

Devices for a Diabetes Epidemic

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Summary:	With an increasing emphasis on tight glycemic control in diabetes care, innovative devices could play a big role, but diabetes is a deceptively complex market. Innovative companies need to differentiate themselves, yet not venture too far outside existing industry dynamics. As the first real-time continuous glucose monitors come to market, a handful of start-ups hopes to be ready for the second generation. Many of these are taking a side excursion into the market for in-hospital glucose monitoring, once a sleepy market but now growing rapidly as outcomes data shows reduced mortality and morbidity in intensively managed hyperglycemic hospital patients.

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With an increasing emphasis on tight glycemic control in diabetes care, innovative devices will play a big role, as long as companies can find the right business models.

Mary Stuart

The race to offer the next innovation in glucose monitoring for diabetes definitely isn't a sprint; it's not even so much a marathon as a demolition derby. Many companies will start out with the pack, but only a handful will survive. Those that do, however, have the chance to operate in a \$6 billion worldwide market for glucose testing—one that is still largely under-penetrated because patients don't test with the daily frequency that they should. Compliance with recommended testing guidelines is still low because of the drawbacks of a glucose self-monitoring paradigm based on the need to draw blood and feed it into a testing device.

Kelly Close, founder and principal of Close Concerns Inc., a San Francisco-based consultancy focused on the businesses of diabetes and obesity, points out that the \$2.8 billion US market share for glucose monitoring is based on an average of roughly one-and-a-half tests a day, far less than the three per day recommended for most people with diabetes. Very simply, if compliance were better, the market would grow dramatically. "Even if we increased testing by, say, half a test a day, the US market would increase by nearly \$1 billion," and patients would benefit, she says.

Diabetes is increasing in incidence, and, without proper intervention, so will a slew of co-morbidities—heart disease, kidney disease, blindness, and limb amputations. According to the American Diabetes Association, there are almost 21 million people with diabetes in the US today: 7% of the population—and only 14.6 million of them have been diagnosed. (One start-up is addressing this gap; *see sidebar, "VeraLight's Perfect Storm in Diabetes Screening."*) Another 41 million have pre-diabetes. The need for cost-effective interventions is clear: 14.6 million people are responsible for some \$92 billion in direct costs in health care today.

Standards of diabetes care are today largely based on outcomes of a landmark study, DCCT (Diabetes Control and Complications Trial), reported in *The New England Journal of Medicine* (NEJM) in 1993, which indicated that intensive treatment to keep blood glucose levels as close to normal as possible reduced the microvascular complications of diabetes. A follow-up study in the NEJM in 2005 called EDIC (Epidemiology of Diabetes Intervention and Complications) showed that tight glycemic control also reduced cardiovascular risks significantly. A mounting body of evidence indicates that glycemic variations—wide swings in glucose levels from peak to valley—may even be as harmful in their own right as sustained periods of hyperglycemia and hypoglycemia, causing problems even if the average blood glucose readings look normal. All of this evidence calls for monitoring technologies and drugs that will better help patients safely maintain tight glycemic control.

Can Innovation Drive Compliance?

Because even a small piece of this market can be lucrative, helping patients achieve greater compliance with testing guidelines spells opportunity for device companies. New technology that makes frequent monitoring of blood glucose easier could enable more aggressive glycemic control regimens. The granularity of diabetes patients would also seem to support a large number of glucose testing options—children in school, middle-aged business people that travel and the homebound elderly can all be diabetic, and they all need something different.

Thus, innovation is occurring in several camps. A number of companies continue to pursue the distant goal of non-invasive glucose monitors; getting rid of the pain of skin-puncture-based testing might be one way to encourage testing frequency. (*See Exhibit 1.*) While many small companies operate here, testing out new optical, acoustic, electrochemical or other ways of measuring glucose in blood, sweat and tears has historically often proven to be a long, arduous, and fruitless course. **FoviOptics Inc.**, which was attempting to

use a retinal analyzer to measure blood glucose in the back of the eye, is only the latest company to pull the plug on the project; many companies before it have suffered the same fate. Trying to target glucose in blood vessels, and separating out its signals from those coming from glucose of a different provenance and age, is simply tough to do, particularly in an instrument that ultimately needs to be operated by consumers and amenable to low-cost manufacturing.

Selected Companies in Non-Invasive Glucose Testing

EXHIBIT 1

Company (Location)	Non-Invasive Technology
EyeSense AG (Grossostheim, Germany)	Spun-out from Ciba Vision, uses fluorescence resonance energy transfer to measure glucose in the eye. System includes eye implant (like a contact lens) and a hand-held photometer.
Calisto Medical (Plano, TX)	Wrist-watch-like <i>Glucoband</i> is based on digitally-processed bio-electromagnetic resonance spectroscopy.
Glucon (Boulder, CO)	<i>Aprise</i> platform combines optical and acoustic technology to localize blood vessels, then measure glucose in vessels.
Lein Applied Diagnostics (Wokingham, Berkshire, UK)	Cell-phone sized meter measures glucose in the eye by measuring the reflectivity of low-power light shined into the eye.
Oculir (San Diego, SA)	Founded by John Burd, founder of LXN Corp. and DexCom. The <i>Mid-IR</i> incorporates a sensor with infrared radiation technology that can be held over the white of the eye. The company says the finished system will be about the size of a cell phone.
Optiscan Biomedical (Alameda, CA)	Measures glucose in the mid-infrared range.
OrSense (Nes Ziona, Israel)	Optical method of determining blood glucose level based on occlusion spectroscopy.
Sensors for Medicine and Science (Germantown, MD)	Small optical sensor with a target life of 6-12 months is implanted under the skin in an outpatient procedure, communicates wirelessly with a hand-held reader.
PreciSense (Horsholm, Denmark)	A microcapsule placement unit places glucose-responding microcapsules in the upper layer of the skin, painlessly. The glucose assay components in the microcapsules generate a fluorescence signal that corresponds to the glucose level. A non-invasive reader uses Fluorescence Resonance Energy Transfer.
Sensys Medical (Chandler, AZ)	Device uses Near Infrared Spectroscopy with self-correcting mechanisms to reduce user error.
VivoMedical (Cupertino, CA)	Electrochemical glucose sensor is disposable transdermal patch that collects sweat and reads glucose levels. Works with hand-held patch reader, integrated into a cell phone.

SOURCE: Windhover's *Strategic Intelligence Systems*; Company reports

Another category includes companies developing a continuous glucose monitor (CGM); they believe that the availability of glucose trend data throughout the day, predictive alarms, and a reduction in finger sticks—a few times a week, instead of the four times daily (at a minimum) finger-stick standard for intensively managed patients—will help patients achieve better glucose control. CGM start-ups are emboldened by the recent approval of first-generation real-time devices from **Medtronic Inc.** and **DexCom Inc.**, although technological and market challenges in this segment remain, most notably on the reimbursement front.

A Deceptively Complex Market

Innovative companies need to differentiate themselves, yet not venture too far outside the razor-blade model that characterizes the industry, which is dominated by four enormous companies: **Roche**, **Johnson & Johnson**, **Abbott Laboratories Inc.**, and **Siemens AG**'s **Bayer Diagnostics**. The Big Four have

entrenched product platforms and marketing relationships; their goals are to maintain their existing diabetes customer base and to try to capture market share from competitors by introducing differentiated products every year. Since many start-ups will be looking to the entrenched players for exit opportunities, they are ill advised to develop technology or business models that rock the boat too much. Start-ups that hope to sell capital equipment for non-invasive glucose measurement, for example, will face great challenges because of this dynamic.

Indeed, Versant Ventures' managing director Beckie Robertson, who was formerly at J&J's diabetes innovator LifeScan Inc. says, "It has been striking to me that over the last five years, all the venture capital attention, all the real innovation in the entrepreneurial community, and to a large extent in the corporate community, has been focused on non-invasive and continuous monitoring. In my humble opinion, the vast majority of the market will continue to be, for a long time, discrete blood based testing, although we're making investments in non-invasive and continuous too."

That's why the founders of Versant portfolio company **Rosedale Medical Inc.** didn't look too far afield for a large business opportunity. Within the existing paradigm of episodic testing, they hope to create a successful business with a technology that aims to increase patient compliance.

A Big Opportunity in Incremental Innovation

Syrous Parsay, founder and CEO of Rosedale Medical, says that episodic testing— that is, the kind of self-monitoring of blood glucose that requires a person to stick himself, get a sample of blood, and quantify that sample—has come a long way over the years, but there is still enough room for improvement that he sees a big business opportunity for Rosedale Medical, although he declines at this early stage to disclose even the nature of his company's device.

Parsay was formerly with LifeScan and Roche, via his former company Amira Medical, a small company which was developing a sampler and meter in one portable unit that could be used to draw blood from areas other than the finger, and which Roche acquired in 2001. [W#200110225] Parsay, who has been in the industry for more than 15 years, says, "Innovation in episodic testing falls into five buckets. These are: accuracy and precision; data management; pain; convenience and hassle-free way of testing; and the social and emotional aspect of dealing with the disease. In terms of accuracy and data management, Parsay says, the field has made great strides. "We understand blood; we understand how accurate it needs to be in order to use it at home. We understand data management, and there are all kinds of contraptions from PDAs to cell phones, to PC-based packages to move the data, so we don't perceive those areas as having significant unmet needs." But about pain, convenience, and the social/emotional component, Rosedale believes it can improve upon the state of the art.

In diabetes, the clinical community has access to a great deal of outcomes data: DCCT, a ten year study, and the UK Prospective Diabetes Study, which began in 1977 and ended in 1998. Parsay says, "We know that the closer you manage your disease, the fewer complications you are going to have. Yet testing frequency is much less than the recommendations and one of the hurdles is the process people have to go through." Parsay says there can be as many as 50 steps involved. "You have a lancing device, you fire a sharp into your body. You squeeze a drop of blood out, you put the blood on a strip—often you have to input a recalibration code first—and you wait around for the device to give you a reading." But often patients have to do the whole operation twice. "The process is open to mistakes, and if you don't get a good reading, you have to repeat the whole thing. It takes about 2–3 minutes to go through the process and most people need a surface to lay all this stuff on," Parsay says. There is also an emotional/social component to this cumbersome process. Many people don't like to test themselves outside of their homes, out of respect for others, or because they don't like to advertise their disease.

"We've had focus groups and many patients say they don't even test themselves because it takes too long and it's inconvenient. They just go by how they feel, and load the syringe and shoot up or adjust their treatment regimen. So there is a huge unmet need in terms of what we can do with episodic testing that we haven't done yet," Parsay says.

Rosedale believes there is a large market opportunity for a company that will integrate all the pieces of the process in a discrete fashion; to provide a tool where a person can better manage disease without having to change his or her lifestyle. "You remove all the errors of calibration coding, or errors due to device usage. You remove sources of error from reagents that might be compromised by handling and exposure to the environment." Parsay says his company's device will allow patients to test themselves whenever and wherever they want, with a decrease in pain as well.

Because the company was spun out of the microfluidics program at **SRI International**'s **Sarnoff Corp.**, developer of the *Songbird* disposable hearing aid and **Insulet Corp.**'s disposable insulin pump, it's a reasonable guess that Rosedale has some kind of integrated disposable. Parsay wouldn't comment, except to say that his company's device will be amenable to low-cost production. "The disease is very expensive, and you need the attention of managed care folks. You can't have a premium-priced product in this category because of the number of competing options. The cost of goods, and the technology used to implement the goals we are talking about will be low-cost."

Parsay believes his company has a good chance of success precisely because it doesn't try to go against industry dynamics "If you want to get a piece of the market, you need to leverage the infrastructure and know-how that's been created over 20 years." A company also needs to serve the multiple constituencies that influence the market, he says. "You have managed care, retailers, and health care professionals. To end up on the shelf of Walgreen's, Rite Aid, or Wal-Mart, you have to have the right type of appeal. If you try to remove the retailers from the equation, their perspective on fulfilling your disposable will be different. Their interest is in store traffic from consumers." Health care professionals must be kept in the loop as well. "They are the backbone of this industry, and their recommendations are key to success," Parsay says.

Rosedale Medical just closed on a \$20 million Series B round with existing investors Thomas, McNerney & Partners and Versant Ventures, as well as US Venture Partners and Investor Growth Capital.

Continuous Glucose Monitoring, but only for a Short Time

At this year's annual meeting of the American Diabetes Association, CGM was a hot topic of discussion, since, after decades of waiting, the first such real-time devices were launched in the months preceding the meeting. (Kelly Close points out that another CGM product, *GlucoWatch*, belonging to "generation zero," as she terms the earliest devices, essentially folded due to a number of problems with reimbursement and user and health care provider acceptance. The patent portfolio was purchased by Animas Corp., acquired last year by Johnson & Johnson for \$539 million). [W#200510215]

Medtronic was the first to launch a CGM device for home use in 2005, the *Guardian* real-time continuous monitor, and then DexCom Inc. received FDA approval for its *DexCom STS* in March 2006. The Abbott *FreeStyle Navigator*, currently under FDA review, is expected to be the next such device to receive approval.

Several start-up companies—like **OrSense Ltd.**, **Sontra Medical Corp.**, **Glucon Inc.**, and **OptiScan Biomedical Corp.**, to name only a few—hope those approvals of these first-generation devices will pave the way for their newer, innovative approaches.

These devices have been long awaited as the missing link in the development of an artificial pancreas, and have recently been regarded as the potential means to help people with diabetes achieve tighter glycemic control and avoid glycemic variability, in light of recently published studies that indicate that sharp swings in

glucose levels may increase oxidative stress, and at any rate, are as harmful in their own right as sustained hyperglycemia or hypoglycemia.

The A1c test, which measures overall glucose control during a three-month period, is important for long-term management, but it is only an average and doesn't reveal day-to-day glucose swings that might be harmful. The A1c is necessary, but perhaps not sufficient for anyone that wants to track glycemic variability. Discrete testing, on the other hand, only indicates a glucose value at a single time-point. Patients thus don't detect many extremes of hypo- or hyperglycemia. Continuous glucose monitoring has the potential to complete that picture.

With CGM, patients can see trends in glucose movement, and devices with predictive alarms can head off episodes of hyperglycemia—which, when really harmful, can send them into the hospital with diabetic ketoacidosis, or hypoglycemia, which can lead to unconsciousness or coma.

The first-generation devices, for their part, are fraught with controversy. A debate swirls around their accuracy—since current devices sample interstitial fluid, rather than blood, glucose status is subject to a time lag of 8–20 minutes, and many believe that accuracy isn't sufficient. Proponents argue that trend data is more important than a single number; the other view holds that patients will be relying on monitors to direct therapy and require accuracy.

Independent of technological approach, however, the real gap in the field at the moment remains the lack of reimbursement: None of the first-generation devices has FDA approval as a replacement for discrete testing, and none of them has reimbursement. Indeed, lack of reimbursement for ambulatory continuous monitoring is a problem that plagues all clinical specialties. (Medtronic has gone furthest down this road, since it is already exploring the right business and reimbursement models for other clinical applications of its CareLink information management network, of which diabetes is a component.) (See *"Remote Patient Monitoring, The Markets Near and Far,"* START-UP, April 2006 [A#2006900088].)

While the major players wrestle with these issues, small companies with continuous monitoring technologies have been shifting their products over to a market in which they believe they might have a better chance: in-hospital glucose management. This market is attractive both because it is largely untapped by the dominant diabetes companies, and because financial incentives favor adoption.

In-Hospital Glucose Management

The historically sleepy hospital glucose monitoring market is poised for rapid growth, as clinical studies showing vastly improved outcomes from in-patient diabetes management are emerging. Here, arguments for adoption can be made in terms of improved outcomes, reduced length of stay, and other types of quantification.

A seminal study by Greet Van den Berghe, MD of the department of intensive care medicine, University Hospital in Leuven, Belgium, in *The New England Journal of Medicine* in 2001 focused attention on the need to aggressively monitor the glucose status of patients in the intensive care unit (ICU). In that initial prospective, randomized and controlled study of 1548 patients, Van den Berghe demonstrated that at 12 months, intensive insulin therapy reduced mortality during intensive care from the 8% experienced by the conventional treatment group to 4.6%.

Van den Berghe's findings have since been reflected in other studies, in particular by Anthony Furnary, MD, a cardiac surgeon at Providence St. Vincent Medical Center in Portland, OR. Furnary observed that 29% of cardiac surgery patients have diabetes, and that patients with diabetes had four times higher rates of complications after surgery, twice the post-operative mortality, and longer lengths-of-stay than non-diabetics. But he has shown at his hospital that by intensively managing diabetic patients through strict

intravenous insulin infusions, death rates were reduced by 60%, and other complications have decreased dramatically as well. Furnary has now studied more the 5600 patients on what he terms "The Portland Protocol."

More recently, a study by Mercedes Falciglia, MD, presented at the June 2006 ADA meeting analyzed a Veterans Affairs database including more than 216,000 admissions to the ICU. The study found that hyperglycemia is associated with an increased risk of mortality independent of the severity of illness, both for patients with undiagnosed diabetes and those with hospital-induced hyperglycemia.

Dan Goldberger, CEO of start-up **Glucon Medical Ltd.**, explains that hyperglycemia has a surprisingly high prevalence in hospital settings—as great as 50% in some hospitals. In addition to those hospitalized with diabetes, many other patients have it but are undiagnosed. Indeed, one benefit of the increased focus on hyperglycemia in the hospital has been an increase in diabetes diagnoses. In addition, a large number of patients without diabetes become hyperglycemic in the hospital, as a result of the body's normal reaction to stress of the surgery, compounded by drug regimens post surgery, most notably steroids.

Glucon, which was founded in 2000 by Israeli scientists Ron Nagar and Benny Pesach, PhD, began with the goal of developing a non-invasive continuous glucose sensor for the self monitoring market, based on photoacoustics. The combination of both optical and sound-based components allows the company to perform targeted spectroscopy, Goldberger says. Historically, the challenge for detecting glucose non-invasively in blood vessels has been separating out the glucose in blood vessels from glucose in other tissue compartments. The photoacoustic technology allows the device to target the vasculature, then measure blood glucose there. That technology is at the heart of the company's non-invasive glucose monitor *Aprise*. At the ADA meeting in June, Glucon presented the results of a 62-patient clinical trial that it says demonstrated that *Aprise* performs favorably in comparison to conventional finger-stick glucose devices.

To capture revenues sooner, however, Glucon has added a development program aimed at the hospital glucose monitoring market, with a completely different product called *OPTImus*. The company's goal with *OPTImus* is to automate for the ICU the process of conventional blood glucose monitoring—not unlike the goal that made the IPO of critical care monitoring company **Visicu Inc.** such a success in April 2006, when it raised \$89 million at a price above its filing range. [W#200630217] These companies share a goal of streamlining the workflow in the staff-constrained ICU.

OPTImus is an automated programmable blood glucose monitor that attaches to an existing vascular access line. Goldberger points out that patients in the ICU generally have some kind of vascular access line in place—a central venous line, an arterial line, or a peripheral IV line. "With *OPTImus*, we put our sterile tubing set in line with the vascular access that is already in place, and we automatically interrupt the flow of IV fluid periodically as programmed by the clinician, withdraw a small sample of blood, and do a conventional glucose oxidase test. The syringe pump that withdraws the sample of blood, the mechanical handling of the glucose test, all of that has been automated by *OPTImus*," Goldberger says.

Support for another in-hospital approach to monitoring came in a paper in the July 2006 *American Journal of Critical Care* (AJCC, 2006;15:370–377). In it, Daleen Aragon presented a study of the nursing work associated with tight glycemetic control and monitoring in the hospital. The task of performing hourly blood glucose monitoring and adjustment of insulin doses was burdensome and costly, Aragon said, requiring up to 2 hours for a single patient in a 24-hour period. That's where **GluMetrics Inc.** believes it can make a difference. In August 2006, it completed a \$9 million Series B financing with new venture investors Versant Ventures and Advanced Technology Ventures to develop a device that "addresses the core requirements of the clinician and the nursing staff in the ICU," according to CEO Bill Markle, who—like Rosedale Medical's Parsay and typical of early-stage medical device company CEOs—won't be too specific about the GluMetrics device. Markle was previously on the executive team of two well-funded critical care start-ups, **Tensys Medical Inc.** and **Masimo Corp.** Pointing to Van den Berghe's recent publication, he says: "The

work quotes high–double–digit improvements across a wide variety of conditions. A 34% reduction in mortality. It's not all that often that you can make that kind of difference." The focus of GluMetrics, he says, is to understand what keeps tight glycemic control from being more widely implemented, and solving those problems with a device that meets the particular needs of the hospital environment.

GluMetric's technology is based on boronic acid–based compounds with unique qualities in terms of their fluorescence as a function of glucose concentration, Markle says. The fundamental discovery came out of the organic chemistry department at the University of California, Santa Cruz. The GluMetrics system, coined *GluCath*, combines the unique properties of this fluorescent chemistry in a catheter–based device small enough for direct placement in the venous periphery. Markle says, "Our technology has some unique advantages that are much better suited to the sicker and less stable patient in the ICU."

Glucolight Corp., founded in April 2003 with funding from individual investors, Matignon Technologies (Paris, France), the Ben Franklin Technology Partners and the Life Sciences Greenhouse Fund of Central Pennsylvania, is initially targeting the ICU with a non–invasive continuous glucose monitor that uses optical coherence tomography and low coherence interferometry. It ultimately aims to be in the consumer self–testing market, but is validating its product in the ICU market. "Our product clamps to a pole; it is the size of a very large IV pump," says Robert Wilkins, VP, medical affairs and business development. "But there is room for further miniaturization. One of the advantages of starting in the ICU market is that you don't need to go down to consumer size in the earliest product launch."

Glucolight's monitor connects to a disposable device that sits on the skin. The disposable is effectively a large, hard contact lens that provides optical coupling between a light source, a light return and sensor system, Wilkins explains. The company is currently engaged in several validation studies.

Glucolight believes that it already has data that demonstrates that it has a sensitive and specific signal, gained from studies of healthy volunteers and subjects with Type 2 diabetes. The company has also taken care to test the system on animal models that are representative of the types of anemic, edematous and sick patient generally found in the ICU environment, to make sure that these physiological factors don't influence readings. The company plans to move into human ICU studies in the fall of this year.

Other companies addressing the hospital market include OrSense Ltd., **OptiScan Biomedical Corp.**, and **Luminous Medical Inc.** (See *Exhibit 2*.)

Selected Start-Ups in Hospital Glucose Monitoring

EXHIBIT 2

Company (Location)	Approach/Venture Backers
Advanced Biosensors) (Mentor, OH)	Wireless continuous glucose monitor measures glucose in the dermis vs. the fatty subcutaneous tissues. Easy self-insertion with less pain since needle is about the thickness of a human hair.
Glucon (Boulder, CO)	<i>OPTIMus</i> automates conventional glucose oxidase testing for the ICU by taking advantage of existing blood access line/Giza Venture Capital, InnoMed Ventures, Infinity Venture Capital, Jerusalem Global Ventures
GlucoLight (Bethlehem, PA)	Non-invasive sensor uses Optical Coherence Tomography and Low Coherence Interferometry/Matignon Technologies, Ben Franklin Technology Partners, Life Sciences Greenhouse Fund.
GluMetrics (Irvine, CA)	System designed for the ICU combines polymer that fluoresces in the presence of glucose, with patient-specific catheter/Versant Ventures, Advanced Technology Ventures.
Luminous (Albuquerque, NM)	Laptop-sized device consists of modules for blood sampling and optical measurement. System automatically draws blood from patient through a standard venous or arterial catheter into a proprietary disposable optical cuvette. Light is transmitted through the blood, and the system analyzes resulting near-infrared absorbance spectrum/De Novo Ventures, Latterell Venture Partners.
Optiscan Biomedical (Alameda, CA)	<i>Optiscanner</i> is in clinical trials/Ascension Health Ventures, NGN Capital, MedVenture Associates, Mitsui, Morgenthaler, Sanders Morris Harris, Wellcome Trust, EGS Healthcare Capital, Hercules Technology Growth Capital, Prism Venture.
OrSense (Rehovot, Israel)	Non-invasive continuous monitoring technology based on occlusion spectroscopy is in clinical trials/Star Ventures, Tamar Ventures, Israel Healthcare Ventures, Unicycle, LTG Development Capital, Madison.

SOURCE: Windhover's *Strategic Intelligence Systems*; Company reports

Kelly Close believes the hospital market, with its prospect for improving outcomes, could exceed \$1 billion if the right incentives were put in place for hospitals to pursue tight glycemic control. Close says, "The costs of increased testing are a pittance compared to the costs borne as a result of uncontrolled diabetes in the hospital and home settings." In order for that market to materialize, however, Close emphasizes that tight glycemic control must be included in the requirements for accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). "Things will change overnight if and when tight glycemic control is put on that list," she says. It's unclear when that will happen, but Close suggests that industry could help JCAHO increase their glacial speed.

Who Can be another TheraSense?

In many respects, this is an old tale: diabetes care would be improved if patient adherence to testing and medication regimens were better, and technology can be brought to bear on the problem. For the past ten years, the industry has witnessed the rise and fall of many a start-up in pursuit of this goal. Today, the story is the same, only the numbers are larger: more patients with diabetes, more companies, a larger market. In some respects, the challenge is even more difficult today than it was even five years ago. Now there is significantly more low-cost competition, more pressure from Medicare. Competitive bidding from the government payers is expected to drive prices lower and squeeze margins, and managed care has become considerably more powerful. More of the costs are being shifted to patients, some of whom, as a result, merely test less. Investors, in turn, have become more wary of investing in novel technologies.

At the same time, if a low-risk approach lies in incremental changes, today it's not as easy to be another TheraSense Inc., as it was in that company's hey-day. (See "*TheraSense's Sweet Spot*," IN VIVO, June 2002

[A#2002800125].) TheraSense succeeded not with a disruptive new medical technology, but by offering a differentiated product that suited existing industry dynamics. Its innovation was a product that would be preferred by patients because it would be less painful. The company achieved more than \$200 million in revenues before Abbott acquired it in 2004 for \$1.2 billion. [W#200410004]

But times were different, then. For one thing, the financial markets were generous: TheraSense raised \$120 million in its initial public offering and a month later raised an additional \$50 million privately. [W#200130298] [W#200130060] Rosedale Medical's Parsay says, "Today, if I told any reasonable investor that I was going to raise \$200 million in capital and then spend it as fast as I could generate revenues, they would tell me to 'Get a life!'".

Having said that, Parsay believes that in one sense, glucose testing companies do have the chance to be TheraSense in terms of the impact that they can have on episodic testing. "There definitely exists at least one, if not more, products that could deal with the inconvenience, the hassle, and the social/emotional barriers of testing, and that could easily become another major acquisition for one of the big players."

Kelly Close agrees that it is harder for a new company to succeed today. "When you could reduce testing from 30 seconds to 15 seconds, that was significant." For the hyper-intensively managed patients (and the most profitable customers), time saved represented half a day a year. "But now that we are at five seconds, and a pretty tiny drop of blood, it's harder and harder to create meaningful incremental changes." There are opportunities, however. "There is always an opportunity to heighten user and health care provider acceptance," Close says. "When I look at the product launches in diabetes that have gone really well, the most successful ones have something in common—simplicity. A number of products have been simple to teach and simple to use. Doctors and nurses have so little time with patients, that the teaching piece shouldn't be lost." She characterizes *Lantus* (long-acting insulin glargine, from **Sanofi-Aventis**) and *Byetta* (exenatide, from **Amylin Pharmaceuticals Inc.**) as standout examples, and she ultimately expects the Insulet disposable insulin pump to be another. "It is easier for a patient to learn to use this technology than to learn about and become comfortable with giving him or herself four shots a day," she says. Finally, in this payer-constrained market, she believes there is a big opportunity to compete on cost: "The power of managed care has heightened incredibly, and we believe the market will be especially receptive to companies that have products in reimbursed categories and that, all else being equal, can leapfrog the competition in terms of cost."

Device Opportunities in Diabetes

EXHIBIT 3

Type of Device	Comment	Selected Companies
Diabetes Screening	Current standard, the fasting glucose test, isn't efficient as widespread screening tool —patients have to fast for 8 hours then have blood drawn at a lab	VeraLight for widespread screening, Neurometrix in diabetic neuropathy, Eyetel Imaging in diabetic retinopathy
Discrete Testing	Opportunities to improve on: pain, convenience, cost	Pelikan Technologies, Rosedale Medical
Ambulatory Continuous Glucose Monitoring	The next hot thing in diabetes, if devices can demonstrate sufficient accuracy to replace finger stick, and gain reimbursement	Medtronic, DexCom, Abbott
Hospital-Based Glucose Monitoring	Emerging market, benefits can be quantified in terms of improved outcomes and reduced length of stay	Glucon, GlucoLight, GluMetrics, Luminous, Optiscan Biomedical, OrSense
Non-Invasive Glucose Monitoring	Accuracy is biggest hurdle, validating glucose from novel sources or other analytes is difficult, lengthy process	EyeSense, Calisto, Oculir, PreciSense, Sensys, VivoMedical, Advanced BioSensors
Drug Delivery: Insulin Pumps	First half of total artificial pancreas; market is still underpenetrated	Animas, Insulet Corp., Medtronic Minimed, Roche Disetronic, J&J
Other Drug Delivery	Alternate vehicles for insulin delivery	Biodel

SOURCE: Windhover's Strategic Intelligence Systems

VeraLight's Perfect Storm in Diabetes Screening

In a US health care system based largely on fixing problems rather than preventing them, looking for diseases in asymptomatic populations has always been controversial. Concerns around cost-effectiveness and the need to definitively link therapies to improved outcomes have prevented the adoption of screening paradigms for more than a handful of conditions. Until 2005 only five screening applications had sufficient cost-utility, in the opinion of the Centers for Medicare & Medicaid Services (CMS), which limited payments to screening procedures for cervical cancer, breast cancer, colorectal cancer, prostate cancer, and bone densitometry. In January 2005, however, the CMS added cholesterol screening and diabetes screening to its list of reimbursed tests, paving the way for **VeraLight Inc.**, a new company developing a non-invasive alternative to the current standard diabetes screening test, fasting blood glucose.

In fact, a number of factors have come together recently, creating the perfect storm for VeraLight's diabetes screening technology, says David Van Avermaete, VeraLight's CEO.

First, payer recognition of the rising economic burden of diabetes is bringing greater focus to the prevention and earlier treatment of diabetes. There are 20.8 million people in the US with diabetes, but only 14.6 million are diagnosed. Patients with diabetes are responsible for \$135 billion in annual health care spending in the US—almost 10% of total expenditures. There are also an estimated 41 million people with pre-diabetes, according to the American Diabetes Association. "If 14.6 million people drive spending of \$135 billion, you can imagine what 60 or 70 million diabetics will do to the system," says Van Avermaete. "Something has to change." While there is increasing pressure to treat patients with diabetes early and aggressively, at the same time, a large number of new drugs for diabetes have come to market, and many new drug class indications that promise to slow the progression of the disease by preserving beta cells or contributing to weight loss are or will soon be in development. (See "Pharma's High Hopes for Diabetes Drugs Revived," IN VIVO, September 2006. [A#2006800159])

Incretins (GLP-1), TZD's (thiazolidinediones), and DPP-4's (dipeptidyl peptidase IV) are all now or eventually will be tested as medications that could prevent diabetes. While a prevention indication is likely years off, according to Kelly Close, founder and principal of Close Concerns Inc., a San Francisco-based consultancy focused on diabetes and obesity, these classes are already billion-dollar classes or blockbusters in the making. "Incretins, in particular, are a mega-billion dollar class in our view," says Close. All told, global sales of diabetes drugs together hover around \$17 billion dollars today, she notes, and certainly have the room to double over the next decade, as the trend toward earlier, more aggressively further develops. All the more reason for new and better screening tools that help the health care system allocate resources in a cost-effective manner, the founders of VeraLight believe.

VeraLight was spun off in 2004 from **InLight Solutions**, a developer of sensor-based measurement systems for life science applications, which was founded by researchers from Sandia National Laboratories and the University of New Mexico. InLight, like so many others, was pursuing the goal of developing a non-invasive glucose monitor. (InLight has also spun out glucose monitoring company **Luminous Medical Inc.**) (*See "Luminous Medical Inc.," START-UP, December 2005. [A#2005900238]*)

Its researchers were using near infrared spectroscopy to try to quantify blood glucose levels. The discovery of the technology's utility in a screening application came about quite by chance, says Van Avermaete.

"The research scientists were pulling out page after page of charts, saying 'Here is a glucose level on a diabetic person, here's one on a non-diabetic person.'" The charts looked the same in terms of glucose levels, Van Avermaete says, and weren't labeled with respect to the health status of each subject. He asked: "How do you know which ones are diabetics?" To which the researchers responded, "You can tell by the shape of the curves. Diabetics always look this way, and non-diabetics always look this way." Van Avermaete told them that if they could use spectral characteristics to classify people independently of their glucose levels, that could be a valuable application. "Three years later, they called me up and said, 'We can do that now.'"

Van Avermaete, a former president of Johnson & Johnson's US division LifeScan Inc. came out of retirement to head up VeraLight. The company is now developing its first product, code-named *Scout*, which uses fluorescence spectroscopy to non-invasively measure advanced glycation end products (AGEs), not glucose, in the skin of a subject's forearm. Skin AGEs are a well known biomarker of diabetes, and have been shown to predict the development of Type 2 diabetes. The company's special know-how is in its algorithms that take into account variations among people—skin color, skin depth variations, and other intrinsic differences—in arriving at a clinically meaningful result. The company also has patents on the wavelength it uses, and its detectors.

In early August, VeraLight raised \$17.5 million in a Series B venture round with investors the Psilos Group, CMEA Ventures, vSpring Capital, Wasatch Venture Fund, Dow Chemical and the Southern Ute Growth Fund. [W#200630417] With those funds, the company has begun hiring: it plans to build 40 clinical prototypes over the next year and conduct a very large pivotal trial—about 5,400 patients at 15 sites. VeraLight will probably implement the trial in the middle of next year, in the hope of getting FDA clearance and launching the product at the end of 2007 or early 2008.

There are many avenues to market for VeraLight. Van Avermaete says that in addition to the major diabetes diagnostic companies, pharma companies would also be interested—"because we will find patients with diabetes for them." Indeed, **Eli Lilly & Co.** has already shown a willingness to partner with companies with other diabetes screening technologies—**EyeTel Imaging Inc.** in diabetic retinopathy [W#200420215], and **NeuroMetrix Inc.** in diabetic neuropathy. There are also several other potential marketing partners among an eclectic group of organizations, Van Avermaete says.

VeraLight will first target the dozen or so national and regional companies that conduct corporate and community-based screening. "We have a perfect product for this—non-invasive and semi-portable, so you

can take it to an employee site and screen a lot of people very efficiently," Van Avermaete says. "It's a consolidated audience—any one of them would be interested in buying 50–100 devices or more, and they don't deal with third party reimbursement. The testing is paid for either by the employer or the individual. That is a good starting place for us because we don't know how long it will take to get Medicare and third party reimbursement," he goes on. VeraLight estimates that this first market could yield approximately \$2–3 million screens per year.

Pharmacy clinics represent the next potential market. These are small labs located next to pharmacies, which offer perhaps a dozen services like pregnancy and strep throat testing, cholesterol screening, and inoculations. There are about 200 such pharmacy clinics in the US today. They wouldn't be worth mentioning, Van Avermaete says, except that every significant retail chain and mass merchandiser—Walgreen's, CVS, Long's, Wal-Mart, Albertson's and Target—is piloting them now. "Pharmacies like them, because they represent incremental store traffic—people buy stuff while they're there. They walk out of the clinic with a prescription and walk over to the pharmacy to get it filled. Insurance companies like the concept, because for select tests, it's cheaper than going to a physician. Patients like it, because rather than going to a pediatrician and then waiting to get a lab result, they can get it all done the same day for a third of the price." Van Avermaete points out that CVS Corp.—the country's largest pharmacy chain with about 6,100 stores—recently bought MinuteClinic, which has 83 outlets in ten states, and plans to increase this number to more than 500 by the end of 2007. "Very quickly this can go from a little cottage industry to 10,000 or more pharmacy clinics. Our test is perfect for a pharmacy clinic—it is non-invasive, you don't have to handle blood, and you can get a result in 60 seconds. In addition, pharmacies love attracting people with diabetes to their store, because they spend 25 times more than the average person."

VeraLight will also target a third consolidated market—integrated delivery networks (like Kaiser Permanente or Geisinger Health System). These are attractive, he says, because they are close to being self-insured; they don't rely as much on Medicare or third party reimbursement. "We could go to them and say, 'You have 6 million members in your plan. If we screen all of those at risk for diabetes, we would find a million or more with undiagnosed pre-diabetes or diabetes, and you can intervene with those and capture significant savings over the next few years.'" Other potential markets include reference lab outpatient centers, where a non-invasive screening test could help with logistical problems. The current standard of blood glucose fasting tests for diabetes, for which people can't eat or drink anything except for water for eight hours prior to the test, causes the labs to be extremely busy in the morning, and less so in the afternoon. Physicians' office labs represent a final target market, although one that is less consolidated and more difficult to address for a device company.

In order to mitigate customer risk associated with large capital purchases, VeraLight is exploring a business model that combines a low capital purchase with a postage meter-like test fee. "We might sell our device at close to break—even for us, for less than \$5,000, but we might have a test counter so users can then pay by the test. Every time a user runs the test, we would charge them \$6, for example, and they would get a billable report for \$12, so they would generate \$6 in revenue for each test. Under this scenario, a typical target customer would likely get a payback in about 2–3 months."

Van Avermaete says he is excited about the ability of his company's technology to make a difference. "We now have interventions that have been shown to be effective and more are on the way. If we can find everyone that has pre-diabetes and intervene, we can prevent this disease or delay its onset and reduce much of the pain and costs associated with this horrible condition."