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ON RED ALERT

Companies are starting to pay for sophisticated tests to monitor the health of key executives. But these pre-emptive medical strikes may never be widely available - because the drugs industry makes its money from cure, not prevention.

By Christopher Bowe

Even at 7am in south-central Texas, a steamy mist envelops Austin, the state's capital and pre-eminent college town. Monica Seidel cuts through the humidity in an SUV so big it overwhelms the driveway of her destination - a neat, prairie-style house in the old-money neighbourhood of Tarrytown.

Inside, Nick Fox is waiting. Fox, a partner at the law firm Vinson & Elkins, is catching a morning flight to New York City, but before flying, he will give Seidel two tablespoons of his blood. Barefoot and business-casual, he leads his lab-coat-cloaked guest into the kitchen, offers her coffee, then sits down and rolls up his sleeve. "Did you strike?" he asks, in the lingo of oil drilling, as Seidel begins to fill five small vials with his blood.

The 48-year-old with greying, close-cropped hair and goatee is taking a new blood test called the Biophysical 250. His employers have sponsored the \$3,400 analysis because it ratchets up preventative medicine to a new level - taking a detailed snapshot of the body's surveillance system: the cholesterol, immune-system regulators, blood proteins and hundreds of other biological elements that show our bodies are running smoothly... or signal that they're breaking down.

Seidel's employer, Austin-based Biophysical Corp, markets the test to top executives, political leaders, astronauts - the sort of people whose good health could be critical to companies' or governments' fortunes. But the pitch also extols the economic benefits of healthy workers, be it from higher productivity or lower healthcare costs. And the fact that the analysis exists at all tells a bigger story: how the lowly blood test could revolutionise our most basic understanding of the human body.

While genetic testing is the face of personalised medicine, biomarkers - the thousands of distinct substances in the blood, of which the Biophysical 250 measures the best-known - are its backbone and potentially its future. Genetic testing mostly offers clues to disease risk passed down from parents; it is an analysis of static information. But the blood can, in theory, give a real-time view of health risks both inherited and self-inflicted through lifestyle choices. While the biologist Craig Venter's complete genome may reveal he has risk-taking genes and a predilection for sweets, for example, it won't

tell us anything about whether his diet has tipped his body's weaknesses to the brink of disease.

Lee Hartwell, winner of the 2001 Nobel prize in medicine and director of the Fred Hutchinson Cancer Research Center in Seattle, says the current fascination with genetic risk has meant that too little attention is paid to blood biomarkers. "There's a lot of work on inherited genetic risk which is not very useful, that people may find out is a waste of time and waste of money... We're really going to need markers that report on our state of health and state of risk at the current moment."

Biophysical Corp's founder, Mark Chandler, came to a similar conclusion during more than 20 years of working on blood-testing technology. Chandler, a loquacious Texan and immunology expert, began his career disappearing into jungles looking for plant toxins to turn into potential medicines. In the late 1980s, he teamed up with his brother Van to build a blood-screening technology company, Luminex; then in 2002, he started another company, Rules-Based Medicine, which uses a unique technology to reveal hundreds of biomarkers' presence in blood serum.

Rules-Based Medicine hires itself out to pharmaceutical companies looking to measure how a body reacts to a drug. Over the years, Chandler began to hear that researchers at the pharmaceutical companies were testing their own blood along with clinical trial blood samples. They wanted to use the biomarkers to measure their own current state of health. "That's when the light came on," says Chandler. By 2005, he had started a sister company devoted to selling consumers a test similar to that designed for the drugmakers. Fox is one of a few thousand people to have signed up.

While Biophysical Corp doesn't have any serious commercial competitors, it is hardly the only player in the field of biomarkers. Doctors, researchers, pharmaceutical companies and regulators are all scrambling to understand them and discover new ones. The promise is irresistible. Doctors hope biomarkers will help catch disease earlier, or even predict it; drugmakers see them as a potential tool for developing and marketing new medicines; and regulators, particularly in the US, where they are besieged by calls to improve drug safety risk monitoring, are hoping biomarkers can help make the drug approval process more efficient.

All this interest belies the complexity of using biomarkers to diagnose disease risk. Take cholesterol, for example. Elevated levels of the biomarker low-density lipoprotein (LDL, or so-called bad cholesterol) have been linked to increased risk of serious heart disease, heart attack and stroke. But even this link, using a relatively straightforward biomarker, was 60 years and millions of research dollars in the making.

Abner Notkins at the US National Institutes of Health says the usefulness of blood protein biomarker testing will depend on just how biomarker research advances. For diseases with no treatment, prevention or cure, biomarkers may only be useful as a tool in drug development. But for diseases that can be treated or prevented - including heart disease, diabetes and many autoimmune diseases - biomarker monitoring could mean early detection. "They're telling us things about the chronic nature of the disease. They're telling us some things about the severity and maybe some of the ways to prevent it," Notkins says.

He points to diabetes, in particular. Researchers have identified three biomarkers associated with the disease: insulin, an enzyme known as GAD, and a protein called IA-2 (islet antigen 2). A person with no signs of diabetes that has all three of these in the blood has a 60-80 per cent chance of developing diabetic symptoms in five years. The presence of two of them means a 50 per cent risk, and the presence of only one confers a 10 per cent risk.

According to Notkins, this shows that disease doesn't simply turn up out of the blue, but emerges slowly. And that emergence is detectable in the blood. "To me, it's the most important facet to come out of all these studies," he says. "Chronic disease is simmering underneath the surface."

Biophysical Corp's labs are located in a faceless technology office park just north of Austin. When Nick Fox's five vials of blood arrive, they are coded and centrifuged by the company's employees, then handed over to robots which run the tests using computer-controlled pipettes. When the results come through, George Rodgers, Biophysical's chief medical officer, and Alan Moore, director of clinical pathology, lead the team of scientists that discuss them. Rodgers, a slight, soft-spoken man in his fifties, with

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a neatly trimmed grey beard, sits at the head of a long table, joined by Moore, Monica Seidel and two nurses. They are reviewing the results of a 55-year-old woman's test. A spectrum of biomarkers show that the woman's body is in metabolic overdrive. Despite fasting ahead of the test, her metabolism was, at the time the blood was drawn, grinding hard – signs that metabolic syndrome or adult-onset diabetes might be on the horizon. Meanwhile, other biomarkers, including cell signalling markers and those that point to inflammation, also suggest diabetes risk. Rodgers thinks the team should focus its report on the diabetes risk and avoid too many other “red flags” that might distract from that message. “We really don't want to lead anybody on a wild goose chase,” he says.

Biophysical says it discovers a significant potential health problem in about 7 per cent of the people who take its test. In addition to spurring interventions for individuals, it is trying to improve data on reference ranges for each biomarker, aiming to advance the science for the public at large.

Others are signing up to Chandler's vision. Rules-Based Medicine is working on a federal grant from the National Cancer Institute to develop biomarkers, and Sam Zell, the Chicago-based private investor, is interested in investing in the test's technology.

And yet the bigger lessons of biomarker research may not translate quickly into practical applications. In April, Lee Hartwell gave an authoritative and heartfelt speech to cancer researchers entitled “There is Plenty of Information in the Blood”. In it, he argued that biomarker research could lead not just to new treatments, but to a better understanding of the body's information network and internal surveillance system. “We think of the cells, DNA and proteins deposited in blood by tumour cells as trash,” he said. But maybe, rather than mere detritus, each substance is a message in a bottle – messages the body itself reads. “What if all the proteins in the blood are actually being monitored as a network of information by the body?” Hartwell said.

The speech was hopeful in some ways. It suggested that biomarkers could begin to tell us something more general about how the body works as a machine and how it monitors itself. But it also reflected some of Hartwell's disappointment in cancer-related biomarker research and the economics for new diagnostic testing. Biomarker-based diagnostics for ultra-early detection are primitive and “in a surprisingly long period of stasis”, Hartwell tells me.

The trouble is society's tendency to think in terms of treatment rather than prevention – and a medical and healthcare system that reinforce that view. The economics of the industries support drug development – not efforts to create cheaper or more accurate biomarker tests that might predict or detect cancer. Elias Zerhouni,

director of the US National Institutes of Health, told Congress this year that rising healthcare costs demanded a “more predictive, personalised and pre-emptive form of medicine”.

Hartwell says: “The excessive influence of the pharmaceutical companies have bent the whole system out of shape. If you could detect cancers early, you can treat them with radiation and surgery, and don't need these expensive drugs.

“We have a tremendous amount of knowledge about biology and cells, yet most of the intellectual power goes into thinking about therapeutics.”

It's not just the pharmaceutical companies that are to blame. Healthcare payment systems are set up to reward treatments, not diagnostics. Biomarker tests not linked to a drug can often find limited interest from government healthcare payers or insurers. Raymond Woosley, chief of the Critical Path Institute, a consortium helping the FDA improve use of some biomarkers for drug testing, says: “Today, you can charge a fortune for a drug, but not a diagnostic.”

About two weeks after Monica Seidel drew Nick Fox's blood, Biophysical sends him the results. Its report colour-codes biomarker levels, from red for risk to

green for neutral. Fox's health looked good, with only two minor signals to watch. One marker showed his body was nearing dehydration and his vitamin B12 level was low. The body typically stores three to five years' worth of B12. Deficiencies can signal stomach or intestinal problems, anaemia or nerve problems in the long term.

Fox wasn't terribly alarmed at the results, although he did show them to his doctor at his annual physical a few weeks later. His doctor found the report fascinating, and decided to initiate a periodic check of Fox's B12 levels. He kept a copy of the report, wanting to study the “cool” test results more carefully.

Fox was part of a pilot programme at his law firm, which hopes that in a few years every one of its 300 partners will take the Biophysical 250. Mark Hanson, the firm's director of administration, says that between one-third and one-half of the partners don't even undergo annual physicals; he hopes this quick blood test can help mitigate that liability.

Hanson is willing to pay for the partners to take even such an expensive test because, he says, prevention is good for the law firm. “We live in a world where there is so much emphasis on the shorter term. We're trying to focus on the longer term for the health of our partners and the financial success of our firm.”

“I came out very happy I did this,” Fox tells me on his next trip to New York. He appears more robust now that I know the results of his Biophysical 250 – or maybe it's because he's shaved his goatee. In any case, we do little to counter his potential dehydration, ordering up a few German pilsners. Fox goes on: “I see [the test] as an incredible supplement. But as with any product, I'd think the price needs to come down.”

The future understanding and careful use of biomarkers could depend on whether society and healthcare systems embrace preventative medicine, or continue to see treatment as the priority. Today, medical treatments of \$5,000 are routine, never mind the yearly costs of expensive regimens of pharmaceuticals. It's the sort of money that only raises eyebrows when individuals are forced to pay all of it – that is, when health-insurance companies or governments balk at that price for a predictive tool.

But skyrocketing costs from ageing populations and increasingly unhealthy youngsters mean even developed-world healthcare systems are being forced to take preventative medicine seriously. Back in Texas, Mark Hanson tells me: “It's one of those ‘pay me now or pay me later’ propositions. It is economically a very prudent thing to do. The more we invest at the front end, the more it saves us down the road.”

THE BIOPHYSICAL 250

A typical blood test you'd get at an annual check-up measures 20 to 40 basic biomarkers. What, then, can one learn when 250 biomarkers are measured?

Biophysical's test looks at markers that might signal existence – or risk – of cardiovascular disease; metabolic disorders such as diabetes; autoimmune disease including rheumatoid arthritis and lupus; virus and bacterial diseases like mononucleosis and pneumonia; hormonal imbalances (such as thyroid or testosterone deficiencies); and breast, liver, colon, ovarian, prostate and pancreatic cancers – among others.

It also uses “biomarker stacking”, or looking at multiple biomarkers, to more accurately assess risk. While a normal blood test might examine high-density, low-density and basic cholesterol levels when screening for cardiovascular disease, the Biophysical 250 will look at four additional biomarkers related to heart disease as well as nine others related to inflammation – an immune system reaction to cardiovascular disease.

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