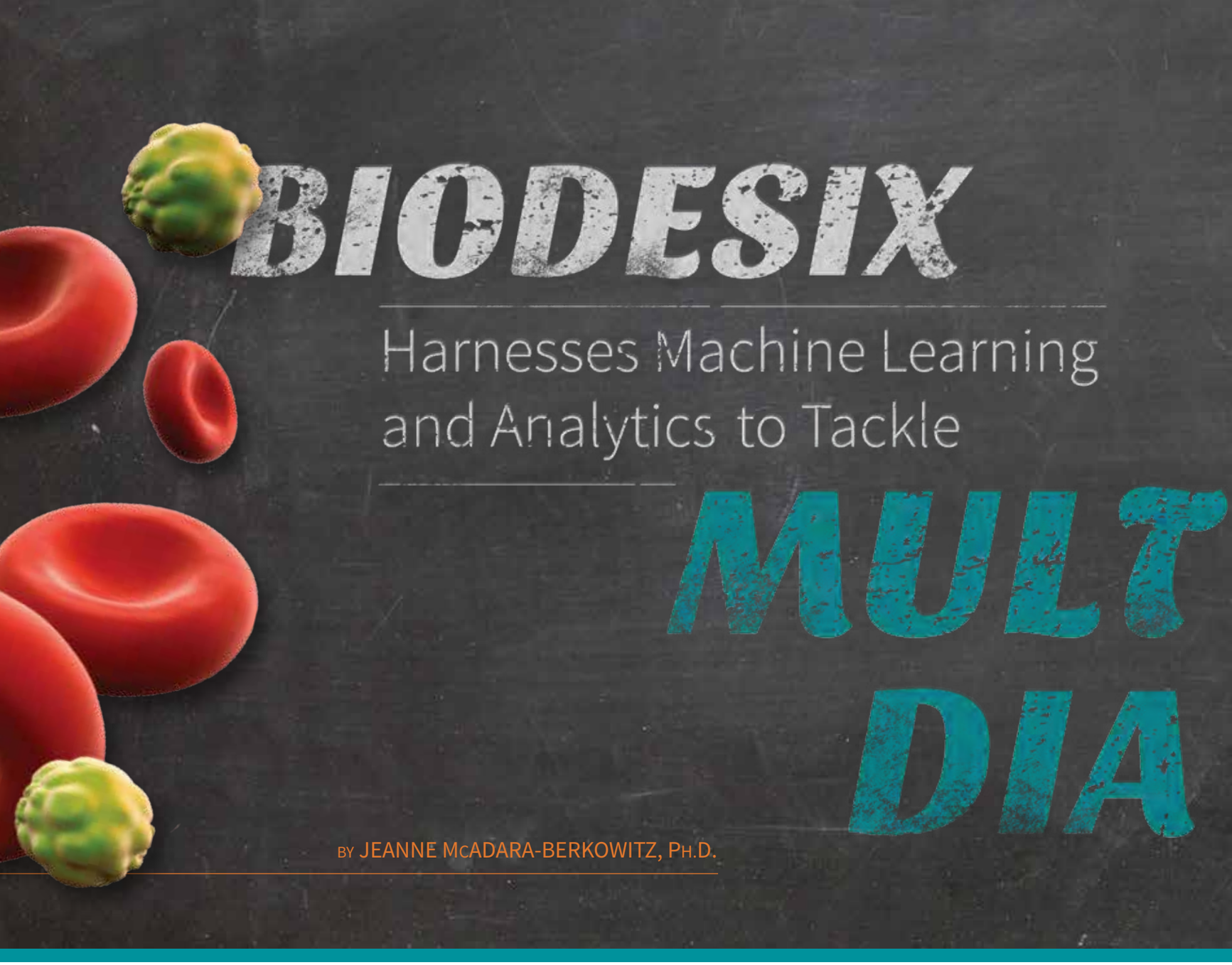


BIODESIX

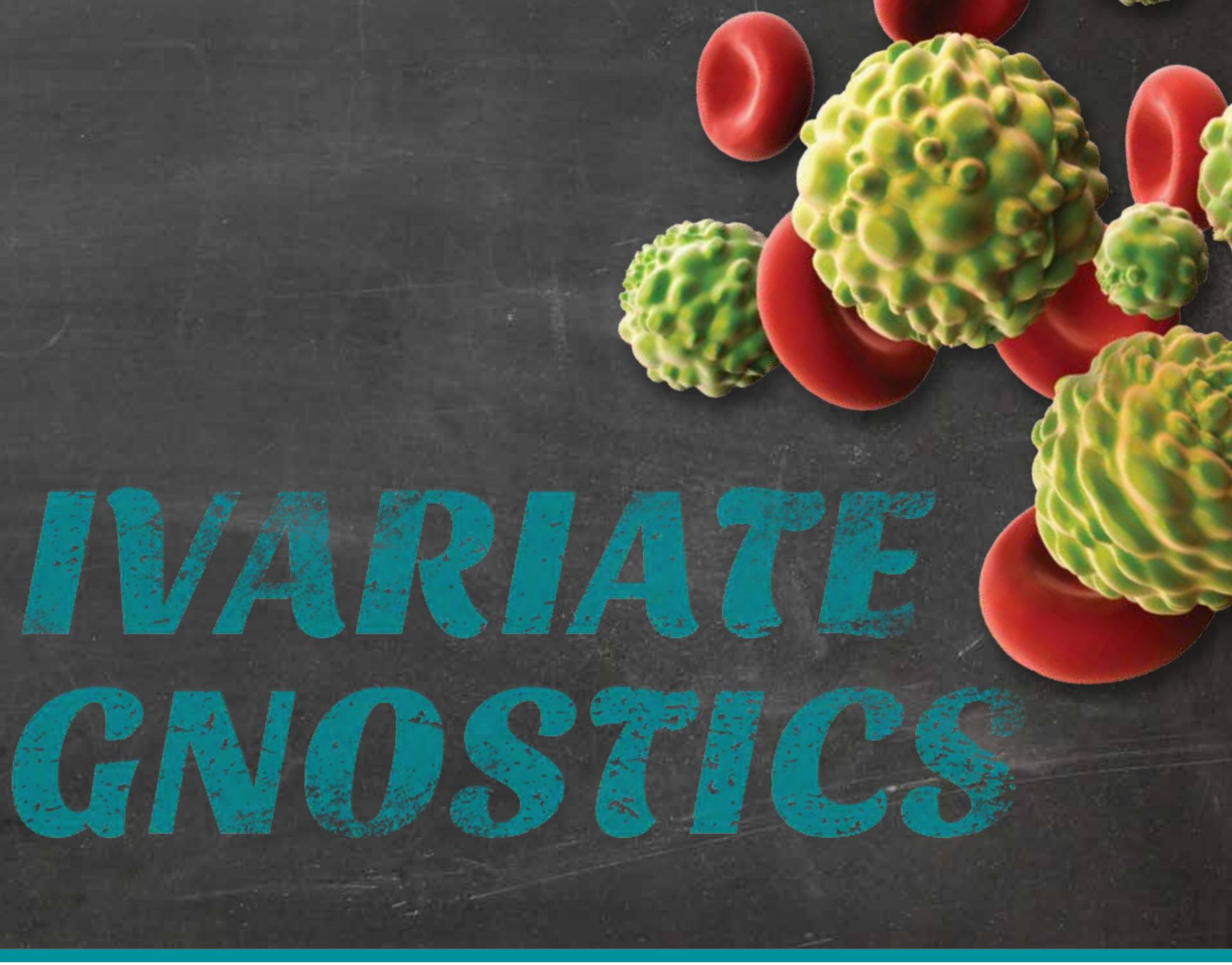
Harnesses Machine Learning and Analytics to Tackle MULT DIA

BY JEANNE McADARA-BERKOWITZ, PH.D.

When Ginny learned that her seemingly innocent, nagging dry cough was actually advanced non-small cell lung cancer (NSCLC), the active, otherwise-healthy 65-year-old was stunned but determined to face her difficult treatment head-on. The therapy was initially effective, but eventually the cancer began progressing again, and Ginny and her oncologist were faced with choosing the next step in treatment. While it wasn't certain which if any of the remaining options would be effective, all of them were likely to cause difficult side effects.

According to the American Cancer Society, more than 1.6 million Americans will be newly diagnosed with cancer in 2014, and that figure leaves out recurrent disease. This means that, like Ginny, millions of patients and their physicians will face the risk-benefit trade offs involved in treatment decisions. The growing availability of companion diagnostics provides some guidance by matching patients with the therapies most likely to be effective and steering them away from treatments that are destined to be ineffective due to a patient's individual genetic makeup.

One such tool is the VeriStrat® test, developed by Boulder-based molecular diagnostics company Biodesix. Like other companion diagnostics, VeriStrat identifies the presence or absence of specific biomarkers in patients with NSCLC. VeriStrat's output helps the oncologist determine the sequence of second-line treatments, including whether the patient should receive erlotinib (Tarceva®), an epidermal growth factor receptor (EGFR) inhibitor, or instead be prescribed an alternative, single-agent chemotherapy.



IVARIATE GNOSTICS

What separates VeriStrat from other companion diagnostics on the market is that it is a multivariate test based on an underlying proteomics-based technology. Unlike tests that amplify a single nucleic acid sequence or detect the presence of a single protein, VeriStrat was developed using a specialized analytics platform, ProTS, which analyzes the output of matrix-assisted, laser desorption ionization (MALDI) mass spectrometry from a small volume of blood serum or plasma. ProTS provides a set of tools for maximizing the usability and reproducibility of individual features in the MALDI spectrum, enabling the detection of complex, clinically relevant and validated signatures from blood serum and other complex samples.

David Brunel
President and CEO of Biodesix

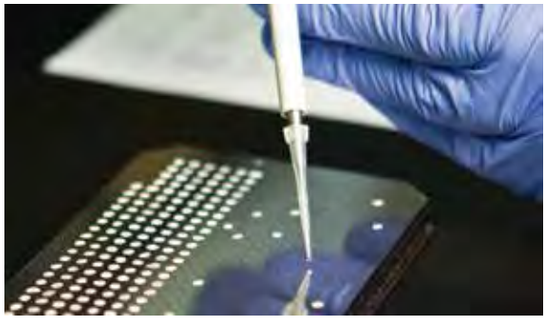
"It's been an exciting couple of years for the field of personalized medicine," says David Brunel, president and CEO of Biodesix. "But efforts like the 1000 Genomes project are only one part of the story; we have to move beyond the patient's genotype toward their actual current state—the phenotype—and we can accomplish that through a series of emerging 'proteomic' technologies."

"We're moving away from an over-reliance on straightforward, single-marker targets like PSA for prostate cancer, CRP for inflammation and cardiovascular disease, or HER2 for breast cancer," he continues.

"For many years there's been interest in multivariate diagnostics and whether they could be used to guide the use of therapy. Now we're finally seeing better tools for answering these clinical questions."

Analytics and algorithms

Multivariate analysis is no simple prospect. Technologies like MALDI-mass spec, genome-wide association studies and other complex clinical analyses generate a lot of data—enough that the development of specialized computational methods designed to deal with and analyze those data has been critical.



VeriStrat, developed by Biodesix, identifies the presence or absence of specific biomarkers in patients with NSCLC, which helps the oncologist determine the sequence of second-line treatments.

Biodesix has approached the diagnostics problem by drawing on the expertise of mathematicians, physicists and software engineers to develop specialized analytics, capitalizing on the advancements in machine learning going on outside of diagnostics.

According to Brunel, the team at Biodesix is working to adapt these analytics to address the specific problems encountered when trying to develop validated tools for improving the practice of medicine.

"One point of difference in our field is that we may have large datasets for each patient, but generally we have very few patients in the initial study population," says Brunel. He says this situation can potentially lead to over-fitting problems, because the analytics will always be able to find correlations through random chance. Biodesix's challenge is to build diagnostics that can be validated beyond the patients in the initial study and can therefore be generalized to larger populations.

"What we've done is to create a set of tools that help us identify useful features that are differentially expressed in patients with and without the disease we're interested in," says Brunel. "We then move on with another set of tools that use 'deep-learning' algorithms. These are similar to the algorithms that Facebook and Google use to continually extract utility from the vast troves of data they collect, from recognizing faces to reminding you that certain friends have been less attentive lately."

Potentially useful or discriminating features that have been identified then go through an iterative refinement process with the eventual goal of creating a validated classifier for clinical prediction. Such tools could help identify patients at risk for disease, diagnose the presence of active disease, guide treatment decisions and avoid interventions that would be unnecessary or even harmful.

A new era of diagnostic medicine

"One example of this application would be a test for early ovarian cancer in women with abdominal masses," says Brunel. "Only about three percent of such masses are ever found to be cancerous, but getting to that answer often requires multiple invasive surgeries that sometimes, in themselves, create opportunities for metastasis. It would be so much better to have a blood test to help rule out cancer before surgery is performed."

Brunel notes that the potential applications for this approach are nearly limitless. "We're interested in this new era of diagnostic medicine, where in some cases it will still be used strictly to guide intervention for acute disease, but its ultimate use will be to monitor health to maintain optimal wellness."

"As the technologies for measuring genes, proteins, metabolites and the many specific variations in each of these classes of molecules improves and costs decline, we see diagnostic development becoming more of an 'in silico' practice," he continues. "The exciting thing about our technology is that it is indifferent to whether the biological attributes being analyzed are proteins or genes or data from a physiological monitor, or even a combination of those. This is an evolution and a revolution that we want to be a part of."

Using VeriStrat, Ginny's oncologist learned that the recurrent cancer had a reasonable probability of being susceptible to treatment with erlotinib, tipping the risk-benefit equation in favor of that treatment strategy. Although the outlook for patients with advanced metastatic cancer is still difficult, the knowledge gave Ginny's team confidence that they were not wasting precious time on an ineffective treatment.