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TRANSENTERIX: MANAGING REVOLUTIONS IN SURGERY

Whether single-port surgery or NOTES is the true next revolution in surgical procedures, TransEnterix believes it has the answer to both.

- Minimally invasive surgery, performed through a number of ports to create access and enable visualization, manipulation, and dissection, promised to revolutionize surgical techniques two decades ago, but ultimately fell short of changing the way surgeons perform the majority of surgical cases.
- Part of the problem: surgeons were uncomfortable with the devices developed to enable more complex procedures. TransEnterix's solution: surgical tools that adapt the flexible catheter technology behind interventional cardiology to general surgery.
- TransEnterix's novel approach not only allows surgeons greater dexterity in performing complex procedures, but also enables them to do surgical cases through a single access port, using the body's umbilicus.
- So-called single-port surgery has its skeptics, but it's gaining momentum. The question for TransEnterix: how will single-port surgery play out against the surgery's newest technique—natural orifice transluminal endoscopic surgery, or NOTES?

BY DAVID CASSAK

For all of the change that minimally invasive approaches brought to surgery two decades ago, the MIS (minimally-invasive surgery) revolution has fallen something short of complete. While conversion to MIS or laparoscopic techniques was rapid and remains at nearly 100% in gall bladder removal (cholecystectomy), other procedures have taken longer to convert and have come nowhere near the same rate of penetration—thus procedures such as bowel resection and appendectomy are only performed laparoscopically about 50% of the time; in an area like cardiac surgery, penetration rates have stalled at much lower numbers.

A large part of the pushback came because surgeons found that more complex procedures were difficult to do with the rigid instrumentation that was perfect for lapaproscopic cholecystectomy. There were two solutions for solving the problem of MIS' lax penetration beyond lap choly: improve the instrumentation and/or improve the surgical techniques.

For much of the late 1990s and early 2000s, no one did much of either. Innovation in surgical instrumentation and devices, in particular, lagged, with few, if any, breakthrough technologies beyond a robotics industry that grew by fits and starts. But beginning a few years ago, surgeons themselves began to experiment with new ways of doing minimally invasive surgery that would build on and improve conventional MIS techniques. One new approach centered on so-called single-port surgery: replacing the multiple trocar-created access points through which surgery is done—sometimes as many as five different ports—with one single access port; the other NOTES, surgery performed through natural orifices of the body, requires no surgically created ports at all.

Both single-port surgery (SPS) and NOTES would enhance many of the benefits of multi-port surgery such as reduced pain and trauma for the patient and quicker recovery times. But neither is without its skeptics: single-port surgery critics argue that the benefits of such an approach are little more than cosmetic, while even NOTES advocates concede that the current buzz is based on little real clinical evidence.

To most people's minds, single-port surgery is the nearer-term prospect, but NOTES is the true revolution, with single-port simply a way station until the clinical bona fides of NOTES are clearly established. But for some time at least, the two will be competitive: if you have a really effective single-port technique, why bother with NOTES? Neither, however, is likely to represent anything like a real fulfillment of the MIS revolution without one more thing: an agile technology that enables either or both new surgical approaches to be performed. NC-based **TransEnterix Inc.** believes it has just such a technology, created through the marriage of MIS tools and the flexible catheter technology of interventional cardiology.

A CARDIOLOGIST'S TRICKS

When Richard Stack's mother and brother each had laparoscopic surgery a couple of years ago, it was clear that the surgery was anything but minimally invasive. Yes, the surgery was performed through a series of ports, enabling access and visualization and the procedure itself, rather than through

large, open incisions. And yes, Stack's relatives saw some of the purported benefits of minimally-invasive surgery: reduced pain and trauma for the patient, easier technique forthe surgery. But by the time the surgery was done, those benefits seemed dminished by the multi-port strategy, and Stack began to wonder if there wasn't a better way to do surgery.

Soon after those procedures, Stack, a physician and pioneer in interventional cardiology and founder of **Synecor LLC**, a North Carolina-based incubator with an impressive track record in device-company creation, approached Aurora Pryor, MD, the surgeon who had performed the surgeries, to talk about what seemed like a relatively invasive approach to less-invasive surgery. Stack had already begun to hear about a surgical approach called NOTES (natural orifice transluminal endoscopic surgery), a procedure by which surgeons cross the lumen (abdominal wall, colon, esophagus, etc.) to perform surgery in the peritoneal cavity, thorax, etc., accessing the surgical space through one of the body's natural openings. "That just seemed like something that could easily be done through a catheter," he recalls. Within a couple of years, Stack and Pryor would launch TransEnterix, a North Carolina-based surgical device company with a platform technology that company officials believe will put it in the vanguard of a second revolution, after MIS itself, that is coming to surgery.

From the beginning, Stack had been intrigued by the possibility of using flexible catheters in surgery—interventional cardiology, after all, rests on innovative ways to deploy catheters—and working with Aurora Pryor, who now serves on TransEnterix's SAB, he began to develop a series of surgical tools that would combine the flexible catheters of interventional medicine with access through a single port, rather than the multi-port approach currently used in MIS. "It was pretty clear that we could use the same catheter technology [that had been used in interventional cardiology] but instead of making four or five penetrations of the abdomen wall, we'd just go in through the umbilicus, which is already a natural scar," he says. "We thought we'd put everything through a catheter and get the same kind of orientation we'd get if we'd penetrated the wall, but with no holes."

Indeed, Stack insists that far from a departure from Synecor's core interventional cardiology expertise, TransEnterix is, in some ways, a natural extension of its original mission and a fulfillment of its vision. First, he notes, interventional cardiology itself is and long has been "arguably ahead of other areas of medicine in trying to create less-invasive alternatives to surgery." The early pioneers in interventional medicine, folks like Andreas Gruentzig, John Simpson, and Stack himself, simply took on "the biggest opportunity in surgery, which was heart surgery."

Moreover, notes Stack, who counts several major innovations in interventional cardiology among his accomplishments, much of the development of technology and technique that appeared first in interventional cardiology would lay the groundwork for the new revolution that is now taking place in general surgery. (*See "Richard Stack, MD: Filling the Cath Lab Pipeline,* IN VIVO*, June 2006*.) "The methods, materials, and skill-sets that we took to a very high level of development in the cardiovascular arena," says Stack, will be the same ones that TransEnterix—and others—brings to other surgical specialties. "Part of our vision [at Synecor] was to figure out how to take what we've learned in 25 years of transforming the field of interventional medicine and apply it to those areas that haven't yet been transformed by interventional techniques," says Stack. "And frankly, [general] surgery was a no-brainer."

SEVEN STEPS

TransEnterix was officially launched at the end of December 2007, but Synecor officials had already done a significant amount of work on the company's technology before the official launch, creating what CEO Todd Pope calls "a single-port access platform in surgery." The platform combines both a proprietary access approach and a wide range of instruments—some still to be developed—that enable a variety of surgical procedures, some of which will be proprietary to TransEnterix, some not. It is this comprehensive approach in terms of both clinical reach and procedural capability that makes the technology a platform, say company officials.

Interestingly, Synecor officials didn't start out trying to develop a single-port system; rather, blending perspectives from both interventional medicine and current surgical approaches, the idea was simply to create better tools for use in minimally invasive surgery to, as Todd Pope puts it, "enhance the laparoscopic experience." In fact, some of the instruments TransEnterix has developed have never been used in general surgery before.

That said, TransEnterix has tried, as far as possible, to replicate a traditional laparoscopic procedure, but with the benefit of single-port access. For example, company officials note that early market research showed that surgeons like the traditional triangulation of visualization and manipulation, with the camera in the middle and various instruments coming to the (closed) operation site from the sides.

In addition, surgeons want to be able to use as many of the tools they currently use as possible—graspers, clip appliers, dissectors, etc.—and they like to be able to retract organs, such as gall bladders, without exchanging instruments: TransEnterix's four-channel system allows surgeons to do just that, whereas most other single-port approaches today, which have only two or three channels, don't. "We don't want to have to ask surgeons to do anything differently," says Pope.

A REVOLUTION CUT SHORT

Better, more flexible instrumentation would likely also make more complex MIS procedures faster—slow, difficult-to-perform cases are a major reason MIS penetration beyond lap choly has lagged. Perhaps just as importantly, given the high success rates of multi-port laparoscopic surgery, any single-port innovation, no matter how effective, has to be affordable said the surgeons. TransEnterix's market research suggested that surgeons would pay a small premium for better devices, but not much more. "They don't want to pay double to do what they're currently doing," says Pope.

As noted, key to TransEnterix's approach is a flexible catheter technology borrowed or adapted from interventional medicine. The great promise and success of minimally invasive surgery as it evolved in the 1980s, when penetration rates of laparoscopic cholecystectomy were starting a rapid ascent toward 90% in the US, hit a wall several years later as surgeons and some product companies tried to extend the MIS revolution to other procedures such as hernia repair and appendectomy. Today, 95–97% of gall bladder removals are done minimally invasively; by contrast, only about half of all bowel resections and appendectomies are done in that manner.

Success in bringing MIS to even more complex surgeries such as orthopedics and cardiac surgery stopped even shorter, and by the early years of this decade the so-called minimally invasive surgery revolution was something less than a full revolution.

Certainly no one would deny that the notion of shorter incisions and laparoscopic surgery has re-crafted surgical techniques and changed the way many thought about procedures. But the number of surgical cases done routinely through small ports is far smaller than the predictions of just a few years earlier suggested they would be by now. Notes Pope, "Twenty years ago, most people assumed that a lot of procedures would move as fast to laparoscopic techniques as laparoscopic cholecystectomies did. That didn't happen then, and it still hasn't happened."

Certainly, the MIS revolution has evolved beyond lap choly—today, lap choly represents only about 40% of the MIS procedures. And some analysts predict that MIS penetration will begin to ramp up dramatically as technology and training fall into place—a 2006 study done by The Advisory Board Co. projects that penetration of some procedures, such as gastric bypass and appendectomies, will within five years reach levels close to current gall bladder removal rates.

Still, there are a number of reasons why the MIS revolution that came to cholecystectomy never really took off more broadly—in orthopedics, for example, there's been a shift toward smaller-incision surgery, but the widely touted two-incision surgery proved a failure. In cardiac surgery, the debate over off-pump and on-pump MIS seemed ultimately to be beside the point. For one thing, there's always a general conservatism, particularly in surgery, where things such as tactile sensation and visualization play such a vital role. But certainly one reason for MIS's half-hearted revolution is that the technology to enable more complex procedures, in general surgery as well as in cardiac and orthopedics, never really materialized. Thus, even surgeons who wanted to use less-invasive techniques in doing surgical cases other than lap choly often found themselves working with rigid instruments that were difficult to use and that made the procedure more time-consuming, particularly when compared with the open procedures that were easy to do and that usually produced great results.

AMID DEBATE, DEVICE COMPANIES BET ON SINGLE-INCISION LAPAROSCOPY

The following is adapted from an article to appear in the June/July 2009 issue of Medtech Insight

One of the most recent trends in minimally invasive surgery is to minimize the number of laparoscopic incisions during major abdominal surgery by accessing the peritoneal cavity via the umbilicus using a single skin incision. There are various names and acronyms for these single-incision approaches (*See Exhibit 1*), but no matter what you call it, single-incision laparoscopy introduces additional constraints to the conventional laparoscopic environment and requires surgeons to use new flexible and articulating instruments and novel access platforms to perform these surgeries. Over the last two years, medical device companies have been racing to develop enabling technologies for single-incision laparoscopy, but the approach is controversial and its future appears uncertain as surgeons debate the cost/benefits of the single-incision laparoscopic approach.

There are several theoretical benefits to the approach, including the potential for less pain, lower costs, shorter lengths of stays, and less blood loss, but the techniques have yet to demonstrate any clear economic or clinical benefits beyond cosmesis. At the same time, some are questioning the very safety of these procedures and whether improved cosmesis merits the cost of new equipment, extended operating room time, and added risk potential, as it is technically difficult given existing tools and techniques. Moreover, because it requires an incision in the umbilicus that is larger than those made for conventional laparoscopy, the approach could obviate all of the theoretical benefits and increase the risk of umbilical herniation, concerns that can only be proven or disproven over time.

Most would agree that a large, randomized, controlled clinical trial is needed that compares patient outcomes for single-incision and multi-port laparoscopic surgery. If such a trial shows only a cosmetic benefit for the single-incision approach, it could provide support to those opposed to the technique and limit the growth of these procedures. On the other hand, surgeons currently performing these procedures say improved cosmesis is enough justification to move forward with the technique as there is a subset of patients who do not want a visible scar on their abdomen and it is the doctor's job to make their patients happy. For these doctors, consumer demand has already driven patients into their offices because of word of mouth and/or hospital press releases trumpeting the doctors' ability to perform "scarless" surgery.

Many are questioning whether the single-incision approach is being driven by industry, the most likely to profit from the sales of new technologies, and by physicians who want to be schooled in the technique to gain a competitive advantage over their peers. And although skeptical physicians believe the approach is more hype than help, many of these skeptics are seeking training in the technique in fear of being "left behind" and of losing patients to hospitals and peers who are marketing themselves as leaders in this area—-a phenomenon that happened to many physicians when lap cholys were first introduced into clinical practice. At this year's meeting of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) held in Phoenix in April, the lectures on single-incision surgery were standing room only. And while interest in the technique appears high, rhetoric at the meeting suggests there is little consensus on single-incision surgery among surgeons, who provided live feedback on the subject at the microphone, via audience response surveys, and in questions submitted wirelessly during some of the panel discussions.

In spite of the debate, a "scarless" approach continues to be the holy grail of surgery and almost every device manufacturer competing in the market for rigid and flexible endoscopic technologies seems to be jumping on the single-incision bandwagon. With a market potential that is huge by most estimates, single-incision technologies could be the next big thing, or the next big bust. Either way, the flexible and articulating technologies being developed for the single-incision approach have the potential to benefit all of laparoscopic surgery, and the winners will likely be those companies able to develop the most innovative and cost-effective technologies.

TransEnterix's device addresses those problems through a proprietary, flexible catheter technology that accesses the operating space through a single port, in this case, the patient's umbilicus. The device itself has four working channels that, once deployed, allow the surgeon to use a number of different tools, such as manipulators, dissectors, clip appliers, and suturing devices, to name just a few, as well as visualization systems.

Clearly, the TransEnterix device represents an advance on conventional minimally invasive surgery tools. Todd Pope notes that currently, minimally invasive abdominal surgery is done through four or five portals, all created with a trocar. "We think we can do the same procedure through just one access, the belly button," he says. And that brings other benefits: for example, managing several instruments through multiple ports often requires additional staff in the OR and can be disorienting to surgeons who, instead of moving instruments themselves, have to direct others to do so. TransEnterix's device allows most procedures to be done with a single operator, which gives the surgeon more control over the procedure and is also a cost-saver for the hospital.

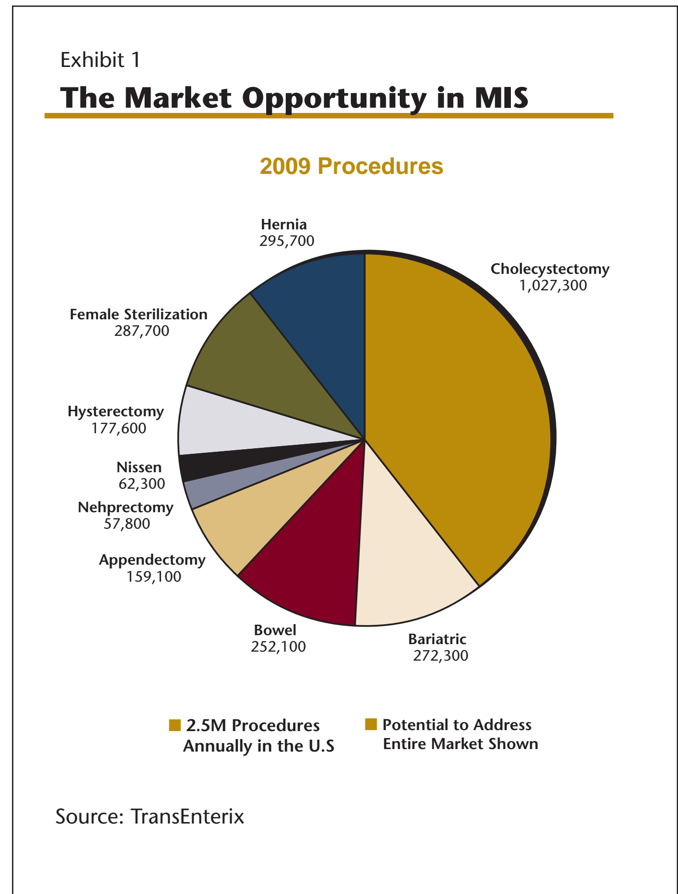
Of course, not everyone is convinced that single-port surgery is an improvement over the current standard: multi-port MIS. Some surgeons claim that the benefits, at this point, of single-port surgery have yet to be proven in valid clinical trials and appear to be mostly cosmetic. For such skeptics, single-port surgery is really just a more-expensive approach to MIS without benefits to justify the higher device costs. (*See sidebar, "Amid Debate, Device Companies Bet on Single-Incision Lap."*) TransEnterix officials counter that what they're doing isn't just enabling better laparoscopic surgery, but, through their innovative flexible catheter technology, they are teeing up what Pope calls "a new way to do surgery." "We're introducing catheters that have proven their ability to snake through [the vasculature of] the heart and brain."

Perhaps more to the point, TransEnterix isn't positioning itself just against the current, multi-port approach to MIS; it also must compete with what some see as a kind of second revolution in MIS: the trend toward NOTES or surgery performed through natural orifices. Todd Pope concedes that "many procedures are looking to advance into natural orifice procedures," but TransEnterix's goal is to "establish a beachhead in single-port surgery," he says. "We believe single-port surgery through the umbilicus is a huge, near-term opportunity."

"There's a lot of momentum right now around single-port surgery," says Pope. "With our technology, there's just no reason to have four or five trocars any longer," he goes on, drawing a distinction between TransEnterix's approach and other single-port approaches. But others are picking up on the opportunity. At the recent Society of American Gastrointestinal and Endoscopic Surgeons meeting, **Covidien Ltd.** launched its Single-Incision Laparoscopic Surgery (SILS) device and **Ethicon Endo-Surgery Inc.**, a **Johnson & Johnson** operating company, met privately with doctors to highlight its initiatives in this area. Notes one industry analyst: "Single-port surgery is here. Other than NOTES, it was the most discussed emerging surgical method" at this year's SAGES.

Exhibit 1

The Market Opportunity in MIS



Source: TransEnterix

THE PROBLEM WITH NOTES

Though they are, in the near term, somewhat competitive approaches—why do NOTES if single-port surgery works just as well, and vice versa—NOTES and single-port share one goal: so-called "scarless surgery," which will likely make this next revolution in surgery even more consumer-driven than the first-generation MIS was, pressuring surgeons to adopt the techniques even more.

Despite the limitations of second-generation MIS, penetration of laparoscopic procedures has transformed surgery, certainly in the US, but even around the world. TransEnterix officials note that there are currently some 2.5 million laparoscopic procedures performed each year in the US, about one million of which are gall bladder procedures. Laparoscopic hernia repair accounts for another 300,000 procedures and tubal ligation, bowel resections, and hysterectomies round out the remaining procedures with around 250,000 laparoscopic procedures each year. And more and more of those are going toward single-port access.

And as the market grows, so does the opportunity. Notes Pope, "we could get single-digit market share and be an incredible success." But not if surgeons are already looking past single-port access to NOTES. Given the success of MIS, the appeal of NOTES—accessing the operating space through the mouth, the rectum, or the vagina—is clear. If operating through small ports represented a huge benefit over traditional open surgery, the ability to do the same procedure without actually poking holes with a trocar has even greater benefits in the terms most often used to describe the benefits of MIS generally: less patient trauma and less blood loss, shorter procedure and quicker recovery times, etc.

Still, for all the current buzz around NOTES, there are skeptics. Many industry observers point to the scanty clinical evidence around NOTES and small number of procedures performed to date and argue that it's simply too soon to talk

about NOTES in any kind of practical sense. Even those who remain convinced that NOTES will be an important approach in the future concede that single-port surgery is more likely to be adopted sooner.

Moreover, TransEnterix officials note that there are issues that have arisen around NOTES that have led some to resist, if not reject, the new approach. One is simple technical feasibility; several of these procedures or approaches remain to be clinically validated through rigorous studies, though there are major protocols now underway. Related to that are training, staffing, and reimbursement issues that arise because most NOTES procedures are new and not fully vetted.

Exhibit 2

The Surgeons' Requirements

- Triangulation
- Retraction
- Low Profile Port – Minimum 4 Working Channels
- Common Tools: Grasp, Clip, Cut, Dissect, Cautery, Suction/Irrigation
- Affordability
- Procedure Time – Comparable to Current Surgery
- Single Operator

Source: TransEnterix

In addition, there may also be some resistance on the part of both patients and surgeons for what might be called psychological reasons—the idea of having surgeons access the operating space through one's rectum or vagina may simply turn off some patients. Nor is such a response simply emotional—the consequences of something going wrong with some NOTES procedures are likely to be significantly greater than with a conventional portal-driven MIS or even an open procedure.

TransEnterix officials say that such concerns are reduced if not outright eliminated by the company's single-port approach. For example, there's established reimbursement for single-port surgery, not for NOTES. And most of the training and adoption issues surrounding single-port are smaller than for natural orifice approaches. Indeed, note company officials, unlike with NOTES, surgeons doing surgery through a single-port are essentially doing the same thing they do in multi-port surgery—they're just doing it through a single access point.

COMING HOME

Soon after closing its Series A financing, a late December 2007 round that raised $20 million, TransEnterix began building its management team, from the start targeting seasoned executives with significant experience in both medical devices and, in most cases, minimally invasive surgery—a common, if somewhat expensive strategy of Synecor companies. Thus, Todd Pope was global president of interventional cardiology giant **Cordis Corp.**, a Johnson & Johnson operating company, just before accepting the job at TransEnterix in early 2008.

Though his most immediate experience had been in cardiovascular devices, Pope's career in devices goes way back, with stints at a number of start-ups as well as an earlier post at J&J and some time at **Boston Scientific Corp.**, where he was VP of sales and marketing for Target Therapeutics. For Pope, who lived through the first MIS revolution 20 years ago, the opportunity to join TransEnterix was like coming home. "It's really good to be back where I started in laparoscopic surgery," he says.

Pope first got to know Synecor's founders, Richard Stack and Bill Starling, in the early 1990s when he worked in the San Francisco area for Target. Over the years, their paths crossed several times—in the early 2000s, Bill Starling was on the board of a biotech company called Liquidia and was instrumental in recruiting Pope to be CEO—though the opportunity at TransEnterix became real only a couple of years ago when the three met up at an event at Stanford University.

The fact that Research Triangle Park, NC-based TransEnterix represented something of a homecoming to Pope, who was born and educated in the area, made the offer tempting. But for Pope, the real appeal lay in what he saw as a kind of renaissance in MIS technology. Twenty years ago, during the first wave of MIS, there had been "a great deal of excitement around new technology," he says. But, speaking broadly, there hadn't been a lot of investment and development in surgical instrumentation over the past dozen years, with most of the investment dollars going into areas like cardiovascular and orthopedics/spine. Now with renewed interest in single-port and NOTES, says Pope, "Small companies are starting to spring up, big companies are beginning to invest, and everybody's getting excited again."

A CULTURE OF CUSTOMER INTIMACY

In addition to Pope, TransEnterix's senior team includes Tom Miller, VP of operations, formerly the CEO of several start-up laparoscopic companies and one of TransEnterix's first employees; Sal Castro, VP of R&D and a veteran of development efforts at US Surgical in the 1990s and spinal cage pioneer Surgical Dynamics; and John Tushar, VP of business development, whose background includes Abbott Laboratories Inc. and Ethicon Endo-Surgery, as well as several start-ups.

Tushar joined TransEnterix last September, not long after the sale of his previous company, **Closure Medical Corp.**, to J&J. (Tushar had run a small technology company between his stints at Closure and TransEnterix.) Impressed by the management team TransEnterix had put together, Tushar says he also saw the potential of the technology immediately: "After seeing the first lab work done, all I could think was, 'This goes well beyond general surgery; this is a platform, a fulcrum so to speak that allows surgeons to not only do surgery, but also a wide range of other things, like ablative therapy and drug delivery and anything that requires imaging and guidance in the abdominal cavity that is a challenge to do today.'" Asked about joining a start-up company in a market dominated by large surgical device companies, Tushar adds, "I never really worried about what Ethicon or US Surgical would do; I saw this as a technology that could disrupt the marketplace."

About TransEnterix's management team, Pope says, "Not only do they all have transferrable skills, but they've also spent much of the past 20 to 30 years in laparoscopic surgery." In addition, Pope notes that one early influence on TransEnterix was brought by the company's chairman, Fred McCoy, who headed Guidant Corp.'s CRM business until Guidant's acquisition by Boston Scientific in 2006 and who joined Synecor in July of 2007. Pointing to Guidant's culture of innovation driven by close collaboration with physicians, Pope says, "We very much want to run a customer-intimacy, innovation model, and I think Guidant did that as well as anyone."

Fred McCoy, too, appreciated Synecor's talent for developing novel technologies and companies. Even before joining, as part of the senior management team at Guidant, he had been well acquainted with Synecor; BioStent, an early Synecor company and a pioneer in bioabsorbable stents, had been acquired by Guidant Corp. in 2003 and, closer to home, Guidant was one of the early investors in another Synecor company, InnerPulse, developers of a percutaneously delivered defibrillator. (*See "InnerPulse: Bringing the Interventional Revolution to CRM,"* IN VIVO, *December 2006.*)

And though CRM, not general surgery, was McCoy's long-time sphere, he says he saw parallels between what TransEnterix was trying to do and what Guidant had done. "First, there was the ability to tap into a large, established market in which disruptive technology could play very effectively for better patient outcomes," he says. "It also struck me that the TransEnterix approach to single-port surgery and NOTES was also very extendable: about as far as the eye could see, it seemed like product iteration was going to be a part of the success equation and that, of course, means customer intimacy, the ability to understand what the customer wants and to deliver that, through rapid, consistent product iteration, refreshing the product line. That was the culture we tried to establish at Guidant."

A RICH DEAL

If Synecor's Series A financing was typical of a Synecor financing, it was anything but typical for most investors. Synecor is known for its rich financings at high valuations, and TransEnterix is no exception (*see "Synecor's Golden Touch,"* IN VIVO, *June 2006*). As noted, the company raised $20 million in its Series A—an exceptional amount for a surgical instrument with a 510(k) regulatory path—at a $20 million pre-money valuation from a group of investors that includes Boston-based SVLS, which led the deal; Synergy Life Science Partners, a venture firm founded by Synecor's founders that for that reason couldn't lead; and Parish Capital, a Raleigh, NC-based fund of funds. (By comparison, InnerPulse raised $16 million on a pre-money valuation of $21 million for a PMA device.) Bill Starling, one of Synecor's founders, notes that because of its incubator role, "One of the virtues of Synecor is that we can be patient and take our time. We reduce risk and build value, and usually get the deal we're looking for."

Fred McCoy notes that typically, a device company yields about 50% of its equity in its Series A financing. For most start-ups, a Series A of between $3 and $5 million is the norm; Synecor's strategy: before yielding half the company, it ought to be worth closer to $40 million. "We try to add enough value so that investors will believe it's worth $40 to $50 million. If we've done what we should have, [the deal] will yield that—we can then hire the best CEOs and technical people and have a comfortable runway," he says.

And notes Richard Stack, it's precisely the expertise built up in Synecor, as incubator, that helps drive value. "What we're able to do is to identify the requisite elements for rapid iteration of innovative products," he says. For example, Synecor's two prototyping labs enable the company "to create novel prototypes very rapidly—we can get feedback from surgeons and turn around new designs in hours, sometimes overnight, where it might take some other company weeks or months." Working closely with the company's SAB, TransEnterix's own device went through eight or nine major iterations over the last year and a half, including 50 to 60 smaller feature changes. Notes Stack, "We then make sure we have the IP under control and wrap the business elements around that."

Such development capabilities are beyond the scope of most companies, even very large ones with deep resources, says Todd Pope. "And I've worked for two of the biggest and best," he adds. Indeed, Pope calls Synecor's capabilities—particularly its closed-loop, physician-driven, rapid prototyping—TransEnterix's "secret sauce." Adds John Tushar, "We probably can't compete with the big companies in terms of manufacturing and sales and distribu-

Exhibit 3

The TransEnterix Effect

Continuous Stream of Innovation

Source: TransEnterix

tion. Where we do have a competitive advantage is in innovation. That's really what we're all about."

Of course, not everyone appreciates Synecor's approach. Bill Starling says TransEnterix got more than its share of turn downs. "We got turned down for a lot of reasons, not all related to the technology, he notes. "We knew we were asking for a lot of value."

Moreover, high valued surgical tools aren't every investor's cup of tea. But Starling says that the right deal in surgical devices can pay off big-time, and he points to a couple of deals, most notably **SurgRx Inc.**, a California company with an energy-based device, which was acquired last year by Ethicon Endo-Surgery for $285 million; J&J's 2005 acquisition of Closure Medical for $370 million; or, in a slightly different space, **Olympus Corp.**'s $1.92 billion acquisition of **Gyrus Group PLC**. Says Todd Pope, "This is a big market with big companies playing in it and a lot of them are acquisitive." Other companies in TransEnterix's space: Ethicon Endo-Surgery and Olympus, as mentioned, as well as major surgical device and products companies such as **United States Surgical**, a division of Covidien, and **Stryker Corp.**, many of which, according to Pope, have efforts underway in single-port surgery and would like to expand them.

MISSING THE BOAT?

About TransEnterix's $20 million pre-money valuation, Bill Staling concedes, "It is a lot of money, but when you look at the inflection curve of value creation, once we get to first-in-man and the 510(k) submission and clearance, there's a quantum leap in value creation. And in our money raising we wanted to make sure that we were close to that and could get to those milestones." From first-in-man to commercial release, says Starling, shouldn't be that far for TransEnterix. Once the company is on the verge of commercialization, it will likely try to raise a second round of financing "to really beef up a large commercialization [effort]," says Todd Pope.

That product launch could, if all goes well, come by the first half of 2010, and when it does, Pope argues, TransEnterix should have a lot of what investors like to see: a novel, arguably disruptive technology that is still a 510(k) device, serving a large market opportunity but with established reimbursement and near to commercialization, with revenues likely within 12 months. Perhaps the only question on investors' minds: in focusing on single-port surgery, has TransEnterix missed the NOTES boat?

Given all of the challenges that face NOTES advocates, the temptation may be to ask whether single-port surgery isn't

SINGLE-PORT OR NOTES: A SURGEON'S PERSPECTIVE

Dr. Aurora Pryor's interest in expanding the range of minimally invasive surgery goes way back. Early on, she was, she says, "active in the NOTES movement" though she hadn't actually done any cases "because I didn't think the technology was good enough to do cases on people."

In fact, Transenterix's technology was originally "designed for a NOTES platform." But, says Pryor, a surgeon at Duke University Medical Center, "we saw that we could use it with single-port surgery and get the same benefits that we were trying to get with NOTES by using a single access through the umbilicus."

By the mid 2000s, Pryor was working with Richard Stack, MD, an interventional cardiologist, and the engineers at Synecor to develop new surgical tools that Pryor says will usher in "the next generation of surgery, instead of NOTES." Synecor's singular innovation was, of course, bringing the flexible catheter technology of interventional cardiology to general surgery. Pryor points out that in the early days of the NOTES revolution, most surgeons—and the companies working with them—"were designing ways to do surgery around an endoscopy platform because those were the tools we had." But that required surgeons to adapt their surgical technique to the technology, rather than the other way around. "To me," she goes on, "it didn't make sense that we should change how we do surgery, because we were already doing surgery well." What TransEnterix sought to do, says Pryor, was to allow surgeons to perform surgery through a single access point, whether a trocar-created port or a natural orifice, that was as close to conventional surgery as possible.

Pryor is, of course, hardly objective about TransEnterix's technology; after all she played a seminal role in its design. But that very role has, as much as anything, thrust her into the heart of the single-port versus NOTES story. And of the current buzz around NOTES and the debate over the different roles of single-port surgery and NOTES, she says, "I think NOTES is the goal on the horizon—if we can accomplish NOTES safely, that's what everybody would like as the target." But, she goes on, right now, that's simply not a realistic near-term target. "I think most people realize that it's single-port surgery that is the achievable goal for making surgery less invasive in the short term."

Even single-port surgery has its limits, however, particularly in the devices currently offered by most companies to enable the approach. Much like the second generation of MIS procedures 20 years ago, single-port surgery has hit a wall, stalling significant penetration. That's because, says Pryor, the tools designed to make it possible aren't, for the most part, tools surgeons like to work with. "What we wanted to do at TransEnterix was to come up with something that was delivered through a very small access, but then could extend and give you all the angles that we're used to using with laparoscopic surgery," she says. "None of the other single-port systems out there do that. They make clumsy instruments through large access sites trying to accomplish the same goal in the end." Pryor says that she does a lot of single-port surgery today and with most instrumentation, "It's awkward and takes longer" to do the surgery.

Surgical residents, too, have difficulty picking up the new technique, "because it's harder" than conventional MIS, she says. "Although I think there are some benefits to [single-port surgery], it's clearly not where it needs to be for a mainstream surgeon to adopt those techniques today." In short, just as with MIS in the 1980s, single-port surgery techniques are being explored, but there's surgeon pushback because most surgeons simply don't like the tools available to them today. The TransEnterix platform, she says, is different. "It rethinks how we get [to single-port surgery] and by rethinking that, makes it much more user-friendly."

enough—if single-port surgery using flexible catheters really can solve many of the technical and procedural problems associated with first-generation MIS, why move to NOTES at all? "That's the debate of the day," says Todd Pope.

Indeed, an article in a recent surgery journal posed the question, "Is Single-Port Surgery a Bridge to NOTES or NOTES a Bridge to Single-Port Surgery?" and asked, if technical difficulties and low patient acceptance continue to limit NOTES and there are better laparoscopic tools coming, why do NOTES? Still, TransEnterix resists pitting the two against each other as competing options. Rather, granted both the hype around and limitations of NOTES, what TransEnterix envisions is a single-port revolution in surgery that is distinct from, but ultimately embraces, NOTES. Richard Stack calls TransEnterix's technology "a transformational, disruptive platform that is going to change all of surgery." TransEnterix is targeting laparoscopic cholecystecomies to begin with, Stack notes, "but after that, we're going after all of surgery." And Todd Pope defends TransEnterix's decision early on to focus on single-port surgery at a time when everyone else was talking about NOTES—"It wasn't a very easy or popular decision," he says. "We were definitely in the minority, but we wanted to focus on single-port surgery." But he adds, "Ultimately we think our technology will be an enabler of NOTES."

A VICIOUS CYCLE

But are revolutions in surgery even possible—and not just one but two, single-port and NOTES, at the same time? Some device industry executives argue that for a variety of reasons, radical, disruptive technology development in surgery is difficult to pull off. For one thing, there's the generally conservative nature of surgeons. Less- or minimally invasive surgery was a true revolution, but really only in a small group of procedures; in other major surgical categories, it's created hardly a ripple. A lot of surgeons simply like doing things the way they've always done them, and all of the innovation in the world won't tempt them. Thus, as noted, although less-invasive approaches have revolutionized general surgery generally, and most particularly cholycystectomy, they have had little impact in cardiovascular surgery (treating angioplasty as a different subsegment) or orthopedics, where in total joint replacement, surgeons have pursued smaller-incision surgery, but nothing like true MIS.

More importantly, because tactile sensation and visualization are so important, sometimes even willing revolutionaries have more recently come up against a kind of technology barrier in advancing laparoscopic surgery. The second generation of MIS in general surgery ran into problems in coming up with tools to do fine manipulations and complex movements within small

And a major part of that re-thinking involves incorporating interventional-oriented designs in the creation of the platform. Pryor says that her experience in working with Richard Stack was "awesome." "I told him that we need to think about NOTES not from the endoscopist's perspective, but from the surgeon's perspective, and he asked, 'Can we make it better by combining it with how [an interventional] cardiologist looks at things?'" The interventionalist perspective was "what surgeons need to gain access and to get the angles they need," she goes on. More to the point, she says of the TransEnterix system, "I don't think this is something I could have come up with on my own, and I don't think [Stack] could have either."

The interventionalist perspective makes an important contribution to how the TransEnterix platform functions from a technical perspective. But will surgeons buy into that perspective? If interventionalist cardiologists tend to be avid new technology adopters, general surgeons tend to be just the opposite: conservative and resistant to innovation and, in particular, disruptive technologies. In other words, might TransEnterix's novel approach to MIS actually work against the company in some way? Pryor believes not. "I think that was truer 10 or 15 years ago," she says. "There was a lot of resistance when the laparoscopy movement first started—a lot of very powerful names in surgery put up barricades and said we shouldn't be doing this. But I think there's been a paradigm shift since then."

For one thing, she notes, laparoscopic surgery itself has gone from a niche procedure performed by a handful of surgeons in the vanguard to the mainstream of surgery. "It's not really a specialty any more," says Pryor. "It's what general surgery has become." In addition, more recently, while the NOTES movement has still to catch on in a meaningful way, it has, says Pryor, made all surgeons "question how we do surgery today. It's made everyone ask whether the box we're looking at is the box we ought to be looking at. Or whether we shouldn't be doing things differently." Younger surgeons, in particular, are much more likely to embrace new ways of doing things, even if that means, for example, adopting procedures and technologies adapted from interventional cardiology. "There's a different thought process right now," she says.

For now, Pryor thinks the future of innovation in MIS lies in improving single-port surgery. Even the TransEnterix device will, she believes, get better. "I think we have a very good device for what we're trying to accomplish," she says. "But there are lots of ways to make it even better for other procedures." More importantly, longer term, as noted, Pryor believes the future lies in NOTES. "I do think there are certain procedures that are perfect for NOTES," she says—trans-rectal colon resection, for example—and she believes it is the TransEnterix platform, as opposed to other NOTES tools, that will enable those procedures to be done.

Ultimately, Pryor believes that, at least where TransEnterix is concerned, the debate between or opposition of single-port surgery and NOTES is a false one. Noting that the original intent of TransEnterix was "to come up with something for natural orifice surgery," she says that the TransEnterix technology "covers everything you would want in a NOTES platform." In the end, rather than seeing single-port surgery and NOTES as different and/or alternative paths, both—at least in TransEnterix's vision of single-port surgery—will wind up in the same place. "What we've come up with is a platform that right now we're advocating should be used for single-port surgery," she says. "But the same platform and operating technique can be used as a delivery system for NOTES as well."

spaces, leading to much lower penetration rates in procedures such as hernias and appendectomies. Robotics was going to be an answer, but for all of the success of companies like **Intuitive Surgical Inc.** or **MAKO Surgical Corp.**, they've hardly created the kind of revolution that, by analogy, angioplasty brought to cardiac surgery.

For these and other reasons, some industry observers note a kind of vicious cycle: surgeons haven't been particularly eager to adopt many of the novel approaches and technologies that have come about recently, and device companies get easily discouraged about developing new instrumentation. Interventional cardiology's eager early adopters have created a whole industry—arguably the largest subsegment of the medical device industry—and the multinational giants that dominate that industry. Minimally invasive general surgery has radically changed the way surgeons think of doing many cases, but hasn't created anything on a similar scale.

Richard Stack argues that there has been technological innovation in surgery over the past 20 years, "but it's been incremental, not disruptive."

But TransEnterix officials believe that general surgery *is* receptive to disruptive technology. The shift from laparotomy to laparoscopy attracted "a lot of innovation," argues Richard Stack. The move to a second-generation MIS in general surgery failed, he insists, not because surgeons were resistant, but because for the most part, there wasn't any true innovation. "There just wasn't anything really new," says Stack. "What they were seeing was the same old same old." True, surgeons can be conservative, he says. But that was part of the equation. "These aren't the kind of people who kid around," he goes on. "They're attracted to the real deal—that's why they go into what is a very hands-on kind of medicine. They won't accept anything that's just window dressing—it has to be something truly better."

John Tushar agrees. Looking back at the wide range of device technology designed for laparoscopic surgery, he says that most of it has been "derivative." "We've seen new trocars come on the market, different forms of energy-based devices, new tools for cutting and stapling, but what we've seen is derivative improvements in those areas." Particularly among the larger, market-leading instrument companies, technology enhancements tended to be small in scale, what Tushar calls "point solutions," and purposely so. "They tended to be minor improvements because they had a large market share and it was costly to protect that share," he says. Thus, when the market leaders brought out new products or acquired new technologies, they looked specifically for small enhancements that would make surgery easier, but that would also protect the procedures—and the tools already created to enable them. "The shift from open surgery to laparoscopic surgery required a huge conversion and took 20 years," says Tushar. No big company was going to start from scratch. Indeed, though it rests on many of the same procedural approaches as conventional laparoscopic surgery, Tushar notes that "the conversion from multi-port surgery to single-port surgery is a different story."

Moreover, given the success of conventional MIS, TransEnterix officials know that the innovation barriers are high. Converting surgeons from open to closed procedures was hard enough; getting surgeons to switch to single-port surgery has its own challenges. "There's some tough criteria," notes Todd Pope. "You have to have easy access, flexible movement, and great visualization. And you have to train people easily and they have to get great results, because that's what they get today [with conventional MIS]. And I hadn't seen a technology that offered that until I saw the TransEnterix technology."

A ROLL-UP OPPORTUNITY

Richard Stack argues that there has been technological innovation in surgery over the past 20 years or so, "but it's been incremental, not disruptive—nothing that broke the mold." Todd Pope agrees: after an initial burst of new technology development soon after laparoscopic surgery was introduced two decades ago, the past 10 years have been characterized by what he calls "a static innovation curve."

But Stack believes that far from being unreceptive, surgeons—even general surgeons—are willing to embrace new technology. They've watched what has happened in cardiovascular medicine, with the revolution brought by catheter-based approaches, and are intrigued. "Having spoken with the top thought leaders, these guys remind me of the initial pioneers in interventional cardiology," he goes on. "They have the same mind-set—they say a lot of the same things."

More importantly, what Synecor brought with its background in interventional medicine wasn't just a new mind-set, but an expertise in flexible cathether technology—which brought with it the ability to infuse fine motor movement in the instrumentation—that represents a significant improvement over the rigid instruments that characterized even the second-generation MIS tools. Fred McCoy notes that "once you free [the procedure] from the idea that you have to create ports with trocars, it opens up some very interesting possibilities." And Richard Stack insists that most surgeons get it—by blending perspectives from interventional cardiology and general surgery, "they can see that you create something entirely new, a new paradigm."

Indeed, Todd Pope notes that as surgeons do more and more cases using the TransEnterix devices, the possibilities of the technology become clear. "It's like a *V8* moment," he says. "They suddenly realize all the things they can do." That's why TransEnterix officials believe that the company's real opportunity lies not just in converting the current lap choly procedures to single-port access, but also in branching out to many of the procedures now done on an open basis. Pope notes for example that even today, only about 50% of bowel resections are done laparoscopically. "I think we're going to see more of those procedures done laparoscopically because of what we're doing," he says.

More importantly, TransEnterix says that the appeal of its platform isn't restricted to high-volume thought leaders. Company officials have begun to show the system at meetings like American College of Surgeons and SAGES, and, they say, even low-volume surgeons are enthusiastic, once they've done a case or two. "We

believe our technology has to be able to be used by the masses," says Todd Pope. "That's the only way we're going to transform this market."

TransEnterix executives clearly see their device as a platform that will be used by a large number of surgeons and that can enable an ever larger number of procedures. But that opportunity also brings challenges: how can TransEnterix possibly hope to develop all of the different instrumentation necessary to make possible this growing number of procedures?

Some of the adjunct instruments will be developed by TransEnterix itself. But company officials know now that, particularly in the beginning, they can't possibly do it all themselves. That leaves two options: alliances with small companies that are developing instruments with narrower applications or, a roll-up of such companies. Pope notes that there are dozens of small companies with interesting technology that, particularly given today's tough financing climate, "may not make it through. There's a lot of great IP out there that companies are much more willing to either sell or license." Indeed, given the current venture financing climate, TransEnterix's late 2007 round of $20 million now seems less an act of hubris than one of prescience. "Normally, companies at our early stage of development wouldn't be aggressive in looking at new technologies, but because we're well funded, we can afford to," Pope says.

SOLVING NOTES

Pope says that TransEnterix has "a fairly strong appetite to roll up certain technologies." And TransEnterix may be uniquely poised for that kind of roll-up because from the beginning the company has seen its technology as a platform that enables all aspects of single-port surgery, access as well as visualization and surgical tasks. Following on his point about large companies, John Tushar says that there are a lot of start-up companies now looking to tap into the growing interest in single-port, but most of them are "point solutions looking for a home." "They're focused on one or two instruments or on access," he says. "They haven't developed a fully integrated system that does both." (In addition, a lot of those companies also started with some other, non-single-port application in mind and have tried to switch over to single-port as that opportunity has taken off, say TransEnterix officials.)

Though TransEnterix executives say they'll work with big and small companies, it's clearly small companies they're thinking about when they talk about their roll-up strategy—and just as clearly, they'd rather own than build, in the long run, because of the value that brings. Still, a roll-up strategy that also embraces TransEnterix's larger rivals, accessing devices already on the market, has one advantage for TransEnterix: by not forcing surgeons to make choices they'd prefer not to make about the instruments they use, open systems should lower barriers to entry for TransEnterix upon commercial launch and allow the company to execute on one critical part of its strategy: a huge market share grab following soon after commercial launch. Fred McCoy predicts that, ultimately, TransEnterix's offering will be a combination of "sole source and open source." And Richard Stack notes that the ability to access novel tools from elsewhere "is really the advantage of the platform." "Our philosophy is to give the doctors what they need," he goes on. "And until we can make a device that's better than the one they're currently using, we have to be able to incorporate what they want to use so they can do the best operation possible."

In some respects, TransEnterix's single-port access approach represents something of a way station on the path to the larger surgical revolution that has led from MIS to NOTES. Fred McCoy insists that "where NOTES will play relative to single-port is yet to be determined. But one thing is indisputable: single-port is going to play first. It's here and now." John Tushar notes that single-port surgery today "is a market with all kinds of momentum behind it. When we talk to surgeons, they all want to do single-port surgery. What's been missing are good tools."

"We're going to take single-port surgery as far as it can possibly go," says Richard Stack. But, interestingly, ultimately, that's NOTES. TransEnterix officials see their platform, with the advantages of a flexible catheter technology, as an improvement not just on open surgery or even conventional laparoscopic surgery, but even on NOTES itself. In fact, rather than standing as an alternative to NOTES, TransEnterix argues that its single-port access technology will ultimately help to make the NOTES revolution real.

But given the potential problems with NOTES, why even bother? Why not just stop at single-port access through the umbilicus? TransEnterix officials insist that the only real problem with NOTES is that what has passed for natural orifice access until now hasn't really revolutionized surgery. "There are all of these so-called NOTES procedures, but they're not really NOTES," says Richard Stack, "because surgeons still have to put in supplemental ports in order to do the surgery. Nothing I've seen in NOTES really works to my mind. It's all very impractical."

Indeed, says Stack, such cheater ports diminish the value of NOTES—not only is NOTES surgery often difficult, but because of the ports, the risk of infection, as well as herniation and surgical adhesions, remains because of the penetration of the skin. "The vision of NOTES is great, but nobody's really figured out how to do it," Stack goes on. "I think the only way to really get there is with flexible catheter technology, and that's where we're going. Our intent is to create a technology that solves the problems associated with NOTES."

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