The Ethics of Pediatric Vascular Composite Allographs

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Life is short,
the art is long,
opportunity fleeting,
experimentations perilous,
and judgment difficult.

Hippocratic Aphorism

If only no child was missing both hands,
or if none had extensive facial injuries.

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or if none had extensive facial injuries.

We are here to consider what to do
in unspeakably difficult circumstances,
aware of the benefits and harm of both doing and not doing.

General Pediatric Treatment Ethical Considerations

- Parents have authority to grant permission for their child to undergo medical care and procedures
- Treatment alternatives
  - Benefits (nature, magnitude, probability, uncertainties)
  - Harms (nature, magnitude, probability, uncertainties)
- How do these play out in a developing human over a lifetime?
- Ultimately, do the benefits outweigh the harms?
- Patient selection (for optimal benefit, minimal harms) and informed consent (and assent) are key ethical processes

VCA Pediatric Treatment Ethical Considerations

- Patient selection (for optimal benefit, minimal harms)
  - Clarifying the nature of this selection process and aiming for consistent use of best practices will further optimize outcomes and minimize risk of bias
- Informed consent (and assent)
  - Information about procedure and outcomes is, of course, vital
  - Structured, guided examination of preferences – and particularly about the tradeoff of quantity of lifespan for quality of life – should be considered
  - Dedicated and empowered patient advocate may be a best practice … note, advocating to either proceed or not proceed

VCA Pediatric Treatment Ethical Considerations

- Distributional ethical concerns, made concrete regarding issue of access to VCA, whether due to eligibility criteria or ability to pay (insurance coverage) or global variation in availability of VCA.
- These in turn raise social justice issues
- Important macro considerations

- Of note, currently, demand for pediatric VCA does not appear to be outstripping supply, so VCA allocation per se is not the same ethical consideration as is the case for solid organs

VCA Pediatric Treatment Ethical Considerations

- Is VCA “experimental”?
- Certainly, VCA is innovative and not standard therapy
- But that does not necessarily make the conduct of VCA “human subjects research”
- N=1 treatments aiming principally to benefit the patient, and the patients themselves, may be poorly served if routed into an IRB framework

Main Points – Hand Transplantation

- Understanding benefits and harms (both magnitude and probability) key to ethical framework & informed consent
  - Benefit depends upon rehabilitation dedication
  - Major harms attributable to immunosuppression

- Quality of Life differences small, loss of years of life figure prominently
  - Small marginal predicted edge for transplant versus prosthesis

- Aversion to years of life lost may offset Quality Adjusted Life Years (QALY) gained
  - Likely individual variation

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Pediatric Hand Transplantation: A Decision Analysis

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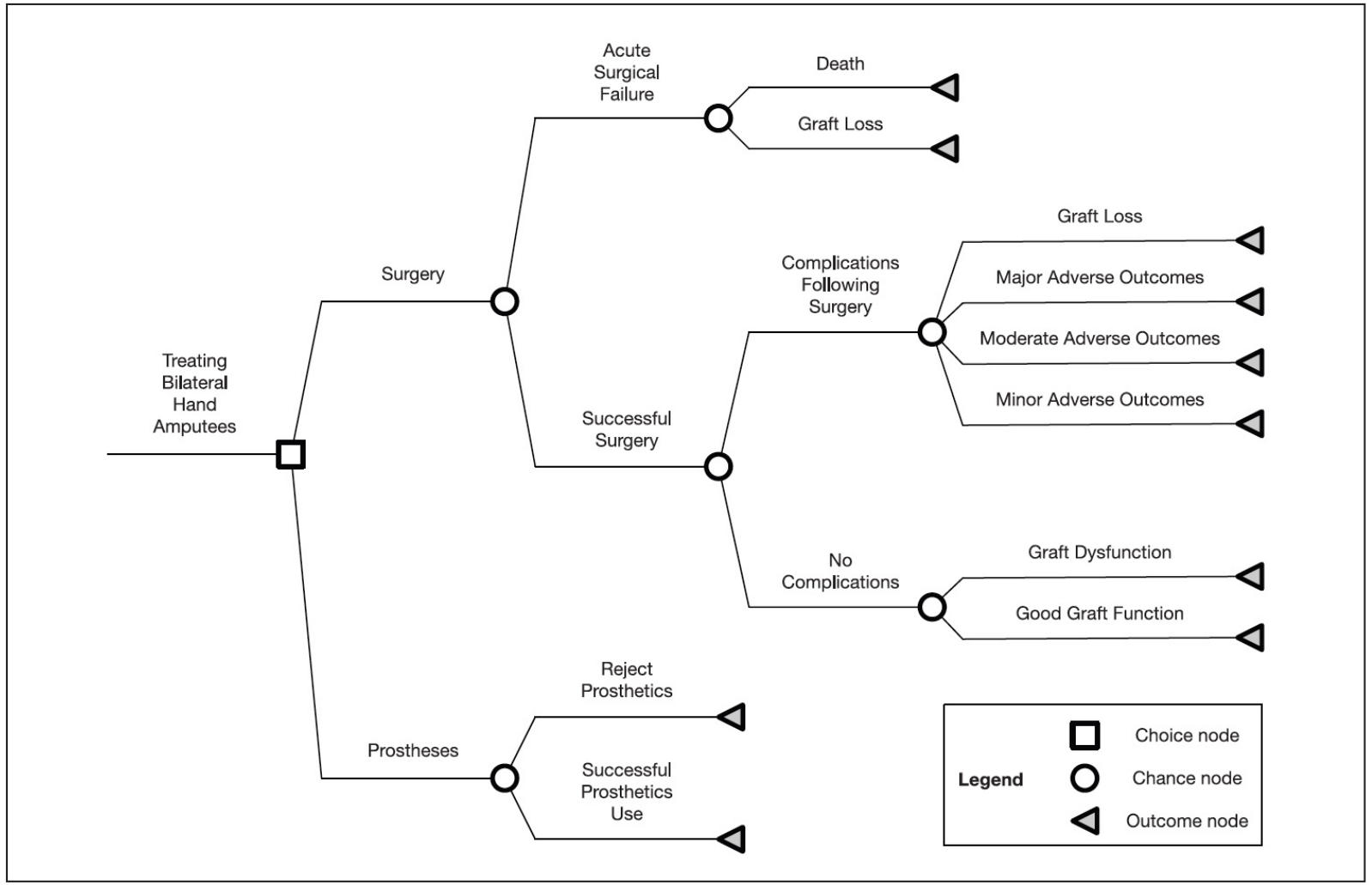


Figure 1. Model decision tree structure.

Table 1. Values of Utilities and Probabilities.

Variable	QOL utility	P	Background information
Healthy VCA following surgery	0.83	.3	0.83 was collected from hand amputee patients using the time-trade off approach. Due to the amputation-specific population, this value has been selected over the values used in the previous 2 decision analyses[11] Research team estimate
Graft failure	0.62[10]	.08[11]	0.62 = Found in CEA registry, from Chung et al.[10] *"Bilateral hand amputation with hand transplant, resulting in graft failure."* *"Out of 24, hands, 2 were lost due to immunosuppression non-compliance and severe inflammation."*[11] (2/24 = 0.08)
Minor complications			
Minor infection	0.8254[12]	.8[13]	For minor infection, the research team used the utility of pneumonia. Discount utilities were not reported in this paper, but are reported in the CEA registry, with pneumonia having a discounted utility from healthy of 0.954. Applied to hand transplant: (1 − 0.954 = 0.0046, 0.83 − 0.0046 = 0.8254)[12] All but 1 patient reported positive for infections[13]
Nonmelanoma malignancy	0.82[14]	.167[15]	0.96 for traditional excision. TTO revealed delta of 0.01-0.03, which was applied to the health utility of a healthy transplant (0.83 − 0.01 = 0.82)[14] 1/6 = 16.7% of bilateral hand transplant patients developed skin cancer[15]
Moderate complications			
Vasculopathy	0.76[16]	.06[17]	Chronic allograft vasculopathy in adult patients. Value was determined by expert opinion.[16] Probability of developing moderate to severe vasculopathy at any age is 6%[17]
Acute rejection	0.81[18]	.71[19]	CEA registry value for a good medical outcome, 3 years' post-acute rejection in pediatric liver transplantation patients. Good medical outcome value of 0.86, therefore a change in value of 0.02. This discounted value was applied to the value of healthy VCA (0.83 − 0.02 = 0.81)[18] "At least 71% of hand transplant recipients reported at least one episode of acute rejection in the first transplant year."[19]
Chronic rejection	0.74[18]	.09[20]	CEA registry value for chronic rejection in pediatric liver transplant patient. Reported value of 0.77, compared to good medical outcome of 0.86, discount factor = 0.86 − 0.77 = 0.09. Discount factor applied to healthy VCA (0.83 − 0.09 = 0.74)[1] "Chronic rejection occurred in 9% of the cohort (n = 167)."[20]
Moderate infection	0.75	.45	Interpolated from mild and major infection Probability interpolated
Chronic kidney disease	0.63[21]	.18[2]	Health utility values found using TTO for 6 subgroups divided based on glomerular filtration rate. Selected sub group with largest sample size, eGFR < 15, reported health utility at 0.77, compared to perfect health at 1. Discount factor = 1 − 0.77 = 0.23. Discount applied to transplant health: 0.83 − 0.23 = 0.6[1] 18% Reported in the current manuscript of the transplantation report through the Children's Hospital of Philadelphia[2]
Hypertension	0.808[22]	.15[23]	Hypertension has a disutility of 0.022. When applied to a healthy hand transplant patient: 0.83 − 0.022 = 0.808[22] Hypertension was reported in 3 out of 33 patients that underwent hand surgery (15%)[23]
Major complications			
Diabetes	0.64[24]	.285[25]	The diabetes health utility was based on a model regarding diabetes-related quality of life, where 0.64 was the lowest reported diabetes health utility with no other complications.[24] 28.5% developed metabolic disorders over the first year, 13% being diabetes mellitus[25]
PTLD	0.6[26]	.095[27,28]	CEA registry value, reported from Evers. Utility value used in a pediatric model of pre-emptive virology screening in bone marrow transplant patients, recognizing monoclonal PTLD. Raw value from Groot et al. No specification on collection method.[26] A range of pediatric incidence after transplant of 4%-15%.[27,28] The expected value is the average of this range.
Major infection	0.69[29]	.117[30]	Value reported from patients with sepsis.[29] Of the transplant patients admitted to the ED, 11.7% had severe sepsis[30]
End-stage renal disease	0.45[31]	.03[32]	CEA Registry reported health utility of 0.62. Paper used TTO, with relative utility compared to perfect health (1 − 0.62 = 0.38). Reduction factor applied to successful VCA base-case (0.83 − 0.38 = 0.45)[31] End-stage kidney disease was reported at 3% in children with nonrenal transplantation[32]
Death from surgery	0	.05	Research team estimate
Death from major complication	0	.1	Research team estimate
Probability of a successful surgery	n/a	.95	Research team estimate
Rejection of prostheses	0.63[10]	.295[3]	Value represents a bilateral amputee using the TTO approach, however this vale represents using a prosthetics, and therefore may be much lower[10] Rejection in children ranged from 10%–49%.[3] The mean of this range was calculated and used as the expected probability factor
Graft dysfunction	0.73	.2	Research team estimated graft dysfunction utility as being halfway between full utility of the graft (0.83) and utility with loss of the graft (0.62). Probability was a research team estimate.

Note. CEA: Cost effectiveness analysis; eGFR: estimated glomerular filtration rate; TTO: time trade off; ER: emergency room; QOL: quality of life; VCA = vascularized composite allograft; PTLD = post-transplant lymphoproliferative disorders.

- Model has within it many different outcomes (variables)
- Model depends upon the values of utilities and probabilities for each of these outcomes

Methods

Assumptions

We created a series of assumptions to guide the model scenario, consistent with standard practice in the development of decision models. The model's assumptions are as follows:

I. The transplant patient is 8 years old, sufficiently mature and motivated to engage in a prolonged intensive rehabilitation program, and with an expected life expectancy of 80 years, unless the patient dies due to complications from the transplants.

- This is a key – and big – and uncertain – assumption.
- Without prolonged diligent engagement in rehabilitation, the magnitude and probability of benefiting drops
- This implies both the child's and a parent's or family's commitment

Brief detour

- We have an intuition that life-saving therapies are governed by different ethics than life-enhancing therapies.
- Why?
  - “You must choose a life-saving therapy so as to not die, but you don’t need to choose a life-enhancing therapy”
  - For life-saving therapies, the clock is ticking … for life-enhancing, one can always wait and do it later
- Notice:
  - Benefit of life-saving therapy usually not assured or unsullied
  - The clock may also be ticking for life-enhancing therapy …

Another assumption

- For the modeling, we presumed that the benefits arising from the functional improvements from the two transplanted hands were not dependent upon the age at which the transplant occurred (other than that a younger patient would have more years to accumulate potential benefits).
- In practice, we did consider whether children might learn better/faster than adults but be less motivated to do rehabilitation.
- We learned, however, that the transplanted hands may have a beneficial impact on the developing brain.
- If this phenomenon turns out to indicate that there is a “critical window” of time for maximal benefit, the “wait until they are an adult” approach would reduce potential benefit.

Discussion

Our model shows that bilateral hand transplant surgery was the favorable decision despite the risks of immunosuppression. Since the difference in QALY values between surgery and prosthetics was minimal, using prosthetics may be the more favorable decision in some circumstances. Most importantly, the patient's and family's willingness to tolerate the immunosuppressive risks and reduce the child's lifespan are key determinants. These factors should therefore be key elements in the informed consent process.

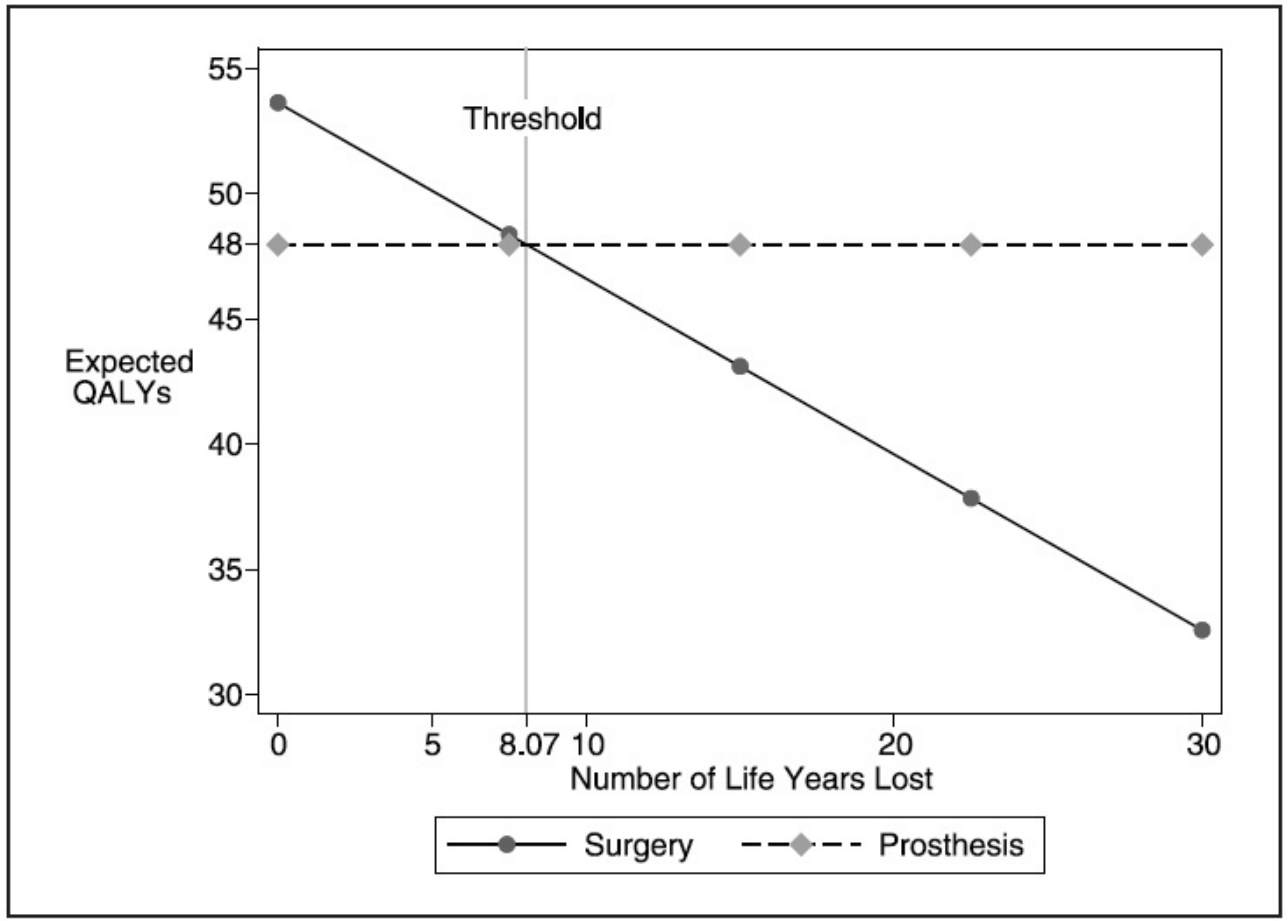


Figure 2. One-way sensitivity analysis on the number of life years lost due to a major adverse outcome. A significant threshold was identified at 8.07 (48 QALY), where if the lifespan is shortened by more than 8.3 years, prosthetics are the favorable decision. QALY = quality adjusted life year.

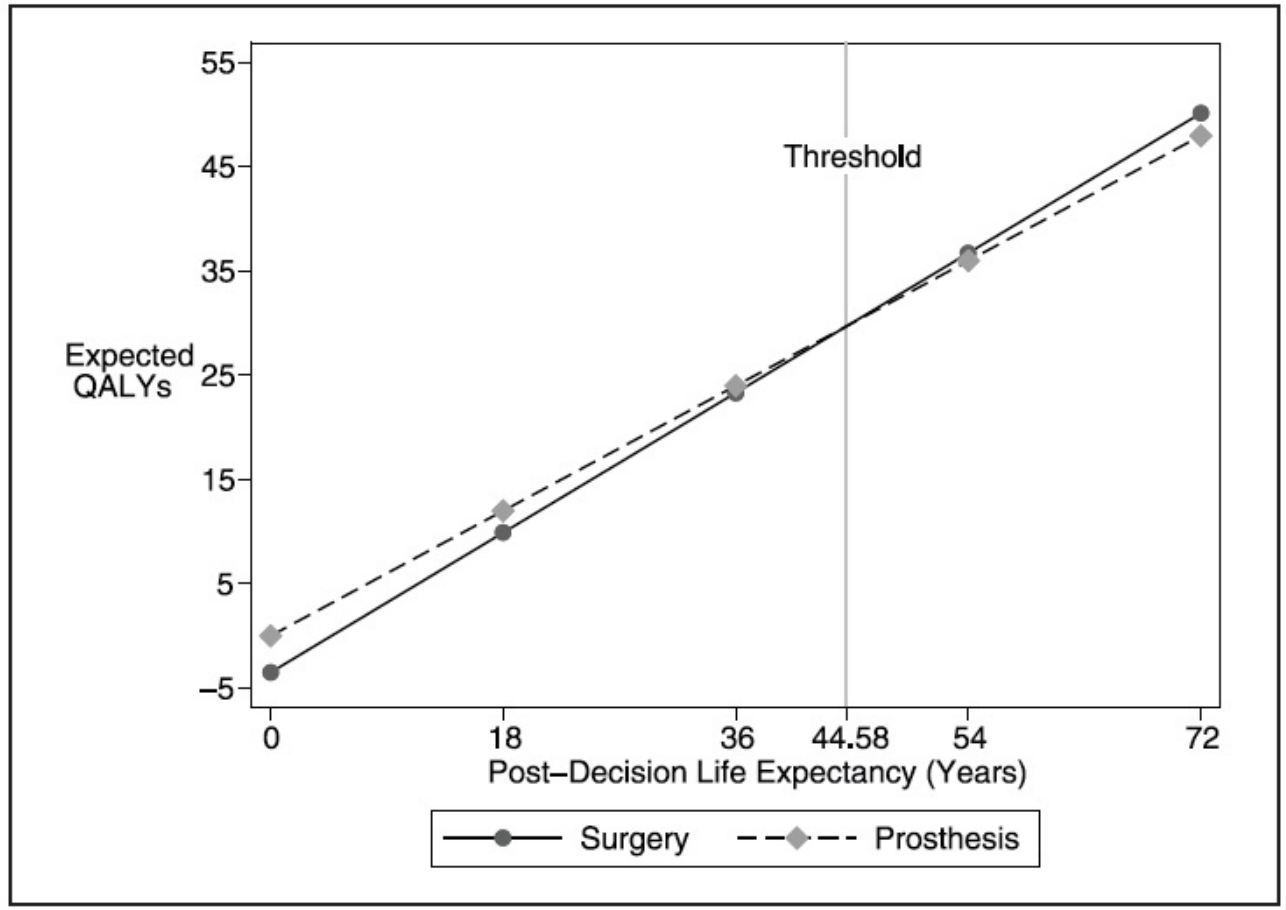


Figure 3. One-way sensitivity analysis on the number of years in the life expectancy, assuming an age of 8 at the decision. A significant threshold is identified at 44.58 years, where once added to the age of decision (8), shows that the patient must live to the age of 52.58 in order for the transplant to be the preferred option. QALY = quality adjusted life year.

Risks of Immunosuppression

The most direct risks related to bilateral hand transplant surgery are related to the post-transplant immunosuppressive regimen. Complications from immunosuppression contribute to a shortened lifespan, as well as potentially life-threatening medical complications. Our model determined that as the risk of developing complications associated with immunosuppression decreases, the decision to perform surgery becomes more optimal. As research continues to focus on reducing the adverse effects of immunosuppression, the decision to operate will become more favorable in more pediatric cases, particularly if the benefits offered by prostheses do not increase.[33] Future research, however, is equally likely to boost the level of acceptability and function of hand prostheses. The net balance of these 2 possible lines of research developments will perhaps be the most important determinants of the future suitability of pediatric bilateral hand transplant.[34]

Reduced Immuno-Suppression Risk

Improved Prosthesis Acceptance & Function

Aversion to loss (of years of life)

- VCA transplants present the tradeoff (potentially) between:
  - Improved quality of life vs Decreased quantity of life

- While the Quality Adjusted Life Years approach of decision modeling takes this into account, individuals likely differ regarding their aversion to trading off:
  - Fewer years of life for greater QOL during earlier years

- We created Aversion Weights (Aw) to examine this potential effect

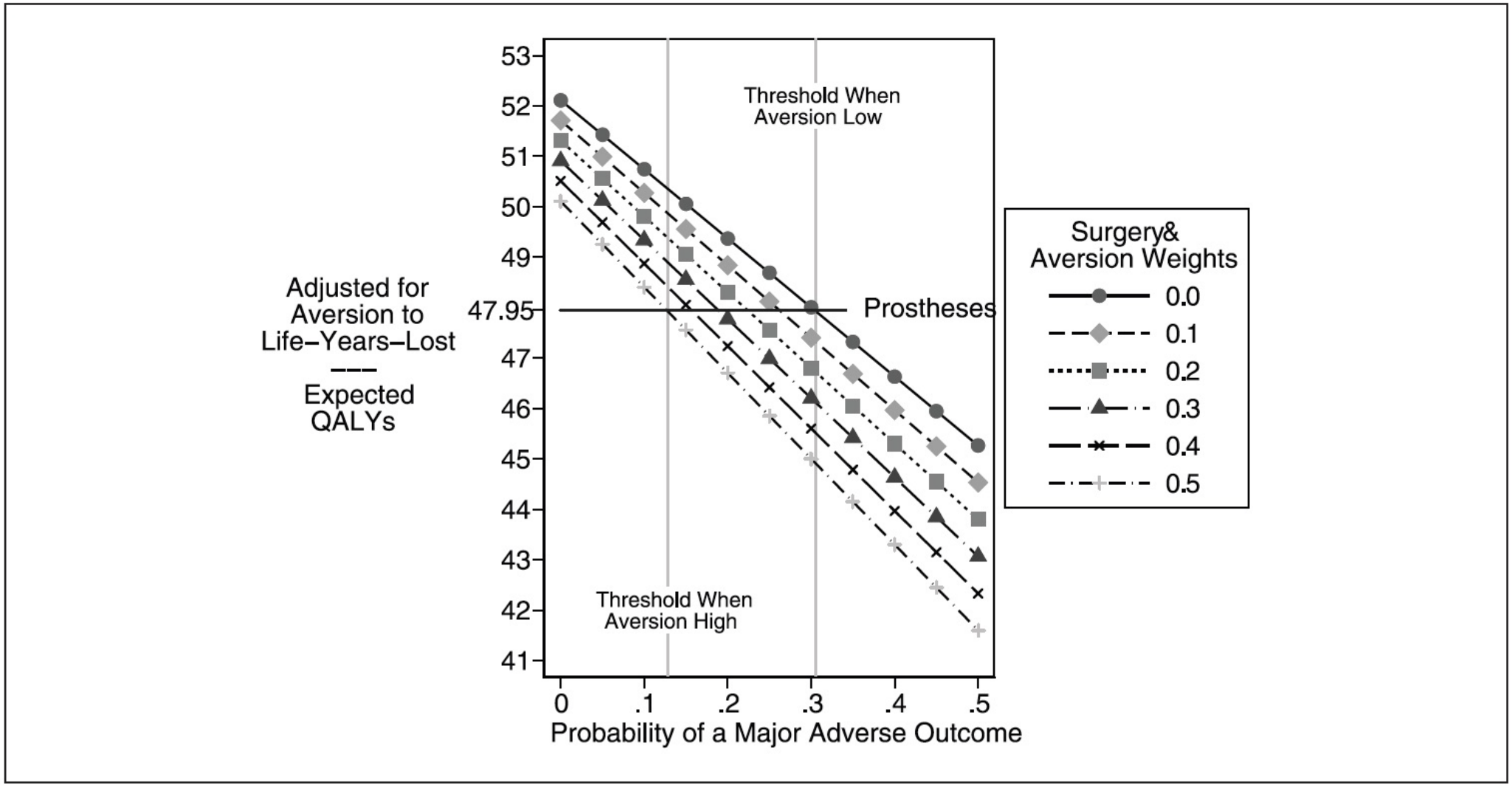
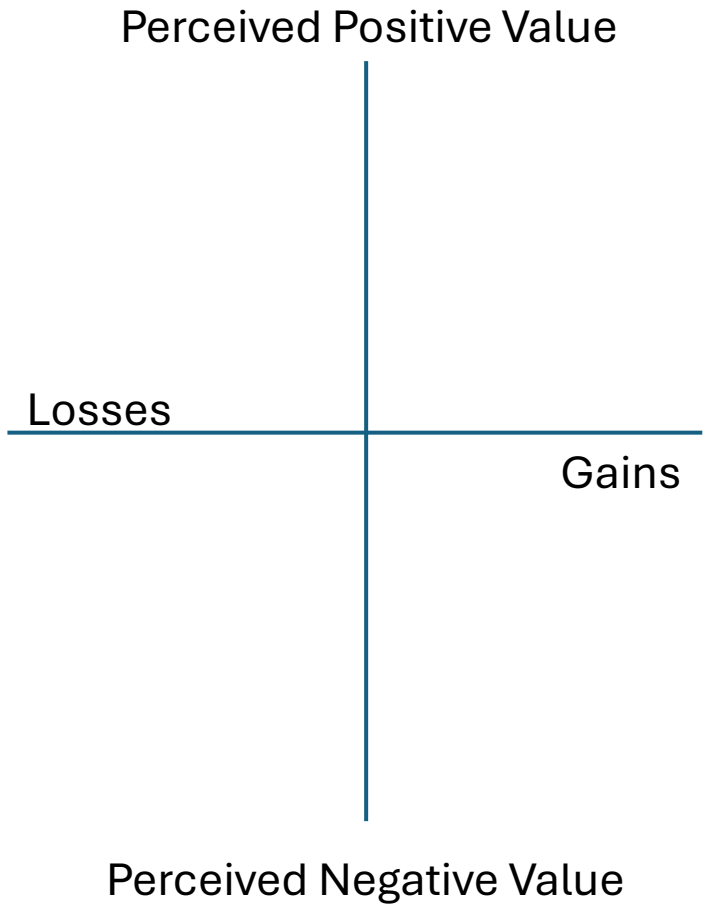


Figure 5. One-way sensitivity analysis on the probability of developing a major adverse outcome, with 5 aversion weights. As the patients (and their family) are more averse to trading life years, the probability of developing a major adverse outcome must decrease in order for surgery to remain the favorable decision. QALY = quality adjusted life year.

Valuation of Years of Life Foregone

By reducing the QALY outcome by the Aw, we were able to demonstrate that regardless of the observed quality of life and life expectancy, an aversion to trading away years of life may be just as important to families when evaluating whether to have the transplant surgery. Exploring this patient and family value may be particularly important during psychological evaluation of a patient (and their family) prior to surgery. Furthermore, as a child matures, he may become more averse to potential lost years of life, which could lead to resentment toward his parents for making the transplant decision on his behalf. Therefore, a comprehensive informed consent process will be particularly important for bilateral hand transplantation surgery, in order to ensure that both parents and children understand to the best of their abilities the risks associated with a shortened lifespan related to undergoing the operation.

Prospect Theory



We hate losses more than we value gains.

Face transplantation

- Quality of life = physical + psychological + social
- Extensive facial disfigurement can radically impair all three
- Causally, people may not perceive the function of the face the way we do hands, but we all are deeply dependent upon our faces
- Childhood and the transition to adulthood are time periods where social and psychological wellbeing are critical.

Thank you.