

Multi-marker Testing—The Power of Diagnostic Panels

a report by

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A Unique Approach to Diagnostics

Biosite Incorporated has always had a unique vision for medical diagnosis. Since its inception in 1988, the company has strived to provide healthcare professionals with innovative and accurate data that is essential to improving patient outcomes. By making this information rapidly available—sometimes right at the patient's bedside—Biosite's diagnostic technologies address the challenges that undermine healthcare excellence, and assists physicians in diagnosing emergent and potentially catastrophic diseases.

In medicine, rapid diagnosis takes priority because treatment cannot be initiated without it. Patients in emergency departments, intensive care units (ICUs) and operating rooms (ORs) can decompensate rapidly or even die during the period of time it takes for traditional diagnostic testing. The last quarter of the 20th century has seen dramatic advancements in imaging, but laboratory testing has not seen similar improvements. The limitations in diagnostics for critical diseases have had a profound effect on the utilization of advanced therapeutics. Revolutionary therapies, such as clot-busting drugs and endovascular procedures for diseases, such as heart attack and stroke, are not widely utilized, even in patients who might benefit, because rapid diagnostics have not previously existed. In the time it takes for a patient to undergo magnetic resonance imaging (MRI) or computerized tomography (CT) and the results interpreted by trained medical specialists, valuable minutes—minutes that might separate therapeutic efficacy from absent benefit—can be lost. Biosite believes that clinical outcomes can be improved and healthcare costs lowered through more widespread use of innovative therapeutics, made possible by a rapid, accurate diagnosis.

While the potential benefit from improved rapid diagnostics has been evident to many in the healthcare industry, a powerful and reliable discovery pathway for proteomics has been elusive. The standard industry model has been watchfully waiting, followed by the in-licensing of already developed single-biomarker tests; this is a model that Biosite views as secondary.

Instead, the priority is to proactively identify important diseases that are inadequately served by existing technologies, and pursue the discovery of biomarkers independently and through collaborations. Research programs that combine in-house biomarker development with clinical trials at leading research hospitals are the hallmark of Biosite's approach, and hold the promise of identifying rapid diagnostic tests where previously nothing existed.

In medical diagnosis, test sensitivity relates to the ability to define a disease when it is present and specificity relates to the ability to confirm when a disease is absent. Biosite's objective is to discover biomarkers that contribute clinically significant improvements to a physician's ability to separate diseased from non-diseased populations. The company's philosophy on diagnostic testing is simple: if a patient with a life threatening condition can be diagnosed more promptly, then the patient can be treated earlier in the disease process, improving the chances of a better outcome. This is why the company targets critical diseases that threaten patients emergently, and in areas where there are a lack of rapid and reliable diagnostics. These are the circumstances in which accuracy and timeliness in diagnosis hold the greatest promise.

The biochemistry of bodily fluids, such as blood or plasma, change as a disease progresses. In most diseases, tissue damage and biological response mechanisms change the blood levels of analytes, enabling them to be potentially utilized as markers of the disease. Analytes that have modified blood concentration, over time, typically also reflect disease severity. Recent advances in the understanding of human biomarkers, including proteins, peptides, enzymes, hormones and other blood-borne molecules have been the catalyst for Biosite's discovery effort. Biosite Discovery—the company's 'unfair advantage'—is a uniquely powerful internal research program that utilizes state-of-the-art antibody development technology and focuses on screening potential biomarkers. The company's discovery programs are capable of screening many potential targets in the process of identifying novel



proteins that can function as ‘disease markers’. Pre-existing collaborations with clinical thought leaders allows for the rapid evaluation of potential tests.

Biosite led in the discovery that, for many diseases, a single molecule may not provide both the sensitivity and specificity required by clinicians. Fortunately, a single biomarker, or marker, is no longer necessary, because Biosite’s portable immunoassay platform can run multiple markers simultaneously. With this in mind, Biosite Discovery not only seeks to identify novel markers, but simultaneously strives to identify panels of markers that provide improved diagnostic utility. This approach allows development of clinically useful diagnostic tests for diseases, which lack single diagnostic markers.

With all of the extraordinary potential power of proteomic based diagnosis, the tests themselves need to simplify diagnostic interpretation, not make it more complicated. The complexity of multiple markers should not result in clinical data that may be confusing for busy clinicians to interpret. Recognizing the complexity that is incumbent with the interaction of multiple markers, Biosite has created a proprietary algorithm, called the MultiMarker Index™ (MMX), which was designed to provide busy healthcare personnel with a test result they can utilize as if it were a single analyte.

Biosite research and development (R&D) uses a proprietary search program to optimize and select combinations of markers based on their overall diagnostic utility. The company then selects the marker combination that contributes most to defining the difference between diseased and nondiseased populations. Once the applicable markers have been selected, an algorithm is defined by the search program—that algorithm becomes the equation to determine a panel’s single MMX value. The Triage® MMX behaves like a single analyte and is a novel way of describing the ability to measure and utilize multiple markers simultaneously.

Biosite’s technology allows the extraordinary diagnostic sensitivity and specificity of immunoassays to be performed at the point-of-care, where they can provide the greatest benefit, particularly in the most challenging hospital environments, such as the emergency department (ED), ICU and OR. These realtime environments demand rapid, accurate and efficient decisions, so the value of immediate-response diagnostics cannot be overstated. Biosite’s Triage products, for instance, directly address 10 of the top 17 reasons patients present to EDs, and provide clear, accurate results in approximately 15 minutes at the patient’s bedside.

Biosite’s diagnostic test pipeline includes panels of markers incorporating the Triage MMX concept that target sepsis, a life-threatening infection, chronic and acute kidney injury, and abdominal pain. The company currently has diagnostic products available for drug screening, myocardial infarction (MI), congestive heart failure (HF), evaluation of shortness of breath, and certain bacterial and parasitic infections. Biosite is also developing its technology to not only better define diagnosis – does the patient have the disease? – but prognosis – is the patient at risk? to determine which patients may need more immediate or aggressive treatment.

The Cardiovascular Diagnostic Challenge

The great challenge of acute care medicine is that vague symptoms, such as chest pain or dizziness, are common in life-threatening diseases, such as heart attack or stroke, but also occur in non-threatening conditions such as indigestion. In the 1980s and early 1990s the standard approach was to admit all chest pain patients to the hospital after sometimes lengthy evaluation in the ED. Standard-of-care at major chest pain centers is now a much more rapid protocol that accelerates the decision to move patients suffering heart attacks to the catheterization laboratory, while at the same time sending a significant fraction of non-emergent patients home. The outcomes of patients suffering acute cardiovascular (CV) emergencies in such systems have improved dramatically, and cost-savings have been significant as well. Much of this improvement has been the direct result of advances in cardiac marker testing.

Unfortunately, such state-of-the-art systems are not yet universal, and the diagnostic technologies remain far from perfect. It is estimated that in the US alone the unnecessary hospitalization of chest pain patients costs more than US\$2.5 billion annually. More accurate diagnosis in the ED could shift much of the care for low-risk patients to the out-patient setting, allowing clinicians to focus on those high-risk patients who truly need to be in the hospital. This is just the type of situation where marker testing can play a significant role.

Since the 1950s, scientists have identified a variety of proteins or enzymes in the bloodstream that are elevated in acute coronary syndromes (ACS), which comprises unstable angina and MI. It is thought that when blood flow to the heart is reduced and heart cells are damaged, an event commonly known as a ‘heart attack’, hundreds of proteins are released into the blood. Currently, several cardiovascular-related markers such as, creatine kinase-MB (CK-MB), myoglobin, B-type natriuretic peptide (BNP) and troponin I are commercially available. All of these markers are available on Biosite’s platform.

In recent years, several large-scale clinical studies have evaluated the early use of multiple, simultaneous markers in the diagnosis of chest pain patients, and demonstrated a clear benefit compared with approaches based on single enzyme tests. Further benefit has been demonstrated for the rapid application of cardiac marker technology at the point-of-care compared with a central laboratory. Biosite has led the way in terms of bringing this technology to widespread use in the management of chest pain patients. Biosite continues to lead the field in integrating currently available markers into a single panel that can be measured on an instrument at the point-of-care.

There has been a paradigm shift in our understanding of acute coronary syndromes, away from an emphasis on coronary occlusion and towards the inflammatory, unstable and thrombosed coronary plaque. Biosite believes that a diagnostic marker panel including molecules associated with different phases of this complex pathophysiologic process will be more useful than the historically accepted single marker approach, which ultimately only focuses on cardiac cell death, or necrosis. In particular, such a panel would potentially provide diagnostically useful data during the early phases of acute coronary syndromes, compared with the standard troponin assay that routinely provides a false negative result during the first few hours of a heart attack.

To address the ACS continuum, Biosite plans to offer a myeloperoxidase (MPO) test in 2006. MPO, the first of

the next-generation cardiac markers, is not an indicator of dead heart cells, but is elevated when the acute coronary inflammation that is central to the disease process is present.

Biosite is also active in developing improved diagnostics for stroke. One of the leading causes of death in the US and the leading cause of long-term disability. It is only in the last few years that potential emergent treatments have been developed. Unfortunately, diagnosis has lagged behind therapeutics, and the majority of patients do not yet benefit from therapies, such as clot-busting drugs and special rescue catheters. CT scans are usually negative in the first few hours after a stroke, and clinicians still must rely on a patient's history and physical examination in making the diagnosis. In busy EDs the opportunity for error, in particular the mistake of sending a patient who has suffered a stroke home undiagnosed, is considerable. Biosite released the first commercial blood test for stroke in Europe in 2005 and continues to perform research in the area of cerebral ischemia.

In summary, Biosite believes that the long anticipated benefits of modern molecular biology will finally come to laboratory testing and the bedside in the next few years. Patients in increasingly greater numbers will experience improved outcomes from advances in therapeutics for diseases as diverse as acute coronary syndromes, stroke and life-threatening infections, because they first had the advantage of advanced rapid diagnostics. ■