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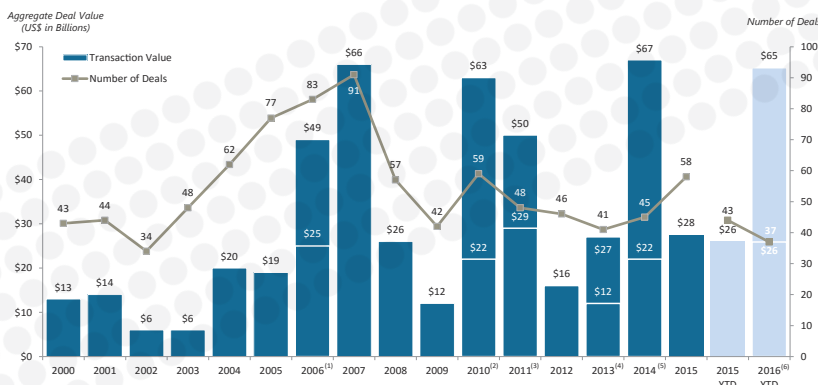
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RefleXion: Using Biology to Guide RADIATION THERAPY

KEY POINTS

■ Medtech investors usually shy away from capital equipment plays because the technology is expensive, the development timelines are long, and selling into a cost-conscious hospital environment today is risky, particularly given the need to unseat an installed base. But RefleXion has been able to raise two rounds of financing, featuring several blue chip investors.

■ RefleXion's novel approach to cancer therapy: combining positron emission tomography (PET) technology with radiotherapy, turning the former into a therapeutic rather than diagnostic tool, to enable real-time, biology-guided radiotherapy.

■ Key to RefleXion's opportunity is a shift in strategy from single tumor therapy to the ability to treat metastatic cancer, a difficult target for conventional radiotherapy because of the diffuse nature of the disease.

■ The interest in RefleXion shown by investors like Pfizer and Johnson & Johnson reflects both a wider context for the company's prospects and a pathway, potentially, to partnerships in the future, particularly with Big Pharma.

by
DAVID CASSAK



All successful fund-raising represents an affirmation of sorts. But for Hayward, CA-based **RefleXion Medical**, the company's recent announcement of a \$52 million Series B, led by a sophisticated family-office (KCK) and with the participation of Johnson & Johnson Development Corporation (JJDC), represented a special kind of affirmation.

Just four years ago, RefleXion was running on fumes, having gone through some early seed capital and grant funding, as the company founders began a search for Series A investors. Worse, early conversations with venture capitalists were decidedly unpromising. Having been turned down by virtually every VC contacted, RefleXion seemed to be the quintessentially un-fundable medtech start-up. The company checked virtually every box on a VC's "do not invest" list: capital equipment, complex technology, potentially long development times and lengthy and difficult sales cycles, to name just a few undesirable attributes.

On the other side of the ledger, however, were some equally compelling positives: a strong management team, backed by an impressive roster of advisors, and, perhaps most compelling of all, RefleXion's promise to revolutionize the treatment of metastatic cancer by incorporating a well-established technology, positron-emission tomography (PET), with a novel approach to zapping tumors. In the end, while it hasn't always been easy, RefleXion has been able to attract some blue-chip investors, including JJDC, KCK, **Pfizer Inc.**, Sofinnova Partners, and Venrock. In the process, this once least-likely of bets has become one of the hottest technology companies in the medical device industry.

Using Signals from Tumors

RefleXion's founders, Sam Mazin and Akshay Nanduri, met in high school in their native Toronto. After high school, each went his own way, Mazin to the University of Waterloo, where he got a degree in computer engineering before moving on in 2002 to Stanford University to pursue a degree in electrical engineering, with plans to go into the communications field. "I didn't have any idea that I would end up in the medical field," he says.

It was in a class in medical imaging, part of his electrical engineering course work, that Mazin came to the concept that would eventually become RefleXion. As he recalls. "It just really blew me away what an elegant application of engineering principles to medicine I was seeing—how CT and MRI scanners work, how ultrasound works—how math produces clinical images. I was hooked." Mazin began searching for an advisor for his PhD thesis and ended up working with Norbert Pelc, ScD, the Chair of BioEngineering at Stanford's School of Medicine, who was doing research on new types of CT scanners. Mazin spent the next five years or so in the radiological sciences lab, earning a PhD on new CT scanners and continuing with post-doctoral studies.

Mazin notes that he saw something interesting in his work in the radiology lab. "The imaging people, the ones who look into the body, and the radiation oncology people, those who treat with radiation, don't really talk to each other a lot," he says. "There were very few joint sessions where the physicists and scientists in one part talked with the physicists and scientists in the other." In fact, Mazin recalls one talk given by a radiation oncologist physicist in 2007 who, discussing the challenges of the field, noted how difficult it is to see the tumors during a course of treatment. "Suddenly the idea just hit me—to use signals coming from tumors themselves to guide radiation." In that kernel, RefleXion was born.

The idea wasn't to assess the shape or size or location of the tumor, Mazin says, but actually to sense it in real-time. "When you're delivering radiotherapy treatment, radiation is invisible; the beam is just going into the patient," he explains. "There's really no way to actually verify where the target is. Because the tumor is inside the body, it's really difficult to have a real-time perspective on what's going on." The body moves with respiration and in radiosurgery, millimeters are crucially important, he notes. Currently, radiation oncologists employ a variety of techniques to help target the tumor, such as implanting gold seeds that establish reference points. "But there's no direct way to actually see where the tumor is," he says.

At the end of the lecture, Mazin had a thought that, in essence, became RefleXion's concept statement. In PET imaging, using radiotracers, couldn't tumors, which emit photons, become beacons? And if so, when a tumor sends out a photon, why can't we just shoot one right back?"

Technically outside his research area, Mazin worked on the idea for another year or so. During this time he was accepted into the Stanford Ignite program offered by the business school to help train scientists on business fundamentals. As the concept began to become real, Pelc introduced him to the Kaufmann Foundation, a Kansas City-based organization that helps entrepreneurs launch companies through educational and other programs, which, at the time, had started a new program designed to help post-doctoral fellows create companies and commercialize technology. At Kaufmann, he ran into medtech industry veteran, investor, and serial entrepreneur, Jay Watkins. Formerly the co-founder and CEO of Origin Medsystems, Watkins is a well-known figure in medtech circles. He later became a VP at Guidant, which acquired his previous company, and subsequently signed on as a venture capitalist at De Novo Ventures for more than 14 years.

A Crazy Idea and a Phone Call

In the late 1990s, Akshay Nanduri was also studying at Waterloo University, where he majored in computer engineering, having stayed close to his high school friend, Sam Mazin. Out of college, he joined a telecom start-up, a six-year stint that lasted until the company was acquired. Having cashed out, Nanduri, like Mazin, left Canada to do graduate work in the US, not at Stanford, but at the Massachusetts Institute of Technology (MIT), where he pursued an MBA at the Sloan School of Management. In 2008, Nanduri got a phone call from Mazin "about this crazy idea in radiation oncology." With no medical background, Nanduri was skeptical at first. "I told him I didn't want to touch it with a ten-foot pole," he recalls. "Plus, I felt it would be difficult to add value in a completely foreign field."

But Nanduri did have an idea: MIT has a business plan competition. "I thought we'd put a team together that could help us understand the implications of the idea." Winners of the competition would receive \$100,000 to be used to start a company.

Reluctant at first, Nanduri became more excited about Mazin's idea as the two did research for the business plan competition. "We interviewed 20 to 25 radiation oncologists, and I got hooked based on the feedback we were getting," he says. "Clearly there was a need for seeing and treating at the same time." There had been other innovative start-ups in the field, he goes on, "but we still felt there was something missing from the market, something clinicians were really hungry for." Mazin's concept, they decided, was exactly what the radiation oncologists were asking for: "for the first time, the tumor was talking to the machine," says Nanduri.

Nanduri and Mazin didn't win the competition—they were semi-finalists in the life sciences track. But the work

on the business plan led the two to create RefleXion, which was launched in 2009 to bring what both claim is an entirely new way to use diagnostic imaging, in this case, specifically positron-emission tomography to deliver therapy to cancer patients.

No Closed Doors

By the time he met Sam Mazin at Kaufmann Labs in 2009, Jay Watkins had begun the next phase of his career, a shift from investing *per se* toward a role as an advisor or mentor to promising medtech projects. “I wanted to move away from being money looking for a place to land and back to being an entrepreneur,” he says. “My goal was to get closer to driving ideas and having a more substantive interaction with the development of companies, more than you get as a venture investor.”

Watkins, who joined the RefleXion board the next year, admits that he was skeptical at first. When Mazin told him that he wanted to build a machine that would combine PET with traditional radiation therapy, Watkins easily saw the obstacles the company would face, particularly in discussions with potential investors, who would push back against a capital equipment project that would have to spend \$10 million just to build a prototype—a project that was raising capital in the worst funding climate in over a decade. “The first thing I asked him was, ‘What else are you working on?’” Watkins recalls. “In 2009 that would have been like pushing a rock up a hill. I mean, there were easier things to do.”

In short, Watkins thought, “Here was someone with, prospectively, a revolutionary idea, but it doesn’t synch with any aspect of the funding environment in any dimension.” Still, inspired by Mazin and his vision, Watkins signed on to help. Though he had been on the board of Rita Medical years earlier, Watkins knew what he didn’t know. “I knew catheter-based cancer therapy [because of the Rita Medical relationship], but I had never spent much time thinking about drug or radiation therapy,” he says. “The long gestation that was the Kaufmann fellowship gave me the time to really swim around with this concept and understand what was going on.”

And the deeper he got into RefleXion, the greater the realization that this would be unlike anything Watkins had experienced in his long career guiding and investing in medical device start-ups. “Sometimes you have to innovate not just the product, but the way you bring it forward,” he says. Certainly, the difficult times medtech start-ups faced coming out of the financial crisis had changed the rules of the game, he goes on, but that merely determined how companies would move forward. The opportunity was still there. “I’ve always believed there is no such thing as a closed door,” Watkins says. “I looked at RefleXion as the ultimate test case for the idea that you can still do great things in an

environment in which everyone is telling you that you can’t do what you’re trying to do.” RefleXion would be “the litmus test to see whether you can innovate a big idea as you swim upstream against all of the obstacles medtech was facing: financing, regulatory, reimbursement. The whole thing was, I thought, a great challenge.”

Elysium: Science Fiction becomes a Reality

As they continued to work on the concepts behind RefleXion’s technology, Mazin and Nanduri had come to believe that even the radiotherapy market leader, **Varian Medical Systems**, had missed the opportunity. “Varian has innovated in x-ray and CT-guided therapy,” says Mazin. “And there are other companies working on MRI-guided radiotherapy systems.” Moreover, certain combinations of PET and radiotherapy were already known, he concedes. “But the way we use PET is fundamentally different,” he says. “It’s what actually enables the principle of real-time biology guided radiotherapy.”

The key to RefleXion’s novel approach to radiotherapy: its system doesn’t actually image the tumor. Instead, it uses the PET signal directly to guide the treatment beam. With conventional PET imaging, “you have to wait for enough of these signals to come out of the patient to form an image,” Mazin explains. “And by then it’s too late. The tumor is moving during that time.”

Mazin notes that the principal difference between PET and other diagnostic modalities, such as CT and MRI, is that the other modalities show anatomical features; PET shows biological features, which is why it’s called a biological imaging modality. That means “you’re seeing function; you actually see an *in vivo* process happen,” he explains. “With PET, you see where the tracer that you injected into the body is going, which depends on whether the cells take up, for example, glucose, a common PET tracer, or not.” That tracer is tagged with a positron emitter. The cancer cells process glucose in much greater quantities than healthy cells, and as they absorb the injected glucose, the tracer sends out signals. “As the cancer cells take up the tracer, they become beacons sending out signals about where the tracer is,” he goes on.

Today, says Mazin, PET is “the gold standard for noninvasively sensing where cancer is in the body. Because it’s so sensitive and specific when compared to CT and MRI, it’s a great way to see if there is a lesion in the patient,” and it is most often used to determine the stage of the cancer. “It’s very difficult to do a full body CT or MRI and see whether there’s a tumor somewhere in the body,” he goes on. “With PET, the tumor just pops out of the image.”

Until now, PET has been used primarily as a diagnostic tool. RefleXion estimates that there are some 1,700 PET machines in the US, and all of the major diagnostic imag-

ing companies—**GE Healthcare**, **Siemens Healthineers**, and **Philips Healthcare**—sell PET systems. But when it comes to radiotherapy, “PET has never really been integrated with a radiotherapy machine,” says Mazin. RefleXion’s system doesn’t so much represent a better PET system; it represents the integration of therapy with diagnostics in PET imaging. In Mazin’s words, the company is all about “combining the best way to see cancer with the best way to locally treat it, noninvasively.” And he compares RefleXion’s system to the machine in the futuristic, dystopian movie *Elysium*: “you lie down in the machine and it just senses where the disease is in the body and treats it without touching the patient. We believe we’re building something like that for cancer.”

But if PET has been around a long time and so has radiation therapy, what makes RefleXion such a hot start-up? The answer: a proprietary piece of capital equipment that can generate a healing effect. “This isn’t as simple as adding a PET imaging system to a radiation therapy system,” says Mazin. “We have to spin our machine at an order of magnitude faster than [the rate at which] radiation therapy systems normally rotate.” RefleXion’s patents—and its novel approach to cancer therapy—revolve around “the concept of responding to individual PET photons coming out of the patient with beamlets of radiation in a very short period of time,” he points out. In addition to some early patents around the concept, RefleXion has also filed patents around additional applications. “Being able to shoot back a beamlet of radiation from a PET photon in a very short amount of time means we have to move multi-leaf collimators very quickly,” Mazin goes on. “We have applied for patents around that because we’re also revolutionizing radiotherapy technology in general.”

Wanted: An Interdisciplinary Skillset

“Sam figured out a way to exploit the underlying physics of PET imaging to solve the most pressing problem in radiation oncology today. No one else is able to do that,” says Akshay Nanduri.

That said, moving from concept to a functioning system brought an entirely new set of challenges, and to address those, RefleXion recruited David Larkin, a controls and robotics expert who spent 14 years at Intuitive Surgical, the robotics company, to be the company’s head of engineering. “That was probably the one area that we underestimated in terms of technology development, and we were lucky to get David,” says Mazin. And while RefleXion’s system isn’t a robot in any sense of the term, Larkin “just has a really good grasp of what it takes to build interdisciplinary and complex medical equipment,” says Nanduri. Adds Mazin, “His real expertise is taking products from concept through to market.”

From an engineering perspective, one of RefleXion’s principal challenges was taking a multi-leaf collimator, the part of the equipment that shapes the radiation beam to the tar-

get, which normally moves very slowly, and enabling it to move at very high speeds. Collimators are “big chunks of tungsten that can stop x-rays,” says Nanduri. “They have to move masses, and we need them to move at the speed of a subwoofer. That was really beyond the limit of most actuation technology, and it was one of our main technical risks. At the beginning, we really didn’t know how much of a risk it was, but David felt it could be done.”

RefleXion’s system doesn’t so much represent a better PET system; it represents the integration of therapy with diagnostics in PET imaging.

A large portion of RefleXion’s Series A capital was devoted to developing multiple models to enable the new type of multi-leaf collimator that RefleXion’s novel radiotherapy equipment needs. In effect, RefleXion’s system is a large, very novel piece of capital equipment and to two people much more comfortable dealing with software than hardware, the technology challenge was great. Mazin and Nanduri relied on a number of advisors and mentors in addition to Jay Watkins, including Jonathan Fleming of Oxford Biosciences, David Auerbach, the co-founder of IMPAC Medical Systems (a very successful radiation oncology start-up, now a division of **Elekta AB**), and Morry Blumenfeld, a former GE-exec and board member at MAKO Surgical. “They put us through the ringer in helping us think about the milestones we needed to reach to reduce the technology risk and how to think of our development program,” says Nanduri. In addition, the company assembled a network of executives from companies like Varian, **Accuray Inc.**, and TomoTherapy (now part of Accuray). “We had all of this input coming through, and we just sorted through it and charted our course,” he goes on.

Hitting Multiple Targets at Once

RefleXion’s most compelling value proposition lies not simply in its ability to treat tumors more effectively, but in its ability to treat multiple targets at one time in cancers that have metastasized, a significant advance over conventional radiotherapy systems. Radiosurgery differs from radiotherapy, Nanduri explains, in its shorter, more concentrated form of treatment. “With radiosurgery, you’re delivering the entire radiation dose in just a few treatments,” he says. Radiosurgery is more effective in controlling tumors, he goes on, but because of the limited number of treatments, “the stakes are so much higher” he says, “so missing a tumor is a major problem.”

On the other hand, he goes on, “with conventional radiotherapy, you’re delivering the entire dose in 30 treatments spread over six weeks.” If the radiation oncologist misses the tumor during one of the treatments, there are 29 other sessions in which to effect therapy. As a result, missing the tumor in any one treatment session “probably won’t have a clinical impact,” says Nanduri.

RefleXion executives point to studies that show that radiation therapy delivered in conjunction with advanced drugs such as targeted agents and immunotherapy is very effective in treating cancers that have metastasized.

“Because the stakes are so high in radiosurgery [for each individual treatment session],” he goes on, it “requires sophisticated imaging and other technologies to make sure [the clinician] is on target.” Clinicians often spend 20 to 30 minutes of each radiosurgery session just making sure the patient is aligned properly and the set-up is just right. “Then they kind of close their eyes and hit ‘Go,’” he says.

Doing that for single tumors is difficult enough; attempting to treat multiple targets in a patient becomes nearly impossible. That’s why radiosurgery is used mostly in early-stage cancers, in an effort to eradicate the disease. “When a patient has multiple sites in their body, radiosurgery is no longer an option because after you go through that whole [set-up] process for one site, you then have to go to the next site and reposition and reimage the patient all over again,” Nanduri says. “It’s a serial modality, just like doing surgery.”

The Goal: Beating both Radiosurgery and Conventional Radiotherapy

In particular, patients who have been diagnosed too late—those whose cancer has begun to progress or has already metastasized—are no longer candidates for radiosurgery. “Once you have more than two metastases in your body, there isn’t really any technology that’s going to offer a local therapy,” Nanduri goes on. When the patient gets to that point, “they’re relying on drugs as their only form of treatment. And drugs do a terrible job at curing the disease,” both because they are often not effective—80% of cancer patients don’t respond to advanced drugs, he points out—and because toxicity concerns limit the amount of drug therapy a patient can undergo.

RefleXion will initially target solid tumor cancers because, Nanduri says, “most solid tumor cancers will metastasize

throughout the body—to the lung, liver, bones, and adrenal glands. And once you have those multiple sites, there’s no treatment option right now that is as good as a local therapy would be” for a single site. That said, he adds, “we also think our technology will be attractive for single sites because we would argue it will be the best radiosurgery system possible.”

Indeed, RefleXion executives point to studies that show that radiation therapy delivered in conjunction with advanced drugs such as targeted agents and immunotherapy is very effective in treating cancers that have metastasized. Their goal is to develop a system that makes the treatment of multiple sites much easier to do and thus more widely applicable. Says Sam Mazin, “We want to make that feasible all over the body.”

RefleXion officials point to other potential benefits of their system. For example, studies show that combining radiation therapy with immunotherapies does not increase the levels of toxicity compared to drug therapy alone. Toxicity resulting from radiotherapy alone is very predictable, says Mazin, and therefore easier to manage or control. “As long as you’re not crossing the toxicity limits in the organs, there’s minimal [additional] toxicity felt by patients” by the combination of radiotherapy and drugs.

In addition, RefleXion also hopes to prove that its approach leads to a lower level of radiation exposure for patients over time. Some patients find that the initial course of radiation therapy was ineffective and the tumor comes back, and unfortunately, the patient becomes more sensitive to radiation in follow-on treatments. “There’s an opportunity for us,” Mazin goes on, “because our technology can reduce the amount of radiation since it’s more focused and targeted.” That’s another area “where we think we’ll have an advantage,” he says.

De-Risking the Platform for Investors

Having launched RefleXion in 2009 with little more than a concept about how to use PET in cancer therapy, Mazin and Nanduri figured they’d need \$11 million in initial funding to bring that concept to life. Early on, they were able to make progress in the development of their idea with relatively little seed funding, around \$550,000. “You can prove a lot of the science with software modeling because these are really physics-based simulations,” says Mazin. “As soon as we incorporated, we were able to leverage our past experience in computer science to de-risk the prospect through software models and experiments.”

They soon acquired raw patient PET scans from Stanford and were able to plug them into their software model to predict the clinical relevance and efficacy of the system through a kind of simulation. With anonymous PET scans, “you can actually replay what those emissions were, the time stamp

of every emission, the coordinates, and in effect simulate the impact of the treatment as if the system actually exists,” Mazin explains. Treating cancerous tumors with radiation is an old concept, he goes on. “So if you know how much radiation was delivered to a particular site, you can predict the likelihood of the tumor being controlled.”

Some radiation oncologists were skeptical at first, however. Accustomed to seeing images, some radiation oncologists found RefleXion’s system, which works on an invisible beam delivering therapy, uncomfortable because there are no images, conventionally considered. “When we first started out, it was much more difficult to educate them,” says Mazin. But the simulations helped a lot, as did a series of publications the company produced about their approach. “Once we started publishing, the clinicians got behind us because we presented the potential of this technology in language they understood,” adds Nanduri.

Still, RefleXion would be able to go only so far on seed funding and simulation models. Nanduri and Mazin began to look for their first round of venture capital. Nanduri concedes that in 2009 as RefleXion was getting off the ground, neither he nor Mazin, brimming with optimism about their idea, really understood the financing obstacles that awaited them. “I was oblivious to the medtech financing scene at the time,” Nanduri recalls. “I was coming out of the mobile software industry,” where investors fell over each other to fund the next hot start-up. “I honestly thought we’d go out, raise \$10 million right away, and be off and running,” he says.

What a Tough Series A Looks Like

It wasn’t just that RefleXion launched in one of the darkest times for funding medtech start-ups. Worse, as a capital equipment, or “big iron” play, as the company founders describe it, RefleXion represented everything conventional venture capital shies away from. And more than a year out from the beginning of the start of the business-plan competition, the pressure was growing. “We needed to raise money soon because we had IP bills that were mounting and we were living off ramen,” says Nanduri.

RefleXion’s seed financing came from angels—radiation oncologists and industry executives who saw the potential of the technology—and though it was, as Nanduri puts it, “a really high quality seed round,” even raising angel money wasn’t easy. “It was painful, a lot of hustling,” he says. “We had to break all of the rules.”

Even some angel investors had reservations, including some radiation oncologists, because the concept was so different from the way PET has traditionally been used. “People have a certain conception of PET imaging,” Nanduri goes on. “They think of it as a great biological tool; that’s

why they use it to stage a disease. But radiation oncologists will rarely use it to plan because PET produces fuzzy images—they’re pretty low resolution compared to MRI and CT.” Because of the quality of the images, many radiation oncologists regarded PET-guided therapy as less accurate than CT-guided therapy. “We actually had to do some education,” he says, noting that radiation oncologists who were “more physics-oriented” usually got the concept and were open to using PET not for the blurry images but for the direct signals.

RefleXion’s seed capital was used to secure some patents, pay some attorney’s fees, and begin studies, which in turn enabled the company to get grants from the National Cancer Institute and the SBIR program. In addition, having earned \$1,000 from the MIT business-plan competition, RefleXion entered other, West Coast contests, including Stanford Basis and the Santa Clara Boomer competition.

The monies from the contests would, however, not do much to help RefleXion’s progress. But, notes Sam Mazin, “it was a great way for us to meet investors and interact with venture capital groups.” Still, as noted, RefleXion’s founders never anticipated the difficulties of raising a first round of capital: the company’s \$11 million Series A financing finally came together in April of 2014, five years after its launch. “We had some dry spells and about six to nine months when we didn’t know if we’d make it,” says Mazin.

Not only were few medical device investors familiar with radiation oncology as an opportunity, most, as noted, had an aversion to capital equipment plays, which often require a lengthy and expensive development timeline and often, too, depend on replacing an installed base with expensive machines. Such considerations only made a difficult financing climate more difficult. “Most VCs wanted to see revenues,” Mazin goes on. “They wanted all risk to be retired.” Adds Nanduri, “The prototype wasn’t going to be enough for them, but we needed the money just to build the prototype. We were years away from revenues.”

Critical to RefleXion’s success in raising capital was the relationship company executives formed early on with Jay Watkins. “From that moment on, we just started going to Jay when we needed advice,” says Mazin. And although it wasn’t easy, by the time the company’s Series A was done, the roster of investors was even more impressive than the seed round: Paris-based Sofinnova Partners, which led the Series A round, Venrock, and pharmaceutical giant Pfizer.

In 2009, Watkins was still at DeNovo Ventures, his former venture firm, and though DeNovo didn’t invest, he did help with introductions to those that did, including Sofinnova’s Antoine Papiernik. “We were able to raise a tiny bit of private capital early on,” Watkins recalls, mostly from angels, with a bit of grant money as well. With that seed capital, he

goes on, “we did the next small thing we could do, which was build a simulation,” while beginning to talk with venture firms. “We worked for two years and got turned down by everybody that we knew who was a possible funding source,” he goes on.

For medtech investors, RefleXion was all about capital equipment and the difficulties of making money in the space; for Pfizer, it was all about advancing cancer therapy.

Even as he was setting up meetings with VCs he knew in the Bay Area, Watkins says, “I knew in my heart of hearts that reaching out to VCs was not going to work.” Watkins kept a list of all of the meetings, with notes in red reflecting the reasons VCs gave for passing on the deal. “I still have the list and they use it at Stanford to teach people what a really tough Series A looks like and how determined you have to be to make it work.” (For more on RefleXion’s financing path, see the sidebar, “*RefleXion’s Financing: Turning Skeptics into Believers*.”) “We got all of the reasons you’d expect,” Watkins goes on: RefleXion hadn’t de-risked the technology enough; the project is capital equipment and nobody invests in capital equipment; it’s a binary outcome and after investing \$11 million there might not be a future for the company; and while the radiation oncology market is large, it isn’t growing.

A Drug Company Steps Up

In the end, says Watkins, two things turned the company’s fundraising efforts around. One was RefleXion’s outreach to a variety of experts—radiologists, radiation oncologists and former industry executives—all “deeply knowledgeable about radiation oncology, the patient profile, and the history of what’s worked and hasn’t,” he says, experts who began to vouch for the technology. “After a while, they went from saying, ‘You’re crazy; this will never work’ to ‘this is a really big idea and if you’re successful, it will change everything,’” he goes on. “Sam was able to cultivate a set of believers among a very experienced and largely skeptical group of people who began to buy into the idea that if we could do this, it would be very important.” In the end, Watkins says, these expert testimonials were “the asset we were building” between the beginning of fundraising efforts in 2011 and the Series A that closed in 2014.

Second, as Watkins puts it, “there was this whole angle that had to do with patients being treated at the intersec-

tion of devices and drugs.” It was at that point that RefleXion broadened its funding search to include Pfizer, which invested in the Series A, and Johnson & Johnson, which came in at the Series B. Even with the testimony of experts, most of the VCs the company met with were skeptical. “We found ourselves in conversations with people whose attitude was, this is an interesting idea and very clever, but is it really as important as you say?” he goes on. “That’s when we opened the conversation to the corporates because you can’t talk about cancer without talking about drugs.”

Indeed, of all of the Series A investors, it is Pfizer that best captures RefleXion’s unconventional route to financing. Says Sam Mazin, “Pfizer was actually the first institutional [investor] group that had any real interest in what we were doing.”

Jay Watkins notes that a meeting with Bill Burkoth, an Executive Director of Pfizer Ventures, was the turning point. “Bill’s perspective was that Pfizer not only participates on the drug side, they also understand the interaction between radiation and drugs.” Suddenly, the funding discussion took on an entirely different tone. “We had gone to see all of the ‘iron’ guys,” says Watkins. “They all sat politely but ultimately said, ‘This will never happen.’” For medtech investors, RefleXion was all about capital equipment and the difficulties of making money in the space; for Pfizer, it was all about advancing cancer therapy. An outlier for medtech investors, for Pfizer, RefleXion “was in their sweet spot,” says Watkins. “It was all about their patient base and how, if it worked, it might even make their drugs more effective.”

Indeed, Pfizer would have and could have taken the whole Series A by itself—for a drug company used to biotech investments, the size of the round and the binary risk involved were minor considerations. Moreover it was obvious that Pfizer had a familiarity with the space that conventional medical-device venture firms lacked. “They have a number of targeted drug therapies for advanced-stage disease in lung and other cancers,” Sam Mazin says. “And studies have shown the benefit of combining their drug with radiation [therapy] for advanced-stage patients if you can hit multiple targets,” which is exactly what RefleXion was aiming at. “With the feedback loop closed, our system allows doctors to hit many targets in one session, much as we do now with radiosurgery.”

“We can pretty much treat all solid tumor cancers,” Mazin goes on. “That’s why Big Pharma is really interested in what we’re doing. And it’s not just Pfizer and J&J; other companies in the pharma space are paying close attention to what we’re doing because radiation is a great orthogonal way of treating cancers: it works with drugs on multiple levels to help the immune system and can de-bulk the disease in general.”

A Second Round of Financing

About the Series A syndicate, Jay Watkins says, “We all understood that nobody can play games. This is a big project and we need a team. We needed people who were comfortable with working with each other, who understood what we were doing and were committed to the idea of going the distance. And weren't going to get that by gaming something and doing a flip. We were going to get that by putting a solid syndicate together.”

And while the success of the Series A financing, when it finally closed, was gratifying, Reflexion management also knew early on that the company's Series B—the \$52 million round announced this summer—would have to be much larger and would therefore be challenging in its own way

Indeed, the sheer size of the second round made Reflexion's next fundraising efforts different than the first. Encouraging for potential second round investors, Reflexion had made important progress in the development of a complex technology. “We came in ahead of schedule and slightly ahead of budget,” Jay Watkins recalls. “And when we turned it [the machine] on, we got exactly what we were looking for.” Reflexion's engineering team vetted the device every way they could think of, he goes on, and in the end, “we did it with duct tape, but we built a prototype that was arguably the best cancer therapy machine in the world.”

In turn, the issues for the second round investors were different as well. Watkins notes that the due diligence efforts of the Series B investors focused on a new set of risk factors, different from the ones that concerned the Series A investors. While Reflexion officials had demonstrated, with its prototype, that biologically-guided radiation therapy is viable, the risks of commercial viability still loomed. “When we said we turned it on and it worked, we didn't turn on a commercial clinical unit,” says Watkins. “What we turned on was a prototype.” Encouraged, Reflexion executives still knew that building such devices, on a scale necessary for a commercially focused company, would be a challenge. “The components that make up those machines are themselves amazing machines. And there are several of them, so we had to solve for each of them. They were like little puzzles inside a bigger puzzle.”

Given that the money raised in of the Series B round was intended to take Reflexion all the way to commercialization, the company had to convince investors that, as Watkins puts it, “what we were able to do at a prototype level we can now do at a commercial level,” where new issues crop up, most notably reliability of the machine and the strength of the supporting services. “It's one thing to turn the machine on and show that it works,” he goes on. “It's another to show that it can be used with patient after patient for years.”

Such concerns are widely appreciated in the medtech industry, says Watkins, “Every big piece of equipment that this industry has built over the years, from radiation therapy machines to robotics, has faced this issue,” and these concerns would therefore be a consideration even for the most enthusiastic investor. “We needed to be very thoughtful about how we mapped out our [commercialization strategy] to make sure we had the right solutions,” he says. “If you think about the role that service and support play in the radiation therapy business, you have to consider how you think through service and support with large pieces of equipment targeting a dispersed customer base.”

Notwithstanding the progress Reflexion had made, says Watkins, as company officials met with Series B investors, “we had proven that we could biologically guide a radiation beam to a tumor in ways that no one had thought possible before. But there were risks remaining and it would have been naïve of us to suggest that we had resolved every issue.” At the end of the day, he says, potential investors wanted to know not whether the machine works, “but whether we could build a business around it.”

In the Clinic, One-Plus-One Equals Three

Indeed, despite the promise of the concept, Reflexion still faced challenges in raising its second round. Part of that was due to the fact that the amount of money the company was looking for was so large; part, says Watkins, “because of the same things we had heard during the first round: ‘It's capital equipment, no one's really innovated in this space for years, there are only so many installations that come up every year and so the upside revenue is capped.’” Even the prestige of the Series A investors wasn't enough to convince people. “We heard a lot of people say, ‘I don't understand why they funded you,’” Watkins goes on. “‘You guys may have the tiger by the tail, but I don't know that I want to hold on to the tiger.’ It was, in many cases, a replay of what we had heard before: ‘You guys are crazy.’” Still, in less than half the time it took to raise the Series A, Reflexion had three term sheets for the Series B and turned two of them down. The third, which the company accepted, was led by the London-based family office KCK Group. (Headed in its California office by Greg Garfield, the former COO of Acclarent, KCK has made investments in a number of medical device companies recently, including Aerin Medical and Mainstay Medical, in which it did a PIPE.)

In fact, there was one important difference between the story Series A investors got and the story that motivated Series B investors to sign on: an important shift in Reflexion's strategy, from single tumor therapy to the ability to treat metastatic cancer. Akshay Nanduri notes, “I think what changed is that as we've built our system, one very promising clinical application has moved to the forefront,” i.e., Reflexion's ability to treat multiple targets at once. “That

completely changed the conversation.” Instead of focusing on the \$4-5 billion single tumor site market dominated by Varian, RefleXion could prove that it can target patients who aren’t well-served by radiation alone. In clinical studies, independent of RefleXion, says Sam Mazin, “we’re seeing compelling survival in metastatic patients who are receiving both radiation and drugs—a kind of one-plus-one-equals-three effect. That’s why we think we’re really on the right track” (see Figure 1).

Planning for the company’s Series B round, RefleXion officials had two options: build a basic prototype with which it could start to treat patients in an effort to collect the first human data; such a round would have been considerably smaller than the \$52 million the company eventually targeted. The second option, and the one the company chose: to finance the company all the way to commercialization, building the system for reliability and installations in a number of cancer centers. “This will very much be a selection process, where RefleXion chooses the early cancer centers we work with and collaborate with on the post-market clinical studies to run along with our pharma partners,” says Nanduri.

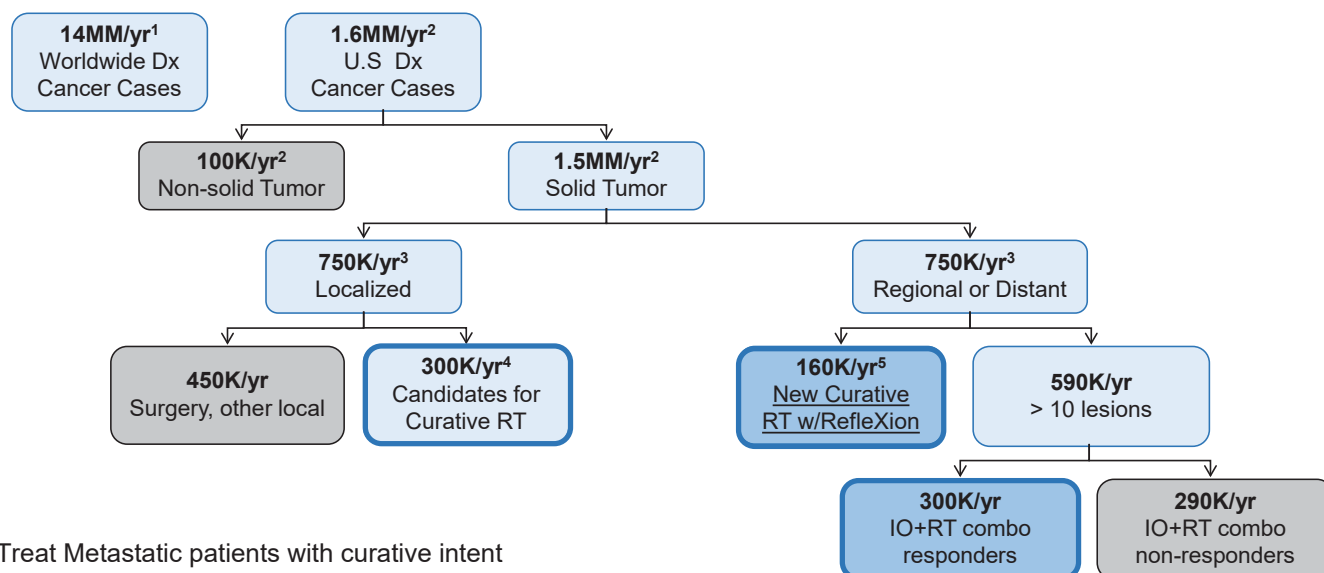
The latter path is possible, says RefleXion, because for all of the clinical promise and therapeutic impact of its system,

the company’s regulatory path is anticipated to follow a 510(k), based on predicates that includes other combined therapy/imaging systems and PET machines. (Systems that combined MRI and radiotherapy also followed this path, RefleXion points out, and set a precedent for the company’s regulatory strategy.)

Beating Cancer

A large part of RefleXion’s appeal and the excitement that surrounds the company—for investors as well as clinicians and patients—lies in the tremendous value that we, as a society, place on treating cancer. Drug companies charge enormous amounts of money for therapies that often prolong lives by a matter of months. RefleXion and its investors are well aware of that, though RefleXion is aiming not just to prolong the life of sick cancer patients but to drive toward remission. “We want to actually beat the disease,” says Nanduri. “And with all of the activity in the pharma industry right now around checkpoint inhibitors and immunotherapies, there’s a real potential for radiation to complement those activities in a significant way.” Indeed, RefleXion believes that radiation therapy lends itself nicely to the same kind of systemic effect that drugs try to achieve.

RefleXion Could Significantly Expand the Number of Radiotherapy Patients Treated with Curative Intent



- Treat Metastatic patients with curative intent
- *Push-button* motion-management for single lesions
- Superior Conventional RT with PET turned off (400K advanced stage patients receive RT for palliation)

1. World Health Organization, 2015 Fact Sheet

2. ACS Facts and Figures 2015

3. NCI SEER Database 2015, <http://seer.cancer.gov/statistics>

4. ACS Treatment + Survivorship Facts + Figures, 2015

5. RefleXion Internal Estimate: Patients with up to 10 lesions in the body

Source: RefleXion

Mazin points to research that goes back to the 1960s suggesting that radiation itself isn't really a local therapy. "They've observed this effect where oncologists would irradiate one tumor and another tumor completely outside the radiation field would respond," Mazin goes on. "And the only way to explain that is that the radiation itself induces an immune response to that particular cancer, promoting the release of antigens from those cells and stimulating the immune system to find those cells elsewhere in the body."

Ultimately, RefleXion's bet is both that radiation will work synergistically with drugs and, just as importantly, that radiation is critical to realizing the therapeutic effects of the drug. "You can develop the most advanced drug on the planet, but it doesn't mean anything if you can't get that drug into the tumor," Nanduri goes on. "We're not trying to replace immunotherapy or drug therapy. We want to work in concert with those advanced drugs on metastatic patients."

That was very likely one of the appeals to Series A and B investor Pfizer and Series B investor J&J, though Sam Mazin says that both pharma investments are purely financial and include no rights to the technology. That said, RefleXion is "working closely" with Pfizer and J&J executives beyond their investment teams as it develops the technology, an approach that, Mazin says, Pfizer and J&J have taken with other companies in which they have made investments. And he says there is the potential for RefleXion to form relationships with other drug companies, just as, more broadly, the drug industry is increasingly relying on partnerships, even among traditional rivals, to bring to market advances in cancer therapy.

Retiring Risk

Rewarding the confidence of their early investors, RefleXion officials say that even at this early stage, physician response to the company's approach has been strong and positive. "We're seeing palpable interest in the system," says Nanduri. He recalls that "for the longest while, Sam and I would sit at the major radiation oncology conference [i.e., ASTRO] at a table we'd commandeered outside the registration area and meet with radiation oncologists from leading centers. And they were all very supportive." As a group, radiation oncologists "have a strong appetite for new technologies," he goes on. "They were very interested in what we were doing."

Today, as RefleXion's progress continues, radiation oncologists come to visit their facilities in Hayward and Mazin and Nanduri take time to visit the oncologists' centers. "They know this is coming," says Nanduri. As noted, encouraged by internal progress and discussions with oncologists, RefleXion raised so much money in its Series B in expectation that the money raised can take the company all the way to com-

mercialization, if all goes well. "We believe we'll be on the market in a few years," says Mazin.

Having developed a working prototype—a piece of equipment that spins ten times faster than conventional radiotherapy systems—the company has addressed technical risk, which was the key objective of the company's Series A. "We've been able to demonstrate that it's technically feasi-

Having developed a working prototype—a piece of equipment that spins ten times faster than conventional radiotherapy systems—the company has addressed technical risk, which was the key objective of the company's Series A.

ble to do what we set out to do," says Sam Mazin. "Now the path we're on is to build a great product." With the money raised in the Series B, RefleXion will hire someone to head their sales effort and do what Akshay Nanduri characterizes as "a lot of market development over the next three years." Adds Sam Mazin, "We'll be in limited production in the beginning, and we are in the process of evaluating those first groups that we're going to partner with."

A Cautionary Tale

Even as the company has earned a reputation as one of the hottest start-ups in the Bay Area, RefleXion officials are cautious in their roll out plans. Behind RefleXion lies the cautionary tale of TomoTherapy, a once hot start-up in the same space that rose quickly only to fade over time. TomoTherapy raised \$45 million in funding, little or none of it from top-tier venture investors, and eventually got to \$150 million in revenue and a \$1B IPO. "It was a phenomenal success for a time," says Nanduri.

But TomoTherapy couldn't sustain that success, a victim of both internal development issues and a quick response by larger competitors that were able to quickly develop upgrades to their own systems and effectively present a competitive offering. (Accuray acquired TomoTherapy in 2011 for \$277 million.) As they look forward to the roll out of their system, RefleXion officials are mindful of TomoTherapy's story.

They're mindful as well of both the enormous amounts of money our society seems willing to pay for promising cancer therapies and the enormous costs those therapies bring. "On the far end of the spectrum, there are centers today that are spending hundreds of millions of dollars on proton therapy," Nanduri says. Even with cost concerns high

and drug pricing under scrutiny, “there’s still an arms-race mentality between premiere centers who are competing for patients,” he goes on.

Down the road, Mazin sees a market for RefleXion’s technology in community hospitals and other non-academic sites, where the focus is less on leading edge research and more on “enabling radiosurgery to be done much more simply.”

However, RefleXion isn’t betting on the fruits of that arm’s-race mentality, says Sam Mazin. “The nice thing about the market we’re entering is that [RefleXion’s success] doesn’t rest on the most advanced application.” Because there’s also a cost and efficiency benefit to the RefleXion system—most notably in more focused and targeted treatments that not only provide for lower radiation exposure but also more efficient delivery of therapy—“[centers] can use our machine to treat patients with single site and limited metastatic disease who would otherwise get conventional radiotherapy or radiosurgery,” he says. Even more, Mazin goes on, “the nice thing about developing a device to try to treat something that drugs are treating is that it could be a lot less expensive than the drug.”

Of course, just as with pharma therapies, the critical metric for RefleXion in its clinical studies won’t be cost or cure, but survival. Mazin notes that RefleXion’s initial roll out will likely bias toward academic centers and leading cancer centers rather than community hospitals seeking to upgrade their oncology programs. “We want to get the clinical research interest from those centers and have that process start as soon as possible,” he says.

Down the road, though, Mazin sees a market for RefleXion’s technology in community hospitals and other non-academic sites, where the focus is less on leading edge research and more on “enabling radiosurgery to be done much more simply.” Asked about the role of KOLs in RefleXion’s roll out, Mazin says the company’s desire is to reduce its need for or dependence on thought leaders in adoption. RefleXion’s goal isn’t just to enhance cancer therapy, but also to make it easier to access and more ubiquitous. Mazin notes that “because of the inherent uncertainties in the current treatment process,” centers delivering radiotherapy need a physicist on hand. “The idea is to reduce that requirement,” he says. “We’re not going to eliminate it, but hopefully we

can reduce it.” Cancer patients who live nearby will always favor leading centers like MD Anderson, Sloane Kettering, or UCSF; for those who don’t live close to those kind of facilities, RefleXion’s technology will, hopefully, enable much better treatment options for more patients, better in terms of both disease state and geography.

A Binary Bet Pays Off

Still, won’t RefleXion be fighting a battle, in today’s economic climate, against an installed base that cost-conscious hospitals will be reluctant to replace? “The good news is that we’re developing a PET machine married to a traditional radiation therapy machine,” says Jay Watkins. When hospitals find themselves wanting to buy a new piece of equipment, he argues, “they can buy a traditional radiation therapy machine or they can buy a radiation therapy machine that has a PET imaging component, which opens them up to doing a lot more for their patients and with partners than they can with those other machines.” In those cases where the radiation oncologists need a basic radiation therapy machine, “they can just turn the PET off.”

In addition, Watkins goes on, beyond Pfizer and J&J, RefleXion has also begun to explore partnerships with Big Pharma around clinical trial programs, another potential plus for hospitals, particularly those that already are participating in clinical trials for drug companies. “At the end of the day, there are going to be some really interesting partnering opportunities,” he says. “In fact, we’re already having those discussions.”

For now, if the company’s clinical progress validates the buzz that surrounds it, RefleXion’s biggest challenge may be justifying to radiation oncologists its plans for a more cautious roll out. “We don’t know whether, over the next few years, as we’re going to market, those pressures will come,” says Sam Mazin. “Would we be willing to put a system on the market earlier than we’d like, one that is not commercially ready but at least ready to treat patients? We believe a methodical approach to a commercial device would best serve both RefleXion and patients.”

With the satisfaction of someone proven right, Jay Watkins praises RefleXion’s investors for their willingness to fund a project no one else would. “It was a completely binary bet,” he says. “When we turned on the machine, it worked better than the simulation. But had we turned the machine on and not gotten what we did, we probably would have had to shut this down. And so the thing I find impressive about our investors, both the Series A and Series B investors, is that they were willing to sign up for that risk. They were handed a victory on milestones that they knew weren’t guaranteed. They knew what they faced and were willing to stand in for it.” 🟡

RefleXion's Financing: TURNING SKEPTICS INTO BELIEVERS

Antoine Papiernik jokes that he spent the first six months after being introduced to RefleXion trying to kill any investment. For RefleXion's early investors—Papiernik, of Paris-based Sofinnova Partners who led the company's Series A, and Colin Cahill, Vice President at Venrock, also a Series A investor—the company offered a checklist of all the things that medtech investors typically don't like in a deal: a capital equipment play in a relatively unpopulated space, a potentially long and capital-intensive development path, a lengthy sales cycle targeting increasingly cost-conscious hospitals, competing against an installed base, and, at the end, a limited number of potential acquirers.

"I did try to kill the deal," says Papiernik. "I didn't really know anything about radiotherapy except that it's an oligopoly and the equipment is very expensive." But, he goes on, "I really liked those two guys [i.e., Sam Mazin and Akshay Nanduri], and so I decided to look into it more." Sofinnova had, independently, begun to look at some opportunities in radiopharmaceuticals used in radiation therapy and Papiernik recalled meeting Sam Mazin a couple of years earlier at the suggestion of Jay Watkins. At the time, Papiernik wasn't really interested in RefleXion, but "took the meeting just to please Watkins," he says. As his interest in radiation therapy picked up, however, so did his interest in the start-up Watkins had introduced him to.

The more due diligence Papiernik did on RefleXion, the more the project grew on him. "We just started calling people, and every call suggested there was something there." And this was before RefleXion had shifted to tar-

get metastatic cancer, says Papiernik. About the company's original vision, "We thought, if this works, it will be huge. The oligometastatic piece was the cherry on the top." After making more than 40 calls to a wide range of experts in the field—physicians, physicists, and industry executives—"I came to the conclusion we had to do the deal," he says.

Papiernik cites two other considerations that argued on behalf of the deal—a strong IP portfolio and, perhaps more importantly, the team that Mazin and Nanduri had assembled, including a number of key KOLs and industry gurus such as Morry Blumenfeld, a long-time General Electric executive with an extensive background in diagnostic imaging technology development, who was an early advisor. "When I saw they were involved, I knew there was something there," he says.

Pfizer had already done considerable due diligence of its own by the time Papiernik began to syndicate the deal. One of his early pitches was to the Palo Alto offices of venture capital firm Venrock. Colin Cahill, the Venrock investor who oversees the firm's investment in RefleXion, had independently met Sam Mazin through Juan Pablo Mas of the venture firm Action Potential and had much the same response initially that Papiernik had. "It had every checkmark against it," he says. "But it also had a compelling unmet clinical need, a young and very talented team, and a very orthogonal approach."

Given the noted reservations about capital equipment investments—long and costly development timeframes and lengthy sales cycles—Cahill ar-

gues that it's hard to get excited about a capital equipment deal "unless there's a chance that it will be dramatically different." And to Venrock, that's what RefleXion offered. "It was very intriguing," he says of RefleXion's technology. "I had never seen anything like it; I had never seen anyone using biology to guide [the delivery of] energy."

Cahill concedes that in most cases, "We would not have spent a lot of time thinking that [a capital equipment company like RefleXion] was in our sweet spot." At the same time, he goes on "we try to be open-minded and agnostic" about the different kinds of opportunities Venrock is presented with. "It's in our DNA to be open to things that haven't made sense 20 times in a row because we're looking for that one big deal, the comp breaker," he goes on. "The last ten capital equipment deals may not have made sense, but we felt this one could be enormous."

Still, Cahill says, "there was a lot of work to do to get comfortable" with the deal. The fact that Sofinnova "had done six months of heavy lifting" in due diligence "and Pfizer had already decided they wanted in," helped convince Venrock that RefleXion was worth a closer look. Pfizer's interest was particularly reassuring: though it approached its investment as a financial play, the drug company has a major franchise in oncology. Says Cahill, "They understand the potential value of this to cancer patients and cancer therapies."

One issue for Venrock, says Cahill, was whether RefleXion was really as novel and differentiated as it seemed. "Could one of the big kahunas in

this space [i.e., companies like Varian and Elekta] pivot a little bit and squash them?” he wondered at the time. “We had a lot of work to do.” For Venrock, such longer-range issues were as critical to the deal as the technical risk. “We are fine taking technical risk but want to do so when we have high confidence in the downstream value,” says Cahill, who notes that technical risk was factored into the Series A valuation. “And in this case, because regulatory and reimbursement are relatively straightforward—more straightforward than they are for a lot of other medtech companies—and because if it works, it’s very differentiated, the commercial/regulatory/reimbursement overhang should be reduced.”

From the technical standpoint, says Cahill, “RefleXion nailed their two or three Series A risks, and they did it faster and on less money than we expected.” That’s not to say that the company has it all solved, he goes on. “Sam and Akshay are great founders, but this is a huge effort. You need physics, electrical engineering, mechanical engineering, and medicine, all woven together, and you have to get the work flows right in a very competitive environment out there.”

A seasoned investor in biopharma companies, Antoine Papiernik, too, worried about the special challenge of investing in a capital equipment company. Calling capital equipment an “unreasonable” place in which to invest, he notes that some capital equipment companies can require more money than a biotech company to get their technologies to market. But RefleXion “isn’t just any capital equipment opportunity,” he goes on. For one thing, the company’s anticipated 510(k) regulatory path should make commercialization faster and less expensive. The fact that radiotherapy is a well-established therapy

is also a plus, says Papiernik. “The clinical rationale is incredibly solid compared to other capital equipment [start-ups],” he says.

But if radiotherapy has a well-established protocol, it also has a well-established competitive landscape. “It is an oligopoly, and that’s a minus,” says Papiernik, noting the

“RefleXion nailed their two or three Series A risks, and they did it faster and on less money than we expected.”

—Colin Cahill

small universe of potential acquirors and partners in the space. As RefleXion and its investors think about potential exits, radiotherapy leaders like Varian and Elekta come obviously to mind; so do large diagnostic equipment companies like General Electric and Siemens, who have begun to focus as much on therapy as diagnostics. The investments made by Pfizer and Johnson & Johnson also raise the question whether Big Pharma might see a sufficient strategic value to make them potential acquirers, though that seems less likely.

Instead, says Papiernik, “With so few companies to sell to, the only real option for [RefleXion] is to build a stand-alone company.” That will mean funding the company all the way to commercialization, which was a driving rationale in the com-

pany’s \$52 million Series B. That’s not an easy path in a market where the installed base can be an obstacle, though Papiernik is confident RefleXion can handle the challenge. “The bad news about capital equipment is that a \$5-8 million piece of equipment is difficult to sell,” he says. “The good news is that at \$5 to \$8 million a pop, you don’t have to sell 10,000 [units] to succeed. The entire market, globally, is around 10,000.”

That’s not to minimize the challenges that RefleXion faces in building a stand-alone company. Papiernik points to TomoTherapy, an early radiation therapy company as a cautionary tale. “They had a great device, but they brought it to market too early,” he says. Conversations with several former TomoTherapy executives revealed some of the pitfalls the company ran into. “It was a great device,” says Papiernik, “but they spent the first two years servicing the first devices they put on the market,” he goes on. “That was a huge issue.” Varian’s competitive response—an upgrade to its own system that came close to doing what TomoTherapy had hoped to do—made commercialization even more difficult. “That was very difficult to fight against,” says Papiernik. “As we started interviewing ex-TomoTherapy people, we kept asking ourselves, are we facing the same situation? Or is ours different? We decided ours would be different.”

The notion that RefleXion will more likely become a stand-alone company makes it by itself an unconventional play in medical devices, where acquisitions remain the most likely form of exit, and it also led to an unusually large financing featuring non-traditional investors, including a corporate venture fund, Johnson & Johnson Development Corp. (JJDC) and a large family office, KCK, which led the Series B round.

"I'm not going to lie," says Papiernik. "Most traditional VCs still have a hang-up about capital equipment." That's why the Series B features unconventional investors. But he insists that raising the Series B was considerably easier than the Series A—RefleXion executives concede they were running on fumes by the time their first round closed. Moreover, Papiernik argues that in today's medtech investing climate, RefleXion knew from the beginning that it couldn't take a conventional or traditional path to syndication. "If you do that, you wind up going to the same people that you've always gone to, and they either don't have money to invest or they don't like capital equipment," he goes on.

"I think it was ultimately a very nicely balanced round with some very good people," Papiernik says. And while the role of blue chip investors such as Sofinnova, Venrock, and

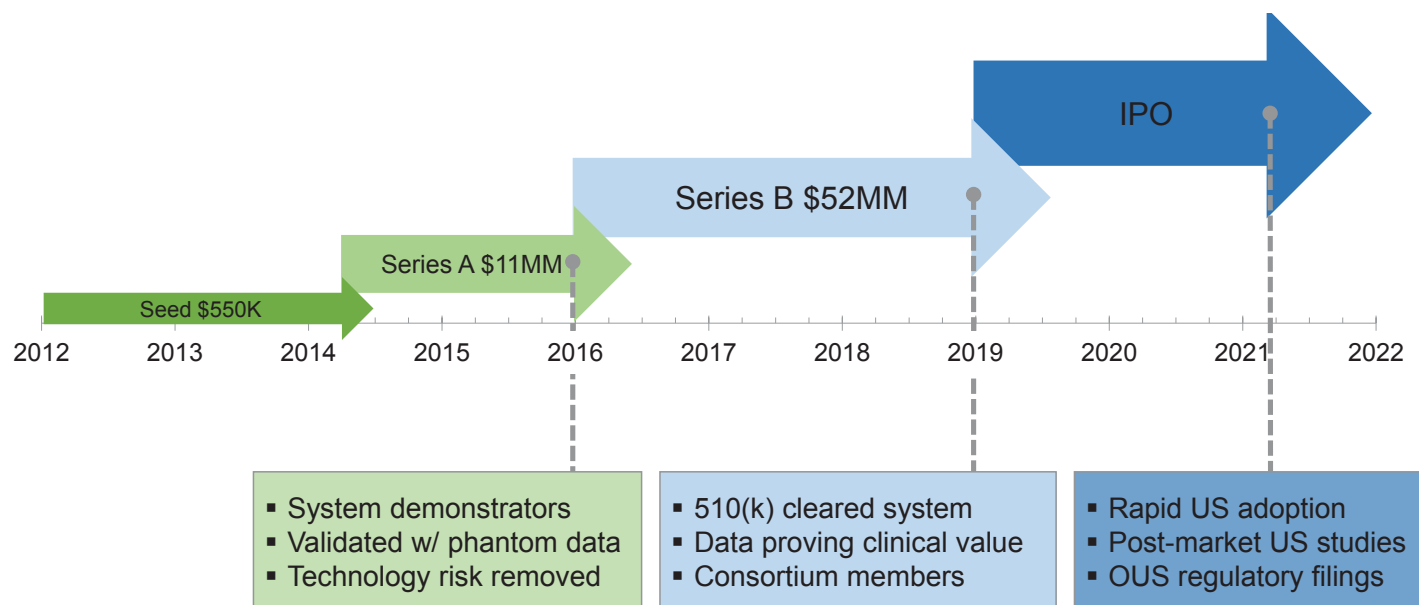
Pfizer undoubtedly helped convince the next group of investors, he argues that RefleXion's ability to resolve most if not all of the technical issues it faced early on was a large part of the company's fundraising success. "There were these gaping questions we needed to answer [before a second round could be raised], including can we actually build this? Can we turn the gantry at 60 RPM?" he says. "These were not trivial." By the time RefleXion went out to raise money again, Papiernik argues, "questions about the feasibility of the technology were basically answered. The challenge now is to make sure we have an approved, commercially viable machine. That's the next step, and it's a different sort of challenge."

The \$52 million that RefleXion raised in its Series B should, says Papiernik, "lead us to a commercial device. We may need to raise more money to create a viable company,

but with this money, we should be able to make and sell a device" (see Figure 3). Looking ahead, Venrock's Colin Cahill argues that "there's a major set of value-creating milestones that are going to take place over the next three years," including turning the company's current prototype into a viable product, getting through the regulatory process, completing the first clinical studies, and driving the first sales. "Those are dramatic inflection points for the company." Even with the large amount of money just raised, RefleXion "needs to be able to go to market in a capital efficient way, with a product that really works and the hope that three years from now, we'll have the option of either going public or raising money at a great price to drive commercialization." Of course some people will remain skeptical until RefleXion is a huge success, he says. "But I think a lot of skeptics were turned into believers with this financing." 📄

—David Cassak

RefleXion's Series B Financing Round



Source: RefleXion