grants from funding agencies such as the "Canadian Institutes of Health Research" (CIHR) could facilitate VCA programs and myoelectric prosthetics to develop. Finally, societal perception of the burden of disease suffered by hand amputees requires better public awareness. In a recent survey of 1000 participants on the attitudes towards VCA, more respondents indicated that hand allotransplantation should be paid out-of-pocket rather than by government programs when compared with solid organ transplantation (251). No survey has been done looking at perception of who should pay for myoelectric prosthetics, but one can suppose it will be comparable to the later.

In this thesis, the last objective was to perform a cost-benefit analysis in the context of the socioeconomic setting of the Canadian healthcare system. Because of the lack of data published on the actual costs of previously performed upper extremity allotransplantation and myoelectric prostheses worldwide, the current evidence is based on simulation models of health technology assessments. Although imperfect, these economic analyses are the most common tools employed by healthcare regulators when deciding about the implementation of novel treatments or interventions. Table 15 summarizes the main findings that compare both treatments head-to-head with respect to costs.

Table 15 – Head-to-head comparison of costs for VCA and myoelectric prostheses

	VCA	Myoelectric prostheses
Total cost per patient for a 30-year lifespan - unilateral	735 647 $ / patient	393 120 $ / patient
Total cost per patient for a 30-year lifespan - bilateral	747 837 $ / patient	786 240 $ / patient
Total cost in Canada (6800 patients) for a 30-year lifespan - unilateral	5,00 billion $	2,67 billion $
Total cost in Canada (6800 patients) for a 30-year lifespan - bilateral	5,09 billion $	5,35 billion $
Incremental cost-utility ratios	780 061 $ / QALY	75 895 $ / QALY
Cost savings in Canada for a 30-year lifespan - unilateral	5,04 billion $	9,49 billion $
Cost savings in Canada for a 30-year lifespan - bilateral	4,95 billion $	6,82 billion $

Our findings demonstrate that a unilateral and bilateral hand transplantation would cost 735 647 $ and 747 837 $ respectively for a 30-year lifespan in a Canadian patient. In comparison, a patient that benefits from a myoelectric prosthesis would cost to the healthcare system approximately 393 120 $ for a unilateral and 786 240 $ for a bilateral device over the same time span. Based on the raw costs alone, a unilateral myoelectric prosthesis is more cost-beneficial than a unilateral hand transplantation, whereas VCA becomes more advantageous in bilateral amputees.

When analysed as a function of incremental cost-utility ratios, it would take 780 061 $ to increase the QALY of a patient by 1, whereas the ICUR plummets to 75 895 $ with myoelectric prostheses. However, both interventions surpass the accepted threshold of acceptability (66 516 $ / QALY), and as such should not be covered by taxpayers based on this cost-benefit analysis. That being stated, when the costs of producing myoelectric prostheses will decrease in the upcoming years with newer technologies such as 3D printing, ICURs may drop below the accepted threshold and could then become an argument for coverage in a universal healthcare system.

Another interesting finding from this cost-benefit study relates to the gains obtained from return to work in this patient population. Considering that the published literature reports rates of 66% and 80% of return to work for VCA and myoelectric prosthetics respectively, treating 6800 Canadians with the later intervention would produce costs savings of 2,13 billion $ over 30-years in the best care scenario. If only 5% of the 6800 Canadian amputees were treated, the cost savings with myoelectric prostheses becomes 224 million $.

Finally, when subtracting the lifetime costs of each procedure from the expected benefits, upper extremity allotransplantation would save 5,04 billion $ to the healthcare system over 30 years for a unilateral amputee and 9,49 billion $ with a myoelectric prosthesis. *Based on these results, we recommend that resource allocations for treatment of unilateral amputations should favor myoelectric prostheses*. In comparison, allotransplantations of the upper extremity and myoelectric prostheses in the bilateral amputee would save 4,95 billion $ and 6,8 billion $ to the healthcare system over 30 years. *Based on these results, both treatments demonstrate similar cost-benefits, with a slight advantage for myoelectric prostheses.*

4.5 Future directions

Many refinements can still occur with upper extremity VCAs and myoelectric prostheses. Decreasing the risk of chronic rejection through donor-specific tolerance remains the main barrier to expansion of indications for upper extremity allotransplantation. By minimizing side effects of immunosuppression in the long run, surgeons can accomplish a safer transfer with superior functional outcomes, both motor and sensory. Research in the field of VCA immunology is ongoing, with novel approaches investigating whether the immune system can tolerate the co-existence of donor and recipient cells through chimerism (252,253). Donor bone marrow and stem cells are injected during the induction therapy in order to develop tolerance to donor antigens in VCA (67). Only 1% of circulating donor lymphocytes are needed to achieve sufficient tolerance. Results published in the literature seem to demonstrate an improvement in successful graft take of VCA (254).

It is also likely that indications for VCA will expand beyond posttraumatic conditions, and include cancer patients, vascular/septic amputations, and congenital deficiencies as well. To date, there have not been any cases of upper extremity VCA performed on cancer patients, but there is a precedent in the literature of facial VCA on oncological patients. Indeed, there have been four patients with plexiform-type neurofibromatosis (benign lesions but with 10% lifetime risk of malignancy) and one patient with squamous cell carcinoma of the mouth who have received a face transplant (255). Of these, only the later succumbed to cancer recurrence. There are ethical considerations that are considerable due to the high risk of recurrence and de novo malignancy, and therefore the risk-benefit evaluation of VCA in the oncologic patient remains unacceptable at this time for non-lifesaving procedures.

Additionally, there have not been any cases of VCA for congenital deficiencies, but the closest example was achieved in an eight-year-old child who had sustained bilateral amputations of his hands after a staphylococcal sepsis at the age of two (256). Being already immunosuppressed due to a kidney transplant, this arguably constitutes the best indication for a bilateral upper extremity allotransplantation to date. The patient has reported complete recovery of function (257), which demonstrates the tremendous potential for rehabilitation in children. Whether this can be reproduced in congenital deficiencies remains to be seen, considering that cortical integration of the transplanted limb might be impossible if it was never present at birth.

On the other hand, developments in the field of myoelectric prostheses continue to blossom. Recent publications focus mainly on incorporation of pattern recognition technology and artificial intelligence. Computer algorithms based on the assumption that movement intent can be recorded from activation patterns of specific muscles have been shown to allow simultaneous control of multiple joints and thus improve task completion (258). Deep learning and artificial intelligence have also been postulated to control for the problem of feature extraction of EMG signals which would facilitate pattern recognition (259).

Another breakthrough stems from the discovery that sensory nerve fibers from transferred nerves in targeted muscle reinnervation can grow through muscles and innervated the overlying skin, allowing for sensory feedback to be transmitted from myoelectric devices. This phenomenon is termed “transfer sensation” and it corrects one of the main functional disadvantages of myoelectric prostheses compared to allotransplantation: the capacity to feel the arm/hand (163).

Future prospects of upper extremity prosthetics also include the incorporation of electroencephalograms (EEG) and electrocortograms (ECog) to supersede EMG for control of the devices (260). EEG-controlled prosthetics could use electrodes on the scalp to control movements of an upper extremity whereas ECog would use invasive electrodes inside the brain where targeted body movements would be measurable. When signal noise corrections and minimally invasive techniques for electrode placement will be developed, these techniques could be well-suited even for patients with spinal cord injury.

Finally, the most important current developments for myoelectric prosthetics reside in minimizing production costs while maximizing performance. Indeed, using low-cost materials and incorporating 3D printing technology to create bionic arms will solve the important issue of cost-benefit (261). Pushed a step forward, bioprinting is a particular approach for the fabrication of tridimensional tissues integrated into bioelectronic systems (262). This is not the realm of science fiction, but rather becoming a reality in which bioelectrodes can be personalised to an individual’s anatomy and used to control a device with the same exactitude and precision as a human hand.

Bibliography

[1] Matias CM. Edwin Boldrey and Wilder Penfield's Homunculus: From Past to Present. World Neurosurg. 2020 Mar;135:14-15.

[2] Parkes CM. Psycho-social transitions: comparison between reactions to loss of a limb and loss of a spouse. Br J Psychiatry. 1975 Sep;127:204-10.

[3] McDonald CL, Westcott-McCoy S, Weaver MR, Haagsma J, Kartin D. Global prevalence of traumatic non-fatal limb amputation. Prosthet Orthot Int. 2021 Apr 1;45(2):105-114.

[4] Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil. 2008 Mar;89(3):422-9.

[5] Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. South Med J. 2002 Aug;95(8):875-83.

[6] Nawijn F, Westenberg RF, Langhammer CG, Chen NC, Eberlin KR. Factors Associated with Primary and Secondary Amputation following Limb-Threatening Upper Extremity Trauma. Plast Reconstr Surg. 2020 Apr;145(4):987-999.

[7] Health Quality Ontario. Composite Tissue Transplant of Hand or Arm: A Health Technology Assessment. Ont Health Technol Assess Ser. 2016 Jun 1;16(13):1-70.

[8] Jang CH, Yang HS, Yang HE, et al. A survey on activities of daily living and occupations of upper extremity amputees. Ann Rehabil Med. 2011 Dec;35(6):907-21.

[9] Kooijman CM, Dijkstra PU, Geertzen JHB, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain. 2000 Jul;87(1):33-41.

[10] Geraghty TJ, Jones LE. Painful neuromata following upper limb amputation. Prosthet Orthot Int. 1996 Dec;20(3):176-81.

[11] Grob M, Papadopulos NA, Zimmermann A, Biemer E, Kovacs L. The psychological impact of severe hand injury. J Hand Surg Eur Vol. 2008 Jun;33(3):358-62.

[12] Roșca AC, Baciu CC, Burtăverde V, Mateizer A. Psychological Consequences in Patients With Amputation of a Limb. An Interpretative-Phenomenological Analysis. Front Psychol. 2021 May 26;12:537493.

[13] Meyer TM. Psychological aspects of mutilating hand injuries. Hand Clin. 2003 Feb;19(1):41-9.

[14] Tennent DJ, Wenke JC, Rivera JC, Krueger CA. Characterisation and outcomes of upper extremity amputations. Injury. 2014 Jun;45(6):965-9.

[15] Solarz MK, Thoder JJ, Rehman S. Management of Major Traumatic Upper Extremity Amputations. Orthop Clin North Am. 2016 Jan;47(1):127-36.

[16] Shue S, Wu-Fienberg Y, Chepla KJ. Psychiatric Disease after Isolated Traumatic Upper Extremity Amputation. J Hand Microsurg. 2021 Apr;13(2):75-80.

[17] Klapheke MM, Marcell C, Taliaferro G, Creamer B. Psychiatric assessment of candidates for hand transplantation. Microsurgery. 2000;20(8):453-7.

[18] Trautwein LC, Smith DG, Rivara FP. Pediatric amputation injuries: etiology, cost, and outcome. J Trauma. 1996 Nov;41(5):831-8.

[19] Amadeo K. The Rising Cost of Healthcare by Year and Its Causes. Available at: https://www.thebalance.com/causes-of-rising-healthcare-costs-4064878. Accessed August 30th, 2021.

[20] Blough DK, Hubbard S, McFarland LV, Smith DG, Gambel JM, Reiber GE. Prosthetic cost projections for servicemembers with major limb loss from Vietnam and OIF/OEF. J Rehabil Res Dev. 2010;47(4):387-402.

[21] Inkellis E, Low EE, Langhammer C, Morshed S. Incidence and Characterization of Major Upper-Extremity Amputations in the National Trauma Data Bank. JB JS Open Access. 2018 Apr 24;3(2):e0038.

[22] Statistics Canada. Table 13-10-0409-01 Life expectancy at birth and at age 65, by province and territory, three-year average. Available at: https://doi.org/10.25318/1310040901-eng Accessed August 30th, 2021.

[23] Statistics Canada. Table 14-10-0060-01 Retirement age by class of worker, annual. Available at: https://doi.org/10.25318/1410006001-eng. Accessed August 30th, 2021.

[24] Statistics Canada. Table 11-10-0190-01 Market income government transfers, total income, income tax and after-tax income by economic family type. Available at: https://doi.org/10.25318/1110019001-eng. Accessed August 30th, 2021.

[25] Jović NJ, Theologou M. The miracle of the black leg: E astern neglect of Western addition to the hagiography of Saints Cosmas and Damian. Acta Med Hist Adriat. 2015;13(2):329-44.

[26] Kohlhauser M, Luze H, Nischwitz SP, Kamolz LP. Historical Evolution of Skin Grafting-A Journey through Time. Medicina (Kaunas). 2021 Apr 5;57(4):348.

[27] Tobin GR, Breidenbach WC 3rd, Ildstad ST, Marvin MM, Buell JF, Ravindra KV. The history of human composite tissue allotransplantation. Transplant Proc. 2009 Mar;41(2):466-71.

[28] Harrison JH, Merrill JP, Murray JE. Renal homotransplantation in identical twins. Surg Forum. 1956;6:432-6.

[29] Morris P. Joseph E. Murray (1919-2012). Nature. 2013 Jan 10;493(7431):164.

[30] Peacock EE Jr. Some problems in flexor tendon healing. Surgery. 1959 Mar;45(3):415-23.

[31] Peacock EE Jr, Madden JW. Human composite flexor tendon allografts. Ann Surg. 1967 Oct;166(4):624-9.

[32] Gilbert R. Transplant is successful with a cadaver forearm. Med Trib Med News. 5 (1964), p.20.

[33] Gilbert R. Hand transplanted from cadaver is reamputated. Med Trib Med News. 5 (1964), p.24.

[34] Murray JE. Organ transplantation (skin, kidney, heart) and the plastic surgeon. Plast Reconstr Surg. 1971 May;47(5):425-31.

[35] Jones JW Jr, Ustüner ET, Zdichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. Surgery. 1999 Aug;126(2):384-8.

[36] Benhaim P, Anthony JP, Ferreira L, Borsanyi JP, Mathes SJ. Use of combination of low-dose cyclosporine and RS-61443 in a rat hindlimb model of composite tissue allotransplantation. Transplantation. 1996 Feb 27;61(4):527-32.

[37] Barker JH, Jones JW, Breidenbach WC. Closing remarks. Transplantation proceedings. 1998;30(6):2787.

[38] Dubernard JM, Owen E, Herzberg G, et al. Human hand allograft: report on first 6 months. Lancet. 1999 Apr 17;353(9161):1315-20.

[39] Hettiaratchy S, Butler PE, Lee WP. Lessons from hand transplantations. Lancet. 2001 Feb 17;357(9255):494-5.

[40] Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. N Engl J Med. 2000 Aug 17;343(7):468-73.

[41] Ravindra KV, Buell JF, Kaufman CL, et al. Hand transplantation in the United States: experience with 3 patients. Surgery. 2008 Oct;144(4):638-43; discussion 643-4.

[42] ABC News. U.S. Hand Transplant Patient Doing Fine. Available at: https://abcnews.go.com/Health/story?id=118039&page=1. Accessed August 30th 2021.

[43] Petruzzo P, Revillard JP, Kanitakis J, et al. First human double hand transplantation: efficacy of a conventional immunosuppressive protocol. Clin Transplant 2003;17:455-460.

[44] Schneeberger S, Petruzzo P, Morelon E, et al. 20-Year Follow-up of Two Cases of Bilateral Hand Transplantation. N Engl J Med. 2020 Oct 29;383(18):1791-1792.

[45] Petruzzo P, Lanzetta M, Dubernard JM, et al. The International Registry on Hand and Composite Tissue Transplantation. Transplantation. 2010 Dec 27;90(12):1590-4.

[46] Kinsley SE, Lenhard NK, Lape EC, et al. Perceived Success in Upper-Extremity Vascularized Composite Allotransplantation: A Qualitative Study. J Hand Surg Am. 2021 Aug;46(8):711.e1-711.e35.

[47] Bosch X. Surgeon denied ethics approval for face transplantation. Lancet. 2004 Mar 13;363(9412):871.

[48] Siemionow M, Agaoglu G. Allotransplantation of the face: how close are we? Clin Plast Surg. 2005 Jul;32(3):401-9.

[49] Brown CS, Gander B, Cunningham M, et al. Ethical considerations in face transplantation. Int J Surg. 2007 Oct;5(5):353-64.

[50] Devauchelle B, Badet L, Lengelé B, et al. First human face allograft: early report. Lancet. 2006 Jul 15;368(9531):203-9.

[51] Strome M, Stein J, Esclamado R, et al. Laryngeal transplantation and 40-month follow-up. N Engl J Med. 2001 May 31;344(22):1676-9.

[52] Hofmann GO, Kirschner MH, Wagner FD, Brauns L, Gonschorek O, Bühren V. Allogeneic vascularized transplantation of human femoral diaphyses and total knee joints--first clinical experiences. Transplant Proc. 1998 Sep;30(6):2754-61.

[53] Levi DM, Tzakis AG, Kato T, et al. Transplantation of the abdominal wall. Lancet. 2003 Jun 28;361(9376):2173-6.

[54] Mackinnon SE, Doolabh VB, Novak CB, Trulock EP. Clinical outcome following nerve allograft transplantation. Plast Reconstr Surg. 2001 May;107(6):1419-29.

[55] Birchall M. Tongue transplantation. Lancet. 2004 May 22;363(9422):1663.

[56] Jiang HQ, Wang Y, Hu XB, Li YS, Li JS. Composite tissue allograft transplantation of cephalocervical skin flap and two ears. Plast Reconstr Surg. 2005 Mar;115(3):31e-35e.

[57] Fageeh W, Raffa H, Jabbad H, Marzouki A. Transplantation of the human uterus. Int J Gynaecol Obstet. 2002 Mar;76(3):245-51.

[58] Hu W, Lu J, Zhang L, et al. A preliminary report of penile transplantation. Eur Urol. 2006 Oct;50(4):851-3.

[59] Lanzetta M, Nolli R, Vitale G, Magni F, Radaelli I, Stroppa L. Hand transplantation: the Milan experience. Polish Journal of Surgery. 2007;79(12):762-72.

[60] Carroll D. A quantitative test of upper extremity function. J Chronic Dis. 1965 May;18:479-91.

[61] Bernardon L, Gazarian A, Petruzzo P, et al. Bilateral hand transplantation: Functional benefits assessment in five patients with a mean follow-up of 7.6 years (range 4-13 years). J Plast Reconstr Aesthet Surg. 2015 Sep;68(9):1171-83.

[62] Kaufman CL, Breidenbach W. World experience after more than a decade of clinical hand transplantation: update from the Louisville hand transplant program. Hand Clin. 2011 Nov;27(4):417-21.

[63] Cavadas PC, Landin L, Thione A, et al. The Spanish experience with hand, forearm, and arm transplantation. Hand Clin. 2011 Nov;27(4):443-53.

[64] Hautz T, Engelhardt TO, Weissenbacher A, et al. World experience after more than a decade of clinical hand transplantation: update on the Innsbruck program. Hand Clin. 2011 Nov;27(4):423-31.

[65] Jablecki J. World experience after more than a decade of clinical hand transplantation: update on the Polish program. Hand Clin. 2011 Nov;27(4):433-42.

[66] Jablecki J, Kaczmarzyk L, Domanasiewicz A, et al. Result of arm-level upper-limb transplantation in two recipients at 19- and 30-month follow-up. Ann Transplant. 2012 Jul-Sep;17(3):126-32.

[67] Schneeberger S, Gorantla VS, Brandacher G, et al. Upper-extremity transplantation using a cell-based protocol to minimize immunosuppression. Ann Surg. 2013 Feb;257(2):345-51.

[68] Shores JT, Higgins JP, Lee WP. Above-elbow (supracondylar) arm transplantation: clinical considerations and surgical technique. Tech Hand Up Extrem Surg. 2013;17(4):221-7.

[69] Dellon AL, Curtis RM, Edgerton MT. Reeducation of sensation in the hand after nerve injury and repair. Plast Reconstr Surg. 1974 Mar;53(3):297-305.

[70] Landin L, Bonastre J, Casado-Sanchez C, et al. Outcomes with respect to disabilities of the upper limb after hand allograft transplantation: a systematic review. Transpl Int. 2012 Apr;25(4):424-32.

[71] Chen ZW, Yu HL. Current procedures in China on replantation of severed limbs and digits. Clin Orthop Relat Res. 1987 Feb;(215):15-23.

[72] Shores JT, Brandacher G, Schneeberger S, Gorantla VS, Lee WP. Composite tissue allotransplantation: hand transplantation and beyond. J Am Acad Orthop Surg. 2010 Mar;18(3):127-31.

[73] Schneeberger S, Landin L, Jableki J, et al. Achievements and challenges in composite tissue allotransplantation. Transpl Int. 2011 Aug;24(8):760-9.

[74] Manske P. The sound of one hand clapping. J Hand Surg Am. 2008 Sep;33(7):1037-8.

[75] Lanzetta M, Petruzzo P. A Comprehensive Functional Score System in Hand Transplantation. In: Lanzetta M, Dubernard JM, Petruzzo P, Eds. *Hand Transplantation*. Vol. 1, 1st ed. Milano: Springer; 2007:355-362.

[76] Singh M, Sisk G, Carty M, et al. Functional Outcomes after Bilateral Hand Transplantation: A 3.5-Year Comprehensive Follow-Up. Plast Reconstr Surg. 2016 Jan;137(1):185-9.

[77] Salminger S, Vujaklija I, Sturma A, et al. Functional Outcome Scores With Standard Myoelectric Prostheses In Below-Elbow Amputees. Am J Phys Med Rehabil. 201 Feb;98(2):125-9.

[78] Shores JT, Malek V, Lee WPA, Brandacher G. Outcomes after hand and upper extremity transplantation. J Mater Sci Mater Med. 2017 May;28(5):72.

[79] Morales ID, Kaufman C. What can we do when complications ensue? Round table discussion with case illustrations. Paper presented at: 11th Meeting of the International Hand and Composite Tissue Allotransplantation Society; 2013; Wroclaw, Poland.

[80] Alolabi N, Augustine H, Thoma A. Hand transplantation: current challenges and future prospects. Transplant Research and Risk Management. 2016;9:23-9.

[81] Petruzzo P, Lanzetta M, Dubernard JM. International Registry On Hand and Composite Tissue Transplantation. Transplantation. 2014;98:44.

[82] MacKay BJ, Nacke E, Posner M. Hand transplantation--a review. Bull Hosp Jt Dis (2013). 2014;72(1):76-88.

[83] Rohrich RJ, Afrooz PN. Just Because You Can, Doesn't Mean You Should. Plast Reconstr Surg. 2017 Nov;140(5):1073-1076.

[84] Mathes DW, Schlenker R, Ploplys E, Vedder N. A survey of north american hand surgeons on their current attitudes toward hand transplantation. J Hand Surg Am. 2009 May-Jun;34(5):808-14.

[85] Jones NF. Concerns about human hand transplantation in the 21st century. J Hand Surg Am. 2002 Sep;27(5):771-87.

[86] Brenner MJ, Tung TH, Jensen JN, Mackinnon SE. The spectrum of complications of immunosuppression: is the time right for hand transplantation? J Bone Joint Surg Am. 2002 Oct;84(10):1861-70.

[87] Nassimizadeh M, Nassimizadeh AK, Power D. Hand transplant surgery. Ann R Coll Surg Engl. 2014 Nov;96(8):571-4.

[88] Beauchamp TL, Childress JF. Principles of Biomedical Ethics. New York: Oxford University Press. 1973.

[89] Varelius J. The value of autonomy in medical ethics. Med Health Care Philos. 2006;9(3):377-88.

[90] Siegler M. Ethical issues in innovative surgery: should we attempt a cadaveric hand transplantation in a human subject? Transplant Proc. 1998 Sep;30(6):2779-82.

[91] Germann G. Bilateral hand transplantation--indication and rationale. J Hand Surg Br. 2001 Dec;26(6):521

[92] Lees VC, McCabe SJ. The rationale for hand transplantation. Transplantation. 2002 Sep 27;74(6):749-53

[93] Dumont M, Sann L, Gazarian A. Bilateral hand transplantation: Supporting the patient's choice. J Plast Reconstr Aesthet Surg. 2017 Feb;70(2):147-151.

[94] King WT, Heubi JE. Comprehension Testing in Informed Consent. AJOB Empirical Bioethics. 2014;5(3):39-54.

[95] Munyaradzi M. Critical reflections on the principle of beneficence in biomedicine. Pan Afr Med J. 2012;11:29.

[96] Pellegrino ED, Thomasma DC. The conflict between autonomy and beneficence in medical ethics: proposal for a resolution. J Contemp Health Law Policy. 1987 Spring;3:23-46.

[97] Page K. The four principles: can they be measured and do they predict ethical decision making? BMC Med Ethics. 2012 May 20;13:10.

[98] Slatman J, Widdershoven GAM. Hand Transplants and Bodily Integrity. Body & Society. 2010 Sept;16(3):69-92.

[99] Jablecki J, Kaczmarzyk L, Patrzalek D, Domanasiewicz A, Chełmoński A. A detailed comparison of the functional outcome after midforearm replantations versus midforearm transplantation. Transplant Proc. 2009 Mar;41(2):513-6.

[100] Kostro JZ, Hellmann A, Kobiela J, et al. Quality of Life After Kidney Transplantation: A Prospective Study. Transplant Proc. 2016 Jan-Feb;48(1):50-4.

[101] Chang J, Mathes DW. Ethical, financial, and policy considerations in hand transplantation. Hand Clin. 2011 Nov;27(4):553-60.

[102] Kaufman CL, Blair B, Murphy E, Breidenbach WB. A new option for amputees: transplantation of the hand. J Rehabil Res Dev. 2009;46(3):395-404.

[103] Petruzzo P, Lanzetta M, Dubernard JM, et al. The international registry on hand and composite tissue transplantation. Transplantation. 2008 Aug 27;86(4):487-92.

[104] Sifferlin A. 'I Can Do Absolutely Nothing.' The First American With a Double Hand Transplant Wants Them Removed. Available at: http://time.com/4419959/double-hand-transplant-surgery/. Accessed August 30th, 2021.

[105] Koulmanda M, Pomahac B, Fan Z, Murphy GF, Strom TB. Hand transplants and the mandate for tolerance. Curr Opin Organ Transplant. 2014 Dec;19(6):545-51.

[106] Tobin GR, Breidenbach WC, Klapheke MM, Bentley FR, Pidwell DJ, Simmons PD. Ethical considerations in the early composite tissue allograft experience: a review of the Louisville Ethics Program. Transplant Proc. 2005 Mar;37(2):1392-5.

[107] Kanitakis J, Jullien D, Petruzzo P, et al. Clinicopathologic features of graft rejection of the first human hand allograft. Transplantation. 2003 Aug 27;76(4):688-93.

[108] Cooney CM, Siotos C, Aston JW, et al. The Ethics of Hand Transplantation: A Systematic Review. J Hand Surg Am. 2018 Jan;43(1):84.

[109] Cooney WP, Hentz VR. Hand transplantation--primum non nocere. J Hand Surg Am. 2002 Jan;27(1):165-8.

[110] Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant. 2007 Jun;7(6):1506-14.

[111] Schneeberger S, Lucchina S, Lanzetta M, et al. Cytomegalovirus-related complications in human hand transplantation. Transplantation. 2005 Aug 27;80(4):441-7.

[112] Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006 Dec 20;296(23):2823-31.

[113] Dobbels F, Vanhaecke J, Dupont L, et al. Pretransplant predictors of posttransplant adherence and clinical outcome: an evidence base for pretransplant psychosocial screening. Transplantation. 2009 May 27;87(10):1497-504.

[114] Organ Procurement and Transplantation Network. Programming VCA Allocation in UNet. Available at: https://optn.transplant.hrsa.gov/governance/public-comment/programming-vca-allocation-in-unet/. Accessed August 30th 2021.

[115] Government of Canada. Cells, Tissues and Organs. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/cells-tissues-organs.html. Accessed August 30th 2021.

[116] McDiarmid SV, Azari KK. Donor-related issues in hand transplantation. Hand Clin. 2011 Nov;27(4):545-52.

[117] Siemionow MZ, Rampazzo A, Gharb BB. Addressing religious and cultural differences in views on transplantation, including composite tissue allotransplantation. Ann Plast Surg. 2011 Apr;66(4):410-5.

[118] Anker AE, Feeley TH. Asking the difficult questions: message strategies used by organ procurement coordinators in requesting familial consent to organ donation. J Health Commun. 2011 Jul;16(6):643-59.

[119] Transplant Québec. FAQs. Available at: https://www.transplantquebec.ca/en/faqs. Accessed August 30th 2021.

[120] Weinstein MC, Torrance G, McGuire A. QALYs: the basics. Value Health. 2009 Mar;12 Suppl 1:S5-9.

[121] Brugger U, Plessow R, Hess S, et al. The health technology assessment of the compulsory accident insurance scheme of hand transplantation in Switzerland. J Hand Surg Eur Vol. 2015 Nov;40(9):914-23.

[122] Chung KC, Oda T, Saddawi-Konefka D, Shauver MJ. An economic analysis of hand transplantation in the United States. Plast Reconstr Surg. 2010 Feb;125(2):589-98.

[123] Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. Value Health. Jan-Feb 2009;12(1):80-7.

[124] Braithwaite RS, Meltzer DO, King JT, Jr., Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008 Apr;46(4):349-56.

[125] Nerlich AG, Zink A, Szeimies U, Hagedorn HG. Ancient Egyptian prosthesis of the big toe. Lancet. 2000 Dec 23-30;356(9248):2176-9.

[126] Museo Galileo. Iron hands and wooden limbs. Available at: https://exhibits.museogalileo.it/nexus/enex.php?c[]=49117. Accessed August 30th, 2021.

[127] Putti V. Historical prostheses. *Scritti Medici.* 1925;IX(4 to 5) First published La chirurgia degli organi di movimento

[128] Thurston AJ. Paré and prosthetics: the early history of artificial limbs. ANZ J Surg. 2007 Dec;77(12):1114-9.

[129] Meier RH. History of Arm Amputation, Prosthetic Restoration, and Arm Amputation Rehabilitation. In: Meier RH, Atkins DJ, Eds. *Functional Restoration of Adults and Children with Upper Limb Amputation*. Vol. 1, 1st ed. New York: Demos Medical Publishing; 2004:1-8.

[130] Huaroto JJ, Suarez E, Vela EA. Wearable mechatronic devices for upper-limb amputees. In: Boubaker O, Eds. *Control theory in biomedical engineering. Applications in physiology and medical robotics.* Vol. 1, 1st ed. Cambridge: Acaemic Press; 2020:211-212.

[131] Childress DS. Historical aspects of powered limb prostheses. Clin Prosthet Orthot. 1985;9:2–13.

[132] Reiter R. [A new electrical arts hand]. Grenzgeb Med. 1948 Sep;1(4):133-5.

[133] Sherman ED. A Russian Bioelectric-Controlled Prosthesis: Report of a Research Team From the Rehabilitation Institute of Montreal. Can Med Assoc J. 1964 Dec 12;91(24):1268-70.

[134] Behrend C, Reizner W, Marchessault JA, Hammert WC. Update on advances in upper extremity prosthetics. J Hand Surg Am. 2011 Oct;36(10):1711-7.

[135] Battye CK, Nightingale A, Whillis J. The use of myo-electric currents in the operation of prostheses. J Bone Joint Surg Br. 1955 Aug;37-B(3):506-10.

[136] Parker P, Englehart K, Hudgins B. Myoelectric signal processing for control of powered limb prostheses. J Electromyogr Kinesiol. 2006 Ddec;16(6):541-8.

[137] Weir RF, Troyk PR, DeMichele GA, Kerns DA, Schorsch JF, Maas H. Implantable myoelectric sensors (IMESs) for intramuscular electromyogram recording. IEEE Trans Biomed Eng. 2009 Jan;56(1):159-71.

[138] Muceli S, Farina D. Simultaneous and proportional estimation of hand kinematics from EMG during mirrored movements at multiple degrees-of-freedom. IEEE Trans Neural Syst Rehabil Eng. 2012 May;20(3):371-8.

[139] Hahne JM, Biessmann F, Jiang N, et al. Linear and nonlinear regression techniques for simultaneous and proportional myoelectric control. IEEE Trans Neural Syst Rehabil Eng. 2014 Mar;22(2):269-79.

[140] Hudgins B, Parker P, Scott RN. A new strategy for multifunction myoelectric control. IEEE Trans Neural Syst Rehabil Eng. 1993 Jan;40(1):82-94.

[141] Tenore F, Ramos A, Fahmy A, Acharya S, Etienne-Cummings R, Thakor NV. Towards the control of individual fingers of a prosthetic hand using surface EMG signals. In *proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Lyon, France; August 23-26, 2007.

[142] Englehart K, Hudgins B, Parker PA. A wavelet-based continuous classification scheme for multifunction myoelectric control. IEEE Trans Biomed Eng. 2001 Mar;48(3):302-11.

[143] Gaston RG, Bracey JW, Tait MA, Loeffler BJ. A Novel Muscle Transfer for Independent Digital Control of a Myoelectric Prosthesis: The Starfish Procedure. J Hand Surg Am. 2019 Feb;44(2):163.e1-163.e5.

[144] Wright FV. Measurement of Functional Outcome With Individuals Who Use Upper Extremity Prosthetic Devices: Current and Future Directions. JPO Journal of Prosthetics and Orthotics. 2006 Apr;18(2):46-56.

[145] Lock BA, Englehart K, Hudgins B. Real-time myoelectric control in a virtual environment to relate usability vs. accuracy. In *Proceedings of the MEC'05 conference, UNB*, Fredericton, New Brunswick; 2005.

[146] Wright V. Prosthetic outcome measures for use with upper limb amputees: a systematic review of the peer-reviewed literature. JPO Journal of Prosthetics and Orthotics. 2009;21(9):3-63.

[147] Biddiss EA, Chau TT. Upper limb prosthesis use and abandonment: a survey of the last 25 years. Prosthet Orthot Int. 2007 Sep;31(3):236-57.

[148] Miller LA, Stubblefield KA, Lipschutz RD, Lock BA, Kuiken TA. Improved myoelectric prosthesis control using targeted reinnervation surgery: a case series. IEEE Trans Neural Syst Rehabil Eng. 2008 Feb;16(1):46-50.

[149] Kuiken TA, Dumanian GA, Lipschutz RD, Miller LA, Stubblefield KA. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. Prosthet Orthot Int. 2004 Dec;28(3):245-53.

[150] Mioton LM, Dumanian GA. Targeted muscle reinnervation and prosthetic rehabilitation after limb loss. J Surg Oncol. 2018 Oct;118(5):807-14.

[151] Dumanian GA, Ko JH, O'Shaughnessy KD, Kim PS, Wilson CJ, Kuiken TA. Targeted reinnervation for transhumeral amputees: current surgical technique and update on results. Plast Reconstr Surg. 2009;124(3):863-9.

[152] Gart MS, Souza JM, Dumanian GA. Targeted Muscle Reinnervation in the Upper Extremity Amputee: A Technical Roadmap. J Hand Surg Am. 2015 Sep;40(9):1877-88.

[153] Cheesborough JE, Smith LH, Kuiken TA, Dumanian GA. Targeted muscle reinnervation and advanced prosthetic arms. Semin Plast Surg. 2015 Feb;29(1):62-72.

[154] Kuiken T. Targeted reinnervation for improved prosthetic function. Phys Med Rehabil Clin N Am. 2006 Feb;17(1):1-13.

[155] Agnew SP, Ko J, De La Garza M, Kuiken T, Dumanian G. Limb transplantation and targeted reinnervation: a practical comparison. J Reconstr Microsurg. 2012 Jan;28(1):63-8

[156] Hargrove LJ, Miller LA, Turner K, Kuiken TA. Myoelectric Pattern Recognition Outperforms Direct Control for Transhumeral Amputees with Targeted Muscle Reinnervation: A Randomized Clinical Trial. Sci Rep. 2017 Oct;7(1):13840.

[157] Kuiken TA, Miller LA, Lipschutz RD, Lock BA, Stubblefield K, Marasco PD, et al. Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study. Lancet. 2007 Feb;369(9559):371-80.

[158] Kuiken TA, Marasco PD, Lock BA, Harden RN, Dewald JP. Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. Proc Natl Acad Sci U S A. 2007 Dec;104(50):20061-6.

[159] Hebert JS, Olson JL, Morhart MJ, et al. Novel targeted sensory reinnervation technique to restore functional hand sensation after transhumeral amputation. IEEE Trans Neural Syst Rehabil Eng. 2014 Jul;22(4):765-73.

[160] Yao J, Chen A, Kuiken T, Carmona C, Dewald J. Sensory cortical re-mapping following upper-limb amputation and subsequent targeted reinnervation: A case report. Neuroimage Clin. 2015 Jan;8:329-36.

[161] Kim PS, Ko JH, O'Shaughnessy KK, Kuiken TA, Pohlmeyer EA, Dumanian GA. The effects of targeted muscle reinnervation on neuromas in a rabbit rectus abdominis flap model. J Hand Surg Am. 2012 Aug;37(8):1609-16.

[162] Souza JM, Cheesborough JE, Ko JH, Cho MS, Kuiken TA, Dumanian GA. Targeted muscle reinnervation: a novel approach to postamputation neuroma pain. Clin Orthop Relat Res. 2014 Oct;472(10):2984-90.

[163] Cheesborough JE, Souza JM, Dumanian GA, Bueno RA, Jr. Targeted muscle reinnervation in the initial management of traumatic upper extremity amputation injury. Hand (N Y). 2014 Jun;9(2):253-7.

[164] Mitton C, Donaldson C. Resource allocation in health care: health economics and beyond. Health Care Anal. 2003 Sep;11(3):245-57.

[165] Neumann PJ, Goldie SJ, Weinstein MC. Preference-based measures in economic evaluation in health care. Annu Rev Public Health. 2000;21:587-611.

[166] Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5-21.

[167] National Library of Medicine. Health Economics Information Resources: A Self-Study Course: Module 4. Available at: https://www.nlm.nih.gov/nichsr/edu/healthecon/04_he_02.html Accessed September 18th 2021.

[168] Arnold D, Girling A, Stevens A, Lilford R. Comparison of direct and indirect methods of estimating health state utilities for resource allocation: review and empirical analysis. BMJ. 2009 Jul;339:b2688.

[169] Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. Psychol Rev. 1956 Mar;63(2):81-97.

[170] Parkin D, Devlin N. Is there a case for using visual analogue scale valuations in cost-utility analysis? Health Econ. 2006 Jul;15(7):653-64.

[171] Arnesen T, Trommald M. Roughly right or precisely wrong? Systematic review of quality-of-life weights elicited with the time trade-off method. J Health Serv Res Policy. 2004 Jan;9(1):43-50.

[172] Finnell SM, Carroll AE, Downs SM. The utility assessment method order influences measurement of parents' risk attitude. Value Health. 2012 Sep-Oct;15(6):926-32.

[173] Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ. 1986;5(1):1-30.

[174] Martin AJ, Glasziou PP, Simes RJ, Lumley T. A comparison of standard gamble, time trade-off, and adjusted time trade-off scores. Int J Technol Assess Health Care. 2000 Winter;16(1):137-47.

[175] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press, 2005.

[176] Jansen SJ, Stiggelbout AM, Wakker PP, Nooij MA, Noordijk EM, Kievit J. Unstable preferences: a shift in valuation or an effect of the elicitation procedure? Med Dec Making. 2000;20(1):62-71.

[177] McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247-63,

[178] Ferreira PL, Ferreira LN, Pereira LN. How consistent are health utility values? Qual Life Res. 2008 Sep;17(7):1031-42.

[179] Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996 Jun;29(6):602-8.

[180] Waljee JF, Kim HM, Burns PB, Chung KC. Development of a brief, 12-item version of the Michigan Hand Questionnaire. Plast Reconstr Surg. 2011 Jul;128(1):208-20.

[181] Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. Health Serv Res. 1972 Summer;7(2):118-33.

[182] Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med. 1977 Mar 31;296(13):716-21.

[183] Torrance GW, Feeny D. Utilities and quality-adjusted life years. Int J Technol Assess Health Care. 1989;5(4):559-75.

[184] Drummond, M. F., Stoddart, G. L., & Torrance, G. W. *Methods for the economic evaluation of health care programmes.* Oxford: Oxford Medical Publications, 1987.

[185] Shale CM, Tidwell JE, 3rd, Mulligan RP, Jupiter DC, Mahabir RC. A nationwide review of the treatment patterns of traumatic thumb amputations. Ann Plast Surg. 2013;70(6):647-51.

[186] Cobbett JR. Free digital transfer. Report of a case of transfer of a great toe to replace an amputated thumb. J Bone Joint Surg Br. 1969 Nov;51(4):677-9.

[187] Foucher G, Medina J, Navarro R, Nagel D. Toe transfer in congenital hand malformations. J Reconstr Microsurg. 2001;17(1):1-7.

[188] Govila A. Improvisation in wrap-around toe-to-thumb transfer. Acta Chir Plast. 1993;35(3-4):101-10.

[189] Cheng G, Fang G, Hou S, et al. Aesthetic reconstruction of thumb or finger partial defect with trimmed toe-flap transfer. Microsurgery. 2007;27(2):74-83.

[190] Buncke HJ, Rose EH. Free toe-to-fingertip neurovascular flaps. Plast Reconstr Surg. 1979;63(5):607-12.

[191] Foucher G, Merle M, Maneaud M, Michon J. Microsurgical free partial toe transfer in hand reconstruction: a report of 12 cases. Plast Reconstr Surg. 1980;65(5):616-27.

[192] Lee DC, Kim JS, Ki SH, Roh SY, Yang JW, Chung KC. Partial second toe pulp free flap for fingertip reconstruction. Plast Reconstr Surg. 2008;121(3):899-907.

[193] Frykman GK, O'Brien BM, Morrison WA, MacLeod AM. Functional evaluation of the hand and foot after one-stage toe-to-hand transfer. J Hand Surg Am. 1986;11(1):9-17.

[194] Wei FC, Carver N, Lee YH, Chuang DC, Cheng SL. Sensory recovery and Meissner corpuscle number after toe-to-hand transplantation. Plast Reconstr Surg. 2000;105(7):2405-11.

[195] Lin PY, Sebastin SJ, Ono S, Bellfi LT, Chang KW, Chung KC. A systematic review of outcomes of toe-to-thumb transfers for isolated traumatic thumb amputation. Hand (N Y). 2011 Sep;6(3):235-43.

[196] Kim HD, Hwang SM, Lim KR, Jung YH, Ahn SM, Song JK. Toe Tissue Transfer for Reconstruction of Damaged Digits due to Electrical Burns. Arch Plast Surg. 2012;39(2):138-42.

[197] Kim HS, Lee DC, Kim JS, Roh SY, Lee KJ, Yang JW, et al. Donor-Site Morbidity after Partial Second Toe Pulp Free Flap for Fingertip Reconstruction. Arch Plast Surg. 2016;43(1):66-70.

[198] Stevens KJ, McCabe CJ, Brazier JE. Mapping between Visual Analogue Scale and Standard Gamble data; results from the UK Health Utilities Index 2 valuation survey. Health Econ. 2006 May;15(5):527-33.

[199] Li YK, Alolabi N, Kaur MN, Thoma A. A systematic review of utilities in hand surgery literature. J Hand Surg Am. 2015;40(5):997-1005.

[200] Alolabi N, Chuback J, Grad S, Thoma A. The utility of hand transplantation in hand amputee patients. J Hand Surg Am. 2015;40(1):8-14.

[201] Chung KC, Walters MR, Greenfield ML, Chernew ME. Endoscopic versus open carpal tunnel release: a cost-effectiveness analysis. Plast Reconstr Surg. 1998;102(4):1089-99.

[202] Pet MA, Ko JH, Vedder NB. Reconstruction of the traumatized thumb. Plast Reconstr Surg. 2014;134(6):1235-45.

[203] Lipton HA, May JW, Jr., Simon SR. Preoperative and postoperative gait analyses of patients undergoing great toe-to-thumb transfer. J Hand Surg Am. 1987;12(1):66-9.

[204] Chung KC, Wei FC. An outcome study of thumb reconstruction using microvascular toe transfer. J Hand Surg Am. 2000;25(4):651-8.

[205] Morrison WA, O'Brien BM, MacLeod AM. Thumb reconstruction with a free neurovascular wrap-around flap from the big toe. J Hand Surg Am. 1980;5(6):575-83.

[206] Vergara-Amador E. Second toe-to-hand transplantation: A surgical option for hand amputations. Colomb Med (Cali). 2015 Jun;46(2):71-4.

[207] Venkatramani H, Bhardwaj P, Sierakowski A, Sabapathy SR. Functional outcomes of post-traumatic metacarpal hand reconstruction with free toe-to-hand transfer. Indian J Plast Surg. 2016 Jan-Apr;49(1):16-25.

[208] Lam WL, Wei FC. Toe-to-hand transplantation. Clin Plast Surg. 2011;38(4):551-9.

[209] Lloyd A, Hayes P, Bell PR, Naylor AR. The role of risk and benefit perception in informed consent for surgery. Med Decis Making. 2001 Mar-Apr;21(2):141-9.

[210] Shekelle PG, Wachter RM, Pronovost PJ, et al. Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices. Evid Rep Technol Assess (Full Rep). 2013 Mar;(211):1-945.

[211] Shauver MJ, Nishizuka T, Hirata H, Chung KC. Traumatic Finger Amputation Treatment Preference among Hand Surgeons in the United States and Japan. Plast Reconstr Surg. 2016;137(4):1193-202.

[212] Park SH, Eun SC, Kwon ST. Hand transplantation: Current status and immunologic obstacles. Exp Clin Transplant. 2019;17:97-104.

[213] Sartori M, Durandau G, Dosen S, Farina D. Robust simultaneous myoelectric control of multiple degrees of freedom in wrist-hand prostheses by real-time neuromusculoskeletal modeling. J Neural Eng. 2018;15:066026.

[214] Raveh E, Portnoy S, Friedman J. Myoelectric prosthesis users improve performance time and accuracy using vibrotactile feedback when visual feedback is disturbed. Arch Phys Med Rehabil. 2018;99:2263-2270.

[215] Strbac M, Isakovic M, Belic M, et al. Short- and long-term learning of feedforward control of a myoelectric prosthesis with sensory feedback by amputees. IEEE Trans Neural Syst Rehabil Eng. 2017;25:2133-2145.

[216] Efanov JI, Shine JJ, Darwich R, et al. French translation and cross-cultural adaptation of the Michigan Hand Outcomes Questionnaire and the Brief Michigan Hand Outcomes Questionnaire. Hand Surg Rehabil. 2018;37:86-90.

[217] Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: New outcome measure for primary care. BMJ. 1992;305:160-4.

[218] Hoang-Kim A, Pegreffi F, Moroni A, Ladd A. Measuring wrist and hand function: common scales and checklists. Injury. 2011;42:253-258.

[219] Maia MV, de Moraes VY, Dos Santos JB, Faloppa F, Belloti JC. Minimal important difference after hand surgery: A prospective assessment for DASH, MHQ, and SF-12. SICOT J. 2016;2:32.

[220] Shores JT, Brandacher G, Lee WP. Hand and upper extremity transplantation: An update of outcomes in the worldwide experience. Plast Reconstr Surg. 2015;135:351e-360e.

[221] Petruzzo P, Dubernard JM. The International Registry on Hand and Composite Tissue allotransplantation. Clin Transpl. 2011:247-253.

[222] Atallah R, Leijendekkers RA, Hoogeboom TJ, Frolke JP. Complications of bone-anchored prostheses for individuals with an extremity amputation: A systematic review. PLoS One. 2018;13:e0201821.

[223] Bleichrodt H, Johannesson M. Standard gamble, time trade-off and rating scale: Experimental results on the ranking properties of QALYs. J Health Econ. 1997;16:155-75.

[224] Krabbe PF, Essink-Bot ML, Bonsel GJ. On the equivalence of collectively and individually collected responses: Standard-gamble and time-tradeoff judgments of health states. Med Decis Making. 1996;16:120-132.

[225] Efanov JI, Wong C, Guilbault C, et al. Investigating patients' perception of microvascular free toe flap for reconstruction of amputated thumbs: A guide for surgeons during informed consent. J Reconstr Surg. 2018;34(9):692-700.

[226] Kubiak CA, Etra JW, Brandacher G, et al. Prosthetic rehabilitation and vascularized composite allotransplantation following upper limb loss. Plast Reconstr Surg. 2019;143:1688-1701.

[227] Salminger S, Sturma A, Roche AD, et al. Functional and Psychosocial outcomes of hand transplantation compared with prosthetic fitting in below-elbow amputees: A multicenter cohort study. PLoS One. 2016;11:e0162507.

[228] McClelland B, Novak CB, Hanna S, McCabe SJ. Using decision analysis to understand the indications for unilateral hand transplantation. Hand (N Y). 2016;11:450-455.

[229] McCabe S, Rodocker G, Julliard K, et al. Using decision analysis to aid in the introduction of upper extremity transplantation. Transplant Proc. 1998;30:2783-2786.

[230] Salminger S, Roche AD, Sturma A, Mayer JA, Aszmann OC. Hand transplantation versus hand prosthetics: Pros and cons. Curr Surg Rep. 2016;4:8.

[231] Majzoub RK, Cunningham M, Grossi F, Maldonado C, Banis JC, Barker JH. Investigation of risk acceptance in hand transplantation. J Hand Surg Am. 2006;31:295-302.

[232] Bertrand AA, Sen S, Otake LR, Lee GK. Changing attitudes toward hand allotransplantation among North American hand surgeons. Ann Plast Surg. 2014;72 Suppl 1:S56-60.

[233] McTaggart-Cowan H. Elicitation of informed general population health state utility values: A review of the literature. Value Health. 2011;14:1153-1157.

[234] Wei HI, Do NT, Din RY, Lin CH, Lin CH. Attitudes of hand surgeons and hand reconstruction patients toward hand allotransplantation in Taiwan. Ann Plast Surg. 2020;84(1S Suppl 1):S107-s11.

[235] Vakhshori V, Bouz GJ, Mayfield CK, Alluri RK, Stevanovic M, Ghiassi A. Trends in Pediatric Traumatic Upper Extremity Amputations. Hand (N Y). 2019 Nov;14(6):782-790.

[236] Canada Go. Canada Pension Plan Disability Benefit – How much could you receive. Available at : https://www.canada.ca/en/services/benefits/publicpensions/cpp/cpp-disability-benefit/benefit-amount.html2018. Accessed September 3rd 2021.

[237] Canada S. Archived - Life expectancy at birth and at age 65, by province and territory, three-year average. 2017; Available at : https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=CSD&Code1=2466023&Geo2=PR&Code2=24&SearchText=Montreal&SearchType=Begins&SearchPR=01&B1=All&TABID=1&type=1. Accessed September 3rd 2021.

[238] Canada S. Retirement age by class of worker. 2021. Available at : https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1410006001. Accessed September 3rd 2021.

[239] Canada S. Canadian Income Survey. 2019. Available at : https://www150.statcan.gc.ca/n1/daily-quotidien/210323/dq210323a-eng.htm. Accessed September 3rd 2021.

[240] CADTH. About the Health Technology Assessment Service. Available at: https://www.cadth.ca/about-cadth/what-we-do/products-services/hta2018. Accessed September 3rd 2021.

[241] Robbins NL, Wordsworth MJ, Parida BK, et al. A Flow Dynamic Rationale for Accelerated Vascularized Composite Allotransplant Rejection. Plast Reconstr Surg. 2019;143(3):637e-643e.

[242] Efanov JI, Izadpanah A, Bou-Merhi J, Lin SJ, Danino MA. Applying Health Utility Outcome Measures and Quality-Adjusted Life-Years to Compare Hand Allotransplantation and Myoelectric Prostheses for Upper Extremity Amputations. Plast Reconstr Surg. 2022 Mar 1;149(3):465e-474e

[243] McGimpsey B. Limb Prosthetics Services and Devices Critical Unmet Need: Market Analysis. 2017; Available at: https://www.nist.gov/system/files/documents/2017/04/28/239_limb_prosthetics_services_devices.pdf. Accessed September 3rd 2021.

[244] McGimpsey B. Limb Prosthetics Services and Devices Critical Unmet Need: Market Analysis. 2017; Available at:

https://www.nist.gov/system/files/documents/2017/04/28/239_limb_prosthetics_services_devices.pdf. Accessed September 3rd 2021.

[245] Resnik L, Meucci MR, Lieberman-Klinger S, et al. Advanced upper limb prosthetic devices: implications for upper limb prosthetic rehabilitation. Arch Phys Med Rehabil. 2012 Apr;93(4):710-7.

[246] Chan A, Kwok E, Bhuanantanondh P. Cost of Ownership of Upper Limb Prostheses: A Retrospective Analysis. In *Proceedings of The Canadian Medical and Biological Engineering Society*, Ottawa, Ontario; May 21-24, 2013.

[247] Fernández A, Isusi I, Gómez M. Factors conditioning the return to work of upper limb amputees in Asturias, Spain. Prosthet Orthot Int. 2000 Aug;24(2):143-7.

[248] Hollenbeck ST, Erdmann D, Levin LS. Current indications for hand and face allotransplantation. Transplant Proc. 2009 Mar;41(2):495-8

[249] National Library of Medicine. HTA 101: II. Fundamental Concepts. Available at: https://www.nlm.nih.gov/nichsr/hta101/ta10104.html Accessed September 18th 2021.

[250] Department of Defense. Reconstructive Transplant Research. Available at: https://cdmrp.army.mil/rtrp/ Accessed September 3rd 2021.

[251] Sarwer DB, Ritter S, Reiser K, et al. Attitudes Toward Vascularized Composite Allotransplantation of the Hands and Face in an Urban Population. Vascul Comp Allotranspl. 2014;1(1):22-30

[252] Szajerka T, Klimczak A, Jablecki J. Chimerism in hand transplantation. Ann Transplant. 2011 Jan-Mar;16(1):83-9.

[253] Wu S, Xu H, Ravindra K, Ildstad ST. Composite tissue allotransplantation: past, present and future-the history and expanding applications of CTA as a new frontier in transplantation. Transplant Proc. 2009 Mar;41(2):463-5.

[254] Gorantla VS, Brandacher G, Schneeberger S, et al. Favoring the risk-benefit balance for upper extremity transplantation--the Pittsburgh Protocol. Hand Clin. 2011 Nov;27(4):511-20, ix-x.

[255] Sosin M, Rodriguez ED. The Face Transplantation Update: 2016. Plast Reconstr Surg. 2016 Jun;137(6):1841-1850.

[256] Amaral S, Levin LS. Pediatric and congenital hand transplantation. Curr Opin Organ Transplant. 2017 Oct;22(5):477-483.

[257] Amaral S, Kessler SK, Levy TJ, et al. 18-month outcomes of heterologous bilateral hand transplantation in a child: a case report. Lancet Child Adolesc Health. 2017 Sep;1(1):35-44

[258] Lu Z, Stampas A, Francisco GE, Zhou P. Offline and online myoelectric pattern recognition analysis and real-time control of a robotic hand after spinal cord injury. J Neural Eng. 2019 Jun;16(3):036018.

[259] Samuel OW, Asogbon MG, Geng Y, et al. Intelligent EMG Pattern Recognition Control Method for Upper-Limb Multifunctional Prostheses: Advances, Current Challenges, and Future Prospects. *IEEE Access.* 2019;**7**:10150–10165.

[260] Bandara DSV, Arata J, Kiguchi K. Towards Control of a Transhumeral Prosthesis with EEG Signals. Bioengineering (Basel). 2018 Mar 22;5(2):26.

[261] Ccorimanya L, Watanabe R, Hassan M, Hada Y, Suzuki K. Design of a myoelectric 3D-printed prosthesis for a child with upper limb congenital amputation. Annu Int Conf IEEE Eng Med Biol Soc. 2019 Jul;2019:5394-5398.

[262] Ngan CGY, Kapsa RMI, Choong PFM. Strategies for neural control of prosthetic limbs: from electrode interfacing to 3D printing. Materials (Basel). 2019 Jun 14;12(12):1927.