

Urine test can diagnose, predict kidney transplant rejection

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Analysis of three biomarkers in the urine of kidney transplant recipients can diagnose—and even predict—transplant rejection, according to results from a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. This test for biomarkers—molecules that indicate the effect or progress of a disease—offers an accurate, noninvasive alternative to the standard kidney biopsy, in which doctors remove a small piece of kidney tissue to look for rejection-associated damage. The findings appear in the July 4 issue of the *New England Journal of Medicine*.

"The development of a noninvasive test to monitor kidney transplant rejection status is an important advance that will allow doctors to intervene early to prevent rejection and the kidney injury it causes, which should improve long-term outcomes for transplant recipients," said NIAID Director Anthony S. Fauci, M.D.

Following a kidney transplant, patients receive therapy to prevent their immune systems from rejecting the organ. Even with this [immunosuppressive therapy](#), approximately 10 to 15 percent of kidney recipients experience rejection within one year after transplantation.

Typically, a biopsy is performed only after a transplant recipient shows signs of kidney injury. Although the procedure seldom causes serious complications, it carries some risks, such as bleeding and pain. In addition, biopsy samples sometimes do not give doctors an accurate impression of the overall state of the kidney because the samples are

small and may not contain any injured tissue.

"Potentially, a [noninvasive test](#) for rejection would allow physicians to more accurately and routinely monitor [kidney transplant recipients](#)," said Daniel Rotrosen, M.D., director of NIAID's Division of Allergy, Immunology and Transplantation. "By tracking a transplant recipient's rejection status over time, doctors may be able to modulate doses of [immunosuppressive drugs](#) to extend the survival of the transplanted kidney." In the study, part of the NIH-funded Clinical Trials in Organ Transplantation (CTOT), investigators at five clinical sites collected urine samples from 485 kidney [transplant recipients](#) from three days to approximately one year after transplantation. Researchers led by Manikkam Suthanthiran, M.D., of Weill Cornell Medical College in New York and Abraham Shaked, M.D., Ph.D., of the University of Pennsylvania School of Medicine, Philadelphia, assessed the urinary cell levels of several biomarkers that previously have been associated with rejection.

Statistical analysis revealed that a group of three urinary biomarkers formed a diagnostic signature that could distinguish kidney recipients with biopsy-confirmed rejection from those whose biopsies did not show signs of rejection or who did not undergo a biopsy. The biomarkers include two messenger RNA molecules that encode immune system proteins implicated in transplant rejection and one noncoding RNA molecule that participates in protein production. The researchers used the signature to assign values to each urine sample and identify a threshold value indicative of rejection. With this test, they could detect [transplant rejection](#) with a high level of accuracy. The investigators obtained similar results when they tested a set of urine samples collected in a separate CTOT clinical trial, thereby validating the diagnostic signature.

To determine whether the urine test also could predict future rejection,

the scientists analyzed trends in the diagnostic signature in urine samples taken in the weeks before an episode of rejection. The values for patients who experienced rejection increased slowly but steadily leading up to the event, with a characteristic sharp rise occurring approximately 20 days before biopsy confirmed rejection had occurred. In contrast, the values for patients who did not show any clinical signs of rejection remained relatively constant and under the threshold for rejection. These findings suggest that it might be possible to treat impending rejection before substantial kidney damage occurs.

"The test described in this study may lead to better, more personalized care for [kidney transplant](#) recipients by reducing the need for biopsies and enabling physicians to tailor immunosuppressive therapy to individual patients," said NIAID Transplantation Branch Chief Nancy Bridges, M.D., a co-author of the paper. The CTOT cooperative research consortium provided the infrastructure and collaborative environment needed to conduct the large, rigorous, multicenter study that established the efficacy of this biomarker-based test, Dr. Bridges noted.

More information: M Suthanthiran et al. Urinary cell mRNA profile and acute cellular rejection in kidney allografts. *New England Journal of Medicine* [DOI: 10.1056/NEJMoa1215555](https://doi.org/10.1056/NEJMoa1215555) (2013).

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