Transforming Organ Transplantation

transonic
THE MEASURE OF BETTER RESULTS.

Contents

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Introduction

by Daniel Foster

This is primarily a technical booklet, but to begin, we're going to speak from the heart, because respect for this subject demands it. Organ donation is beautifully sophisticated and advanced in the way that only cutting-edge technology can be, but at its core, organ donation isn't scientific—it's human. It's not about technology. It's about people.

Specifically, it's about the people who matter to you.

Throughout history, much has been said about maternal love. Mothers' sacrifices for their children have become the stuff of legend. Even animals are not beneath the respect of our matronly mythology. An Appalachian tale tells the story of a farm on fire, and the mother hen who herded her chicks into a corner of the henhouse, shielded them with her wings, and died in the flames so that her children could live.

Despite their simplicity (or perhaps because of it), stories like this one can help ground us in the modern world. They remind us that life is a privilege. But our species has moved beyond mythology into technology. We have traded our creaking rocking chairs and fireside tales for blaring televisions and dazzling smart phones.
Does this mean that our ability to tell such stories is fading? Does it imply that we are distracted by flashier, but shallower things?

No. It means we have evolved to new heights of caring.
Organ donation is a paramount example.

It was 7:30AM, and Robin was drifting off to sleep. An anesthesiologist was pressing an oxygen mask over her face and repeating simple questions. "What's your full name, Robin? Where do you live?" The sound was soothing—familiar questions being asked in a tone that became gentler as she drifted away. Presently, Robin found that she couldn't remember her full name. Then all was black and quiet.

In the next OR, another woman was already asleep. This woman was older, maybe a bit more careworn, but the resemblance was strong. She was, after all, Robin's mother. Robin was twenty-one years old, and for twenty of those years, she had struggled with kidney disease. Recently she had been very sick, weak, and increasingly unable to sleep or eat.

But Robin was not alone in her struggle.

Robin's doctors had finally decided it was time, so mother and daughter entered the hospital together, and soon, they would leave together too.

By 9:30, the surgeons had opened Robin's abdomen and readied the cavity. A nurse came through the OR door, wheeling a cart with a grey-white kidney in a cold solution. The kidney had belonged to Robin's mother, but soon it would be part of Robin. The surgeons carefully studied the kidney, memorizing the location and size of each of the mother's vessels, which they would meticulously stitch to the daughter's. After flushing the organ, they lowered it into its new home inside Robin, and began the complicated, delicate task of grafting part of one person into another.

When the last stitch was complete, the surgeons waited and watched as the kidney began to perfuse. Within minutes it had turned from grey-white to pink—the color of life and health.

The surgery was a success. The gift of life was given. Both Robin and her mother recovered.

This is why we have created the booklet you hold in your hands: because you have the power to give life. You may not be a mother, and you may not have a child named Robin, but there are thousands of "Robins" in this world who need your gift. Please register as an organ donor so that you can help us build a better world for all our children—whatever their names may be.

Thanks for all that you do,

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Organ Donation

The road to organ transplant is long and rocky. Wait times can seem even longer. Organ recovery staff sometimes go days without sleep as they fight to save lives. Recipient hopes rise and fall as they struggle with their failing organs. Organ transplant is one of the most vital, and yet least understood processes in medicine. Join us for the next few pages to learn more about this modern miracle.

Background

The treatment for organ failure is as varied as the organs themselves. For kidney failure, the patient can be placed on hemodialysis until a kidney becomes available. For heart failure, a patient might have a mechanical circulatory device such as a left ventricular device implanted as a bridge until transplant. When the condition deteriorates to the point that it can no longer be managed, the doctor will speak to the patient about an organ transplant. With the patient's permission, the doctor will refer the patient to a Transplant Program in a nearby major medical center.

Initial Contact

First, a transplant team examines the patient's medical record, speaks to the doctor, and ultimately decides whether the patient might be a good candidate. If so, the patient is contacted to come to the center for evaluation. A credit analyst from the hospital also contacts the patient to discuss medical coverage and the costs of transplant surgery *(see sidebar on right)*.

Cost of Organ Transplants in the U.S.

Heart-lung or kidney-heart: **$2.6M**

Heart: **$1,664,800**

Bone marrow-allogenic: **$1,071,700**

Liver: **$878,400**

Autologous bone marrow: **$471,600**

Kidney: **$442,500**

Cornea: **$32,500**

Source: Transplant Living, a UNOS project.

Evaluation

Following insurance approval, the patient undergoes a battery of bodily-system tests to determine if transplant is the best course. Tests can include an ECG, a heart cathetization, an exercise stress test, etc.

Wait

Once approved, the patient (with condition notes) is added to the transplant waiting list. The wait for a donor organ depends on avalibity and severity of need, so the patient's condition is continually monitored. When an organ becomes available, the medical center's transplant coordinator contacts the patient to come to the hospital immediately for the transplant.

Transplant Surgery

The patient is taken into surgery and placed under general anaesthesia. Surgical staff work quickly and carefully to implant the donated organ. Following surgery, the patient is taken into recovery. After spending a day in recovery, the patient is moved to the ICU to recuperate before being released.

Wait Time for Transplant Organs

Kidney – **5 years**
Pancreas – **2 years**
Kidney / Pancreas – **1.5 years**
Liver – **11 months**
Heart – **4 months**

Source: https://www.donors1.org/patients/resourcesfor-transplant-patients/the-waiting-list/

Post-Transplant

The patient returns home with instructions to carefully follow the guidelines for diet and exercise, and to take the prescribed anti-rejection medications. Follow-up appointments with the hospital's transplant team will be a life-long process.

Organ Donation & Transplantation Steps

Organ Donation

The following are the basic steps in **organ donation recovery**.

Transport

A specialized team of emergency medical technicians and paramedics begin life-saving efforts at the scene. During transport of the patient to a hospital, they contact emergency room physicians.

Treatment

When the team arrives, emergency room doctors and nurses evaluate injuries and continue life-saving measures through administration of medicine, IV fluids, blood transfusions, and/or placing the patient on a ventilator.

Intensive Care

When vital signs stabilize, and as the medical team continues life-saving measures, the patient is transferred to an intensive care unit (ICU), where a physician performs tests to assess the patient's brain and organs.

Brain Death Declared

Brain death is diagnosed as an irreversible loss of blood flow to the whole brain. After brain death, the donor's body is supported by artificial means, such as a ventilator.

Evaluation

Specially-trained medical practitioners from an organ procurement organization (OPO) arrive at the hospital to assess if the patient is medically suitable for organ donation.

Consent/Authorization

The doctor informs the family of the patient's death. Then, someone from the OPO, or specially-trained hospital staff, talks to the family about donation. If the patient registered as a donor in their state or on the national registry, that information is shared with the family and the OPO family counselor explains the donation process and answers any of the family's questions. The OPO and hospital work together to support the family and honor the patient's wishes. If the patient has not registered with a state or national registry, the patient's family takes time to think and ask questions before they decide. The donation decision is easier if the family has previously discussed donation.

Placement

The donor's blood type, height, weight, the hospital ZIP code, etc. are entered into the United Network for Organ Sharing (UNOS) national network, and the organ allocation process begins. Appropriate candidates are found based on the best match. Timing is crucial at this step and during recovery.

Organ Recovery

The donor is taken to an operating room where the donated organ is surgically removed and sent to the transplant hospital where the recipient is waiting. The donor is treated with honor and respect throughout the donation process.

Funeral

After donation, the donor is taken to a funeral home, and the OPO works with the funeral director to honor the donor and donor family's funeral wishes. An open casket funeral is possible after organ donation.

Follow-up

A few weeks later, the OPO sends a letter to the donor's family letting them know which organs were donated. The names of any recipients are kept confidential. Most OPOs continue to provide donor families with support such as bereavement counseling and assistance planning memorial events. If donor families and recipients wish to correspond with each other, their OPO's can provide coordination and communication guidelines.

Brief History of Organ Transplant

The stage for orthotropic organ transplantation was set in the early 20th century by two Frenchman, Mathieu Jaboulay, a surgeon who practiced medicine in Lyon, and Alexis Carrel. In 1902, Jaboulay became a professor of clinical surgery. Carrel was one of his students. In 1906, Jaboulay attempted to save two kidney-failure patients by transplanting a pig kidney into one, and a goat kidney into the other. In both cases, he joined renal vessels to brachial vessels. Both transplants failed and both patients died.

Alexis Carrel was determined to find a way to sew vessels together. He realized that he needed better needles, finer thread, and a masterful suturing technique. Legend has it that he took lessons from a famous lace embroideress in Lyon. He ultimately succeeded in sewing two vessels together, for which he was awarded the Nobel Prize in Physiology in 1912.

In 1936, Yu Yu Voronoy, a Ukrainian surgeon working in Kiev, transplanted human kidneys into a series of six patients dying from acute renal failure from mercury poisoning. All the transplants failed, largely because of a failure to appreciate the deleterious effect of warm ischemia.

In the 1950s, specialists began using kidneys from live donors. The surgical technique for kidney transplant involved placing the kidney extraperitoneally in an iliac fossa, where the external iliac vessels are easy to access and the bladder is close by for anastomosis to the donor ureter. This technique is still used today.

The immune response causing organ rejection remained a serious challenge. The first successful kidney transplant occurred by avoiding an immune response altogether, when Joseph E. Murray's team at what is now Boston's Brigham and Women's Hospital transplanted a kidney from Ronald Lee Herrick to his identical twin brother.

Technological breakthroughs continued. They include controlling the immune response with chemical immunosuppressants and devising preservation solutions to enable prolonged periods of *ex vivo* organ storage. In 1954, the kidney was the first human organ to be successfully transplanted.

Organ Transplant Timeline of Firsts

Organ Transplants

from Jan 1, 1998, to Dec. 31, 2020, (UNOS)

Kidney	492,576
Liver	181,976
Heart	79,562
Lung	43,585
Kidney/Pancreas	25,445
Pancreas	9,029
Heart/Lung	1,363

1999

First successful adult-to-adult living donor liver transplant

1990

First successful living donor lung transplant

1989

First successful living donor liver transplant

1988

First successful split liver transplant

1987

First successful intestinal transplant

1986

First successful double-lung transplant performed

1983

Cyclosporine introduced

1983

First successful single-lung transplant

1981

First successful heart-lung transplant

1968

First successful heart transplant; First successful isolated pancreas transplant

1967

First successful liver transplant

1966

First simultaneous kidney/pancreas transplant

1954

First successful kidney transplant

1906

First anastomosis performed by Alexis Carrel in Lyon, France

Liver Transplantation

It wasn't until 1967 before Thomas Starzl successfully performed a liver transplant at the University of Colorado Health Sciences Center. Through extensive animal research, Starzl identified two needs: one, cooling the liver before transplantation; and two, maintaining venous return using veno-veno bypass to shunt blood from the inferior vena cava (IVC) and portal circulation to the superior vena cava. These innovations, along with improvements in patient selection, perioperative management, and post-operative immunosuppression, have made liver transplantation feasible for patients in liver failure.

Heart Transplantation

At Stanford University, Norman Shumway worked out the operative strategy for transplanting a heart from a donor to a recipient in a series of animal experiments. It involved cooling the heart and leaving part of the atria in situ to reduce the number of anastomoses required. However, it was Christiaan Barnard of Cape Town, South Africa who performed the first human heart transplant in 1967. Over the next year, more than 100 cardiac transplants were performed around the world. Results were poor. It was only after the introduction of immunosuppresant cyclosporine in the early 1980s that cardiac transplantation became widespread. It was also during the 1960s that the first lung transplant was performed, but the patient ultimately died of renal failure.

By the 1980s, cyclosporine provided sufficient immunosuppression to permit successful liver, kidney, pancreas, heart, and lung transplantation. Transplantation emerged as a viable treatment of organ failure.

References: statnews.com/2017/03/05/thomas-starzl-obituary/

Organ Donation Worldwide

Organ donation can be a life-saver for persons with organ failure. Every donor can save eight lives and enhance 75 more. In 2019, 153,863 organs were donated worldwide according to the Global Observatory on Donation and Transplantation (GODT).

In 2020, Spain and the United States had the highest rates of organ donation rate of 38 people per million population. Other countries with high rates of donation are Croatia (25.37 per million), Portugal (24.8 per million), and France (23.13 per million). China, with its 1.5 billion population, had one of the lowest rates of 3.61 donations per million inhabitants.

(Note: 2020 donation figures were uniformly less than 2019 donation figures due to the pandemic.)

Category	U.S.	Spain	Europe*	Russian Federation	Japan	Global 2020
Population	331 Mil.	46.8 Mil.		145.9 Mil.	126.5 Mil.	7.8 Bil.
Deceased Donors (DD)	38.03	38.97	12.37	3.92	0.61	4.7
After brain death	28.29	24.7	10.51	3.79	0.54	3.63
After circulatory death	9.74	13.27	1.86	0.13	0.07	1.04
Kidney: Total	71.43	57.74	25.88	7.7	13.42	11.37
Deceased Kidney	55.62	52.2	18.9	6.63	1.11	7.34
Living Kidney	15.81	5.53	6.97	1.08	12.3	4.03
Liver: Total	26.91	22.09	10.89	3.83	3	4.52
Deceased Liver	25.42	21.86	8.96	2.67	0.5	3.36
Living Liver	1.47	0.24	1.92	1.16	2.5	1.07
Heart	11.23	5.94	2.97	1.72	0.43	1.08
Lung	7.85	7.18	2.22	0.08	0.59	0.79
Pancreas	2.91	1.56	0.7	0.11	0.22	0.26
Small Bowel	0.27	0.09	0.05	0.01	0.02	0.02
Total Organ Tx	120.59	94.59	42.7	13.45	17.68	18.04

**Excluding Spain and the Russian Federation*
Source: GODT http://www.transplant-observatory.org/

Global Observatory on Donation and Transplantation

The most comprehensive worldwide source for organ donation and transplantation data is the United Nations' World Health Organization (WHO). It collaborates with the Spanish Transplant Organization, Organización Nacional de Trasplantes (ONT) to collect global data.

2020: # of Global Organ Transplant Centers

Kidney	88
Liver	74
Heart	63
Lung	51
Pancreas	51
Small Bowel	51

Source: GODT http://www.transplant-observatory.org/

Its mission is to:

- Increase safe, effective transplantation of cells, tissues, and organs
- Encourage donation of human material for transplantation
- Ensure ethical and technical practices
- Ensure effective national oversight, traceability, and appropriate surveillance of adverse events
- Promote international cooperation to prevent exploitation of the disadvantaged through transplantation tourism.
- Prevent black market distribution of human tissue.

The WHO Global Database includes 194 member states in the six regions: Africa, the Americas, the Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific. The database aggregates about organizational structures, legislative systems, and activities related to organ donation and transplantation. These questionnaires are sent annually to the WHO's member states.

UNOS Organ Transplantation Stats in the U.S.

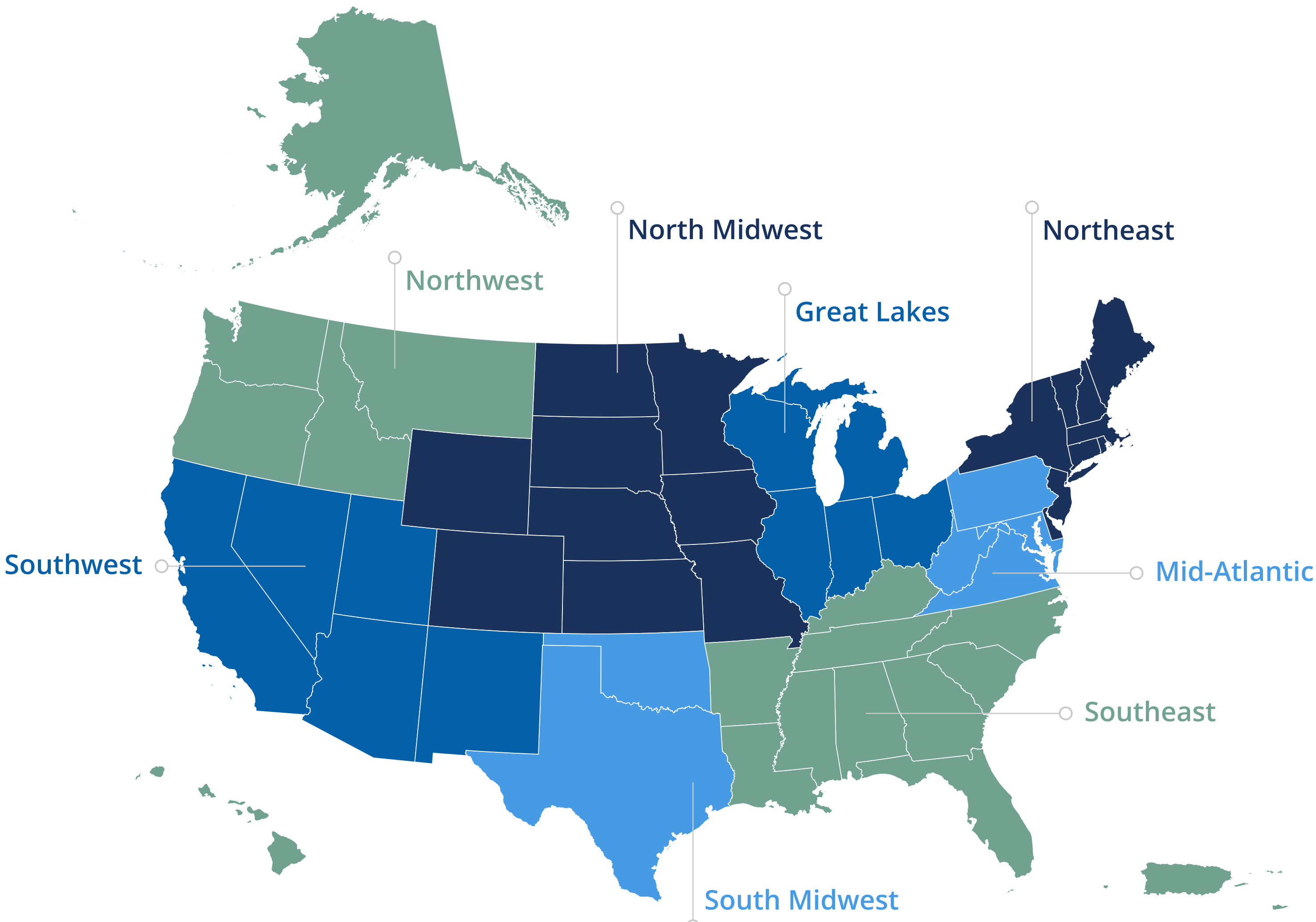
In 1986, the United Network for Organ Sharing (UNOS) received its federal contract to operate the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients. The following year, UNOS began collecting medical data on donor and transplant recipients, transplant centers, histocompatibility laboratories, and organ procurement organizations to enter data into the OPTN database. Transplant professionals enter some pre-transplant information about both candidates and recipients and post-transplant information about recipients on organ specific OPTN data collection forms. Information used to reconcile donor and recipient data about the transplant is entered on a Donor Organ Disposition record.

The number of deceased organ donors and deceased-donor organ transplants performed in 2020 in the United States reached all-time highs of 32 per million inhabitants. UNOS reports that in the first half of 2021, 21,061 organ transplants were in the U.S.

- Organ donation from deceased donors is up 15% over last year.
- There were 900 more deceased donors, people who provided one or more organs to save and enhance the lives of others between January 1 and June 30 of 2021 than there were during the same period in 2020.
- The drop in donors caused by the COVID-19 pandemic was offset by high numbers early in 2021.
- There were 242 more donors in the first half of 2020 than in the first half of 2019.
- Deceased donor organ transplants are up by 11% in 2021. A total of 17,821 deceased donor transplants were performed in the U.S. in the first half of the year compared to 15,933 in the first six months of 2020.
- 2020 marked the 10th consecutive record-breaking year for organ donation from deceased donors and the eighth in a row for deceased donor transplants.
- 106,669 men, women, and children are on the waiting list for a transplant, which is the lowest backlog since 2009. The list topped 124,000 at its height in 2014. In the U.S., organ donors are required to register on a national database. As of 2018, over half of the U.S. population had been registered as organ donors.

How Organ Matching Works

When a transplant hospital accepts a person as a transplant candidate, it enters the patient's medical data into the UNOS computerized network. When an organ procurement organization gets consent for an organ donor, it also enters medical data—i.e. the donor's blood type, body size and the location of the donor hospital—into UNOS' network. Using the combination of donor and candidate information, the UNOS system generates a "match run," a rank-order list of candidates who will be offered each organ. This match is unique to each donor and each organ. The candidates who appear highest in the ranking are in most urgent need of the transplant, and/or those most likely to have the best chance of survival if transplanted.



Organ Demand

Kidneys are the most frequently transplanted organ in the world followed by the liver and the heart. The two organs that are needed most frequently are kidneys and livers. According to the United States Department of Health and Human Services, about 83 percent of the people on the national transplant waiting list are waiting for kidney transplants and about 12 percent are waiting for liver transplants. Most people wait for three to five years for a kidney transplant. As of February 2, 2019, there were 120,000 people waiting for life-saving organ transplants in the US. Patients over 50 years of age experienced the longest median waiting times.

Kidney Transplantation Success

Adult kidney transplantation is perhaps the greatest success among all the procedures; more than 270,000 initial transplantations have been performed since 1970. Receiving a cadaveric graft doubles a patient's chances of survival, and a living-donor graft quadruples them, compared to those who remain on the waiting list. Across all such procedures, 1.37 million life-years (4.4 yr/recipient) have been added; the median survival time among recipients is 12.4 years, compared with 5.4 years among those on the waiting list.

Liver Transplantation Success

More than 50% of liver transplant recipients survive for seven years, in comparison with approximately 25% of patients on the waiting list. Adult cadaveric liver transplantation nearly quadruples the median survival time, from 3.1 to 11.1 years. The most remarkable impact is in the pediatric population where survival duration often exceeds 25 years.

Heart Transplantation Success

Similarly, seven-year survival rates are seen in heart transplantation: more than 50% of recipients survive, compared with approximately 25% of individuals on the waiting list. In adult recipients, the median survival time is 9.4 years, in comparison with 2.4 years among patients awaiting a heart. The heart must be donated by someone who is brain-dead but is still on life support. The donor heart must be in normal condition without disease and must be matched as closely as possible to the recipient's blood and/or tissue type to reduce the chance that their body will reject it. In pediatric recipients, the median survival time is 12.8 years. Overall, heart transplantation has added approximately 270,000 life-years (mean, 4.9 yr/recipient).

Organ Transplantation Challenges

Complexity of Organ Matching Guidelines

> *Income, celebrity status, race, or religion play no role in determining allocation of organs.*

When an organ donor becomes available, all the patients on the national waiting list are compared to that donor. The rules for matching donor organs with patients on the transplant list vary by organ.

General matching criteria includes the following:

- Medical urgency
- Blood/tissue type and size match with the donor
- Genetic makeup
- Time on the waiting list
- Proximity between the donor and the recipient

Local individuals who need organs generally receive preference when an organ becomes available in their area. Donor organs are distributed locally first, and if no match is found they are offered regionally, and then nationally, until a recipient is found.

Donor Hesitancy Results in Fewer Organ Donations

> *17 people die each day because the organ they need is not available*

Even though 2020 was another record-setting year for transplantation in the United States not everyone who needed a new organ received one. More than 107,000 people in the U.S. need a lifesaving organ transplant. Of those, 65,000 are candidates on an active waiting list.

To receive an organ transplant, three criteria must be met:

1. An organ must become available,
2. The donor's organ and transplant recipient must be compatible,
3. The donor organ must be viable after transfer from the donor site to the recipient site.

> *One organ donor can impact the lives of up to eight transplant recipients through donations of heart, liver, kidneys, pancreas, lungs, and intestines.*

One tissue donor can help hundreds of people. Cornea donors give the gift of sight to two people. Skin donors help burn victims recover from traumatic injuries. Bone, heart valve and tendon donors help many people return to health. Organ donation is a genuine "gift of life."

Donor hesitancy keeps many potential donors from agreeing to donate one or more of their organs. Many are confused or have questions about what it means to be an organ donor.

Misconceptions about organ donation abound and include the following:

MYTH #1: If I am in an accident and the hospital knows that I'm designated as a donor, the doctors and staff won't try to save my life.

FACT: Although this is the number one reason people don't put "organ donor" on their driver's license, in actuality, hospital staff will do everything they possibly can to save your life. According to the Gift of Life Donor Program, "An individual must be in a hospital, on a ventilator and pronounced brain dead to donate organs. Gift of Life Donor Program is not notified until life-saving efforts have failed. The transplant team is not notified by Gift of Life until permission has been given by the deceased's family."

MYTH #2: My family will be charged if I donate my organs.

FACT: The organ donor's family is never charged for donating. The family is charged for the final efforts to save your life, but the costs for organ removal go to the transplant recipient.

MYTH #3: Only the deceased can donate organs.

FACT: Living donor donation, mainly for kidneys, has changed the landscape of organ donation in recent years. A kidney from a deceased donor may last 10-12 years; a living-donor organ can last 10-20 years or even more. Transplantation from a living donor can also be planned and scheduled, so the patient getting the organ can have family around to help.

MYTH #4: Many religions forbid organ donation.

FACT: All major religions including Roman Catholicism, Islam, most branches of Judaism, and most Protestant faiths not only support organ donation but encourage it as an act of generosity and compassion.

> *Celebrity and financial status*
> *are not considered in organ allocation.*

MYTH #5: People who have donated organs can't have an open-casket funeral.

FACT: Organ and tissue donation doesn't interfere with an open-casket funeral. Through the entire donation process, the body is treated with care and respect. Because the donor is clothed and lying on his or her back in the casket, no one can see any difference.

MYTH #6: Kidney donors must be family members.

FACT: Many donors are altruistic. Doctors match the donor to the patient using various criteria, including blood type.

MYTH #7: Only young and healthy people can be donors.

FACT: There is no set age limit for organ and tissue donation. The decision to use your organs is based on strict medical criteria, and doctors evaluate each potential donor on a case-by-case basis.

MYTH #8: Rich and famous people go to the top of the list when they need a donor organ.

FACT: The rich and famous aren't given priority when it comes to allocating organs. They are treated no differently than anyone else.

Length of Time of Organ Viability Ex Vivo

Heart: **4-6 hours**
Lung: **4-6 hours**
Liver: **8-12 hours**
Pancreas: **12-18 hours**
Kidney: **24-36 hours**

Source: UNOS

Assuring Donated Organ Arrival & Maintaining Their Viability during Transport

To assure that they will receive a donated organ, surgeons often personally go to hospitals to collect and transport hearts, lungs, and livers, which survive for a limited time out of a body *(see box on previous page)*. But kidneys and pancreases, which have longer shelf lives, often travel commercial, as cargo. As such, they can, on rare occasions, end up missing connecting flights or be delayed like lost luggage.

Static Cold Storage (SCS)

Cadaveric donor organs are primarily transported via cold storage (on ice) in a picnic cooler to the transplantation site. This static cold storage (SCS) preservation creates a race against time, because the organ begins to decompose once it is removed from its donor. The purpose of organ preservation is to slow or arrest these changes. With SCS this is achieved primarily by cooling, but cold storage can limit the utilization of donor organs and negatively impact outcomes. Only 2-3 out of 10 donated thoracic organs can be used for transplant.

References: pennmedicine.org; edars-sinai.org/blog/myths; mayoclinic.org; health.ucsd.edu/

Normothermic Machine Perfusion (NMP)

The rapidly advancing technology of *ex vivo* normothermic machine perfusion (NMP) holds promise for improved preservation, better assessment, and even reconditioning of organs before transplant. And while many questions remain regarding the implementation of this still-young technology, NMP has already had an important impact on transplant medicine by expanding the donor pool. This allows surgeons to assess and successfully transplant organs that once would have gone unutilized.

NMP approximates "near physiologic" conditions of temperature, nutrients, and oxygen outside the body, enabling the organ to function much as it would within the body.

Its benefits are:

- Equal safety as static cold storage (SCS).
- Extended time that organs can be maintained before transplant. This potentially allows organs to be transported greater distances, for recipients to travel further to the hospital for surgeons to have more flexibility to schedule more optimal surgical times, and to increase surgical time for complex cases.
- Possibility for organs that might once have been rejected to become acceptable for transplant.
- Expanded donor pool.

Three companies currently lead the development of *ex vivo* NMP devices. TransMedics is developing a transportable Organ Care System for heart, lung, and liver. OrganOx is developing a metra-transportable perfusion device for liver, and XVIVO Perfusion is developing a non-transportable XPS lung perfusion system.

A fourth company, Lung Bioengineering, has focused on making perfusion technology more widely accessible by developing a centralized, free-standing perfusion facility to serve multiple organ transplant hospitals. The facility employs both the XPS and the Toronto EVLP System developed at University Health Network in Toronto, Ontario, Canada.

Hypothermic Machine Perfusion (HMP)

Hypothermic machine perfusion (HMP) of kidneys offers an alternative to static cold storage. The technology might also provide a platform active graft repair, making it particularly attractive for higher-risk kidneys.

Potential HMP benefits include:

- Maintaining the patency of the vascular bed
- Providing nutrients & low demand oxygen to support reduced energy demands
- Removing metabolic by-products and toxins
- Accessing of cytoprotective agents and/or immunomodulatory drugs
- Increasing available assays for organ viability assessment & tissue matching
- Facilitating changes from emergency to elective scheduled surgery with reduced costs and improved outcomes
- Improving stabilization or rescue of ECD kidneys or organs from NHBD that increase the size of the donor pool
- Benefiting transplant center economics and reducing health care costs
- Providing an *ex vivo* platform for non-transplantable organs to be used for research.

Reference: Taylor MJ, Baicu SC. Current state of hypothermic machine perfusion preservation of organs: The clinical perspective. Cryobiology. 2010 Jul;60(3 Suppl):S20-35.

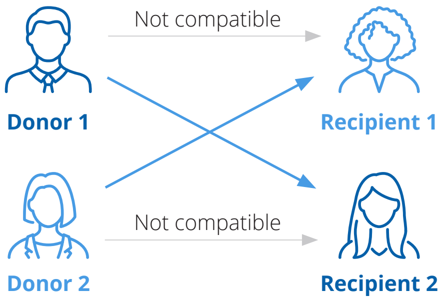
Spotlight on Expanding the Donor Organ Pool

Kidney Paired Donation (KPD)

There are times when a transplant candidate has someone who wants to donate a kidney to them, but tests reveal that the kidney would not be a good medical match. Kidney paired donation (KPD) gives that transplant candidate another option. In KPD, living donor kidneys are swapped so each recipient receives a compatible transplant.

How it Works

If the recipient from one pair is compatible with the donor from the other pair, and vice versa—the transplant center may arrange for a "swap"—for two simultaneous transplants to take place. This allows two transplant candidates to receive organs and two donors to give organs though the original recipient/donor pairs were unable to do so with each other.

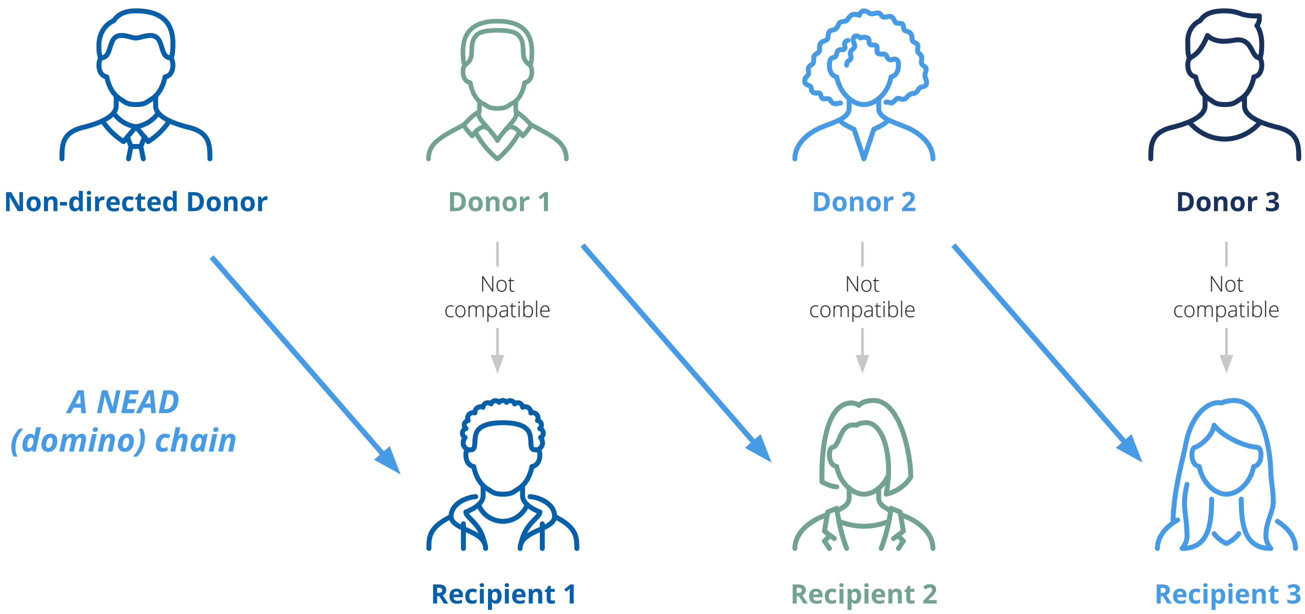


Never Ending Altruistic Donor (NEAD)

A NEAD chain takes a group of incompatible donor-recipient pairs and matches them with other pairs in a similar predicament to create a domino effect of donation. This technology was pioneered at John Hopkins University under direction of Robert A. Montgomery, MD, PhD, then director of the Johns Hopkins Comprehensive Transplant Center. This occurs when several people who need transplants have friends or relatives who are willing to donate but aren't compatible. A chain of surgeries is planned in which each would-be donor is matched with a compatible recipient. Altruistic donors, who are willing to give a kidney to anyone, are used to fill in the gaps.

In fact, it was an altruistic donor who initiated the chain. Just like falling dominoes, the altruistic donor kidney went to a recipient from one of the incompatible pairs, that recipient's donor's kidney went to a recipient from a second pair, and so on. The last remaining kidney from the final incompatible pair went to a recipient who had been on the United Network for Organ Sharing (UNOS) waiting list. In this way, each recipient receives a kidney from a stranger, and transplants are enabled that otherwise would not have taken place. Involving multiple hospitals created even more possibilities for matches.

Kidney Paired Donation (KPD)



Historic Eight-Way Multi-Hospital Kidney Transplant

In 2009, surgical teams at the Johns Hopkins Hospital in Baltimore, Barnes-Jewish Hospital in St. Louis, INTEGRIS Baptist Medical Center in Oklahoma City and Henry Ford Hospital in Detroit made transplant history when they successfully completed the first eight-way, multi-hospital, domino kidney transplant. The transplant involved eight donors and eight organ recipients. The formidable logistics for performing all the surgeries required a multihospital team of eight anesthesiologists, 16 nurses and nine surgeons.

The model serves as a blueprint for a national KPD program in which kidneys will be transported around the country, significantly expanding the kidney organ donor pool.

Reference: Gentry SE, Montgomery RA, Swihart BJ, Segev DL. The roles of dominos and nonsimultaneous chains in kidney paired donation. Am J Transplant. 2009 Jun;9(6):1330

Spotlight on Immunological Improvements

Desensitization

Thirty percent of kidneys donated by live donors are immunologically incompatible because recipient antibodies attack the new kidney. Desensitization of the recipient is one strategy used to overcome such incompatibility. Desensitization removes the antibodies from the recipient to lessen or eliminate immune response to the allograft.

Combined Kidney and Bone Marrow Transplant

Combining a kidney transplant with a hematopoietic stem (bone marrow) cells from the same donor induces a state of immune tolerance in the recipient that decreases (and ideally stops) the use of immunosuppressive drugs. This is particularly appealing in young recipients because, over time, immunosuppressive drugs can be toxic.

Transplant Trailblazing Is His Passion

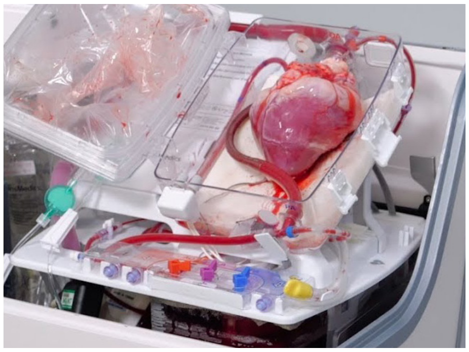
Robert Montgomery MD, PhD

As a transplant surgeon and chief of the New York University Langone Transplant Institute, Dr. Montgomery is renowned for his trailblazing in the field of transplantation. While at Johns Hopkins University, he was the lead surgeon in the first 2-way, 3-way, 4-way, 5-way, 6-way, and 8-way domino-paired donations and in the first 10-way open chain donation. For this, he was credited in The Guinness Book of World Records with performing the most kidney transplants in one day. Dr. Montgomery holds a PhD in immunology from Oxford University and is considered an authority on desensitization. He was instrumental in developing a treatment protocol to remove antibodies from a patient's blood prior to kidney transplant. This procedure reduces risk of rejection, and doubles the patient's life expectancy compared to those who remain on dialysis. He also helped develop a protocol that combined kidney and bone marrow transplants to prevent rejection of donor organs in immune-incompatible patients and eliminate the need for immunosuppressive therapy. He also was among the first transplant surgeons to promote the idea of using HCV-positive organs, after the new generation of antivirals proved capable of quickly clearing the virus. A practitioner of what he avows, Dr. Montgomery's own heart transplant in 2019 was from a hepatitis C+ donor.

Spotlight on Organ Preservation During Transport

TransMedics Group Inc.

TransMedics is a world leader in portable extracorporeal warm perfusion and assessment of donor organs. Headquartered in Andover, Massachusetts, the company was founded to address the unmet need for more and better organs for transplantation. TransMedics Organ Care Systems are fully portable, multi-organ, normothermic preservation and assessment technology that mirrors human physiology, minimizes ischemia, and provides the ability to optimize the organ during transport.



OCS Heart System by TransMedics.

In September 2021, the company received FDA clearance to market its Organ Liver Care System (OCS) for use with organs from donors after brain death (DBD) and after circulatory death (DCD). The OCS Liver System is indicated for the preservation and monitoring of hemodynamics and metabolic function which allows for *ex vivo* assessment of liver allografts from DBD and DCD donor livers.

Earlier in the month, the company received FDA clearance for its OCS Heart System indicated for the preservation of DBD donor hearts deemed unsuitable for procurement and transplantation. The OCS Heart System is now the only FDA approved device indicated for *ex-vivo* perfusion and assessment of both donor hearts and lungs as an alternative to the antiquated cold storage preservation. The approval of the OCS Heart System follows FDA approval and subsequent commercialization of the OCS Lung System.

Waleed Hassanein founded TransMedics to develop such organ care systems. The company leverages proprietary core technologies across multiple organs. Transonic's transit-time ultrasound technology is one of those technologies. Transonic Tubing Flowsensors measure the volume of flow within the circuits that perfuse the donor organ during transport.

TransMedics Founded to Improve Organ Transport

Waleed Hassanein

Born in 1958 near Cairo, Egypt, Waleed Hassanein dreamt of becoming a pilot. His parents wanted him to become a doctor. They prevailed so he studied medicine in Cairo and London and moved to Washington DC intending to become a heart transplant surgeon.

As a Georgetown University Medical Center resident, his plan changed after he saw the picnic cooler in which the donor heart had been transported during his first heart transplant surgery. He was startled, and knew that there had to be a better way - a more physiological way to transfer organs from donor to recipient. Waleed set out to develop a better solution for organ transport. He envisioned an enriched artificial blood circuit that would keep organs functioning during transport. A heart would continue beating, lungs would continue expanding and contracting, and livers would continue to produce bile. He founded TransMedics and realized that dream.

This revolutionary technology allows physicians and institutions to maximize the potential of donor hearts, lungs, and livers while monitoring each organ throughout the entire process. This ensures transplant teams can preserve organs in optimal condition.

The systems mimic the human body through warm, oxygenated blood perfusion that maintains the organ in a living, functional state. As a result, the lung breathes, the heart beats, and the liver produces bile. Diagnostic assessment of perfusion makes it possible to analyze organ function and viability, which allows for therapeutic intervention through replenishing oxygen and nutrients.

A recent clinical trial compared post-transplant outcomes with and without use of the OCS Heart System. The OCS Heart was used to resuscitate and assess hearts from a group of DCD donors, which were compared to a group of cold-storage hearts from brain-death donors. The goal was to assess the effectiveness and safety of OCS Heart technology, and to expand the heart donor pool to include DCD donors. The trial achieved its primary clinical objectives by meeting the primary effectiveness endpoint of 6 months patient survival post-transplant which was 95% for OCS DCD arm vs. 89% for DBD Control arm. “These results are tremendously exciting and confirm our belief that the OCS Heart System is a transformative technology that allows us to safely utilize donor organs that were previously never considered,” said Dr. David D’Alessandro, surgical director of heart transplantation at Massachusetts General Hospital and the co-principal investigator for the OCS DCD Heart Trial. “We now have a unique technology which will allow us to offer this life saving therapy to more patients than ever before.”

To date, OCS has been used in more than 2,100 transplants worldwide. Going forward, TransMedics hopes to gain broader indications for use for OCS Lung, Heart, and Liver. As the ability for OCS to extend and save lives is consistently demonstrated, and economic benefits are documented, the reimbursement environment can be expected to improve in many regions around the world, thus facilitating adoption of the technology. Ultimately, the goal is that every donated organ that is salvageable should be handled in a way that maximizes its viability for life-saving transplantation. (Waleed Hassanein - Sustaining Transplant Organs)

Spotlight on Surgical Transplant Refinements

Surgeons always strive to improve surgical protocols and tailor them to the needs of each patient.

Procedural refinements and new surgical tools used during transplant surgery include:

Laparoscopic Kidney Removal

In 2020, 5,700 persons in the U.S. became living organ donors. Most of these donations were kidneys removed from a donor and transplanted to a recipient. Laproscopy (pioneered at the beginning of the 21st century) is less invasive than traditional nephrectomy. Laparoscopic kidney removal minimizes surgical trauma, and reduces recovery time. It uses two or three small incisions, each about a half-inch long, on the abdomen through which rigid plastic tubes or "ports," are inserted to guide surgical instruments and scopes into the body. The scope visualizes the procedure which is then magnified and projected on television monitors in the operating room. Finally, a six inch incision is made several inches below the belly button to extract the kidney. More recently, robotic surgical tools are complementing the laparoscopy.

Creating Protocols for Novel Transplants

Organs with well-established protocols for transplant include the heart, lungs, liver, kidneys, intestine and pancreas. Tissues that can be transplanted include heart valves, bone, tendons, ligaments, skin, and parts of the eye such as the cornea and/or sclera.

Hand Transplants

A few transplant centers worldwide are approved to transplant hands for those who have had one or both hands amputated. During a hand transplant, the patient receives one or two donor hands and a portion of the forearms from a person who has died. The first successful hand transplant was performed in 1999. The first U.S. hand transplant was performed a few months later. Today, more than 100 hand transplants have been performed around the world. Hand transplant surgery is more complex than a solid organ transplant because it involves several tissues, skin, muscles, tendons, bones, cartilages, fat, nerves, and blood vessels.

Facial Transplant

A facial transplant is a treatment option for some people with severe facial disfigurement. It is an intricately complicated, personalized medical procedure by a multi-disciplinary team to replace as much as 100 percent of the recipient's facial tissue with that of a deceased donor. The surgery can integrate many different functional components, such as nose and lower eyelids as well as different tissue types including, skin, muscles, bones, arteries veins and nerves. New techniques and technologies such as surgical rehearsal, 3D printing and virtual reality through 3D modeling are used for preoperative planning for the long, extensive surgery. By 2021, more than 45 patients had received full or partial face transplants at institutions around the world.

Integration of Volume Blood Flow Measurements into Protocols

Measuring blood flow during a transplant procedure provides a quick assessment to confirm an acceptable surgical result, or to alert the surgeon to potential problems while they can be readily addressed. For example, flow-assisted surgery during liver transplantation informs the surgeon if both the hepatic artery and portal vein are functioning.

Spotlight on Clinical Research

Liver4Life - Ex Vivo Regeneration of the Human Liver

Wyss Zurich, a Swiss company, is developing a novel therapy for liver regeneration outside of the body. Project Liver4Life is being created by a world-class team of engineers, biologists, clinicians, and quality and regulatory experts.

Liver4Life Platform

Conceived and initiated by Prof. Pierre-Alain Clavien, the project includes:

- Surgical resection of a small healthy piece of the liver from the patient
- Growth of this piece outside of the body in a perfusion machine until a sufficient size is reached
- Retransplantation of the regenerated liver into the original patient while removing the remaining diseased part.

Current perfusion systems are not able to keep a liver alive outside of the body long enough for growth and regeneration. The challenge of the project is to extend the viability of liver tissue outside of the body and allow its growth.

Reference: wysszurich.uzh.ch/projects/wyss-zurich-projects/liver4life/

The liver has a unique capacity among human organs to regenerate itself. A liver can regrow to a normal size even after up to 90% of it has been removed. Liver resection (surgical removal of the diseased part of the liver) for the treatment of liver cancer has been carried out for a few decades, but many tumors are inoperable because excising them would require removing a fatally large section of the liver. Mentored by Pierre-Alain Clavien, Philipp Rudolf von Rohr, Mark Tibbitt and led by Project Manager Max Hefti, the Liver4Life project will allow surgical resection for patients with formerly inoperable liver cancers. In addition, the capability to perform autologous transplantation will avoid the need for life-long immunosuppression and its side effects.

This novel regeneration strategy could also be used in allogenic liver transplantation. With this approach, a healthy donor liver will be split into a couple of parts that will be grown in the perfusion machine, yielding more than one transplantable organ. Thus, the organ donor pool would be increased, which would help to alleviate the existing donor organ shortage.

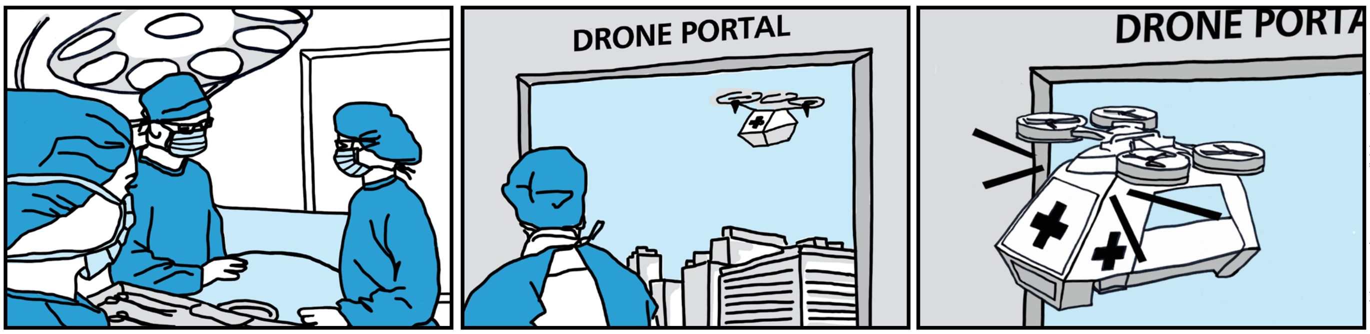
Wyss Zurich Is Translating Science into Life Improvements

Hansjörg Wyss

Wyss Zurich is a joint venture of the University of Zurich and ETH Zurich (Swiss Federal Institute of Technology Zurich) to unite world-leading experts from both institutions into multidisciplinary teams to pool their knowledge and expertise. Made possible by a December 2014 $120,000,000 donation by Swiss entrepreneur and philanthropist Dr. Hansjörg Wyss, Wyss Zurich was established to foster translational research focused on developing treatment protocols and clinical therapies, novel technologies, and intelligent systems in the emerging fields of Regenerative Medicine and Robotics. Traditionally, there has been a long delay between scientific discovery and its widespread application. Dr. Wyss wants to change this: “Breakthrough discoveries in medical and technological fields must be made available as soon as possible for the benefit of mankind.”

What's Ahead

Organ Transplant in 2030?



"We're ready. Where's the donor heart?" **"Here it comes!"** **"Organ 9264. Viable and ready for transplant."**

Organ transplantation is a story of remarkable achievement and ongoing challenges. While organ transplantation has made great strides since the first successful kidney transplant in 1954, the demand for organs far exceeds the supply. This underscores the need for innovation in organ transplantation. Existing tools and methods need to be refined. New technology (*ex vivo* organ perfusion and bio-engineered organs) must be continually developed. Advances in the transplantation of additional organs including hands, uteri, face, and composite tissue.

Immunosuppression

The goal of transplantation is to induce a state of specific unresponsiveness, or tolerance, to a transplanted organ in the donor. The discovery of the immunosuppressant effects of cyclosporine changed the transplantation landscape forever, dramatically improving the results of kidney transplantation and providing sufficient immuno-suppression to permit successful liver, pancreas, heart, and lung transplantation Unfortunately, immuno-suppression can cause diabetes and toxicity in patients. Today, immunosuppression is achieved through a combination of agents with different sites of action and different side-effects. A regimen will vary according to the perceived immunosuppressive challenge that the transplant poses, with more powerful immunosuppression being used where the risk of rejection appears highest. Similarly, different organs and different diseases require different protocols. While immunosuppression advances have reduced the incidence of acute rejection, chronic organ damage remains a problem. For instance, a case of influenza can sabotage immunosuppression. Consequently, extensive research continues to determine the best combination of immunosuppressants for each type of organ transplant.

Organ Perfusion during Transport

Organ perfusion during transport remains the Achilles heel of transplantation. Existing NMP and HMP technologies will continue to improve, allowing organs to be preserved in a state that mimics the natural conditions within the human body. Recent evidence suggests that unsuitable lungs may be “reconditioned” *ex vivo*, increasing the number of organs available for transplant.

Bio-engineered Artificial Organ Technology

Another strategy to increase the donor pool for transplantation is the generation of artificial organs. This technology requires construction of 3D scaffolds upon which progenitor cells are grown into a functional remodel. At the forefront of this technology is Pittsburgh-based Carnegie Mellon Bio-engineered Organs Initiative. Its vision is to save lives by increasing the number of available organs. Their multi-disciplinary research team is designing, creating, and testing a new generation of long-term replacement organs engineered from a combination of bio-printed cellular and synthetic materials. They hope to one day eliminate the need for organ donation.

Bioengineering requires broad collaborative effort. Tissue engineers work with researchers in biomaterials, cellular mechanics, and 3D printing to create cardiac tissues and tissue-based artificial lungs.

Xenotransplantation

Xenotransplantation is the transplantation of living cells, tissues, or organs from one species to another. Although the concept is more than a century old, it was considered ethically controversial to transplant organs, cells, or tissues from an animal to a human. When significant immunological advances were made during the 1960s, interest in xenotransplantation resurfaced. Now, particularly with the long wait for donor kidneys, xenotransplantation has regained momentum. In September 2021, a milestone was reached at New York University’s Langone Transplant Institute when a kidney grown in a genetically engineered pig (sans the enzyme the human body would first attack) was transplanted into a brain dead human recipient on life support. The kidney functioned for the length of the 54-hour trial. Research clinicians observed that the recipient’s body was producing normal transplant levels of urine and creatinine, and there were no signs of the body rejecting the organ. This breakthrough bolsters the hope that organs grown in animals might eventually be used to decrease the wide gap between donor organ supply and demand.

Summary

It is through the ongoing innovations and efforts of scientists, biomedical engineers, transplant researchers, and clinicians that organ transplantation has improved year after year. In 2021, organ transplants in the U.S. alone are expected to exceed 40,000.

Although donor organ availability continues to be a problem. More than 106,000 potential recipients are currently awaiting a transplant in the U.S. Increased awareness of the impact a person can make through donation could change perceptions and enlarge the donor pool.

Together, we must work to advance these technological breakthroughs into clinical practice.

Transonic Systems Inc. is a global manufacturer of innovative biomedical measurement equipment. Founded in 1983, Transonic sells "gold standard" transit-time ultrasound Flowmeters and Monitors for surgical, hemodialysis, pediatric critical care, perfusion, interventional radiology, and research applications. Transonic also provides pressure and pressure volume systems, laser Doppler Flowmeters and telemetry systems.

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