

White Paper

STATE OF THE ART IN POINT-OF-CARE *IN VITRO* DIAGNOSTICS: A SOLUTION FOR MONITORING RECURRENT MYOCARDIAL INFARCTION

ABSTRACT

Patients that experience a major cardiovascular event, like a heart attack or cardiac arrest, are at high risk for recurrent incidence, especially during the first year. People who experience recurrent heart attacks are at much higher risk for cardiovascular complications or sudden cardiac death. Therefore, it is important to monitor patients closely for risk factors such as inflammation, tissue healing and oxidative stress during the first few weeks to a year after the first cardiovascular event.

BioMEMS has developed a rapid PoC CVD test panel, to monitor risk and provide opportunities for intervention that may prevent recurrent heart attacks. Our platform uses ultra-high sensitivity multiplexed electrochemical immunoassays in a novel biological microelectromechanical system (BioMEMS) to produce an automated answer with one-button operation and minimal training. The ease of testing allows patients to monitor their risk anytime, anywhere, or to provide clinicians with rapid, actionable results at PoC.

KEY POINTS

- Point-of-care screening (PoC) for high-risk factors, such as inflammation and oxidative stress, after a major cardiovascular event is essential to reduce the risk of recurrent incidence and mortality
- Biomarkers linked to inflammation, oxidative stress, tissue healing and other cardiovascular health indicators could give valuable insight into lifesaving preventative measures
- A cardiovascular disease (CVD) test panel based on the BioMEMS diagnostic platform is exceptionally well suited for PoC screening and monitoring of high-risk factors for recurrent heart attacks
- The BioMEMS ultrahigh-performance platform delivers previously unattainable non-invasive detection and quantification of biomarkers at PoC, with cost and time efficiencies that outperform and displace most lab-scale and POC analyzers for disease, metabolic and nutritional biomarkers.

INTRODUCTION

Patients recovering from a heart attack are at high risk for recurrent myocardial infarction

Cardiovascular diseases (CVDs) are the number one cause of death and disability worldwide [1]. Every 40 seconds, a person in the US experiences an acute myocardial infarction (AMI), or heart attack, amounting to medical intervention expenditures of hundreds of billions of dollars annually [2,3]. About a quarter of heart attack cases are recurrent MI (RMI), a common occurrence after a heart attack that poses a higher risk of cardiovascular complications and death, especially during the first year [4-6]. Monitoring patients during this period is essential to reduce the risk of RMI and the potential for sudden cardiac death.

Survival from a major cardiovascular event depends on how much damage was done and how quickly it can be treated. The risk of death and complications is predicted by inflammation, oxidative stress, and tissue healing [7-15]. Inflammation describes the body's reaction to injury and infection and plays a major role in the risk of arterial plaque rupture [15]. During the immune response, white blood cells and their signals circulate the bloodstream, which can interfere with the normal repair process and cause the coronary artery to become obstructed.

Flagging inflammation risk factors can reduce inflammation levels

and lower the risk for RMI [16]. However, it is difficult to motivate healthier lifestyles without knowledge of ongoing damaging or pending progression to life-threatening disease. Convenient screening of high-risk patients is critical to prevent RMI.

Current diagnostics fail to provide actionable data regarding complications and impending death [7-14, 17]. Improvements in monitoring and screening at-risk cardiovascular patients are needed for anticipating imminent clinical outcomes.

A point-of-care and over-the-counter diagnostic platform for monitoring patients' at-risk for RMI

BioMEMS has developed a handheld point-of-care (PoC) *in vitro* diagnostic (IVD) device and cardiovascular disease test panel (disposable cartridge) that provides results in under 3 minutes. Our diagnostic platform is exceptionally well-suited to screen and monitor heart health risk factors, such as systemic inflammation, oxidative stress, wound healing, and infection. The CVD test panel can be performed in clinical and non-clinical settings for more frequent monitoring, establishing personalized trendlines, critical thresholds, and enabling predictive modeling.

BioMEMS Analyzer and CVD Test Panel Offers:

- Ease-of-Use – does not require a highly trained operator or special setting
- Rapid Results – provides results in minutes
- Ultra-High Sensitivity/Specificity – picomolar sensitivity and specificity
- Cost Effective – less expensive than standard laboratory testing
- Remote Patient Monitoring – mobile with cloud-based record management

Inflammation Risk Factors:

Cigarette Smoking
Excessive Alcohol Use
Obesity
Immobility
Metabolic Syndrome/
Prediabetes
Hypertension
Sleep Apnea
Anxiety/Depression
Autoimmune Disease
Periodontal Disease
Infection

Bikunin urinalysis CVD panel

The CVD Test Panel uses Bikunin as a biomarker for identifying cardiovascular risk. Bikunin is one of the main anti-inflammatory response mediators that promotes tissue and organ repair and is often associated with inflammatory conditions, as it is found in high concentrations in the urine of patients suffering from acute and chronic inflammatory diseases. Bikunin is clinically used to treat acute circulatory failure, sepsis, ischemic injury, post-cardiac arrest mode, and pancreatitis and provides multi-organ protection [21-42]. Monitoring Bikunin in the presence of markers for oxidative stress can indicate tissue damage infection, and poor immune response. The panel is of special value for adult populations within 1-2 weeks of an AMI for reducing the recurrence of a heart attack by directing treatment which improves patient outcomes [43-50, 8].

Clinical utility	Response of panel	Treatments/Expected outcome
Healthy tissue repair	In the presence of oxidative stress, Bikunin indicates tissue damage.	Improved inflammation through exercise, nutrients, and vitamins.
Reduced cardiovascular event	Reduced Bikunin demonstrates healing during CVD events, and oxidative stress products predict a lack of inflammation inhibition.	Cardio-protecting therapies to reduce tissue damage, necrosis, and RMI.
Improved response to infection	Bikunin and oxidative stress increase with infection.	Identification of infection and treatment with antibiotics.
Impaired Immune system	Low Bikunin in the presence of high infectious indicates a poor immune response.	Anti-infective immune therapies. Identification of macrophage phagocytosis deficiency and impaired ability to clear pathogens.

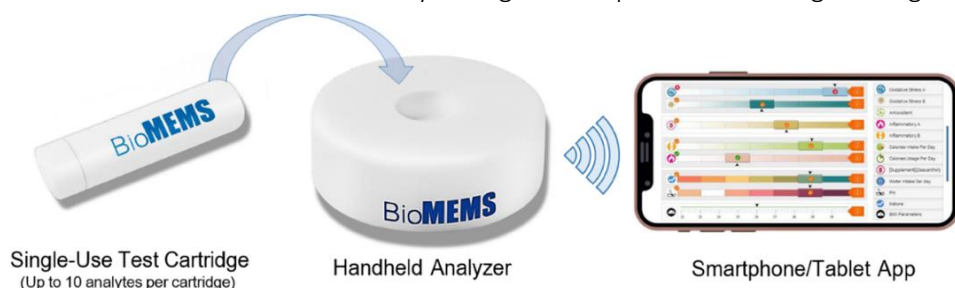
CVD Test Panel biomarkers include Bikunin (immune response), HNE-Albumin (oxidative stress), albumin (liver/kidney), RBC (Hb), WBC Lysed, WBC intact (immune system)

BioMEMS DIAGNOSTICS PLATFORM DESIGN AND WORKFLOW

Precisely measure any biomarker in any biofluid at high sensitivity in less than 5-minutes

The BioMEMS test platform is built around an electrochemical immunoassay (EC-IA) system with the unique capability of processing complex biofluid samples rapidly using size exclusion filtration passed through a proprietary microelectromechanical sensor array. A single-use capture and sensing cartridge is combined with a handheld analyzer that

activates the cartridge and ports raw results via Bluetooth to a sophisticated normalizing and analytics app that can be downloaded to most smart devices. Results are typically available within 5 minutes of obtaining the biofluid sample, with picomolar sensitivity and specificity.



Designed to overcome the limitations of complex laboratory analyzers and chip-based diagnostics

The BioMEMS platform is designed to surpass the challenges and limitations of currently available technology. The design allows for processing samples such as whole blood, serum, plasma, urine, wound fluid, bronchial lavage, and sputum. Sample amounts required for measurement range from 1 μ L to 1 mL. The biomarkers can be whole cells or cell-free markers, and the platform can be configured to detect a broad range of targets, from individual pathogens to small molecular

entities. The single limiting factor is the availability of an affinity agent that binds or interacts with the biomarker or pathogen of interest. This means that hundreds, if not thousands, of unique assays can be created from the currently available pool of 200,000+ assays, antibodies, probes, and reagents using the same capture and sensing technology.

When a test cartridge with a biofluid sample is inserted into the analyzer base, the cartridge captures, concentrates, and purifies analyte molecules by affinity

BioMEMS Advantage:

- Complex biofluid sampling
- Small sample requirement
- Detects broad range of targets
- Concentrates and purifies analytes to reduce background noise
- Small and disposable test cartridges
- Prevents user from interacting with testing components
- Short assay run time
- Ultra-high sensitivity and analyte specificity
- Requires small amount of antibody reagents
- Does not require confirmatory sampling
- Low test cartridge manufacturing cost
- Low operating cost
- Internal standard
- Highly customizable

surface capture on a microfiltration sensor membrane. The surfaces of individual microwells are chemically modified to allow rapid removal of background signals while concentrating the analyte(s) of interest with antibodies or other affinity agents on the sensor surface. The removal of background signals from the desired analyte gives the immunoassay reagents the ability to operate under ideal conditions and generate clean results without interferences. This simple and efficient process does not have the legacy problems of competing methods, where the analyte fails to bind to separation surfaces consistently.

Engineered to be small and disposable, the test cartridge is designed to prevent the user from interacting with the chemistry, affinity reagents, or the biofluid sample itself. The unique configuration

allows for filtration and detection simultaneously, effectively reducing assay run time. The design allows for ultra-high sensitivity electrochemical assays within a single microwell, each such microwell representing an individual immunoassay result. Ultimately, this requires far smaller amounts of antibody reagents in the cartridge to achieve a quantitative result that is faster and more accurate than other IVD products. Furthermore, confirmatory sampling is unnecessary as the cartridge is designed for the captured and purified analytes to be released on demand for confirmatory testing by orthogonal methods (liquid chromatography-mass spectrometry, PCR, etc.).

Creating new diagnostic tests faster at lower cost while delivering high performance and value

Combining high sensitivity and analyte specificity with microscale dimensions greatly reduces the cost of test cartridge manufacturing. The miniaturized, disposable test cartridge design also drives down operating costs, as the system uses an internal standard for live electrochemical calibrations in each sample, thereby successfully eliminating maintenance that comes with the current state of laboratory-scale or POC equipment.

The BioMEMS platform is intended to displace conventional laboratory tests that lack the sensitivity or specificity needed to measure pre-clinical to clinical levels of biomarkers, toxins, and pathogens at extremely low concentrations. Especially in applications with the most difficult and esoteric targets where sensitivity and specificity are vital, i.e., infectious disease, chronic disease monitoring, cardiac testing, cancer testing, and endocrinology.

MARKET AND COMPETITIVE ANALYSIS

BioMEMS diagnostic platform has clear advantages over its competitors

There are competing technologies that we can supplant by providing faster results and cheaper tests with greater accuracy at PoC. PCR, flow cytometry (FC), lab-on-a-chip (LOC), MEMS, and lateral flow (immunochromatographic, IC) devices have strengths and weaknesses. However, the BioMEMS diagnostic platform overcomes the limitations of lab analyzers and chip-based diagnostics and has clear advantages over its competitors.

	BioMEMS	PCR	FC	LOC	MEMS	IC
PoC	Yes	No	No	No	No	Sometimes
Sensitivity	High	Varies	Varies	High	High	Varies
Specificity	High	Varies	Varies	High	High	Varies
Assay Time	<5 min.	4-6 hrs	2-72 hrs	<20 min	<20 min	10-30 min.
Target Format	Broad Range	DNA/RNA only	Proteins/antigens	Broad Range	Broad Range	Proteins/antigens
High Throughput	Yes	Yes	Yes	Yes	Yes	Yes
Background Noise	Low	Varies	Varies	Low	Low	Varies
Simple Multiplexing	Yes	Limited	Limited	Limited	Limited	Limited
Universal Label System	Yes	No	No	No	No	No
Low-Cost Manufacturing	Yes	No	No	No	No	Yes

Growing incidence of chronic disease, such as CVD, fosters demand for POC diagnostics

BioMEMS platform applications include Home Care Devices, IVD, Medical Devices, and Pharmaceutical & Biological Research. The global market for PoC was valued at USD 46.7 billion in 2021 and projected to grow from USD 36.4 billion in 2022 to 51.9 billion by 2029, exhibiting a CAGR of 5.2% [51]. The demand for quality PoC diagnostics increases with acute and chronic diseases worldwide, and CVD continues to rise.

Summary Statement

The BioMEMS CVD panel is of value for adult populations within 1-2 weeks after a major heart attack to monitor risk factors for a potential second cardiovascular event. Reporting elevated or otherwise unfavorable test results in advance of a recurrent heart attack may well result in a clinical outcome with both cost saving and life-saving attributes.

ABOUT US

BioMEMS Diagnostics is a Michigan-based startup developing a breakthrough diagnostics platform to deliver high-need, high-complexity diagnostics at PoC, even in resource-limited settings.

Our firm has developed a biomarker-agnostic, biofluid-agnostic, universal biomedical MEMS sensor array that vastly improves the processing speed and sensitivity of antibodies, probes and other affinity agents. Instead of designing an expensive, single-purpose LOC, conventional MEMS or microTAS for specific biomarkers or diagnostic targets, our hybrid BioMEMS test platform can accept and optimize most any commercially available, clinically relevant reagents and probes, with the potential to develop hundreds of new tests very quickly while exponentially driving down the cost of manufacture and administration. This contemplates a massive shift in the creation and deployment of POC diagnostics.

We are actively looking for collaborations, pilot programs, venture funding, strategic partnerships, joint ventures and the like to demonstrate the capabilities and possibilities offered by our diagnostics platform. Our R&D effort, led by Chief Science Officer Michael J. Pugia, Ph.D., is breaking new ground. The prospective applications include but are not limited to infectious disease, metabolomics, fertility, healthy aging, even nutritional biomarkers at point of care, at home or public health screening.

The Team

Michael J. Pugia, Chief Science Officer – Ph.D. Biochemistry, 450+ US and international patents, 100+ publications, former Siemens senior scientist, co-founder Indiana Biosciences Research Institute (IBRI), previously Bayer *in vitro* diagnostics (IVD) lead R&D scientist

Zane R. Baird, Director, Laboratory Operations – Ph. D. Analytical Chemistry, 40+ patents and papers, formerly Siemens and Indiana Biosciences Research Institute (IBRI) R&D lead assay development scientist

Matthew J. Hymes, VP Business Development – M.S., MBA, 20 years in biotech and medtech, previously segment lead for infectious disease & microbiology at Illumina, formerly VP Strategic Partnerships RapidBio.

Andrew A. Dahl – Founder & Executive Chairman, Interim CEO – As CEO led ZIVO Bioscience to re-IPO and Nasdaq listing summer 2021. Various consulting and management roles in medtech/biotech startups since 2003. Prior experience in Fortune 50 business consulting and marketing planning as CEO, Dawber & Company, Inc.

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