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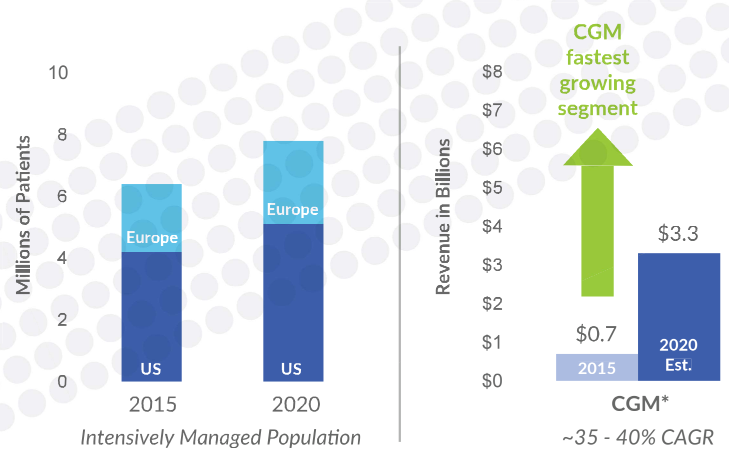
MARKET TRACK *See page 14*

Global Diabetes Device Market Opportunity



Analytics 4 Life: Using AI to Diagnose Coronary Artery Disease at the Point-of-Care

Analytics 4 Life has been stealthy until recently, but on the eve of the completion of its clinical trials has unveiled a new modality that uses AI to measure disease, one that makes sense of electrical signals that can be measured noninvasively. The company's target application—coronary artery disease—checks off all the boxes of qualities required for the success of a disruptive and valuable application of AI, including a large clinical need, and a machine-learning application that can be trained by a sufficient volume of high quality input and outcomes data. If successful, the company will improve the efficacy, efficiency, and economics of CAD diagnosis.

by
MARY STUART

Artificial intelligence (AI) is one of the most exciting new technologies applied in the healthcare industry today. When complicated and massive sets of input data can be correlated with large, carefully curated bodies of patient outcomes data, machine learning, a type of AI, can do a far better job than humans at making sense of clinical patterns. And AI has the potential to make existing technologies—sensors, smartphones, cloud storage platforms, and medical imaging devices, for example—much more powerful.

Starry-eyed visions of AI look for it to predict the future—which patients will develop disease or exacerbations or symptoms of the diseases they have, or for computers to do the complex analysis to enable personalized patient care. Machine learning, or, the ability of computer algorithms to learn continuously from data, will certainly, and in the not-too-distant future, underpin all sorts of processes in medicine, whether directed at understanding the individual patient or the entire system of healthcare, from diagnosis to treatment, from precision medicine to population health.

Machine learning is already being incorporated into many medical applications where sufficient data exists, in terms of inputs and outcomes, to train algorithms, for example, in care pathways that involve medical imaging. Here, data captured by traditional imaging modalities like x-ray or MRI can be analyzed to identify patterns (the emergent condition pneumothorax, for example, from an analysis of x-rays, an application of **GE Healthcare**) more quickly than humans can, or, to reconstruct from two-dimensional data three-dimensional images that help improve surgical or other processes relying on visualization. (The latter is the goal of **Synaptive Medical**. *See "Synaptive Medical: Connecting Surgery, Imaging and Data to Improve Outcomes,"* The MedTech Strategist, *January 31, 2017*.) There are many such near-term applications under development in medicine today, which use machine learning to extract more clinical meaning from data that is already being gathered by conventional imaging, monitoring, or diagnostic technologies.

But one company, **Analytics 4 Life** (A4L), is using AI to develop a brand new modality for measuring disease, one that makes sense of electrical signals that can be measured from the body's surface.

And the company's target application—coronary artery disease—checks off all the boxes of qualities required for the success of a disruptive and valuable application of AI. First, there is a large clinical need. The process for diagnosing coronary artery disease (CAD), which is the leading cause of death across the globe, is not cost effective. It's an ideal application for machine learning, A4L's founders believe, because the company can access large volumes of clinical data and train it with reliable outcomes data derived from diagnostically effective but invasive coronary angiography—the ground truth in CAD diagnosis.

Founded in 2012, Analytics 4 Life has been stealthy. Nearing completion of a two-stage, 3000-subject clinical trial of its *CorVista* platform, which will happen at the end of November, and with the announcement of the raising of a large financing round, however, it is emerging from the shadows.

In late September, A4L announced that it raised $25 million in a Series B financing, bringing its fundraising total to date to $35 million. Its reliance on non-traditional investors, notes president and CEO Don Crawford, has helped the company keep its novel and disruptive technology under wraps until the appropriate time. "We have funded the entire project with a syndicate of family offices and accredited investors across the globe, including investors in Europe, Hong Kong and China," he says.

Crawford has executed this strategy successfully before, having garnered the same kinds of non-VC funding for Sapheon Inc., the developer of a device for the treatment of venous reflux disease, which he co-founded and led. Covidien (**Medtronic plc**) acquired Sapheon in 2014 for $238 million, seven years after its founding.

Indeed, ticking off the final—and most important—requirement for success, members of A4L's management team all have track records of success in the roles they've undertaken. Greg Davis, executive VP and chief operating officer, was the CEO of Tryton Medical, the developer of stents for bifurcations (its stents are now on the market with distribution partner Cardinal Health), and he subsequently founded Medcelerate, where he focused on supporting the growth and exit strategies of young medical device companies.

Analytics 4 Life founder and chief scientific officer Sunny Gupta possesses an unusual breadth of background in the disciplines important for medical applications of AI. Gupta is a polymath and engineer who studied bioengineering, electrical engineering, and computer science at the University of California-Berkeley and the University of Toronto. At the latter, he studied in the department chaired by Dr. Geoffrey Hinton, known as the 'godfather' of artificial intelligence. Hinton is now the chief scientific officer of the newly-created Vector Institute of Artificial Intelligence in Toronto. (A4L is housed in the same building as the Vector Institute, in **Johnson & Johnson**'s JLABS incubator. *See "J&J's New Approach to Innovation: An Interview with Bruce Rosengard,"* The MedTech Strategist, *May 12, 2017.)*

Artificial Intelligence Makes Sense of Novel Physiologic Signals

Sunny Gupta came to Analytics 4 Life with both a background in biomedical signal processing and a personal interest in studying heart disease, for family reasons. He sought to collect electrical energy signals produced by the body (the brain and heart in particular) in a unique way, process them mathematically, and employ computer science to analyze them and create images of the heart.

The company's technology operates on a study of mathematics and physics called phase space, a method for representing states of dynamic systems, which has previously been used, for example, for studying particles in accelerators, or the propagation of light. A4L's proprietary approach to this field is *Phase Space Tomography*, and the first medical application that employs AI with *Phase Space Tomography* is *CorVista*. This technology is covered by multiple issued US patents (with other patents pending).

Phase Space Tomography "can't be easily explained by waving your arms and pointing to pictures," admits Crawford, but very simply, he says, the company creates multidimensional images of voltage gradient data captured from multiple viewpoints on the body using computer reconstruction. "Phase space is a science that takes a time-series of data, and through mathematical manipulation, removes the element of time, creates a plot or a graphical image of energy data, and superimposes it onto a 3D image."

By way of illustration of the concept underlying phase space modeling, Greg Davis describes the pendulum. "The pendulum is one of the simplest examples of a dynamic system. As it swings back and forth, if you were to record the position of the end of the pendulum over a one-minute period of time, you would see an arc or a line. Every single point in that arc and line is a data point. But if you plot position versus velocity, you take the element of time away and will see a full circle that represents the back-and-forth movement of the pendulum. This circle represents every phase of the dynamic system." The heart is a much more complicated dynamic system but the principle is the same. By measuring the phase shift or the movement of many points of energy and applying machine learning to the millions of data points collected from a patient, the company aims to come up with images that reveal ischemic regions of the heart.

Davis notes that significant coronary artery disease (defined by the American College of Cardiology as any major coronary artery that is blocked by 70% or greater), restricts blood flow to the heart tissue beyond the blockage, causing ischemia. A4L's *CorVista* is thus a functional assessment; it is measuring the impact of blocked arteries on the heart muscle.

Today's CAD Diagnostic Paradigm: Inefficient, Costly, and Burdensome for Patients

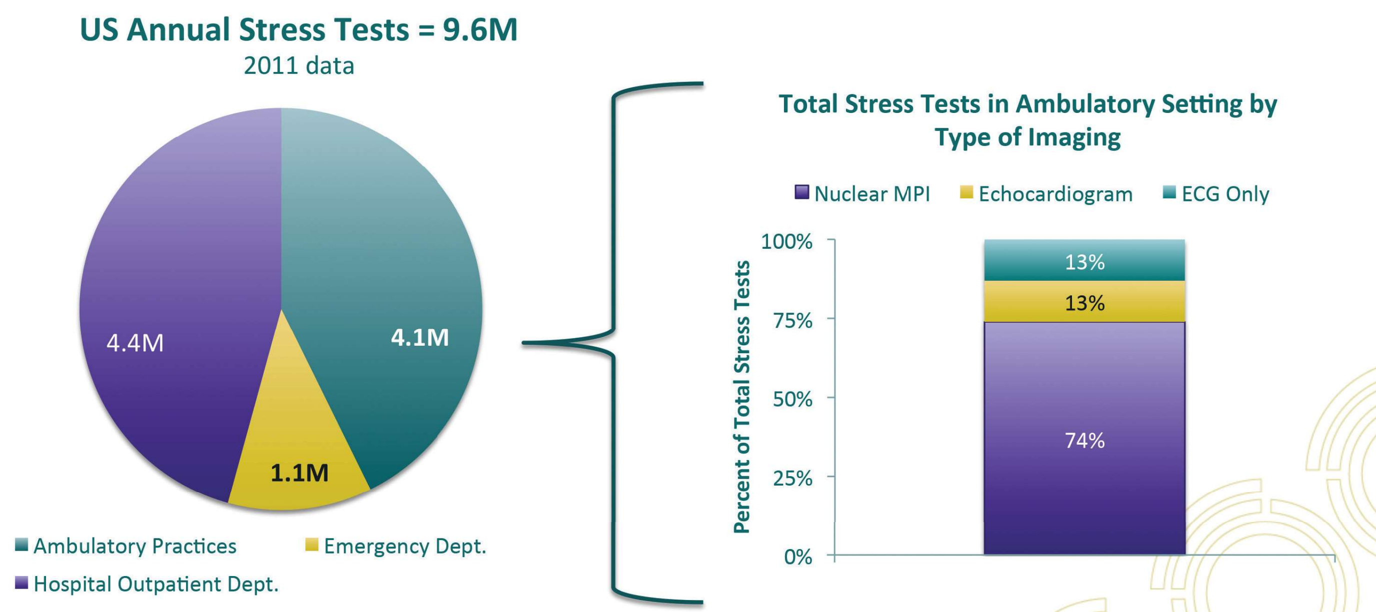
Surprisingly, although cardiology is often regarded as the most advanced specialty in medicine, particularly with respect to the diagnostic and therapeutic tools that have been developed over the past 30 years, the process of diagnosing CAD is still quite flawed.

Coronary angiography is indeed a powerful diagnostic tool; it shows physicians images revealing the extent and location of blockages in coronary arteries, and also gives them a chance to treat those blockages on-site in the catheterization lab. But it's an invasive, expensive procedure. As such, patients flow through one or several non-invasive diagnostic modalities prior to cardiac catheterization—ECG Stress Test, Stress Echo, Nuclear Stress Test, CT Angiography or MRI Angiography—to

Figure 1

US Annual Volume of Stress Tests

Nearly 10 million stress tests are performed in the US per year, mostly in the ambulatory practice and hospital outpatient settings. In ambulatory practices, nearly 75% of stress tests are myocardial perfusion imaging (nuclear stress) tests; at that rate, the number of US nuclear stress tests exceeds 7M per year.



S2N 2012 National Ambulatory Medical Care Survey
2012 National Hospital Ambulatory Medical Care Survey (NHAMCS)
Madsen T et al. Utility of the emergency department observation unit in ensuring stress testing in low-risk chest pain patients. Crit Pathw Cardiol. 2009

Source: Analytics 4 Life

determine eligibility for the cath lab based on their likelihood of having significant CAD worth treating. This protocol has shortcomings, since, after many layers of testing that delay definitive diagnosis and increase healthcare costs, only 30-40% of patients who get a diagnostic angiography actually have significant disease.

Each year, some ten million patients (in the US) go to their healthcare providers or the emergency room with cardiac symptoms such as chest, jaw or arm pain. The clinician will look at the patient history and risk factors for cardiac disease, and if the patient appears to be in an intermediate to high risk group, will refer him or her to a cardiologist for testing. The first test might be a basic ECG stress test, which involves monitoring the heart while a patient runs on a treadmill for 10-15 minutes. Or, the cardiologist might recommend a nuclear stress test, which might mean that the patient has to schedule an appointment at another facility that has a nuclear cardiologist on staff. There might be some time lost between the referral and the actual testing appointment. The patient has to fast the night before, have blood drawn in the morning of the test, and, after nuclear isotopes are mixed in with the blood, which is reinjected into the patient, to endure a period of waiting—an hour or more—for the distribution of the isotopes throughout the body.

"That's an expensive test, at $750-$1500 per procedure," says Crawford, "and you have to recognize that from the time the patient first complained of symptoms to the test result, we might be talking about two or three weeks." According to the company's estimates, there are seven million nuclear stress tests in the US each year, accounting for more than $5 billion in costs to the healthcare system (*see Figure 1*).

If, as a result of the nuclear stress test, the cardiologist deems the patient to be at risk of significant coronary artery disease, then the patient is referred for a coronary catheterization, perhaps involving a different facility, a different clinician, another period of waiting, and another procedure fee of approximately $2,000-$3,000. At that point, the patient has probably been worked up for a number of weeks, maybe even a month or more. "After all of these diagnostic tests by a number of physicians, you would think that by the time you got to the cath lab, there would be a high probability that you have CAD, right?" says Crawford. Not so. "Roughly 60-65% of patients don't have disease that needs to be treated in the cath lab, after all of this workup, expense, and anxiety."

That was the problem that Analytics 4 Life set out to solve, and it's well on its way to offering a solution.

Off-the-Shelf Sensors Yield an Advanced Diagnostic

CorVista's workup begins with off-the-shelf sensors, which are placed in a three-dimensional configuration on the body in order to collect voltage gradients from the surface of the body. That allows the system to make measurements from six different viewpoints, all synchronized to within ten femtoseconds. Over the course of the 3-minute testing period, the system gathers 10 million data points. The large volumes of data can be collected and used to train computer algorithms that identify patterns of disease. The company developed its machine-learned algorithm by pairing physiologic signals from about 1500 patients with clinical outcomes data.

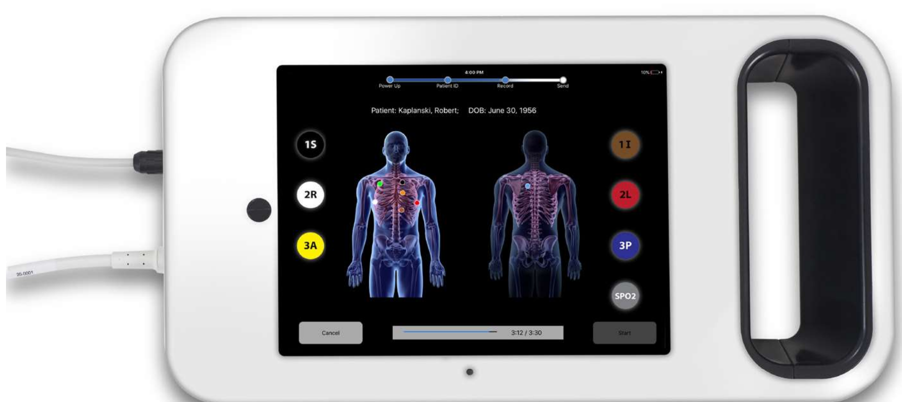
Using *CorVista* is straightforward. A hand-held device, called the *Phase Signal Recorder,* collects the signal data from the patient and transmits it to a secured, cloud-based repository called the *Phase Signal Data Repository (see Figure 2).* From here, the machine-learning-based algorithms analyze the data in the cloud to identify and display the probability of ischemic regions in the heart in the form of a graphical report for physician interpretation.

Although Davis notes that none of the hardware components are novel, the company did configure a highly sensitive device that incorporates the sensors, recording electronics, and radios for wirelessly transmitting data to the cloud. In

Figure 2

PSR Signal Collection

Caution—Investigational Device. Limited by Federal Law to Investigational Use. CorVista™ is not available for commercial distribution.



Source: Analytics 4 Life

addition, the company's approach to processing, analyzing and reporting the data back to physicians is innovative, yielding, in a timely fashion, a report that the company hopes will enable physicians to assess the presence of disease related to significant blockages and recommend further treatment in a single office visit (*see Figure 3*).

Quality of Data is Key

As noted, the company is just about to wrap-up the second stage of its clinical trial conducted at thirteen sites across the US. The pivotal stage of the study is a prospective, blinded, non-randomized, paired comparison trial to test the machine-learned algorithm's ability to detect significant CAD, as verified by results obtained through a cardiac catheterization procedure. The trial is enrolling patients who complain of CAD symptoms and who were already referred to catheterization, while excluding any patients that have already been diagnosed with CAD.

In this study, before the catheterization procedure, patients receive a *CorVista* scan. They subsequently undergo a coronary angiography procedure that "gives 100% truth on the status of that patient," says Crawford, by showing which arteries are blocked and which aren't. "We are essentially in the final stages of a pivotal trial, and we expect to submit all of this data in a *de novo* 510(k) application in the first half of 2018."

Davis notes that the company is in the advantageous position of being able to use patients as their own controls, "so all 30 billion data points collected from subjects are source-verified prospective data. For every subject, we can tell you the exact time, the patient, the physician, and the location of that recording." Crawford adds, "The fidelity of our clinical data is almost unsurpassed in this new field of medical machine learning, and that will become one of our key identifying factors going forward."

Just the Beginning

The company is waiting for the insights from its clinical trial, and then the large task of developing the market will begin on its first application. And additional potential applications for its platform lie ahead—assessing heart failure and neurological diseases, for example.

Crawford notes that, as with any new medical technology, physicians will need time to learn how to work with the new data and images, just as they had to do when MRI was introduced 40 years ago. It will also take experience with the new modality to determine where it fits in the care pathway.

*CorVist*a won't entail significant capital investment; it will be offered on a fee-per-test service model based on its cloud computing platform. "Practices won't have to maintain expensive equipment, or keep extra highly trained technicians on staff," comments Crawford, "and patients won't have to undergo injections of contrast agent or schedule appointments in different facilities." If it works, and Crawford claims that clinical trial results to date look promising, *CorVista* could possibly enable the treating physician to determine, at the first visit, whether the patient is a candidate for angiography or not. The economic implications would be great, not only because it might help diagnose disease sooner so that it can be treated in a timely manner, but in terms of the avoidance of additional test costs (as much as $1500 for a nuclear stress test, as noted above).

As its initial market strategy, says Crawford, "We are not trying to replace other tests. We are providing the clinicians with another tool they can work with. Of course, over time, they, and hospital systems might find out that it's easier to administer, and that the quality of the service is more desirable."

Clinical trial data will be out soon. And if all goes well, Crawford says, "We have a trifecta—we are benefitting the patients, providers, and payors."

Figure 3

Physician-Patient Consultation CorVista Portal

Caution—Investigational Device. Limited by Federal Law to Investigational Use. CorVista™ is not available for commercial distribution.

Source: Analytics 4 Life