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## DNA on the Loose: Next-Gen Blood Tests Tap Free-Floating Genetic Material

**Tests using floating nucleic acids could diagnose disease, monitor pregnancy and weed out "mad" cows**

By Barbara Juncosa

Free-floating messages in the bloodstream could soon provide a unique window into the body. Researchers worldwide are racing to decipher circulating genetic material for better ways to diagnose disease, monitor pregnancy, and even improve [food safety](#).

Circulating [DNA](#) and RNA—temporary gene copies that act as blueprints for protein production—was first discovered in 1948. Researchers still do not fully understand how the free-floating genetic fragments (chemically referred to as nucleic acids) survive outside the protective barriers of cells, but recent technological advances now allow scientists to comb through these tiny messages for clues about human health.

Traditional genetic screens, such as [paternity tests](#) and criminal profiling, utilize the abundant DNA stored in the nuclei of circulating blood cells. Although these tests shed light on a person's genetic inheritance, they do not provide insights on the current health of specific tissues and organs—information that could potentially be gleaned from the free [nucleic acids](#).

Debate about the exact origins of circulating DNA and RNA continues, but dead cells from all areas of the body certainly contribute to the pool with new evidence mounting that living cells also release nucleic acids, perhaps enabling cell-to-cell communication over vast distances in the body, says Asif Butt, senior research fellow at King's College London.

Even healthy patients have circulating DNA and RNA, says Michael Fleischhacker, a molecular biologist at Charité-Universitätsmedizin Berlin hospital, but individuals with chronic disease such as cancer, [inflammatory bowel disease](#) and systemic lupus typically harbor increased levels of these messages in their blood. Simply monitoring the overall concentrations of nucleic acids in circulation, however, does not provide sufficient information about any one condition, prompting scientists to hunt for genetic targets specific to particular diseases.

Cancer researchers, for example, are seeking out patterns of chemical modifications and [mutations](#) detectable in the circulating gene fragments that are unique to malignancies. This approach could allow physicians to profile [tumors](#) without invasive sampling, says David Hoon, a molecular oncologist at the John Wayne Cancer Center Institute in Santa Monica, Calif.

The long-term goal is to identify genetic guides that can point physicians to a tumor's location as well as patterns that are characteristic of its stage to determine and monitor treatment and disease progression in patients, says Brian Durie, an oncologist at the Cedars-Sinai Medical Center's Samuel Oschin Comprehensive Cancer Institute in Los Angeles.

Fleischhacker cautions, however, that preparing these tests for routine cancer screening is likely to take a few years, because today's sensitive techniques can also detect rare mutations in healthy people that are of no clinical consequence.

Perhaps the most successful application of testing circulating DNA to date has been in the area of prenatal care. In the late 1990s researchers first recognized that fetal DNA could be detected in the mother's blood, albeit at very low levels, opening the door for noninvasive testing during pregnancy.

Traditional methods for examining fetal DNA, such as [amniocentesis](#), require removing a sample of amniotic fluid surrounding the baby, increasing the risk of miscarriage, says Diana Bianchi, professor of pediatrics at Tufts University School of Medicine in Boston. Analysis of the mother's blood, on the other hand, could allow physicians to safely monitor the fetus and mother throughout the pregnancy.

In the U.S. and Europe, blood tests have already been approved for the diagnosis of rhesus D incompatibility—a condition in which a mother produces antibodies against her fetus due to the absence of the blood factor in her own body. Gender screening is also performed in Europe for families at high risk of passing on genetic disorders linked to the X chromosome. Bianchi says blood tests for Down's syndrome could be available in the near future.

Beyond cancer and prenatal testing, circulating nucleic acids could help physicians track a broad range of diseases, including stroke, heart attack and complications from diabetes. Butt's team has already identified several genetic markers important for diagnosing (and potentially predicting) [diabetic retinopathy](#)—damage to the eye's retina. Currently, only annual comprehensive eye tests can detect the condition, which is a leading cause of blindness in adults in the U.S., according to the National Eye Institute in Bethesda, Md.

Even the safety of animals stands to get a boost from testing circulating DNA. Researchers last month announced that chronic wasting disease in elk and bovine spongiform encephalopathy ([mad cow disease](#)) in cattle could be diagnosed up to six months before symptoms show up.

The only way to confirm a case of these diseases right now is to examine an animal's brain postmortem, says study leader Christoph Sensen, director of the Sun Center of Excellence for Visual Genomics at the University of Calgary in Alberta. But by comparing the circulating DNA profiles of sick and healthy animals, Sensen's team was able to identify disease-specific genetic patterns for diagnostic use in live animals. Providing a cheap method for testing all livestock in slaughterhouses, Sensen says, will be important for certifying the safety of meat exports and preventing future disease transmission to humans.

Although blood has been the primary focus for work on circulating nucleic acids, some researchers are now looking to test other bodily fluids. [Urine](#) is a particularly attractive candidate as it could provide an alternative source for testing circulating DNA and RNA in the developing world where drawing blood can be impractical, notes Timothy Block, co-founder of the Hepatitis B Foundation and a virologist at the Drexel University College of Medicine in Philadelphia.

With such broad applications, King's College's Butt agrees that the future of this technology is bright, but cautions that commercial partners will be key for developing clinical tests in the coming years.

Howard Urnovitz, CEO of Chronix Biomedical, Inc., in San Jose, Calif., is already looking for companies in the diagnostic field to help commercialize his company's bioinformatic approach to computationally mining thousands of sequenced circulating DNA fragments from healthy volunteers and patients for diagnosing and tracking specific diseases, including [multiple myeloma](#) (a cancer of disease-fighting plasma cells that is incurable but treatable), breast cancer and multiple sclerosis.

Despite the pressing need for identifying and validating new disease markers, Peter Gahan, a cell biologist at King's College, is optimistic. "Funding was virtually nonexistent five to 10 years ago," Gahan says, but "we are already beginning to get markers that could enter into predictive medicine."