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Umbilical Cord Blood for Transplantation – a Brief Summary Page # 1-2

Transplanting umbilical cord blood stem cells for the treatment of blood disorders and cancers was once controversial. Today, research has proven cord blood to be a viable alternative to peripheral blood and bone marrow stem cell sources, especially for those who have a hard time finding an HLA-matched donor from a registry. In some cases, using cord blood as a stem cell source has demonstrated superior transplant outcomes.

Islet Autologous Transplant for Chronic Pancreatitis Page # 3-4

Chronic pancreatitis causes irreversible damage to pancreatic structure and function and can interfere with a patient’s lifestyle. If the underlying cause of chronic pancreatitis resists medical treatment, a pancreatectomy may be necessary to prevent debilitating pain and life-threatening symptoms associated with necrosis and sepsis. A pancreatectomy would render the patient completely dependent on insulin injections and enzyme replacement therapy for life, however, the procedure combined with autologous islet cell transplantation, may present a sustainable option for chronic pancreatitis patients.

The New Kidney Allocation System (KAS): Basics and Trends Page # 5-6

Recent changes in the kidney allocation system have prioritized hard-to-match patients. Kidney transplant candidates who are very highly sensitized, are ABO blood-type incompatible, or have been on dialysis for many years are now receiving transplants at a higher rate. Another key change to the allocation system affects how recipients are matched to deceased donor kidneys, with a new focus being longevity predictability based on clinical data. Following three years of discussion and planning, UNOS/OPTN implemented these changes in December 2014 and has been tracking and reporting on significant trends and outcomes.

Current Use of Cord Blood

The National Marrow Donor Program (NMDP)/Be The Match is the world’s largest marrow match program and registry that assists with the matching of unrelated donors and allogeneic transplant patients. Their registry lists over 12.5 million potential donors and more than 209,000 UCB units. Through international connections, NMDP/Be The Match has provided access to over 24.5 million potential donors and more than 622,000 UCB units.

Figure 1: These two graphs from the NMDP/Be The Match program demonstrate the increased use of UCB over the last 7 years, although use has remained steady or slightly declined in the last 2 years. ¹

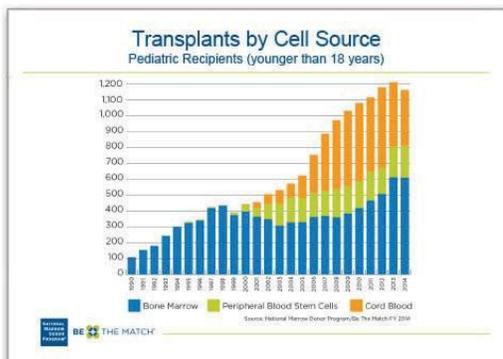
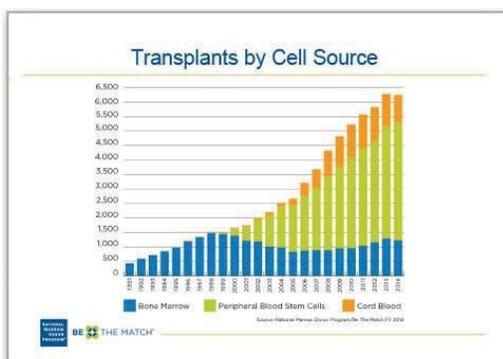
Umbilical Cord Blood for Transplantation

A Brief Summary — 2015

Hematopoietic stem cells are derived from three sources for transplant purposes: bone marrow (BM), peripheral blood stem cells (PBSC), or umbilical cord blood (UCB). The purpose of transplanting these therapeutic stem cells is to allow them to differentiate and proliferate into healthy white cells, red cells, and platelets following ablation. The ablative/ablation therapy (also known as the preparative/conditioning regimen) is given to the patient prior to the transplant and effectively destroys the patient’s own diseased/cancerous bone marrow and stem cell population.

There are two types of hematopoietic stem cell transplants. **Autologous transplants** use the patient’s own PBSC or BM after the ablative therapy. In these cases, the patient would not need to be treated with lifelong immune-suppression, as the infused cells are an exact match. **Allogeneic transplants** utilize stem cells derived from a related family donor or an unrelated donor and require lifelong immune-suppression and surveillance for rejection symptoms. Approximately 65 percent of allogeneic transplants are performed using PBSC, 20 percent are performed using BM-derived stem cells, and the rest using UCB stem cells.

A smaller number of allogeneic transplants utilize UCB as their source of stem cells and represent a different set of potential risks and benefits. These cells are collected from umbilical cords after delivery of a newborn baby, and the cells are cryo-preserved at an approved center for later use. UCB stem cells can be cryo-preserved for years;



¹ <https://bethematchclinical.org/Resources-and-Education>. Data accessed 10/2/15

The relationship between the number of stem cells infused at time of transplant and the recipient's body size plays an important role in the overall success of UCB transplant. Total nucleated cells, or TNCs, is the complete stem cell count of a cord blood unit and is derived from a standardized lab test. For transplant purposes, the TNCs are calculated by kilograms of body weight and a way to measure the volume of stem cells to be infused into the recipient.

Each UCB unit contains a low volume of stem cells. Due to their small size, pediatric patients typically require only one unit of UCB, while adult patients usually require two units – commonly known as the double cord. In 2014, approximately 30 percent of pediatric allogeneic transplant patients received a UCB transplant in comparison to 12 percent of adult allogeneic transplant patients.

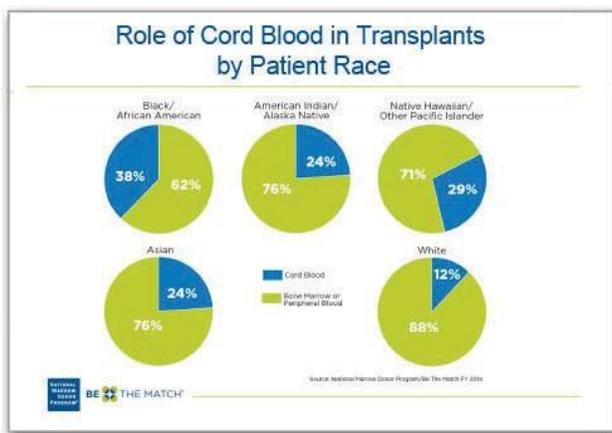
Advantages of UCB Transplantation

The availability of UCB provides a significant advantage over PBSC and BM procedures. Because UCB stem cells are stored at a cord blood bank, they can be available in as short of time as one week compared to the several months required to identify and confirm an unrelated PBSC or BM donor.

Patients who receive cord blood are less likely to develop acute or chronic graft-versus-host disease (GVHD) than those who have a PBSC or BM stem cell transplant. UCB transplants carry less risk of transmitting blood-borne infectious diseases when compared with transplants that use PBSC or BM of related or unrelated donors.

Another advantage of UCB is the greater availability of acceptable stem cells for transplantation of patients from diverse racial and ethnic minority backgrounds. Because Human Leukocyte Antigen (HLA) mismatch is better tolerated in UCB transplantation, the use of this stem cell source has been particularly beneficial for these patients who have traditionally had more difficulty finding a suitably matched BM or PBSC donor on volunteer donor registries. The NMDP/Be The Match data for 2014 show overall UCB transplantation rates of 29 percent for minority patients and 12 percent for white patients.

Figure 2: The accompanying chart shows the relative rates of UCB use by patient race.²



² <https://bethematchclinical.org/Resources-and-Education>. Data accessed 10/2/15

³ Masatsugu, T., et.al. "Comparison of Cord Blood Transplantation with Unrelated Bone Marrow Transplantation in Patients Older than Fifty Years." *Biology of Blood and Marrow Transplantation*. March, 2015. Vol.21, Issue 3, Pages 517-525.

⁴ Vanderson, R., Broxmeyer, H.E. "New Approaches for Improving Engraftment after Cord Blood Transplantation." *Biology of Blood and Marrow Transplantation*. January 2010. Vol. 16, Issue 1, Pages S126-S132

In general, there is greater latitude in HLA matching with UCB – especially with patients that have unusual tissue types. Recently, a retrospective review of transplant outcomes for patients over 50 years old was conducted for UCB transplants and unrelated BM transplants.³ The results demonstrated that patients with 7/8 allele-matched unrelated BM cells had the same 2-year survival outcome as patients with 4/6 – 6/6 allele-matched UCB cells (39 vs 38 percent, respectively).

Disadvantages of UCB Transplantation

One significant disadvantage of using UCB stem cells is the fact that engraftment takes longer for recipients, leaving them susceptible to post-transplant infections for a prolonged period of time. Once the infused stem cells have made their way into the bone marrow, the process of engraftment begins. Stem cell engraftment refers to the proliferation of new immune and blood-forming cells in the bone marrow. The number of cells needed for the best chances of engraftment and survival is based on the weight, age, and disease status of the recipient. Because the TNC count is lower in a unit of UCB, patients who receive this source tend to experience slower engraftment than those patients who receive the larger stem cell volumes from PBSC or BM transplants. Engraftment following a PBSC or BM transplant can generally occur within 15 to 20 days. Conversely, engraftment following a UCB transplant can take anywhere between 25 to 42 days. This results in a longer hospital for monitoring of life-threatening infections and engraftment outcome.

Research efforts continue to reduce the engraftment time and improve success rates after UCB transplants.⁴ Techniques and approaches include strategies relating to donor choice, engraftment, use of multiple donors, and accessory cell transplantation.

Costs of UCB Transplantation

The financial impact of UCB stem cell transplantation to the insurer and the family is significant. The estimated cost of a unit of UCB is \$60,000 (roughly double that of BM and PBSC sources). Additional costs are also associated with longer hospital stays for surveillance and possible treatment of life-threatening infections. However, the cost is balanced by the reduced risk and severity of GVHD and reduced time waiting for a transplant.

Islet Autologous Transplant (TP-IAT) for Chronic Pancreatitis

Each year approximately 15,000 Americans are diagnosed with chronic pancreatitis, resulting in over 56,000 hospitalizations. These patients suffer chronic, progressive and debilitating pain, multiple hospitalizations, opioid medication abuse and addiction, and significant quality of life dysfunctions. In addition, these patients are at increased risk for adenocarcinoma of the pancreas. The diagnosis is made mainly in middle age with twice as many men affected as women but children can also be affected. In many cases, genetic mutations cause children to be more susceptible to chronic pancreatitis.¹

The initial treatment for these patients has not changed appreciably over the past 20 years and includes medical management, drainage procedures, bowel rest with diet modification, and chronic percutaneous feeding tubes or total parenteral nutrition (TPN). Often, patients will have a co-morbid condition of diabetes with insulin dependence. When treatment options fail to relieve the symptoms, a total or subtotal pancreatectomy is sometimes performed.

Performing a total pancreatectomy will result in an iatrogenic type of diabetes labeled as 3c diabetes. Islet-autologous transplant after a total pancreatectomy (TP-IAT) was first performed in 1977 at the University of Minnesota to reduce the risk of this surgically induced diabetes. Since then, this procedure has become a viable option for patients that fail other treatments, with a goal of relieving the pain and reducing the burden of insulin dependence and diabetes. Currently, there are 12 centers in the U.S. performing the procedure.

Islets of Langerhans

Within the pancreas are areas called Islets of Langerhans, which contain the key endocrine cells. The largest proportion of cells in the islets is the beta cells which comprise approximately 65 percent of the islets and produce insulin. The counter-regulatory hormone to insulin is glucagon which is produced by the other main cells of the islets, the alpha cells. Patients with surgical removal of the pancreas develop type 3c diabetes with the total loss of both insulin and glucagon production. These patients often have brittle diabetes with all the manifestations of high and low blood sugars on their system.²

Patient Selection

One of the most difficult aspects for clinicians to determine is which patients would benefit from the procedure. Since the procedure is irreversible, it is the last resort for these patients and does not come with a guarantee that it will reduce or eliminate the most debilitating symptoms. The goal of the islet-cell transfusion is not necessarily to eliminate insulin dependence, but to reduce the risk of brittle and difficult to control diabetes. A successful procedure would eliminate the source of pain and replace the dysfunctional beta and alpha cells that normally control endocrine functions.

Evaluation should include confirming that pancreatitis is the primary diagnosis, determining that the pain is of pancreatic origin, monitoring the presence of diabetes, assessing the beta-cell mass, assessing the patency of the portal venous system, evaluating for liver disease, and determining immunization status.³

Since some of these patients may have had previous surgeries and a partial pancreatectomy, their overall chances for success may be lowered due to the reduced number of available beta cells that can be isolated and re-infused back into the patient. Therefore, it is incumbent on the medical team to keep this option in mind when recommending treatment for patients with episodes of acute pancreatitis, or flares of “acute on chronic” pancreatitis.

Most institutions consider active substance abuse, pancreatic malignancy, and poorly controlled psychiatric illness as major contraindications. However, if a patient can demonstrate management of their pain medications, and eliminate active substance abuse, they may qualify for the TP-IAT procedure.⁴

Total Pancreatectomy with Islet Autologous Transplantation

The TP-IAT procedure includes the removal of the patient’s pancreas, followed by isolation of the islet-cells in a special laboratory, and subsequent infusion of the islet cells into the patient’s portal vein. In most cases, the patient remains in the operating room while the cells are isolated in the lab. The cell isolation can be carried out in several ways, but generally involves a series of digestive enzymatic solutions and mechanical techniques to break apart the pancreas. The tissue is analyzed to determine the number of cells present, is then centrifuged, and the resultant cells are washed and prepared for the final step. After isolation, the cells are returned to the operating room and infused into the patient’s portal vein. These cells must engraft into the liver and start producing insulin. In some centers, the pancreas is transported to an FDA-approved islet isolation lab at the facility for this preparation. Some centers collaborate with another center to perform the islet cell isolation, but this type of remote isolation is associated with longer periods of cold ischemia, an additional surgery, and additional transportation and lab fees.⁵

Outcomes

Since the total pancreatectomy leaves the patient as a surgery-induced insulin dependent diabetic, the additional procedure of autologous islet-cell transplant is to prevent or minimize the surgical diabetes. Because the cells come from the patient, there is no need for immune-suppression. The number of islets transplanted is an important prognostic factor for insulin independence. A key factor to successful outcomes is the number of cells isolated and transfused. Minimizing the impact of post-surgical diabetes is the desired end result, and insulin independence is an important added bonus. Another key indicator of post-transplant success is reduction in pain control measures. Various studies have reported pain-free outcomes ranging from 23 to 82 percent.⁶

Approximately one-third of TP-IAT patients will become insulin free and one-third will require minimal insulin management. The remaining patients will continue to require daily insulin and 10 percent will result in complete graft failure. Patients who experience complete graft failure have exhausted all transplant options, and they remain with the significant risk of brittle diabetes.

¹ Bellin, M., et.al., “No Islets Left Behind: Islet Autotransplantation for Surgery-Induced Diabetes”, *Curr. Diab. Rep.* (2012) October; 12(5) 580-586. Doi:10.1007/s11892-012-0296-1

² Bellin, M., et.al. “No Islets Left Behind...”

³ Kesseli, S.J., et.al. “Total Pancreatectomy with Islet Autologous Transplantation: The Cure for Chronic Pancreatitis?” *Clinical and Translational Gastroenterology.* (2015) 6, e73:doi:10.1038/ctg.2015.2

⁴ Kesseli, S.J., et.al. “Total Pancreatectomy...”

⁵ Kesseli, S.J., et.al. “Total Pancreatectomy...”

⁶ Kesseli, S.J., et.al. “Total Pancreatectomy...”

Current research is underway to determine if other areas of islet cell implantation, such as the peritoneum, might yield a better function of the cells. It could mean that the patient would receive partial transplantation in the liver and a portion in another area of the body.⁷

Cost-Benefit

The average cost of the transplant phase of the procedure, using a laboratory at the facility is \$300,000. These costs must be measured against the overall costs of multiple hospitalizations, procedural care, medications, TPN and other feeding tube management, and lost productivity.

The decision to undergo a TP-IAT is a difficult one – both for the transplant team and the patient. The outcomes are mixed and the patient might be trading a condition of chronic pain for one of diabetes. As research and experience increases, one can expect to see changes in patient selection criteria that will help identify the best candidates for TP-IAT.

⁷ Kesseli, S.J., et.al. "Total Pancreatectomy..."

The New Kidney Allocation System (KAS): Basics and Trends

What is the new KAS and why was it implemented?

The number of solid organ transplants that occur in the U.S. is largely limited by the number of deceased organs consented for donation by the decedent or their immediate family. Access to this supply of deceased organs, which is fairly stable and far from meeting the demand, is managed by United Network for Organ Sharing (UNOS) and Organ Procurement and Transplantation Network (OPTN), along with organ procurement organizations (OPOs) managing the regions from which the organ is obtained. The methodology that UNOS and the OPOs use to assign organs to potential recipients is determined by an allocation system designed to make matching criteria more consistent, to create equitable wait-list times across the OPO, and to ensure that the right patients are receiving the right organs.¹ It is important that organ allocation systems are reviewed as demand changes and researchers learn more about transplantation.

The new KAS was implemented on December 4, 2014 with the goal of better serving an increasingly diversified waitlist and improving transplant outcomes within underserved demographics. Patients are being added to the UNOS kidney waitlist at an increasing rate which extends the wait time to transplant, creates a growing pool of hard-to-match candidates, and causes some patients, having waited several years on the list, to be transplanted in a sicker condition. The new KAS goals reported by UNOS are:

1. Make better use of available kidneys
2. Improve transplant opportunities for candidates who are difficult to match
3. Minimize unanticipated effects on key groups of kidney candidates²

The OPTN/UNOS Transplantation Committee recently issued its 6-month post-KAS implementation report that gathers data across all OPOs to measure the short-term impact of the new system. It will take time and data to judge the long-term impact of the new system on key indicators like patient and graft survival outcomes.

Making better use of available kidneys: KDPI and EPTS

For several years, the rate of transplants where the donor age differed from the recipient age by greater than 15 years has been increasing. The new KAS aims to correct such large age disparities and tries to ensure that expected patient outcomes match expected graft outcomes. The new KAS is based on a dual-classification and longevity-matching criteria using characteristics and values about the deceased organ and the patient receiving that organ. Separate scores are generated for both the deceased kidney and the potential recipient.

The kidney's score is called the Kidney Donor Profile Index (KDPI) score,³ ranges from zero to 100 percent, and predicts the likelihood of graft failure and how long the kidney is likely to continue functioning in comparison to other available kidneys. A lower score designates a kidney predicted to function longer than other available kidneys with lower risk of failure.

Some key aspects used to determine a deceased kidney's KDPI score

Some key aspects used to determine a deceased kidney's KDPI score are:

- Age of donor
- Height and weight of donor
- Ethnicity of donor
- Whether the donor died from stroke, brain and/or cardiac death
- Donor history of hypertension and diabetes
- Donor exposure to the Hepatitis C virus
- Serum creatinine as a measure of kidney function

Similarly, transplant candidates will be assigned a score called the Estimated Post-Transplant Survival (EPTS) score, which also ranges from zero to 100 percent, to predict how long a candidate will need a functioning kidney compared to other waitlisted transplant candidates.

Some aspects used to determine a candidate's EPTS score are:

- Age of Candidate
- Length of time on dialysis
- Having received a previous transplant, of any organ
- Current diagnosis of diabetes⁴

The KDPI scores and the EPTS scores are then analyzed to determine the best possible match. The closer the two scores, the closer the "match" between the kidney and the potential recipient. A KDPI score of 80 percent implies that the deceased kidney has an expected risk of graft failure that is higher than 80 percent of all deceased donor kidneys and is expected to remain functioning longer than only 20 percent of other available kidneys. Likewise, an EPTS score of 80 percent implies that the candidate is expected to need a functioning kidney longer than only 20 percent of other candidates on the UNOS waitlist. Ideally, a deceased kidney with a KDPI score of 80 percent will then match a transplant candidate with an EPTS score of 80 percent.

An example from the lower end of the scoring scale would describe the most robust kidneys and recipients. For instance, a KDPI score of 20 percent would estimate that the kidney is among the 20 percent of kidneys expected to function the longest. This kidney would then be "matched" to a patient with an EPTS score of 20 percent, who would be among the 20 percent of patients needing a kidney the longest. If for some reason a deceased kidney is not accepted by any of the candidates who match it, then it will be offered to another candidate regardless of EPTS score.⁵

Improving transplant opportunities for hard-to-match, highly sensitized and pediatric candidates

Patients who are sicker and/or older may not be able to handle long-term dialysis and would be assigned a higher EPTS score to match a deceased kidney with a higher KDPI score. Children and adolescents (under 18) are at risk for having development problems if they wait too long for transplant, so they would be given priority to be matched with the top 35 percent of deceased kidneys in the pool (organs with the longest predicted longevity).

¹ "How Organ Allocation Works." Organ Procurement and Transplantation Network. U.S. Department of Health & Human Services. <<http://optn.transplant.hrsa.gov/learn/about-transplantation/how-organ-allocation-works/>>.

² "New data shows kidney allocation system continues to achieve goals." UNOS Transplant Pro. <<https://www.transplantpro.org/news/education/early-data-suggest-kidney-allocation-system-meeting-key-expectations/>>. Published 11/5/15.

³ KDPI Calculator can be found here: <https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/>

^{4,5,6} The OPTN/UNOS Kidney Transplantation Committee. "The New Kidney Allocation System (KAS) Frequently Asked Questions." Organ Procurement and Transplantation Network. US Department of Health & Human Services. <https://optn.transplant.hrsa.gov/media/1235/updates_to_kas_faqs_october_2015.pdf>. Pp 5-7.

Highly sensitized patients with high calculated panel reactive antibody (CPRA) levels will be given a slightly higher priority than before, and very highly sensitized patients (those with a CPRA of 98 percent or higher) will be given a much higher priority. Candidates with rarer blood types will have a higher priority over those with more common blood types.

Finally, those on dialysis before being listed will have new wait times calculated based on when dialysis began. This again may present more opportunities for hard-to-match patients, such as ethnic minorities, to transplant sooner. It is important to ensure that a patient remains in contact with their transplant team at the facility so that the most accurate EPTS score and waitlist time is on file with UNOS.⁶

Is the new KAS meeting expectations and what trends need to be monitored more closely?

The OPTN/UNOS Kidney Transplantation Committee's 6-month, post-KAS "Out-of-the-gate" monitoring report, published on June 26, 2015, identifies four significant changes to how kidneys are being allocated. Their findings indicate:

- **An immediate 6-fold increase in transplants for very highly sensitized patients (CPRA of 99-100) from 2.5 to 17.7 percent in December 2014.** This rapid increase may well represent the initial "bolus" effect of having a new priority calculated for these patients that were previously difficult to match under the old system. As these patients are transplanted, the number of patients on the wait-list has dropped and a new state of equilibrium is developing. Further evidence of this is represented by a more current rate of 12.6 percent reported in May, 2015.
- **"Non-local transplants" increased from 21 to 33 percent.** An increase in non-local transplants was expected due to the regional and national priority of the highly sensitized patients and the regional redistribution of the high-KDPI kidneys if a local match was not identified.
- **Decrease in number of longevity-mismatched patients.** Longevity-mismatched patients (as defined by the age difference in excess of 15 years between the donor and recipient) decreased from 49.5 percent to 45 percent. The average donor-recipient age difference also dropped from 18 years to approximately 16 years.
- **Increase in transplants for African-American recipients from 31.5 to 38 percent of transplants.** This trend may be related to the new wait-list time based on initial dialysis start dates that compensates for delays in registration on the wait list.

Other statistically-significant trends that need further monitoring include:

- **Decrease in zero-mismatch transplants from 8 to 4.5 percent.** This is perhaps related to the increase in transplants performed for the highly sensitized patients who have a higher priority for a donor kidney, even if they do not have a zero mismatch with the donor.
- **Increase in kidney discard rate from 18.5 to 20.3 percent.** This concerning statistic describes the proportion of kidneys that are recovered but not transplanted for various reasons. The discard rate had historically been 18.3 percent, but for the 6 month period post KAS implementation, the rate has increased to 20.3 percent. Early data suggests the increase in discard rate came from kidneys with the higher KDPI scores, but did not affect the overall rate of deceased kidney transplants. Statistically significant, it bears close watching by the OPTN/UNOS Kidney Transplantation Committee to determine if any policy or practice changes are warranted.⁷

While early, it appears the new KAS is meeting most expectations and improving the match between the patient's needs and the availability of kidneys. With over 100,000 people on the waitlist, and an average of only 900 transplants per 30 days, this change will not radically reduce the disparity. But for those most difficult to match and those with longer dialysis times, the new KAS system seems to be meeting its stated goals.⁸

⁷ OPTN/UNOS Kidney Transplantation Committee. "Kidney Allocation System (KAS) 'Out-of-the-gate' monitoring report." Organ Procurement and Transplantation Network. US Department of Health & Human Services. <http://optn.transplant.hrsa.gov/media/1178/kas_report_06-2015.pdf>. Published 6/26/15.

⁸ "Organ Donation and Transplantation Statistics. National Kidney Foundation, Inc. <<https://www.kidney.org/news/newsroom/factsheets/Organ-Donation-and-Transplantation-Stats>>."