STATE OF THE ART IN POINT-OF-NEED & AT-HOME *IN VITRO* DIAGNOSTICS: A SOLUTION FOR PROMOTING HEALTHY AGING & LONGEVITY

ABSTRACT

The escalating global investment in anti-aging solutions, encompassing remedies, treatments, and diagnostics, is a testament to the significant growth of this market. In 2022, the anti-aging market was valued at an impressive USD 63.01 billion and is forecasted to surge to USD 106.65 billion by 2030, as reported by Vantage Market Research, Inc. This expansion is driven by an aging demographic eager to slow down, or even arrest, the aging process.

In the United States alone, individuals annually spend over $30 billion on dietary supplements and a myriad of anti-aging products, often without concrete evidence of their efficacy. The effects of these products are not only elusive but also highly variable, impacting users in diverse ways and not always yielding beneficial results. This uncertainty underscores the urgent need for a scientifically robust method and system capable of accurately evaluating the effects of diet and supplementation in the comfort of one's home and in so doing, tailoring a precise, highly personalized regimen for healthy aging.

BioMEMS is at the forefront of addressing this need with its innovative Point-of-Need/At-Home urine test kit, designed for regular assessment of the influences of nutritional choices, hydration, sleep, and physical activity, along with any additional factors that users opt to monitor. Our solution integrates ultrahigh-sensitivity multiplexed electrochemical immunoassays within an advanced biomedical microelectromechanical sensor array (BioMEMS), encapsulated in a single-use, disposable test cartridge. This cartridge is used with a handheld analyzer that instantly transmits test results to our proprietary mobile app on any paired smart device, ensuring privacy and convenience at home.

This pioneering approach not only empowers individuals to make informed decisions about their anti-aging regimen but also paves the way for a new era in personalized health and wellness, directly from the comfort of one's home.

KEY POINTS

- Point-of-Need monitoring (PoN) of key aging factors, such as "silent" inflammation and oxidative stress, serves to guide individuals toward healthy lifestyle choices while also serving as an early warning system for future problems.

- Biomarkers linked to inflammation, oxidative stress, tissue healing, immune response and cardiovascular health provide valuable and timely insight into life-extending and life-saving preventative measures.

- BioMEMS ultrahigh-performance platform technology delivers previously unattainable, non-invasive monitoring of biomarkers at PoN, with cost and time efficiencies that outperform many traditional lab methods.

INTRODUCTION

Slowing or even stopping the aging process is of great consequence to many of the world's affluent, greying inhabitants. Much has been publicized regarding the genetics of aging, but little about how a healthy lifestyle can ultimately impact the expression of inherited genes or ameliorate poor lifestyle choices made earlier in life.

The study of healthy and unhealthy bodily processes

Nutrigenomics is the study of nutritional inputs that can alter, and in some cases, selectively halt the expression of an individual's inherited genetic code, or positively impact an individual's disease state regardless of genetic predisposition. Metabolomics is the study of metabolites, or more precisely and individual's metabolic profile, to measure healthy or unhealthy bodily processes. BioMEMS research and product development is at the nexus of nutrigenomics and metabolomics — measuring the impact of diet, supplementation and hydration on a functioning organism — in this case, an aging human being.

Inflammation/OS Risk Factors:

Cigarette Smoking

Excessive Alcohol Use

Obesity

Immobility

Metabolic Syndrome/ Prediabetes

Hypertension

Sleep Apnea

Anxiety/Depression

Autoimmune Disease

Periodontal Disease

Sun Exposure

Medical science has for centuries battled epidemics of infectious diseases, invented new methods and technologies to intervene in trauma, injury and impairment, and vastly improved overall life expectancy. Today's top health problems can be traced to lifestyle choices: Type 2 diabetes, heart disease, stroke, and certain forms of cancer can be attributed to a poor diet, lack of physical activity and proper hydration.

Fact: 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, responsible for medical intervention expenditures in the hundreds of billions annually [2,3]. Heart problems are closely correlated to Type 2 diabetes, which in turn develops when a poor diet and inactivity results in obesity, to be followed by insulin resistance.

The best strategy to avoid age-related, lifestyle-induced health problems is to adopt healthy behaviors — easily said but difficult to maintain in most developed, post-industrial societies that value leisure and self-indulgence.

Establishing a baseline for healthy aging

This advice is of little comfort to aging individuals confronting the prospect of unknown risks and problems in their golden years. Establishing a baseline for healthy aging is the first order of business. Most individuals exert ordinary care in maintaining their health, such as regular

BioMEMS Healthy Aging & Longevity Test Panel Offers:

- Ease-of-Use – does not require a highly trained operator. Can be self-administered at home
- Rapid Results – provides results in minutes
- Ultra-High Sensitivity/Specificity – picomolar sensitivity and specificity
- Cost Effective – less expensive than standard lab tests
- Remote Monitoring – mobile with cloud-based record management

visits to the doctor and dentist, and certainly not ignoring troubling symptoms. In the US, most presume that when their physician advises them that their annual blood test results are negative and suggests losing some weight

along with regular exercise that they are somehow generally healthy. That is not the case. They are merely not sick at the time of the annual test. The overwhelming majority of medical diagnostic tests are designed to detect and measure disease, injury, impairment or deficit. In other words, precisely what's wrong, not necessarily what's right, regarding an individual's state of health.

Although general observations can be drawn by skilled clinicians from diagnostic test results that are generally normal or negative, it is difficult to diagnose levels of "healthiness" absent some troubling symptoms or observed pathology. This is especially pointed because "healthiness" varies greatly between individuals. This is particularly true when aging and obesity are introduced into the equation. Due to genetic factors, disease, injury, impairment or lifestyle choices, most people age at different rates, much the same way as children grow and mature unevenly.

Aging factors – obvious and unobvious

The impact of lifestyle choices such as excessive alcohol, tobacco or drug consumption on aging varies significantly from one individual to another. While some may exhibit resilience in coping with the detrimental effects of substance abuse, others may experience profoundly negative effects. Beyond these obvious and pronounced effects, the rate and nature of aging differ among individuals, influenced by varying degrees of obesity and other factors. The underlying causes, be they genetic, related to the interaction between diet and genetics (nutrigenomics) or more subtle factors that elude traditional diagnostics methods – are critically important to identify. By detecting and quantifying these important aging indicators at subclinical levels, we can aim to not only decelerate the aging process but also to potentially delay the onset of age-related diseases and decline, thereby offering significant health benefits over the short and long term.

BioMEMS scientists take the position that measuring optimal metabolic efficiency or function is the best approach to assessing the state of healthy aging. By deductive reasoning, if an individual is functioning at optimal metabolic efficiency (very difficult to achieve) for their individual biometrics, they very likely can't be harboring even the pre-conditions favorable for the onset of disease, deficit or suffering from an undiscovered injury.

Therefore, if there exists the ability to detect and measure optimal metabolic efficiency with exceptional precision, anything that subtracts from that optimal status, however slight, may not escape notice: A food

sensitivity, a minor topical infection, even something like chronic plantar fasciitis or a badly stubbed toe can cause the numbers to change.

This is not to suggest that every minor trouble is identified and run to ground, rather that something other than a healthy bodily process is in play and there is sufficient sensitivity and capacity to detect a change, without necessarily identifying it.

Empowering an individual to detect, quantify and see trendlines for aging factors form over time creates compelling, positive reinforcement of healthy lifestyle choices.

Results, response and behavior modification

There is a significant benefit in establishing a baseline for metabolic efficiency. Changes in diet or supplementation can be tracked and monitored for their beneficial or deleterious effect, along with changes in activity, sleep, hydration and the like. As stated in the abstract, Americans spend billions on special diets and dietary supplements, mostly on faith. Most, if not all, have no idea whether the supplements they consume help, hurt, or do nothing at all. There is a demonstrated need for a healthy aging test that would allow individuals to add or subtract various supplements or foods and determine which may contribute to metabolic efficiency and/or positively impact aging factors.

When discussing aging factors, the appearance of aging and the sense of well-being are foremost in the minds of aging consumers. The prevailing scientific consensus is that the very same factors contributing to systemic healthiness affect the appearance of skin and hair. For example, excessive free radicals in the bloodstream destroy elastin and collagen, causing wrinkles and sags, and when combined with sun exposure, deal a double dose of accelerated skin aging.

Empowering individuals to control their own aging factors in the privacy of their home goes beyond quality of life and the appearance of aging. The risk of death and various disease states is predicted by inflammation, oxidative stress, and tissue healing factors [7-15].

Establishing metrics and context

Detecting and measuring subclinical inflammation and stress levels can provide consumers with truly actionable information and the tools to actively manage same. This is not intended to replace conventional medical care and interventions, but rather complement the work of healthcare providers by reducing the risk of disease and infirmity as individuals age, especially asymptomatic
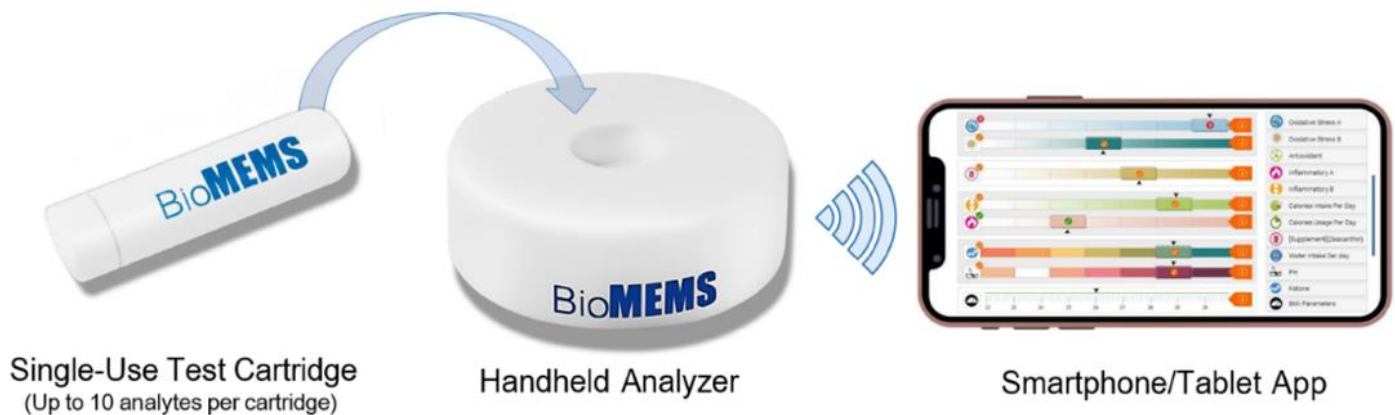
heart conditions [16]. It is difficult to motivate healthier lifestyles without firsthand knowledge of ongoing damage or pending progression to life-threatening disease.

Conventional diagnostics may not provide actionable data regarding deteriorating health and potential complications [7-14, 17]. There is a compelling need to bring awareness and actionable information to the consumer and enable informed decisions based on scientifically sound data presented in an actionable, interactive format that promotes and reinforces healthy behaviors. BioMEMS has moved forward to develop a set of diagnostics targets to best assess aging factors, and also a platform technology to detect and measure those diagnostic targets using urine or saliva, to be self-administered at home by the consumer. The results are ported to any paired smartphone and can be uploaded to the cloud for sharing with care providers

BioMEMS DIAGNOSTICS PLATFORM DESIGN AND WORKFLOW
Precisely measure any biomarker in any biofluid at ultrahigh sensitivity in less than 5-minutes

Single-Use Test Cartridge
(Up to 10 analytes per cartridge)

Handheld Analyzer

Smartphone/Tablet App

The BioMEMS test platform is built around an electrochemical immunoassay (EC-IA) system with the unique capability of processing complex biofluid samples rapidly by passaging 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 analytics app that can be downloaded to most smart devices. Results are typically available within 5 minutes of obtaining the biofluid sample, with single-digit 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 at Point-of-Need. The design allows for processing samples such as saliva, urine, wound fluid, sputum, bronchial lavage, cerebrospinal fluid, plasma, whole blood and serum. The platform can be configured to detect a broad range of targets and biomarkers, from individual pathogens to small metabolites. The system is designed to utilize a broad range of affinity agents that bind, detect and measure biomarkers or pathogens of interest. Hundreds of unique electrochemical assays can be created and optimized for the BioMEMS platform, many derived from previously clinically validated and commercialized diagnostics tests that are currently processed in hospital and commercial laboratories. When a test cartridge with a biofluid sample is inserted into the handheld analyzer and activated, the cartridge isolates, concentrates, and purifies analyte molecules by affinity surface capture on a microfiltration sensor membrane. The surfaces of individual microwells are chemically modified to allow rapid, efficient 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 target gives the immunoassay reagents the ability to operate under ideal conditions and generate clean results without interferents. This simple and efficient process does not have the legacy problems of competing methods, where the target analyte fails to bind to separation surfaces consistently.

Engineered to be small and disposable, the BioMEMS 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 ultrahigh sensitivity electrochemical bioassays within a single microwell, where each such microwell represents an individual immunoassay test 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 at Point of Care and Point of Need.

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.

COMPETITIVE ANALYSIS METHODS

BioMEMS diagnostics platform advantages over competing diagnostic methods

There are competing technologies that we can supplant by providing faster results and cheaper tests with greater accuracy at PoC or PoN. 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 at PoC, PoN and At-Home.

	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

Healthy aging/longevity test panel

The selection of biomarkers and corresponding assays constitute the core features of a healthy aging/longevity test panel, which can then be processed using the BioMEMS hardware and software platform. The healthy aging test panel is composed of ten (10) tests that detect and measure biomarkers for inflammation, oxidative stress, tissue damage, immune health, digestive health, energy levels, and insulin resistance, among others. Some of the biomarkers can provide more than one data point, and in combination with other biomarkers, provide enhanced metrics and insights into complex bodily functions. For example, bikunin can function as a biomarker for identifying systemic inflammation, the effects of oxidative stress, as well as 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. It can be detected at elevated concentrations in the urine of patients suffering from acute and chronic inflammatory diseases [21-42]. Monitoring bikunin in the presence of markers for oxidative stress can indicate tissue damage infection, and poor immune response. By including

bikunin, the panel is of special value for cardiac health, monitoring key biomarkers well before they enter the clinical or pathological range [43-50, 8] and serving as an early warning trendline. Other biomarkers, such as those measuring elevated advanced glycation products (AGE's), when combined with lipid peroxidation and nitrosative stress biomarkers, help inform consumers of visible aging as elastin and collagen are degraded.

Aging population explosion fosters demand for anti-aging remedies, treatments and diagnostics.

BioMEMS platform applications include Home Care Devices, IVD, Medical Devices, and Pharmaceutical & Biological Research. The global market was valued at USD 63.01 billion in 2022 and is projected to reach USD 106.65 billion in 2030. The demand for accurate, actionable PoN and at-home diagnostics increases with the aging population, as well as acute and chronic age-related diseases continue to rise.

BioMEMS Diagnostics is actively developing its healthy aging & longevity test panel and testing platform. We are also fully engaged in developing technical and strategic partnerships to bring the test panel and the testing platform to market.

As a core strategic principle, BioMEMS aims to partner with a larger, established global brand to launch its test panels and testing platform on a global scale. In so doing, we intend to de-risk the vagaries of market launch and acceptance, establish predictable cashflow and focus on developing new test products and scaling up manufacturing capabilities.

This strategy allows BioMEMS to grow quickly, scale its production capacity rapidly and establish itself as a market leader at Point of Need and At-Home settings, providing access to previously unattainable diagnostics capabilities where they are needed most.

Clinical utility	Response of panel
Healthy tissue repair	In the presence of oxidative and nitrosative stress, bikunin indicates tissue damage.
Cardiovascular efficiency	Reduced bikunin demonstrates healing during CVD events, and oxidative stress products predict a lack of inflammation inhibition.
Improved response to infection	Bikunin and oxidative stress increase with infection.
Healthy immune response, sustained response capacity	Low bikunin in the presence of elevated infectious biomarkers indicates a poor immune response.
Lipid peroxidation and oxidative stress	Elevated oxidative stress may reveal poor management of reactive oxygen species (ROS), free radicals
Elastin and collagen destruction, degraded cell function	Elevated Advanced Glycation End Products (AGE's) degrade cell functions that manage free radicals
Energy and energy Conversion	Efficient digestion and resulting energy conversion by muscles, organs
Nitrosative stress	The presence of NOS products indicates acceleration of various aging factors
Insulin resistance and metabolization	Biomarkers that monitor insulin output relative to absorption

NEW INFORMATION
A newly published UK-based proteomics study of 50,000 individuals has revealed that a "sparse protein model" of less than 20 key proteins present in blood or urine are predictive of significant health problems as much as 20 years into the future. BioMEMS scientists are reviewing this new development and will approach the study authors and global health brands with a proposal to create a new and novel test kit that detects and measure up to 10 key protein biomarkers.

ABOUT US

BioMEMS Diagnostics, Inc. is a Michigan-based startup developing a breakthrough, patent-pending diagnostics platform delivering high-need, high-complexity tests at Point-of-Care (PoC), Point-of-Need (PoN) and At-Home.

Our firm has developed a biomarker-agnostic, biofluid-agnostic, universal biomedical MEMS sensor array that vastly improves the processing speed and sensitivity of diagnostic tests currently performed in hospital and centralized laboratories. Instead of designing an expensive, single-purpose lab-on-a-chip (LOC), conventional MEMS or micro total analysis systems (µTAS) for specific diagnostic targets, our hybrid BioMEMS test platform can accept and optimize most any commercially available, clinically relevant immunoassays and antibodies, with the potential to develop dozens of new and novel 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 seeking technical 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 & Technology 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, precision medicine, precision nutrigenomics, nutritional optimization at point of care, point of need, at home or public health screening.

The Team

Michael J. Pugia, Chief Science & Technology 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, VP R&D – Ph. D. Analytical Chemistry, 40+ patents and papers, formerly Siemens and Indiana Biosciences Research Institute (IBRI) R&D lead assay development scientist

Jacob R. Kapala, Lead Engineer – multiple degrees in math, physics and engineering, previously lead engineer at Indiana Integrated Circuits, responsible for all firmware & software design, and device electronic engineering

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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