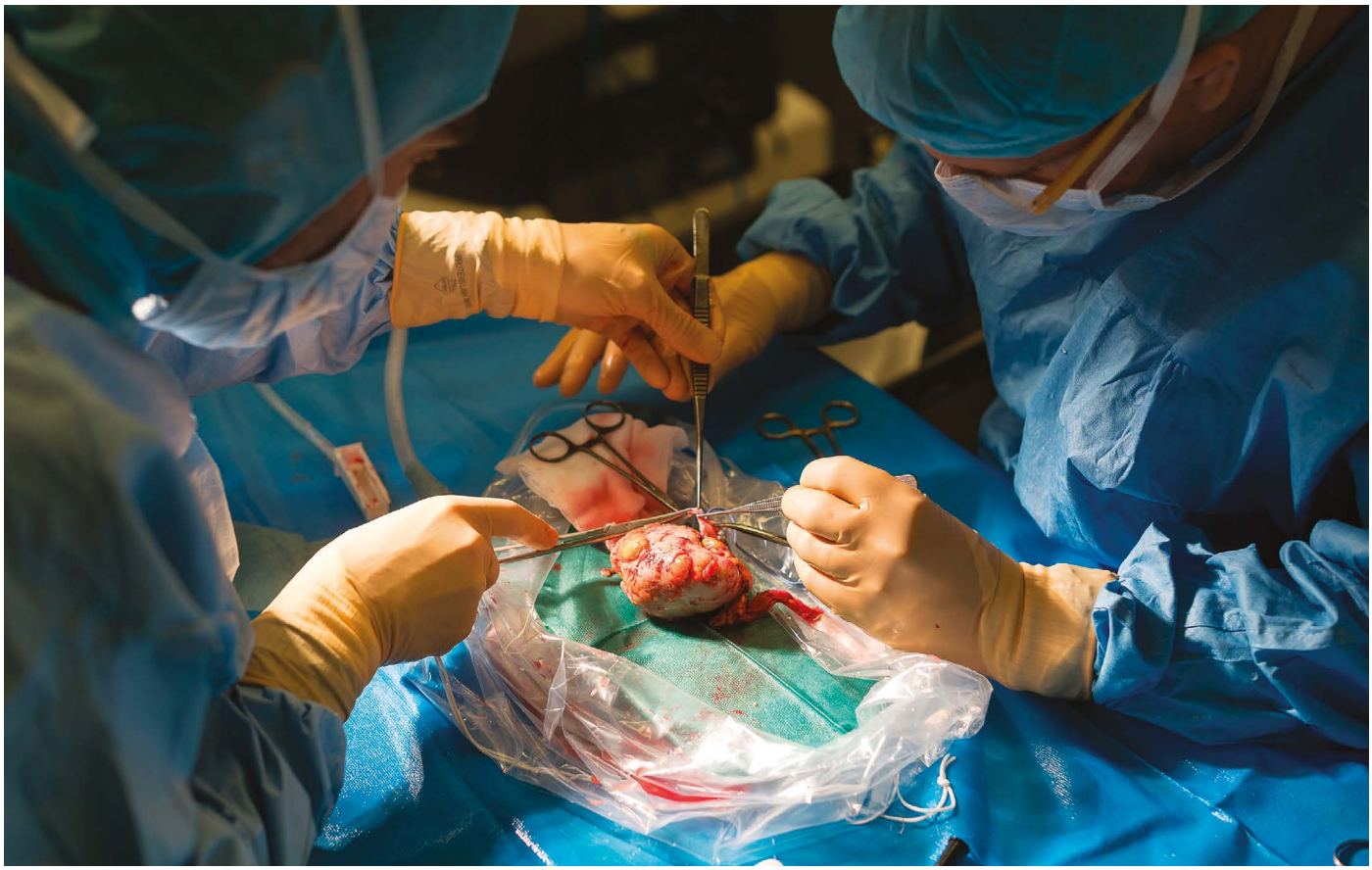
News in focus



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A kidney is removed from a donor, in a standard transplant procedure.

FIRST PIG KIDNEYS TRANSPLANTED INTO PEOPLE: WHAT SCIENTISTS THINK

The genetically modified organs seemed to function for more than two days, but some researchers are sceptical that the experiments had value.

By Sara Reardon

Kidneys from pigs that had been genetically modified to have human-like immune systems worked successfully when transplanted into two people who had recently died, the team that performed the experiments has reported[1]. Although the organs seemed to function, some researchers question the value of the experiments and argue that clinical trials in living people are the only way to find out whether transplants from pigs can help to alleviate the shortage of human organs.

Researchers have transplanted pig organs into non-human primates with great success: one baboon lived for more than two years with a genetically modified pig heart[2]. But baboons' immune and metabolic systems are different from humans', and certain immunosuppressive drugs routinely used in human organ transplants don't work in non-human primates, says Robert Montgomery, a transplant surgeon at New York University (NYU) in New York City who led the experiments. People who have recently died, he says, are "the closest thing we're going to get to a living human without the risk of harm".

In their transplant tests, which they performed in September and November 2021, Montgomery and his colleagues used pigs that had been genetically engineered to lack a gene coding for a protein called alpha-1,3-galactosyltransferase (αGal). The pig version of αGal triggers the human immune system to reject xenotransplants (organs transferred from a different species). With each kidney that the researchers transplanted, they also transplanted a pig thymus, an organ that produces immune cells and helps the body to accept the foreign organs.

They tested these "thymokidneys" in two

people who had been declared legally dead one to two days earlier because they did not have discernible brain function. The researchers did not remove the patients' own kidneys, but grafted the pig kidneys to the veins and arteries that carried blood to and from the recipients' legs. They then monitored the kidneys' function and the patients' immune responses for 54 hours — a limit imposed by NYU's ethics board and based on the amount of time typically required to harvest a person's organs for transplantation.

In a paper published on 19 May in *The New England Journal of Medicine*, the researchers said that the patients showed no immediate immune reaction to the organs[1]. Montgomery calls this "very reassuring", although he says that a later immune reaction might have arisen if the patients had been kept on life support for months. The amount of urine that the patients produced increased after the transplant and the amount of creatinine — a bodily waste product — decreased, suggesting that the pig kidneys were working as intended.

Genetic modifications

Other researchers, however, are sceptical of the results. For one thing, the pigs used in the study were missing only one gene, despite research showing that modifying three or more genes helps the human immune system to accept the organ[3]. "It's a pig that's not relevant to what we need to know," says David Cooper, a transplant surgeon at Massachusetts General Hospital in Boston. Montgomery says that some of the immune response could be controlled using drugs.

Moreover, it's difficult to tell whether the pig kidneys were functioning or whether the urine and creatinine were actually coming from the patients' own kidneys. "You can't interpret the results," says Paige Porrett, a transplant surgeon at the University of Alabama at Birmingham. In January, she and her team published results from their own study[4] in which they removed both kidneys from a person who had been without brain function for five days. After testing whether the patient's antibodies would attack the pig organ, they transplanted two kidneys from a pig with 10 genetic modifications and monitored the deceased patient for 74 hours.

Like Montgomery's team, Porrett's team saw little immune reaction against the organs. But although the pig kidneys produced some urine, they did not process creatinine, suggesting that they weren't functioning properly. Porrett suspects the reason for this was that the patient's metabolic systems were shutting down because he had been dead for five days.

Cooper is not surprised by either group's findings: research in baboons and human serum had already shown[5] that primate immune systems won't immediately reject a pig organ that lacks αGal. The unanswered questions, he says, are whether the human immune system will attack the organ months later and whether the organ will continue to function.

Montgomery and Porrett say that it might be medically possible to extend the experiment, because some people can survive for months after being declared brain dead. But doing this for research purposes creates ethical problems, says Rebecca Pentz, a bioethicist at Emory University in Atlanta, Georgia. According to a set of guidelines[6] that she authored in 2005, researchers should maintain people who have irreversible loss of brain function on life support for only one day, unless there are valid scientific reasons to extend the period.

Still, Pentz says that the NYU study followed the regulations set by the researchers' ethics board. "It's a smart use of the newly dead," she says. "I do think xenotransplantation — if we can work out the science — is going to be an ethical advance because we can save more human lives."

Partly because of such limitations, Cooper and others argue that it's time to start transplanting animal organs into living people — something that has been only partially successful so far. In January, researchers at the University of Maryland got special permission from the US Food and Drug Administration (FDA) to perform the first emergency transplant of a genetically modified pig heart into a man who was certain to die otherwise. The man died two months later.

Porrett and Cooper's groups are applying to the FDA to start small clinical trials that would transplant genetically modified pig kidneys into humans. The kidney is the ideal organ to start with, Cooper says, because, unlike a heart, it can be removed if problems arise and the patient can be placed on dialysis. "It should be done cautiously," he says.

1. Montgomery, R. A. *et al. N. Engl. J. Med.* **386**, 1889–1898 (2022).
2. Mohiuddin, M. *et al. Nature Commun.* **7**, 11138 (2016).
3. Estrada, J. L. *et al. Xenotransplantation* **22**, 194–202 (2015).
4. Porrett, P. M. *et al. Am. J. Transplant*. https://doi.org/10.1111/ajt.16930 (2022).
5. Kuwaki, K. *et al. Nature Med.* **11**, 29–31 (2005).
6. Consensus Panel on Research with the Recently Dead. *Nature Med.* **11**, 1145–1149 (2005).

HOME TESTING FOR SYPHILIS GAINS SUPPORT IN WAKE OF COVID

With cases of sexually transmitted infections growing, researchers hope self-tests could stem the tide.

By Carrie Arnold

Cases of sexually transmitted infections (STIs) have been on the rise in some countries. Even the COVID-19 pandemic — which locked down life in many ways — hasn't halted the trend. In April, the US Centers for Disease Control and Prevention (CDC)reported that the first year of the pandemic saw 133,945 cases of syphilis, a 52% increase since 2016 (go.nature.com/3gcfcim; see 'Resurgence').

And this is probably an underestimate, the CDC says, given that health-care clinics had to limit in-person visits at the start of the pandemic, and STI surveillance programmes found their resources shifted elsewhere. The situation sparked a push for at-home tests for syphilis and other STIs.

Encouraged by the popularity of at-home tests for COVID-19, self-testing has been embraced by many, including policymakers and people in marginalized populations. In January, a California law went into effect that requires private health insurers to cover the cost of at-home STI testing. Supporters say that self-testing has the benefit of allowing individuals to collect samples in the privacy of their homes, free from any stigma that might be associated with attending clinics, and that it allows people from all backgrounds and income levels to test frequently.

But the shift could also have trade-offs — some of them similar to those experienced for COVID-19, cautions Shweta Patel, a gynaecologist at the University of Alabama at Birmingham. With at-home tests, people do not receive the counselling that comes with in-person testing, and public-health departments might lose valuable statistics. Users must report their own results, and perform their own contact tracing to inform others that they might be in need of testing, Patel says, and this doesn't always happen.

Still, during the pandemic, self-testing for COVID-19 proved to be useful, says Natalie Cramer, deputy executive director of programmes at the National Alliance of State and Territorial AIDS Directors in Washington DC. She adds that it's past time for a