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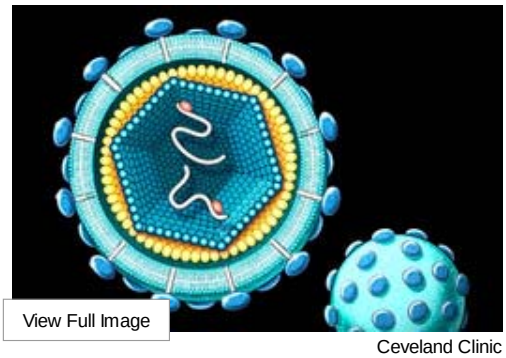
Seeking New Blood-Supply Test

By AMY DOCKSER MARCUS

Scientists are racing to develop tests for a retrovirus called XMRV, which could be used to determine if the blood supply is tainted and to assess how many people may be infected.

The impetus behind the drive is a paper published in the journal Science last year that reported a link between XMRV and chronic fatigue syndrome. Public health officials were alarmed that close to 4% of healthy people used as controls in the study were infected with XMRV. That could mean as many as 10 million Americans are infected.

XMRV has gotten a lot of attention because, like HIV, it is a retrovirus. This means the virus cannot be eradicated from the body, only controlled. There is some preliminary evidence that XMRV may be transmitted sexually or through transfusions. While the retrovirus has been linked to certain diseases, scientists don't yet know if it actually causes any disease.



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Right, XMRV; left, cross-section of the retrovirus.

The virus doesn't appear to replicate as frequently as HIV, making it challenging to detect. How labs handle blood samples before they test for XMRV may have an impact on results, some researchers believe. Some labs haven't been able to find it in people with chronic fatigue syndrome or prostate cancer, which have both been linked to the retrovirus. There has also been debate over the criteria used to define patients with chronic fatigue syndrome. These issues have made it challenging to come to a consensus on how many people are actually infected and whether or not XMRV poses a health risk.

Tests are in the works at a number of labs, including the Centers for Disease Control and Prevention and the National Cancer Institute as well as Abbott Diagnostics, a division of Abbott Laboratories, and Gen-Probe Inc. Roche Diagnostics says it expects to have a test for research purposes ready in months. Michael Busch, director of the Blood Systems Research Institute in San Francisco and a member of a federally funded blood-working group studying the potential impact on the blood supply, says the group pushed for companies to get involved early on in developing XMRV tests because they have technology that allows them to screen thousands of samples quickly. This kind of capacity "is critical to support our research studies and resolve the questions about XMRV," Dr. Busch says.

Various labs have their own tests but not everyone has been able to find XMRV in patients. If it turns out that XMRV is associated with diseases, there will be a need to screen large numbers of people and fast, reliable methods to test for it.

A key challenge is that these are still early days in understanding XMRV. Researchers usually calibrate tests against clinical samples that everyone agrees are positive and negative for the virus. A successful test would correctly determine which samples are infected. In the case of XMRV, there isn't yet scientific consensus. Some labs have said they cannot find XMRV in blood samples from patients that other labs have deemed positive.

To get around that problem, researchers at Abbott, Cleveland Clinic and Emory University created their own positive samples by using blood from monkeys that were infected with XMRV in the lab. "There is always doubt about human samples, but there are no ifs, ands, or buts about the animals being infected," says Robert Silverman of Cleveland Clinic, whose lab is working with Abbott and receives research funding from the company. Dr. Silverman also could receive royalty payments from Abbott because of XMRV patents licensed to the company.

Researchers from the three institutions developed tests that identify antibodies to three key proteins of XMRV, or xenotropic murine leukemia virus-related virus. The presence of antibodies indicates exposure to the virus.

Walter Kierans of Abbott Diagnostics says they were able to find virus in the blood of the rhesus macaque monkeys immediately after being infected, but that amount was virtually undetectable in the blood within a few weeks. This could provide one explanation for why it has been hard for some labs to find the virus in the blood of patients. Low levels of virus doesn't mean that XMRV isn't harmful, Dr. Kierans said. Another retrovirus, HTLV, is also found in low levels in the blood but causes leukemia in some infected people.

Rachel Bagni, a scientist with a government contractor working with the NCI, developed an XMRV antibody test using blood from patients with chronic fatigue syndrome provided by the Whittemore-Peterson Institute in Reno, Nev., whose researchers led the team that published the Science paper. For healthy controls, Dr. Bagni used blood from healthy blood donors whose blood tested negative for known pathogens typically screened for by blood banks.

To be declared positive, the blood had to show antibodies for three or more XMRV proteins. The test was able to detect XMRV but it will likely be refined once more clinical samples become available, Dr. Bagni said. She cautioned that the presence of antibodies doesn't determine if someone has an active infection. Antibodies mean that someone was exposed to the virus at some point in time.

Mary Kearney, an NCI researcher, took a test she developed for HIV and adapted it to measure the amounts of XMRV in patients' blood. The test, called X-SCA, is so sensitive that it can pick up a single particle of XMRV in a milliliter of blood. She says the test could be useful in the treatment of patients infected with XMRV because the test can measure viral loads before and after therapy.

Carl Hull, president and CEO of Gen-Probe, which has been working with the XMRV blood-working group, says the company has an early version test that looks for the genetic material of XMRV in the blood. There is a window between when someone is infected and when the body starts making antibodies that can be picked up by testing. Gen-Probe says its test enables detection very early, without waiting for signs of an immune response.

Mr. Hull says the test can be run on an instrument that allows for high volume testing, which could be useful in screening blood donors. "We can run 1,000 samples in 14 hours," he says.

Paul Kortschak of Roche Molecular Diagnostics says Roche is still in the earliest stages of developing a research test. He said Roche wants more "specific proof that XMRV is a virus of concern and it is possible to transmit through blood transfusions."

Another effort attempts to find XMRV specifically in men with prostate cancer because some research has linked the virus to that disease. Studies have found the virus in prostate-cancer tissue, but Eric Klein, a prostate-cancer

surgeon at Cleveland Clinic, says doctors want a way to avoid having to do tissue biopsies. Instead, researchers in Dr. Klein's and Dr. Silverman's labs, developed a test that can detect XMRV genetic material in urine. Biopsies sample only a small part of the prostate and can miss cancer. A urine test that looks at secretions from the whole prostate potentially could be more comprehensive. In data presented by the Cleveland Clinic researchers at an NIH XMRV workshop in September, 26% of 120 prostate-cancer patients had XMRV in the urine, compared with 8.5% of healthy controls.

Now that so many researchers have developed early versions of different tests, the next step is to see how they work outside a research setting. Dr. Busch says the federal blood working group is creating a set of positive and negative clinical samples that all labs can use, and has sent out blood to various labs to use as they fine-tune their tests.

The working group is developing a protocol that instructs labs on how to handle and process the blood, he says. For instance, discrepancies in the number of days that elapse between the time the blood is drawn and tested could make a difference in results, Dr. Busch says.

"When there is a new agent that we don't know a lot about, it's always a process," he says.

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