REVIEW

The Baltimore Criteria for an ethical approach to penile transplantation: a clinical guideline

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SUMMARY

Significant advances and increasing acceptance of vascularized composite allotransplantation (VCA) have contributed to emerging success of penile transplantation. The aims of penile transplantation are fourfold: adequate urinary function, enabling natural erections, restoration of erogenous sensation and appearance of external male genitalia. Successful penile transplantation also requires limiting risks and managing complications of lifelong immunosuppression. Given the limited experience with this procedure, potential recipients must understand that penile transplantation is not currently standard of care and long-term functional outcomes are unknown. Moreover, these transplants are associated with complex ethical issues. Nevertheless, as the efficacy and safety of penile transplantation are being evaluated, clear indications for transplant are needed. Although preliminary recommendations have been proposed, a more comprehensive framework is needed. We performed a literature review for English language publications related to penile transplantation and ethics. Based on the results of the search, a review of prior recommendations, and our experience performing the first whole male genital allotransplantation including penis, scrotum and abdominal wall; screening and identifying potential donors and recipients for the procedure; and addressing the associated ethical issues, we propose guidelines for responsible penile transplantation: The Baltimore Criteria for an Ethical Approach to Penile Transplantation.

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Introduction

Historically, complex genitourinary (GU) reconstruction was most commonly performed for congenital defects, gender incongruence or following oncologic resection. More recently, complex traumatic GU injuries have resulted from improvised explosive devices (IEDs) in military conflicts [1,2] sometimes involving loss of the entire penis, scrotum, testes, perineum and abdominal wall. Many patients with these injuries have associated physical symptoms, especially impaired urinary voiding and sexual dysfunction [3]. Additionally, they often suffer devastating psychosocial distress, commonly manifesting with feelings of loss of identity, and suicidality [4,5]. Technical progress and increasing acceptance of vascularized composite allotransplantation (VCA) have advanced penile transplantation as an innovative reconstructive option for these individuals. The functional

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goals of penile transplantation are to provide a phallus with the ability to urinate, achieve erection and ejaculation. Unlike uterine transplantation, penile transplantation is not performed for reproductive purposes as donor germline tissue (i.e. testes) are not considered for inclusion with penile transplantation [6]. Successful VCA also promises to result in improved quality of life through increased intimacy between sexual partners, improved social integration, and feelings of masculinity. Nevertheless, VCA requires lifelong immunosuppression with its associated toxicities and high costs.

Should the efficacy and safety of penile transplantation become better established, clear indications for transplant and clinical practice guidelines will be needed. Preliminary steps have been taken to address this need. For example, a research protocol has been developed that delineates the technical and logistical aspects of the procedure [7]. In addition, some ethics protections have been employed for early penile transplants and recommendations regarding them have been offered [8–11]. However, a more comprehensive ethical framework, akin to that which is available for uterus transplant that is often referred to as the "Montreal Criteria", is not currently available for penile transplantation [12–14].

Given our experience performing the first whole male genital allotransplantation including penis, scrotum and abdominal wall with successful achievement of urinary and sexual function; screening and identifying multiple potential donors and recipients for the procedure; and addressing the associated ethical concerns, we propose guidelines for the responsible practice of penile transplantation. To this end, we first review the ethical issues that have arisen with the technical progress of penile transplantation. We then propose a set of appropriate indications for penile allotransplantation as well as the infrastructure needed for the responsible practice of penile transplantation: "The Baltimore Criteria for an Ethical Approach to Penile Transplantation".

Materials and methods

In February 2019, we performed a comprehensive literature review from inception to 13 February 2019 using three databases: PubMed, Scopus, and Google. Our aim was to select articles related to penile transplantation, including its historical development, experimental data, clinical results, expert consensus, public opinion and associated ethical issues. We excluded articles (i) unrelated to penile transplantation or (ii) not written in English. We searched with the key words "penis transplantation", "penile allotransplantation", "penis vascularized composite allotransplantation", and "penis transplantation ethics". Relevant English language articles, including original research, reviews (systematic and literature) and media reports, were selected for inclusion. Results are shown in Fig. 1.

Based on the literature, several of the authors (LMN, AJN, CC, DSC, YMR, RJR) created an initial draft of relevant considerations for an ethical approach to penile transplantation. A larger group was then formed composed of plastic surgeons, transplant surgeons and bioethicists who were part of the team who performed the world's first total penile and scrotum transplantation at Johns Hopkins Hospital. Over the course of six months, the group held several discussions to refine these considerations. Then, using the Montreal Criteria for Ethical Feasibility in Uterus Transplantation [12,13] as a model, we created the Baltimore Criteria for an Ethical Approach to Penile Transplantation, which builds upon the foundation laid by prior recommendations [8–11] while incorporating the current approach developed and used at Johns Hopkins.

The development of penile transplantation

The limited availability of appropriate animal models poses a challenge to preclinical studies of penile transplantation. In the few available reports, rats are the most commonly used model. The feasibility of allogeneic penile transplantation through nonvascular anastomosis [15] and then with arterial anastomosis to the distal corpus spongiosum [16] were demonstrated successfully in rat models. Autotransplantation rat models have also been used to evaluate the viability and function of a re-planted phallus with varying levels of success [17,18]. Additionally, a study with dogs showed similar success with allograft survival and restoration of urinary function [19]. Extending beyond nonhuman animal studies, a deceased donor study identified important anatomic details that had key implications for surgical technique [20]. Further, an ex vivo model was developed to assess rejection and its effects on erectile function [21].

The first human penile transplant was attempted in China in 2006. The recipient, a 44-year-old man, had sustained a traumatic injury to his penis. Although a technical success, the graft was explanted after 14 days due to psychological rejection [22,23]. In 2015, the first successful human penis transplant was performed in a 21-year-old man in South Africa who had sustained a penile injury during cultural circumcision [24]. Two

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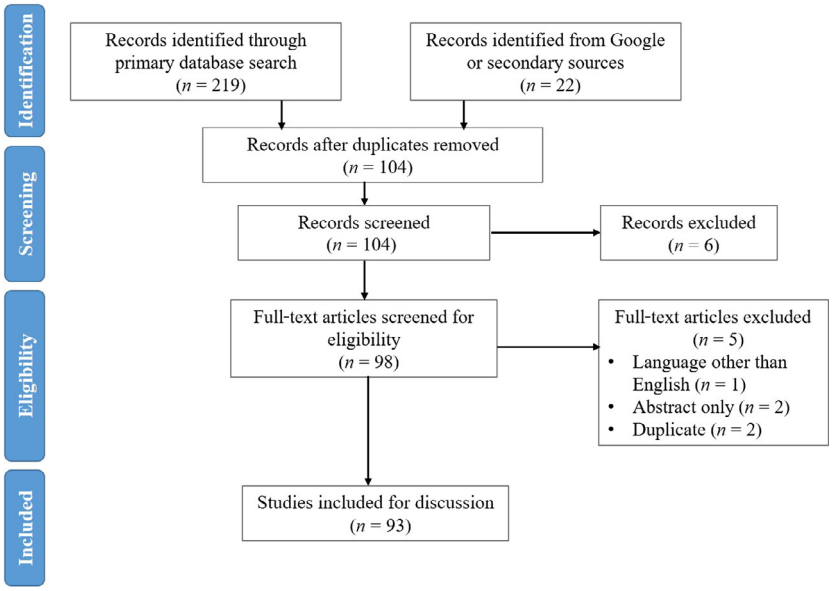

Figure 1 Literature review.

years following this landmark surgery, the recipient had regained abilities for urination, erection, orgasm and ejaculation [25,26]. In 2017, the same group performed its second deceased donor penis transplant [27]. Just prior to this, in 2016, a partial penile transplant from a deceased donor to a 64 year-old man following a penile amputation due to oncologic treatment was performed in the USA [28,29]. By six months following the operation, the patient had recovered sensation, adequate voiding function and partial erectile function. In 2018, the entire penis, scrotum (without testes) and part of the abdominal wall were transplanted from a deceased donor to an injured veteran who sustained a substantial injury to the abdominal wall and pelvic region caused by an IED [30]. One year after the transplant, the patient is voiding without difficulty and has return of erogenous sensation and the ability to obtain a full erection. Most notably, he reports his transplanted penis feels "normal" [31].

Ethical considerations of penile transplantation

The promising results above suggest that penile transplantation may become a realistic alternative to autologous reconstruction [32]. However, with technical successes come ethical challenges (Fig. 2). With a total of five procedures performed to date, penile transplantation at this stage is still appropriately considered experimental. The paucity of long-term data coupled with the prospect of lifelong immunosuppression is powerful risks that must be considered carefully when considering the possibility of transplantation. Although recent experiences have been salutary, earlier penile transplants were fraught with controversy surrounding informed consent and the harmful effects of immunosuppression [34]. While sharing similar ethical concerns with face and upper extremity VCA transplants in regard to balancing the life-threatening risks (immunosuppression) in exchange for improved quality of life, the intimate nature of the penile allograft arguably sets it apart, given the associated psychological burdens and potential effects on sexual relationships. For example, a patient's sexual partner may be unable to accept the graft as belonging to the recipient patient, thereby straining intimacy.

Preliminary recommendations to help navigate such difficult issues have been previously proposed [8–11]. These include recommendations regarding candidate selection, balancing benefits and risks, informed consent of the donor and recipient, use of a patient advocate and the funding implications of penile transplantation as a standard of care. However, despite its current experimental status, penile transplantation may be moving closer to becoming clinical practice. It is, therefore, imperative to establish clear ethical guidelines for clinical practice. In addition, a more comprehensive framework is needed.

Beauchamp and Childress' bioethical principles are a familiar approach to addressing issues in medical practice and research [35,36]. Table 1 summarizes the bioethical considerations associated with penile transplantation. The strengths of principlism include its structured approach to elucidate action-based solutions to complex ethical issues. However, this approach is

	Preclinical studies	Human trials	Ethical recommendations
2003	Nonvascular anastomosis of allogeneic PTx (rat)		
2004			
2005	Autotransplantation of phallus (rat)		
2006		Posttrauma recipient; explanted (China)	
2007			
2008			
2009	Arterial anastomosis of allogeneic PTx (rat)		
2010			Ten guiding principles for PTx
2011			
2012			
2013	Autotransplantation of phallus (rat)		
2014	Deceased donor study of PTx	Postcircumcision recipient; successful (South Africa)	OPTN/UNOS Final Rule on VCAs including PTx
2015			
2016	Allotransplantation of phallus (dog)	Postoncogenic recipient; successful (USA)	
2017	Immunosuppressive effects on penile function (ex vivo model)	Postcircumcision recipient; successful (South Africa)	Preliminary recommendations for ethical practice
2018		First GU Tx; post-trauma recipient; successful (USA)	

Figure 2 Timeline of preclinical studies, human trials and key ethical recommendations relating to penile transplantation [22–24,27–29,33]. *GU*, genitourinary, *OPTN/UNOS*, Organ Procurement and Transplantation Network/United Network for Organ Sharing, *PTx*, penis transplantation, *Tx*, transplantation, *VCA*, vascularized composite allotransplantation.

arguably incomplete. For example, a principlist approach can inadvertently overlook the moral virtues that are essential to ethically sound action, whereas virtue ethics provides an approach that privileges ways of acting. At the risk of oversimplification, principles may help elucidate *what to do* whereas virtues capture *how to* take an appropriate action. Some virtues that are especially relevant to the medical profession include prudence, trust, compassion, benevolence and intellectual honesty [47]. It has been suggested that both principles and virtues are needed to provide a balanced ethical approach [35,48].

The Baltimore Criteria for an ethical approach to penile transplantation

The Baltimore Criteria for an Ethical Approach to Penile Transplantation (Fig. 3) delineates four primary categories that incorporate both the principles and virtues for when and how determinations of ethical appropriateness for penile transplantation are being made: patient and donor selection, consent and privacy, postoperative concerns and institutional requirements.

Patient and donor selection

The process of patient and donor selection requires a thoughtful deliberation about choices surrounding indications of penile transplant, specific patient and donor selection and management of potential risks. Here the ethical principles of nonmaleficence and justice govern actions guided by the virtue of prudence.

Indications for penile transplantation

To date, most discussions about penile transplantation have focused on traumatic aetiology. In this context, extremity amputation related to IEDs and blast injuries

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Table 1. Beauchamp and Childress' four bioethical principles applied to penile transplantation

Bioethical principle	Key points	Relation to penile transplantation
Autonomy	*Self-determination* *Recipient informed consent* *Donor informed consent*	• Patients' wish for self-determination can often come into conflict into the physician's doctrine of "do no harm" • Therapeutic misconception occurs when individuals do not understand that the purpose of clinical research is to generate knowledge and participants may not benefit from the intervention [36]. Valid informed consent would require not only therapeutic misconception to be managed but for external pressures to be absent • Donor consent presents an additional challenge. All current penile transplants have been obtained from deceased donors. Thus, the decision falls to others. These decision makers must be given enough information and privacy to come to decision
Beneficence	*Improved quality of life* *Identity*	• For patients with severe genitourinary injury, transplant offers a chance of relief from psychological and physical anguish, and thus an improved quality of life. The metrics for success in penile transplantation mimic the goals of reconstruction: the creation of a functional (sexual and urinary) and aesthetic penis [37,38] • Gender identity has also been proposed as an important function of the penis [39], and its restoration can have profound psychological benefits [26]
Nonmaleficence	*Immunosuppression* *Physical risks of major surgery* *Psychological distress*	• The primary risk associated with vascularized composite allotransplantation is long-term exposure to immunosuppressants [40]. High-dose immunosuppression predisposes to infections, end-organ damage and malignancy [41]. Immunosuppression can present a threat to patient longevity in an otherwise healthy patient • There are physical risks related to surgery, in addition to risk of rejection. Novel strategies for monitoring allograft rejection also need to be created and evaluated. Due to the influence of vasculature on erectile function, graft rejection, even treated, has implications for function and thus, patient satisfaction • Postoperatively, patients can experience psychological distress that can be of sufficient severity to warrant removal of graft [22,23,42]
Justice	*Alternative treatment* *Established allocation criteria are needed* *Penile transplant may provide equity* *Penile transplantation is costly*	• Established alternatives currently exist to penile transplantation that bypass the need for immunosuppression, such as neophalloplasty, lengthening and replantation [43] • Allocation of resources should be according to need. Thus, an algorithm is needed to ensure equitable access to treatment • However, these alternatives carry their own limitations, such as a high complication rate [44,45] and the need for multi-stage surgeries. Thus, penile transplantation provides an option to those who do not qualify for the reconstructive approach, enabling equity in this select patient population • Penile transplantation is an expensive procedure that will benefit a select few. Additionally, it is still unclear who the costs will fall to. In the initial stages before integration into the healthcare system, it is imperative that the financial burden does not fall solely on the patient, thereby creating a selection pressure towards wealthy recipients

may compromise reconstructive donor sites. Conventional reconstruction is often precluded in such patients due to inadequate donor sites for autologous tissue transfer thus suggesting a priority for transplant. However, a lack of reconstructive options is not alone an indication for penile transplant. Previous recommendations emphasized penile transplantation as a last resort [9], following failed conventional reconstruction. Yet some have questioned the prudence of amassing failed reconstructive attempts before transplantation [49]. Consequently, surgeons should aim to preserve reconstructive options as part of a contingency plan in the event of allograft failure. The rationale for this is threefold. First, the superior functional and aesthetic outcomes of transplant may outweigh its associated risks. Second, there may be limited to no salvage options may

The Baltimore Criteria for an Ethical Approach to Penile Transplantation

Selection

1. Recipients should be adults who have suffered traumatic (following ≥ 6 months of recovery) or oncologic (with 5 year remission), significant phallus loss, or were born with ambiguous genitalia, and for whom other reconstructive options are infeasible or unacceptable to the patient.
2. Candidates who have passed clinical, physical and psychological assessment, and are seeking to achieve return of function (aesthetic, urinary and sexual).
3. Deceased donors (aged 16-65 years) should be matched for age (within 5 years) and skin tone when possible, with a healthy and functioning potential graft.

Consent and privacy

1. Recipients must provide informed valid consent (e.g. psychological and mentally capable, free from coercive influences). This would include demonstrating an understanding of the limitations and risks, including rejection and graft loss.
2. Given that express donor consent is unlikely in penile transplant, materials should be provided to the donor's respresentative who may act as surrogate decision makers to give informed consent.
3. Privacy of both donors and recipients must be protected and confidentially assured.

Postoperative concerns

1. Recipients should have a strong social support network with access to long-term psychological care. This care should also be made available to loved ones.
2. Long-term support of financial costs (e.g. surgery, immunosuppressive regime, psychological aid) must be identified before the procedure. This may include support from the institution, charitable donation, the patient or a third-party payer.

Institutional requirements

1. Adequate surgical trials and patient specific surgical planning should be achieved prior to transplantation. This should be accomplished with institutional support.
2. Procedures must occur at approved OPTN/UNOS transplant centers with a multidisciplinary team approach (e.g. reconstructive surgery, urology, psychiatry, infectious disease, and bioethicists), as per the OPTN Final Rule[1].
3. Protocols should undergo review by peers and an institutiional ethics committee. Wide dissemination should be encouraged to enable transparency.

[1] Electronic Code of Federal Regulations. CFR §121.4(e)(3).

Figure 3 The Baltimore Criteria for an ethical approach to penile transplantation. *OPTN/UNOS*, Organ Procurement and Transplantation Network/United Network for Organ Sharing.

be available for penile reconstruction if the transplant fails. Third, the uncertainty of graft longevity warrants preserving "back-up" reconstructive options.

Candidate eligibility

Allocation of life-enhancing grafts such as penile transplants ought to follow that of life-saving transplantation: allocation of resources is based on equity, priority and net benefit [50,51]. Judicious patient selection can help achieve these goals.

Thus far, the ethical difficulties associated with the use of a life-enhancing transplant in children [52–56] and donor matching concerns have limited penile transplantation to adults. It seems appropriate that this restriction should currently remain in place until additional evidence regarding the safety, efficacy and feasibility of penile transplants is available to inform the ethics analysis for several reasons. First, the potential risks associated with transplants are higher in children when compared to adults. For instance, they will be exposed to maintenance immunosuppression for a much longer period of time and are more likely to experience long-term toxicities related to this exposure such as cancer [57]. Additionally, adherence to an immunosuppressive regime may also present challenges, particularly in adolescence. Second, whether and when children can provide adequate consent is unclear and parental permission during childhood may not be ethically sufficient in these circumstances. Parents may provide permission for penile transplant, but once in adulthood those who received the transplant may disagree with the decisions that were made on their behalf and the long-term implications for them. Third, paediatric penile transplant is further complicated by donor matching, which presents a daunting

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challenge. For example, it would be inappropriate to transplant an adult-sized phallus to a child, but the alternative of an age-congruent phallus carries a risk of psychological distress in adulthood due to an age-incongruent phallus. Fourth, media interest has been high for the penile transplants completed thus far, and it is reasonable to expect a great interest when the first paediatric penile transplants are performed. Such intense scrutiny may negatively impact paediatric patients. Fifth, the lifespan of penile transplant is currently unknown, and it is possible that child recipients will require another transplant. Accordingly, alternative reconstructive options may be more appropriate until adulthood. Therefore, until penile transplantation becomes an established treatment, ethical barriers currently preclude children from being candidates for penile transplantation.

The penile transplants performed thus far have been limited to patients within the reconstructive or traumatic population, which helped to justify the potential risks. We propose expanding the eligibility criteria to include patients with oncologic extirpation who have a 5-year history of remission. We base this expansion on the following justifications. First, careful patient selection should minimize the risk of cancer recurrence in transplant recipients. The largest cohort study of penile cancer recurrence [58] to date reported that all regional and distant oncologic recurrence of penile cancer occurs within five years following resection. Most local recurrences occurred almost exclusively in men who had undergone penile preserving treatment. Given that any remaining native penile skin can be resected at the time of transplant, the risk of local, regional and distant recurrence of disease is negligible [29]. We also recommend that patients should also have significant penile loss before consideration of penile transplant. Similar to prior recommendations [10,11], the decision to proceed with transplant should be made when conventional reconstruction is deemed unsatisfactory and unable to meet the needs of the patient. Such decisions should be made following discussion not only with the patient but also with the plastic surgeons, urologists and transplant physicians and mental health professionals.

In addition, we believe the criteria should be expanded to include cis-gender men with congenitally ambiguous genitalia given that the functional abnormalities and severe psychological distress associated with congenitally ambiguous genitalia in an adult may warrant transplant. After all, outcomes from conventional reconstructive techniques are generally poor [44,45]. Although risks of penile transplantation are higher, the function of transplanted phallus may be superior to that of conventional reconstruction. Further deliberation regarding penile transplantation in transgender men is needed as described below.

Managing potential risks

Penile loss may not be regarded by some as being as socially disabling as facial disfigurement nor as functionally disabling as upper extremity loss. Therefore, penile transplantation may be subject to increased scrutiny when assessing its risks and benefits; an assessment that must be sensitive to emerging data regarding the procedure. The value of improved quality of life through improved urination, sexual function and aesthetic appearance needs to be balanced against the risks posed by lifelong immunosuppression, major surgery, and allograft failure or rejection. To be eligible for penile transplantation, candidates must be screened to ensure that they are physically suitable, able to understand the risks and potential benefits and deemed to be able to adhere to a lifelong immunosuppressive regime [30]. While the implementation of an immunomodulatory regime [59] has minimized the need for maintenance immunosuppression, concerns still persist for psychological and social risks.

Although penile transplantation may reduce psychological burdens, the possibility of post-transplant distress should not be underestimated [22,23,43]. Nonlife-saving transplantation holds unique challenges. Visible organs form an obvious component of the individual's identity [60]. Therefore, penile transplantation may alter the recipient's self-image in addition to affecting personal relationships. A resultant incongruence between a recipient's self-image and their reflection in the mirror can provoke psychological rejection and even requests for graft explantation. Psychiatric screening is used to assess suitability for transplantation and select out those without sufficient support to manage the associated burdens [61]. The experience from the first reported penile transplant described earlier underscores the need for careful psychiatric evaluation when determining whether a particular patient is an appropriate candidate for the procedure. Criticism of that initial procedure focuses heavily on the psychological rejection of the penile graft by the recipient and his wife [62,63]. Of note, psychological rejection was not uncommon in early life-enhancing transplants [43], such as upper extremity transplantation [64].

Donor selection

A major hurdle in any transplantation is donor graft recovery due to limited donor availability. The level of safety and quality of human tissues for transplantation must be maintained and optimized. This should entail a standardized process for donor selection and long-term follow-up, with a record maintained of any postoperative adverse events or outcomes. In addition to medical considerations including HLA matching and ensuring a healthy donor phallus (free of vascular disease, diabetic complications or sexually transmitted infections), attention should be paid to recipient preferences. The physical appearance of donor phallus must be congruent to the recipient's appearance and discussed candidly prior to listing, in hopes of limiting psychological stress post-procedure.

Although living donation is a medically and ethically accepted practice for certain life-saving and life-enhancing transplants [65], the use of such donors is not generally considered appropriate in penile transplantation due to the associated unacceptable loss of function suffered by the donor. Indeed, past recommendations have only discussed use of a deceased donor [8–11]. Nevertheless, gender reassignment surgery offers a potential source of living donors. Somewhat analogously, women donate their uteruses once they feel the function is no longer needed. However, the surgical viability and design of a penile transplant procedure from a living donor are still not fully understood. Currently, when performing feminizing genital reconstruction, the penile skin is used for vaginal reconstruction and the resultant denuded penis is inappropriate for transplantation. Therefore, further studies are needed to investigate this approach. Should there be preliminary evidence that such an approach is feasible, there will need to be careful deliberation about the appropriate criteria to implement in this setting. While this controversial issue is beyond the scope of this paper, these criteria will likely need to include some assurance that the decision to undergo gender reassignment surgery was made prior to the decision to donate a penis and there will be critical issues associated with ensuring confidentiality.

Consent and privacy

Those considering penile transplantation must have a clear understanding of the risks and potential benefits of the procedure. However, communicating these issues may be especially complex given positive media accounts of successful transplants. Here, the principle of respect autonomy is paramount guided by the virtue of trust. Clinicians are entrusted with the duty of protecting the interests of both donors and recipients.

Informed consent of the recipient

An appropriate transplant candidate must understand the physical and psychological risks and will be able to weigh them against the potential benefit of improved quality of life. To promote autonomy, recipients should have access to accurate information on the benefits and risks of penile transplantation, in addition to details on alternative procedures. Voluntary choice regarding whether to pursue a penile transplant must be assured, either through use of an independent patient advocate and/or one-to-one psychiatric screening, as previously recommended [11]. Media coverage can cause misinformation and widen the gulf between patient expectations and the true functional and cosmetic outcome of penile transplantation. Penile transplant is not a panacea, and assessment of potential psychological or emotional impairments to consent should also be undertaken. Physicians are ultimately responsible for judging whether a patient has adequate decision-making capacity and if valid consent can be obtained.

Informed consent of the donor

It is likely that family members will function as surrogate decision makers for deceased donors. Specific and separate permission must be sought for VCA donation; it is not included in the blanket consent indicated by the organ donor designation on a driver's licence or donor authorization card. Therefore, penile donation is determined by the donor's authorized representative [66]. Those seeking donations must provide accurate information about penile donation and transplantation that is sensitive to the very recent death of a family member.

Privacy

Following standard deceased transplant donation privacy practices, no information about the donor should be revealed without the express written consent of the donor family. It is possible that the donor family would wish to disclose penile donation but that the recipient would not wish to have his information disclosed. In such cases, the press or public may attempt to identify the recipient without the recipient's consent. For these reasons, policies and procedures should include donor

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family education as to the recipient's right for nondisclosure. Additionally, potential transplant recipients should be made aware of the possibility of donor family disclosure during the screening and consent processes.

Postoperative concerns

Penile transplantation, like medical practice in general, should strive towards patient-centred care. The ethical principle of justice supports the pursuit of penile transplants in certain situations. Postoperatively, recipients must have access to care and monitoring to ensure the continued wellbeing based on the ethical principles of beneficence. Virtues of compassion and benevolence are essential in implementing these obligations.

Recipient care

In a manner similar to other VCA transplants, longitudinal care is needed to maximize benefits and minimize medical and psychological risks. Extensive psychological counselling should be incorporated into pre- and post-transplant care to reduce the risk of transplant reversal and ensure the patient integrates the new graft with their sense of identity and bodily integrity [60]. Safer sex counselling is an essential part of recipient care because certain sexually transmitted infections may be particularly devastating. Given the intimate nature of penile transplants, sexual partners and others close to the patient should be involved in care if the recipient so wishes. Relationship counselling can be an essential component of pre- and post-transplant care. This also provides an opportunity to ensure the recipient has a stable and strong support network to aid with emotional adjustment post-transplant. In some instances, use of a patient advocate may be appropriate. The advocate acts with the recipient's best interests as their priority and may also provide support to others close to the patient, with the aim of improving the overall adjustment to the transplant. Patient advocates may also assist recipients in medication adherence and rehabilitation schedules.

Funding concerns

In 2018, 64% of US healthcare professionals were in favour of penile transplantation [40]. Two of the concerns identified by respondents were the lack of established donor sources and the impact on healthcare resource utilization. This is reiterated in earlier recommendations [9–11]. Considering the high expense associated with VCA, some may question whether penile transplantation can be justified. However, given the potential benefits of successful transplant – both physically and psychologically – in appropriate cases penile transplantation indeed seems justifiable. Of note, the costs of penile allotransplantation are comparable to that of other transplants [67]. Additionally, due to its small select target population, penile transplant is unlikely to be performed frequently enough to pose a large economic burden.

Nevertheless, even if penile transplants become standard clinical practice, there will likely be funding gaps from insurers. Therefore, institution performing the procedure must be willing and able to absorb costs for what may be the life of the transplant.

Institutional requirements

Penile transplantation cannot be reduced to a single event; rather, clinical care must continue over time. The ethical principle of beneficence requires that physicians maintain a persistent adherence to high quality of care of recipients and do so with compassion.

Ensuring safety

Penile transplantation is only appropriate when there is infrastructural capacity and sufficient clinical expertise to maximize safety and success. Moore proposed standards for ethically acceptable surgical innovation that offers a robust model upon which to identify such requirements. Following Moore's standards, any clinician seeking to perform penile transplantation should have the support of an institution with a strong basic science and clinical multidisciplinary team on hand [68,69]. Penile transplantation is a large undertaking, and institutional support is necessary for success. Those involved must possess sufficient expertise to embark on the task. This is addressed through stringent surgical team training, achieved through a combination of knowledge and adequate technical experience through laboratory trials. Extensive clinical experience in the techniques needed to perform the surgery, such as microsurgical reconstruction experience in the anatomical region, is also critical. Institutions seeking to conduct penile transplants should have experience with other more established VCA transplantation protocols, such as hand and face, thus making the transfer of skills possible.

Preclinical trials and preliminary data from human penile transplantation suggest that a valid and tested

immunologic regime specific to penile transplantation is an indispensable component of the postoperative care [59]. However, those involved must have knowledge of the rejection monitoring schedule and any contingency plans in the event of allograft failure.

Regulatory oversight

In the United States, VCA transplants are subject to the policies and bylaws of the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) [33] who act as a regulatory body and record outcomes. As such, penile transplant must occur within approved OPTN/UNOS transplant centres. Given the current state of limited experience with penile transplants, they should be considered to be research procedures and an Institutional Review Board should provide oversight along with a formalize approach to data monitoring, such as a data safety and monitoring board, as previously recommended [8–11].

Transparency and peer review should help promote a high ethical and research standard. At this stage of development, part of the goal in pursuing penile transplants is to generate generalizable, replicable knowledge that can be disseminated and further advance the field. All outcomes, good and bad, should be transparently published to inform others of the associated pitfalls and successes. This might involve participation in a transplant registry. An additional objective is to identify previously unknown risks and facilitate their correction in order to minimize harm to recipients.

Future considerations

We propose the Baltimore criteria to enable responsible continued development of penile transplantation. However, we recognize there is a need for additional deliberation and future adaptation in order to deliver optimal patient care. Should more favourable long-term outcomes be realized, it may be appropriate to broaden the scope of potential recipients. In the current framework, eligibility for penile transplantation includes those with traumatic or oncologic cause of penile loss, and genetic males born with ambiguous genitalia. However, the pool of candidates may be expanded in the future.

In the case of micropenis, it is important to establish the threshold at which transplant is considered therapeutic versus a form of "enhancement", a point of early debate in face transplantation [70]. While we argue for the inclusion of patients with congenitally ambiguous genitalia, a key distinction between these two patient subsets is the arguably limited functional impairment experienced by those with a micropenis.

The potential use of penile transplantation as a part of gender confirmation surgery presents different challenges, surgically and societally. As described earlier, work is needed on feasible surgical approaches before considering its use for transgender men. A recent survey in the United States in 2017 revealed that 40% of respondents believe that being transgender is a choice [71]. This could pose problems in seeking donations in this setting. Accordingly, education of the public and strategies to overcome the potential bias against donation of penile grafts for reconstructive transplantation are needed [69,72].

Importantly, restoration of fertility through concomitant transplantation of donor testes is not currently a goal of penile transplantation. Indeed, the US transplants that have been performed thus far have not included testes transplantation due to issues surrounding germline transfer from donor to recipient. Ethical considerations regarding the fathering of children via testes donation from a deceased donor preclude such a transplant from current and future considerations. However, further discussion of this complex issue is beyond the scope of this paper.

Conclusion

The Baltimore Criteria for an Ethical Approach to Penile Transplantation provides guidelines for candidate selection, identifying potential donors, maintaining the best interests of patients and addressing ethical and logistical concerns.

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Conflict of Interest

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