A DREAM COME TRUE

BY ROBERT GRACE

Predictive healthcare via point-of-care diagnostics will reshape medicine by improving outcomes and slashing healthcare costs

"The future of healthcare is predictive medicine." So declares Rey Parel, an evangelist on the topic, at the end of every one of his emails.

The San Francisco-based scientist and plastics engineer has devoted himself since 1985 to helping develop medical devices that improve healthcare outcomes. He also is director/angel investor to several medical device startups in the U.S. and Canada, including mFluiDx Inc. of Berkeley, Calif.

"Imagine," as Parel says, "a world where disease could be predicted before it happens, instead of diagnosed and cured by drugs or surgery. Where doctors could change a patient's lifestyle, diet and exercise and prevent the disease." With 24 patents and more than 60 medical devices to his name, Parel says his mission in life is nothing less than "medical emancipation" for patients.

Several companies are tackling the challenge of predictive medicine in a variety of ways, with plastics and advanced processing techniques aiding the cause in nearly every case.

- For Fluxergy, it is low-cost, multimodal, point-of-care (PoC) diagnostic devices the company refers to as a "lab in a box."
- For Micropoint Bioscience Inc., it's a microfluidics based PoC device that detects BNP (brain type natriuretic peptide), a cardiac marker antigen that is produced in the heart in minute quantities before the advent of arrhythmia. (Note: microfluidics is the technology of fluid manipulation in channels with dimensions in the tens of micrometers.)
- For Guardant Health, it's a liquid biopsy test that captures and profiles circulating tumor DNA in the blood stream to detect the earliest stages of cancer.

And, before all this, it was the work of Parel and others at PerkinElmer in the early 1990s to develop incredibly thin, uniform "thermocycler tubes" made of polypropylene that were used to execute polymerase chain reaction (PCR) technology applied in DNA testing.

The fact is that the early detection of biomarkers that reveal the potential onset of serious medical conditions can assist doctors in prescribing corrective actions to patients and quite often help individuals avoid the costly and risky consequences of hospitalization.

Diagnostics and COVID

Never has predictive medicine been so vital as now, in the midst of a global pandemic. Dr. Ali Tinazli was chief commercial officer of Irvine, Calif.-based Fluxergy this past spring when he wrote: "The rapid spread of COVID-19 … has demonstrated that current diagnostic testing methodology is too slow and too inaccessible to address today's dramatically changing healthcare challenges. New technologies are needed immediately that provide fast, accurate

"Imagine a world where disease could be predicted before it happens, instead of diagnosed and cured by drugs or surgery.

- Rey Parel

and low-cost tests directly at the point of care."

The clinical and cost-management needs for such solutions are readily apparent and urgent, especially in today's environment, continued Tinazli, who remains on Fluxergy's board but recently assumed a new role as CEO of lifespin GmbH of Regensburg, Germany.

"To realize the full potential to democratize health testing for consumers, important gaps in technology must still be overcome, including the ability to deliver multimodal and multiplex testing panels utilizing molecular diagnostics (e.g., PCR), immunoassays, chemistry and cytometry—functionalities that identify DNA, RNA, proteins, metabolites and cells." Fluxergy's platform, Tinazli suggests, is very promising as a means to successfully address these critical gaps.

Dr. Ali Tinazli

Diagnostics, he adds, represent less than 2 percent of the total worldwide healthcare spend (according to 2017 World Bank data), and yet they influence more than 60 percent of critical healthcare decision making.

The 8-year-old Fluxergy—which also makes veterinary healthcare products and plans to supply tests for the food industry as part of its core efforts to be seen as a "one health" company—launched its first commercial human product, a COVID-19 test kit, in March. The firm aims to be producing 100,000 test kits per month by year's end, with an eventual goal of up to 1 million kits per month, says CEO and co-founder Tej Patel. It is selling the kits in Europe, Asia and the Middle East, but has yet to gain the necessary approvals in the U.S. The firm plans to launch a series of equine tests later this year, and a couple more human assays by first quarter 2022, he says.

Recognizing the potential benefits of being able to use testing more routinely and comprehensively at the point of care to catch illnesses earlier and promote overall long-term wellness, Tinazli notes that "the field of medicine is increasingly transitioning to a more systematic approach that focuses on the "4Ps," i.e., predictive, preventive, personalized and participatory."

In the precision medicine or 4P model, he says that comprehensive health testing could play a vital role, delivering repeated longitudinal measurements (i.e., more frequent testing) with a broader range of biomarkers (e.g., blood and urine panels) to monitor the health status, manage acute and chronic care conditions, and better quantify wellness and even predict—ideally even prevent—disease.

> **The rapid spread of COVID-19 … demonstrates that current diagnostic testing methodology is too slow and too inaccessible to address today's dramatically changing healthcare challenges. New technologies are needed that provide fast, accurate and low-cost tests directly at the point of care.**

New Test Options

A few companies, including Fluxergy, are developing innovative diagnostic testing solutions intended specifically for the PoC, providing the necessary combination of ease of use, small sample requirements and significant cost-effectiveness. Fluxergy's system offers the added ability to potentially deliver sophisticated multimodal and multiplex "sample-to-answer" testing solutions.

These new technologies would enable providers and ultimately even consumers at the PoC to cost-effectively conduct many of tests that are currently only performed at centralized labs. In other words, this would give PoC providers the quality and precision of central lab testing but make it less expensive and closer to patients. Fluxergy's Patel sees this as finally unlocking the true potential of diagnostics to play a far greater and more important role in the early detection and ongoing monitoring of health status, where and when it matters most—at the point of care.

The aim is to make testing devices with multimodal/multiplex testing capabilities widely available on a distributed basis at PoC locations, ranging from doctors' offices and urgent-care centers to clinics and retail pharmacies.

Imagine, Patel said in a mid-August telephone interview, if diagnostic testing became so accessible and affordable that the average person could be tested monthly, instead of once a year during an annual physical. One of the keys to Fluxergy's efforts involves creating a single device that can effectively handle a wide range of tests, including molecular, immunoanalyse, chemistry and cytometry. Currently, different tests are typically needed for each of these, which can be slow and costly, and often can be processed only by central labs.

Fluxergy says it is developing a multimodal/multiplex in vitro "health testing ecosystem," leveraging artificial intelligence (AI) that delivers what's needed to power the transformation to the diagnostic care model—namely, precision, ease-of-use and cost-effectiveness.

Its FluxergyCard is essentially an entire "laboratory on a card," a highly integrated, modular cartridge used for handling samples with advanced microfluidics and proprietary printed circuit board (PCB) technology with the potential to provide highly accurate and fast sample-to-answer testing. Unlike other PoC in vitro diagnostic technologies, which tend to focus on only one modality, such as either PCR or immunochemistry assays, the FluxergyCard has been designed to allow for a comprehensive variety of assays and panels.

Key Role for Plastics

Since these microfluidic test cards must be single-use, disposable devices, it is vital that they can be manufactured quickly, inexpensively and in great volume. This is where plastics technology plays a key role. Fluxergy uses polystyrene and polycarbonate (PC), among other materials, to injection mold these parts.

Tej Patel

"It would not be possible to achieve our goal without plastics," Patel says.

Separately, the unit designed to read the test cartridges, called the FluxergyAnalyzer, is a

> **The early detection of biomarkers that reveal the potential onset of serious medical conditions can assist doctors in prescribing corrective actions to patients and quite often help individuals avoid the costly and risky consequences of hospitalization.**

proprietary device featuring a homogenous multi-sensor system that's designed to eliminate the need for multiple heterogeneous laboratory analyzers and has the potential to accurately detect a range of markers from molecules to cells. Its enclosures are mostly made of metal now, but Patel hopes to transition these to plastics, most likely PC. The device also employs some 3D-printed nylon parts.

Fluxergy's aim is to deliver results in as little as 10 to 45 minutes, at any number of PoC locations, from clinics to walk-in pharmacies.

The final part of the firm's ecosystem is FluxergyWorks, a sophisticated, cloud-based user interface capable of analyzing and disseminating test results data to users while maintaining cybersecurity and meeting U.S. federal HIPAA (Health Insurance Portability and Accountability Act) law requirements.

Patel says Fluxergy, with close to 100 employees in its Irvine headquarters, is producing some 40,000 cartridges a month, with the aim of reaching 1 million units per month. Additionally, he says it will be able to make about 250 analyzers per month, depending on demand.

The key, says lifespin's Tinazli, is to gain a better understanding of the human body—of your human body, he emphasizes, on a personal level, but to do that one needs testing and data. "Early detection can prevent hospitalization," he notes. Vehicle technology now offers "lane assist" to alert drivers if they are drifting into another lane, and smartwatches can tell wearers to get up and stretch and move. These are preventive actions, and the same can apply to healthcare diagnosis and treatment, with the right tools.

Echoing Patel, Tinazli states that "plastic is the key for democratization of health testing." Indeed, given its many applications, "the entire healthcare industry is a plastics industry."

Tinazli, born in Germany to Russian and Turkish parents, earlier in his career worked for HP, Sony and Applied Biosystems (now Thermo Fisher Scientific). During his last stint with Sony, in 2014 to 2015, he served as vice president and head of business development and sales at DADC BioSciences Americas in Cambridge, Mass. While there, he directed efforts to leverage Blu-Ray optical disc manufacturing technology to make 24-array polymer discs for healthcare testing, specifically for single-molecule detection of immunoassays.

At HP in Palo Alto, Calif., Tinazli successfully led the corporate-wide healthcare strategy to put microfluidics based on inkjet printing technology into the context of highly decentralized health testing to lower cost burdens in health systems.

He describes his new venture, lifespin, as "a health data insights company that can map human health and well-being on a metabolic level." The aim is to detect with novel biomarkers, at very early stages, neurological diseases such as Parkinson's, multiple sclerosis and cancer.

Early Detection of Disease

Early detection of cancer is the focus of Silicon Valley startup Guardant Health, whose chief executive officer and co-founder Helmy Eltoukhy was Parel's former boss about a decade ago at San Diego-based biotech company Illumina Inc. Guardant uses a technology called ctDNA liquid biopsy, which detects tiny bits of cancer DNA floating in a patient's bloodstream, using a small blood sample.

Liquid biopsy detects and interrogates cell-free DNA, not

Fluxergy sells its COVID-19 test kit in Europe, Asia and the Middle East, and is awaiting U.S. approval for the product. Courtesy of Fluxergy

Fluxergy wants to increase production of test cards to 1 million per month. Shown is the manufacturing plant in Irvine, Calif. Courtesy of Fluxergy

circulating tumor cells, to detect very early-stage cancers in the human body. Eltoukhy has been quoted as saying, "We aren't far away from creating blood tests that can be used to detect the earliest stages of cancer."

Micropoint Bioscience, meanwhile, was funded initially by China, and has offices in Shenzhen as well as in Grenoble, France, while making U.S. headquarters in Santa Clara, Calif. The firm also is all about identifying key markers at early stages, in this case potentially fatal heart conditions, including arrhythmia. Its device, mLabs ImmunoMeter, is an immunoassay diagnostic platform, based on Micropoint's patented microfluidic technologies and advanced fluorescence detection, using small samples of blood.

Micropoint CEO Nan Zhang has said that MicropointBio's mission is "to improve patient care by providing rapid, accurate, reliable and low-cost diagnostic products at point of care." The device was initially tested for D-Dimer (a protein released by blood clots) in 2013 but, she says, now boasts a suite of diagnostic assays for the early detection of AMH, Cardiac Panel 3, NT-proBNP, PCT and Troponin I (a marker for heart muscle damage), hs-Troponin I (a marker for acute thrombosis syndrome), and D-Dimer and BNP. (Note: The Micropoint Bioscience web site states that products are not available for sale or marketed in the U.S. at present.)

The aim [of Fluxergy's technology] is to make testing devices with multimodal/multiplex testing capabilities widely available on a distributed basis at locations ranging from doctors' offices and urgent-care centers to clinics and retail pharmacies.

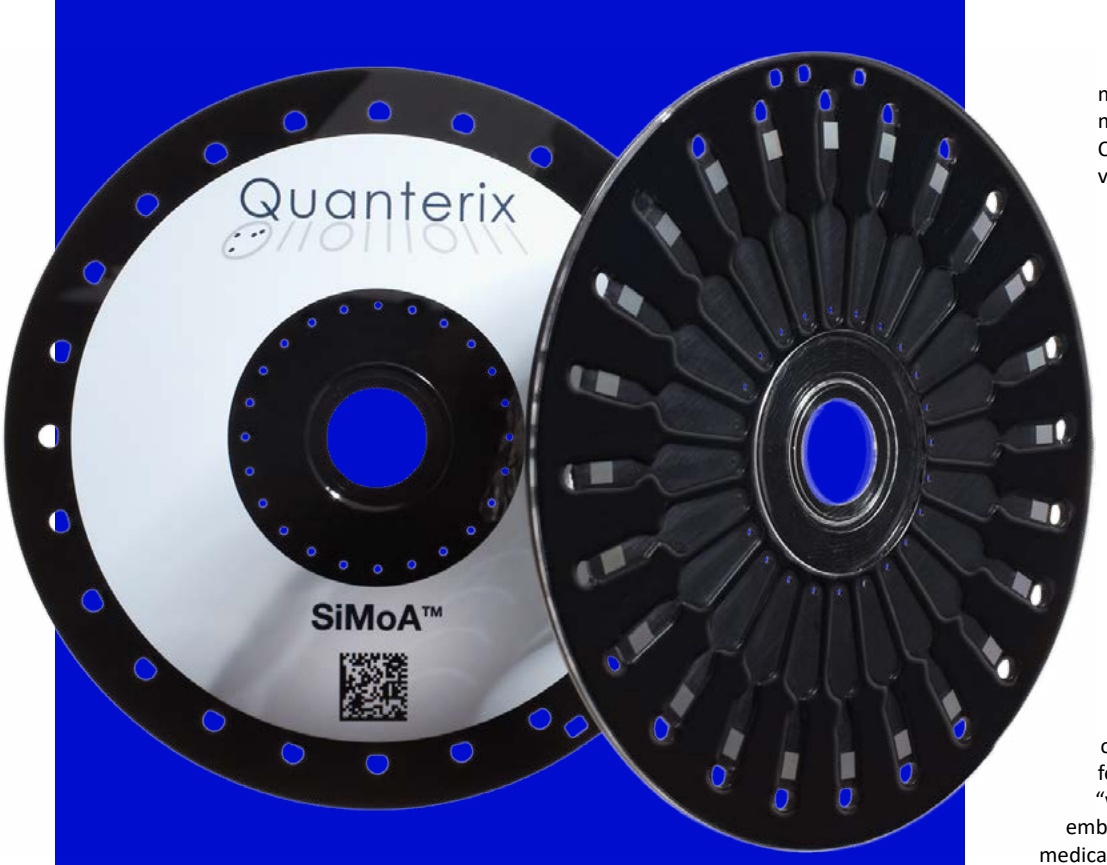
PCR Back Story

A key to many of these developments can be traced back 30 or more years to the development of a technology called polymerase chain reaction, or PCR.

Parel—a board member of SPE's Golden Gate Section in California since 2009—recounts a 1989 meeting in which he was introduced to Kary Mullis, an American biochemist who four years later won the Nobel Prize in chemistry for his invention of PCR. Mullis told Parel and his colleagues: "I want you to design a tube that is so thin and so uniform in thickness, it has never been done before in plastic." Why plastic? Because, Mullis said, "we will produce millions and millions of these 'thermocycler tubes,' and they have to be manufacturable and cheap, robust and accessible to ordinary folks."

Parel, a 67-year-old Filipino native who came to the U.S. in 1985, recalls that Mullis explained PCR to him and his colleagues as follows: Imagine our DNA chain as a railroad track twisted like a helix. Under heat, this railroad track unravels into a straight track. The polymerase enzyme takes base pairs from other sections of this railroad track and puts it in the same sequence as the DNA sequence to be copied. And it does this hundreds, millions, even billions of times.

As a young plastics engineer, Parel said the



Ali Tinazli oversaw efforts at Sony DADC BioSciences Americas to leverage Blu-ray optical disc technology to make 24-array polymer discs for healthcare testing. Courtesy of Ali Tinazli

concept of amplifying, or making copies of DNA was not only foreign but mind-boggling.

Mullis, who died in August 2019, stressed that the thermocycler tube wall thickness must be incredibly uniform, so uniform in fact that it was virtually impossible to produce using the plastics technology available at the time, some three decades ago. But molding technology has advanced tremendously, so that such precision is easily accomplished now.

In 1991, Parel and his colleagues at PerkinElmer responded to Mullis' challenge by developing the GeneAmp PCR System, and the ultra-thin, ultra-uniform PCR thermocycler tube was a reality. "I certified the polypropylene material that is still used today in all your labs," recounts Parel. (At the time that isotactic PP homopolymer was a Himont grade known as PD701; now it is LyondellBasell's Pro-fax PD702.)

A First in Microfluidics

In 2000, while working at Aclara Biosciences (now Monogram Biosciences, acquired by LabCorp), Parel says he helped produce the first polymer-based microfluidics chip in the industry. At the time, it still was a struggle to enable replication of micron-sized plastics features, he recalls. A decade later, when Parel and Tinazli met, Illumina leveraged Sony DADC Biosciences technology to injection-compression mold a credit-card sized PCR chip with 2.8 million wells, with each well 30 microns in diameter.

And why plastics for that application? The answer is excellent performance at a fraction of the price. Consider, Parel says, that at the time it cost about $0.30 cents per square centimeter for a silicon-glass chip and $0.03 per square centimeter for the same chip molded in cyclic olefin polymer (COP). Today, the material cost is a fraction of that.

Previously, Topas Advanced Polymers' cyclic olefin copolymer was the polymer of choice for microfluidic chips, but now Zeon Corp.'s Zeonor COP is finding favor. Both materials have the same glass-transition temperature, Parel says, but the Zeonor resin has a higher thermal decomposition temperature, higher heat deflection and higher vicat softening temperature, which indicates better heat stability all around, as well as outstanding optical properties and very low extractables.

He notes that PCR became the engine that revolutionized research to sprout new fields in DNA sequencing, genomics, bioinformatics and the like, further spurring the plastics industry to develop techniques, machinery, tools and polymers to meet the demanding challenges of replicating increasingly smaller features. "The result," he notes, "was the plastic microfluidic chip embedded in almost every diagnostic medical device today."

At the heart of these disease-predicting devices, Parel states, are novel developments in nano-biosensors and ultra-sensitive DNA detection.

This advent of so-called "prognostic medical devices" is really one of the most exciting developments in healthcare in the last 10 years, according to Parel. "I liken it to the growth of the electric car industry, in the

Micropoint Bioscience mLabs ImmunoMeter immunoassay diagnostic platform tests for a wide range of disease markers. Courtesy of Micropoint Bioscience

The first prototype of the PCR 96-well tray. Courtesy of Rey Parel (Left) **Aclara Biosciences Inc. pioneered the development of microfluidics, or lab-on-a-chip technology, with the industry's first plastics microfluidic chip, called LabCard.** Courtesy of LabCorp (Right)

"Plastic is the key for democratization of health testing." Indeed, given its many applications, "the entire healthcare industry is a plastics industry."

— Ali Tinazli

face of opposition from the big automakers, and their eventual embrace of the EV (electric vehicle) technology. The same holds true with preventive healthcare. I recall the strong opposition of the pharmaceuticals [producers], HMOs and big medical device companies, because of vested interests and expensive drug pipelines."

But now, together with the development of point-of-care technology, this new class of medical devices is starting to be developed not just by small startups but by the major pharma and biomedical OEMs.

Enabled by the powerful engine of polymer-based microfluidics, "Reverend Rey," as he is known to some of his colleagues, continues to preach the gospel that "the future of healthcare is predictive medicine." Amen, Rev.

More information on predictive diagnostic developments is available from the companies interviewed for this article.

Fluxergy - www.fluxergy.com

Guardant Health - www.guardanthealth.com

lifespin GmbH - www.lifespin.de

mFluiDx Inc. - www.mfluidx.com

Micropoint Bioscience - www.micropointbio.com ■