APRIL 2025 | Vol. 12, No. 4

MedTech STRATEGIST

Type 2 Era to Transform US Insulin Pump Market

Mary Thompson

The Unique View of the Surgeon-Scientist: Luis Savastano

Mary Stuart

Start-Ups Overcome Drug Delivery Drawbacks

Colin Miller

The Viscogliosis' Holistic Approach to Back Pain

Wendy Diller

THE UNIQUE VIEW OF THE SURGEON-SCIENTIST: LUIS SAVASTANO

Vascular neurosurgeon Luis Savastano brings a unique perspective to device invention as he straddles the surgical and endovascular worlds. While practicing medicine, he spends equal time on translational medicine. We profile two of the start-ups he founded, Endovascular Engineering and Endovascular Horizons.

▶ MARY STUART


LUIS SAVASTANO

Because surgeons and other interventionalists work directly with patients, they are in the best position to understand problems in medicine long before innovators in academia or industry go to the drawing board to invent the tools that might advance care. Cerebrovascular surgeon Luis Savastano, MD, PhD, is perhaps the rare clinician who delivers those solutions himself, as the founder of two start-ups, **Endovascular Engineering** and **Endovascular Horizons**, both profiled below, spending as much time on translational medicine as on clinical practice.

Referring to himself as a hybrid vascular neurosurgeon, he treats problems of the neuroanatomy and is part of a select group of clinicians in this country—just a few dozen—who possess both endovascular and microsurgical skills for treating conditions of the brain and spine. Says Savastano, "It's a long, hard training to get there, but you can provide unique care to patients, because you have no bias one way or another. You understand both options—surgery and endovascular—and you can choose what is best for that patient, because there are always subtleties."

The hybrid perspective also lends itself to out-of-the-box thinking when it comes to innovation. "We have the skill sets to fix a problem, both from an open surgical approach or an endovascular approach. Being able to see things from both sides helps you understand the limitations and the opportunities for innovation and breakthrough."

His start-up Endovascular Horizons, which has a novel way of providing transvascular access to the brain, is a great example of that dual perspective. When neurosurgeons do surgery to drain subdural hematomas, a situation where blood pools on the surface of the brain, one of the most common neurosurgical problems, "We are looking at the vasculature, the brain, and fluid collection from the outside. When we do endovascular embolization of the middle meningeal artery [to dry up the subdural membranes and prevent further bleeding], we see the inside of the arteries by injecting contrast and navigating tiny catheters and wires from a peripheral access. There is only a millimeter of tissue separating both spaces, and that's what we bridge with the technology we've developed," he says.

Savastano was born in England, grew up in Italy, and moved to Argentina, where he completed medical school at the Universidad Nacional de Cuyo, graduating as valedictorian and first of his class at age 23. There, he again distinguished himself from other medtech inventors by gaining a firsthand understanding of the architecture of the human body through his work as an assistant professor of anatomy. "In parallel with medical school, for seven years I was a member of the Anatomy Dissection Academy, a group of medical students and anatomists who do prosections of human cadavers for research and to teach medical students anatomy," says Savastano. In contrast to the usual representations of anatomy in the textbooks that medical students rely on, "I was learning, from hundreds of dissections in human cadavers, how the human body is really constructed. When you dissect, you go layer by layer, which gives you a fundamental understanding of the relationships between different parts of the body, structures and organs."

After finishing his MD in 2009, Savastano went on to earn a biomedical engineering PhD at his alma mater, with a *summa cum laude* thesis focused on intravascular imaging. In 2012, he joined the University of Michigan in Ann Arbor as a neurosurgery resident, where, while gaining a surgical education, he started his entrepreneurial journey. Because of his background in intravascular imaging, Savastano was recruited as a scientific adviser and eventually chief medical officer of VerAvanti, a company working on a new breakthrough optical technology based on scanning fiber endoscopy. "At VerAvanti, I was very lucky, so early in my career, to be exposed to seasoned medtech executives like CEO and founder Gerald McMorrow," who previously brought the *GlideScope* and *BladderScan* devices to the international markets as CEO of Verathon. "I started to understand how device start-ups are structured, the different roles in the team and how they evolve overtime, and the complexities of going from early prototypes to clinical use." Things that you don't learn in medical textbooks, he says.

A Clinician Becomes a Scientist

In 2015, as Savastano was doing a fellowship in endovascular neurosurgery at the University of Michigan, he ran a translational research group. Around that time, the landmark clinical trials (MR CLEAN, ESCAPE, EXTEND-IA) studying a new category of stroke thrombectomy devices from **Medtronic** (Covidien, at the time), **Stryker**, and **Penumbra** were published. Savastano says he had a lot of exposure to the devices during his fellowship. "When we were able to open the arteries early, it was almost a miracle. The patients bounced back."

But back in 2015, the devices failed to lead to reperfusion in 30-40% of patients, and sometimes it took hours to achieve success. "There was clearly an opportunity to make a huge difference by improving the technologies and the techniques."

Savastano stresses that he was fortunate, because the University of Michigan "has a tremendous engineering

college and university next to the hospital, and there was a particular mechanical engineering lab that was keen to work with physicians." A team of engineers was assembled with the goal of understanding why and how thrombectomy devices worked, and how they failed. "The team fit was perfect, as we all shared the same passion for testing and building new tools."

The team started by collecting all the clots that were removed from patients during stroke thrombectomy procedures and subjecting them to mechanical testing to understand how clots behave under the application of mechanical forces. Savastano recalls, "Days were long, but I never had so much fun." By day, he says, he was a neurosurgery resident at the hospital, assisting the staff surgeons with cases and collecting clots and devices. "At night, I would head to the engineering lab, where the team had all the models ready to test the devices I had used earlier that day."

The team created phantoms, human cadaver models, and clot analogs to study the mechanism of action of the devices that were then being used in hospitals. "It was basically grab and pull; you navigate the arteries, grab the clot, and pull it out," he continues. It wasn't a perfect solution; they discovered, for example, in the process, there was the potential to damage the vessel or to fragment the clot so part of it remained behind.

That work had two fortuitous consequences for the translational team, Savastano explains. "First, because we published the work and models we'd developed and validated, many start-ups and big companies came to our lab to test the devices in their development pipelines, new catheters, new stents." Second, the team of engineers and the neurosurgeon realized that there might be a better way to remove clots than by grabbing and pulling. "Maybe we could instead navigate a small catheter to the clot and ingest the clot *in situ* without pulling on it, rather than having bigger and bigger catheters like everyone else." They envisioned a small catheter that, once navigated to the clot, could capture, ingest it, and remove it. "That's how we conceptualized and invented a new thrombectomy technology, which is a suction catheter that engages the clot and reshapes it, so it can travel down the catheter." That was the invention around which Endovascular Engineering was founded as a spin-off from the University of Michigan, and how Savastano became a physician-entrepreneur.

From Idea to Patient in Five Years

After Savastano completed his neurosurgery training in 2019, he spent three years on the faculty at the Mayo Clinic (Rochester, MN). He was subsequently recruited by the University of California, San Francisco (UCSF). "My job at both institutions was to be a 'surgeon-scientist' blending a busy clinical practice—hundreds of cases per year—with the running of a translational research lab, which in my case was very focused on understanding and developing new surgical technologies and procedures." Today he heads the multidisciplinary Transcatheter Neurosurgical Technologies Lab (TNT, for short) at UCSF, which brings together physicians, neurosurgeons, biomedical engineers, mechanical engineers, CAD engineers, and materials scientists. "And of course, we collaborate throughout the institution and with other institutions as well."

TNT uncovers major unmet clinical needs in the hospital, the OR, or at the bedside, he says, and does fundamental translational research and incubates new technology. The solution can be a new device, a new procedure, or both, that impacts clinical care. "The goal is to close that cycle within five years, that is, from idea to patient in five years."

Savastano urges more clinicians to become involved in creating the solutions to the medical problems with which they, in directly caring for patients, are intimately familiar. "This is super exciting, and it's not necessarily 'pie in the sky.' All physicians want to help patients, and through innovation we can have a tremendous impact, in our lifetime." A surgeon helps one patient at a time, he continues, "but when we develop a new device or technique for something that didn't have a cure before, we can potentially affect hundreds or thousands of patients for generations. You make a huge difference."

Writing patents, prototyping new products, benchtop and animal testing, planning and executing clinical trials and fundraising are often outside a clinician's core skill set. "They will certainly need a multidisciplinary team behind them. It takes a village to make this happen!" Savastano admits. But that shouldn't discourage would-be physician-entrepreneurs. His message to them: "You are not alone. There are probably lots of resources at your institutions, for example, the office of tech transfer, or if you're at an academic institution, there are likely to be scientists and engineers willing to team up with you."

Before undertaking the journey, Savastano advises physician-inventors to make sure they use their unique domain expertise and perspective to truly understand what is happening in their patients. "Medical problems are typically complex and easier to unravel when deconstructed in smaller chunks."

After doing that exercise and reaching the root cause of the problem, "think about solutions, try to build the simplest one, and test it over and over." That can be done in many ways, he continues, like creating phantoms that are easily controllable, before moving on to cadavers, then animals, while optimizing the device along the pathway. "You will find a thousand ways that the device doesn't work and learn tremendously in the process. If you persist, you are eventually likely to generate the

proof of concept to convince more people to join your team, and to attract funding. And you keep moving."

Savastano cautions that "many things that we believe are new, probably even most of them, have been tried before, and have, for one reason or another, failed. So it's really, really important to understand what has been done before, so we don't repeat the mistakes of the past."

Finally, the inventor must adopt the mindset of "The Man in the Arena," he states, referring to a speech by Theodore Roosevelt that emphasized striving for worthy goals and taking action. "This is hard to do, and most things are not going to be successful, and by successful, I mean impacting the lives of our patients and their families in extraordinary ways." Only a minority of ideas get there. That being the case, "You have to know that it is something that is worth doing. You have to enjoy the journey; you can't be desperate to cross the finish line."

Which is, fundamentally, good advice for most of life.

Endovascular Horizons: The Dawning of a Transvascular Age in Neurology

Chronic subdural hematoma (CSDH), a bleed that occurs between the innermost layer of the skull and the brain, is one of the most common conditions neurosurgeons treat. In the US each year surgeons treat approximately 60,000 patients with CSDH to alleviate dangerously high intracranial pressure, most of them over the age of 65 (the incidence in that age group is 100 cases per 100,000 people). A subdural hematoma can happen to anybody after a head trauma, but the elderly are disproportionately affected because of the brain shrinkage they experience as they age, which stretches the veins bridging the brain to dura making them susceptible to rupture. In addition, older people are more likely to already have a higher bleeding risk because they're taking blood thinners for co-morbidities.

The conventional treatment for CSDH involves surgically drilling one or two burr holes in the cranium (or removing part of it) and aspirating out the clot and fluid. Following this surgical procedure, patients will proceed to the ICU with the drain protruding from the skull to complete the drainage process, where they will remain for one to three days.

Because chronic subdural hematomas have a high rate of recurrence within three months of the surgical evacuation procedure (20-30%, according to varying estimates), in the past 10 years a new intervention has been introduced to avoid re-bleeding into the subdural space by drying up the blood supply to the dura—embolization of the middle meningeal artery (MMA) to take it out of commission. Following the surgical drainage procedure, during the same hospitalization, the patient is transferred to the cath lab to have the minimally invasive embolization procedure.

Last year saw the publication of the results of at least four randomized clinical trials showing the benefit of this endovascular procedure. Embolise, which studied the *Onyx* embolic agent of Medtronic, demonstrated that the intervention lowered the CSDH recurrence rate from 11% to 4%. In the STEM trial (sponsored by **Balt/Boston Scientific**), administration of the *Squid Liquid* lowered recurrence from 36% to 16%.

Having firsthand experience with both these procedures, Luis Savastano, then a vascular surgeon and a professor of neurosurgery and radiology at the Mayo Clinic (Rochester MN), was bothered by the complexity of two different procedures in frail, elderly patients—two different medical teams for two different settings (the OR and the cath lab), both requiring anesthesia. "Now we have one patient with one problem and we're doing two procedures to fix the problem: surgery to drain the fluid and decompress the brain, and embolization to decrease the likelihood of re-bleeding," he recalls.

In causing the 70- to 80-year-old treatment population more discomfort and a longer hospital stay, a two-procedure treatment paradigm is not ideal. Ever the surgeon-scientist, Savastano asked himself, "What if we could drain the fluid differently?"

He considered, "If [during MMA embolization] we're already going inside the vessels with catheters and wires to block the artery, we could go further with an intentional perforation of the artery and drain the dura transvascularly."

That was the simple premise, he states, but executing it would be difficult. "There was no endovascular technology purpose-built to enter and cut through vessels that are long and thin, with vents and loops, very deep in the head. Predicate devices, models, phantoms, cadavers, and animal models didn't exist." Savastano and his team acknowledged the challenge.

At the same time, he says, every decade or so there is a breakthrough innovation in the brain. In the '80s and '90s, pioneers began placing wires and catheters inside the vasculature to accomplish aneurysm coiling, the occlusion of ruptured arteries, or the unblocking of arteries with stents and thrombectomy devices. "Those were endovascular procedures for vascular problems. That has been a great evolution for patients." But he continues, "We're still limited by vascular walls."

Breaking Through the Limits

Savastano wanted to kick off the next evolution in neurosurgery and neuroscience. "We thought if we could break that limit, the vascular wall, we could use the natural corridors of our bodies,

the arteries and veins, to get anywhere we want, even inside the head. We could exit the vasculature to treat non-vascular problems."

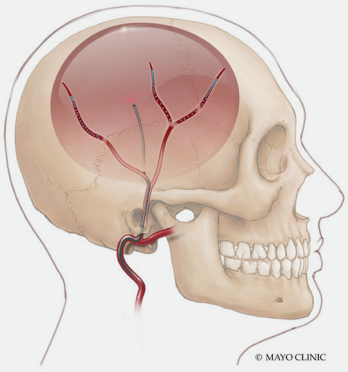
With a license from the Mayo Clinic to technology he invented, Savastano founded Endovascular Horizons in 2020. Its solution begins after embolization of the MMA to occlude distal vasculature using conventional endovascular access and techniques. After MMA occlusion, a proprietary wire is delivered through the catheter in the lumen of the MMA and is activated to perforate the artery wall and dura. The wire has safety features that allow it to self-orient and control the depth of perforation. An aspiration catheter is then guided through the opening in the MMA to the subdural hematoma to vacuum out the fluid. After the drainage step is completed, the system is pulled back into the MMA, the transvascular access site is occluded, and the system is removed (see *Figure 1*).

The company is conducting its first-in-human trial in Buenos Aires, Argentina, led by neurosurgeon Pedro Lylyk, MD, at Clinica la Sagrada Familia. More than a dozen patients have been treated so far. The study has recruited patients at high risk of CSDH recurrence (because they're on blood thinners and/or have brain atrophy). The procedure begins with MMA embolization, then the subdural fluid is drained transvascularly. If, during six-month follow-up the investigator deems that the patient needs more fluid drained, they will return for surgical drainage. (As of this writing, most patients are out six months and none have required surgical drainage).

Savastano reports that they have intentionally enrolled patients with all types of non-acute subdural hematoma, and they have been consistently able to drain the fluid without adding much time to the embolization procedure. In addition, he notes, while elderly patients undergoing conventional surgical drainage and long hospital stays often require physical therapy or rehabilitation post-discharge, anecdotally, they've seen patients in the study wake up from anesthesia, move, talk, and go home one or two days after the procedure. "That is the vision: to be able to do one endovascular procedure that decompresses the brain and gets the patient back to normal as soon as possible, while also embolizing the artery to prevent re-bleeding so the patient doesn't need another procedure."

Figure 1

Endovascular Drainage of Subdural Hematoma



Source: Endovascular Horizons

On an NIH grant (Blueprint MedTech) and seed funding from "friends and family" the start-up has demonstrated proof of concept—that its platform is feasible, safe, and effective. The company will be out fundraising this year to support a pivotal trial in the US and FDA clearance. The FDA has already granted its Breakthrough Device designation for the therapy.

Taking an endovascular approach to the intradural space is only the first step, says Savastano. "This is the beginning of a transvascular field. What we have developed is a technology and procedure to gain access to the intracranial space and the brain without surgery. There is no reason why we cannot inject medications or different therapies, or implant electrodes for epilepsy or brain-computer interfaces, for example, without opening the head. These are the endovascular horizons." Hence the name of the company.

Endovascular Engineering: *Hēlo PE Thrombectomy System* Is Small but Acts Big

It hasn't been long since Inari Medical commercialized the first mechanical thrombectomy device purposefully built for treating venous disease, and specifically, pulmonary embolism (PE), a dire situation in which blood clots block the pulmonary arteries. Inari received FDA clearance for its *FlowTriever* system in 2018.

Inari, now part of Stryker by way of an acquisition valued at $4.9 billion, and Penumbra, with the *Indigo Aspiration System* for PE that gained FDA clearance in 2020, have, in the ensuing years, firmly established thrombectomy as an effective and potentially safer and more predictable treatment for intermediate- and high-risk PE than thrombolytic drugs. Solidifying the role of the devices in patients with intermediate-risk PE, Inari's landmark randomized controlled trial PEERLESS, presented at the TCT conference in late 2024, pitted mechanical thrombectomy against catheter-directed thrombolytic drugs. Thrombectomy won; patients thus treated exhibited less clinical deterioration, used fewer intensive care services, enjoyed a greater rate of early recovery at 24 hours, spent less time in the hospital, and experienced a lower 30-day readmission rate.

While it's still early in the evolution of a new therapy, it has been long enough for next-generation innovators to take note

of the shortcomings of first-generation devices, chief of which is the trade-off between delivering a device with a large enough lumen to capture significant levels of clot, but not so big that it damages the anatomy on the way in.


DAN ROSE

Dan Rose, CEO of next-generation PE thrombectomy company Endovascular Engineering, was formerly the CEO of LimFlow, which developed an innovative treatment for chronic limb-threatening ischemia, shepherding it through an acquisition by Inari. Rose says that today the majority of PE cases are done by vascular interventionalists (cardiologists and radiologists) using very large diameter (24 Fr) catheters. These must be inserted through an access site in the groin and navigated through two chambers of the heart, across two valves, and into the pulmonary artery. "There are challenges to using large catheters across the heart in PE. They do allow you to take out a lot of clot, but these patients are hemodynamically unstable. There are noted complications associated with using such large-bore devices."

On the other hand, Penumbra has been using smaller aspiration catheters (12 Fr and 16 Fr) but it's very challenging to collect enough thrombus through a small-bore catheter. "The choice presents a clear trade-off. You can opt for a big pipe, big pull, lots of thrombus captured, but you must also accept the inherent risks associated with navigating it through the heart and vasculature. Alternatively, you can use a smaller catheter that clogs a lot and removes much less clot per pass." The challenge is fundamentally one of physics, he notes. "The smaller the bore, the more restricted the internal diameter, which directly limits what you can pull through with suction alone. These physical constraints create real clinical limitations."

To avoid that trade-off, Endovascular Engineering (or E2, as it is affectionately known) is developing a thrombectomy device that "goes in small and acts big," says Rose.

An Inventive Clinician

The start-up was founded in 2019 by Luis Savastano, while he was working in translational medicine at the University of Michigan, with a license to the technology from that institution. He didn't start with PE, however; the invention came out of work he and his team were doing to study the mechanisms of thrombectomy when used in stroke patients, where the goals and challenges of getting clot out in one pass were similar.

His idea was a catheter with a funnel containing a spinning element. The clot would be aspirated toward the funnel and macerated inside it. "The ability to break down clots before they go into the catheter allows you to deploy smaller and much more flexible catheters," explains Rose, "which are basically more attractive for any endovascular purpose, whether for access, navigation, or therapy."

Savastano presented the idea and proof-of-concept results at a "shark tank" event for life sciences companies sponsored by the University of Michigan. It so happened that James Eadie, MD, managing director of Santé Ventures, was in attendance. Says Savastano, "He liked the technology and basically said, 'We are going to fund the company and build it together.'"

To transform the university research prototypes into clinical grade devices, E2 hired an experienced engineering group, Inventure Group (Menlo Park), which is run by Mike Rosenthal and Scott Baron, two medical device engineers with several successful exits behind them. (Both are now at E2, Rosenthal as co-founder and chief operating officer, and Baron as chief technology officer.)

It soon became evident that the technology had an unprecedented capacity to ingest clots but would be difficult to implement in the brain. "It was technically challenging to build at a very small scale," says Rose. "You need a level of precision in the brain due to the small caliber of vessels that is less critical for other applications."

However, it didn't take the team long to realize they possessed a technology well suited to deep vein thrombosis and PE. The company pivoted to both applications but is prioritizing PE. "At the time, Inari was chasing the same space with different strategies and it was growing. The team at E2 saw they could bring something differentiated with a lot of value," recalls Rose. Savastano adds, "Thrombectomy technologies for stroke have evolved tremendously in the last 30 years but are relatively nascent for PE. At E2, we decided to take all the knowledge and science we had accumulated for stroke thrombectomy to make a quantum leap in PE thrombectomy."

Aiming for the First Pass Effect

Designed to engulf an entire clot in a single pass, E2's *Hēlo PE Thrombectomy System* is a 16 Fr compatible (moderate bore) catheter with the flexibility to navigate the sharp anatomical bends that occur as it navigates through the inferior vena cava, the right atrium, the right ventricle, and up into the pulmonary artery. "There are steerable primary and secondary curves in the device that allow you to navigate difficult to reach anatomy and orient yourself in multiple different directions through the procedure to get the funnel near the thrombus," Rose says.

Once advanced to the clot, the system deploys a 24 Fr funnel with an atraumatic tip designed to minimize vessel trauma. The operator activates aspiration and engages the spinning element

with a button press on the device handle, drawing the clot into the funnel and efficiently macerating the clot into smaller pieces that are aspirated out. The device doesn't have to be removed and reinserted to treat an additional location. "You just use the compound bends inside the device to reorient to a new area. You can actually snake the catheter throughout the pulmonary tree without having to rewire and renavigate, which is key to getting to a single-pass procedure," Rose points out.

Engineering the Workflow

Beyond the advantages of a smaller-bore catheter that can capture large clot volumes, the company has several other innovations that make the procedure faster, easier, and more reproducible with fewer people needed in the room, according to Rose.

"We've thought very long and hard about the procedural flow and how to advance it into the modern era. We shouldn't require multiple additional people in the room, we shouldn't have to open 17 packages to do one of these procedures. There should only be one pass of the device," Rose asserts. Users report several passes for the device of the largest competitor, he says, because when the device becomes clogged, or needs to be repositioned, it needs to be taken out and put in again. "Every time an operator goes across the pulmonary valve, a large catheter is lying on an already distended heart." That's a known, says Rose, because one of the mandates for treating PE patients is an abnormal right ventricle to left ventricle ratio. (The right ventricle is supposed to be slightly smaller than the left). "Putting a large catheter across the heart can stress a ventricle that is already strained, especially when you go in multiple times and leave it resting across two valves inside the heart for, say, an hour."

Figure 2

Hēlo PE Thrombectomy System

Source: Endovascular Engineering

Hēlo addresses other shortcomings of current procedures; for one, the blood loss that occurs during aspiration. "Aspiration thrombectomy devices aren't only sucking out thrombus, they also remove blood," Rose points out. Mechanical thrombectomy "takes blood from a patient who isn't healthy to begin with, so there has been a push to integrate blood return systems into these devices." (Inari has developed one, called *FlowSaver*.) Rose says E2 has developed an advanced blood return system that allows the physician, as they're pulling clot from the body, to separate the clot from the blood and return the blood back to the body. "Why wouldn't we want to offer our physicians the option to return a patient's own blood into their body? It's all done right there in the sterile field within an arm's reach of the physician and smoothly integrated into the procedural flow, which is not true for other systems."

Pivotal Moment

In November 2024, E2 presented results of the pilot phase of its ENGULF study, which enrolled 25 patients at eight centers in a prospective, single-arm study. First assessing the safety, feasibility, and efficacy of the *Hēlo PE Thrombectomy System,* investigators found that embolectomy was successfully achieved in all patients, was safe and effective in treating acute PE, and provided a notable reduction in thrombus, as assessed by computed tomography angiography and core-lab adjudicated. The company is now close to completing enrollment for the pivotal phase of ENGULF, with a target of 181 patients.

A $42 million Series B round raised in February will help it complete this final phase. The round was co-led by 415 Capital and S3 Ventures, with the participation of Panakès Partners, M&L Healthcare, and strong support from founding investor Santé Ventures. Two global strategic investors made substantial commitments alongside the company's early strategic investor Cordis.

E2 wants to solve an unmet clinical need; 12-50% of patients who present to medical care with a PE die. The company believes it will be a strong competitor in a market where, in the US, 900,000 patients with PE need treating each year. Today a $1.65 billion market, the PE thrombectomy market remains 88% unpenetrated. "We know the market is waiting for a smaller device that's more effective and efficient, a complete system designed specifically for PE," says Rose.

Posted on MyStrategist.com April 16, 2025