Why Have So Many Intravascular Glucose Monitoring Devices Failed?

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Abstract

Secondary to the inherent limitations of both point-of-care and central laboratory glucose technologies, continuous glucose measurement has recently enjoyed a high level of investment. Because of the perceived advantages by some of measuring in the intravascular space compared to the subcutaneous tissue, a number of technologies have been developed. In this review, we evaluate nine systems that have shown promise, although only one of these has been cleared for sale in the United States. The detection methodology, regulatory status, technical issues, and company circumstance surrounding each technology are examined.

Keywords

continuous glucose monitoring, FDA approval, intravascular monitoring

In ambulatory populations and for in-hospital use, many have long felt the need for continuous glucose measurement (CGM). Point-of-care (POC) measurements are labor intensive and there is growing concern regarding POC products that are not intended for the critically ill.[1] The glucose values measured with subcutaneous systems may not correspond to central laboratory values and exhibit various lag times.[2,3] What is required is a system that accurately and reliably monitors continuous glucose levels. A noninvasive system that provides reliable values on a continuous basis would be ideal, but the difficulties associated with developing a clinically accurate system have been well documented.[4-6] As a result, there have been many attempts to develop systems that measure intravascular glucose, but this has proved challenging.

Improved outcomes following cardiac surgery with intense insulin therapy (IIT), a version of which is known as the Portland Protocol©,[7] indicated the value of closely controlling glucose levels. The enthusiasm for IIT has waned, owing to serious complications from hypoglycemic events,[8] but the need for accurate perioperative monitoring has continued and many believe that intravascular systems remain the best hope. Systems that extract glucose from interstitial fluid have not found widespread acceptance, largely due to the short lifetime of the collection fibers and the need for frequent recalibration (these systems will not be described here). This article describes true intravascular blood measurement devices, either measuring *in vivo* or after removal of a sample of blood (*ex vivo*).

Although we will describe nine systems, three US companies have gone out of business, and a fourth has not yet applied for FDA approval. Products with the Conformité Européenne (CE) mark are available in the European Economic Area (EEA), but those systems have had regulatory challenges in the United States.

Issues That Apply to All Systems

These units are designed for perioperative and critical care use, and this places a substantial burden on accuracy, short lag time, and reliability. Intravascular systems are designed as alternatives to central laboratory analyses and POC strip and meter systems, and many provide continuous glucose readings. Until recently, no POC systems had been cleared by the FDA for critically ill patients, and official communications have appeared warning against "other off-label uses of glucose meters [which] include the monitoring of glycemic control of non-diabetic patients in hospitals; use on critically ill patients."[9] However, in September of 2014, Nova Biomedical's Stat Strip was cleared for this patient population.[10]

Every system must have a means of vascular access—central venous catheter (CVC), arterial, or peripheral venous—and materials in contact with the bloodstream are affected to varying degrees by "foreign-body responses." This has been described elsewhere in detail,[11-13] but the clinical consequence of thrombus formation can be severe. CVC

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Table 1. Characteristics of Intravascular Glucose Monitoring Systems.

System, company	Detection technology	Sampling site	Measurement site	Regulatory status	System status	Technical issues
GlucoScout, Via Medical	Electrochemical, glucose oxidase	Peripheral venous	*Ex vivo*	FDA 510(k) cleared	On market, EEA and US	Unheparinized glucose-containing infusion volume
GlucoClear, Edwards LifeSciences	Dexcom electrochemical, glucose oxidase	Peripheral venous	*Ex vivo*	CE Mark	On market, EEA	Corporate support?
Automated blood glucose monitor, Luminous Medical	Near-infrared; then electrochemical glucose oxidase	Peripheral venous, arterial	*Ex vivo*	None	Company closed	Regulatory approval; detection technology
OptiScanner 5000, OptiScan Biomedical	Mid-infrared, plasma	CVC, peripheral venous	*Ex vivo*	CE mark	On market, EEA	Unheparinized infusion, drug interferences?
OPTImus, IntelliDX	Electrochemical	Peripheral venous	*Ex vivo*	None	Company closed	Funding?
GlySure CGMS, GlySure	Boronate fluorescence	CVC	*In vivo*	CE Mark	In development	Nonthrombic sensor; interferences?
Glucath, Glumetrics	Boronate-quenched fluorescence	Peripheral venous, arterial	*In vivo*	None	Company closed	Thrombus formation
Glucoset, (originally Invivosense)	Boronate optomechanical	Peripheral venous	*In vivo*	None	Under development	Interferences?
Autosampler, Cascade Metrix	Electrochemical	Peripheral venous	*Ex vivo*	None	Under development	Development progress?

clots may result in pulmonary emboli and clots from arterial catheters can result in peripheral ischemia. Subcutaneous sensors have different challenges than intravascular catheters, but most foreign materials will cause an inflammatory reaction, and diabetes can exacerbate these effects.[14] Heparin, which is sometimes added to mitigate the risk of thrombi in bloodstream catheters, may cause erroneous coagulation tests[15] and may also increase the incidence of heparin-induced thrombocytopenia.

To date, the only US-cleared system for intravascular glucose measurement is the Via Medical Glucose Monitor (International Biomedical, Austin, TX).[16] Several proposed systems measure glucose using either near-infrared (NIR) or mid-infrared (MIR) spectroscopy instead of the more traditional amperometric or colorimetric methodologies. Possibly as a result of the unsuccessful noninvasive glucose systems using spectroscopy, obtaining approval with this modality has been more difficult (see Luminous Medical, Inc and OptiScan Biomedical below).

Intravascular systems measure glucose using a wide variety of detection techniques, including amperometry, NIR and MIR spectroscopy, fluorescence spectroscopy, and optomechanical interferometry. See a summary of each technology in Table 1.

FDA-Cleared System

Via Medical

The sole device currently cleared in the United States is the GlucoScout (Via Medical).[16] It accesses blood from a peripheral vein, withdraws 1.2 ml of blood for glucose oxidase electrochemical analysis, and then returns the blood together with 6 ml of nonheparinized calibration solution (Figure 1). It initially performs a 2-point calibration, and then calibrates at 82 mg/dl before each measurement.[17]

Ganesh et al[17] described the GlucoScout performance compared to the HemoCue® β-glucose analyzer and showed 86% of points in the Clarke error grid[18] "A" zone, 11% of points in the "B" zone, and 2% of points in the "D" zone (Figure 2).

Abandoned Systems

Luminous Medical

Luminous Medical, Inc (Carlsbad, CA), a spin-off of InLight Solutions, Inc (Albuquerque, NM), developed an ex vivo system that withdrew a blood sample from a peripheral vein into a cuvette, measured the glucose concentration using NIR spectrometry, and then returned the blood with about 6 ml of heparinized saline (personal communication, R. Robinson). Following each patient measurement, the system was flushed with saline that was pulled into a waste reservoir. Partial least squares (PLS) analysis was used to calculate the glucose results for each sample. Their results are shown in Figure 3 with the fluid management system shown in Figure 4 (personal communication, R. Robinson).

In 2009, company representatives met with the FDA in a "pre-IDE" meeting[19] to gain feedback for 510(k) premarket notification for the system as a class II device, but were unsuccessful.[20] Proposed "predicate devices" for the system included the Via Medical Glucose Monitor (see above), the SureStep Pro Glucose Monitor (LifeScan, Inc, Milpitas, CA),

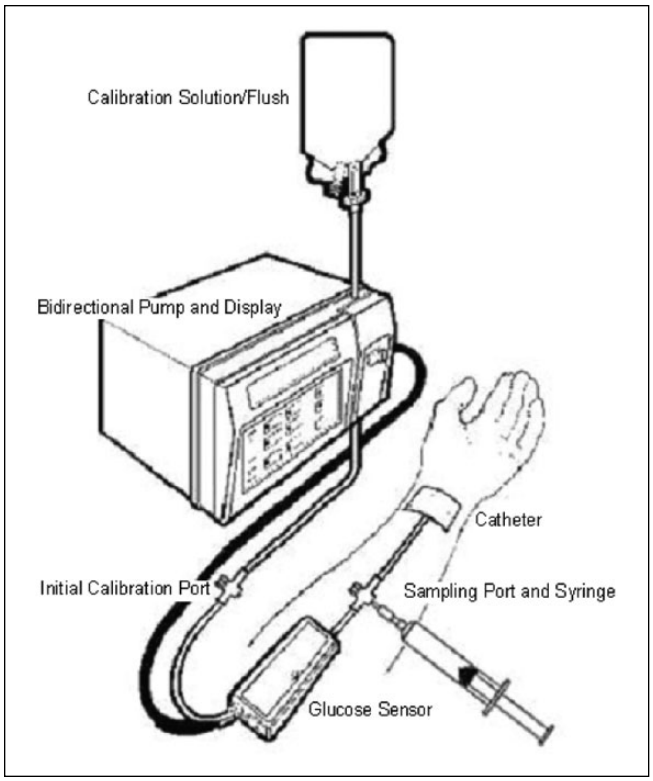

Figure 1. Via Medical GlucoScout.[18]

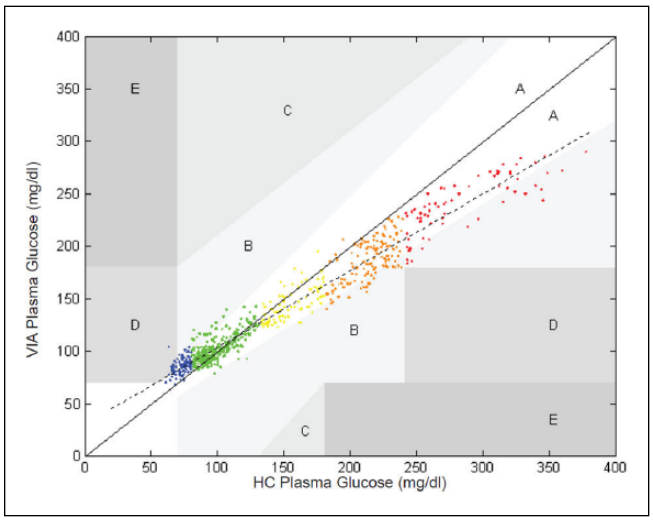

Figure 2. Via Medical GlucoScout (uncorrected) Clarke error grid.[17]

a traditional POC meter, and the Avoximeter 4000 Co-oximeter (International Technidyne Corporation, Edison, NJ), an NIR blood oxygen monitor.

The FDA reportedly[20] indicated that none of these devices were suitable as predicate, that they had deemed the device "truly novel," and that unless a more traditional method of detection was employed, a premarket approval (PMA) application would be required. Even though Luminous Medical had secured the rights to a glucose oxidase-based detector in 2009,[21] the time and cost needed to comply with the requirements of either a new detection system or a PMA proved to be beyond the company's resources, and it closed operations in 2011.[20]

While pulse oximetry using visible/NIR measurement is well established (leading to the FDA clearance of the Avoximeter 4000 Co-oximeter in 1996[22] along with many earlier devices), no glucose measurement system using this technology has yet been approved by the FDA,[5] and any future systems using this technology would be expected to require a PMA as a class III device.[23]

Glumetrics

Glumetrics, Inc (Irvine, CA) employed technology based on a boronate chemical quenched fluorescence sensing element (Figure 5), originally developed at the University of California, Santa Cruz.[24] Their *in-vivo* sensor, called Glucath, had the sensing reagent attached to the tip of a fiber optic probe (308 in Figure 6).

The sensor was deployed through a peripheral venous catheter, with blue light traveling down an optical fiber to the sensor. Green fluorescence increased in proportion to increasing glucose concentration. Glucose results (Figure 7) for 20 patients were reported, showing 95% of all points in the "A" Clarke zone, and a mean absolute relative deviation (MARD) of 7.9%.[26]

In a corresponding study with the sensor implanted in a radial artery, of 437 paired sensor and reference values, 353 (80.8%) were within 20% of the reference value when the blood glucose was ≥4.2mmol/l (75 mg/dl). The aggregate MARD was 13.0%, with the MARD for individual sensors ranging from 4.7% to 33.5%.[27]

Even though the Glucath sensor was coated with a heparin-based coating to inhibit thrombus formation, the sensor had problems with thrombus formation in one cohort of patients,[28] while a second study detected only clinically insignificant thrombus in five of 21 patients.[29] In a small observational study,[30] the authors state, "Poor IA-CGM (intra-arterial continuous glucose monitoring) system performance (> 11% MARD) in 3 subjects was attributed to optical signal variability associated with routine patient care activities and the administration of 3 interfering medications (mannitol, citrate, glubionate). The company did not obtain additional funding and has since closed shop."

IntelliDX

A system named OPTImus (IntelliDX, Santa Clara, CA) was reviewed in 2007,[31] when it was reported to have a "MRAD" of 15.0% compared to reference, but no description of the measurement technology was provided; the system was

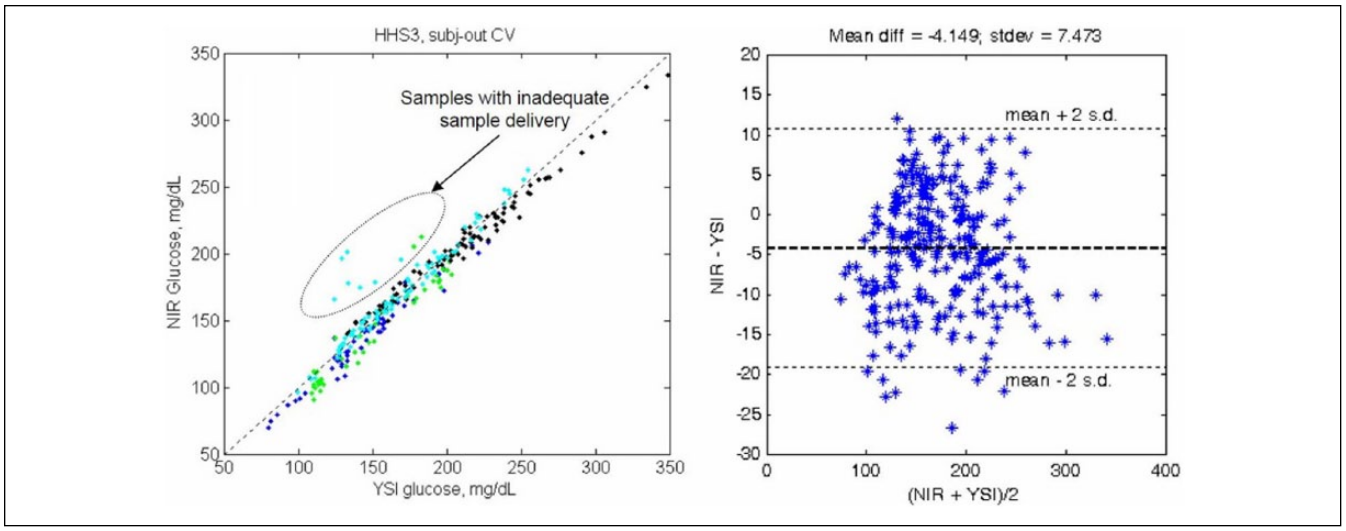

Figure 3. Performance of Luminous Medical automated blood glucose monitor.

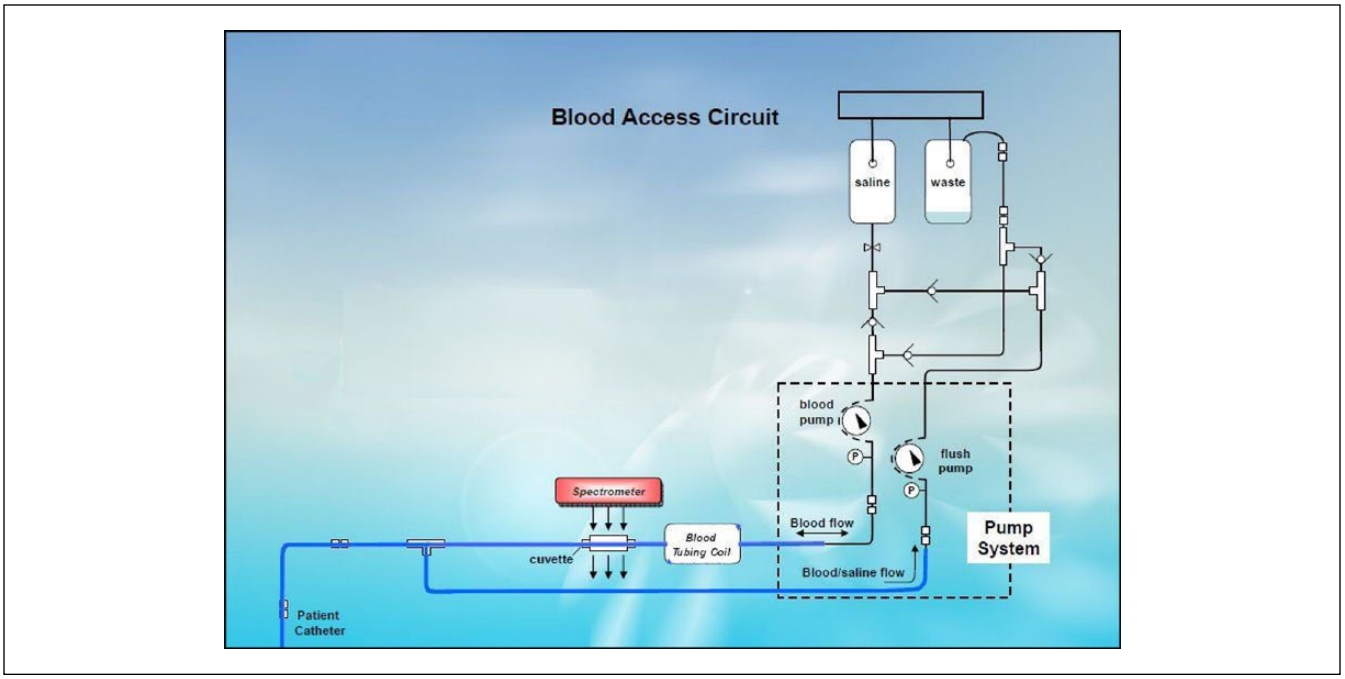

Figure 4. Luminous Medical automated blood glucose monitor blood access circuit.

identified in that report only as the "Glucon OPTImus under development." Another report[32] described the company as being out of business.

Systems in Development

OptiScan Biomedical

OptiScan Biomedical (Hayward, CA) has an intravascular system, the OptiScanner 5000®[33] (CE mark granted in 2011), and announced in April 2014 three-site-pivotal studies.[34,35] Results obtained with an earlier version appeared in 2005[36] and 2006,[37] and a new system, the OptiScanner 6000, which the company says "will be designed to automatically measure and trend glucose, hemoglobin and central venous oxygen saturation levels,"[38] has been announced.[39]

The OptiScanner connects to a venous catheter[40] and withdraws 3.0 ml of blood, of which 120 µl is heparinized, separated to plasma by centrifugation, and analyzed in a cassette by MIR spectroscopy, with approximately 2.8 ml returned to

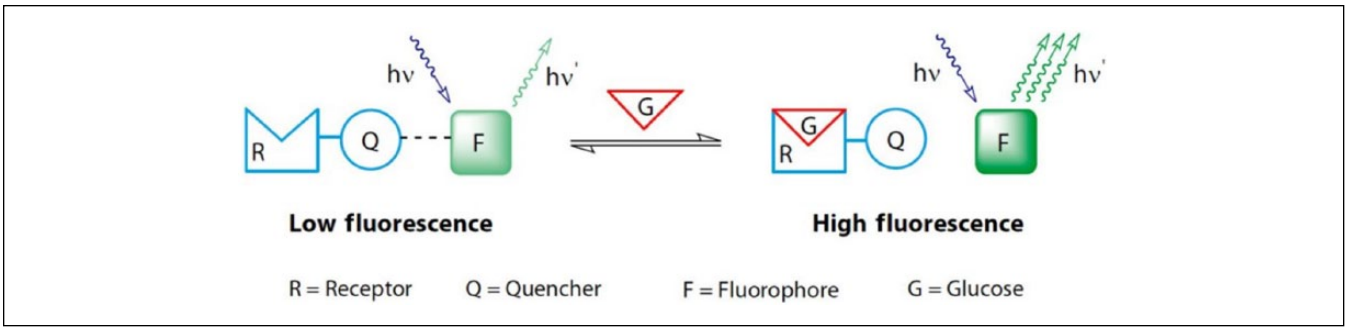

Figure 5. Glumetrics chemistry scheme.[26]

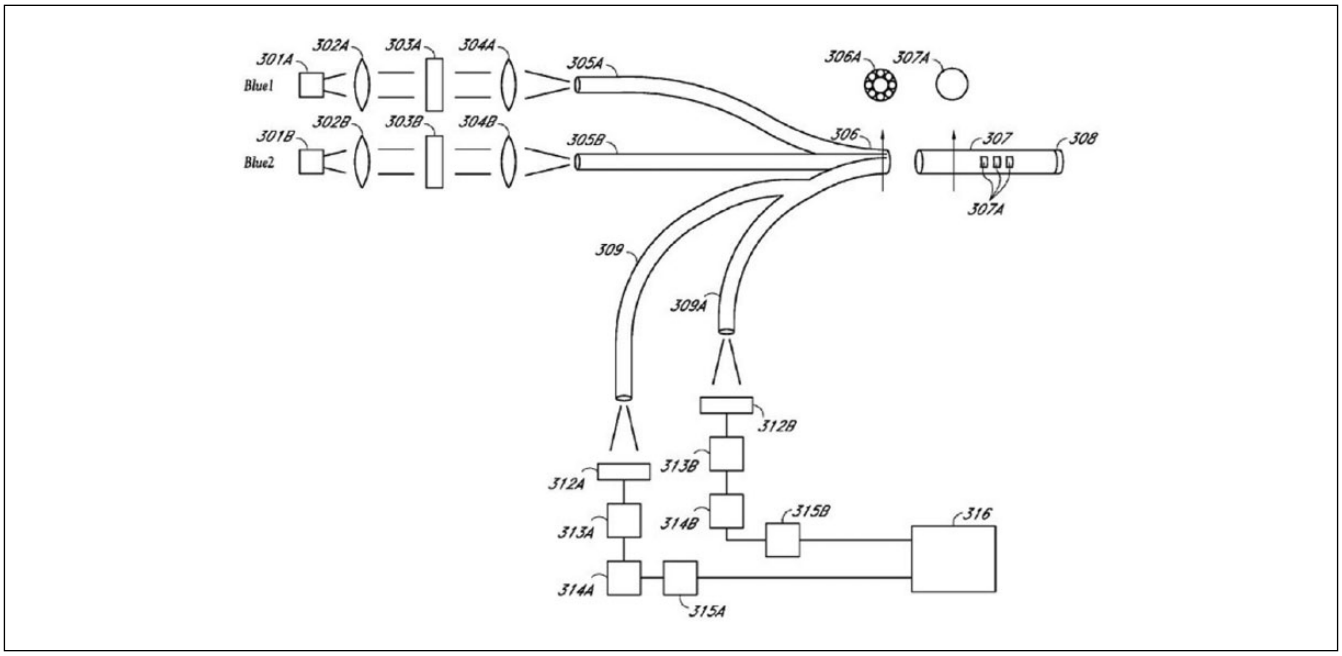

Figure 6. Glumetrics fiber optic sensor.[25]

the patient (Figure 8). There is no heparin in the returned blood.[40] With measurement every 15 minutes, patient blood loss is approximately 10 ml per day, while an additional 144 ml per day of saline is infused.

A University of Amsterdam[42] report of the system with CVC access, indicated a number of problems with the system, including occlusion alarms in 32 of 101 patients (24 of which could not be resolved), and interferences that required elimination with additions to an "interference library" for hydroxyethyl starch, IgG, propofol, albumin, cephalosporins, lactate, phosphate, and mannitol. The authors note, "While the device was designed for critically ill patients it had not yet been tested *in vivo*, and specifically, in critically ill patients at the ICU bedside. The present study expands the experience with the devices and shows that the devices could perform accurate glucose level measurements."

Following corrections for all the identified interferences, the 463 results for the remaining 71 patients are shown in Figure 9. The authors concluded, "The blood glucose measuring devices we used needed calibration for several previously unrecognized interferences. Thereafter, accuracy of the device for measuring plasma glucose levels in "our cohort" of critically ill patients improved, but external validation is highly recommended."

GlucoClear

Edwards LifeSciences (Irvine, CA) has developed the GlucoClear System (CE mark for a first generation system in 2009[43]) and a second-generation system, GlucoClear 2, in 2013.[44] It uses a dual electrochemical detector developed by Dexcom (San Diego, CA), and withdraws a 40-µl blood sample that is returned with a heparinized glucose solution with about 1.25 ml of 200 mg/dl (or 100 mg/dl[45]) heparinized glucose solution. A study of the first-generation system[46] reported 99.5% of the results in the Clarke error grid "A" and

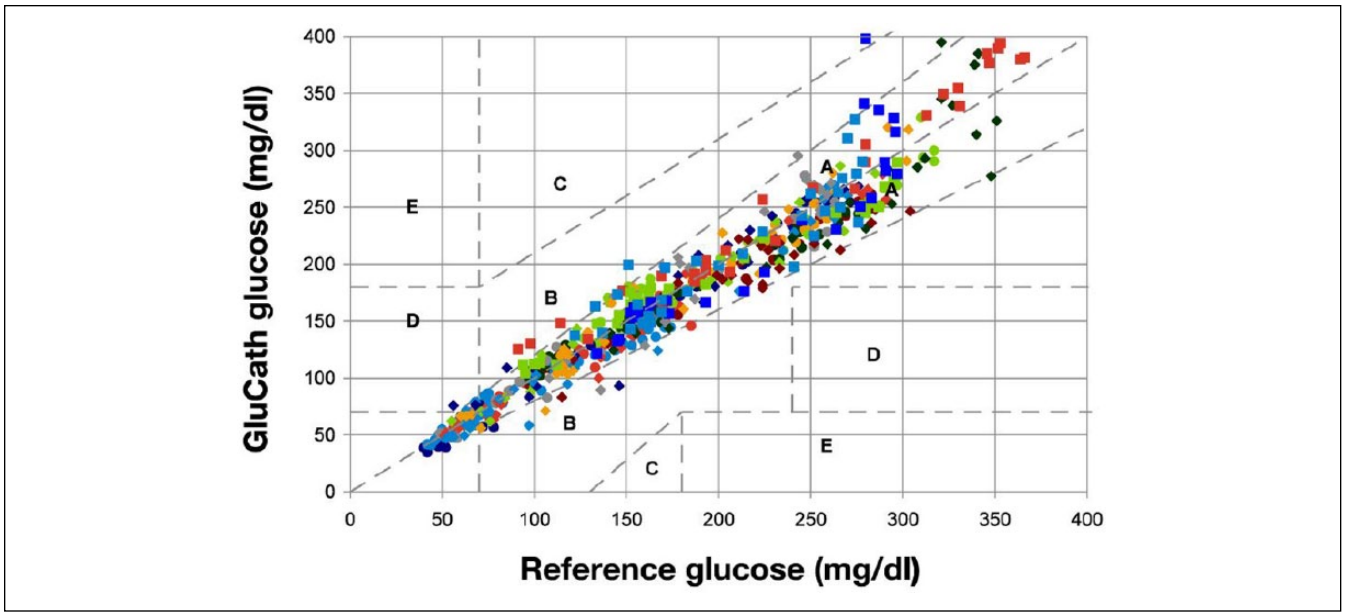

Figure 7. Glumetrics venous Clarke error grid plot.[26]

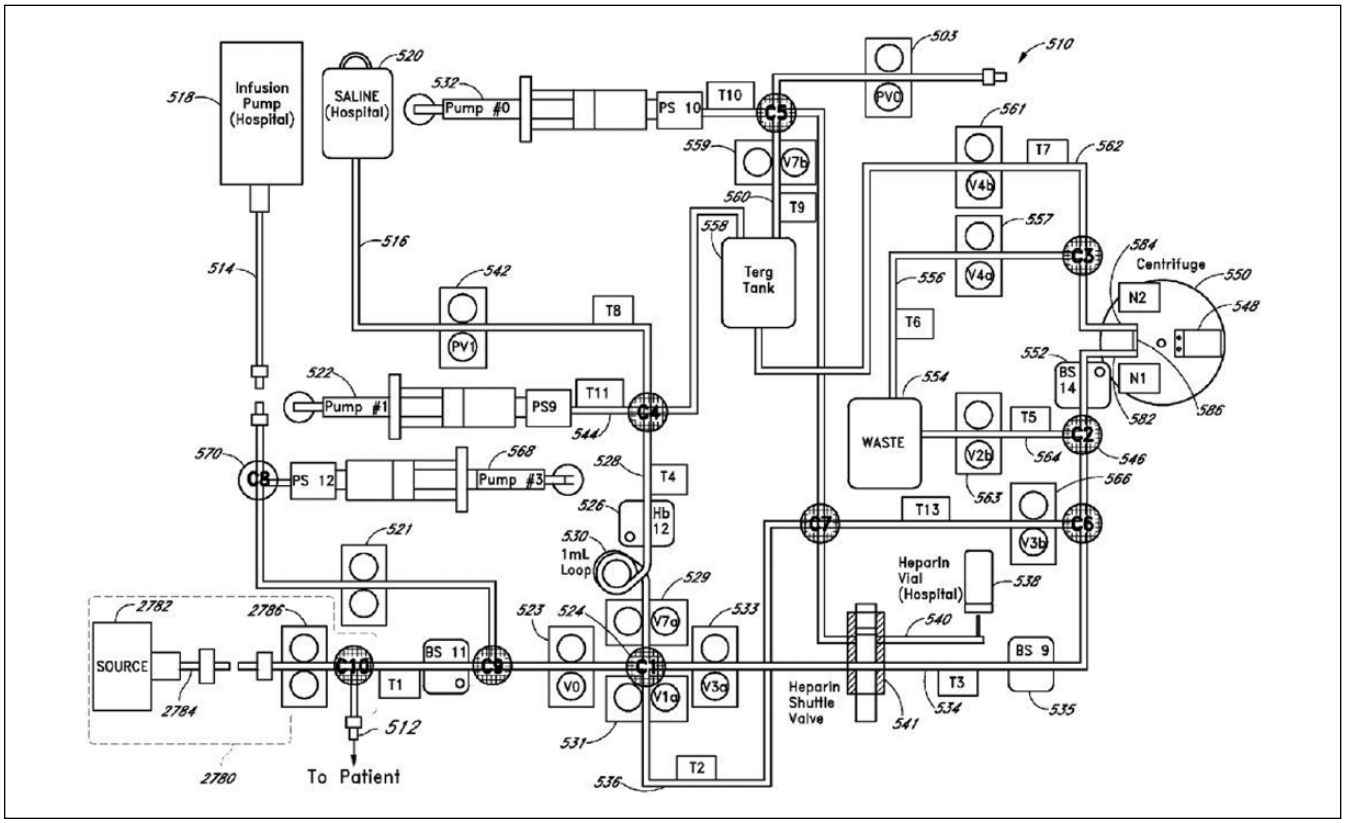

Figure 8. One version of the OptiScanner fluidic diagram.[41]

"B" zones. An ICU study using the newer GlucoClear2 indicated 99% "A" zone and 1% "B" zone points with 4578 results compared to reference, and a MARD of 4.9%.[47] At the quoted 200 mg/dl glucose concentration, less than 20 IU of heparin and 20 mg of glucose are delivered to the patient per hour.

In October 2014, Edwards stated, "…the company is redirecting the resources from its Glucose monitoring program

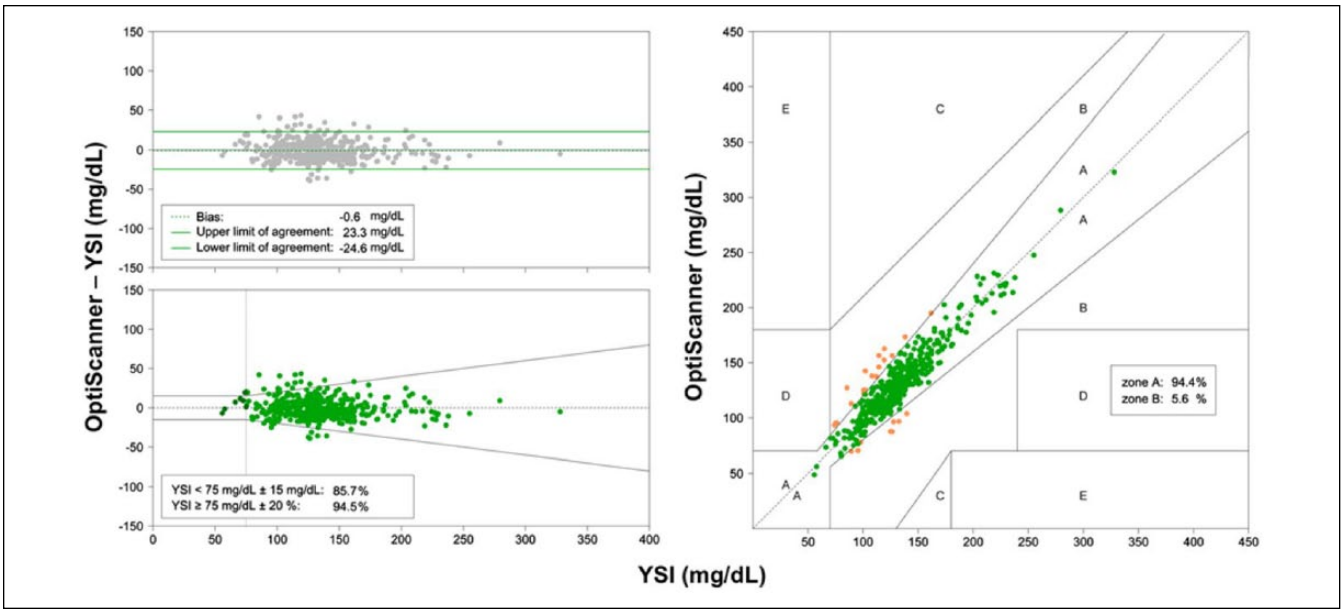

Figure 9. OptiScanner performance after interference corrections.[42]

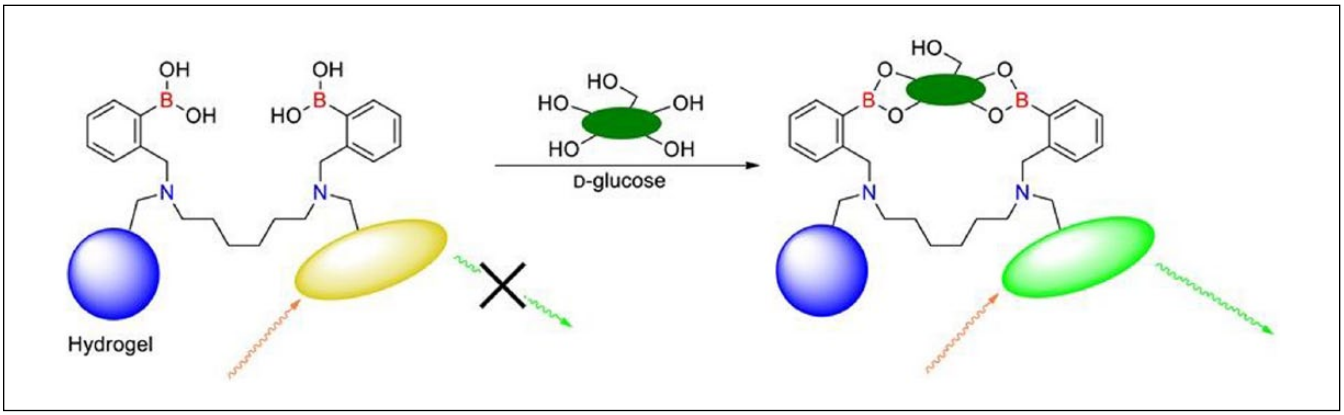

Figure 10. GlySure fluorescent sensor system.[52]

to its [Enhanced Surgical Recovery] initiative, and The Company recorded a $5.0 million charge in the third quarter of 2014 to write-down assets related to its automated glucose monitoring program. The charge related primarily to intellectual property, fixed assets, inventory and severance expenses."[48] In response, Edwards's CEO and chairman Michael Mussallem stated, "We are still discussing what might happen with that program. We do think it's very valuable. We have accomplished a great deal. We have a commercial product, clear path to commercialization in the U.S., a CE mark in Europe, and so we are considering strategic options in that, including partnering."[49]

GlySure

The GlySure system (Oxfordshire, UK) uses a direct fluorescence boronate-sensing element (Figure 10) at the tip of a fiber optic probe inserted into the jugular vein (rather than the quenched fluorescence chemistry employed by Glumetrics). Results reported from a 34-patient study stated "The 456 sample values recorded by the monitor based on 8-hour calibrations were correlated . . . and the MARD for the study was 9.40%. . . . 89.23% of the data fell within zone 'A' . . . with the rest falling within zone 'B.'"[50] An earlier abstract reported a 24-patient study at what appears to be the same institution and quoted a MARD of 7.70%, with 92.7% of the data zone "A," 6.8% in zone "B," and by difference, 0.5% in zone "D."[51]

Glucoset

The Glucoset system (Glucoset AS, Trondheim, Norway) is an *in-vivo* hydrogel matrix sensor at the end of an optical fiber that responds to changes in the diameter of the hydrogel

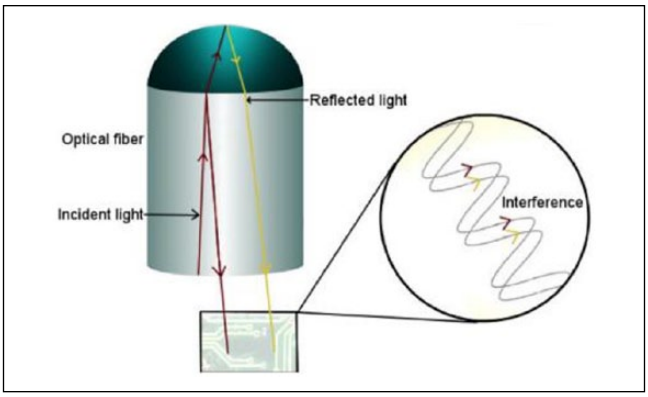

Figure 11. Glucoset sensing system.[53]

by an interferometric optical measurement (Figure 11). When 3-phenylboronic acid complexes with glucose, it causes cross-linking, which changes the diameter, causing a change in the path of light sent down the fiber.

This system was originally developed by Invivosense ASA in Trondheim, Norway, which went out of business in 2009.[55] Results of a porcine study were reported in 2011,[55] but no human results have been published to date.

Cascade Metrix

Cascade Metrix, Inc (Indianapolis, IN) is developing the CMI Automated Glucose Monitoring System that is reported to be in the "pre-clinical prototype stage."[56] According to the company's website, "CMI expects to obtain EU CE mark in Q1 of 2015 and to begin commercial product shipments following clearance. FDA 510k would be filed in [the second] half of 2015."[57] A 2008 publication described the automated sampling system, comparing proposed detection systems with preliminary *in vitro* results.[58] A recent patent describes both a flow-through mid-infrared sensor and an automated electrochemical test strip and meter measuring system that is integrated with the sampling unit.[59]

Conclusions

Although many intravascular glucose measurement systems, employing differing access sites, sampling, and detection technology have been under development, some for many years; to date, only 1 system has been cleared or approved for sale in the United States. The difficulties encountered have been equally diverse, including difficulties in regulatory approval, thrombic events at the sensor tip for *in vivo* systems, unexpected drug interferences, and possibly inconsistent manufacturer support. Without doubt, the controversy regarding tight glycemic control in hospital ICUs has contributed substantial uncertainty to the development path and probable commercial success of these systems.

Abbreviations

CE, Conformité Européenne; CGM, continuous glucose measurement; CVC, central venous catheter; EEA, European Economic Area, IIT, intensive insulin therapy; MARD, mean absolute relative deviation; MIR, mid-infrared; NIR, near-infrared; PMA, premarket approval; POC, point of care.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JLS served as a consultant to Luminous Medical for intravascular glucose and Edwards (for noninvasive glucose measurement technologies, not intravascular glucose) in 2008. MJR is a frequent scientific advisory board member for Roche Diabetes Care, Inc and is an employee of Vanderbilt University. NIVG Consulting discloses no conflicts of interest.

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