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APNICURE: Unmasking Sleep Therapy With An Alternative To CPAP

Sleep apnea is now widely recognized as an underlying factor for major CV diseases and metabolic disorders, making it a huge market opportunity. CPAP, a safe and effective treatment, has long been available but people don't want to use it. ApniCure hopes that by avoiding the masks that patients hate while using the differential pressure therapy that doctors and payors like, it can unlock this potential blockbuster market.

- Sleep apnea is increasingly recognized as contributing to serious cardiovascular diseases and metabolic disorders.
- Yet, CPAP has been around for 30 years as a safe and effective treatment for OSA.
- The problem is patients hate CPAP and are reluctant to use it, largely because they don't want to wear a face mask while sleeping.
- ApniCure is looking to leverage the effective components of CPAP without using a mask in the hope of increasing patient compliance and unlocking a potentially huge market opportunity.
- The sleep therapy market is attracting increased investor and entrepreneurial interest, bringing a variety of technology approaches to address the different etiologies of sleep disorders, with many limited to specific niches. ApniCure plans a broad product line to address many clinical needs in this space.

BY STEPHEN LEVIN

Sleep medicine is a relatively recent clinical specialty, yet obstructive sleep apnea (OSA) – the most prevalent sleep disorder – has long been one of the most vexing clinical challenges facing the medical device industry. The science of sleep medicine has grown exponentially over the last 30 years, producing groundbreaking research revealing the extent to which sleep disorders have a significant impact on a multitude of serious cardiovascular diseases and metabolic disorders. The state of sleep therapy, however, has remained largely stagnant. The most effective therapy continues to be what it was in 1981 when CPAP (continuous positive airway pressure) was invented. Unfortunately, CPAP remains almost as unpopular with patients today as it was then, mainly because it requires patients to wear cumbersome, uncomfortable facial masks while sleeping.

As a result, while the OSA population continues to increase as a result of both improvements in diagnosis and the growth of contributing risk factors like obesity, the percentage of patients being treated remains low, with large numbers of unmanaged patients not even bothering to get diagnosed because they know that CPAP is their likely treatment. Nevertheless, the market opportunity remains compelling and as a result, this has been a space that has been attracting increased interest from device investors and entrepreneurs.

Redwood City, CA-based **ApniCure Inc.** is one of a number of recent sleep start-ups looking to come up with a better alternative to CPAP. The company's new therapy relies on differential pressure to keep the airway open, but with negative, rather than positive pressure. ApniCure's use of air pressure is similar to CPAP with one big difference: its device uses a mouthpiece, not a mask, which the company believes will enhance patient comfort and compliance.

ApniCure's strategy has evolved along a path that reflects the traditional device innovation model of creating value through incremental improvement of an existing technology. But the irony for ApniCure is that the traditional model has recently come under attack in this era of health care reform and comparative effectiveness. These days, payors question whether additional clinical improvements alone justify the increased cost of subsequent product iterations. Phrased differently, will payors continue to reimburse for incremental innovation? ApniCure is betting that in the OSA market there is still room for this traditional approach, particularly since it has the potential to significantly increase the number of patients diagnosed and treated in what could emerge as a blockbuster opportunity.

THE LEGACY OF HEARTPORT

Matt Vaska, ApniCure's founder, was barely familiar with sleep apnea when his father was diagnosed with the condition in 2005 and complained to his son, the medical device engineer, about how the required therapy – CPAP – was so unwieldy and uncomfortable that he wasn't able to use the machine as he should. Up to that point, Vaska's experience had been primarily in the cardiovascular space. He started in the device industry immediately after completing his undergraduate and master's degrees in mechanical engineering at **Stanford University** (before any kind of biomedical engineering program existed there, never mind the Stanford Biodesign program). After graduating, he joined Stryker Endoscopy in 1991, due, he says, more to "the fact that I needed a job and they were recruiting," than a specific interest in medical devices.

After spending three years at Stryker working on manufacturing and design engineering for light sources, endoscopes and cameras, Vaska was recruited by a former colleague to join what was probably the hottest device start-up of the mid-1990s: Heartport Inc. The company was known primarily for developing the *PortAccess* system, which enabled surgeons to employ a minimally invasive approach to a number of cardiovascular surgical procedures, including coronary artery bypass graft (CABG) surgery, through a series of small holes or punctures rather than large incisions. This technology was initially so promising that Heartport went public in 1996 and raised $97 million, and then saw its market cap top $1 billion, all before recording any sales. The company never lived up to that promise, however, ultimately crashing as part of the ill-fated device IPO class of 1996-97 – a time that saw companies fail because they went public prematurely and wound up disappointing investors. Heartport was eventually acquired by **Ethicon Inc.**, a **Johnson & Johnson** operating company, for $81 million in stock in 2001.

While Heartport wasn't successful as a company, its legacy lives on in a number of different areas. Perhaps most notable is the group of former employees that have moved on to prominent positions in the device industry over the years; among them John Stevens, MD, Heartport's co-founder and now president and CEO of **HeartFlow Inc.**, a cardiovascular imaging company (and an investor in ApniCure), and Hanson Gifford, one of the leaders of **The Foundry Inc.** incubator.

Another important part of Heartport's legacy is its IP portfolio, which extended well beyond minimally invasive cardiac surgery. In fact, some of the key patents relating to the development of TAVI (transcatheter aortic valve implantation) by **Edwards Lifesciences Corp.**, the market leader, came from Heartport.

For Vaska, Heartport was "an amazing place to work so early in my career because there were so many smart, high-energy people there, and we could focus on a wide range of innovative projects." Indeed, Vaska worked in a cardiac arrhythmia group that was looking to develop an alternative to a complex, surgical approach for atrial fibrillation (AF) called the Maze procedure that had been developed by James Cox, MD, a prominent St. Louis-based surgeon. The Heartport engineers had come up with the idea of using cold energy by applying cryo probes to create the same lesions in the heart (designed to halt the arrhythmias) as surgeons were doing using traditional surgical tools. Vaska was assigned to this R&D team after it had already come up with this basic approach, and he recalls cautioning the group that, while Jim Cox loved the idea, there were only a small number of surgeons capable of and willing to perform the Maze procedure, meaning that even with the cryo approach, this was likely to produce a technology that would only be adopted by a small group of clinicians.

> **"It's great to have a KOL supporting your technology, but that may not be the best person to judge whether that device can be successful commercially."**
>
> **– Matt Vaska founder & CTO, ApniCure**

Vaska's advice reflects a cautionary tale that Heartport and other start-ups often fail to heed. According to Vaska, "We often wind up drinking too much of our own Kool-Aid. That's especially true when a key opinion leader embraces your technology; the result is you can really get ahead of yourself." That is what happened with the atrial fibrillation project. "With AF, only a small number of doctors are even capable of performing the Maze procedure, and since it is generally not a life-threatening condition, not many patients are willing to undergo this kind of major procedure," he notes. Similarly, too, with other projects at Heartport, most notably the PortAccess system, one of the major issues that wound up undermining the company was that the tools and procedures were too complex for the comfort level of most surgeons, which meant they could only be employed by a small number of the most skilled surgeons, thereby significantly limiting potential adoption. "It's great to have a KOL supporting your technology, but that may not be the best person to judge whether that device can be successful commercially," Vaska advises.

For the Maze/AF project, Vaska suggested coming up with an easier procedure that more surgeons could perform, and one that would be less traumatic, thereby making it more attractive to AF patients. The result was a minimally invasive, rather than open surgical procedure, that involved accessing the heart externally, which was easier for clinicians and more attractive to patients. The R&D team adopted Vaska's approach and was making significant progress on developing this new system, including filing several key patents, at a time when Heartport was running out of money and looking to dramatically scale back the scope of their operations. Numerous R&D projects were cancelled, with the Maze/AF system slated to be one of them.

Vaska believed the R&D team had advanced the project to the point where it could become a viable commercial technology. "We had figured out an approach to perform a Maze-type procedure on a beating heart, accessing it externally, and were convinced that this was something that a large number of patients and clinicians would be interested in," he explains. Intent on keeping the project alive despite Heartport's deteriorating financial condition, Vaska approached the company's executive team and proposed spinning this technology out of Heartport into a start-up company. "We suggested that, instead of shutting this project down,

Heartport give us the IP around this technology in exchange for stock in the start-up, and they accepted," he says. The result: the creation of Epicor Medical Inc. in 1999. Epicor was later acquired by **St. Jude Medical Inc.** in 2004 for $200 million. According to Vaska, Heartport's stake in Epicor ended up providing Ethicon a financial return amounting to a substantial portion of Heartport's 2001 sale price.

Vaska wound up being the only Heartport employee who joined Epicor. He launched the company with Mike Sweeney, then an entrepreneur-in-residence at Interwest Partners, a venture firm that had made the initial investment in Epicor. Sweeney became CEO to get the company started, and was then succeeded by Casey Tansey, another Heartport alum (who is now at US Venture Partners [USVP] and is an investor in and board member of ApniCure). Vaska credits Tansey with driving Epicor's acquisition by St. Jude.

Having gotten a taste of life as an entrepreneur, Vaska left St. Jude shortly after the Epicor deal to pursue other device ideas he had come up with, primarily a cardiac assist pump. Working out of his garage in Palo Alto, CA, Vaska began experimenting with prototypes and talking with VCs about his pump project. "I learned some valuable lessons during this time, including how to pitch a story and understanding that your project needs to fit within the parameters of what venture investors are looking for. The pump story didn't sell well to the VCs because it's a very long-term play," he explains.

It was about this time that Vaska's father was diagnosed with obstructive sleep apnea and was calling his son across the country to complain about the CPAP therapy prescribed for his condition. "My dad generally tries to be a compliant patient, but he really struggled with using a CPAP machine," Vaska recalls. His father's complaints sparked Vaska's interest and he started researching OSA and its treatments.

OSA COMES OF AGE

Vaska found that sleep medicine, a relatively recent clinical specialty, is an area that has seen significant expansion over the past decade on all fronts: improved clinical understanding, greater physician interest, and more therapeutic options. The problem is that while there are more types of treatments available today, when it comes to OSA the only one that remains effective for the vast majority of patients is the original treatment: CPAP, which is rejected by most patients because it is so uncomfortable to use.

The whole field of sleep-related disorders, including obstructive sleep apnea, is relatively young; sleep clinicians generally point out that these conditions have only been studied seriously for roughly 30 years. Sleep is often compared to nutrition as an area that, until relatively recently, received scant attention in medical school. Much of that is changing, particularly for OSA.

> **"Patients are now pushing the doctors, telling them, 'I'm snoring, I'm sleepy; do you think I have sleep apnea?'"**
>
> **– Richard J. Schwab, MD**

Richard J. Schwab, MD, a leading sleep physician and co-director of the Sleep Center at the University of Pennsylvania Medical Center (and consultant to ApniCure), notes that sleep is now a regular part of medical school curriculum. "Typically there are multiple lectures in med school on sleep, so doctors know more about the area now. Also, many hospitals, including Penn, have in-patient sleep consult services where we're doing sleep studies on patients in the hospital, so that also increases the visibility of sleep disorders," Schwab says. "There are still a lot of patients who aren't familiar with sleep problems and a large part of that is probably because there's still wide variation in awareness among primary care physicians, some of whom know about sleep issues, while many others don't." Part of what is driving increased physician awareness is greater patient knowledge of sleep disorders, particularly OSA, drawn largely from the Internet. Schwab points out that "Patients are now pushing the doctors, telling them, 'I'm snoring, I'm sleepy; do you think I have sleep apnea?'"

While relatively little is known about many of the nearly 80 different disorders that comprise the field of sleep medicine, knowledge is increasing around the group of diseases categorized as sleep-disordered breathing, of which OSA is the most prevalent. (OSA, as the name implies, is a respiratory disorder, caused by a breathing obstruction, to be distinguished from central sleep apnea, which is a neurological condition. The two are treated differently, although patients may suffer from both concurrently, while others will suffer from just one or the other.)

That improved understanding of OSA extends both to the etiology of the disease itself, as well as to its accompanying co-morbidities. Just a decade or so ago, the main concern with apnea was sleep disruption and the impact that the resulting fatigue and daytime sleepiness had on daily activities, e.g., the dangers it poses to certain professions such as long-haul truckers. Now all forms of apnea are recognized as possible co-morbidities, risk factors, catalysts, or even causal agents for many serious diseases including cardiovascular conditions like atherosclerosis, myocardial infarction, hypertension, stroke, and heart failure. Apnea also has a strong association with metabolic disorders, including obesity and diabetes. According to Schwab, "While there haven't been a lot of randomized, controlled trials in this area, there have been many observational studies that demonstrate an increased risk of all of the major cardiovascular problems, including sudden death, along with clear links to the whole metabolic syndrome."

Although the precise etiologies are still being studied, it is clear that the intermittent hypoxia (reduced oxygen) and release of stress hormones that occur every time an apneic stops breathing and gasps for breath, which happens to these patients numerous times per hour, have serious clinical consequences. These clinical consequences also take an economic toll. A 2010 Harvard Medical School study estimated the economic cost of unmanaged moderate to severe OSA in the US to be anywhere between $65 and $165 billion, roughly $3,000 per patient annually, comprised largely of the health care costs of related diseases, traffic and workplace accidents, and the loss of workplace productivity.

Obstructive sleep apnea is essentially a mechanical problem. A patient's upper airway will narrow while sleeping, resulting in repeated breathing stoppages. The main anatomical causes for this narrowing

are large tonsils, a large tongue, excess fat in the neck, flabby tissue, a long soft palate or uvula, or a certain jaw structure. Incidence of the disease increases with age, since the loss of muscle tone that goes along with aging contributes to these anatomical obstructions. When a sleeping person with apnea breathes in, he or she creates negative pressure in the upper airway (behind the tongue and soft palate) that causes the upper airway to collapse. This often produces the vibration that triggers snoring, but more dangerously, can result in the complete blockage of the airway, or an episode of apnea.

As noted, there are several different anatomical causes of apnea and physicians are still in the early stages of precisely diagnosing specific causes for specific patients; in some people the condition is largely caused by the soft palate, while for others, the issue may be related to the tongue and/or tonsils. (ApniCure's first product, the *Winx* system, is designed to treat patients in whom OSA is caused primarily by soft palate problems, which is the largest group among OSA etiologies, comprising about half of all obstructive apnea patients.) As a result, different therapies may be more or less effective depending on the underlying anatomical cause of the condition. It is still early in the field as far as matching new therapies up with the patients who can most benefit fit from them, and the complexities around how patients come in for diagnosis and fragmented referral patterns don't help. (*See"Sleep Apnea Devices: The Changing Of The Guard "* — START-UP, *October 2010*.) CPAP retains an important advantage in that it is the only therapy that has been demonstrated to be generally effective in treating all forms of OSA.

Sleep disorders are diagnosed through sleep studies, which use polysomnography monitors to measure a variety of factors to determine how often a sleeping patient stops breathing. (Sleep studies were previously conducted exclusively in sleep labs that were initially hospital-based and then, because of the attractive reimbursement, led to the growth of free-standing sleep centers. Recent reimbursement changes now allow sleep studies to be done at home, which may also contribute to market growth by making diagnosis easier.) Based on the number of apnea episodes per hour, patients are diagnosed with either mild, moderate or severe OSA, with the latter two categories generally requiring treatment.

NOBODY LOVES CPAP

The irony behind sleep apnea is that for all of the serious complications associated with the condition, CPAP is a relatively simple therapy that is safe and effective for nearly all OSA patients. There are several different types of CPAP in addition to the traditional variety, including machines that automatically titrate themselves, and bi-level machines that provide dual pressures. But they all employ the same principle: there is a small console that generates airflow through a tube that is connected to a mask that the patient wears on his or her face when sleeping.

The irony behind sleep apnea is that for all of the serious complications associated with the condition, CPAP is a relatively simple therapy that is safe and effective for nearly all OSA patients.

The masks can either just cover the nose or the full face, and they blow air into the pharynx, creating positive pressure that basically acts like what Schwab calls "a pneumatic splint to keep the airway open." That enables the patient to continue breathing and prevents episodes of apnea. CPAP is safe for nearly all patients; probably the biggest complaints over the years, Schwab notes, include dry sinuses or runny noses, which he says have largely been ameliorated by adding humidification components to the machines.

According to Schwab, CPAP is generally effective in treating nearly all OSA patients who can tolerate the treatment. And that's where the problem lies. Many people are unable to tolerate the restrictiveness of sleeping with a mask on their face, tethered by a large tube to a bedside machine blowing air all night. For patients to receive the full benefit of the therapy, nightly usage is required, but patient compliance has long been the primary problem with CPAP. As Schwab notes, "The real issue is not whether the therapy will produce side effects, or whether it's going to be effective; it's whether or not the patient can and will use it." And if they start using it, will they continue to use it? More than 50% of CPAP users discontinue the therapy within the first year.

Many patients can only tolerate CPAP for a few hours each night, while others may start out using it regularly but eventually stop using it completely. The reasons patients most commonly give for not using CPAP are that it is difficult to use because it restricts motion in bed, involves multiple mask/strap adjustments for proper fit and to avoid air leaks, causes humidification problems including dry sinuses and headaches, and is inconvenient for travel. Other patients also report problems with claustrophobia caused by the mask, and difficulties getting used to the noise of the blowing air.

Indeed, the problems with non-compliance are now easily quantified because recent technological advances enable CPAP machines to track how long the devices are actually used through the use of smart cards. The patient brings the card in to his or her physician, who downloads the data to show exactly how long that patient used the machine each night. Future iterations will employ wireless cloud computing that will enable physicians to download this data without the patient having to bring the card to the office.

As a result of this new technology, sleep physicians now have the ability to do what most other physicians (along with product companies and payors) only wish for: to quantitatively monitor patient adherence to therapy regimens. (ApniCure has built a similar capability into its device.) "If I have patients with high blood pressure, I don't know if they are taking their medications," Richard Schwab points out. "But for my CPAP patients, I know exactly how many days and hours they are using the therapy." Some of the machines even record factors such as mask leakage, thereby providing a measure of relative efficacy. This is a feature that, in this era of comparative effectiveness, can potentially be a boon for high compliance therapies and problematic for low compliance treatments like CPAP. This technology both creates opportunities for companies that can develop technologies with higher compliance rates than CPAP – ApniCure's strategy – while also providing sleep physicians with usage data they previously lacked, which they can also use

to try to increase compliance. Schwab, for example, sees this as an opportunity to improve patient care, noting, "It is now much easier for me to effectively manage my patients."

At the Penn Sleep Center, improvements in patient care can be seen in the high compliance levels that Schwab and his colleagues are able to achieve. Schwab estimates that, industry-wide, only half of CPAP patients consistently use their machines. Yet at Penn, the compliance rate is around 80%. Schwab is quick to point out that there is a lot more that goes into driving up compliance than new smart card technology; just as important are consistent patient follow-up, and specialized care such as mask clinics to ensure devices fit properly. But the larger point is that Penn has to go to great lengths to even get an 80% compliance rate, which means that even with intense management 20% of patients can't or won't use CPAP. For most sleep physicians, 50% compliance is still considered good.

POOR COMPLIANCE = GOOD OPPORTUNITY

When Matt Vaska was starting his due diligence in 2006 to familiarize himself with the sleep apnea field, the high level of patient dissatisfaction with CPAP jumped out as a device opportunity. The market is huge and the patients that are dissatisfied with CPAP represent only the tip of the iceberg. The real market expansion opportunity lies in the so-called watchful waiters (the large numbers of patients who think they might have sleep apnea but, knowing that CPAP is the likely therapy, refuse to get diagnosed or treated).

Estimates place the actual level of diagnosed OSA patients in the US at as low as 10%. It's difficult to determine exactly how large the total patient population is, but estimates place the number in the US at anywhere from 18 to 50 million people based on prevalence, estimated at 9% to 24% of men and 4% to 9% of women between the ages of 30 and 60. According to ApniCure, more than 20 million Americans have moderate or severe OSA, with more than 1.5 million new patients diagnosed annually. The current global market is estimated to be around $4 billion, divided pretty equally between its two primary product segments: CPAP devices and polysomnography equipment (sleep testing monitors).

In addition to the size of the market and patient dissatisfaction with current therapy, Vaska also identified another key factor that led him to think this would be a viable device opportunity: the nature of the prospective therapy. "Sleep apnea is a mechanical problem, having to do with the movement of the soft palate and tongue," he explains. "I didn't have a solution in mind, but I thought, 'Well, I'm a mechanical engineer, I should be able to come up with a better way to do this.'"

In looking to design an improved sleep apnea device, Vaska drew on his previous device experience to come up with possible options. He first looked to his background in surgical devices to see if he could design a device to essentially grab the soft palate and tongue and pull them forward. "I quickly found out that you can't touch any of those tissues because you cause a severe gag reflex," he notes.

ApniCure estimates that more than 20 million Americans have moderate or severe OSA, with more than 1.5 million new patients diagnosed annually. Yet, as few as 10% are being diagnosed and treated.

Vaska also drew on lessons he had learned at Heartport and Epicor about matching a therapy with the severity of the disease. In Vaska's view, "If patients feel they can live with a problem – if there isn't an immediate severe impact – they are less likely to try an invasive solution like a surgical procedure or an implant."

He found that establishing those parameters narrowed down his options. "The question became, how can I move tissue without touching it?" he says. Vaska's solution: negative pressure, the opposite of CPAP. Instead of using air to create positive pressure to move tissue and keep the airway open, he wanted to essentially create a vacuum in the front part of a patient's mouth, which the body would then look to fill by naturally moving the soft palate and tongue forward, producing the same result as CPAP – keeping the airway unobstructed.

POSITIVE BENEFITS FROM NEGATIVE PRESSURE

In 2007, self-funded and working out of his garage, Vaska began experimenting with different ways of building an effective prototype. "Fortunately, the tools and parts I was using to design this device were pretty inexpensive, mostly a bunch of sports mouth guards, some acrylic, wire and glue, and then I would use a flashlight and a mirror to look at how the device fit in my mouth" he explains, hardly the high-tech R&D he had done at Heartport and Epicor.

Vaska quickly realized that it would be difficult to create a vacuum in the back of the throat, which is where it was needed to keep the airway open. "Once you create a vacuum in the mouth, it doesn't want to propagate to the back; the tongue will immediately move to fill that void by rising to the roof of the mouth. When I first tried it, I could feel that nothing really moved because the vacuum wasn't getting to the back of the mouth," he recalls.

His solution: use a small plastic plate to prevent the tongue from moving to the roof of the mouth and filling that vacuum. "As soon as I tried that, I could feel my soft palate move," he says. That was Vaska's "Ah ha" moment. The next step was figuring out how he could confirm and document the efficacy of his negative pressure technology with tools more reliable than the flashlight and the mirror.

Vaska knew that he had to capture the anatomical changes that the negative pressure device produced in the mouth in some kind of imaging format. His idea was to perform a 3D CT scan of his head with the device in his mouth. Vaska downloaded the necessary prescription form for the CT scan from a local imaging lab's website and then realized that he would need a clinician to sign it. That's where living in the Bay Area became a huge advantage. Vaska had an upcoming appointment with his dentist in Palo Alto to get his teeth cleaned, and while he was in the chair, explained his idea and asked his dentist, who was probably not unaccustomed to hearing about new technology ideas from patients, if he would sign the prescription and he agreed. (Vaska later gave his dentist stock options out of appreciation.)

Vaska then brought this crude proto-

type device into the imaging lab where they didn't hesitate at all when he explained what he wanted to do, again another advantage of being in the Bay Area. "In other parts of the country the imaging lab would probably have said, 'You're not coming in here with that thing.' But they were used to inventors coming in to vet new ideas. Not only did they not complain, they helped operate the prototype system while I was in the CT scanner," he notes. Vaska did one scan without the device and then several others with the device at multiple pressures. Once he learned how to read the CT images, he found that they clearly confirmed that the negative pressure moved the tissue to keep the airway open, as he had hoped. "The movement was very obvious and that was the instant I knew that my approach could definitely work," he says.

Vaska immediately set about filing for patents and putting together a business plan. At that point, he says, he had to decide whether to talk to investors to raise money, or whether to put a small team together to further develop the technology. "I decided that this was an interesting enough opportunity to bring together a team of really good people that I had worked with before because I figured that would also help with the fundraising process." Vaska reached out to Chris Daniel, with whom he had worked at both Heartport and Stryker, and two engineers who had been at Epicor, Jonathan Podmore and Jed Crowe. "I showed the technology to them, and asked if they wanted to launch a company around it as co-founders. While they didn't know the sleep space, they thought the idea was interesting and all agreed to join," he says. All three are still with ApniCure – Daniel is EVP of operations, Podmore is VP of R&D, and Crowe is a director of R&D.

Seeking business advice for the new venture, Vaska met with John Stevens, his former boss at Heartport. "John is a good strategic thinker and I thought he might be a good person to have on our board," Vaska recalls. Stevens was so impressed with ApniCure's technology that he offered to invest on the spot, taking Vaska by surprise. "I didn't even know John was an investor, and we weren't looking for investors then; so I told him we weren't quite ready to raise money," he says.

Vaska had also promised his former Heartport and Epicor colleague Casey Tansey, who was then a VC at US Venture Partners, that he would get the first look at ApniCure. Realizing that the company was building momentum more quickly than anticipated, Vaska met with Tansey, who immediately brought him into USVP's next partners' meeting to pitch ApniCure. USVP was interested but not prepared to finance the company immediately; they wanted to perform due diligence and have additional internal discussions, whereas John Stevens kept calling Matt Vaska, eager to invest immediately.

Vaska had taken the unusual approach – almost unheard of within the device industry – of developing the prototype and forming the company without vetting the technology with any clinicians, an approach made riskier by the fact that he had no experience in and relatively little knowledge of sleep medicine.

The company was faced with a tough, but good choice: either wait for USVP to deliver a term sheet, which at the time seemed pretty likely, and go with the relative security and deeper pockets of a venture firm, or accept John Stevens' offer, which would provide the immediate cash they were looking for, and wait to take on venture funding in their next round. Matt Vaska says he relied on some good advice from friends who had been through this process before. "They advised me that, at this point, the company really only needed money; we had already put a good team together. USVP seemed interested for the future, so we went ahead and accepted John's offer," he explains. Stevens invested $2 million in ApniCure's Series A round in December 2007. As it turned out, USVP came back just a couple of months later and invested the same amount at the same valuation in what became a two-tranche round.

Around the same time, ApniCure was looking to begin to establish the clinical bona fides of its negative pressure technology with leading sleep physicians. Vaska had taken the unusual approach – almost unheard of within the device industry – of developing the prototype and forming the company without vetting the technology with any clinicians, an approach made riskier by the fact that he had no experience in and relatively little knowledge of sleep medicine. "Fortunately, the company found that it was as easy to generate enthusiasm from clinical advisors as it was from investors."

As he began looking for sleep doctors in the Bay Area, Vaska found a friend who was an elementary school teacher of the children of Jed Black, MD, director of the Sleep Clinic at Stanford University Medical Center. His friend made an initial introduction to Black, who was highly skeptical at first, based on Vaska's email description, but agreed to meet with him. Vaska brought Black CT scans of the negative pressure technology in November of 2007, and those images apparently changed Black's mind. As it turns out, Black and Stevens were close friends, completely unknown to Vaska. The result turned out to be doubly beneficial to ApniCure: Stevens was even more secure in his investment based on the recommendation of his friend, the sleep expert, and for Black, the company had increased commercial standing, beyond that of a typical device start-up, with Stevens as an investor. " (Around the same time, through a colleague's introduction, Vaska also vetted his idea with Andrew Goldberg, MD, a sleep physician at UCSF Medical Center. Black and Goldberg remain key clinical advisors to ApniCure.)

A NOVEL MECHANISM IN A FAMILIAR FORM

Flush after having raised a $4 million Series A round slightly ahead of schedule, ApniCure moved out of Vaska's garage and into a small office in Redwood City, with its sights set on refining the device and completing a first-in-man (FIM) trial. Vaska admits that as a veteran of two cardiovascular device companies, the simplicity of the clinical trials process for a sleep device "was a breath of fresh air. In fact, I don't know if I can ever go back

Exhibit 1

ApniCure's Winx Sleep Therapy System

SOURCE: ApniCure

to do another CV technology."

For one thing, ApniCure never did an animal study; not surprisingly, there is no animal model for this type of sleep device (as opposed to surgical approaches to sleep disorders, which require preclinical animal work). More importantly, since ApniCure's device is not a permanent implant, the company was able to conduct its clinical trials under the non-significant risk investigational device exemption (IDE) process. According to Matt Vaska, "This meant we didn't even have to go to the FDA to approve our clinical trials; we only needed the approval of regional institutional review boards (IRBs). That made it really easy for us to get clinical data."

By late 2008, ApniCure had refined its first product, a negative pressure device called the Winx system, to the point where it was ready for first-in-man usage. Matt Vaska describes the mechanism of action for the ApniCure device as "pressure differential therapy without a mask."

The Winx sleep therapy system, like CPAP, has three basic components, and the first two are similar in both devices: a portable console and tubing. However, the Winx device has a mouthpiece, instead of a CPAP mask, which is the component that OSA patients appear to find most objectionable. (*See Exhibit 1.*)

According to Vaska, the Winx console is much smaller and quieter than a typical CPAP console because instead of blowing air, it's basically creating a vacuum. The console is also able to electronically store patient usage data. The Winx tubing is also much smaller than CPAP's. ApniCure employs a soft, flexible mouthpiece that is fitted to each patient (it comes in ten pre-made sizes and is designed to be fitted in the sleep lab).

In Vaska's view, "One of the things that is compelling for physicians is that Winx is not totally different than CPAP, which is the therapy they are most familiar with. Even though people sometimes think our device works very differently than CPAP, the mechanism of action is still a pressure differential. The bottom line is that if you want to move tissue, you have to create higher pressure in the airway and lower pressure elsewhere in the mouth; both therapies accomplish that, but we do it with negative pressure."

From a patient's perspective, the big difference between the Winx system and CPAP is the use of a mouthpiece instead of a mask. ApniCure is betting that this will greatly enhance patient comfort and help drive increased compliance. One of Matt Vaska's pet peeves is that he believes CPAP is undeservingly credited with having high efficacy rates. In his view, "CPAP is effective in the sleep lab, where they can guarantee that people use it. But if patients take CPAP home and they don't use it, then it's not a truly effective therapy for those people. So one of the things we're trying to do is change the paradigm on how people think about the effectiveness of CPAP."

A patient using the Winx system inserts the mouthpiece and pushes the single button on the console, which automatically sets and maintains the necessary vacuum level. Winx users have to keep their mouths closed, so for some patients this may require a change in habit and those who can't keep their mouths closed won't respond as well because they will lose suction, but according to Vaska, breathing is much more normal than with CPAP. He also points out that, because the Winx tubing is much slimmer and more flexible than CPAP's, it is easier for a patient to sleep in a variety of positions. One difference: the tubing collects a small amount of saliva generated during sleep as a result of keeping the mouth closed, and that liquid is deposited in a small cup located in the console, which is emptied and cleaned after each use.

As to the mechanism of action, Richard Schwab believes the Winx device may actually create a dual effect. First, the system generates negative pressure that pulls the soft palate forward toward the front of the mouth, which also seems to pull the tongue forward as well. "Simply pulling these things forward, by itself, will open the airway," he explains. "In addition, the device may be stabilizing the airway because it generates continuous pressure, which makes it less likely the airway will

collapse." (*See Exhibit 2.*)

Once the Winx system was ready for human clinical trials, ApniCure took advantage of its non-significant-risk status and initiated a highly iterative design-build-test process. "Although iterating your design quickly with human trial feedback obviously has a lot of advantages, you have to be careful interpreting results on the fly. We didn't realize it at that time, but we've learned that there can be a lot of variability, night to night and patient to patient, in sleep therapy, more so than with other kinds of therapy," Matt Vaska explains. As a result, a small data set might not reveal all that much about the therapy because of the chance that there will be very mixed results. Fortunately for ApniCure, they got good responses in their first cohort of 11 patients, demonstrating the initial efficacy of the Winx system.

The success of the FIM trial sparked ApniCure's investors to begin looking for additional VCs for the firm's next round, even though the company was not in immediate need of cash. The timing was not ideal, occurring in the middle of the economic downturn – a particularly difficult time for device companies to raise money because of the ongoing contractions among device investors. But Vaska says, "We have always done our financings in a kind of preemptive way, going out before we really needed the money, and that has worked out well for us."

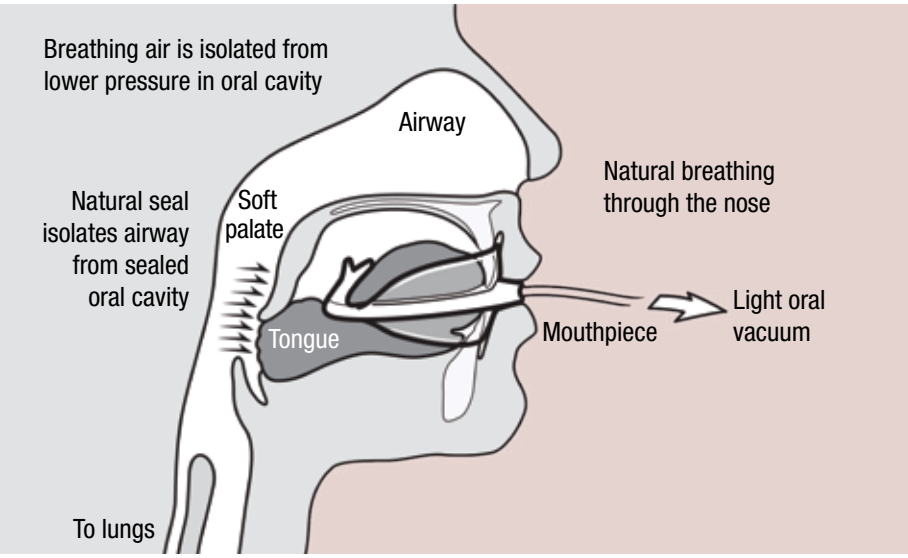
That proved to be the case once again for ApniCure. For the Series B round, Casey Tansey introduced Dana Mead of Kleiner Perkins Caufield & Byers to Vaska, and, like Tansey and John Stevens, Mead was immediately interested in investing in the company. Mead notes that Kleiner Perkins has a strong interest in the sleep space, with two other sleep companies in KP's device portfolio: **Inspire Medical Systems Inc.**, a spin-out from **Medtronic Inc.**, developing an implantable hypoglossal nerve stimulator, and **Breathe Technologies Inc.**, which is a respiratory therapy company focusing primarily on COPD, that is also working on a sleep project. According to Mead, "Sleep disorders represent such a huge market that it is the kind of area where not all conditions are going to be well-treated by a single technology. There will be room for a number of companies and products along the treatment continuum."

Kleiner Perkins came in as the only new investor in ApniCure's 2009 Series B round, which raised $13 million at what Vaska says was more than a 50% step-up in valuation, which again is particularly notable given the economic climate. Dana Mead then joined the company's board.

One year later, ApniCure closed its Series C round, again raising money before it needed to, with this investment also driven by a referral from a current investor. In this case, John Stevens introduced Barry Uphoff of Capricorn Investment Group, an investor in Heartflow, to ApniCure. Uphoff led the $38 million Series C round and also joined the board. With that round, ApniCure had raised a total of $55 million and was in good shape to complete its clinical trials, apply for both FDA 510(k) and CE mark approval, and prepare for commercialization

Exhibit 2

Winx System's Mechanism Of Action



SOURCE: ApniCure

BUILDING FOR COMMERCIALIZATION

With its financing secure for the immediate future, and its clinical trials and regulatory processes underway, the next major challenge for the company was to begin building the infrastructure necessary to take the company from a technology-development venture to a commercial organization. To do this, change would have to start at the top. Matt Vaska is the first to point out that his primary interests and skillset lie on the R&D side of the house, and he led the efforts to find a new president/CEO with a commercial background, preferring to fill the chief technology officer role, while also serving as chairman.

Vaska's successor, like Vaska, turned out not to have any prior background in the sleep area. Steve Carlson joined ApniCure in July of 2011 with more than 25 years of sales and marketing experience, primarily in aesthetics and orthopedics, having worked for **Allergan Inc.** and Orquest, with the latter being acquired by **DePuy Inc.**, a J&J operating company, during his tenure. Also, like Vaska, while he was considering whether to join ApniCure, Carlson had a parent – his mother – diagnosed with OSA, so he too, learned first-hand about the disease and the problems patients have with CPAP.

Carlson says there were two factors in particular that convinced him to join ApniCure. One was that he believed there was the potential for ApniCure to become a true platform technology company, with a number of offerings for both sleep and airway management generally. Also, ApniCure was well-financed, which, according to Carlson, meant "We wouldn't have to be chasing financing milestone after financing milestone, and instead could focus on the business. Not often these days do you find a start-up that doesn't have to raise another financing round before going commercial." In fact, the company does not have another financing milestone requirement. "That means we can

build this company to a cash break-even basis in the next two or three years," he says. "If we do additional financings, it will be because our early success means the inflection curve is steeper than expected and requires more operating cash."

Once he joined the company, Carlson's biggest immediate challenge was ApniCure's impending 510(k) clearance submission. The company eventually received FDA clearance in May of this year, albeit in a process that Dana Mead says took longer than expected, a result that is becoming more the rule than the exception among device companies awaiting agency action. There was some thought that ApniCure might be able to avoid a longer process as a result of its non-significant risk status, but that proved illusory. According to Mead, "The FDA set the bar pretty high for ApniCure. Fortunately, the company had done a lot more clinical work than is often done for a non-significant risk device." This enabled ApniCure to draw on its clinical data and address the agency's questions without having to do additional clinical work. The company also received CE mark approval for the Winx system earlier this year, although they have no immediate plans to begin selling in Europe, choosing instead to concentrate their initial commercialization efforts in the US.

ApniCure's FDA clearance was supported by the clinical data from the company's ATLAST feasibility trial. This was a multicenter, prospective, single-arm study that covered 63 patients at six US sites. The patients used the Winx device for a month with a subsequent study following patients for three months. Patients were identified as responding to the therapy if they experienced a 50% or greater reduction in their AHI and if the actual number of breathing stoppages was reduced to 20 or fewer per hour. (AHI stands for Apnea Hypopnea Index, a measure of the number of times a patient's breathing is significantly limited by at least 50% for at least 10 seconds; up to five per hour is considered normal, 5 to 15 is mild, 15 to 30 is moderate, and above 30 is severe, with the latter two categories typically requiring treatment.)

Patients enrolled in the study were not screened as to the etiology of their OSA, even though, as noted, the Winx system is not designed to treat all apnea patients, and is effective primarily on those with soft palate disease, which clinicians estimate comprises around half of all OSA patients. Of the 63 patients, 26 responded to the therapy, a clinical success rate of 41%. And of the 26 responders, 20, or 77%, had fewer than 10 events per hour. Matt Vaska also notes that three-month follow-up data indicated that patients were continuing to use the device, and that there was a strong treatment effect found even in the most severe patients. According to the consoles' electronic data measurement system, patients used the system for an average of six hours per night on 90% of nights with no serious adverse events. "The overall results of the trial demonstrated that Winx could produce results comparable to those of CPAP, in a large and easily identifiable group of patients" Vaska explains.

> **"The FDA set the bar pretty high for ApniCure. Fortunately, the company had done a lot more clinical work than is often done for a non-significant risk device."**
>
> **– Dana Mead, Kleiner Perkins**

In addition to the pending FDA submission, another issue immediately facing Carlson was that, while ApniCure had filed several patent applications when the company was launched, none had yet issued when he joined the company in the middle of last year. "That meant there was some uncertainty regarding how much real IP protection we would have," he says. Since then, ApniCure has seen three of its primary patents issued without any challenges, leaving the company with very broad claim structure. And the company also has a number of additional patents pending.

While the initial pending regulatory and IP issues were successfully resolved shortly after Steve Carlson joined the company, another significant issue presents more of a long-term challenge: reimbursement. OSA is largely handled by private payors, with only around 20% of the patient population covered by Medicare, although that may increase as the population continues to age. Steve Carlson notes that the company is still in the early stage of discussions and negotiations with payors on how they will handle Winx reimbursement.

Just as ApniCure, in order to increase clinicians' comfort levels with a new technology, has emphasized to physicians the many ways in which the Winx device is similar to CPAP in terms of how it is used and its basic mechanism of action, so too is the company emphasizing to payors how its device is much like CPAP, but with the opportunity to have much greater patient compliance and therefore improved outcomes in the hope that Winx can be covered by the existing codes and guidelines. "We think that approach is resonating," Matt Vaska explains, "because we're hearing from insurance companies that it's CPAP compliance is a real challenge" although he cautions that the company's conversations with payors are just getting started.

Both systems also employ a razor/razor-blade model where the companies look to the disposable components as their significant revenue drivers, as opposed to the consoles. According to Vaska, the manufacturing and selling costs of the Winx and CPAP systems are pretty comparable in large volumes, so ApniCure would be comfortable obtaining coverage in line with current CPAP reimbursement coding levels. And he adds, "We also save the payors money by not needing a humidifier and other components."

There are those who suggest that Winx is not a positive pressure device like CPAP, a perspective that could make reimbursement more difficult. Matt Vaska's response: "Winx is a pressure differential device, has strong clinical data across all severities of sleep apnea, and has shown highly favorable compliance, so we think we're in a good position."

ApniCure has already hired national accounts managers to call on managed care institutions and self-insured large employers to get what Carlson calls "a good understanding of how we fit in the current reimbursement structure, especially in terms of achieving parity with CPAP." The reimbursement effort is designed to build a foundation underlying the company's early commercialization efforts.

Steve Carlson points out that ApniCure

has also begun building out its marketing group and will start to put salespeople on the ground in key regions. "We're going to undertake a centers-of-excellence-focused controlled launch," he explains. "Our focus is to go deep and slow, and keep it well-structured. That's the best way for us to make sure we maintain a good fit with the sleep clinicians' practices so that the doctors and patients understand how patient and user-friendly this technology is." According to Carlson, ApniCure chose this rollout strategy because "the sleep universe today is highly influenced by key opinion leaders, who themselves are highly influenced by clinical data." The reliance by KOLs on clinical data is also why the company chose to pursue a more rigorous clinical trials approach than might have generally been required for a non-significant risk device. To date, ApniCure has treated more than 300 patients with more than 3,000 nights of therapy, and is planning additional clinical studies. In Carlson's view, "Everything starts with clinical data and experience, and how meaningful that is to clinical practice, to patient compliance, and to utilization."

BREAKING NEW COMPETITIVE GROUND

ApniCure's heavy reliance on building clinical data to drive adoption, while not unusual for most companies introducing new device therapies, is atypical for many non-significant risk products. For ApniCure, such a strategy makes sense because not only is the company attempting to introduce a new type of treatment, it is also trying to break into a market that has long been dominated by a single therapy that is basically controlled by two large companies – **ResMed Inc.** and **Philips Respironics**, (a division of **Royal Philips Electronics NV**) – each of which has roughly a 40% market share. In Steve Carlson's view, "Because there has been so little innovation in this marketplace, apart from masks and CPAP, we believe we need to continue to generate clinical data so that physicians know how our device fits into their practice along with CPAP."

ApniCure defines clinical data more broadly than the way that concept is commonly understood in other specialties. This goes back to Matt Vaska's emphasis on the need to change the paradigm in terms of discussing the effectiveness of CPAP to take into consideration the therapy's low utilization rates. "We take a view different than that of traditional clinical data," Carlson explains. "It's not just a matter of whether a treatment is effective in lowering AHI. Any discussion also has to take into consideration endpoints like utilization and compliance in order to really help physicians understand what's the best treatment modality that a patient is going to use at home, as opposed to what may work effectively in a sleep lab."

ApniCure is also looking to take advantage of the fact that, in the 30 years since CPAP was developed, no other viable therapy has emerged to broadly treat OSA. Each of the other potential therapies currently available or in development also carries significant issues that discourage patient adoption and, at best, is limited to particular segments of the overall OSA patient population.

Oral appliances provide the most widely used alternative to CPAP. These are designed to pull the lower jaw in front of the upper jaw and in doing so also pull the tongue forward, keeping the airway open. There are many of these devices on the market because they are generally non-proprietary. Effectiveness and compliance are hard to measure, but Richard Schwab estimates that these appliances are effective in roughly 60% of patients – they address a smaller segment of the population than CPAP, but they have higher compliance rates. In his view, one of the drawbacks to oral appliances is that a patient must go through the process of having the device custom-fitted by a dentist and only after the device comes back from the dental lab can the patient take it home to see if it works and if they can tolerate its use. A patient also has to pay for the appliance before finding out if works for them, a cost of around $1,500 that may not be covered by insurance. By comparison, the Winx's mouthpiece is fitted immediately and the patient can see if it works and if they can tolerate it, without having to pay for it in advance.

As noted, there are several possible surgical procedures for OSA. According to Schwab, the most effective procedure is probably maxillary mandibular advancement, where the maxilla and mandible (essentially the upper and lower jaw bones) are actually moved forward, but that generally requires wiring the jaw closed for as long as a month. There is also a procedure called uvulopalatopharyngoplasty (UPPP), which is a traumatic, painful surgery that involves removing tissue from the back of the throat. "There really isn't good data suggesting that any of these surgeries is effective in treating OSA; maybe they work 50% of the time at best and there's some placebo effect there," Schwab explains. "As a result, we don't recommend the surgery unless somebody has gone through CPAP and an oral appliance and can't tolerate either, and they have significant apnea that needs to be treated."

Against this landscape of ineffective or unattractive therapies, several start-up companies, in addition to ApniCure, are attempting to develop better alternative OSA treatments. They range from simple disposable products to surgically implanted devices, but one thing they have in common is that none involve a face mask.

Ventus Medical Inc. has received FDA clearance for its *Provent* therapy, which involves disposable Band-Aid-like devices that fit over a patient's nostrils and contain valves that regulate breathing to keep positive pressure in the airway when exhaling. In addition, several companies, including the aforementioned Inspire, **ImThera Medical Inc.**, and **Apnex Medical Inc.** (for which Schwab is a consultant), are exploring hypoglossal nerve stimulation devices, which are implanted in a patient's chest much like a pacemaker except with leads going to the nerve under the jaw that controls the tongue instead of to the heart.

Richard Schwab has used the Provent nasal valves with his patients, and says they generally found them hard to tolerate. "It's just like CPAP – you have to educate people how to use it, and while I haven't had great experience with Provent, there are some papers that suggest it doesn't work too badly, so I'm going to give it a second chance," he says. The hypoglossal nerve stimulation devices won't be available in the US for at least a couple of years, and Schwab predicts these will only be a treatment of last resort. In his view, "It looks like this approach may be effective, but this will also require a major procedure and a permanent implant. It will probably only be an option for patients with severe apnea who can't tolerate CPAP and don't want to have surgery."

IT'S LIKE CPAP, BUT DIFFERENT

Many new devices and procedures have been proposed for OSA, yet the competitive landscape appears to look pretty much the same as it always has. So far, no other therapy has been able to match CPAP's ability to effectively treat all types

of OSA patients. Each new therapy from the companies mentioned above appears to have its own drawbacks either in terms of ease of use or applicability and will likely be confined to serving specific niches of the OSA market.

Indeed, even ApniCure falls into that group, at least initially. As noted, Winx's current clinical data only support the potential to treat roughly half of all OSA patients. Steve Carlson insists that the company has plans for a robust product pipeline that will provide devices to eventually serve all OSA patients, including those whose apnea results primarily from tongue and mandibular advances, as well as combination therapies and devices that can be actuated mechanically. Other market segments that ApniCure is also looking at include pediatrics, snoring, hospital airway management, and dental appliances.

In the meantime, the company is looking to establish itself as the leading alternative to CPAP in the soft palate segment. "Initially, Winx is going to be used for people who can't tolerate CPAP," Richard Schwab predicts. Whether the ApniCure device will replace CPAP as a first-line therapy for those patients will depend largely on both clinical data and reimbursement coverage, areas in thatthe company intends to aggressively pursue. Schwab points to the fact that "Oral appliance companies did head-to-head studies comparing their devices with CPAP, and while the appliances didn't work quite as well as CPAP, they found that patients tolerated appliances better and that has helped them gain a foothold in the market. If ApniCure does a head-to-head with CPAP, they may see similar results, which may result in more sleep physicians using this as a first-line treatment. But we're not there yet."

ApniCure will be trying to walk a fine line in challenging CPAP, a therapy whose strengths and weaknesses are well established. The company needs to align Winx with CPAP, in terms of physician acceptance and reimbursement, also highlighting the new therapy's differences so that patients who currently find CPAP too cumbersome to use will see the benefits of Winx, a strategy ApniCure is betting will significantly expand the market.

In this way, ApniCure's strategy is a throwback to the traditional device innovation model, which historically has been based on incremental innovations to existing technology. In this era of health care reform and comparative effectiveness, that traditional model has come into question, with industry and payors wondering if there still is a market for incremental innovation based primarily on improving clinical, as opposed to economic, outcomes. In ApniCure's case, the answer might be Yes. Here, incremental innovation may finally be the key to unlocking what for 30 years has been a huge, but largely untapped market. In this case being a lot like CPAP, just better, may prove to be enough.

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