State of the Art Review
Blood Glucose Measurement And Monitoring Technologies - Abbreviated Report

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ABSTRACT

Introduction:

To describe alternative approaches, technologies, and products for glucose measurement under development and available in the consumer and clinical markets, and compare them with the market-ready Clinical Sentinel IP created, developed and refined by TecMed, Inc.

Method:

Compile and compare published data and descriptions for glucose measurement and management from the approaches, technologies, and products first described above. Data will include published accuracy data, specifications, costs, reliability, convenience, and efficacy.

Results:

Currently utilized systems with regulatory approval for use in critical care have common challenges that include lack of accuracy, high cost , complexity, timeliness and reliability. Systems under development have not sufficiently addressed most of these challenges. Continuous glucose monitoring systems (CGMS) have not proven effective for blood glucose management in critical care and perioperative environments with accuracy problems continuing. Improvements in sensor reliability and predictive algorithms have provided some improvement in accuracy, but daily fingerstick calibration and reimbursement issues continue to hinder broader adoption. Proposed and approved integrated continuous monitor-insulin pump “artificial pancreas” designs are showing promise and bolstering market growth in CGMS, but have existing and newly introduced challenges to address. Growth in CGMS is adding pressure to the already beleaguered conventional blood glucose monitoring market segment. The majority of non-invasive glucose monitoring technologies that are under development are recycled technologies with few new entrants outside of the hype of Google and Apple involvement.

Conclusions:

TecMed’s Clinical Sentinel IP remains the only technology that has provided automation and accuracy at the levels recommended by healthcare professionals for appropriate glycemic management in critically ill patients that provides a viable solution for government mandated inpatient blood sugar targets and reimbursement penalties.

INTRODUCTION

Diabetes is now the sixth leading cause of death worldwide resulting in more than 1.6 million deaths in 2015. There are currently an estimated 422 million people with diabetes globally. The total annual direct and indirect costs attributed to diabetes is $825 billion. In developed countries, treatment costs for diabetes and complications resulting from it are estimated to be between 10% and 18% of national health care expenditures.

The combined markets for medical devices, diagnostics, therapeutics and treatments for diabetes are in excess of $55B annually. In 2016 the consumer diabetic self-monitoring and clinical blood glucose monitoring markets totaled nearly $15B.

It is fundamentally understood that more appropriate management of blood glucose within the euglycemic or normoglycemic range ("true" or "normal") provides better patient outcomes and lowers costs for hospitalized patients and delays, or eliminates, the onset of severe and costly diabetes related complications for self-monitoring diabetics. The limitations for providing the accuracy and reliability necessary for more appropriate management by products that are currently available to the consumer and clinical markets have been demonstrated in numerous peer-reviewed and published studies.

The intellectual property (IP) comprising TecMed's core Clinical Sentinel IP provides automated solutions with accuracy and precision at the levels requested by healthcare professionals to meet their blood glucose management specifications, which have been driven largely by government regulation and associated reimbursement penalties. The Clinical Sentinel IP is incorporated in highly advanced device designs (Technology Readiness Level 8-9) for automated patient blood glucose measurement (monitoring) during on-bypass open-heart surgery, perioperatively (before, during and after surgery, in critical/intensive care environments, and laboratory analysis instrumentation.

BACKGROUND

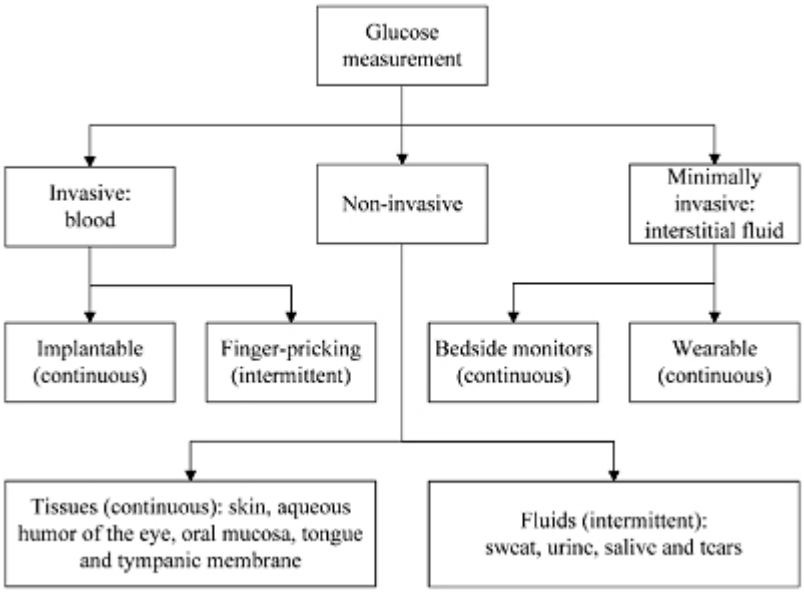
The following describes numerous technological approaches and products for the measurement of blood glucose for consumer diabetic self monitoring and clinical point of care measurements for inpatient populations. Both consumer and clinical methodologies are discussed to reflect the off-label utilization of consumer devices and technology in clinical settings. The use of consumer devices in clinical settings is a source of growing and critical concern for hospitals, healthcare professionals, and regulatory agencies.

Management of blood glucose in critical/intensive care environments, for critically ill patients and those undergoing major surgical procedures is even more complex and has further amplified the shortcomings of current products, methods and technologies.

Common drawbacks and weaknesses described more fully herein continue to challenge existing approaches, technologies and methods. These issues include lack of accuracy, immediacy, reliability, robustness, and cost effectiveness. The technological approaches explored include, but are not limited to, electrochemistry, fluorescence, spectroscopy, optical coherence tomography, differential imaging, photoacoustics, temperature, chromatography, light sensors, metal oxide sensors, bioelectrical impedance, refractometry, reflectometry, interferometry, ellipsometry and polarimetry.

These varying technological approaches are further distinguished across more than two hundred companies, universities, and research laboratories who are applying these measurement techniques to a variety of substrates that include, and should not be considered limited to, blood, blood components, interstitial fluid, urine, saliva, tears, aqueous humor, sweat, exhaled breath, cerebrospinal fluid, skin, skin components, retinal tissue, iris folding, cheek mucosa, and other cellular tissue. These measurement techniques are being applied to the various substrates listed above through techniques that are invasive, minimally invasive, and non-invasive. The resulting simplified matrix is illustrated below (Medical Engineering & Physics 2008):

The pursuit of technology for improving the lives of 100's of millions of diabetics worldwide, as well as improving the outcomes of hospitalized patients and reducing healthcare costs has been well documented for at least the past two decades. The focus has primarily been on the realization of non-invasive (needle-free) glucose measurement technology that provides the necessary accuracy for therapeutic decisions (insulin administration) without added cost. In the hospital setting, invasive access to patients is less of an issue, while accuracy, timeliness, cost and labor-intensive caregiver engagement are the priorities. Until the completion of the Clinical Sentinel IP, there was no automated inpatient blood glucose measurement technology that could provide the accuracy and reliability required for appropriate blood glucose management without excessive cost and repeated caregiver intervention.



Accuracy

It is undeniable that monitoring and managing blood glucose concentration in diabetics slows or stops the onset of more severe complications associated with diabetes. These complications include amputation, blindness, kidney failure, and cardiovascular disease. The annual cost of diabetes worldwide is now in excess of $825B.

Accuracy is critical in blood glucose monitors (BGM's). Recent studies have demonstrated the inaccuracy and lack of reliability in numerous blood glucose monitoring systems, including those that have achieved regulatory approval in the U.S. and Europe. Less than 50% of BGM's evaluated met regulatory approval specifications. Results from these studies, led to the proposed creation of an independent European Institute of Technology Evaluation and Quality Control. ***The medical literature demonstrates that adverse clinical outcomes are associated with the use of inaccurate BGM's.***

Additional studies have identified inaccurate BGM's as the cause of rising HbA1c results in self-monitoring diabetics. Glycated hemoglobin testing (HbA1c) provides a measure of blood sugar management. Multi-center studies of approved/certified self-monitoring blood glucose systems (SMBG's) showed that in "real world" patients, 20-25% of devices failed to meet either old (+/-20%) or new (+/-15%) accuracy/"trueness" standards. In this study of more than 9,000 patients with type 1 diabetes, ***poor performance of SMBG's correlated with higher HbA1c levels and increased rates of hypo and hyperglycemia. Diabetic patients who feel they cannot rely on meter readings tend to stop monitoring.***

As of 2013, there has been an average of over 32,000 adverse BGM medical device reports filed with the FDA per year and the FDA feels that these adverse BGM events remain largely under-reported. Modeling studies for insulin treated diabetics in the U.S. have shown that monitor accuracy of +/-10% can result in insulin dosing errors approximately 28% of the time, and nearly 50% of the time for accuracy at +/-20%. The economic risks from insulin dosing errors identified in these studies, based only on severe hypoglycemic events, has been estimated at nearly $460M annually in the U.S..

The rising interest in continuous glucose monitoring systems (CGMS) has also been impacted by the accuracy of BGM's that almost predominantly rely on BGM's for daily calibration. It is generally understood and agreed that accurate BGM's will provide better continuous monitoring and more appropriate diabetic monitoring and management compliance.

In hospital settings, and even more so among critically ill patients, blood glucose management has become a crucial factor in assessing and managing patient outcomes and economic impact. The role of metabolism in illness and healing continues to become more clearly understood. Time in targeted blood glucose range has become predictive of patient outcome, and increased the demand for more frequent measurement with greater accuracy. Interest has been growing rapidly in automated measurement and continuous monitoring systems that have demonstrated improvements in diabetic HbA1c values, reduced hypoglycemic events, and lower daily/weekly average blood glucose concentrations that are indications of appropriate blood glucose management.

Glucose Measurement Fundamentals - Testing Media

Whether optical or electrochemical, invasive or non-invasive, glucose monitoring techniques have been developed based on measurements of glucose in a number of bodily fluids. A brief overview of the various media follows, including inherent advantages and challenges associated with each of them.

Blood

Whole blood and blood components account for the overwhelming majority of testing methods. Blood components include serum, interstitial fluid, aqueous humor, plasma and other serum ultra filtrates/microdialysates.

The most common testing methods are invasive and involve drawing venous, arterial, or capillary blood samples that are subsequently tested with laboratory instruments, point of care analyzers, or consumer blood glucose monitors. Alternatively, sensors may be imposed within blood vessels or into tissues to measure glucose in blood or from the interstitial fluid bathing cells that is derived from blood. Blood samples are often processed to remove cells and other components to allow for measurement of plasma glucose concentrations. Typical blood glucose concentrations range from 40-600mg/dL (~2.2-33mM).

The advantages of blood based measurements include well established analytical techniques, low cost instrumentation and relatively continuous and reliable procedures. The downside for such measurements stems mainly from the invasive nature of the sample extraction and include pain, inconvenience, waste, time, and infection risk.

Urine

Urine is one of the most widely studied media, mainly because it is non-invasive and painless. The approaches are generally affordable, portable, simple to use, and test strips are cheaply and easily manufactured.

Glucose concentrations in urine are very low, the accuracy of urinalysis is typically poor, requires frequent calibration and is highly susceptible to interferences associated with patient hydration and fluid volumes. Average urine glucose concentrations range from 50-100mg/dL (3-6mM).

Saliva

Saliva testing is also non-invasive, painless and safe for children and adults. Samples are generally easy to collect and testing methods affordable and easy to mass produce.

Glucose concentration in saliva is very low, testing requires very high sensitivity and specificity (selectiveness) to provide reliable results. Salivary glucose concentrations normally range between 0.14-3.78mg/dL (0.008-0.21mM). Lag between blood and saliva glucose concentrations

may not be suitable for therapeutic treatment for diabetics using insulin. Saliva is also dependent on hydration that can interfere with measurement accuracy.

Sweat
For the most part, sweat collection is minimally or non-invasive and collection of sufficient sample volume is generally not a problem.

However, as with saliva, glucose concentrations are quite low typically between 5-20mg/dL (0.277-1.11mM), testing sites are subject to irritation, measurements are often inaccurate due to inconsistent lag time, hydration levels, and physiological changes in sweat composition that can interfere with testing.

Tears
Normal tear production provides a fairly accessible media for a non/minimally invasive measurement that is continuously replenished. According to the literature, it is less susceptible than sweat and urine to dilution/hydration interference. Numerous testing methods have been proposed/studied that are cost effective (cheap).

The problem with tear-based glucose measurement has been mainly with a poor correlation between blood glucose and tear glucose. Ranging between 0.18-10.8mg/dL (0.1-0.6mM), glucose concentration in tears is relatively low necessitating very high sensitivity and specificity (selectivity). Interference from high lactate levels, variable pH, and other compounds-physiological factors have added to the complexities of this approach.

Breath
Breath analyzers provide an approach that would be straightforward, non-invasive, and easy to use. However, the results and analysis are influenced by multiple confounding factors and other biomarkers, and their correlation to blood glucose concentrations are not well defined. At 0.5-21ppm, the acetone concentration is extremely low and subject to interferences.

Testing Methods

Electrochemical
By far the most common measurement approach for blood glucose/sugar measurement is electrochemistry. Electrochemical biosensors are in their third and fourth generation iterations with advances in electroding, nanomaterials, bioengineered enzymes, selectively permeable membranes, dynamic signal processing, and ongoing advances in predictive/corrective algorithms. Electronic and automated readers for electrochemistry based blood/urine test strips include reflectance and colorimetric analysis that employ optical technologies (photometry, spectrometry, colorimetry) to read electrochemically generated results.

Optical
Optically based sensors have been utilized for a variety of diagnostic purposes over the past decade or so, including scanning thermometers, pulse oximeters, oxygen saturation and hemoglobin monitoring. A number of optically based technologies have been explored for measuring glucose non-invasively and/or less invasively than blood draws and fingerstick methods. Brief descriptions of these technological approaches are provided below and more detailed analysis is provided later in this paper as they relate to specific companies and products that are under development, on the market, and many that have been discontinued or abandoned.

General design limitations and challenges associated with optical glucose measurement approaches include, but are not limited to low absorption, high scatter, poor penetration/radiation of light in tissue, glucose clearing (diffusion coefficients), scarring, skin thickness, hydration, glycosylation, temperature and

other dynamic tissue irregularities.

Spectroscopy
A wide variety of spectroscopy-based technologies and variants therefrom have been investigated for measuring glucose in blood, tissues and bodily fluids. Fundamentally, spectroscopy is the study of the interaction of matter and electromagnetic radiation. Spectroscopic data is often represented by an emission spectrum, which is a plot of the response of targeted interest as a function of wavelength and frequency.

Near Infrared Spectroscopy
Near infrared (NIR) spectroscopy utilizes both the absorption and scattering phenomenon of light when it is directed over sample tissues/fluids up to a depth of a few millimeters. Changes in molecular specific vibrational information resulting from the light and tissue interactions are measured in the absorption and scattering phenomenon (fingerprint/spectral bands) in the near infrared domain (750-2500nm spectrum).

Limitations of NIR spectroscopic approaches include the weak spectral bands of glucose that overlap the stronger bands for water, hemoglobin, proteins and fats. In addition, the effect of solute (glucose) on the reflective index of a medium is non-specific and is common to other soluble analytes (interfering compounds). Physical and chemical parameters such as blood pressure, body temperature, skin hydration, and albumin concentrations can also interfere with glucose measurements. Environmental parameters including changes in temperature, humidity, CO2 and atmospheric pressure can also affect measurements. NIR measurements can also be confounded by measurements of glucose in different media, from blood and interstitial fluid respectively.

Mid-Infrared Spectroscopy
Mid-infrared (mid-IR) measurement is based on analysis of both the absorption and scattering phenomenon of light when it is directed over sample tissues/fluids up to a depth of a few micrometers (um). Changes in molecular specific vibrational information resulting from the light and tissue interactions are measured in the absorption and scattering phenomenon (fingerprint/spectral bands) in the near infrared domain (2500-10000nm spectrum). Mid-IR approaches benefit from increased absorption and decreased scattering due to the higher wavelength. Mid-IR spectroscopy has an advantage over NIR in that the spectral bands are sharper (more distinct) as opposed to NIR bands that are often broad and weaker.

The primary limitation of utilizing mid-IR is relatively poor penetration, but includes the same confounding and/or interfering compounds as NIR.

Raman Spectroscopy
Laser light is used to induce oscillation (vibration) and rotation in glucose molecules. The excitation of the molecules effects the emission of scattered light, and is dependent on the concentration of the solute (glucose) molecules. This relies on inelastic scattering (Raman scattering) of monochromatic light usually in visible, near infrared, and near ultraviolet range. Most commonly, Raman spectroscopy is utilized to measure glucose in the aqueous humor of the eye or dermal/sub-dermal layers of skin.

Several variants of Raman spectroscopy have been investigated including spatially offset Raman spectroscopy (SORS), surface enhanced Raman spectroscopy (SERS), spontaneous Raman spectroscopy (SRS), and polarization or Raman optical activity (ROA). Spatially offset Raman provides for the retrieval of Raman scattering beneath an obscuring surface from a scaled subtraction of two spectra taken at two spatially offset points. Surface enhanced Raman utilizes gold or silver to enhance the electric field excitation, increasing signal strength. Spontaneous Raman exploits the temperature dependence of the Raman spectra of molecules, while Raman

optical activity relies on small differences in the intensity of Raman scattering from chiral molecules (intensity and/or polarity of components of the scattered light).

Raman spectroscopy provides sharper and less overlapped spectra than NIR, with modest interference from luminescence and fluorescence phenomena. Low cost, fixed wavelength lasers can be used. There is an expectation from proponents of this approach that advances in surface-enhanced Raman techniques may improve sensitivity and signal acquisition time.

Limitations associated with Raman spectroscopy include instability of laser wavelength and intensity, long spectral acquisition times (motion errors), and common problems of interference from other molecules and compounds.

Impedance Spectroscopy
Dielectric spectroscopy provides an experimental analysis for characterizing electrochemical systems. The technique measures impedance at a specific frequency or over a range of frequencies to quantify the glucose concentration as a function of permittivity (opposition to the flow of alternating current at different wavelengths or frequencies), based on energy storage and dissipation properties of biological tissues that can be correlated with glucose concentration. The dielectric spectrum is measured in frequencies ranging from 100Hz to 100MHz. Fundamentally based on the decrease in sodium and increase in potassium in red blood cells in response to variation in blood glucose. The resulting change in the cell membrane potential reflected in permittivity and conductivity are reflected in the changing dielectric spectrum. Wrist and finger cuff based devices measuring red cells in the blood and tissues have been, and continue to be investigated.

Limitations include hydration, disease state, red cell health, exercise, rapid electrolyte concentration fluctuations and effects of pharmaceutical/therapeutics.

Photo-Acoustic Spectroscopy
Acoustic detection of the effect of absorbed electromagnetic energy (particularly light) correlated to the spectrum associated with absorbing components of the sample (tissue or fluid). Most common approach is modulated laser light excitation of the sample in a range of 10-10kHz, and employing a lock-in amplifier for amplitude and phase for its specific frequency. Measurement is made of the changes in acoustic response associated with changes in glucose concentration. Light absorption causes localized heating that generates ultrasonic pressure waves detectable by microphone. In clear media, the photoacoustic signal is a function of the laser light energy, the volume thermal expansion coefficient, the speed of sound, the specific heat and the light absorption coefficient.

Fundamental limitations include limited pathlength (penetration), high water absorption, temperature dependence, overlapping bands/spectra, and week absorption at short wavelengths. Variability in cell membrane associated with disease, metabolic, or physiological conditions also interfere with measurements.

***Optical Coherence Tomography*/Interferometry**
Principally, optical coherence tomography (OCT) measures the echo time delay of backscattered light in a sample through the characterization of the interference intensity obtained when the light coming through, or reflected from, the sample and the light reflected in a reference surface overlap.

The technique is sensitive to motion artifacts, changes in temperature, minute changes in source/detector angle, and poor penetration capabilities. Penetration is further affected by thickness of skin, hydration, and pigmentation.

Fluorescence

In general, fluorescence approaches are based on the generation of, or changes in the generation of, fluorescence of molecules in human tissues/fluids when excited by light at specific frequencies. It is generally understood that ultraviolet light between 340-400nm provides measurable fluorescence from glucose in solution, and that the fluorescence intensity is dependent on the glucose concentration.

Affinity-based glucose binding fluorescent chemistry techniques employ sensors coated with chemicals with glucose specific binding sites (boronic acid derivatives and others) for activation of fluorescence emitting enzymes and molecules (glucose indicator hydrogels). These glucose sensors are implanted intravascularly (measuring blood), or subcutaneously (measuring interstitial fluid).

Fluorescence monitoring limitations include matrix effects, skin thickness, pigmentation, and hydration, as well as interference from luminescence, scatter, absorption, quenching and competitive/non-competitive inhibitors.

Thermal Spectroscopy -Temperature Modulated Reflectance Spectroscopy

Thermal spectroscopy measures glucose as function of the infrared radiation or emission of naturally occurring infrared light energy corresponding to glucose, or based thermal modulation (cooling/heating tissue) to measure based changes in energy absorption correlating to the changing temperature. Infrared radiation can be increased by imposing additional infrared light and measuring the additive reflected and emitted energy. Measurements of glucose have been explored in the skin of the forearm, palm of the hand or finger. The ear can also be utilized, with the sensor inserted in the ear canal and measure made from the IR radiation from the tympanic membrane.

Variation of body and skin temperature are strong confounding elements. Illness and other natural dynamic and periodic physiologic parameters (sweating, fever, flushing, etc.) effect skin and tissue temperature.

Electromagnetic Sensing

Electromagnetic sensing measures the dielectric parameters of blood/interstitial fluid using electromagnetic coupling between two inductors. The coupling of the inductors is modified by variations in the dielectric parameters of the solution (blood/interstitial fluid), glucose concentration can be estimated from those variations. When a voltage is applied to the primary inductor the signal produced at the second inductor is utilized to calculate glucose concentration. Frequencies currently under investigation range from 2.4-2.MHz. Frequency optimization is highly dependent on temperature.

Limitations include large dependence on temperature, hydration (electrolyte concentrations). Fundamentally, the dielectric parameters of blood and interstitial fluid depend on numerous related and unrelated components in addition to glucose.

Fluid Harvesting / Iontophoresis

Iontophoresis is based on the flow of low electrical current through the skin, between an anode and cathode positioned on the skin surface. An electrical potential applied between the anode and cathode causes migration of sodium and chloride ions from beneath the skin towards the cathode and anode respectively. Uncharged molecules (such as glucose) are carried along with the ions by connective flow (electroosmosis), that causes interstitial glucose to be transported across the skin to be collected at the cathode where a glucose sensor is placed for a direct measurement. For a typical range of iontophoretic current densities (<0.5mA/cm^2), glucose extraction is in an approximately linear relationship with the density and duration of the iontophoretic current. Measurement sites have typically been at the wrist in the form of a watch;

alternative designs have been explored in the form of patches.

Primary limitations include skin reactions that lead to skin irritation, and inflammatory events that confound measurements. In addition, there are fundamental challenges due to the length of time required to draw the sample to the cathode/sensor, and interference from sweat, humidity or other events effecting skin and/or interstitial conductivity/permissivity.

Polarimetry

Optically active solutes (such as glucose), are chiral molecules. These solutes effect the angular rotation of the polarization plane of light as the light transverses solutions containing them. The amount of rotation is related directly to the concentration of the solute that is in solution. Non-invasive measurement of glucose in humans by means of polarization changes is one of the earliest and longest investigated approaches. Inherent advantages include the ability to use visible light that is easily available and recent developments in the miniaturization of optical and electrical components to facilitate manufacturing. Most common measurements are made from/through aqueous humor of the eye.

Challenges include high sensitivity to scattering, reflection, absorption that diminish signal. Sensitivity is described in the literature as poor due to additional optically active (chiral) molecules present in human fluids containing glucose, including ascorbate (vitamin C) and albumin. Variations in temperature and pH can also effect changes in angular polarization, and a greater understanding of the time delay between changes in blood glucose and glucose concentrations in aqueous humor is being explored. Methods must be adapted to address movement of the eyes and corneal rotation that can also impact measurements.

REVIEW/RESULTS

This review will begin with clinical monitoring systems that might be construed as direct competition for the Cardiac Surgical Sentinel, Critical Care Sentinel, and Perioperative Sentinel instrument/device designs. Currently available clinical monitoring systems are minimally invasive or invasive. At this time there are no commercially available non-invasive products in the market. Several non-invasive approaches that may be modified for clinical or hospital utilization are under development and will be discussed later. Invasive (fingerstick) blood glucose monitoring systems are described more fully later on, although two systems will be described here that have achieved regulatory approval in the U.S. for use with critically ill patients.

The majority of continuous and fingerstick glucose monitoring systems are electrochemically based and provide a measurement based on the product of an enzymatic reaction. This electrochemical approach is discussed in much greater detail under the “Invasive” section further on in this paper. Regardless of how the sample is acquired, invasive or minimally invasive, electrochemical systems have inherent limitations and challenges that include, but are not limited to, pH, temperature, oxygen saturation (altitude), humidity, hematocrit (red cell concentration), interfering compounds, and need for predictive algorithms.

Fluorescence-based measurement has been incorporated into several testing systems with attempts to overcome quenching, chemical interferences, skin thickness, pigmentation, sensor fouling, confounding chemistries and non-linear response across the full physiological range (40-600mg/dL).

Point of Care - Portable Laboratory (In Situ) Devices

In Situ, portable laboratory devices provide smaller footprint laboratory bench analysis in the hospital ward but continue to experience difficulties in gathering wide spread adoption for glucose monitoring. The accuracy is comparable to central laboratory devices, and these units are often utilized as reference standards for published studies. The accuracy is defined differently than ISO 15197, and these devices must be routinely calibrated and certified to achieve certification accuracy equal to 2% at 450mg or +/-

9mg/dL equal to about 12% at or below 75mg/dL. The most common format is for individual patient test cartridges for physiological/metabolic panels. The cartridges range in cost from $10-$20, but the real expense in utilizing these instruments is in the liquid reagents utilized for testing, calibration, and maintenance, as well as the time and expense of drawing tubes of blood from patients.

Point of care testing (POCT) devices come in handheld and benchtop formats that provide more timely access to data in emergency care situations, but the debate between laboratorians, clinicians and administrators continues as to the cost and execution of new and emerging POCT technology when compared with conventional laboratory testing.

MINIMALLY INVASIVE

The term minimally invasive describes glucose monitoring systems that do not require a fingerstick or blood draw. It becomes confusing in many clinical systems that claim to be “noninvasive” because the system merely attaches to existing vascular access lines (IV, central line/PICC). The majority of continuous monitoring systems, for inpatient monitoring or consumer diabetic self-monitoring, are at least minimally invasive at this time. Non-Invasive and invasive monitoring systems will be discussed in detail later in this document.

Continuous/Real Time - Glucose Monitoring Systems - Clinical

Historically, continuous (real-time) monitoring systems have been based on implantable sensors, intravascular (indwelling) catheters or subcutaneously implanted micro-needles or microdialysis catheters. Sensors measure whole blood, interstitial fluid, or serum ultrafiltrate from microdialysis. As an alternative, drawing blood, interstitial fluid or ultrafiltrate to a flow through sensor unit is an approach that has been, and continues to be utilized.

Pursuit of automated bedside monitoring and management of inpatient blood glucose levels goes as far back as the 1980's Miles Laboratory Biostator, Nikkiso STG-22, and the Olmatic GmbH Glucostator. These systems embodied many of the same challenges that remain in the current pursuit of closed loop “artificial pancreas” technologies. These instruments are large (as much as 70lbs), complex, expensive, use large volumes of blood (up to 50mL/day), have demonstrated accuracies in the +/- 20% range at best, are challenged by confounding-interfering chemicals, and are complex, difficult, and costly to maintain. Each of these systems draw blood from the patient to a sensor or test cell where blood sugar is measured by electrochemical or enzyme-based colorimetric analysis. Of the three, Olmatic still lists the Glucostator as a laboratory research and investigational device, and Nikkiso is continuing development with published trial studies from 2015 with results in the +/-25mg/dL (averaging approximately +/-18% across physiologic range 40-600).

At this time, two fingerstick-test strip systems have been approved for clinical glucose measurements leading to therapeutic adjustments. The NovaStat (Nova Biomedical) and Informa II (Roche Diagnostics) have both achieved POCT12-A3 certification, which minimally requires that 95% of readings be within +/-12.5% of reference values. Hospital protocols often require that tests are rerun for measurements that are outside of the normal glycemic range (80-120mg/dL). Off label use of other consumer blood glucose meters and test strips has been long debated and proposed changes in regulatory certification for clinical utilization have been set aside for the past several years. Testing with these devices costs about $20/test and 80% of that cost is labor. In addition, when off label measurements indicate the need for therapeutic adjustment, blood must be drawn for laboratory analysis that costs another $60 and easily adds another 20-30 minute delay before measurement data is delivered. Physiologically, blood glucose concentration changes take about 5-7minutes in healthy patients, minimizing the value of data received 30-40 minutes later.

The need for accurate, automated, and timely measurements for appropriate management has continued to grow over the past three decades with the increased understanding of the benefits of appropriate blood glucose management in hospitalized patients (diabetic and non-diabetic) in terms of lower costs and better patient outcomes.

There are challenges that apply to all invasive/minimally invasive continuous monitoring systems utilizing intravascular and subcutaneous patient access that have not yet been sufficiently addressed. Indwelling catheters and sensors are subject to "foreign-body responses", edema/swelling, fluid retention, inflammatory cascade/immune cell recruitment, thrombus (blood clot) formation and other effects leading to sensor/signal degradation, fouling and failure. Sensor failure rates as high as 30% have been reported in studies. The clinical consequences of thrombus formation intravascularly (within blood vessels) can be quite severe, including pulmonary emboli and peripheral ischemia.

Several measurement methods and systems have been developed or are under development for the purposes of providing automated blood glucose measurement in hospitalized patients, and more specifically for critical care and surgical environments. The clinical point of care glucose measurement segment (in hospitals) accounts for approximately 20-25% of the total blood glucose measurement market that is approaching $15B worldwide. Reports from 2016 place the continuous glucose monitoring market at just under $1B with only 3-4 participants (Abbott, DexCom, Medtronic, and Sensionics)

Continuous/Real-Time Glucose Monitoring Systems - U.S. FDA Approved Clinical Systems

In general hospital wards, skilled nursing facilities (long-term care and rehabilitation hospitals), and clinicians offices off label use of handheld blood glucose meters (BGM's) abounds, in many cases with glucometers that have been specifically designed for clinical utilization, ***but not for critical care and/or surgical environments or for making therapeutic decisions*** (administering insulin/glucose). For critically ill patients and patients undergoing major surgical procedures, ***only POCT12 approved /certified BGM's can be utilized.***

Alternatively, blood can be drawn and sent to the hospital laboratory for analysis or by smaller portable lab units located in their unit. In either event, results are not timely, and repeated engagement of the care provider is time consuming. In a twelve hour shift, nurses can spend 20% or more of their time monitoring and managing glucose. The hospital cost for each fingerstick glucose test is nearly $20, the vast majority of which is labor. Laboratory costs including blood draw, processing and analysis ranges from $40-$60 depending on utilization of portable in situ devices or the central laboratory. Repeated engagement to draw capillary (fingerstick) or venous blood (tube) also increases the possibility for infections for the patient and care provider.

Continuous/Real-Time Glucose Monitoring Systems - CE Certified Clinical Systems

The future of clinical continuous glucose monitoring systems (cCGMS), can be seen in overseas markets. European countries require CE Mark (Conformite' Europe'ene). Historically, achieving CE Mark was easier than the U.S. FDA, but the global regulatory landscape is changing. A push towards global harmonization of regulatory standards is driving increasingly more stringent specifications for approval that are adding to cost and time-to-market. The specifications under which most blood glucose meters have been approved for CE Mark in an accelerating state of change. Specifications were tightened in 2009, 2013 and again in 2015, and the latest change with the publication of EN ISO 15197:2013 included the provision that blood glucose meter manufacturers had a three year transition period before the newer specification would go into effect as the EN ISO 15197:2015 that does not provide for "presumed conformity".

The 2015 specification includes a cessation of presumption of conformity, meaning that existing meters, strips and control solutions approved under the 2003 or 2009 standards may lose their CE mark if they cannot meet the newer (2013) standard. The date of implementation is June 30, 2017. Manufacturers have had more than three years to demonstrate conformity with the newer standard, but it will impact the smaller players in the market who may not have the resources for ongoing regulatory battles.

From the perspective of healthcare professionals, patients, government and private payers, and patient advocacy groups this change addresses a growing concern that once approved, blood glucose monitoring systems are essentially never checked again to ensure continued safety and efficacy, until people are injured or killed. It is part of the argument about off label use of BGMs that are CLIA-waived devices; CLIA standards require periodic review to maintain their certification and FDA approval under ISO 15197:2013 does not.

The market for automated blood glucose monitoring in critical care and perioperative settings has been growing steadily, and at an accelerating pace. The Affordable Care Act created penalties that have added to the demand in this arena. The current market is at about $4M with a little more than half of that in the U.S., that has several companies, including our organization (TecMed, Inc.) working diligently to get into the marketplace.

Continuous/Real Time - Glucose Monitoring Systems - Closed-Loop "Artificial Pancreas"

The artificial pancreas is the long awaited pinnacle achievement in diabetic blood glucose management. The market is being driven in part by consumers cobbling together systems from available components for DIY artificial pancreas systems. Given the dangers of insulin administration, the uncertainties of meter accuracy and reliability, and the questionable delivery accuracy of glucose pumps, it is a leap of faith to combine existing devices and compound those risks for convenience. With that having been said the following provides an introduction into the "Wild West" and conceivably a look into the future of fully closed loop, non-biological artificial pancreas technologies. Only one has been approved by the FDA (Medtronics 670G)

A few fundamentals on the way in, the bundle of technologies for the majority of these systems include a continuous monitoring system with transmitter, receiver, and management software platform; a programmable insulin pump, tubing kit (for most), insulin, basal/bolus management software platform; an artificial intelligence platform, a virtual glucose management system (BGMs) that learns user patterns and trends and provides guidance to the main system management platform that assumes control of both CGM and pump, that interfaces wirelessly with smartphone, PC, and cloud so that data can be shared with physicians so that they can provide better guidance to patients. An additional pump, tubing kit, and management system can be added in the creation of "bionic" pancreas designs that include glucagon administration. The system can be expanded even further with additional pumps, tubing kits, and management software for therapeutics like Pramlintide or incretin mimetics to augment insulin and/or glucagon, respectively.

Continuous Glucose Monitoring Systems - Consumer

The benefits of continuous blood glucose monitoring, and more specifically with CGM integrated with insulin pumps are to improve A1c, time in normal blood sugar ranges, and reduced hypoglycemic events. More time in normoglycemia is the fundamental goal of blood glucose management. The benefits have been demonstrated in 30 year studies, and include: 53% decrease in retinopathy, 45-48% decrease in retinal detachment/cataract surgery, 39% reduction in overall kidney disease, 51% reduction end stage renal disease, 69% reduction in kidney damage and amputations, 30% reduction in peripheral neuropathy,

42% reduction in cardiovascular disease, and 57% decrease in heart attack or stroke. ***These studies have shown that more appropriate management of blood glucose, testing at least 4 times a day, delays the onset (by an average of 15 years) and slows progression of these costly, painful, and deadly complications associated with diabetes.***

Studies have demonstrated improvements in A1c and reduced hypoglycemia from advances in pump and monitoring technologies, when compared with conventional BGM and multiple daily injection (MDI) regimens. Technologies and treatments for these improvements are costly and reimbursement varies widely between payers and plans for both government and private payers. Average annual cost for conventional fingerstick BGM is approximately $1,700, with multiple daily insulin injections this increases to nearly $4,000, and the move to a pump pushes the cost to nearly $6,000. Adding the cost of CGM systems with average costs of another $5-$6,000 provides an understanding of why the markets are so large. ***Without insurance the average annual cost for diabetes supplies is over $11,000 in the United States.*** Most people have insurance that covers some of the cost, but diabetics are still paying, through increasing premiums and deductibles and, in some scenarios, an inability to choose the medications or technologies that they want, because of what is reimbursable.

The past decade has seen improvements in reliability, accessibility, and convenience in consumer continuous glucose monitoring systems (CGMS). ***Accuracy has improved, but only incrementally***, and the majority of systems still require calibration with fingerstick blood glucose monitoring systems that are struggling to achieve measurement accuracy within +/-15% of reference devices. As a caution, some accuracy claims are based on comparisons of CGM systems versus the same BGM that was used to calibrate the system. Achieving measurements within +/-15% of results obtained from a device that provides accuracy of +/-15% at least 95% of the time is not a measure of real accuracy.

CGMS Market dominated by three players in order of market share as through December 2016, Dexcom, Medtronic and Abbott. Of what is reported as a $956M market, a recent report shows Dexcom revenues totaling approximately $445M, Medtronic with $380M, Abbott with revenues from CGMS of $130M. The report also showed $30M in overseas revenue from Senseonics new long term implantable product. The CGMS market segment has the strongest growth potential and has grown from $275M in 2014 to $956M in 2016.

NON-INVASIVE BLOOD GLUCOSE MEASUREMENT

The pursuit of truly noninvasvie blood glucose monitoring methods has been going on for three decades, and probably longer. Current methods are costly, inconvenient, painful, messy, and insufficient in the eyes of many for the task of appropriate blood glucose management. The demand from the diabetic and healthcare professional community for noninvasive and more accurate technology is growing increasingly vocal. Numerous approaches have been investigated over the past thirty years and none have produced a commercially viable device after the expenditure of more than $3B in institutional capital, and a reportedly equal amount of private investment.

Many have been lured in by the relative simplicity of making in vitro glucose measurements under controlled research laboratory conditions. The challenge of making those measurements from the human body under normal environmental and physiological conditions has proven dauntingly elusive.

INVASIVE BLOOD GLUCOSE MEASUREMENT

Summary
Electrochemical based finger-stick and test strip blood glucose measurement devices are the most common form of invasive blood glucose measurement devices. In alternative iterations the approach is used for measurement of glucose in blood serum and/or urine in high throughput laboratory instrumentation (and consumer urine strips) :

Principle
Glucose reacts with an enzyme; hydrogen peroxide is released and change in electrical potential is measured as an electrical signal. In the latest generation sensors, oxidation-reduction chemistry provides measurable changes in electrical potential without utilizing enzymes.

Measurement
Capillary blood from finger tips; or alternative sites such as forearm or thigh. Alternative site testing is further limited by recommendation from the FDA that alternate sites should only be utilized during those times when blood glucose is not changing rapidly. The FDA recommends using only finger tip blood measurements when insulin is taken, when blood sugar is low, if patient is unaware of symptoms of hypoglycemia, results do not agree with how patient feels, after eating, after exercise, when sick/ill, or when stressed. Alternate site tests should never be used to calibrate a continuous glucose monitoring system or to calculate insulin dosing.

Limitations
Inconvenient and painful, with accuracy limitations at or near the current ISO standards for 97% of measurements falling within +/- 15% of reference values. Accuracy and reliability of measurement can be further hindered by limitations of temperature, humidity, altitude and interfering compounds including, but not limited to Acetaminophen (Tylenol), maltose, icodextrin, vitamin C supplementation (ascorbic acid), prescription drugs, antibiotics and blood preservatives. Devices seem easy to use, but training is required to optimize results and both consumer and clinic levels.

Advantages
Low-cost, high volume automated manufacturing, relatively robust system, quick results (3-5 seconds), lends itself to scaling for miniaturization. Market, diabetic population, familiarity with the devices and procedures.

History
Invasive technologies, devices, approaches, and products are those that require drawing blood and or implanting intravascular catheters. The majority of invasive techniques are based on electrochemical measurement, widely recognized as fingerstick and test strip systems. The overwhelming majority of commercially available glucose measurement products are based on the measurement of hydrogen peroxide released when glucose is bound to one of several enzymes deposited on an electrode (“enzyme electrodes”). The most commonly utilized enzymes are glucose oxidase (GOX), glucose hexokinase (GHK), and glucose dehydrogenase (GDH). Increased specificity and reduced cross reactivity with other sugar molecules (maltose) have been achieved through recombinant DNA enzyme offerings such as flavin adenine dinucleotide dependent glucose dehydrogenase (GDH-FAD) or nicotinamide adenine dinucleotide (phosphate) glucose dehydrogenase (GDH-NAD) or (GDH-NADP).

Nearly all measurement systems are derived from the anlaysis of changes in amperometric, potentiometric, coulometric, and voltammetric signals based on the amount of hydrogen peroxide that is produced in accordance with changes in the glucose concentration and enzyme substrate binding/activation levels. Portable (in situ) laboratory devices and blood gas anlayzers, as well as numerous high throughput hospital/reference laboratories often employ spectrometer analysis to quantify colorimetric (color intensity based) measurement of peroxide release.

First generation sensors were effectively electrode, substrate (enzyme) and the base charge across the electrodes. In second generation sensors, higher conductivity precious metal sensors, and more complex predictive algorithms were employed to correct for the non-linear enzymatic response, hematocrit, and temperature. Third generation sensors included organo-metallic conjugate additions (ferrocene, ferrocyanide & pyrolidines) to substrate-electrode that reduced measurement dependence on oxygen and improved sensitivity.

While third generation biosensor technology has advance, improvements in manufacturing methods (printable electrodes) and signal analysis (mediated amperometric, variable potentiometric, and multi-point analysis methods/algorithms), as well as multiple sensor systems that provided data to correct for temperature, available oxygen, and signal baseline correction were also realized. In addition, modifications were made to allow capillary draw of smaller blood samples and exclusionary membranes employed to reduce cellular and charged particle interferences. Affinity capture techniques where molecules are embedded in the membranes that bind selectively to interferences have been explored, ***but the improvements in measurement do not appear to have merited the added complexity and cost.***

The latest generation of electrochemistry based blood glucose meters have a handful of common “bells and whistles” that have over the past decade been incorporated in one form or another into the device designs of nearly all of the manufacturers in this segment. These design advances include sub-microliter blood testing volumes, autocoding (replacing coding chips for test strips), automated plasma calibration, capillary fill, blood volume checking, alarms and timing functions, wireless connectivity to cell phones/computers, blood sugar measurement data storage, data sharing and management applications, hematocrit correction, temperature correction, alternative site testing capabilities (AST), audible reporting, and auto strip ejectors to reduce handling of used strips.

A more recent trend is the miniaturization of entire systems to fit them into more convenient all-in-one formats that include meter, strips, lancing device and lancets compact enough to fit in a cell phone, or device that can be attached to cellphones or computers (via USB). Taking that in another direction, manufacturers have recognized sensory, dexterity and vision limitations and created designs with larger displays for results and larger/wider test strips that are easier to manipulate.

Fundamental accuracy has not improved to meet the target defined by medical professionals in their presentation at the FDA open house on glucose sensors in 2012 to provide meaningful improvement in disease management. The demand for greater accuracy prompted the FDA to propose new standards to tighten the minimum accuracy specifications for blood glucose meters in 2013. The proposed standards met with tremendous push back from the industry and were not implemented as proposed. The FDA amended the specifications to require that only 95% of measurements be within +/-15% of reference measures, and that 99% of all measurements must be within +/-20% of the reference device measurements. Additionally, these new specifications would not go into effect until after May 31, 2016, to allow the industry time to make necessary improvements.

Current Companies & Products in the Market

Note: In 2015, 62% of the $11B test strip market was held by four companies listed in order of market share.

Roche - $2.13B
Johnson & Johnson -Lifescan - $1.92B
Ascensia (formerly Bayer) - $1.55B
Abbott - $1.25B

ADVANCED BIOSENSOR RESEARCH

The large and growing diabetes markets are encouraging researchers in the public and private sectors to put a tremendous amount of effort into the field of glucose biosensors that go beyond the capabilities of the first three generations described previously in this section.

Carbon nanomaterials have similar dimensions as redox proteins, and can be used as effective electrical connectors with redox enzymes commonly used in electrochemical sensors. The result is an enhancement of second generation technique providing faster response times and higher sensitivity at extremely low working electrical potentials. More work needs to done regarding control of the chemical and physical properties of carbon nanotubes (CNT), specifically in the areas of toxicity and fabrication.

Cost effective fabrication of CNT nanoelectrode arrays (NEA's), have produced much higher currents than single nanoelectrodes and replaced expensive electronic devices, which improved signal to noise ratio leading to ultrasensitive (CNT-NEA) sensors for chemical and biological sensing. Further improvement in CNT-NEA's for biosensor applications requires predictable assembly and well ordered structures. Novel nano-technology such as soft lithography and nanoprint lithography offer promising approaches for addressing those issues.

Development of CNT's in non-particulate forms such as continuous CNT fibers provides a solution to particulate cellular-toxicity issues, and allows for CNT utilization in implantable sensors for in vivo testing. Even with shorter response times and faster electron transfer there is still a long way to go before full implementation of CNT fibers in biosensing applications, as seen in a couple of the proposed breathalyzer designs described earlier.

How to make consistent and reproducible graphene and sensors from such material in large volumes is still an area of concern and uncertainty. Additionally, graphene is highly hydrophobic and easily contaminated by various species, mainly solvent hydrocarbons used in the microfabrication process.

Non-enzymatic sensors providing direct oxidation of glucose from embedded redox proteins can address the issues of expensive and fragile enzymes. More recently the incorporation of nanomaterials into non-enzymatic sensors provided enhanced sensitivity and faster response. Research into biosensor applications for graphene and CNT applications has expanded dramatically. Hybrid metallo-nanomaterial sensors are showing tremendous promise, but they have issues with pH that significantly limit their use as a replacement for conventional and third generation non-enzymatic electrochemical sensors.

DISCUSSION

The demand for automated and frequent blood glucose measurement with the accuracy required for appropriate management of blood glucose in hospital inpatient settings is being driven by a converging focus on lowering healthcare costs and improving patient outcomes. Patients, healthcare professionals, patient advocacy groups and the families of patients are pushing for technological innovations that promote faster, better and more complete healing. Government and private payers, along with healthcare administrators add to that drive with a greater focus on lowering costs. The Affordable Care Act imposed new penalties based on patient outcomes and costs that are adding urgency to these focused objectives.

In the clinical monitoring arena little has changed in the past decade. In most cases, inpatient blood sugar is still being tested with handheld BGM's or laboratory devices that are handheld, in situ benchtop, or located in central laboratories. In either event, the existing protocols and procedures have demonstrated continued poor results in terms of hospital acquired complications and adverse events that add to healthcare costs and negatively impact patient outcomes. Both the importance and difficulty of appropriate blood glucose management increase dramatically in perioperative and critical care settings.

Dynamic shifts in metabolism, fragile patients, therapeutics, hydration, temperature, and a host of additional physiological responses severely challenge the practices that are currently in place.

With that in mind, regulatory agencies have imposed higher standards for accuracy and reliability for devices that are utilized in those settings. Only a couple of devices have met the standards, and one of those in just this past year. Four automated products are available, that have not gathered traction in the marketplace due to common issues of size, complexity, cost, using too much blood, and insufficient accuracy and reliability.

With nothing else available, the status quo has continued with off label use of CLIA-waived BGM, and either POC or central laboratory devices. Several approaches are under development, most with a focus on intravascular or subcutaneous sensors. Whether implanted subcutaneously or placed in central or venous vasculature, common issues with immune response, sensor degradation, infection, occlusion, thromobosis, and lack of accuracy due to environmental, therapeutic and physiological challenges have hindered progress.

As an alternative, systems drawing blood to or through testing or measurement devices have shown promise, but have been hindered by several of the challenges described previously. There are a couple of optically based approaches that are attempting to address several of those issues. Introducing artificial intelligence and interference libraries to a system that utilizes only microliter quantities of blood for each measure, while returning the unused portion to the patient offers a potential solution. Unfortunately, it also creates new potential problems in terms of complexity, human error when care providers are entering patient data, and increased cost in both time and money to get to market. The difference between a Pre-Market Approval application and a 510K submission, along with the potential difference between Class II and Class III medical device classification can increase costs exponentially.

The fundamental system requested/demanded by healthcare professionals for appropriate blood glucose management in perioperative and critical care settings will provide automated and timely measurements at a frequency of at least once per hour and optimally at not greater than 10-minute intervals. The system will need demonstrated accuracy and precision for blood glucose measurements that are within 5% of reference laboratory measurements at least 99% of the time without adding additional cost or repeated caregiver engagement.

The importance of accuracy or “trueness” of measurement has been demonstrated in studies analyzing the incidence of severe hypoglycemic events resulting from insulin dosing errors at varying levels of glucose measurement accuracy. The difference between +/-15% and +/-5% reflected a difference in dosing errors of 1 in 3 as opposed to 1 in 5 respectively. The calculated savings from this reduction in dosing error related hypoglycemic events was shown to be nearly $500M/annually. Additional savings from reduction in hospital acquired infections (40-50%) and shorter hospital stays (avg. 1.8 days) can be attributed to appropriate blood glucose management. These improvements in outcomes can also provide cost savings of approximately $6-$8,000 per patient. For the 6M critical care patients admitted to critical care units in the U.S. annually, the savings can be in excess of $40B annually in the U.S. alone.

The technologies and products in this market segment, and under development for this market segment, have a long way to go to meet the accuracy, reliability, timeliness, and cost parameters demanded by healthcare professionals, patients and patient advocacy groups, as well as, government reimbursement agencies, private payers (insurance) and hospital administrators, whose primary focus is economic.

Significant strides have been made in consumer CGM systems over the past decade, with the introduction of longer lasting, more accurate and robust/reliable sensor systems. With that having been said, improving accuracy from nearly +-25% to systems that can achieve accuracy in the range of +/-15 percent in real world use by average consumers is no small achievement. Unfortunately, this can lead to high incidences of insulin dosing errors that lead to significant health risks and added cost. Advances in sensor technology that have increased the effective use of sensors from three days to seven days, and up

to 90 days is an important step on the path to the development of an implantable artificial pancreas.

Existing CGM's and those under development continue to perform poorly in published studies of their use in critical care and surgical environments with diabetic patients.

An economic review of the past 3-5 years in the diabetic blood glucose monitoring market shows annual declines in conventional blood glucose fingerstick and meter systems. Conventional BGM revenue is down nearly 27% cumulatively over the past five years. Much stronger and accelerating growth has been seen in the CGM segment of the market with double digit cumulative annual growth for the same period. The strength of the CGM market segment is supported by advances in sensor technology, the integration of insulin pumps with CGM, and improvements in insulin pump technologies, as well as the integration of CGM and pump along with predictive management software to provide patient guidance in hybrid closed loop "artificial pancreas" platforms.

Adoption of CGM has been slowed by inconsistent and unclear reimbursement policies that limited access and utilization. Recent changes in regulatory and reimbursement policies are adding strength and momentum to this market segment, which has grown from just under $300M worldwide in 2014 to just short of $1B in 2016. New policies have been implemented providing reimbursement for "therapeutic" CGM; defined as those that can be utilized for insulin dosing. Only the Big Three (DexCom, Medtronic and Abbott) currently have FDA approved systems and/or systems pending FDA approval that meet the therapeutic threshold.

With an eye on the growth and strength of this market segment, a number of new CGM systems and technologies are under development or undergoing clinical trials for regulatory approval applications. Of those reported herein the majority are hybrid closed loop systems incorporating existing approved meters, pumps, connected diabetes management software, and integrated system management software. Much is being made of studies incorporating Big Data and artificial intelligence designed to create personalized guidance and calibration for integrated "artificial pancreas" systems.

The fundamental challenges common to these systems remain accuracy, reliability, cost and complexity. Accuracy has not improved beyond the +/-15% regulatory threshold. A couple of manufacturers have internal or sponsored studies that have demonstrated the first single-digit accuracy results at +/-9%. Unfortunately, third party researchers and user based studies have not been able to duplicate those results. Reliability of CGM sensors has continued to be challenged with bad and/or early sensor failure rates that can exceed 10%.

It is important to note here that conventional diabetes management with BGM + metformin has an average annual cost of $1,700. The introduction of reliable insulin pumps provided better management adherence and improved A1c and reduced hypoglycemia over BGM and manual insulin injection at a cost of between $4-$6,000 annually. The move to CGM provided more frequent data than BGM at a cost of approximately $5,000 annually. Without reimbursement and widely varying private payer coverage the slow adoption over the first half of the decade is understandable. Longer term implantable CGMS for up to 90-days have entered the market, and sensors are under development for up to 18 months of use. Unfortunately, nearly all of these systems are adjunctive and cannot be used for dosing insulin or other therapeutics. Given the need for continued fingerstick testing between 2-4 times a day to calibrate CGM systems the cost, complexity, and inconvenience continues to hamper adoption.

The future of CGMS is trending toward integrated systems that are complex and require more support in the form of user training, coaching and guidance that increase costs. This is expected to be the case with the added complexity and components in "bionic pancreas" systems that provide CGM, insulin delivery, glucagon delivery, basal therapeutic (pharmaceutical) delivery systems, personalized optimization software, physician connected guidance and the systems operations software platforms to integrate all of these components, especially without improving the accuracy of the measurement data upon which everything is dependent.

The size of the market is drawing participants that are introducing subscription, “pay as you go”, systems that provide 24/7 coaching, training and expert guidance, at attractive early rates. Whether or not these introductory rates will provide sustainable business models remains to be seen. The markets are certainly large enough with more than 400M diabetics worldwide.

The dream of accurate, reliable and continuous noninvasive blood glucose monitoring is still very much alive, with numerous technologies and approaches under development. After three decades a couple of devices have achieved CE and FDA approval for adjunctive use and with significant consumer warnings in their product packaging. Limitations and challenges in the noninvasive arena continue to be physiological, environmental and physical. Measurements that are relatively straightforward in controlled laboratory settings become increasingly difficult in real world environments with numerous constantly changing interferences, artifacts and measurement matrices that are in constant states of motion and flux.

A disturbing trend in noninvasive glucometry is the recycling of failed technologies and approaches. Companies come and go, researchers move on to other companies, or start their own, continuing the development of technologies that have not met with success. In researching this document it was not uncommon to find 3 and 4 company names attached to technology and device designs that are still “two to three years from commercialization”, by their own admissions.

None of the new noninvasive glucose monitoring (NIGM’s) approaches are demonstrating accuracy that is better than fingerstick or CGM systems, which is disconcerting given the expenditure of more than $6B and three decades in the pursuit. Advances in miniaturization, micro-electronics, optical components and manufacturing capabilities are expected to support development of noninvasive monitoring.

Conventional invasive and inconvenient blood glucose monitoring (BGM) is being challenged on several fronts. Increasingly stringent regulatory specifications, trends towards globally harmonized standards that may include aftermarket quality/safety monitoring, large numbers of participants in the market, and pressure from CGM/integrated hybrid artificial pancreas technology, and reimbursement reductions driving down profitability are expected to continue hampering this market segment.

The original Big Four included Roche, Johnson and Johnson, Abbott and Bayer, which collectively owned 80+% of the market. That cumulative market share has dropped to 60% or less over the past five years, and strip reimbursement in the U.S. has been slashed by 68%. Several foreign companies have ceased to market glucose monitors and strips in the U.S. and are concentrating on markets that have retained profitability. Of the Big Four, Bayer sold their diabetes division to KKR/Panasonic (now Ascencia Health), Johnson and Johnson is looking to sell their diabetes care divisions, Roche could not find suitors in their brief look at selling their diabetes monitoring division 3-4 years ago, and Abbott has pivoted to bring long-term implantables and CGM systems to market, while continuing to market conventional BGM’s.

Adding to these pressures, low cost devices and strips are being manufactured under distribution agreements with WalMart, WalGreens and other highly cost competitive global behemoths. It should come as no surprise that accuracy and reliability are less important than cost in this market segment. The market segment has seen some innovation in all-in-one designs that provide greater convenience, and in business models providing month subscriptions that include unlimited test strips, coaching and 24/7 access to expert guidance.

Technological advances in biosensor technology may lead to advances in continuous and non-invasive monitoring technologies as nanomaterials and hybrid metallo-nanomaterial sensor systems continue in their development. Greater sensitivity and specificity, along with improvements in robustness of the sensors and development of cost effective manufacturing methods are demonstrating promising results, but it is generally agreed that most are still years from commercial application and viability.

CONCLUSION

After completing a review of more than two hundred companies, there has been very little improvement in accuracy in conventional fingerstick BGM, CGM or NIGM systems. A handful of clinical monitoring systems are under development, one optically based device has shown promise and has received CE Mark.

Optiscan Biomedical is engaging in talks with the FDA before completing preparations for a PMA application, and may provide a predicate device for a 510k path for the next optical system into the market, if the Optiscanner 6000 is approved. Their accuracy is in the +/-12% range and their system includes blood return to patients.

Continuous monitoring systems and more recently hybrid integrated "artificial pancreas" systems have performed poorly in perioperative and critical care studies.

No product or technology has a demonstrated accuracy of +/-5% that has been achieved with the device designs incorporating the Clinical Sentinel IP created and developed by TecMed, Inc.

Disclaimer

The company and organization data and information incorporated in this document are deemed to be accurate and true, but the authors do not guarantee the correctness of the content included from outside sources or the conclusions provided herein.

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