Short Communication

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GalSafe Pig Organ Xenotransplantation: A Bright Future for More than 800,000 Americans

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Over 54 percent of US citizens are registered as organ donors, however, fewer than 1 percent of deaths result in useable organs [1]. By a large margin, kidneys are the most commonly transplanted organ, followed by liver, heart, lungs, and pancreas. Typically, kidney failure is due to diabetes or severe hypertension. In 2021, it is estimated that more than 800,000 Americans live with kidney failure but their wait times for a human kidney can range from four months to six years depending on a multitude of factors: blood type, geographic location, disease severity, immune system activity, and numerous other factors.

For Americans suffering from kidney failure, each must have their blood cleaned via hemodialysis, a process that entails commuting to a dialysis center and spending at least four hours daily, three times weekly, attached to a machine simply to remain alive. If the person is healthy enough to qualify for the kidney transplant waiting list, only 65 percent will receive a kidney in time. Hemodialysis is necessary when the patient has 10 to 15 percent of their kidney function left, and the kidneys no longer remove enough wastes and fluids to keep the patient healthy [2]. In fact, the longer the person is on dialysis, the smaller the chance that a successful kidney transplant becomes. All these disheartening statistics help explain the huge market for xenotransplantation, the use of animal organs, i.e. pig organs into humans [3].

For more than half a century, scientists have attempted several transplants of monkey, chimpanzee, and baboon organs into humans mainly because these nonhuman primates are our closest genetic ancestors. Sadly, none of these surgeries were successful because of infection and rejection of the transplants [4]. In 1984, a newborn with a life-threatening heart defect received a baboon heart and the eventual organ rejection allowed the newborn to live for 21 days. For scientists, this was an historic milestone. However, Harvard geneticist George Church published a 2017 landmark study proving that pigs will be the future of xenotransplantation.

Prior to the breakthrough by George Church, all plans of using pigs as organ sources were thwarted by fear that viruses from the pigs, known as retroviruses, could infect humans through the pig organ transplants. Under the guidance of George Church, "scientists took pig cells and edited them using the gene-editing technology CRISPR-Cas9 to target and hinder their virus-related DNA. They then cloned those edited cells and developed an embryo. Those embryos were implanted into sows and then became piglets." George Church's breakthrough is this: all 37 piglets were born without retroviruses, meaning these gene-edited piglets could not infect humans through organ transplants. Today, these gene-edited piglets are called "GalSafe Pigs" and they are approved by the Food and Drug Administration (FDA) [5]. Additionally, scientists have turned to pigs for the future of xenotransplantation because pigs grow faster than monkeys, their organs are roughly the same size as humans, and the American public now seems open to consider such transplantations [6].

At a molecular level, natural pigs have an alpha-gal sugar genome on the surface of the pig's cells that humans do not, and this causes allergic reactions as well as swift organ rejection in some people. Without advanced gene editing technology, if these alpha-gal genomes are introduced into a human body, a process called hyperacute rejection takes place. Essentially, hyperacute rejection means that the human immune system will register the alpha-gal sugar genome as foreign and mount an attack on the foreign molecules. This attack is the central reason why many transplanted animal organs fail. Using CRISPR-Cas9 technology to genetically tweak and eliminate the problematic alpha-gal sugar genome leads to the creation of GalSafe Pigs.

The most recent statement from the Food and Drug Administration (FDA) regarding GalSafe pigs is noted as follows: "tissues and organs from GalSafe pigs could potentially address the issue of immune rejection in patients receiving xenotransplants, as alpha-gal sugar is believed to be a cause of rejection in patients." Regarding the widespread approval of xenotransplantation, the agency noted that its approval does not extend to xenotransplantation until more paperwork is submitted for review. One key improvement is the use of GalSafe pigs that have additional human genes that help the recipient's body accept the new organ. As of this writing, there have been two successful pig-to-human transplants that survived the 48-hour mark known for swift organ rejection. The fact that both surgeries took place in the last 6 months helps demonstrate how close scientists are to another significant breakthrough.

Both surgeries took place at NYU Langone Health Center in New York City. The first attached a GalSafe pig kidney to a brain-dead human on life support and found the organ functioning for 54 hours, surpassing the critical 48-hour mark with no major issues stemming from the human immune system attacking the transplanted organ.

The leading surgeon Robert Montgomery, declared that this successful GalSafe pig kidney xenotransplantation could possibly pave the way for clinical trials in patients with end-stage kidney failure within the next few years [7].

This January 2022, the second surgery took place at the same hospital in New York City. For this GalSafe pig heart transplant surgery, the patient was in such poor health from terminal heart disease that he was ineligible for a human transplant and could not receive an artificial heart pump. It was unknown how the terminally ill patient would fare after the surgery, but he

accepted to proceed with the surgery after the FDA approved through its "compassionate use" provision. Although the patient reached the 48-hour mark without any organ rejection and later survived 2 months following the surgery, the cause of death was not immediately clear [8].

The hemodialysis process requires a doctor to perform minor surgery to the arm to make an access into the patient's blood vessels. Both the dialysis machine and a dialyzer (special filter similar to an artificial kidney) are used to cleanse the patient's blood. The dialyzer has two parts, one for the patient's blood and another for a washing fluid called dialysate, and a thin membrane separates the two parts. Blood cells, protein and other important things are too big to pass through the membrane and therefore remain in the blood. Smaller waste products, such as urea, creatine, potassium, and extra fluids pass through the membrane and are washed away [9]. In cases of acute kidney failure, dialysis may only be needed for a short time until the kidneys get better. However, when chronic kidney disease progresses to kidney failure over time, the kidneys do not get better and the patient will need dialysis for the rest of their life, unless they are a recipient of the over 24,669 kidney transplants performed in 2021 [10].

More than 90 percent of Americans with kidney failure, what Medicare calls End-Stage Renal Disease (ESRD), have medical care coverage under Medicare. The patient must have worked for a minimum of 40 quarters (10 years) in order to qualify for Medicare covering most of the treatment costs. Oftentimes Medicare covers other treatment costs not related to kidney disease. People with kidney failure are fortunate to have Medicare Part B medical insurance to cover many kidney dialysis medical services and supplies, including:

- Inpatient dialysis treatments at a hospital for special care;
- In a Medicare-certified dialysis facility or your home, known as outpatient dialysis treatments and outpatient doctors' services;
- Home dialysis training, which includes instructions for you and the person helping you with your home dialysis treatments;
- Home dialysis equipment and supplies, which includes the dialysis machine, water treatment system, basic recliner, alcohol wipes, sterile drapes, rubber gloves and scissors;
- Most dialysis drugs for outpatient or home dialysis, such as injectable, intravenous and oral medications; and
- Laboratory tests and other services that are part of dialysis and which may be costly while awaiting transplant surgery.

If the patient is selected for a kidney transplant, both Medicare Part A (Hospital Insurance) and Medicare Part B (Medical Insurance) will require the patient to cover 20 percent of the Medicare-approved amount. Medicare will cover the kidney transplant only if it is performed in a hospital that is Medicare-certified to perform kidney transplants. As of this writing,GalSafe pig kidney transplants are in the acute research stages and to date, these costs are not covered by Medicare [11].

Without a doubt, the authors believe that the future is bright for GalSave pig organ xenotransplantation. The CRISPR gene editing technology is currently in its infancy and expected to evolve with significant improvements by 2030.

Although nearly 25,000 kidney transplants were covered by Medicare Hospital Insurance and Medicare Medical Insurance in 2021, more than 800,000 Americans now suffer from kidney failure. In other words, there are at least 32 patients suffering of kidney failure for every kidney transplant performed in 2021 [12]. It is clear that a more efficient solution must be created, and it appears that Harvard geneticist George Church, and other creative geneticists and researchers are on the right track to solve such a critical problem.

Keywords:

Xenotransplantation, Kidneys, Animal organs, GalSafe Pigs, Kidney failure.

Conflict of Interest

The authors declare no competing financial interest.

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