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## CLEERLY'S PERSONALIZED APPROACH TO HEART ATTACK RISK

Despite advances in cardiology, most heart attacks occur without warning. Cleerly has developed a cardiology care management system, based on image analysis and AI, to help clinicians personalize a patient's heart attack risk so they can determine who needs intensive management—and who doesn't.

MARY STUART

eart disease is the number one killer in the world, an unsolved problem that has inspired much innovation from the pharmaceutical and medtech industries. But despite many advances, the field of cardiology is still not good at understanding which patients are most likely to suffer a myocardial infarction.

We've all had the same experience: someone we knew who seemed to glow with good health who then died unexpectedly of a heart attack; the thin, active, healthconscious person who went out for a run and never came back. In fact, more than half of all heart attacks occur in people in whom there were no warning symptoms, and after the event, outcomes are rarely good. Approximately one-third die within the first month, onethird go on to develop heart failure, and only a third survive without major complications and go on to live a normal life.

For cardiologist James Min, MD, that personal experience happened when he was taking care of critically ill patients in the ICU. He faced a young man, 36 years old, who'd had a massive heart attack. The patient survived, but Min thought, "I'm on the wrong side of the healthcare curve; I need to be on the preventive side rather than treating late-stage disease."

Min, an expert in coronary artery disease, took action. He co-founded the prevention-focused HeartHealth program, a collaboration between the Dalio Institute of Cardiovascular Imaging at NewYork-Presbyterian Hospital (for which Min served as the director) and Weill Cornell Medicine. "Our HeartHealth program took a very different approach to preventing heart attacks than other preventive programs," Min says. Fast forward several years and, "with four faculty members taking care of some very sick people, we never witnessed a single heart attack in our patients."

The program's secret was its focus on quantifying and characterizing actual heart disease—which is the atherosclerosis that builds up silently in the walls of the heart arteries—rather than on indirect markers of heart disease. The historical approach to cardiovascular prevention has relied upon surrogates of heart disease, such as risk factors like cholesterol, blood pressure, diabetes, and smoking.

At the core of the HeartHealth program was an analysis of a patient's heart through a noninvasive coronary computed tomography angiography (CCTA) scan. "Through an array of multicenter clinical trials we performed when we were in academic medicine, we learned what was most important for pinpointing and quantifying cardiovascular risk." Interestingly, Min says, when researchers ranked the features in order of importance, the top features were all related to the amount and type of heart disease a patient had, rather than how old or young the patient was, whether they were a man or a woman, black or white, or whether they had a comorbidity like diabetes.

In addition to providing patient care, the team also designed a series of clinical trials to see how different types of plaque affected outcomes, and what measures could influence the natural history of the disease to reduce heart attacks.

As noted, the HeartHealth program worked; it prevented heart attacks in an at-risk population. Unfortunately, it wasn't a scalable approach to patient care. The image annotation alone required many hours per patient. "We could do that, because we had the luxury of being supported by a very generous philanthropic donor," Min notes. "We had 20 CT technologists just circling images all day long."

To help this new medical paradigm reach a wider audience, Min founded **Cleerly Inc.** in 2017 to create the needed scalability with a software solution. Using millions of annotated CCTA images, the start-up created algorithms to quantify and characterize atherosclerosis and all its attendant features. "We wanted to standardize and personalize the approach to heart disease through an end-to-end closed-loop care pathway that would enable us to consistently identify and characterize, educate, implement, treat, and track disease over time to prove therapeutic success in patients before they suffer a heart attack event."

To date, Cleerly has raised about \$60 million in two financing rounds with the participation of venture capital investors Vensana Capital, LRVHealth, New Leaf Ventures, DigiTx Partners, and Esplanade Ventures. Clinically focused investors include Cigna Ventures (the venture capital arm of the health insurance company), and the American College of Cardiology.

### **Precision Heart Care**

If you want to prevent heart attacks, notes Min, "Symptom-based care isn't an ideal approach, because then you are looking for late-stage disease. If you only look for symptoms, you will miss the majority of people who suffer heart attacks with no antecedent warning."

Cleerly's goal is to provide clinicians, patients, and other stakeholders with decision support derived from the most relevant information—the presence, quantity, and type of atherosclerotic plaque in a particular patient far enough in advance that prevention is still possible, when patients can change their habits and at a point when clinicians can intensively treat those who are at the highest risk to alter the course of the disease.

In 2007, Min made a television appearance on The Today Show. When discussing then co-host Matt

Lauer's coronary CT scan, Lauer asked if what he saw on the image was "the good or bad kind of plaque." Min recalls that he answered that there was no such thing as a "good" plaque. "But I was wrong. Some types of plaque are unstable and dangerous, and these are the strongest predictors of heart attack. There are other plaques that are very stable and safe and might even protect against heart attacks." Some patients in the HeartHealth program had serial CT scans over the course of several years, and Min says clinicians learned that intensive patient management didn't make the plaques go away but it did result in changes of the composition and morphology of the plaques." They turned unstable into stable plaques. This is personalized care. Precision heart care."

With multiple 510(k) clearances in hand, Cleerly now offers a digital care platform that generates reports for all the stakeholders in the care pathway, including clinicians—such as primary care physicians, advanced practice providers, cardiologists—and imaging specialists, to help them understand the importance of the disease phenotype without needing expertise in advanced imaging.

Indeed, Justin Klein, MD, a co-founder and managing partner at Vensana Capital (which, as noted, is a Cleerly investor) believes Cleerly's software approach will help clinicians who read and interpret cardiac CTs do a better job, and more swiftly. "It would take about eight hours for a radiologist to read and curate every part of the coronary tree the way Cleerly's system does, so they have to focus only on the vessels they perceive are most relevant to patients' symptoms." In minutes, Klein notes, "Cleerly can get a read on the entire coronary tree and generate multiple types of reports for different stakeholders with the perspective and level of detail they require."

Patients also get a report (geared to a nonmedical layperson) so they can fully understand the test and their results, and what that implies for their risk going forward. Quantitative tools available through Cleerly's digital care pathway enable patients and their care team to track heart disease changes—both good and bad—over time to help patients and physicians personalize guidance of lifestyle changes and medical treatment.

Although Cleerly's system offers information that was never before clinically available, it still operates seamlessly within the existing medical workflow and guidelines. Cleerly comes into play when patients present with chest pain, at which point they should undergo a CCTA scan, the basis for Cleerly's analysis. In 2021, the American College of Cardiology and the American Heart Association issued a Level 1A recommendation based on the highest quality evidence for the use of CCTA in the evaluation and diagnosis of chest pain, which is a strong secular tailwind for the start-up in driving CCTA uptake. "We can improve the diagnostic certainty and the kinds of information that can be extracted from the scan," notes Min. In this regard, Cleerly is useful for all patients across the entire continuum of disease severity, which is a big reach for a start-up.

## The Entire Continuum of Care and Stakeholders

It would be great to prevent myocardial infarctions in asymptomatic patients by identifying their risk—that is, to address those numerous times when death from a heart attack was the first symptom—but that is a quite distant screening application, and not the company's business model. In the fee-for-service model, "You just can't get payors to adequately cover early diagnosis and prevention," says Min.

But stakeholders operating in value-based healthcare delivery models find Cleerly particularly attractive. "For organizations that are either at risk and/or capitated, there is a finite bucket of resources allocable to heart disease evaluation and treatment. If you want to reduce costs and improve outcomes at the same time, the answer is simple: focus on prevention," Min advises. Under those scenarios, he notes, "All of the clinical and economic incentives are aligned to keep the patient healthy, to get the disease treated as early as possible, and to do that with the minimally invasive interventions that are the least expensive," goals that Cleerly serves.

So far, says Min, the company has experienced a warm reception in value-based healthcare delivery models such as ACOs (accountable care organizations), at-risk provider networks, Medicare Advantage, and self-insured employers. "There are a lot of places where prevention and keeping people healthy adds marked value and reduces cost." He notes that the start-up's first two large accounts were major self-insured employers, and that in a few fee-for-service models Cleerly takes on risk, which aligns with the company's values. "We get paid if we deliver value, both clinical and economic," Min says.

To gain reimbursement for the fee-for-service environment, the company has generated a large data corpus of scientific evidence. "We were founded on science, and we will always stand for science."

Meanwhile, Cleerly has launched several large-scale clinical trials. "These landmark studies serve as a foundation to help us constantly adapt to new technologies in the marketplace and new medications that might be developed," Min explains.

The company recently enrolled more than 10,000 patients with known multiyear outcomes, including some who have undergone serial CT scans, to learn how disease phenotypes correlate to outcomes, and how treatments influence disease outcomes. The start-up has also designed a series of large-scale multicenter trials to prove the diagnostic accuracy of its platform "against every conceivable gold standard," Min notes, including expert readers, quantitative coronary angiography, intravascular ultrasound, fractional flow reserve, optical coherence tomography, and nearfield infrared spectroscopy. Min points out that two of those studies have been published in the Journal of Cardiovascular Computed Tomography and the Journal of the American College of Cardiology, with the rest publishing soon.

Cleerly has also launched an international multicenter registry called CONFIRM2, which will enroll up to 200,000 patients with a follow-up of at least four years to evaluate associations between its CCTA image findings, clinical presentations, and the software's ability to identify heart attack risk.

In terms of stakeholders on the strategic side, Justin Klein notes that a broad array of companies might be interested in Cleerly's platform. "You could imagine interest from imaging device companies involved in the coronary cath lab, or companies developing stents and interventional cardiology tools. This is an important category for them, given the patient volumes and the magnitude of the clinical need."

Pharmaceutical companies developing drugs for cardiovascular diseases or diabetes could—and have, Klein points out—used Cleerly to determine how their drugs might be disease-modifying for atherosclerosis, because of Cleerly's ability to track longitudinally. Finally, "Payors and providers, frankly, are embracing this whole approach to being more proactive and less costly to deliver better, personalized cardiovascular care," Klein says.

As noted, Cigna was one of the co-investors in the most recent financing round. Cigna isn't just focused on fee-forservice insurance and Medicare Advantage; it also has an interest in benefits management, where it would like to optimize its spend for cardiovascular care and diagnostics.

## The First Digital Care Pathway to Prevent Heart Attacks

Two decades ago, there was a great flurry of innovation around the detection of "vulnerable plaque." The idea was that if we could identify a bad plaque most likely to rupture and cause a thrombotic event—it would look like an inflamed pocket of lipids with a thin cap—we could treat it and avoid a heart attack. As noted in the list of detection modalities that Cleerly is comparing its platform against in terms of the diagnostic accuracy of



\$36,000,000 Private Placement

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Internally, Min says, Cleerly's team often asks the rhetorical question, "Do you ever wonder why we use noninvasive imaging to prevent the most common cause of cancer, but not the most common cause of death?" The answer of course, is that now we should.

its algorithms, many of the technologies born in the era of vulnerable plaque exist in cardiology today—intravascular ultrasound, optical coherence tomography, and near-field infrared spectroscopy. But the notion of vulnerable plaque is limited and the term obsolete.

Many things come together in the etiology of a heart attack, Min notes. "There might be a situation—a patient is shoveling heavy snow and suffers a heart attack. You can't predict that by simply looking at an image. There is also an inflammatory process—images can't help you much there either. A heart attack also requires a thrombotic event. Blood has to clot, and we can't see that in advance, either." There are too many unknowns to accurately identify a vulnerable plaque, Min says, but the totality of all the dimensions of data offered by whole-heart disease phenotyping allows the precision to support physicians in identifying those at higher and lower risk. "The high-risk plaques we have identified in our prior research are the strongest early predictors of who will have a heart attack and who won't. We can get extremely important clinical information when we comprehensively characterize and quantify the disease process."

When asked who or what Cleerly's competition is, Min says that in early discussions (before they completely understand what Cleerly is doing) potential partners or investors might compare Cleerly to imaging or software companies using artificial intelligence to increase the diagnostic yield of CT (and MedTech Strategist has written about a few; see, for example "Cardiac AI Pushes Human Limits," MedTech Strategist, January 25, 2021). But Cleerly is not an imaging company. "We are a personalized, standardized, comprehensive care management platform. We identify and characterize disease and we help to educate all the medical stakeholders—nurses, primary care doctors, and cardiologists—so they can treat according to the stage of the coronary disease and track quantitatively to prove therapeutic success. And in the case of failure, medical professionals and patients can intensify therapy and lifestyle changes until they achieve success." In short, it is precision heart care to support the personalization to heart attack prevention. Min says he doesn't see any competition in terms of companies offering similar products.

Justin Klein notes, "We do see barriers to entry based on how Cleerly's proprietary AI-based algorithms and approach to cardiac CT were developed, and the types of clinical trials they've done to validate their algorithms. We think we have a nice first-mover advantage in this approach, and a technology advantage over what others could do to try to replicate these products."

#### **Prevention Is Possible**

While Cleerly has introduced the first digital care pathway for the prevention of heart attacks, in oncology, the second most fatal disease after coronary artery disease, this paradigm already works well. Min finds direct parallels between oncology and cardiology. "Heart disease is not a single disease, any more than cancer is. There are many different kinds."

In oncology, early detection, and an assessment of the extent of cancer are accomplished by imaging; cancer is then characterized and staged by other innovative tests—biomarkers and liquid biopsies, for example. Therapy can be personalized, and the response to treatment assessed using serial imaging.

Internally, Min says, Cleerly's team often asks the rhetorical question, "Do you ever wonder why we use noninvasive imaging to prevent the most common cause of cancer, but not the most common cause of death?" The answer of course, is that now we should (see Figure 1).

Min sums up why: "One, we now have a safe, accurate, and noninvasive tool that can comprehensively extract disease phenotype. Two, there is a full toolbox of treatments—if there were only one treatment, we would just give it to everybody. But we have a dozen classes of medications we can use to effectively treat atherosclerosis. Three, we never understood the vascular biology until we looked at heart disease longitudinally, and now we understand that it is a dynamic process that changes over time to higher- and lower-risk states."

Having met those three criteria, he says, "We are ready to systematize early diagnosis and prevention." But, he adds, "I dream of the day where we have the sufficient evidentiary foundation and policy guidelines for universal screening for heart disease in a manner similar to the way we screen for breast, colon, and lung cancers."

In the near future, the company is focused on commercial execution, on "working with the right customers where we can offer the greatest clinical value in a way that reduces overall costs for the healthcare system. That will allow us to lead with an enormous clinical value proposition while ensuring economic attractiveness to our partners," Min says.

This year, Cleerly will submit additional products for FDA clearance, which are "unique products that have never before existed in the field of cardiology."

#### Figure 1

#### **Oncology Provides Model for New Paradigm in Coronary Artery Disease**

Cleerly's personalized approach to CAD prevention emulates the success in preventive care paradigms for cancer, including breast, colon, skin and lung, where a five-step process has improved patient survival.

#### **FIVE STEP PROCESS**

**01** EARLY DIAGNOSIS THROUGH IMAGING In oncology, imaging includes mammography, colonoscopy, skin examination, and low-dose chest CT. In the CAD paradigm, comprehensive coronary phenotyping by noninvasive CCTA (Cleerly analysis) helps the cardiovascular clinician to determine and address cardiovascular disease risk.

In oncology, disease stage is determined by the presence of tumor,

presence, extent, and severity of disease. In the CAD paradigm, this

is accomplished through evaluation of plague burden, type, location,

and vascular remodeling, as identified through the Cleerly analysis.

lymph node involvement, and metastasis, which represents the

02 STAGING OF DISEASE

**03** CLASSIFICATION OF TYPE OF DISEASE

> 04 PERSONALIZED MEDICINE

05 response assessment In oncology, the disease type is classified through imaging, histopathology, and/or genetics. In the CAD paradigm, CCTA-based quantitative "virtual histology" of plaques within all coronary arteries and their branches is performed by the Cleerly analysis.

In oncology, staging and classification of disease guide treatment decisions for surgery or adjuvant chemotherapy. In the CAD paradigm, the ACC Innovation Prevention Working Group has defined a logical stepwise pilot approach to CAD prevention based on the Cleerly analysis. This approach integrates the totality of contemporary medications and evidence to support individualized treatment.

In oncology, assessment of therapeutic response is performed using serial imaging. In the CAD paradigm, serial CCTA (Cleerly analysis) can be performed when indicated to assess whether the disease has stabilized or is progressing. The algorithm would intensify therapies when needed.

Source: "A Digital Care Pathway to Prevent Heart Attacks," Cardiology Magazine, February 19, 2021, American College of Cardiology, Innovation at ACC

The company will continue to build on its evidence with studies like those cited above. Says Klein, "This is definitely a paradigm-changing opportunity, and there is a lot of work for us to do." But Klein likes one aspect that makes things easier. "Because this is a software solution, there is a very scalable opportunity here, and by that, I mean that software can be deployed in a bunch of different ways, on site, at imaging centers, or in the cloud. It is an efficient way of going to market when you have a significant volume of patients to manage."

Min, the mission-driven clinician and patient advocate, says, "What we understand about vascular biology is pretty constrained to middleaged white males," who have historically represented the bulk of participants in clinical trials. "Women present differently than men, and disease might present differently among blacks, whites, Hispanics, Asians, and other populations. So, by personalizing heart care, we end up democratizing it. We look at each person as an N-of-1, not an N-of-million. That allows us to hone in and treat someone as an individual rather than a population." MTS

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