genomeweb

Heart Transplant Monitoring Test From TAI Diagnostics Validated in New Study

Jan 22, 2020 | Madeleine Johnson

NEW YORK – A noninvasive molecular diagnostic test to anticipate heart transplant rejection has shown to have a nearly 100 percent negative predictive value in a recent evaluation.

Developed by Milwaukee, Wisconsin-based TAI Diagnostics, the laboratory-developed test uses fraction cell-free donor DNA in a recipient's blood as a biomarker of heart transplant viability. The assay, called MyTAIHeart, is the company's first though TAI Diagnostics is also developing longitudinal monitoring tests for other types of solid organ transplants.

The firm is a molecular diagnostics reference lab co-founded by Aoy Tomita-Mitchell, a professor of surgery and biomedical engineering at the Medical College of Wisconsin, and Michael Mitchell, a pediatric cardiothoracic surgeon also at MCW.

The team previously founded Ariosa Diagnostics, a noninvasive prenatal testing firm that was acquired by Roche in 2015 for $625 million. The two then moved to the Medical College of Wisconsin where they founded TAI Diagnostics in 2014.

Frank Langley, CEO of TAI Diagnostics, said in an interview that the genesis of TAI Diagnostics was a patient of Mitchell's with venous access issues that complicated taking biopsies of the heart — the standard way to monitor transplants.

MyTAIHeart focuses on heart transplants. From initial donor and recipient samples, the firm takes a baseline signature of 94 SNPs in genomic DNA. It can then detect and quantify donor DNA in the transplant recipient's blood and calculate a donor fraction. These cfDNA levels serve as a biomarker of viability, with rising donor fraction indicating a potential for transplant rejection.

As described in *PLoS One* last week, the assay was compared to a biopsy of the donor heart tissue, called an endomyocardial biopsy (EMB). Paula North, a professor of pathology at the Medical College of Wisconsin and chief laboratory officer of TAI Diagnostics, explained in an email that while EMB is considered the gold standard for heart transplant monitoring, it is problematic.

The EMB procedure involves accessing the heart through the vascular system. Because the heart can be failing in one part and healthy in another, multiple biopsies are often taken each time, a procedure that requires anesthesia.

Pathologists then analyze biopsies of donor hearts using histology to detect acute cellular rejection (ACR) and antibody-mediated rejection (AMR), North said. These two kinds of rejection are distinct and would have different treatments. Unfortunately, the "rejection grade" assigned by the pathologists tend to have low concordance between experts, North said, and approximately 20 percent of rejection cases are "biopsy negative."

One advantage of MyTAIHeart is that it is a noninvasive test, which North said is particularly applicable in patients with limited vascular access, which is "a relatively common problem in transplant patients."

Furthermore, it can also be useful in stable patients after the first year post-transplant, and in patients who are too ill to undergo anesthesia and invasive biopsy. It is also a relatively inexpensive option compared to EMB that can potentially allow increased frequency of monitoring to detect rejection before it becomes clinically evident, she said.

North, who also practices surgical, clinical, and molecular pathology at Children's Hospital of Wisconsin and serves as medical director of the TAI clinical reference laboratory, said the MyTAIHeart test can be used to stratify probability of moderate to severe ACR in heart transplant recipients. In the *PLoS One* study, she and her co-authors showed that the test had a greater than 99 percent negative predictive value based on a cut-off value of fraction of donor DNA in the transplant organ recipient's blood.

There are a handful of other noninvasive options for monitoring heart transplant rejection, but North said these have significant limitations compared to the MyTAIheart test.

For example, the CareDx Allomap test is a competing technology that measures leukocyte gene expression rather than cell-free DNA. Although the test is cleared by the US Food and Drug Administration, it is not indicated for use in pediatric patients or for use before 55 days after a transplant.

"We can test heart transplant patients who are two months of age or older, and we can go as early as eight days post-transplant, which is critical because that is when rejections often occur," Langley said

Because the test uses multiplex PCR, it is also less expensive, with a shorter turnaround time and a higher sensitivity than next-generation sequencing, North said. The patient's total cfDNA level is also reported and has independent clinical value, she added.

North noted that the MyTAIHeart test is not intended to completely replace EMB, "which can provide uniquely advantageous morphological, immunohistochemical, and molecular diagnostic information," but rather to complement it.

Langley said there is growing clinical adoption of the MyTAIHeart test, and he expects that the PLoS validation will enhance that positive trajectory. The firm is also cosponsoring a multicenter National Institutes of Health study, with Phase I data recently published in *The Journal of Heart and Lung Transplantation*.

Additionally, "Our cell-free DNA testing is a platform technology, and we are pursuing a pan-organ strategy, developing products for every organ," Langley said. Future tests will apply the same technology to lung, kidney, and liver transplants, he said.

The company is also working with United Therapeutics — a company developing therapies for pulmonary arterial hypertension as well as lung transplant-related applications — to develop a companion diagnostic for their *ex vivo* lung perfusion program, Langley said.

For TAI Diagnostics, being situated in the Milwaukee area has helped support the development of its technology, according to company executives.

Milwaukee, and Wisconsin generally, have been striving to become a regional incubator of biotech, according to two non-profit groups in the area. At the Milwaukee Institute, Executive Director Kathleen Gallagher and her team support regional economic development.

In health and life sciences, the biggest player in the Milwaukee region is the Medical College of Wisconsin, Gallagher said. It has more than $200 million in research expenditures, and although MCW had historically struggled with tech transfer, they brought in a new director of their office of technology development who is now closing in on 10 startup licenses since arriving two years ago, Gallagher said.

Additionally, GE Healthcare also has a very large presence in Milwaukee, Gallagher said, and the Versiti Blood Center of Wisconsin has also fostered some spinouts. Milwaukee is also home to Aldrich Chemical, which later became Sigma-Aldrich, and was acquired in 2014 by Merck for $17 billion.

Other diagnostics firms in the Milwaukee area include Retham Technologies – a firm developing tests for heparin-induced thrombocytopenia - and Right Patient Right Drug or RPRD Diagnostics, which spun out from MCW and has since partnered with St. Jude Children's Research Center to offer pharmacogenomic genotyping.

Promiss Diagnostics is also developing a non-invasive, machine-learning clinical diagnostic test for ovarian cancer and raised $400,000 earlier this month from the University of Wisconsin, Madison's Wisconsin Alumni Research Foundation, with investment from a local venture fund affiliated with Northwestern Mutual called Cream City Venture Capital.

Nearby, Madison is home to Epic Systems, the dominant electronic health records company in the US, as well as Exact Sciences, Luminex, and Promega. Other diagnostics companies in the Madison area include Gregor Diagnostics, a spinout of Lucigen called Eden, GoDX, BluDiagnostics, NeuroPointDx, and Capio Biosciences.

TAI Diagnostics' Langley, who was formerly the president of a non-profit called BioForward Wisconsin — which fosters the growth of biotech, diagnostics, and medical device firms in the state — noted that there also happens to be a particularly strong microcosm of transplant-related biotech in the area as well, with Pel-Freeze Clinical Systems, a company that developed pretransplant HLA typing technology, as well as Immucor, a company with a transplant focus in the vicinity.

"There is significant transplant expertise and talent that resides in Milwaukee ... and there is a tremendous amount of scientific and technical capability here," Langley said.

Filed Under PCR Molecular Diagnostics Cardiovascular Disease Genomics: Clinical Implementation North America heart transplant organ transplant transplant rejection cell-free DNA

Sign Up for Newsletters