WIRED

<< Back to Article

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You've Got Drug-Resistant TB! The Ultimate Diagnostic Device.

Thomas Goetz 07.24.07 | 2:00 AM

Charles Daitch, CEO of Akonni Biosystems, has introduced the TruDiagnosis system to identify deadly pathogens quickly and cheaply.
Photograph by Michael Schmelling

In April 1989, the Centers for Disease Control and Prevention announced an audacious goal. In a report titled *A Strategic Plan for the Elimination of Tuberculosis in the United States*, the CDC declared that by the end of the 20th century, the number of TB cases in the US would drop to 10,000 a year — down from 22,000 in 1985. And by 2010, the scourge would be eradicated from our shores. "A great nation such as ours can carry out this plan," the authors wrote with an enthusiasm unusual for the buttoned-up agency. "It is time to commit to a tuberculosis-free society!"

It was stirring rhetoric — but that's about all. Instead of falling, cases of TB initially shot up, reaching almost 27,000 in 1992. In 2000, instead of 10,000 cases nationwide, there were still nearly 17,000. The surprising trend, revealed in a 1999

assessment of the plan's failure, could be attributed to several factors. For one thing, the arrival of HIV created an immunity-compromised population acutely susceptible to infection. For another, state and local agencies, misreading the statistics and assuming TB was under control, scaled back their surveillance, screening, and treatment programs. Meanwhile, the CDC hadn't recognized the emergence of new strains of TB that proved impervious to courses of typical antibiotics.

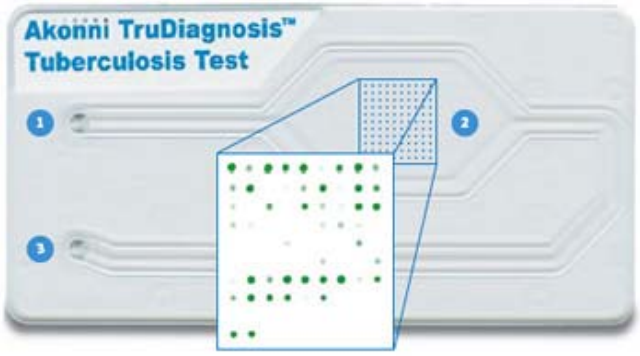
All of these problems could have been addressed by better detection and diagnosis. But the CDC was slow to spot new risks and slower yet to bolster its network for monitoring infectious disease.

Almost 20 years after the CDC's plan, our inability to diagnose and track infectious disease quickly and accurately remains a serious problem. Take the case of Andrew Speaker, the Atlanta attorney with drug-resistant TB whose international odyssey was front-page news this past spring. Using conventional diagnostics, it took the CDC four months, by Speaker's account, to definitively identify his particular strain as extensively drug-resistant, or XDR, TB. That lag meant he was wandering about, potentially exposing thousands to a deadly strain of TB untreatable with most antibiotics. Better diagnostics would spot such a risk earlier. What's more, the fact that Speaker was able to evade quarantine and then slip back into the country demonstrates the inadequacy of our surveillance network. Better diagnostics could improve screening at airports and border crossings. And though Speaker's illness was a novelty in the US, XDR TB is despairingly prevalent worldwide, with half a million cases and climbing. Better diagnostics would give health authorities a weapon to stop that march.

The traditional way to do a quick diagnostic test for TB hasn't changed much since Robert Koch first identified the bacteria under his microscope in 1882. The technique, known as sputum microscopy, calls for sticking a piece of bloody phlegm under a microscope, adding a stain, and looking for the bacteria. That method takes only a few hours but misses about half of all cases. For a definitive diagnosis, labs still rely on the gold-standard technique: a culture. This was first developed by Julius Petri in 1877: Place the sputum in a dish, add nutrients, and let it sit for a few weeks. If there's TB, the sample will grow a colony of telltale bacteria. To use the terms of epidemiology, this method has 97†percent specificity (meaning it catches 97 percent of true negatives) and 80†percent sensitivity (meaning 20 percent of negative tests are actually true positives). Those figures are considered quite high, standing as benchmarks for any competing test.

The problem with cultures is that they take a long time — three weeks or more — to produce a definitive result. In those three weeks, antibiotics may be fortifying the bacteria's resistance rather than curing the patient. In those three weeks, a TB patient goes back into the population and spreads disease. In those three weeks, the bacteria have enough time to escape our grasp. What's needed, then, is a new way to diagnose the disease: one at least as fast as the sputum microscopy test, as accurate as the culture, and refined enough to differentiate between garden-variety bacteria and drug-resistant strains. What's needed is nothing less than a new gold standard.

Those tests might finally be at hand. There is a crop of diagnostic tools on the horizon, portable devices that can detect infectious disease with a degree of accuracy that measures up to that of lab-based cultures. Dozens of companies are investing hundreds of millions of dollars to develop these new tools. Some of the funding comes from venture capitalists ; some comes from the Defense Department (which sees infectious disease as an ideal vehicle for bioterrorism) and from the Bill & Melinda Gates Foundation (which has invested $155 million in diagnostics since 2000 as part of its fight against TB, malaria, and other infectious diseases). The new approach blends the values of the technology sector, in which products live or die based on how well they scale toward cheaper, simpler versions, with the priorities of global public health, which holds that if a solution isn't cheap and simple to use, it may as well not exist. The result is an emphasis on cost, speed, size, and simplicity. It's a formula that could change the way infectious disease is detected and treated.



How TruDiagnosis Works
1) A few microliters of DNA sample are dropped onto a cartridge the size of a business card.
2) The sample flows over an array of probes that test for six TB genes and 88 strain-specific mutations.
3) The card is inserted into a reader that uses a laser to detect which dots light up, indicating a genetic match.

To find Akonni Biosystems, you need to stay vigilantly off course. First make a beeline toward the nation's third-largest biotech center, in Rockville, Maryland — but veer 30 miles northwest toward the town of Frederick instead. Then aim for the legendary USAMRIID, the US Army Medical Research Institute for Infectious Diseases, where much of Richard Preston's *Hot Zone* takes place — but keep going 2 miles south to the tiny campus of Hood College. Finally, step inside Rosenstock Hall but climb till you reach the attic. There, Akonni has secured a few cramped offices and a bit of lab space to devise what may be one of the most promising diagnostic devices in the field.

At 38, Charles Daitch, Akonni's freckle-faced founder and CEO, still has the aw-shucks demeanor of someone far removed from the vanguard of biotech. But his low-profile approach has kept Akonni's 21 employees focused on the task at hand: perfecting a diagnostic device that is faster and more accurate than anything now available.

Daitch calls his tool TruDiagnosis. It combines advances in microfluidics (miniaturized pumps and channels), microarrays (micron-sized sensors affixed to a chip), and engineering into what could be the ultimate medical gadget: a handheld device that, using a small sample of blood or spit, reveals in mere minutes every pathogen inside the body. It would work in hospitals, in labs, in the field, perhaps even in homes. TruDiagnosis is Akonni's twist on so-called molecular diagnostics, the promising discipline that detects the presence of a bacteria or virus when only a few molecules of DNA, protein, or other biomarkers are present. Akonni's tests look for small segments of DNA from a specific pathogen, a method that emphasizes detection of telltale genetic fragments rather than start-to-finish genetic sequencing. This simpler approach lets Akonni exploit economies of scale, which can mean the difference between life and death in global medicine. The smallpox vaccine was deployed worldwide, all at once, because it was cheap to produce — it scaled. But HIV antivirals do not scale, and their high cost puts them out of reach for millions of people.

Akonni's technology is based on a microarray technique developed at the Argonne National Lab in the 1990s. At the time, Daitch was working as an engineer on a related bioweapons project funded by the Pentagon. Motorola then licensed Argonne's technology but failed to find a viable application. Daitch was there to pick up the license, and in 2003 he founded Akonni.

Four years later, molecular diagnostics has become a crowded field. There are more than 100 companies in the game, each offering a slightly different technology (quantum dots, antibodies, and so forth). The industry was pioneered by Affymetrix, which first commercialized the microarray in the early 1990s. Affymetrix's GeneChip uses many thousands of molecular probes to analyze reams of complex genetic information looking for, say, genetic markers that correspond to a disease. But such detail comes at a price. An Affymetrix system, which includes cartridges, software, a scanner, and a "fluidic station," lists for around $375,000, and each test runs about $250 to $500. High cost, low volume.

Akonni, instead, is going low-cost, high-volume. The TruDiagnosis system has two parts: the credit card sized array, which can be tailored to detect combinations of diseases or strains of a particular disease, and the device that processes and reads the array.

Right now, Akonni's reader is about the size of a Nintendo Wii console. Daitch is producing a prototype for a handheld device that looks very much like an iPod. But making it work is a challenge more worthy of the iPhone — cramming three functions onto one tidy package.

First, the system has to prepare the sample; starting with a glob of mucus or blood or saliva, it must wash out all the particles and DNA signals you don't want and isolate the ones you do want. This can happen on the array itself and requires some microscopic pump-and-valve fluid mechanics .

Second, the device must amplify the DNA of the possible pathogen, in a process known as polymerase chain reaction, or PCR. This basically involves splitting a strand of DNA in two, mixing it with a primer, replicating those two halves into two wholes, splitting the strands again, and so on. In a lab, PCR takes place in a machine the size of a suitcase. But microscale chip-based PCR is now possible.

Third, the system must read the genetic signature. The DNA is washed over an array of dozens of polymer probes primed with fragments of genetic material known to correspond to certain pathogens. Wherever there's a match, the DNA sticks, forming a pattern of fluorescent dots. The last step: The card is inserted into a reader, which interprets the pattern for indications of Ebola or influenza or some other disease.

TruDiagnosis is made of cheap injection-molded plastic. It's small enough to carry into the field and use outside a lab. And it produces results in an hour or less. "Anyone should be able to use it without much training," Daitch says. "This is what we're focused on." He wants to make it so cheap that the cost of the TruDiagnosis reader is negligible, something nonprofits or foundations can buy in bulk and give away. The target price is under $5,000. Individual tests will be priced from $50 in the US to less than $10 globally. That's scale.

Akonni has developed tests for a score of pathogens, from smallpox and anthrax to lesser-known bugs like the Lassa virus and methicillin-resistant *Staphylococcus aureus*. Most of these are drawn from the CDC's list of bioterrorism agents, guided by the preferences — and funding — of an alphabet soup of Defense Department agencies, like USAMRIID, DTRA

(Defense Threat Reduction Agency), and the Air Force's EOS (Epidemic Outbreak Surveillance) program. Akonni's first test, though, was developed with the CDC for tuberculosis.

TB has been a scourge of humanity for thousands of years, long enough to have earned a number of names (phthisis, the White Death, consumption) and to have taken an inconceivable number of lives. (Some estimates hold that TB has caused 3 billion deaths in human history, perhaps the greatest killer of all time.) Today, 2 million people worldwide die of TB annually, even though the pathogen would prefer not to kill us. It would rather we stay alive so it can continue to spread, something it does quite well. Fully one-third of humanity — some 2 billion people — carry TB. Most of those carriers have so-called latent infections and will never develop symptoms. But for 10 percent, the bacteria can lie dormant for as long as 20 years until something (we just don't know what) triggers the bacteria to attack the host, leading to an active case of TB.

The discovery of antibiotics in the 1940s provided the first opportunity to actually cure tuberculosis. But it also started a race with evolution that we're destined to lose, as the bacteria responds to the antibiotics by morphing into ever-more-hardy strains. Multidrug-resistant tuberculosis, or MDR TB, first took hold in the 1990s and is defined as resistance to isoniazid and rifampicin, the two most powerful anti-TB drugs. Its more lethal cousin XDR TB is resistant to not only these first-line drugs but also to fluoroquinolones, the last-resort antibiotics that can cause severe side effects, including depression and musculoskeletal problems. The cure rate for XDR TB is only about 50 percent in the general population; among people with lowered immunity, a stunning 85 percent will die. "It's the hot zone of the moment," says Tom Shinnick, lab director of the CDC's project on tuberculosis eradication. "Physicians are treating it with standard regimens, and the patients are failing the regimens. In the meantime, they're out there spreading the disease." A rapid test that would detect TB down to the particular strain, Shinnick says, "would make a tremendous difference."

One afternoon in late February, Daitch treats his team to beer and garlic fries at the local bar he co-owns. Darrell Chandler, Akonni's chief science officer, and I tick off the various scientific disciplines that are coming together in the TruDiagnosis system. There's physics in manipulating the fluids. Microbiology, because you must isolate the bacteria or virus. Genetics, obviously, because it's all about DNA. Chemistry . Biostatistics . Computer science. Optics. And to put it all together... "Engineering!" says Daitch, who it turns out was half-listening to our list-making. "Don't forget engineering!" He's right — it all comes down to an engineering problem. "This isn't just one lab on a chip; it's many totally different industries on a chip, one piece of plastic. So many people don't get that. Lots of people are doing the pieces, but we're trying to do it all in one."

Preparation, amplification, interpretation — it's the formula behind most molecular diagnostics. But that doesn't make it an easy thing to pull off. As it happens, on the day of my visit to Akonni, the CEO of CombiMatrix Molecular Diagnostics, a competitor, left "to pursue other opportunities" after the parent company reported huge losses for the quarter and expressed doubts about its "ability to continue as a growing concern." The news makes Daitch and his team happy they're not publicly traded — but also a little nervous about other rivals in the field. Several firms already have products on the market. The Food and Drug Administration has approved two DNA tests for TB, by Roche and Gen-Probe, but neither has displaced the old- fashioned culture. Cepheid, based in Sunnyvale, California, has a single-use cartridge-based device called the GeneXpert, which integrates sample prep, PCR, and reading into a package about the size of a laptop. Cepheid is already testing for anthrax in US postal facilities and is developing tests for several other infectious diseases, including TB. And the FDA is reviewing Nanosphere's Verigene system, which uses gold nano particles to detect single strands of nucleotide. Different approaches may work better for different diseases, so no single company is likely to dominate the market.

Akonni, meanwhile, recently completed a test for MDR TB that, in about an hour, delivers results with 91 percent sensitivity and 99 percent specificity — exceeding the accuracy of a culture . Daitch says a test that recognizes the particular strains of XDR TB should be ready by year's end. Both diagnostics will be available to hospitals next year, for research purposes only. If all goes well, Daitch will start the process of FDA approval in late 2008. The public health community is counting on Daitch — or someone else — getting this right. "This is crucial," says Marcos Espinal, executive secretary of the World Health Organization's Stop TB Partnership. "If we want to halt TB by 2015, we need new tools. With the current tools, we will not make it. It's that simple."

By current tools, of course, Espinal means those developed more than a century ago. At the time, Koch's microscope and Petri's dish represented a huge shift in health care: They shook medicine free from diagnosis based on *symptoms* and let scientists pursue *causes* instead. Molecular diagnostics pushes medicine back even further, to *risks*. That means treatment based on the likelihood of getting a disease. If a microarray test is precise enough, doctors could detect a pathogen even before it goes to work, allowing them to intervene far earlier than we do now. Indeed, before disease as we understand it has even started.

Deputy editor Thomas Goetz (thomas@wired.com) *wrote about metabolic syndrome in issue 14.10.*