Cell-free DNA detects pathogens and quantifies damage

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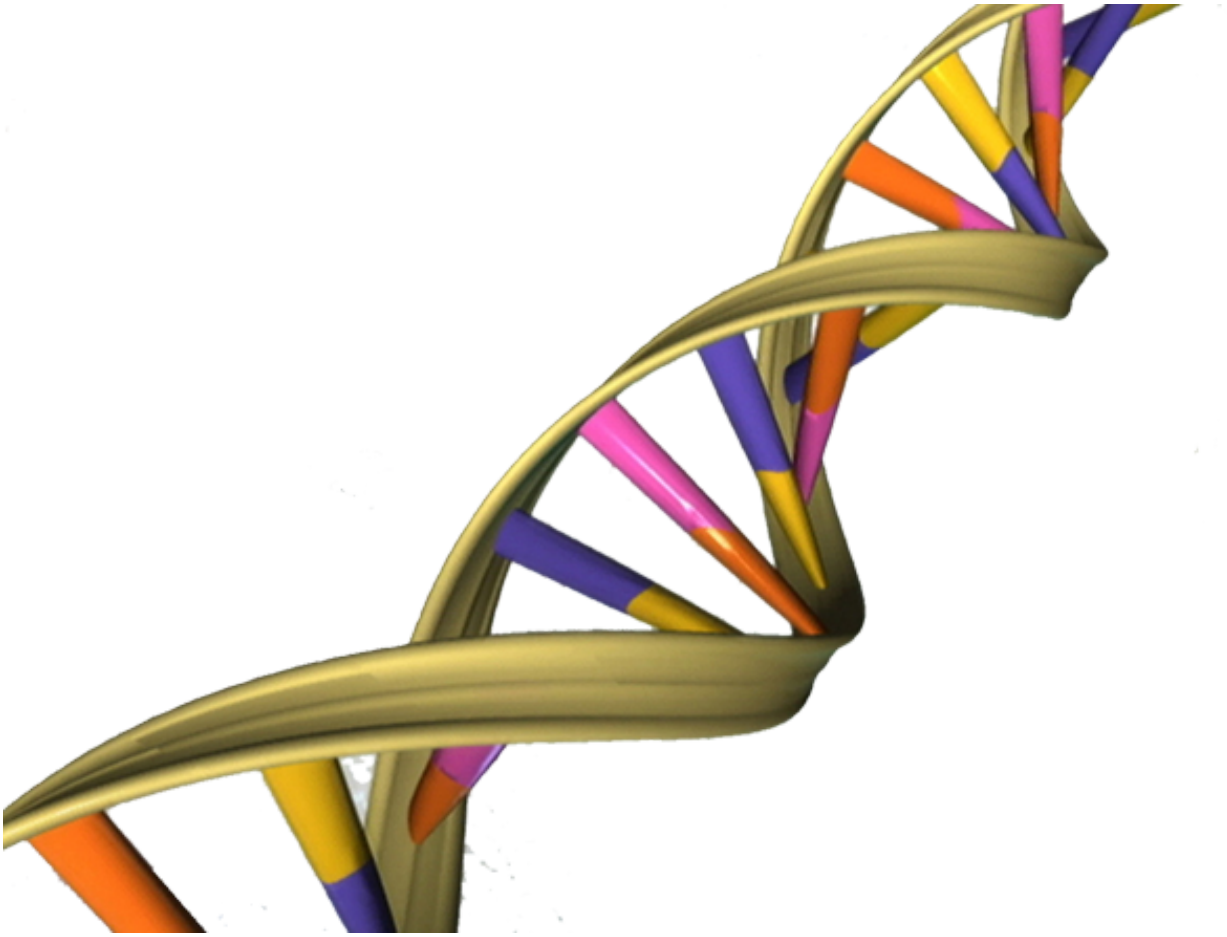

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A common problem in diagnosing infectious disease is that the presence of a potential pathogen in the body does not necessarily mean the patient is sick. This can be particularly challenging for the treatment of organ transplant recipients, who often grapple with infection as well as complications related to immunosuppression.

A new Cornell study, "A Cell-Free DNA Metagenomic Sequencing Assay that Integrates the Host Injury Response to Infection," published Aug. 26 in *Proceedings of the National Academy of Sciences*, presents a technique to identify viruses and bacteria in the human body and quantify injuries to organs by using dead fragments of DNA, called cell-free DNA, that roam throughout the bloodstream and urine.

The resulting test is simple, fast, low cost and generalizable enough to identify thousands of bacteria and viruses.

"This really came about through collaboration with clinicians who explained to us this common problem in infectious disease diagnosis," said co-senior author Iwijn De Vlaminck, the Robert N. Noyce Assistant Professor in Life Science and Technology in the Meinig School of Biomedical Engineering. "So we developed an assay that would simultaneously inform us about the presence or absence of a wide range of pathogens, but at the same time would also tell us about the injury of different host tissues. The combined information enables us to more definitively say whether a person is dealing with disease or not."

De Vlaminck and his team partnered with researchers at Weill Cornell Medicine and focused on urinary tract infections in kidney transplant patients.

Lead author and Ph.D. student Alex Cheng used high-throughput DNA sequencing to identify any microorganisms that were present in clinical samples and distinguish them from the host DNA via bisulfite

sequencing, a process in which the cell-free DNA is treated with salt to reveal methylation marks. These marks helped the researchers trace the cell-free DNA's tissues of origin and measure the degree of injury to different host tissues.

"In the field, doctors who try to diagnose infectious diseases and people who run microbiology labs are getting more and more excited about the use of genomic medicine approaches for diagnosis," De Vlaminck said. "But there was still a big gap to assess whether that organism is actually causing disease.

"That's really a critical question," he said. "Because some organisms are just commensals, they live side by side with the host. Our guts are filled with microbes, but those microbes may not be the reason you're suffering from disease. In a way, you're infected. You're colonized, but that's just part of normal biology."

The test is so generalizable that virtually any organism that has a DNA genome can be identified.

"Infectious diseases are a leading cause of disease burden worldwide," Cheng said. "They affect almost every single demographic, and they are not very easy to understand. So to have a test that can potentially help this large amount and wide range of people is exciting."

"Transplant recipients, because of the lifelong drug therapy needed to protect their transplanted organs, are ever at risk for infection-related complications," said co-author Dr. Manikkam Suthanthiran, chief of Nephrology, Hypertension and Transplantation Medicine and Stanton Griffis Ditinguished Professor of Medicine at Weill Cornell Medicine and NewYork-Presbyterian/Weill Cornell Medical Center. "A precise test that informs not only the presence of infectious agents but also the presence or absence of tissue injury is a major step toward personalizing

therapy and making organ transplantation safer."

For co-senior author Dr. Darshana Dadhania, associate professor of medicine at Weill Cornell Medicine and a nephrologist at NewYork-Presbyterian/Weill Cornell Medical Center, the test is especially helpful in diagnosing damage due to BK polyomavirus (BKV) infection. While 25% to 30% of kidney transplant recipients have the virus in their blood or urine, only 5% experience nephropathy, or kidney disease, from the virus, Dadhania said.

"In this investigation, we were able to demonstrate that the kidney-specific urine cell-free DNA is higher in individuals with BKV nephropathy as compared to those with BKV replication alone and those with no BKV replication, suggesting a role for this assay to monitor kidney damage in the face of active viral replication and infection," Dadhania said. "This is particularly important because there is no specific therapy for active BKV replication."

More information: Alexandre Pellan Cheng et al, A cell-free DNA metagenomic sequencing assay that integrates the host injury response to infection, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1906320116

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