# Genetic Testing Takes Guesswork Out Of Diagnosis

Naval Research Lab
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Interpreting a patient's symptoms, then working backward to determine the cause could be made obsolete by a digital and genetic tool that is mistake-proof, faster and rapidly improving. TessArae LLC is accelerating the process of diagnosing infectious diseases using resequencing pathogen microarray (RPM) testing. The process uses tiny computer chips that take details from culture swabs to identify bacteria and virus samples using a portion of genetic code then matches it against a database of known diseases. Even better, after thousands of RPM tests, there have been no false positive results.

The venture merges information technology, medicine and microbiology. RPM begins by removing everything from the sample organism except nucleic acids, permitting genetic codes to be read. What begins as a patient's throat swab contents ends up as a series of pathogen genetic code. When compared against databases of known codes, test results are returned with pinpoint accuracy.

Those details can be critical when doctors need to identify a particular flu, disease variant or even a co-infection — such as during the 2009 flu outbreak. RPM technology quickly detected an H1N1 virus sample even before the organism's genetic sequence was known. When those results did not fit any known flu strain, it pointed to a new influenza. A week later, when the sequence became available, the RPM test sample was a perfect match. More remarkably, the test — developed in 2006 — identified the H1N1 strain several years later. No other test today can do that without specifically being designed against the target organism it seeks to identify.

"The beauty of it is the computer does all the work in converting the sequence into A, C, G, T, " says TessArae Chief Executive Officer Klaus Schafer, M.D. "Even if doctors think they know what they're looking for, they are often wrong or find out too late. This test is especially useful when vague symptoms such as cough or fever are all that is known. I'm a physician by training. Today's process is always to start with a hypothesis and ask, What should I test for? But one only gets results of what one is testing for — so these tests could change our understanding of epidemiology."

Although there are no reliable measures of missed diagnoses, adverse treatment reactions or those made too late to identify and cure patients, RPM's creators say it can remake the delivery of health care. It can reduce errors and improve targeted treatment to provide cost savings, better results, more quickly than current practices.

**From the Air Base to the Lab**

With a story as complex as a prime-time medical drama, RPM technology began as an experiment to spot infectious diseases at U.S. Air Force bases. The path began with concerns over biological weapons in 2001 — when deliveries of anthrax via mail made headlines, prompting research on computer-assisted diagnostics to protect against biological attack.

At the same time, Affymetrix Corp. was pioneering the lab on a chip — computer assisted diagnostics using genetic codes of virus and bacteria samples. Schafer calls RPM microarrays "the software to Affymetrix hardware." By the mid-2000s, genetic medicine was getting recognition for treatments, but diagnostics was still emerging.

Virologist Clark Tibbetts, Ph.D., teamed with RPM co-inventor David Stenger, Ph.D., of the Naval Research Laboratory in Washington, D.C. While serving as a civilian Air Force official, Tibbetts had proposed using RPM predecessor tools to monitor virus and flu outbreaks at Lackland Air Force Base in Texas. Medical teams knew that military installations — especially during initial basic training — were prone to infectious virus outbreaks when recruits came together from all over the world. After Air Force tests, a later proof-of-concept test of RPM was used to safeguard Washington, D.C., during the 2004 presidential inauguration.

Several scientific breakthroughs were combined by the RPM team to increase its capabilities, gradually expanding the number of samples on each array microchip. Up to 70 nucleotides can be scanned simultaneously and quickly compared to genome databases. According to its patent, issued in July 2009, more than a dozen contributors shared credit with the Naval Research Laboratory (NRL).

Building ongoing research relationships and multidisciplinary talents were crucial to commercialization. Joel Schnur, Ph.D., directed NRL's Center for Bio/Molecular Science and Engineering, contributing his experience in transferring nonmedical military technology to the marketplace.

The route from government lab to business plan can be challenging, because of federal regulations on publishing details of intellectual property in full view of companies that might be pursuing similar advances in private, TIbbetts notes, "The key thing is that all parties have an interest in moving things forward. And by starting in and moving outward, TessArae really mastered this genetic testing for inherited diseases, as well as infectious diseases, where

there are chances to leverage the technology and grow more rapidly."

**From Military to Marketplace**

Tibbetts and Schafer left the government to start the company and signed a cooperative research and development agreement with the NRL, giving TessArae time to continue while seeking investors and customers. "Part of the challenge in developing new technology in Washington, D.C., is that it can be a conservative place," Stenger adds. "And what we were trying to do was rather ambitious. I wrote most of the patent applications in 2004. Just before people thought we would fail, they began to see potential to be a real gold standard in medicine."

Those prospects took shape when TessArae opened in Potomac Falls, Va., in 2007. Regulatory approvals from the U.S. Food and Drug Administration and other agencies are still based on polymerase chain reaction (PCR) testing developed in the 1980s. So the company is helping federal officials develop new frameworks for evaluating digital alternatives and modernizing aspects of genetic diagnostics.

Other opportunities for RPM are opening up in unexpected fields, and Stenger notes the database of known genetic codes is growing logarithmically every year, which will advance applications. Beyond current testing for avian influenza, Ebola virus and other human diseases, TessArae received a U.S. Department of Agriculture innovation award for food safety, applying RPM tests to finding obscure, rare diseases in food stock. Single-use tests wouldn't be cost-effective, Stenger says, but can be profitable when multiple tests deliver more results.

> *"Additional applications have emerged in tracking genetic, inherited diseases. Also, because the same condition may affect two people in different ways, having proof — instead of waiting for symptoms or reactions — means patients get treated sooner.*

In 2009, TessArae and Affymetrix collaborated to identify H1N1 flu strains within hours — while the National Institutes of Health used older, slower methods. Outside the medical office, RPM test results will allow doctors to more accurately report a specific strain of influenza and geographically map the spread and speed of outbreaks.

Yet RPM applications intended for soldiers have not been implemented. Commercial prospects and other forces have shifted attention — another unexpected, but not unusual, result in the path of a trailblazing technology, Schnur says.

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