

Prevalence and Distribution of Potential Vascularized Composite Allotransplant Donors, Implications for Optimizing the Donor-recipient Match

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Background: Vascularized composite allotransplantation (VCA) is an emerging and growing field. Little is known about the prevalence and distribution of the adult potential donor population in the United States now that it falls under the oversight of the United Network for Organ Sharing (UNOS).

Methods: We assessed the UNOS database from 2008 to 2015 to estimate the prevalence and distribution of adult potential vascularized composite allograft donors. Donor inclusion and exclusion criteria were developed in a way to minimize risk to recipients and were applied to the dataset. Donors were categorized by factors that influence vascularized composite allograft matching including ABO blood type, cytomegalovirus status, and ethnicity (correlate for skin color) and sorted by UNOS region.

Results: Just under half of all brain dead donors met the inclusion/exclusion criteria. Blood type O, cytomegalovirus+, White donors represented the most frequent donor profile while blood type AB, cytomegalovirus-, Asian donors were the least common. UNOS region 3 had the most and region 1 had the least potential VCA donors per year. Nearly all potential VCA donors were solid organ donors with the liver being the most commonly donated solid organ in this population.

Conclusions: A large portion of the solid organ donor pool would qualify as adult vascularized composite allograft donors in the current UNOS system. These data will assist transplant teams in determining the prevalence and distribution of vascularized composite allograft donors for their individual patients awaiting composite allografts based on relevant matching characteristics in addition to standard transplant criteria. (*Plast Reconstr Surg Glob Open* 2018;6:e1833; doi: 10.1097/GOX.0000000000001833; Published online 18 June 2018.)

INTRODUCTION

Vascularized composite allotransplantation (VCA) is the transplantation of multiple tissue types (skin, fat, muscle, bone, nerve, vessels) as a single functional unit, often referred to as a vascularized composite allograft.

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The first attempt at VCA was made by Gilbert¹ in 1964 with a unilateral hand transplant. Unfortunately, primitive immunosuppression of that era was unable to prevent graft rejection, and the hand was amputated 3 weeks posttransplant.¹ In the 30 years following, improvements in immunosuppressive therapy led to huge advances in the field of solid organ transplantation and opened the door for further VCA research.

The first modern day VCA transplant occurred in 1998 with a unilateral hand transplant performed in Lyon, France.² Though the hand allograft was initially viable, patient noncompliance with immunosuppression therapy led to repeated rejection episodes and eventual amputation of the hand allograft after 2 years.³ A few months after the Lyon hand transplant, the Louisville team in the United States performed a hand transplant on a 37-year-old male who lost his dominant hand in a fireworks

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accident.⁴ The operation was successful, and the patient continues today with a functional allograft 18 years later.⁵ In the years following, there have been multiple successful unilateral and bilateral hand and arm transplantations.⁶⁻⁸

In 2005, 7 years after the first modern hand transplant, the first successful face transplantation was performed.⁹ Since then, the field of VCA transplantation has expanded worldwide and particularly in the United States with 26 United Network for Organ Sharing (UNOS)-approved programs as of 2016 (Fig. 1). World-wide there have been approximately 150 upper extremity transplants and 40 face transplants.^{8,10} In addition, transplantation of the abdominal wall, lower extremities, scalp, ears, larynx, uterus, and penis have been reported.¹¹⁻¹⁶

In the United States, solid organ donation and transplantation oversight is provided by the Organ Procurement and Transplantation Network (OPTN), which is operated by the UNOS under contract with the Health Resources and Services Administration.¹⁷ These governing bodies oversee the operations of 58 organ procurement organizations (OPOs) throughout the country that provide organ procurement and distribution services to donor hospitals and transplant centers, facilitate the consent process, screen for disease, and package and label organs to be transplanted.¹⁸ Until recently, VCAs were considered a “gray zone” since not classified as “human

cells, tissues- or cellular- or tissues based products” and excluded from FDA oversight. Similarly, VCAs were not classified as “organs” and therefore were excluded from the regulations of UNOS.^{18,19} However, as the number of VCA centers increased, it became clear that oversight of VCA procurement and distribution was needed. Considering the similarity between VCA and solid organs, many stakeholders felt that VCA should fall under the jurisdiction and regulation of UNOS/OPTN.²⁰ In 2013, after evaluation of the characteristics of VCAs and the feedback received from the transplant community, the Department of Health and Human Services issued the final rule, effective July 3, 2014, which added VCAs to the definition of “organ” under the governance of the OPTN.¹⁹

The inclusion of VCAs into the final rule allowed for VCA donation to fall under the infrastructure and oversight of the OPTN/UNOS. This transition brings VCA more into the realm of mainstream transplantation, allowing for standardization of policy and protocols for donor screening, allocation, and procurement on the national level and at the individual OPO level. This transition will promote more widespread screening for potential VCA donors, thus allowing for better matching in VCA transplantation. Currently, little is known about the prevalence and distribution of potential VCA donors in the UNOS-based system. To better understand this, we utilized the

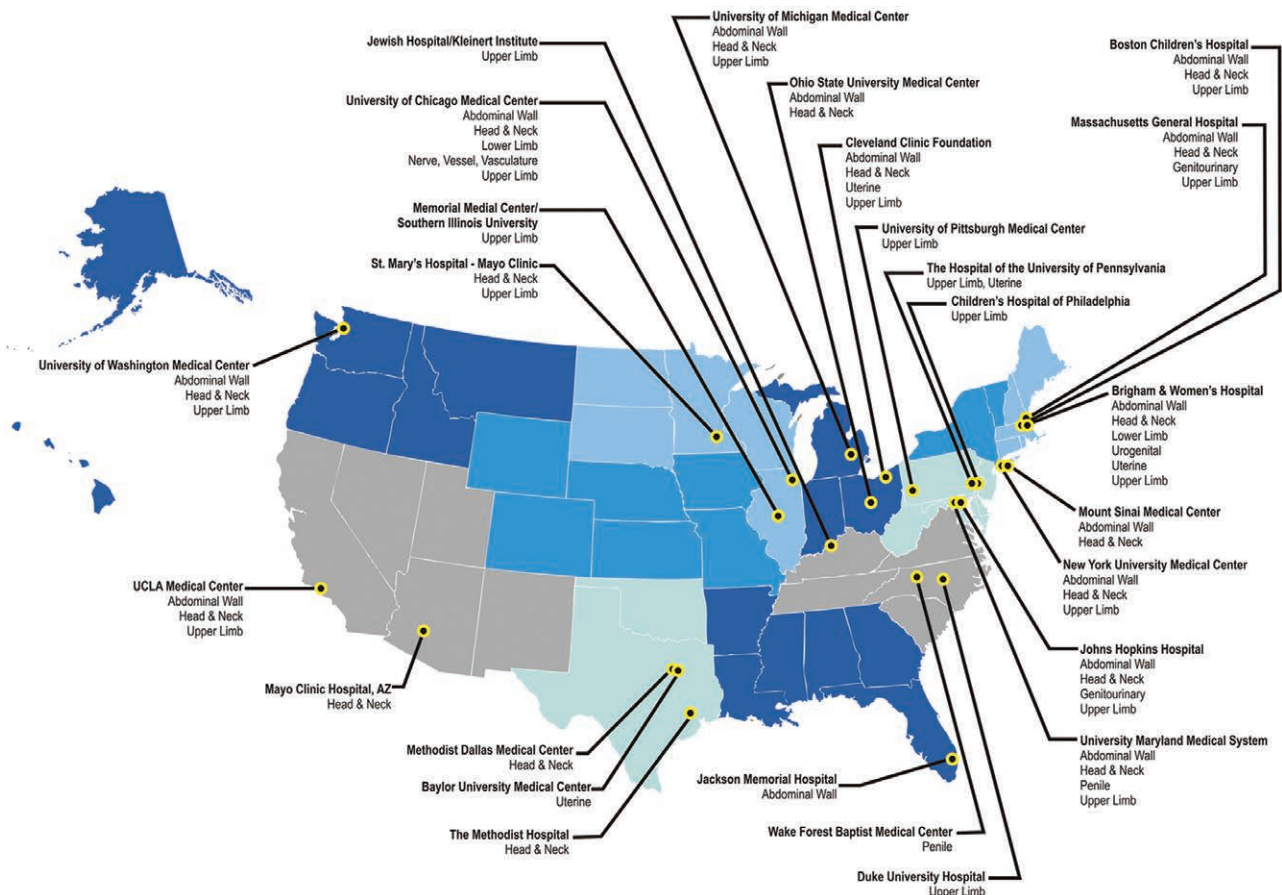


Fig. 1. Map of UNOS-approved VCA centers in United States. Distribution of VCA centers in the United States, and the VCA types approved at those centers (data obtained from the UNOS on June 20, 2016).

UNOS deceased donor database to determine the prevalence, distribution, and characteristics of potential VCA donors. We hypothesize that the potential VCA donor pool will be more than sufficient for the current demand for VCA transplants, which will allow teams to optimize the donor recipient match. This information will help VCA transplant centers better understand the potential donor pool for their individual patients under the UNOS system.

MATERIALS AND METHODS

A custom dataset was obtained from UNOS of all brain-dead donors in the United States from 2008 to 2015. The dataset included de-identified characteristics such as age, sex, ethnicity, height, weight, laboratory values, blood type, viral status, human leukocyte antigen (HLA) type, comorbidities, mechanism of death, and organ dispositions. The study was reviewed by our institutional review board and deemed exempt. Descriptive statistics including frequencies of donor characteristics were performed. To identify the prevalence of potential VCA donors, donor inclusion and exclusion criteria were developed similar to previously described criteria for hand VCA matching¹⁸ that would select for optimal donors with the lowest possible risk to recipients. These criteria included brain dead status, age 18–65, no recent history of malignancy, no Public Health Service increased risk for HIV/Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) transmission, no systemic infections, no severe organ failure (creatinine < 4, AST/ALT < 500), no actual HCV/HBV, and no history of prior myocardial infarction (surrogate marker for vascular disease), among other parameters (Table 1). A prevalence tree was built for various patient profiles based on blood type, Cytomegalovirus (CMV) status, and ethnicity (a rough surrogate for skin color matching necessary to VCA; Fig. 2) by using filters in Microsoft Excel for Mac 2011. The number of male and female potential VCA donors was analyzed since some VCA organs are gender-specific such as face and uterine transplants. Potential donors were separated by UNOS region, and the number of potential donors per year was calculated and averaged over the 8 years of data (Fig. 3).

RESULTS

From 2008 to 2015, there were 57,300 brain dead donors retrieved from the UNOS dataset. In total, 34,192 donors were excluded, 21,566 of which did not meet the inclusion criteria, and 12,636 that met the exclusion criteria. Overall, 40.33% (23,108) of all brain dead donors met criteria as potential VCA donors (Fig. 2). The proportion of potential VCA donors who were male was 59.7% versus 40.3% female. The region with the most potential donors per year was UNOS region 3 with 530 donors per year, whereas that with the least was region 1 with 84 potential donors per year (Fig. 3). The most commonly represented profile was that of white, blood type O, CMV+ donors, representing 16.21% (n = 3,746) of the potential VCA donor population, whereas the most poorly represented was Asian, blood type AB, CMV– donors, representing only 0.01% (n = 2) of potential VCA donor population

Table 1. Inclusion and Exclusion Criteria Used in the Present Study to Determine Prevalence and Distribution of Potential VCA Donors from the UNOS Donor Database

| Donor Inclusion Criteria | Donor Exclusion Criteria |
|--------------------------|---|
| Brain dead donors | DCD donors |
| Donation years 2008–2015 | CDC high risk for HIV |
| Aged 18–65 years | HCV, RPR positive |
| BMI 17–35 | HBV core or surface antigen positive |
| Creatinine < 4 | On 3 or more pressors at incision |
| AST < 500 | Infection blood source |
| ALT < 500 | Insulin-dependent diabetes |
| | Intracranial or extracranial cancer present |
| | Skin cancer present |
| | Prior MI |

BMI, body mass index. AST, aspartate aminotransferase; ALT, alanine aminotransferase; DCD, donation after circulatory death; CDC, Center for Disease Control; RPR, rapid plasma reagin; MI, myocardial infarction.

(Fig. 2). Similar to solid organ donation, across the board Asians and “other,” that is, Multiracial, Native Hawaiian/other Pacific Islander, and American Indian/Native Alaskan ethnicities were the most underrepresented, while whites were the most represented potential VCA donors. Hispanic and Black donors were similar in number and slightly more common than Asian or “other” ethnicities.

The liver was the most commonly transplanted organ in the entire VCA donor population with 86.0% of potential donors having their liver transplanted, whereas intestinal transplants were the least common with only 1.3% of the potential VCA donor population donating this organ. In total, 98.0% of donors deemed eligible for VCA transplantation donated at least 1 organ.

DISCUSSION

VCA transplantation has expanded significantly in the last 2 decades, beginning with the successful transplantation of an upper extremity in 1998. As the field has expanded, many questions remain unanswered, including the prevalence and distribution of potential donors, especially in light of the recent addition of VCAs to the OPTN final rule. The present study assessed the UNOS deceased donor database to determine the distribution and prevalence of potential VCA donors, finding that the adult donor pool appears more than sufficient to supply the currently low demand for vascularized composite allografts. These data provide evidence that finding an acceptable adult donor for VCA recipients will not be the limiting factor for VCA expansion in the future. It also provides a means of indirectly estimating the time it will take to obtain a donor while on the VCA waitlist by knowing the percentage of organ donors with similar profiles.

Currently, there is no standardized protocol when evaluating for VCA donors, and screening protocols vary between OPOs and transplant centers. However, the criteria applied to the UNOS deceased donor database in this study represents a starting point for VCA screening and is consistent with criteria currently used by many VCA centers to screen potential donors.¹⁸ After searching the UNOS database, we found that just over 40% of all adult organ donors meet these initial screening criteria for

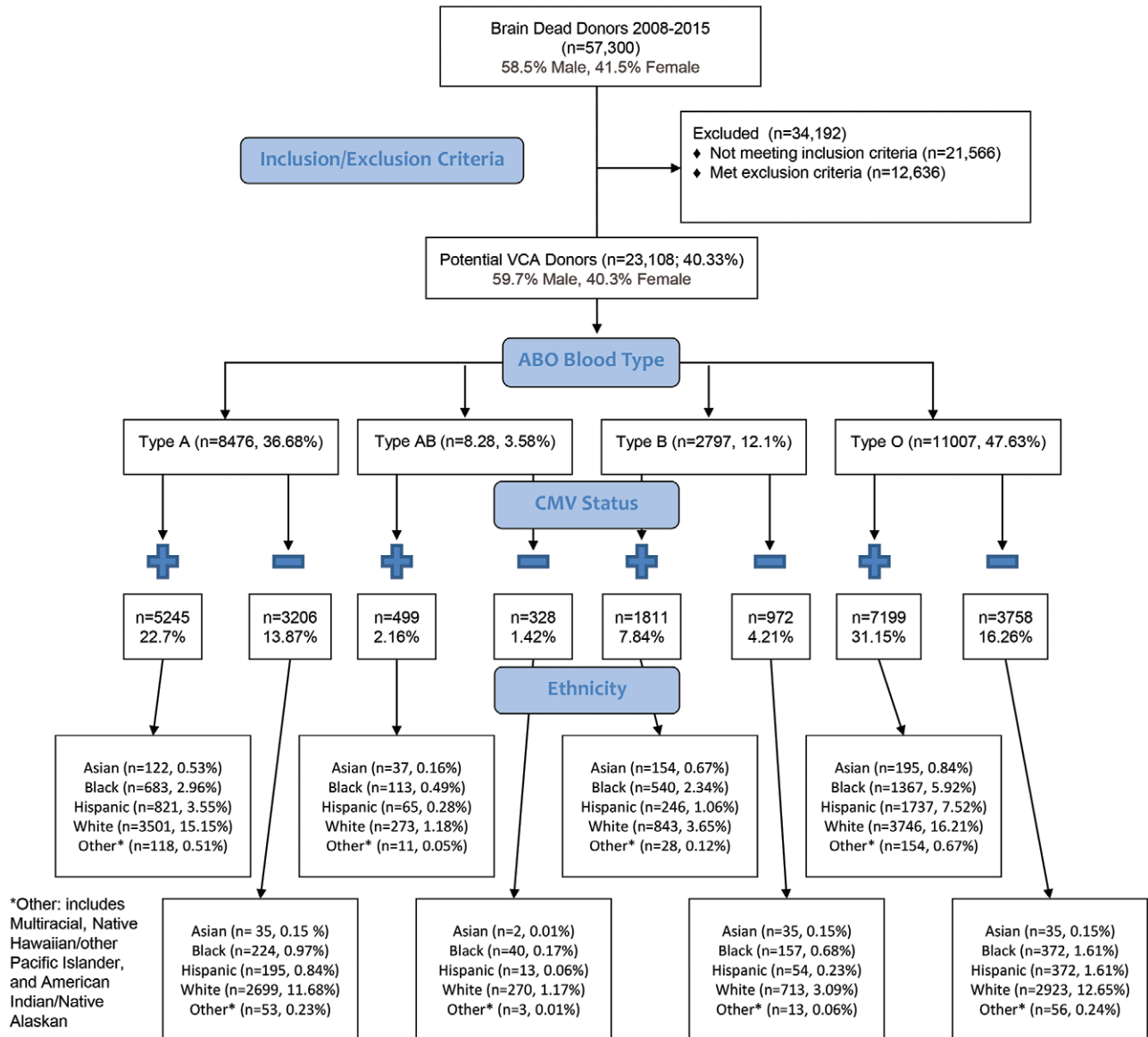


Fig. 2. Prevalence of potential VCA donors from UNOS database 2008–2015.

VCA donation. We acknowledge that this number is only a rough estimate of the potential donors and that many other factors come in to play for individuals waiting for a VCA transplant.

We categorized the estimated number of annual donors into UNOS regions to assess regional variations in donor availability. These data, which closely follow solid organ donation data, will give VCA transplant centers an idea of the number of potential VCA donors each year in their respective areas. Currently, VCAs are allocated first to compatible candidates within the OPO’s region, and then to those candidate’s beyond the OPO’s region.^{21,22} Eligible candidates are sorted by waiting time and must have compatible blood type with the donor, which is similar to the allocation strategies used for solid organs.²² However, solid organ allocation concepts are not completely transferable to VCA allocation because of the requirement to

match factors such as skin color/tone, the low ischemia time requirements of VCAs, and the relative few number of VCA centers. For this reason, the OPTN VCA allocation policies have remained relatively broad.²¹

The findings of this study underscore the importance of having a supportive OPO for the success of VCA. The number of potential VCA donors is not necessarily proportionate to a region’s success in facilitating VCA donation. In the present study, UNOS region 1 had the lowest VCA potential yet has had significant success in facilitating VCA donation. This region has facilitated VCA donation from 11 donors to 12 recipients since 2009 (6 face, 1 face w/ bilateral upper extremities, 3 bilateral upper extremity, 1 unilateral upper extremity, and 1 penis; The American Society for Reconstructive Transplantation annual meeting, November 3–5, 2016, Chicago, Ill.). Thus, another factor in increasing VCA transplants is the commitment of OPOs

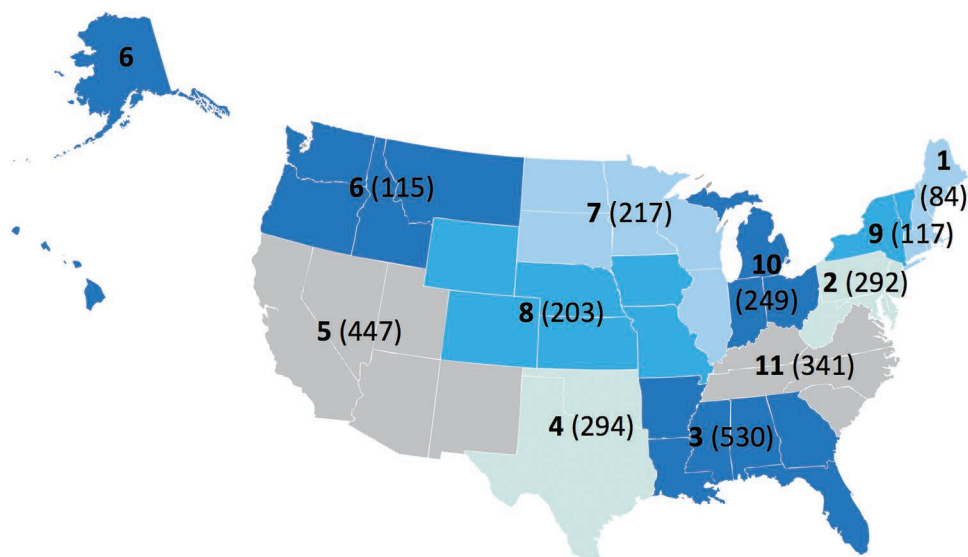


Fig. 3. Distribution of potential VCA donors per year by UNOS region.

to put standard processes and procedures in place to facilitate VCA donation and systematically pursue VCA donation when there is an appropriate VCA candidate match.

Finding a compatible VCA donor is more involved than a solid organ donor. In addition to the typical parameters of ABO blood type and HLA types, the visibility of most VCAs necessitates certain aesthetic variables to be accounted for in the donor allograft.¹⁸ These may include skin color and tone, hair pattern and color, lack of tattoos, and bone size depending on recipient preference. In the current study, after applying inclusion and exclusion criteria to the data set, donors were split into groups based on blood type, CMV status, and ethnicity. Because VCA transplants are not life-saving transplants, it is important to minimize morbidities caused by mismatch in CMV (and Epstein-Barr Virus (EBV)) status, so these are matched whenever possible. We used ethnicity as a rough correlate of skin color, which is an important factor to consider for VCA matching. We acknowledge that this is a very rough estimate of skin color and is only meant to provide a general idea of the prevalence particular VCA donors. We were unable to address bone size as a factor in the database query, as this parameter cannot accurately be judged based on body mass index or other variables available in the deceased donor database. We hope these data will be utilized by VCA centers as a starting point to estimate the prevalence of donors for a given recipient about to be added to the VCA waitlist, and therefore an indirect way to estimate time on the waitlist.

One of the limitations of the study is that we are unable to estimate the percentage of donor families who would actually consent to VCA donation. Under UNOS regulations, specific authorization for VCA donation must be obtained in addition to consent for donation of solid organs.²¹ Obtaining this authorization may be more difficult than for solid organ donation. Unlike solid organs, VCAs are not life-saving donations and alters the physical appearance of the donor's body, which may make some families hesitant to proceed with VCA donation.¹⁸ In ad-

dition, there is a fear that approaching families to obtain consent for VCA may jeopardize solid organ donation authorization. Although this has not happened yet to our knowledge, every effort should be made to prevent this by thoroughly training OPO staff to approach these authorizations with the utmost tact and respect.

Currently, the conversion rate (actual donors divided by eligible deaths) for VCA donation is unknown. Surveys suggest that potential donors are more willing to donate their hands (54.6–80.3%) than their face (44–58.2%).^{23,24} The New England Organ Bank experience from 2009 to 2014 demonstrated a 50% authorization rate of donors approached for VCA donation (International Hand and Composite Tissue Allotransplantation Society annual meeting, April 16, 2015, Philadelphia, Pa.); therefore, a more accurate estimation of VCA donors may be 20% of solid organ donors. Even using the lower end of these estimates, the number of VCA donors exceeds the current demand.

It is important to note that this study was limited by the variables available on the deceased donor registration worksheets (and their accuracy) that make up the UNOS database. An important factor for matching donor and recipient in solid organ and VCA transplantation in the degree of recipient sensitization to other human antigens as measured by the panel reactive antibodies. This variable impacts the number of potential donors for individual recipients and we were unable to account for this in the present study.

Despite an adequate supply of potential adult donors, there currently are very few VCA transplants performed annually in the United States. However, the recent inclusion of VCAs within the final rule definition of organ and subsequent oversight provided by the OPTN/UNOS will establish the necessary infrastructure to standardize the procurement and distribution of VCAs. In addition, OPTN/UNOS oversight of VCAs will raise awareness and help bring VCA transplantation into the forefront of the public and medical community.

The field of VCA transplantation is rapidly evolving. What was once an experimental procedure is now widely accepted as a reasonable alternative to traditional reconstructive strategies and prostheses and is even argued by some as a standard of care treatment for devastating injuries.^{25,26} The present study provides an early attempt to estimate prevalence and distribution of the adult potential VCA donor population in the United States, which may be useful to clinicians in determining the likelihood and indirectly the timing of finding appropriate donors for patients on the VCA waitlist.

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