Urine Test Can Detect Likelihood of Kidney Transplant Rejection

Noninvasive Test More Than 95 Percent Accurate, UCSF Researchers Say

By Scott Maier [1]

A simple urine test can diagnose and predict acute rejection in kidney transplants, leading to an opportunity for earlier detection and treatment, according to a new study by researchers at UC San Francisco.

A test of 601 urine samples showed greater than 95 percent accuracy in determining the risk of rejection following transplant, the researchers said. Their work already has led to the spinoff Bay Area company NephroSant, which plans to launch its first noninvasive test for detecting kidney rejection in the near future.

“Our test can provide a new gold standard of post-transplant monitoring of adults and children,” said senior author Minnie Sarwal [2], MD, PhD, professor of surgery, medicine and pediatrics at UCSF, of the findings appearing online March 18, 2020, in *Science Translational Medicine* [3].

“Our test can provide a new gold standard of post-transplant monitoring of adults and children,” said Sarwal, incoming medical director of the Kidney-Pancreas Transplant Program at UCSF Health. “The high accuracy of the test can allow a physician to minimize unnecessary invasive biopsies for patients with low risk of rejection, and conversely, triage patients with high risk of rejection for customized immunosuppression. As the test is noninvasive, can be conducted at any time and requires approximately one tablespoon of urine, it lends itself to repeat testing for post-transplant immune monitoring.”

Chronic kidney disease (CKD), a gradual loss of kidney function over time, affects one in nine people worldwide, and one in six in the United States. Another one-third of American adults (80 million) are at risk for CKD, and 120,000 people annually develop end-stage renal disease that requires a kidney transplant.

All organ transplant recipients carry some risk of acute rejection. In extreme cases, the donated organ can be injured or even fail, resulting in costly treatments and diminished quality of life.

Occurring in 15 to 40 percent of kidney transplant recipients, acute rejection is generally detected by an invasive biopsy after a drift in the patient’s serum creatinine, and then treated with immunosuppressive medications. However, this drift is not a sure sign of acute rejection and occurs only after substantial organ damage. Some patients can even contract acute rejection without a drift.

In addition to adhering to immunosuppressive drugs and regular clinical visits, ongoing
diagnostic monitoring is essential to monitor transplanted kidney health. However, the current diagnostic methods are suboptimal, requiring blood draws using special tubes and kits for collection.

As a direct ultra-filtered product of the kidneys, urine provides an accurate window into the health of the transplanted kidney, and it is readily accessible and noninvasive to collect.

In the *Science Translational Medicine* study, Sarwal and her colleagues analyzed 601 urine samples from three transplant centers of 332 pediatric and adult kidney transplant recipients immediately before biopsy, along with 32 biopsy-matched samples obtained a week to eight months before a biopsy-confirmed organ rejection. The analysis was done with an assay developed in Sarwal’s lab called the QiSant assay, which measures cell-free DNA in urine, and detects certain epigenetic changes as well as levels of four other proteins and metabolites, combining these features in a ?Q-Score? that distinguishes organ rejection from stability.

The Q-Score has been shown to strongly correlate with both T-cell and antibody-mediated tissue rejection injury parameters, as measured from kidney transplant biopsy samples paired with the urine samples. Once acute rejection is detected above the diagnostic threshold, the higher the Q-Score, the greater the underlying injury from organ rejection.

In a comparison of 111 random Q-Score samples to 103 independent samples of rejection or no rejection, the Q-Score result was similar to paired biopsy results and clinical pathology diagnoses in determining whether the transplanted kidney was undergoing acute rejection, both antibody-mediated rejection and T cell-mediated rejection, or stable and healthy. The assay was 95.6 percent accurate in determining high-vs.-low risk of organ rejection in both adults and children.

In addition, unlike blood determinations of circulating free DNA (cfDNA) that require assessing its ratio between the transplanted organ and the overall blood sample in the donor, and therefore cannot be used to assess rejection in repeat transplants or multi-organ transplants from different donors, the Q-Score detects rejection in repeat transplants and across a wide range of recipient ages spanning both childhood and adult, Sarwal said.

These study findings support previous research by Sarwal and her colleagues showing these same six urine markers could detect different stages of kidney injury and were more sensitive for detecting early kidney injury than estimated glomerular filtration rate (eGFR), serum creatinine or the onset of excess protein (proteinuria).

Looking at multiple biomarkers and not just cfDNA enables the assay to provide a comprehensive analysis of the kidney, both before and after transplantation, Sarwal said. The analysis process itself is simpler than other similar tests by not requiring sequencing or sequence information.

With adjustments to the algorithm, the same biomarkers can be applicable for testing the potential of CKD in the remaining single kidney in living kidney donors. It also can have clinical relevance for testing kidney function in non-renal organ transplant donors (e.g., heart, liver, pancreas and lung), where damage to the native kidney is likely from chronic exposure to immunosuppression.

The QiSant test will be available to kidney transplant patients and providers for accurate
diagnosis of kidney transplant rejection as a laboratory-developed test through NephroSant’s Clinical Laboratory Improvement Amendments (CLIA) certified lab, Sarwal said.

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Disclosures: The intellectual property (IP) for this assay has been filed and is owned by the UC Board of Regents. Sarwal, Yang, and Sigdel are founders of NephroSant, Inc. (San Francisco, CA), which has licensed the IP for this assay from the UC Board of Regents. Sarwal is on the FDA Science Board and consults or has recently consulted or received sponsored research funds from Bristol-Myers Squibb, Natera, Astellas Pharma, Genentech and Jazz Pharmaceuticals. Vincenti consults for eGenesis Bio, Natera and Sanofi.

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