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A multibiomarker test for predicting CVD: Has its time arrived?

Sue Hughes and Shelley Wood | Jun 20, 2012

Cleveland, OH - Anyone attending the slick **TEDMED** conferences— billed as the "grand gathering of people passionate about imagining the future of health and medicine"—expects to hear about futuristic ideas and mind-boggling technologies. This year, attendees had the chance to go home with what one company believes is a glimpse of things to come: results of an "inflammation test" purporting to predict their risk of heart disease.

Over the course of the four-day meeting, Cleveland Heartlab, a Cleveland Clinic spin-off company, invited to participate at TEDMED, collected blood samples on over 500 delegates who lined up on the red-carpeted lobby of the Kennedy Center Opera House, in Washington, DC. Company founder and chief medical officer of Cleveland HeartLab, **Dr Marc Penn**, later took to the esteemed TEDMED stage to tell the audience just what this new blood test might tell them about their risk of heart disease.

Without question, the holy grail of cardiovascular health today is how to identify those patients who have not yet had a cardiac event but who are at risk of one. In addition to measurements of traditional risk factors such as cholesterol, blood pressure, and glucose levels, there are dozens of other possible biomarkers that have been suggested as maybe correlating with risk, perhaps the most discussed being high-sensitivity C-reactive protein (hs-CRP). But as these tests proliferate, with promotion at meetings like TEDMED, some experts are questioning whether the thirst for better risk prediction—and the money to be made in this arena—is outstripping the science supporting their use.

Dr Marc Penn [Source: Cleveland Heartlab]

Cleveland HeartLab's **CVD Inflammatory Profile** tests for levels of five biomarkers—F_2-isoprostanes, hs-CRP, urinary microalbumin, myeloperoxidase (MPO), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2). The company's website describes the test as having been "designed to more accurately estimate cardiovascular risk for patients who may require more aggressive and comprehensive therapy." It adds that this panel of biomarkers "covers an individual's full spectrum of risk from lifestyle concerns (long-term risk; F_2-isoprostanes) to the development of cardiovascular disease (mid-term risk; hs-CRP and urinary microalbumin) and initiation of an adverse cardiac event (near-term risk; MPO and Lp-PLA_2)."

Cleveland HeartLab was formed in 2009 with four employees to commercialize scientific discoveries for the prediction of heart-disease risk licensed from the Cleveland Clinic. Media coverage of the company's financial performance notes that Cleveland HeartLab has now grown to more than 100 employees and is approaching $20 million in annual revenues, about half of which comes from its inflammation-profile test. Last year, the company moved out of the Cleveland Clinic to a new 27 000-sq-ft premises, after securing $18.4 million in venture-capital funding.

According to CEO **Jake Orville**, just one of the markers in the inflammation profile (MPO) is licensed from the Cleveland Clinic, for which Cleveland HeartLab pays market-rate "single-digit" royalties. (Contacted by heartwire, the Cleveland Clinic declined to comment on how much it is paid for this patent, citing a 'confidentiality provision' in the licensing agreement).The company also sells a range of other tests and pays royalties to several other institutions. Orville says: "We are a small emerging company, with much of the profit going back into research and education."

Of note, the Cleveland Clinic was one of the sponsors of this year's TEDMED meeting, along with companies like Philips, Siemens, and Johnson & Johnson. And Cleveland HeartLab was not the only one offering free screening: attendees also braved long lines to undergo carotid ultrasound screening and glimpse other evolving health solutions.

But while everyone agrees better tools for risk prediction are urgently needed, preventive cardiologists who spoke with **heart *wire*** about the kind of blood tests on offer from Cleveland HeartLab and others agreed that the evidence base does not support widespread use of such an approach at this time, particularly when doctors and patients are doing so poorly at keeping standard risk factors under control. Some, however, say that if patients want to pay for the tests themselves, they may have a limited role.

The case for testing

Penn, who is also director of research at Summa Cardiovascular Institute and professor of medicine at Northern Ohio Medical University, put forward the case for the company's inflammation-profile test. He pointed out to **heart *wire*** that half the people who have an MI have normal lipids, so just measuring cholesterol or LDL is not enough. "MI is caused by both injury and inflammatory response. We have spent 30 years focusing on the injury part. We need to be targeting the inflammation as well. There is no magic bullet to define inflammatory risk. But we have put together a panel of five inflammatory markers to estimate such risk on a spectrum from long-term risk of a cardiovascular event to short-term risk."

Penn explained that F_2-isoprostanes detect oxidation and highlight unhealthy lifestyles such as smoking and obesity. Patients with high levels can benefit from counseling on lifestyle factors such as diet, exercise, and smoking cessation. "Physicians find this measure useful, as it can help gauge whether patients are sticking to healthy behaviors or not. If you can show them with a biochemical test that they are making progress, this can really help in getting them to stick with it."

In terms of more intermediate-term risk, the panel includes hs-CRP and urinary microalbumin. Penn notes that high levels of hs-CRP reflect increased atheroma burden, while the albumin/creatinine ratio is used to measure endothelial dysfunction. "These two together tell us the patient has heart disease."

And finally, to assess near-term risk of an event, MPO and Lp-PLA_2 are markers of vulnerable plaque. Penn says that Lp-PLA_2 is a measure of active vessel-wall inflammation, whereas MPO focuses on the white-blood-cell activity, "so the two results give an idea of plaque vulnerability via two different mechanisms."

Penn says that raised levels of the biomarkers in this panel can signify a 50% increased risk of cardiovascular events on top of Framingham risk factors—ie, a hazard ratio of 1.5—and there are several studies cited on the company's website documenting this.

"It has consistently been shown that individuals with a raised level of either MPO or hs-CRP have an increased risk vs those without raised levels of either, and those with raised levels of both have a higher risk again," Penn claims.

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The evidence base

Penn reports that Cleveland HeartLab runs this panel of tests (which can be can be ordered as a panel or individually) for thousands of doctors on a daily basis and finds at least one of the biomarkers is raised in about 9% to 11% of individuals who have normal lipids. "So we are identifying risk that wouldn't have been found otherwise."

He notes that the company's data set—which he says is currently in press—shows that of 2700 patients who had their MPO and Lp-PLA_2 measured at a preventive cardiology clinic, 5.5% had raised MPO and 4.5% had raised LPA_2. Only six patients had both biomarkers raised.

And speaking at TEDMED, where 60% of attendees took Cleveland Heartlab's inflammation test, Penn said that 40% of those tested had high cholesterol, 20% had abnormal CRP, and 12% had either raised MPO or Lp-PLA_2. Of these 12%, half had normal lipids.

According to Penn, raised levels of these biomarkers underscore the need for improved vascular health. "If the patient has only a high F_2-isoprostane, they might just need a lifestyle change, but if other indices are raised, the doctor may start or increase the dose of a statin and in general be a bit more aggressive in treatment."

Experts skeptical

Most experts polled by **heart *wire*** on the usefulness of this panel of tests were skeptical about its role at present, saying there was not enough evidence of incremental risk assessment over traditional risk factors to justify its widespread use.

Dr Nathan Wong [Source: University of California, Irvine]

Dr Nathan Wong (University of CA, Irvine), who is immediate past president of the **American Society for Preventive Cardiology** and has conducted studies on some of these biomarkers, noted that while there is some evidence for use of hs-CRP, microalbuminuria, and Lp-PLA_2 in risk stratification, and they have been included in some recent guidelines [1], there is limited information on the other biomarkers in this panel.

He added that there are important emerging data regarding MPO and risk prediction in asymptomatic intermediate-risk populations, but evidence is limited for its added benefit over standard risk factors.

Moreover, the data showing added benefit of multiple biomarker indices for incremental risk prediction over standard risk factors in asymptomatic patients without known CAD have not been entirely consistent, "and I am not aware of a paper that has looked at this with the combination of markers suggested in this particular panel."

But he added: "I'm not saying that these tests are not useful. They may well identify higher-risk people who can be treated more aggressively, but we need more data on whether they solicit improvement in physician prescribing patterns, patient adherence to medications or healthy lifestyles, and ultimately improvements in risk factors and clinical outcomes before we can recommend these be routinely used for screening healthy or intermediate-risk populations."

The big question is whether risk can be substantially reclassified by measuring any of these biomarkers.

Another preventive cardiologist specialist, **Dr Steve Jones** (Johns Hopkins University, Baltimore, MD), has views similar to Wong's. "There are innumerable biomarkers that have been identified that could correlate with heart disease risk, but it is very difficult to know if any one of these actually signals an increased risk independent of the traditional Framingham risk factors. It sounds good to construct complex biomarker panels, but the big question is whether risk can be substantially reclassified by measuring any of these biomarkers and whether the outcome can be changed by knowing the result. This really has not been tested for most of the biomarkers in this panel."


Dr Steve Jones

Like Wong, Jones says there is some evidence for measuring hs-CRP and possibly also Lp-PLA2 for incremental risk assessment in intermediate-risk individuals. He points out that the US National Lipid Association recently published a paper on which biomarkers give some independent measure of risk, and "Lp-PLA_2 received a faint endorsement, while most of the others in the HeartLab panel fell into the realms of possibly useful in selected patients" [2].

He adds that "a very good study on the MONICA cohort rated a slew of markers in terms of incremental value over the Framingham risk score and found the best to be troponin I, [B-type natriuretic-peptide] BNP, and hs-CRP" [3].

Jones adds: "The idea of putting a whole load of biomarkers on one panel and if anything comes up positive then you are at increased risk is an attractive but unproven idea. If someone comes to me and their risk is more than trivial but they are not a secondary-prevention patient, I would do the normal Framingham risk scores, and I might also measure hs-CRP and Lp(a). Lp-PLA_2 and MPO are rarely on my list. If I wanted to do something else I would order a coronary calcium. That has a much higher predictive value."


Dr James de Lemos

Jones continued: "If I were making national policy I would ask whether there was enough evidence for everyone at a certain age or risk level to get these tests, and the answer for this panel would be absolutely not. But there is an enormous population out there of 'worried well' who will do whatever it takes to identify risk. This is a substantial part of the market for this panel, but I can't criticize people for such behavior."

Dr James de Lemos (University of Texas Southwestern Medical Center, Dallas) is also unconvinced about the usefulness of the inflammation panel. He commented: "Of the five biomarkers included, only CRP and microalbumin have sufficient evidence to consider clinical application." He says the evidence for CRP, while consistent, suggests only marginal improvements in risk prediction, and "microalbumin is promising, but the therapeutic implications are not yet clear." He adds that the evidence for MPO, LP-PLA_2 and F_2-isoprostanes "is much less robust and quite inconsistent."

Coronary calcium better

Dr Prediman Shah (Cedars Sinai Heart Institute) puts it differently: "Although we all agree that in addition to lipids,

inflammation and immune-system activation play an important role in the pathogenesis of atherothrombosis, systemic markers of inflammation (such as hs-CRP, $LpPLA_2$, MPO, etc) provide only modest incremental prognostic information over and above traditional risk factors, with odds ratios generally around 1.5 to 2.0 at the most. This is useful on a population basis but cannot provide sufficient precision for individual decision making. Therefore, I am not yet convinced that a panoply of these markers are robust enough for routine clinical use."

In response, Penn points out that "a good proportion of doctors are already measuring all the traditional risk factors, but they understand that it is not just about cholesterol and there is more that can be done to pick up those at risk."

Dr Prediman Shah

Many of the physicians who spoke with **heart *wire*** said they'd opt for an imaging test before testing for novel biomarkers. Direct visualization of atherosclerosis with computed-tomography (CT) scanning of coronary calcium, for example, is a much stronger predictor of risk, Wong noted, and "offers incremental prediction far greater than any biomarker or combination of biomarker tests."

Shah, likewise, observed that coronary calcium by CT scan provides the most incremental information for risk prediction. "This shows odds ratios close to about 10, which is huge."

Penn agrees coronary calcium is a good test but argues that it doesn't show how active the disease is. "Some doctors would order our panel to screen, then use a coronary calcium [scan] to quantify the disease."

The worried well

Cleveland HeartLab CEO Orville bemoans the lack of physician enthusiasm. "Academic physicians are difficult to convince," he told **heart *wire*** . They want to see years of outcome data, but they are not the ones who are seeing hundreds of patients. However, studies in support of our tests are there."

In particular he highlighted a new report from the MONICA cohort, showing that individuals with baseline concentrations of MPO in the top tertile had a higher risk of developing heart disease than the bottom tertile, independent of major cardiovascular risk factors [4].

Wong, however, countered that this was a nested case-control study, which is not as powerful as following an entire cohort for outcomes. "This is a good study and did show a positive result, but it didn't look at incremental risk prediction or reclassification. And it suggested only a very modest increase in risk (HR 1.5). It is not what I would consider a powerful biomarker, but I look forward to seeing future studies on this test and others."

Academic physicians are difficult to convince. They want to see years of outcome data.

Orville, for his part, insists the time has come for tests like this one, calling it "an easy affordable test."

The inflammation panel is priced at $200. Orville notes that it is generally not reimbursed by insurance companies for general screening, but it is often covered if the patient has another diagnosed condition such as hypertension.

"There is strong interest in it from doctors, and there are over 100 publications showing good correlations of these biomarkers with cardiovascular risk," Orville said. "Lots of physicians like to see the range of results to understand where their patient is on the spectrum of risk."

One such physician is **Dr Dharmesh Patel** (Stern Cardiovascular Foundation, Memphis, TN), who says he finds the

MPO and Lp-PLA_2 tests useful to identify patients with a near-term cardiovascular risk, even when their basic lipid panel appears acceptable. "Understanding markers of vulnerable plaque/endothelial dysfunction has been especially useful in my intermediate-risk patients and enables me to treat more aggressively where required," Patel said.

Others, according to Penn, also like to use the inflammation panel to monitor a patient's progress.

The company markets the this panel of tests mainly to GPs and cardiologists—mostly community-based physicians seeing middle-aged patients with other risk factors who are often in executive health programs or concierge-medicine settings, where patients generally pay cash for the additional time and services of a doctor, who may offer additional tests such as this one that aren't so easily available through normal channels.

Jones admits there may be place for this type of test in this setting. "This can be attractive to patients, as they feel they are getting the cutting edge." He also says he can see that such a test may be useful for motivating patients. "It may fall short of complete evidence-based scrutiny, but if it engages the patient and encourages behavior change, then some may think it's worth it."

Some people believe that there may be benefit in knowing these values even if you can't prove it.

He says: "Some people believe that there may be benefit in knowing these values even if you can't prove it—even if this just means doctors can show their patients the values are going down with changed behavior or treatment. That may keep them compliant. And there will always be things people purchase on their own accord for which there may not be rigorous evidence but provide reassurance. I am not against that idea."

Jones adds: "If you want third-party payers to pay for these tests, then strict hurdles have to be passed, but if you can construct a believable logical framework for a test, as this lab seems to have done, and people are willing to pay for it themselves, then that is a reasonable approach."

Address the basics first

Wong points to a final key point: neither patients nor doctors are paying adequate attention to standard risk factors, let alone an expensive, as-yet-unproven blood test.

Less than 1% of US adults meet the **American Heart Association**'s Life's Simple 7: targets for body weight, diet, exercise, cholesterol, blood pressure, glucose, and not smoking, Wong notes.

"There are several other similar multibiomarker panels available, and doctors are often interested in the hottest new tests. I don't blame them. But the basics need to be addressed better before we start thinking about fancier biomarker tests for which data are mixed on whether they improve clinical risk prediction."

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