

Products for Monitoring Glucose Levels in the Human Body With Noninvasive Optical, Noninvasive Fluid Sampling, or Minimally Invasive Technologies

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Abstract

Background: Conventional home blood glucose measurements require a sample of blood that is obtained by puncturing the skin at the fingertip. To avoid the pain associated with this procedure, there is high demand for medical products that allow glucose monitoring without blood sampling. In this review article, all such products are presented.

Methods: In order to identify such products, four different sources were used: (1) PubMed, (2) Google Patents, (3) Diabetes Technology Meeting Startup Showcase participants, and (4) experts in the field of glucose monitoring. The information obtained were filtered by using two inclusion criteria: (1) regulatory clearance, and/or (2) significant coverage in Google News starting in the year 2016, unless the article indicated that the product had been discontinued. The identified bloodless monitoring products were classified into three categories: (1) noninvasive optical, (2) noninvasive fluid sampling, and (3) minimally invasive devices.

Results: In total, 28 noninvasive optical, 6 noninvasive fluid sampling, and 31 minimally invasive glucose monitoring products were identified. Subsequently, these products were characterized according to their regulatory, technological, and consumer features. Products with regulatory clearance are described in greater detail according to their advantages and disadvantages, and with design images.

Conclusions: Based on favorable technological features, consumer features, and other advantages, several bloodless products are commercially available and promise to enhance diabetes management. Paths for future products are discussed with an emphasis on understanding existing barriers related to both technical and non-technical issues.

Keywords

invasive, noninvasive, glucose, fluid sampling, minimally invasive, optical

Introduction

Optimal diabetes management requires glucose monitoring at regular intervals or continuously.¹ In the 1970s, the commercial sector responded by developing analytical systems that provided accurate readings of glucose concentrations in capillary blood samples. This technology is commonly referred to as either self-monitoring of blood glucose (SMBG) or assisted monitoring of blood glucose (AMBG) and is recognized as a major advance in managing diabetes. This technology permitted, for the first time, the ability for people with diabetes to monitor their individual glycemia on a daily basis. This technology also enabled the clinical studies that established the benefits of tight glycaemic control in delaying the onset of diabetes complications.^{2,3}

Despite improvements in sample volume requirements, analysis times, and measurement accuracy, the pain, cost, and inconvenience of SMBG technologies are driving the

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commercial sector to develop new analytical devices that are not based on individual blood measurements, but rather on continuous, or near continuous, glucose measurements in non-blood samples. Non-blood glucose sensing technologies have been under development since the mid-1980s, yet relatively few have realized commercialization and received regulatory approval.

This review reports the results of a literature search to uncover a listing of established and nascent commercial products that are based on non-blood glucose sensing technologies. Each product is classified as either of the following:

- (1) Noninvasive optical glucose monitor (NIO-GM),
- (2) Noninvasive fluid sampling glucose monitor (NIFS-GM), and
- (3) Minimally invasive glucose monitor (MI-GM).

These technologies are generally characterized as providing continuous or intermittent glucose measurements with minimal or no pain.

Definitions of Glucose Monitoring Devices

The discovered products are classified according to the following set of definitions.

Invasive glucose monitors. The most recent published definition of an invasive procedure, based on an analysis of almost 400 articles from the medical literature, is “Where purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation.”⁴ By this definition, when a product requires puncturing of the skin with a lancing device, this product is defined as an **invasive glucose monitor (IGM)** device.

Home IGM devices involve collecting a sample of capillary blood by breaking the skin barrier at the subject’s finger with a sharp lancing device.^{5,6} Such IGM systems have been marketed for almost half a century and have undergone continual improvements to require less blood volume and shorter measurement times. Unfortunately, the cost, pain, blood waste, and finger calluses related to this method reduce patient enthusiasm for frequent glucose testing.⁷

Noninvasive optical glucose monitors. Using the above definition of an *invasive procedure*, a technology where the concentration of glucose is measured without inserting a device into the body is considered noninvasive. When a noninvasive measurement involves passing a type of radiation into a vascular region of the body, then the instrumentation is defined as a **noninvasive optical glucose monitor (NIO-GM)**. Typically, the analytical information associated with such measurements is derived from the chemical composition of the

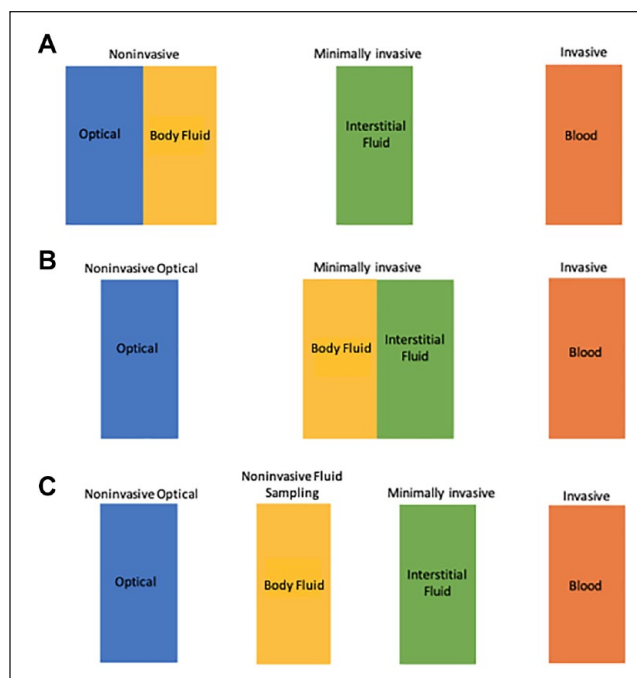


Figure 1. How NIFS-GM technologies have been classified. (A) Previously classified by some experts as a noninvasive technology; (B) Previously classified by other experts as a minimally invasive technology; (C) Classified per our definition in this article as a distinct technology separate from NIO-GM and MI-GM.

interstitial fluid (ISF) contained within the skin matrix. Additional tissue components, such as vascular and intracellular compartments, can also contribute to the spectroscopic response.⁸ Most often, measurement sites correspond to accessible body compartments, such as fingers, extremities, the abdominal wall, or earlobes. Such devices are painless and free of medical waste.

Noninvasive fluid sampling glucose monitoring. A second type of noninvasive measurement involves analysis of a fluid sample that is collected without an *invasive procedure*. In this case, the body fluid, such as tears, sweat, saliva, and urine, is available without puncturing skin and the analytical information is determined *ex vivo*. Once the processes involved in collecting and analyzing a sample are packaged into an integrated product, the system is defined as a **noninvasive fluid sampling glucose monitor (NIFS-GM)**.

The above definition differs from those used in previous reviews that categorize glucose sensing technologies.⁹⁻¹¹ In other reviews, analysis of fluids other than blood are grouped under either the terms minimally invasive or noninvasive, as illustrated in Figure 1A and 1B. The rationale for treating these methods as minimally invasive is based on the fact that these NIFS-GM methods require collection of a body fluid and the analytical measurement does not involve passing

radiation through the body. On the other hand, other reviews place an emphasis on the lack of puncturing skin for NIFS-GM systems, thereby categorized these devices as noninvasive. Developers of such products prefer the term noninvasive over minimally invasive because of marketing advantages.

In our assessment, NIFS-GM systems are distinctive and require a separate designation, as illustrated in Figure 1C. These technologies are uniquely characterized by a lack of puncturing skin, instrumentation applied to the body, a potential for skin trauma, and the need for an established clinically valid correlation between the concentrations of glucose in the fluid and in blood.

Minimally invasive glucose monitoring. The insertion of a sensor into the subcutaneous tissue is an *invasive procedure*, but this procedure is characterized as involving minimal pain and providing glucose concentrations over an extended period with a single insertion. For these reasons, such an approach is defined as a *minimally invasive glucose monitor (MI-GM)*. These technologies are capable of staying in place for periods of days, weeks, or even months while performing glucose measurements repeatedly.

MI-GM devices have been marketed worldwide for the past two decades and serve as the basis for state-of-the-art wearable continuous glucose monitor (CGM) systems. The commercial success of these devices is illustrated by the data presented in Figure 2. For the industry, total revenues exceeded \$1.5 billion USD as of the fourth quarter of 2020.¹²

Technological Approaches for Glucose Monitoring Products

The various glucose monitoring products rely on different technological approaches, as described below.

Technology for noninvasive optical glucose monitoring. NIO-GM involves sending harmless, low-energy radiation through a vascular body site and extracting information about the glucose concentration from the collected signal. In many cases, a selected band of electromagnetic radiation is applied to skin and the diffusely scattered photons are collected. Glucose concentrations are estimated by a multivariate analysis of the resulting spectrum. Several recent review articles provide detailed descriptions of the different NIO-GM technologies currently under development.^{5,13-15} These technologies include near-infrared spectroscopy, mid-infrared spectroscopy, Raman scattering spectroscopy, optical polarimetry, approaches based on microwave and radio wave sensing, and others.^{5,13-15}

Technical hurdles for success of NIO-GM products include issues related to detection limits and selectivity of glucose measurements. Glucose concentrations in blood and ISF are at milli-molar concentrations, which places them at an intermediate level – meaning they are lower than the principal

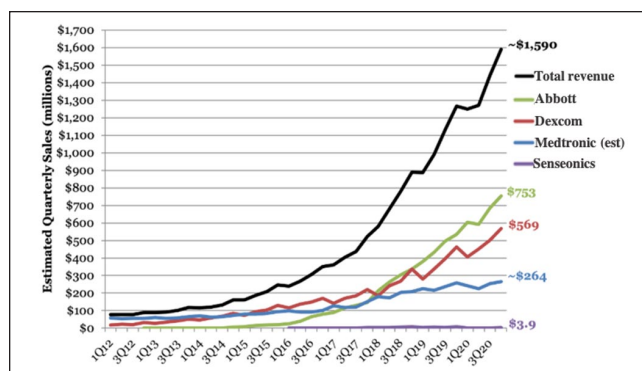


Figure 2. The total quarterly sales for MI-GMs produced by the world's four largest manufacturers as of the fourth quarter of 2020.

Figure adapted from Cai et al.¹²

components of skin and higher than many clinical biomarkers. Still, spectroscopic signals originating from glucose molecules are weak, which challenges the signal-to-noise ratio (SNR) of the instrumentation.¹⁶⁻¹⁹ Fundamentally, the SNR for the instrumentation must be sufficient to enable measurement of the weak signals from glucose over background noise and other sources of instrumental variation. In addition, the measurement signal must be selective relative to all other components of skin, including membranes, glycosylated structures, and soluble compounds within the ISF matrix, such as albumin, urea, amino acids, and ascorbic acid. Ideally, such a selectivity is derived from the chemical structure of glucose, thereby providing a robust basis for measurement accuracy. Depending on the radiation used, a viable NIO-GM has to take into account skin pigmentation, surface roughness, skin thickness, breathing artifacts, blood flow, body movements, and ambient temperature.²⁰ Individual calibration can reduce the impact of the skin's contribution to the results of measurement.

NIO-GM devices have been proposed based on primary or direct glucose sensing as well as secondary, or indirect glucose sensing. Primary measurements involve collecting a signal derived directly from the glucose molecule, while secondary measurements involve measuring a parameter impacted by the concentration of glucose, such as (1) heart rate changes with electrocardiography,²¹ (2) rate of red blood cell aggregation with ultrasound,²² (3) blood volume dynamics with photoplethysmographic measurement of blood,^{23,24} (4) dielectric properties of the skin matrix with diffuse scattering or temperature-modulated localized reflectance,²⁵ or (5) sudomotor dysfunction with electrochemical skin conductance and sweating asymmetry.²⁶

No NIO-GM product has received clearance by the United States Food and Drug Administration (FDA). Although both direct and indirect noninvasive glucose measurements bear the burden of establishing measurement accuracy, this burden can be greater for indirect methods owing to the lack of a selective signature originating from the glucose molecule.

Indirect methods are based on correlations of physiological signals that may be impacted by parameters other than glucose, thereby confounding selectivity and measurement accuracy to a considerable extent. However, machine learning and neural network approaches might provide a successful path for selective indirect glucose measurements.²¹ Successful approaches might require a combination of direct and indirect sources of analytical information. It is possible to quantify glucose in standard solutions and tissue phantoms under idealized conditions by such approaches; however, in the real world, the accuracy and precision of glucose measurements could be inadequate for clinical use. Measurement accuracy over time represents the major analytical challenge of all NIO-GM technologies.

The FDA recently distributed a warning concerning the impact of skin pigmentation on the accuracy of clinical pulse oximetry measurements.²⁷ NIO-GM are potentially subject to the same concerns depending on the wavelength of the probing radiation. Absorption of the incident radiation by melanin, or other skin pigments, will certainly impact signal measurements.²⁸ Substances that may affect skin pigmentation, skin structure, and reflectance properties of the probing radiation include topical medications, cosmetics, cosmeceuticals, and estrogen, as well as tobacco, and alcohol.²⁹ Radio waves and microwaves are not expected to be impacted and infrared wavelengths are also unlikely to be affected, although visible and near infrared wavelengths near the visible spectrum (ie, less than 1 micron can be impacted). The impact of skin pigmentation must be experimentally assessed for each system.

The only approach to developing an NIO-GM product that does not involve measurements in skin, involves direct measurements in the aqueous humor of the eye.³⁰ This approach eliminates the confounding effects presented by the skin barrier, however, none of the products covered in this review is based on this approach.

Although no NIO-GM device has been approved by the FDA, interest in noninvasive measurements is high. In 2020, 343 articles were referenced in PubMed with the search term “noninvasive glucose.” Also, the number of such articles in PubMed has increased progressively over the past 45 years.³¹ Initially, interest in this field was mostly academic, but since the 1990s, a number of companies have been attempting to develop NIO-GM products.³²⁻³⁵

Technology for noninvasive fluid sampling glucose monitoring. NIFS-GM products center on technologies capable of collecting and analyzing samples of ISF, tears, sweat, or saliva. Electrochemical glucose oxidase biosensors are available to determine the concentration of glucose in the collected fluid. Sample collection technologies are specific for the measurement fluid. Reverse iontophoresis enables the collection of a representative sample of ISF without puncturing the skin. Other technologies are reported for measurements in lacrimal,³⁶ and tear fluids.³⁷

Two NIFS-GM technologies have either received clearance from the FDA or have been granted a Conformité Européenne (CE) Mark. The first is the measurement of glucose in ISF samples extracted through the skin surface by reverse iontophoresis.³⁸ This is an active transport system stimulated by an electrical current applied to the skin. The concentration of glucose in the resulting fluid is measured with a sensor patch placed on the skin surface. Glucose concentrations in such samples are two to three orders of magnitude below those in the original ISF, which presents an analytical challenge.³⁹ The SugarBEAT from Nemaura (Loughborough, England) is a NIFS-GM device that uses this method and has received a CE Mark. A comparable approach received FDA clearance in 2001 and was marketed as the GlucoWatch Biographer by Cygnus, Inc. (Redwood City, California).^{40,41} The resulting glucose concentration measurements lacked sufficient clinical accuracy and the device suffered from poor user experience.⁴² A skin permeation process using ultrasound was briefly used more than ten years ago to collect ISF with a sensor placed over the site of skin permeation for an investigational needle-free product,⁴³ and this type of product is still under development.⁴⁴

Technically, urine test strips fall under the definition of a NIFS-GM device. These test strips are ineffective in estimating real-time blood glucose concentrations and are rarely used for making treatment decisions. Urine glucose testing is characterized by the following three characteristics:

- (1) a long and unpredictable lag time between dynamic blood glucose concentrations and urine glucose concentrations,
- (2) a high blood glucose concentration threshold for urine glucose excretion, below which glucose does not appear in the urine, and
- (3) a wide person-to-person variability in this blood glucose threshold concentration where glucose spills into the urine.⁴⁵

For NIFS-GM technologies designed to measure glucose in samples of sweat,³⁷ saliva,^{46,47} and tears,⁴⁸ the actual analytical measurements might be accurate; however, the correlation is poor for glucose levels in these fluids compared to those in blood, and this correlation might be influenced by regionalized physiological stressors or stimuli.⁴⁹ Such correlations have proven difficult to control, thereby raising the possibility that physiology will render such an approach to be impractical for commercialization.

Technology for minimally invasive glucose monitoring. The majority of MI-GM products currently on the market are devices that require the user to insert the sensing element in the subcutaneous space. The sensing element is an electrochemical glucose biosensor which reports a glucose concentration every 1-15 minutes to a receiver located outside the body. The sensor is limited to 10-14 days of operation.

Three generations of biosensor technology are reported for MI-GM devices. Each generation differs by the internal path of electrons associated with the enzyme-catalyzed reaction and the electrochemical detection. In all generations, the enzyme catalyzes the oxidation of glucose to form gluconic acid, thereby producing the reduced form of the enzyme cofactor. The electron generated from the oxidation of glucose is ultimately transferred to either oxygen (first generation), an electron mediator (second generation), or the electrode directly (third generation).⁵⁰ Accuracy of glucose measurements and their resistance to interferences by drugs or other substances have improved with each successive generation of glucose sensors. Third generation sensors are not yet commercially available.⁵¹

As an alternative to electrochemical MI-GM devices, the principles of reversible affinity sensing are available. For this purpose, two molecules, one of which is a glucose binding protein (GBP), are brought together with a dextran derivative. At low glucose concentrations, the GBP forms a macromolecular complex with the dextran-derivative. As the concentration of glucose increases, the GBP will prefer glucose, thereby dissociating the macromolecular complex. The measurement of the glucose concentration is carried out by determining the change in a physical parameter related to this dissociation of the macromolecular complex. Examples of measurements include a change in viscosity,⁵¹ osmotic pressure against a membrane,⁵² or fluorescence.^{53,54} Depending on the measuring principle, the change in the measured quantity is detected with either pressure or optical transducers and the signal is correlated to a change in glucose concentration by a calibration curve.

The Eversense CGM, offered by Senseonics (Germantown, Maryland) is an FDA approved MI-GM device that measures the concentration of glucose by a fluorescence signal generated from a reversible affinity sensing mechanism involving a selective glucose binding protein.⁵³ This device has demonstrated clinical sufficient glucose measurement accuracy for 180 days,^{55,56} although it was initially cleared by the FDA for 90 days of use.^{57,58} This device must be implanted under the skin and removed by a healthcare professional and requires twice daily calibration.

Technological Challenges across Platforms

Regardless of the sensing technology, NIO-GM, NIFS-GM, or MI-GM, the following technical challenges must be considered for each clinically viable product.

Time delays in glucose concentrations between blood and measurement fluids. When blood glucose concentrations change, glucose levels in other physiological fluids, such as ISF, do not show similar changes instantaneously. As a result, differences in glucose concentrations reported from NIO-GM, NIFS-GM and MI-GM devices compared to blood measurements may not reflect inaccuracy in the measurement

technology but may have a physiological basis. The rate of transporting glucose between the different fluids is not instantaneous and time is required for glucose to diffuse between compartments during periods of disequilibrium. Relevant body fluids include ISF within the subcutaneous matrix,⁵⁹⁻⁶¹ extracted samples of sweat,⁶² saliva,⁶³ tears,⁶⁴ or ISF harvested using reverse iontophoresis,¹⁰ and aqueous humor measured from outside the body.⁶⁵

Time lags for glucose concentration measurements have three components: First, a physiological lag occurs as glucose equilibrates by diffusion (a passive transport to or from blood and the body fluid). The impact of this source of time delay depends on the rate of change in blood glucose levels. This physiological lag time can vary between individuals; but tends to be consistent over time for a specific individual for a given fluctuation in the blood glucose pattern. Second, a measurement lag can occur if the sensor's response is slow. Third, a delay can occur owing to the data-smoothing algorithm. Such algorithms can introduce a time delay between the current glucose sensor reading and previous readings to smooth fluctuations, which leads to a delay in the measurement output. This third element of lag time is only relevant for CGM technology and not for spot glucose measurements.^{66,67}

Reported total lag times vary depending on the measurement conditions; however, they generally range between 5 and 20 minutes. Lag times tend to be shorter with NIO-GM and MI-GM sensor methods and tend to be longer with NIFS-GM. In the latter case external glucose sensors measure fluids that must be extracted before the analytical measurement. If a manufacturer provides a single number to represent the lag time in minutes for ISF glucose compared to blood glucose for a glucose sensor, then this number cannot necessarily be relied upon because much of the lag time is dependent on the individual whose lag is being measured.⁶⁰ Furthermore, the lag time can vary depending on activities being performed⁶⁸ or whether the blood glucose concentration is rising or falling.⁶⁹

Skin irritation. SMBG and AMBG capillary blood measurements can lead to calluses and scarring on the punctured finger tips.⁷⁰ MI-GMs and the two categories of noninvasive glucose monitors (of the skin only), NIO-GMs and NIFS-GMs, have shown varying levels of skin irritation that could cause discomfort, scarring, or local skin infections. These skin reactions can be induced by the adhesives used to affix the glucose sensing element to the skin. Such adhesives have been reported to cause skin irritation and even allergic reactions.⁷¹ Stronger adhesives used to facilitate longer wear times can lead to even more pronounced skin problems.⁷² Acrylates being in the adhesives (and also in the plastic material of the sensor housing) are known to induce skin reactions.^{73,74}

Short term studies with MI-GMs that use transcutaneous microneedles to sample ISF have demonstrated minor edema and erythema skin irritation that resolve without treatment.^{75,76}

The use of a powerful laser for NIO-GM measurements poses a risk of pronounced skin damage. NIFS-GM methods sampling from the skin using no needles may cause dermatitis after prolonged collection (e.g., by reverse iontophoresis,¹⁰ skin permeation, or sweat collection⁷⁷). NIFS-GMs that collect fluids from sites other than the skin as well as optical noninvasive glucose monitors have not been reported to cause skin irritation.

Toxicity. The issue of toxicity is more of an issue for MI-GM technologies compared to the other less invasive approaches.⁵¹ For IGM, NIFS-GM, and MI-GM products, there is direct contact between the sensing element and a physiological fluid containing glucose. However, operation of MI-GM devices calls for the sensing element to be inserted into the body for periods of multiple days, which demands safety assurance. For IGM and NIFS-GM devices, the glucose measurements occur outside the body, thereby permitting the use of materials that would be unsuitable for indwelling MI-GM sensors. NIO-GM devices might involve direct contact between the physical glucose sensing element and skin. If so, then toxicity effects of the sensing materials must be evaluated. Manufacturers of NIO-GM systems must also be concerned with adverse effects caused by the energy and power of the probing radiation applied to the skin.

User involvement. Glucose monitoring methods that rely on user action are not well suited for automatic and continuous glucose monitoring. User involvement can be extensive for IGM and some NIFS-GM devices as well as for any bulky NIO-GM devices. Either a minimally invasive implanted sensor or a wearable noninvasive sensor would be suitable for measuring continuous and automatic glucose measurements. In comparison to intermittent measurements, CGM devices can provide the following important information and functions with minimal user inputs or adjustments:

- (1) real-time glucose concentrations including the timing and magnitude of peak responses to food intake, physical activities, and medications,⁷⁸
- (2) a 24-hour recording of changes of glucose levels over time,⁷⁹
- (3) short-term and long-term glycemic trends,⁸⁰
- (4) warnings of impending or surpassed clinically relevant low or high glucose concentrations,⁸¹
- (5) control of an automated insulin delivery (AID) system,⁸² and
- (6) interface with advanced digital systems for diabetes management.⁸³

Methods

Overview

We conducted a database review to survey products for monitoring glucose that did not use invasive blood glucose sampling.

We searched for products using optical noninvasive, fluid sampling noninvasive, and minimally invasive glucose monitoring technologies. We performed four types of searches to find candidate NIO-GM, NIFS-GM, and MI-GM products and their manufacturing companies to be included in our list for this article, and these searches are updated as of December 17, 2020. We listed an NIO-GM, NIFS-GM, or MI-GM product if the product met at least one of two inclusion criteria: (1) clearance or approval by FDA or CE, and/or (2) significant coverage in a news story or press release from a search of the product (or, if the product did not turn up, then a search of the manufacturer) on Google News, indicating the product was reported as viable since 2016. When we discovered a product that would possibly qualify for our list from one of our four sources of information and designated these as “candidate products.” We then performed two types of, what we called, “Inclusion Searches.” The product was defined to meet our first criterion if its manufacturer’s website or a Google search indicated that the product was cleared by FDA or had a CE Mark. The product was defined to meet our second criterion if a search of Google News for an article published since 2016 provided significant coverage, which we defined as at least one paragraph of this product. In summary, we searched for information about candidate products for NIO-GM, NIFS-GM and MI-GM technologies through four information sources. For each discovered candidate product, we applied the two inclusion criteria to determine whether the product would be included on our “identified products” list. Figure 3 presents a PRISMA diagram of how we performed our database reviews to create a list of identified NIO-GM, NIFS-GM, and MI-GM products.

Information Sources for Finding Candidate Products

PubMed. Our first source of information for finding candidate products came from two types of searches in PubMed-referenced journals for articles describing technologies for measuring glucose noninvasively (either optically or via fluid sampling) and minimally invasively. We selected 16 technologies that have been reported to be used for NIO-GM, NIFS-GM, or MI-GM products in review articles about bloodless glucose monitors.^{5,13-15} These 16 technologies included: (1) spectroscopy, (2) Raman scattering spectroscopy, (3) fluorescence, (4) iontophoresis, (5) polarimetry (optical rotation of polarized light), (6) impedance, (7) osmotic pressure, (8) electrochemistry, (9) absorption, (10) scattering, (11) photoacoustics, (12) quantum cascade laser, (13) photothermal detection, (14) photoplethysmography, (15) quartz crystal microbalance, and (16) DNAzyme.^{5,13-15} We performed a set of 16 PubMed searches of technologies with two search terms: one of these 16 technologies + “glucose monitor.” From the articles that we found, we searched each article for a glucose monitoring product and its manufacturer. We also searched for glucose monitoring products

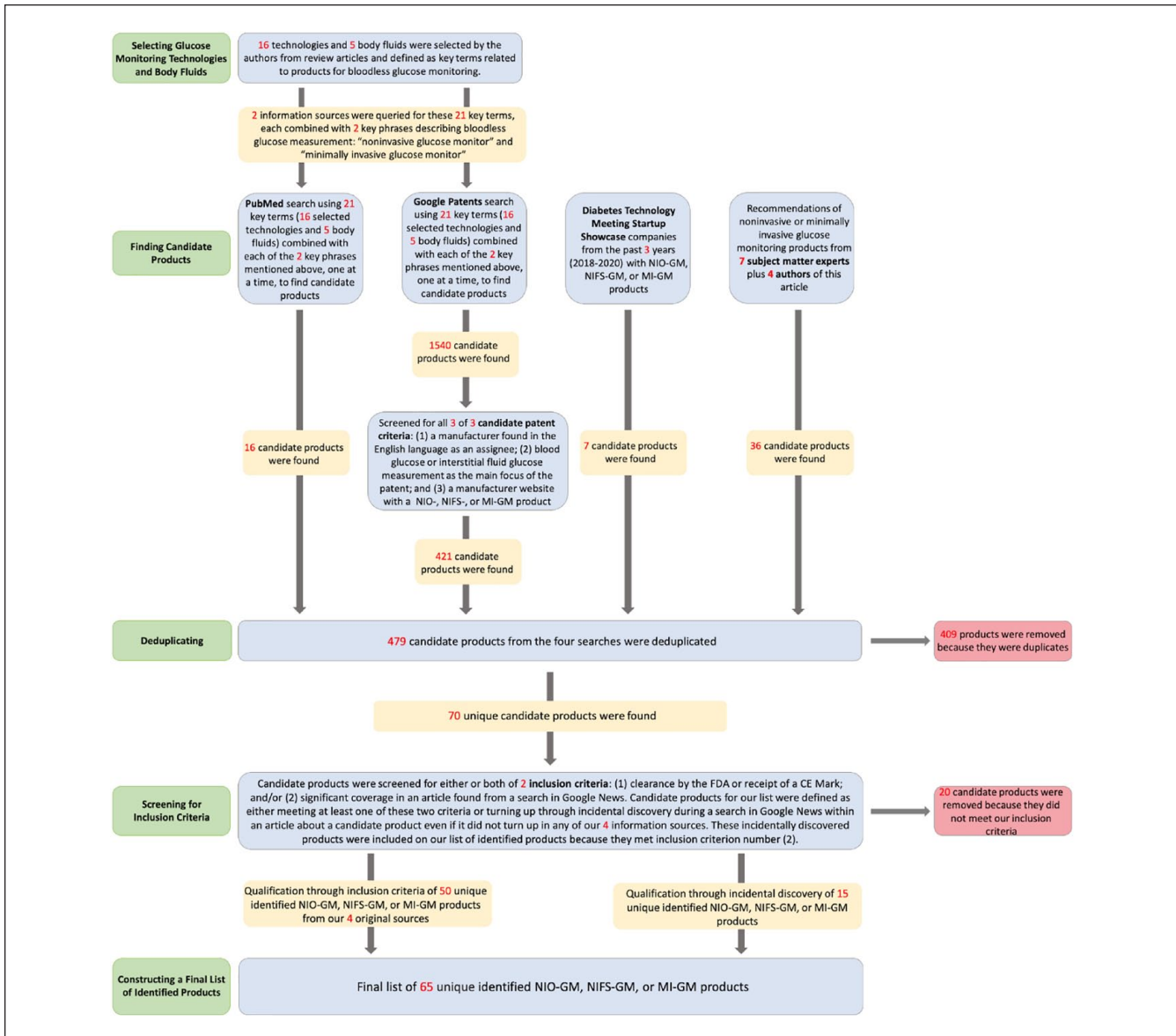


Figure 3. A PRISMA diagram of how we performed our database reviews to create a list of identified NIO-GM, NIFS-GM, and MI-GM products.

Abbreviations: CE, Conformité Européenne; FDA, Food and Drug Administration; NIFS-GM, noninvasive fluid sampling glucose monitor; MI-GM, minimally invasive glucose monitor; NI-GM, noninvasive glucose monitor; NIO-GM, noninvasive optical glucose monitor; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

that measured any of five body fluids that we selected from review articles about bloodless glucose monitors.^{5,13-15,37} These body fluids included: (1) ISF, (2) sweat, (3) tears, (4) saliva, and (5) breath vapor. We performed a set of five PubMed searches of body fluids with two search terms: one of these five body fluids + "glucose monitor." We sorted searches by "best match" and terminated each search after finding no additional relevant articles about glucose monitoring after ten consecutive additional articles. From the articles that we found, we searched each article for a glucose monitoring product and its manufacturer. We upgraded a

candidate product to our identified products list if it met at least one of the two inclusion criteria.

Google Patents. Our second source of information for finding candidate products came from a series of 42 searches in the Google Patents database, each using one of the same 16 key technology terms and five body fluid terms we used in our PubMed search plus either the phrase "diabetes minimally invasive glucose monitor" or the phrase "diabetes noninvasive glucose monitor." We limited this search to active or pending patents published starting from January 1, 2010

using the Google Patents “Date” filter. The Google Patents search engine automatically generated the most relevant patents first and progressively less relevant patents afterward. Each page contained ten patent applications. We elevated a patent to the stage of assessing whether it met our two inclusion criteria for our list of identified products if it turned up in one of our 38 searches and also met three criteria for a candidate patent that we established for our patent search. These criteria specified that a candidate patent had: (1) a manufacturer named in the English language as an assignee, (2) a main focus on measuring glucose in blood or a body fluid, and (3) a manufacturer’s website with an NIO-GM, NIFS-GM, or MI-GM listed as a product. For each of our 42 searches, we reviewed successive pages for candidate patents. We continued reviewing page after page as long as we found at least one new candidate patent per page. If a page contained no such patents, then we reviewed one subsequent page and if that page also contained no candidate patents, then this search was terminated. If a candidate patent was found on one of those two pages, then we resumed searching page after page. For the purpose of termination, if a manufacturer generated more than one patent application during a search, then each subsequent patent after the first candidate patent was not counted as a new candidate patent. However, subsequent patents to a first patent were counted for the total number of candidate patents found, and they were later deduplicated if they were the same product. We upgraded a candidate product to our identified products list if it met at least one of the two inclusion criteria.

Diabetes technology meeting startup showcase. Our third source of information for finding candidate products came from a review of any NIO-GM, NIFS-GM, or MI-GM product presented by startup companies that participated in Diabetes Technology Society’s three Startup Showcases during the 2018, 2019, and 2020 Diabetes Technology Meetings. We used a proprietary database provided by Diabetes Technology Society to find the companies. We upgraded a candidate product to our identified products list if it met at least one of the two inclusion criteria.

Experts in glucose monitoring. Our fourth source of information for finding candidate products came from seven experts in glucose monitoring: (1) Guido Freckmann, MD (Institute for Diabetes Technology GmbH, Ulm, Germany), (2) Avner Gal, MBA, MSCEE, MSc (Iridium Consultancy and Technologies, Ltd., Herzliya, Israel), (3) H. Michael Heise, PhD (South-Westphalia University of Applied Science, Iserlohn, Germany), (4) Jeffrey La Belle, PhD, MS (Grand Canyon University, Phoenix, Arizona, United States), (5) Jeffrey Joseph, DO (Thomas Jefferson University, Philadelphia, Pennsylvania, United States), (6) John Pickup, MD, PhD (King’s College of London), and (7) Mark Prausnitz, PhD (Georgia Institute of Technology, Atlanta, Georgia, United States) and asked them to name a product and/or a

manufacturer developing novel NIO-GM, NIFS-GM and MI-GM technology. We also used information provided by five of the authors (AT, MA, BV, LH, DK) to name similar products and/or manufacturers. We searched every named manufacturer’s website for a product name. We upgraded a candidate product to our identified products list if it met at least one of the two inclusion criteria.

Inclusion Criteria for Upgrading a Candidate Product to an Identified Product

FDA clearance or CE Mark. Our first inclusion criterion for upgrading a candidate product to an identified product was regulatory clearance of a candidate product. We searched the product name in the “Device Name” search box, or the manufacturer’s name in the “Applicant Name” search box of the 510(k) Pre-Market Notification Database of the FDA⁸⁴ to determine FDA clearance. If we were unable to find information on this database, then we also searched the manufacturer’s website for a claim of FDA clearance and/or a CE mark. If a manufacturer’s website did not indicate regulatory clearance, then we also searched the first page on Google using the search terms of the product name or manufacturer’s name + “glucose monitor” + “FDA” and the product name or manufacturer’s name + “glucose monitor” + “CE Mark.” If a product had FDA clearance and/or a CE mark, then we included this information in Table 1 in a column entitled “Which Inclusion Criteria Were Met.”

Google News. Our second inclusion criterion for upgrading a candidate product to an identified product was a mention in a news article from a search on Google News of a candidate product. Such a search followed a termination process similar to the Google Patents search under the “Information Sources for Finding Candidate Products” section. The Google News search generated the most relevant articles first and progressively less relevant articles afterward. In the Google search box, we searched for the product name + “glucose monitor,” then clicked the “News” tab on Google to find news articles. Each page contained ten articles. For each candidate product we discovered from our four sources, we reviewed Google News pages for candidate articles that were published any time on or after January 1, 2016. If the first Google News page did not contain any articles that described the product in at least one paragraph, then we would continue searching the next four pages for an article containing at least one paragraph of information. If the product name + “glucose monitor” did not show any candidate articles, then we would also search the manufacturer’s name + “glucose monitor.” If a news article was found about a product, then we included the reference in Table 1 in a column entitled “Which Inclusion Criteria Were Met.” We included no more than one news article per product in this column as an example, even if more than one article was found on Google News. If no article was found about a product that lacked regulatory

clearance, then we did not include this candidate product on our identified product list.

If an article found on Google News described the product we were searching for within a longer list of products, then we read through the article to see if any of the other products mentioned were already included in our list of candidate products. If any products were not included in the list of candidate products, then we added them to our candidate products. We then passed these incidentally discovered products (not originally found within our four original sources) through our inclusion criteria.

An Additional Scenario for Finding a Candidate Product and Upgrading it to an Identified Product

We upgraded one candidate product to an identified product using different inclusion criteria than the other identified products. An expert suggested the EyeSense (Basel, Switzerland) MI-GM called “FiberSense CGM,” so we then passed the product name + “glucose monitor” and manufacturer’s name + “glucose monitor” through Google News to determine if it fit one of our inclusion criteria. We found an article on Google News describing an NIFS-GM using tears being developed by EyeSense,²²¹ but we were unable to find specific mention of the MI-GM “FiberSense CGM.” The manufacturer’s website did not mention the NIFS-GM product using tears; however, the manufacturer’s website did mention the MI-GM “FiberSense CGM.” We decided to include this MI-GM “FiberSense CGM” in our identified products list because of the article we found in Google News mentioning the manufacturer.

Product Classification

We classified every product on our identified product list of glucose monitors, that did not use invasive sampling, into one of three categories: (1) noninvasive optical (measuring glucose with electromagnetic radiation from a blend of tissue sources including blood, ISF, and cells); (2) noninvasive fluid sampling (measuring a body fluid other than blood or urine extracted without the use of an implanted needle employing a technology requiring contact of the sensor with the fluid, including sweat, and ISF); and (3) minimally invasive (measuring ISF with a sensor inserted or implanted into the skin requiring contact of the sensor with the ISF). All three of these methods are distinct from traditional invasive blood glucose testing, which refers to measuring glucose with a needle that is inserted into the body to puncture a blood vessel so that blood can be in contact with a sensor.

Product Features

We considered 11 features for each NIO-GM, NIFS-GM, or MI-GM product, which were: (1) which inclusion criteria were met, (2) PubMed article, (3) regulatory status, (4)

adjunctive/non-adjunctive status (if cleared by FDA), (5) mechanism of glucose sensing, (6) matrix of glucose sensing, (7) degree of accuracy, (8) interferences, (9) measurement cycle, that is, continuous or intermittent, (10) pricing model, and (11) size/shape. We divided these features into regulatory features (Feature 1-4), technological features (Features 5-8), and consumer features (Features 9-11). We then summarized the glucose sensing technologies and the products that belonged to each category of glucose sensing.

Finding information for product features. Information about product features was obtained from: (1) manufacturer websites, (2) articles found in a PubMed search for identified products, (3) patents found in a Google Patents search, (4) news stories found in a Google News search, (5) results from a Google search. Not every product was described on all five of these outlets (ie, a manufacturer’s website, PubMed, Google Patents, Google News, the first page of results on Google) and in many cases, no information was available about specific features of the listed glucose monitors. For products that have been cleared by the FDA or have a CE Mark, we asked an official from the manufacturer about what were their interfering substances. While we considered lag time between fluctuations in concentrations of blood glucose and NIO-GM, NIFS-GM, or MI-GM system glucose measurements, as well as the presence of skin irritation from contact by the sensor or adhesive around the sensor with the body, to be important technological features, there was not enough reliable published data on the lag times or the status of the skin problems of chronic users for a high percentage of the various products to include more than general statements for all of these products.

Manufacturer websites. To fill information about product features, we first looked through manufacturer websites. In order to find a manufacturer’s website, we performed a search on Google using the search terms: (product name OR manufacturer’s name) + “glucose monitor.” We would look through the first page of Google results to find the manufacturer’s website, which featured details about the product.

PubMed articles. When we discovered a product using the second (Google Patents), third (Startup Showcase), or fourth (experts in the field) initial information sources and the product met our inclusion criteria, we then conducted a PubMed search for articles mentioning identified products. We used the search terms product name + “glucose.” If we found no relevant product-related articles, then we conducted a second PubMed search of the manufacturer’s name + “glucose.” If a PubMed article was found about a product, then we included the reference in Table 1 in a column entitled “PubMed Article.” We included no more than one article per product in this column as an example, even if more than one article was found on PubMed. This search was not an inclusion search, but rather was conducted to find published

references to be used if the product met at least one of our two inclusion criteria. Any PubMed article we found through both the information source search and this search may also have been used to provide information for columns in other tables.

Patents on Google Patents. We searched Google Patents by putting the manufacturer's name under the "Assignee" and using the term "glucose monitor" in the search, which was a different type of search than we initially conducted using Google Patents as a source of candidate products (as described in the third paragraph of the "Methods" section). We used the information found on these patents to fill out information about product features.

News stories found in Google News. We used the same method, as was used under the "Google News" subsection of the "Inclusion Criteria" section, to find news stories in Google News to fill out details regarding product features. We summarized the most important product features in tables.

Results from a Google Search. We performed a Google Search with the (product name OR manufacturer's name) + "glucose monitor" + "the product feature we are looking for (e.g., matrix)" on Google and looked through the first page of results for mention of a patent. We looked through each result to find details about the product feature.

Detailed Explanation for Specific Columns in Tables 1 and 2

Patents under the "Regulatory Status" column in Table 1. The Table 1 column on "Regulatory Status" specifies either clearance by the FDA, clearance by CE, or (if there was no clearance) whether we found a patent or any mention of having a patent. If a product was cleared by a regulatory agency, then we assumed that the product had a patent and we did not specifically search for one. If a product was not cleared by a regulatory agency, then we attempted to identify whether the product had a patent by using the five methods described under the "Finding Information for Product Features" section to identify a patent or mention of a patent. For the "First Page of Google Results" method, we used "patent" as our term for "the product feature we were looking for." If we did not identify a patent through these five methods, then we stated "No patent identified." If a manufacturer reported only patent(s) that could pertain to both a cleared product and a non-cleared product, then for the non-cleared product, we stated "No patent identified."

"Mechanism of glucose sensing" column in Table 2. Just as with the other product features, the mechanism of glucose sensing presented in Table 2 was found using the five methods described under the "Finding Information for Product Features" section. Some manufacturers have developed both

cleared and non-cleared products intended for bloodless glucose monitoring, but we were unable to find details about the mechanism of glucose sensing for their non-cleared products in manufacturer websites, articles on PubMed, articles on Google News, or results on the first page of a Google search. In this case, our source of information would theoretically be the patent if it was available. However, if the patents we reviewed did not call out the product by name, then it was unclear which product the patent was associated with. Therefore, we stated "No information available."

Product Designs

We included examples of product design if the product website included an image and if a manufacturer's official approved our request to publish an image of their product design. We reached out to every manufacturer that had a product design on their website if contact information was available. Representatives from manufacturers of the following products provided a separate image, that was not on the manufacturer's website, for us to use for this article: Dexcom G6, Freestyle Libre 14-day, Freestyle Libre 2, Freestyle Libre 3, GlucoBeam, Gluco Quantum, LifeLeaf, SynerG, and UBand. Every other product image came from the product website.

Advantages and Disadvantages

From the manufacturer's website and the first page of Google results (as per the search method defined in the "Overview"), we determined which identified product had FDA and/or CE clearance. For each cleared product, we evaluated its features and created a list of advantages and disadvantages based on our experience with glucose monitoring technologies and treating people with diabetes. Advantages and disadvantages were not presented for any product which has not received regulatory clearance, because that product might eventually contain different features than what we are currently able to determine.

Results

Summary of Identified Products

We listed 65 identified products based on three categories for the degrees of invasiveness of the sensor relative to the body: (1) NIO-GM, (2) NIFS-GM, and (3) MI-GM technology. The products included 28 NIO-GMs, 6 NIFS-GMs, and 31 MI-GMs. We recorded available information on 12 different features for each glucose monitoring product. We classified these identified products according to (1) headquarter country, (2) which inclusion criteria were met, (3) PubMed article, (4) regulatory status, (5) adjunctive/non-adjunctive status (if cleared by FDA), (6) mechanism of glucose sensing, (7) matrix, (8) degree of accuracy, (9) interferences, (10)

Table I. Regulatory Features of NIO-GM, NIFS-GM, or MI-GM Identified Products (in Alphabetical Order Within Each Category of Invasiveness).

Entry number	Product and manufacturer	Degree of invasiveness	Headquarter country	Which inclusion criteria were met	PubMedarticle	Regulatory status	Adjunctive or non-adjunctive (if cleared by the FDA)
1	No product name; Afon Technology	NIO-GM	Wales	Google News ⁸⁵	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{85,86}	N/A
2	Alerty NI-GM; Alerty	NIO-GM	USA	Google News ⁸⁷	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ⁸⁸	N/A
3	No product name; AnnNIGM	NIO-GM	Russia	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
4	Add on to the Apple Watch; Apple	NIO-GM	USA	Google News ⁹⁰	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{90,91}	N/A
5	BioMKR; Prediktor Medical	NIO-GM	Norway	Google News ⁹²	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ⁹³	N/A
6	Blood Analysis Sensor; Brolis Sensor Technology	NIO-GM	Lithuania	Google News ⁹⁴	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ⁹⁵	N/A
7	CompanionCM; Socrates Health Solutions	NIO-GM	USA	Google News ⁹⁶	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{97,98}	N/A
8	CompanionSR; Socrates Health Solutions	NIO-GM	USA	Google News ⁹⁶	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{97,98}	N/A
9	D-Band; DiaMonTech	NIO-GM	Germany	Google News ⁹⁹	Lubinski ¹⁰⁰	Not cleared by FDA but the manufacturer has submitted a pre-submission to the FDA for the D-Base to the FDA. ¹⁰¹ Has not received CE Mark of approval. Patented technology. ^{102,103}	N/A
10	D-Base; DiaMonTech	NIO-GM	Germany	Google News ⁹⁹	Lubinski ¹⁰⁰	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{102,103}	N/A
11	D-Pocket; DiaMonTech	NIO-GM	Germany	Google News ⁹⁹	Lubinski ¹⁰⁰	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{102,103}	N/A
12	GlucoBeam; RSP Systems	NIO-GM	Denmark	Google News ¹⁰⁴	Pleus ¹⁰⁵	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁰⁶	N/A
13	GlucoFit; GlucoActive	NIO-GM	Poland	Google News ¹⁰⁷	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
14	Gluco Quantum; Genki Vantage Ltd	NIO-GM	China	Google News ¹⁰⁸	None	Not cleared by FDA and has not received CE Mark of approval. Has not received CE Mark of approval but has initiated ISO 13485 certification process. Patented technology. ^{109,110}	N/A
15	Glucosense; Glucosense Diagnostics Ltd	NIO-GM	England	Google News ¹¹¹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹¹²	N/A
16	GlucoStation; GlucoActive	NIO-GM	Poland	Google News ¹¹³	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
17	GlucoTrack; Integrity Applications Ltd	NIO-GM	Israel	Google News, ¹¹⁴ CE Mark ¹¹⁵	Lin ¹¹⁶	Not cleared by FDA. Received the CE Mark of approval June 2013 for DF-F model. Received final CE Mark of approval in March 2014. ¹¹⁵	N/A
18	GlucoWear; GlucoActive	NIO-GM	Poland	Google News ¹⁰⁷	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A

(continued)

Table I. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Headquarter country	Which inclusion criteria were met	PubMedarticle	Regulatory status	Adjunctive or non-adjunctive (if cleared by the FDA)
19	GlucoWise; MediWise	NIO-GM	England	Google News ¹¹¹	Gonzales ⁵	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹¹⁷	N/A
20	Glutracc; Add Care Ltd	NIO-GM	China	Google News ¹¹⁸	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹¹⁹	N/A
21	HELO Extense; Wor(l)d Master Distributors	NIO-GM	USA	Google News ¹²⁰	Gonzales ⁵	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ^{121,122}	N/A
22	HELO LX PRO; Wor(l)d Master Distributors	NIO-GM	USA	Google News ¹²⁰	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ^{121,122}	N/A
23	LIFELEAF; LifePlus	NIO-GM	USA	Google News ¹²³	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ¹²⁴	N/A
24	Movano Wearable CGM; Movano	NIO-GM	USA	Google News ¹²⁵	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ¹²⁶	N/A
25	No product name; Omni Sciences, Inc.	NIO-GM	USA	Google News ¹²⁷	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{90,128}	N/A
26	Sanmina; Sanmina Corporation	NIO-GM	USA	Google News ¹²⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹³⁰	N/A
27	TensorTip Combo Glucometer; Cnoga Medical Ltd	NIO-GM	Israel	Google News, ¹³¹ CE Mark ¹³²	Pfützner ¹³³	Not cleared by FDA. Received the CE Mark of Approval. ¹³²	N/A
28	Uband; Know Labs, Inc.	NIO-GM	USA	Google News ¹³⁴	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹³⁵	N/A
29	Bios; GraphWear Technologies Inc.	NIFS-GM	USA	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹³⁶	N/A
30	gSense; Nutrix	NIFS-GM	Switzerland	Google News ¹³⁷	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
31	NextGen CGM; Echo Therapeutics	NIFS-GM	USA	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹³⁸	N/A
32	Saliva Glucose Biosensor; Gbs Inc.	NIFS-GM	USA	Google News ¹³⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁴⁰	N/A
33	sugarBEAT; Nemauro Medical	NIFS-GM	USA	Google News, ¹⁴¹ CE Mark ¹⁴²	Gonzales ⁵	Has received CE Mark of Approval. ¹⁴² Submitted a premarket approval medical device application to the FDA for its SugarBEAT glucose monitor. ¹⁴³	N/A
34	Tear Glucose Sensor; NovioSense	NIFS-GM	Netherlands	Google News ¹⁴⁴	Geelhoed-Duijvestijn ¹⁴⁵	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁴⁶	N/A
35	AiDex CGM; GlucoRx (Rebranding of MicroTech Medical) ^{146,147}	MI-GM	England	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
36	Biolinq CGM; Biolinq	MI-GM	USA	Google News ¹⁴⁸	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁴⁹	N/A
37	Care Sense Air; i-SENS	MI-GM	South Korea	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁵⁰	N/A

(continued)

Table 1. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Headquarter country	Which inclusion criteria were met	PubMedarticle	Regulatory status	Adjunctive or non-adjunctive (if cleared by the FDA)
38	Cascade CGM system; Waveform	MI-GM	USA	Google News, CE Mark ¹⁵¹	Rebec ¹⁵²	Not cleared by FDA. Received CE Mark of approval in 2019 and usable for people who are over 2 years of age. ¹⁵¹	N/A
39	CT-100; POCtech X Ascensia	MI-GM	POCTech: China Ascensia: Switzerland	Google News, ¹⁵³ CE Mark ¹⁵⁴	None	Not cleared by FDA. Received CE Mark of approval. ¹⁵²	N/A
40	Dexcom G6; Dexcom	MI-GM	USA	Google News, ¹⁵⁵ FDA cleared, ¹⁵⁶ CE Mark ¹⁵⁷	Isaacson ¹⁵⁸	Cleared by the FDA in October, 2019 for use in adults and children over 2 years of age. ¹⁵⁶ Received CE Mark of approval in 2020. ¹⁵⁷	Non-adjunctive ¹⁵⁹
41	Dexcom G7; Dexcom	MI-GM	USA	Google News ¹⁶⁰	None	Not cleared by FDA and has not received CE Mark of approval. No patent identified.	N/A
42	Eclipse 3; iCGM GlySens	Implanted MI-GM	USA	Google News ¹⁶¹	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ¹⁶²	N/A
43	Eversense; Senseonics	Implanted MI-GM	USA	Google News, ¹⁶³ FDA cleared, ¹⁶⁴ CE Mark ¹⁶⁵	Fokkert ¹⁶⁶	Cleared by the FDA for people who are over 18 years of age. ¹⁶⁴ Received CE Mark of approval in 2016. ¹⁶⁵	Non-adjunctive ¹⁶⁷
44	FiberSense Technology CGM; EyeSense	MI-GM	Switzerland	Google News ⁹⁰ (manufacturer is mentioned)	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁶⁸	N/A
45	FreeStyle Libre 1 4 day; Abbott Diabetes Care	MI-GM	USA	Google News, ⁶⁹ FDA cleared, ¹⁷⁰ CE Mark ¹⁷¹	Kudva ¹⁷²	Cleared by the FDA. ¹⁷⁰ Received CE Mark of approval in 2014. ¹⁷¹	Non-adjunctive ¹⁷³
46	FreeStyle Libre 2; Abbott Diabetes Care	MI-GM	USA	Google News, ¹⁷⁴ FDA cleared, ¹⁷⁵ CE Mark ¹⁷⁶	Denham ¹⁷⁷	Cleared by the FDA for adults and children with diabetes ages 4 years and above. ¹⁷⁵ Received CE Mark of approval in 2018. ¹⁷⁶	Non-adjunctive ¹⁷⁸
47	FreeStyle Libre 3; Abbott Diabetes Care	MI-GM	USA	Google News, ¹⁷⁹ CE Mark ¹⁷⁹	O'Neill ¹⁸⁰	Not cleared by the FDA. Has received CE Mark of approval for adults and children with diabetes ages 4 years and above. ¹⁷⁹	N/A
48	Glucomen Day CGM; A. Menarini Diagnostics	MI-GM	Italy	Google News, ¹⁸¹ CE Mark ¹⁸²	O'Neill ¹⁸⁰	Not cleared by the FDA. Waveform partner received CE Mark of approval to release Glucomen day. ¹⁸²	N/A
49	Glunovo i3 CGM; Infinovo Medical Co Ltd.	MI-GM	China	Google News, ¹⁸³ CE Mark ¹⁸⁴	None	No news articles about Infinovo CE Mark. However, LinkedIn page of Infinovo indicates CE Mark has been received as of June 2019. ¹⁸⁴	N/A
50	Glyde CGM; GluSense	Implanted MI-GM	Israel	Google News ¹⁸⁵	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁸⁶	N/A
51	Indigo CGM; Indigo	Implanted MI-GM	Belgium	Google News ¹⁸⁷	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁸⁸	N/A
52	No product name; Integrated Medical Sensors	Implanted MI-GM	USA	Google News ¹⁸⁹	Mujeeb-U-Rahman ¹⁹⁰	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ¹⁹¹	N/A

(continued)

Table 1. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Headquarter country	Which inclusion criteria were met	PubMedarticle	Regulatory status	Adjunctive or non-adjunctive (if cleared by the FDA)
53	No product name; <i>One Drop (acquired Sano Intelligence, Inc., which was developing patch biosensor glucose monitor)</i> ¹⁹²	MI-GM	USA	Google News ¹⁹³	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ¹⁹⁴	N/A
54	K'Watch; PKVitality	MI-GM	France	Google News ¹⁹⁵	Gonzales ⁵	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{196,197}	N/A
55	Lumee; Profusa	Implanted MI-GM	USA	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{198,199}	N/A
56	Medtronic Guardian Connect (Powered by Medtronic Guardian Sensor 3); Medtronic MiniMed	MI-GM	USA	Google News, ²⁰⁰ FDA cleared, ²⁰¹ CE Mark ²⁰²	Sadhu ²⁰³	FDA has approved the Android version of its guardian connect system. ²⁰¹ Received CE Mark of approval in 2016. ²⁰²	Adjunctive ²⁰⁴
57	Medtronic Synergy; Medtronic MiniMed	MI-GM	USA	Google News ²⁰⁵	None	Not cleared by FDA and has not received CE Mark of approval. No patents identified.	N/A
58	Medtronic Zeus; Medtronic MiniMed	MI-GM	USA	Google News ²⁰⁵	None	Not cleared by FDA and has not received CE Mark of approval. No patents identified.	N/A
59	No product name; Metronom Health	MI-GM	USA and Belgium	Google News ⁸⁹	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ^{206,207}	N/A
60	PercuSense CGM; PercuSense	MI-GM	USA	Google News ²⁰⁸	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ²⁰⁹	N/A
61	Sanvita CGM; Sanvita Medical, LLC and LifeScan	MI-GM	Sanvita Medical, LLC: USA LifeScan: USA	Google News ²¹⁰	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ²¹¹	N/A
62	Sencell; Lifecare AS	MI-GM	Norway	Google News ²¹²	None	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ²¹³	N/A
63	SugarSenz; Glucovation	MI-GM	USA	Google News ²¹⁴	None	Not cleared by FDA and has not received CE Mark of approval. Patent pending. ²¹⁵	N/A
64	SynerG; Pacific Diabetes Technologies	MI-GM	USA	Google News ²¹⁶	Jacobs ²¹⁷	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ²¹⁸	N/A
65	TouchCare System A6; Medtrum	MI-GM	China	Google News ⁸⁹	Zhou ²¹⁹	Not cleared by FDA and has not received CE Mark of approval. Patented technology. ²²⁰	N/A

PubMed article refers to the first author of an article indexed in the PubMed database. Abbreviations: CE, Conformité Européenne; FDA, United States Food and Drug Administration; MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sampling glucose monitor; NIO-GM, noninvasive optical glucose monitor; USA, United States of America.

measurement cycle, that is, continuous or intermittent, (11) pricing model, and (12) size/form factor. We divided these features of the 65 identified products along with their manufacturer and degree of invasiveness into (1) regulatory features (Feature 1-5, Table 1), (2) technological features (Features 6-9, Table 2), and (3) consumer features (Features 10-12, Table 3). We presented a summary of the underlying technologies used by each identified product in Table 4. We presented images of product designs for selected identified products in Table 5A (FDA cleared and/or CE marked) and Table 5B (not FDA cleared or CE marked). We presented advantages and disadvantages of regulatory cleared products in Table 6.

Regulatory Features

Table 1 presents five regulatory features of the 65 identified products, including whether they received FDA clearance or a CE mark. Obtaining a CE mark requires proof of safety of the device, however, obtaining FDA clearance, requires proof of both the safety and efficacy of the device.³⁴⁷ Although FDA clearance is more difficult to obtain, it is a more powerful certification.³⁴⁸

Technological Features

Table 2 presents four technological features of the 65 identified products. The next four paragraphs discuss these features.

The first technological feature we considered is the mechanism of glucose sensing, which is the process through which the sensor detects and interacts with glucose. These processes were based on a variety of chemical and physical properties of glucose.

The second technological feature we considered is the matrix where sensing occurs. For each glucose monitor, the sensing of glucose is carried out within a specific matrix. The matrix can be ISF with MI-GMs, ISF, sweat, tears, or saliva with NIFS-GMs, or a combination of ISF, cells, and blood with NIO-GMs.

The third technological feature we considered is accuracy. The accuracy of glucose monitors that are not invasive is typically reported in one of two ways. First, accuracy can be reported as the percentage of data pairs of glucose monitor values compared to reference values falling within various accuracy ranges, such as within 5%, 10%, 15%, 20%, 30%, and 40%. Second, accuracy can be presented as the mean absolute relative difference (MARD) or median absolute relative difference (medARD) of the measured glucose value compared to the reference glucose value. The two values for normally distributed datasets are linked by an approximate conversion factor of 2.5. For example, if a glucose monitor has a MARD of 10% and a set of glucose values is distributed normally, then approximately 95% of its measurements will fall within $\pm 25\%$ of the reference glucose value because $2.5 \times 10\%$ equals 25%. Clinical accuracy is typically reported using an error grid analysis which presents the

risk to a user based on actions taken from a measured glucose value compared to the correct action that would have been based on a reference glucose value. Three widely used error grids for blood glucose have been proposed, and over time they have reflected increasingly more modern expectations of analytical accuracy, understanding of risks of hypoglycemia, and prescribing patterns for modern insulins. The most recent error grid and that which reflects input from the greatest number of diabetes clinicians (compared to earlier iterations of error grids known as the Clarke Error Grid³⁴⁹ and the Parkes or Consensus Error Grid³⁵⁰) is the Surveillance Error Grid.³⁵¹ Each grid presents data pairs in five zones of risk, although the Surveillance Error Grid is constructed so that it is possible to also generate more than five risk zones. Neither analytical accuracy data nor clinical accuracy data was available for every product because not every product has conducted clinical trials or published performance data.

The fourth technological feature we considered was the device's possible interferences or interfering substances that might affect the glucose monitor's accuracy. The accuracy of a glucose monitoring device might be affected by interferences or interfering substances, which are molecules that can interfere with sensing, often because of a similar structure as glucose. These substances are important to identify and characterize to ensure that users understand why or when their readings might be inaccurate.

Consumer Features

Table 3 presents three consumer features of the 65 identified products. The first consumer feature we considered is the measurement cycle, or whether the device makes automatic continuous or intermittent measurements. Any automatic measurement device must be engineered to be small enough to be a wearable device, but an intermittent measurement device does not necessarily need to be built small. The second consumer feature we considered is the pricing model. There are two main models that are used. In the first model, the user purchases the sensor and can make as many measurements as desired during the lifetime of the sensor. In the second model, the patient is charged for each measurement. Combinations of these two models are also possible. One device might require a single large payment for a device that could last for years, while another device might require periodic purchases of consumable parts or else payment of a toll charge each time the monitor is used. The third consumer feature we considered is the size/form factor of the product. A small sized sensor, compared to a large sized sensor, is usually more convenient and preferred by most users. However, a small minimally invasive implanted sensor could break off from its transmitter and be lost under the skin. A small, wearable noninvasive sensor with a streamlined form factor, compared to a large, bulky, free-standing noninvasive sensor, will usually be more costly because component miniaturization and assembly are expensive.

Table 2. Technological Features of NIO-GM, NIFS-GM, or MI-GM Identified Products (in Alphabetical Order Within Each Category of Invasiveness).

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
1	No product name; Afon Technology	NIO-GM	Uses microwave spectroscopy. Sensor analyzes resonance shifts based on microwave signal to detect changes in glucose. Results reported for a clinical trial. ²²²	Blood/ISF ²²²	MARD: 21 ± 9% surveillance error grid: 48.9% in "no risk" zone, 47.1% in "slight risk" zone, 4% in "moderate risk" zone. ^{4%} ²²²	No information available.
2	Alertgy NI-GM; Alertgy	NIO-GM	Uses dielectric spectroscopy. Wristband with integrated Microchip (dielectric sensor). The apparatus senses the electrical membrane permeability of cells and detects if the permeability varies from the norm. It then uses the difference between the measured permeability with the known permeability to sense glucose levels. Frequency range: 100 kilohertz–220 megahertz. Radiowave frequencies. ⁸⁸	Blood/ISF ⁸⁸	No information available.	No information available.
3	No product name; AnnNiGM	NIO-GM	Measuring principle not reported so far. Earlobe clip sensor. No description of their technology provided on their website. ²²³	No information available.	No information available.	No information available.
4	Add on to the Apple Watch; Apple	NIO-GM	Uses absorption spectroscopy with light of certain wavelength to determine the concentration of glucose. ²²⁴	Blood/ISF ²²⁴	No information available.	No information available.
5	BioMKR; Prediktor Medical	NIO-GM	Uses absorption spectroscopy. A near infrared laser is used to generate an absorption spectrum for a certain measurement location of the user. A calibration model is then used to estimate blood glucose values from the infrared spectrum. ²²⁵	Blood/ISF ²²⁵	No information available.	None specified so far, but the device is intended for use in people age 18 or older. It is also only appropriate for use in certain cases. ²²⁶
6	Blood Analysis Sensor; Brolis Sensor Technology	NIO-GM	Based on integrated photonic package designed to measure glucose, lactate and ethanol. Wavelengths included at 1.7–2.5 microns. Uses laser-based sources. ²²⁷	Blood/ISF ²²⁷	MARD: 5.7% Clarke error grid: greater than 97% in zone A ²²⁷	No specific information – claims that ethanol and lactate are not significant ²²⁷
7	CompanionCM; Socrates Health Solutions	NIO-GM	Rotation of plane polarized radiation at a non-defined wavelength through a tissue phantom (mimics ear tissue). Preliminary data presented for several human subject experiments. Technology similar to CompanionSR. ²²⁸	Tissue ²²⁸	Resolution for the measurement of micro-radians: ± 10 mg/dl. ²²⁸	No information available.
8	CompanionSR; Socrates Health Solutions	NIO-GM	Rotation of plane polarized radiation at a non-defined wavelength through a tissue phantom (mimics ear tissue). Preliminary data presented for several human subject experiments. Technology similar to CompanionCM. ²²⁸	Tissue ²²⁸	Resolution for the measurement of micro-radians: ± 10 mg/dl. ²²⁸	No information available.
9	D-Band; DiaMonTech	NIO-GM	Use of photothermal detection of the molecules after excitation with a mid-infrared laser (quantum cascade laser). A mid-infrared laser is used to detect glucose molecules in the ISF. The reflected wavelength is analyzed to gather data on the amount of glucose molecules. Data analysis involves a leave-one data set-out machine learning system. Technology similar to D-Base and D-Pocket. ¹⁰⁰	ISF ¹⁰⁰	No information available.	No information available.
10	D-Base; DiaMonTech	NIO-GM	Use of photothermal detection of the molecules after excitation with a mid-infrared laser (quantum cascade laser). A mid-infrared laser is used to detect glucose molecules in the ISF. The reflected wavelength is analyzed to gather data on the amount of glucose molecules. Data analysis involves a leave-one data set-out machine learning system. Technology similar to D-Band and D-Pocket. ¹⁰⁰	ISF ¹⁰⁰	MARD: 11.3%-12.1% medARD: 6.4%-6.5% Consensus error grid: 98.8%-99.1% in zones A+B ¹⁰⁰	Temperatures outside of the range of 10-30°C may cause inaccurate readings. Temperature or residue on skin can interfere with accuracy. ¹⁰²

(continued)

Table 2. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
11	D-Pocket; DiaMonTech	NIO-GM	Use of photothermal detection of the molecules after excitation with a mid-infrared laser (quantum cascade laser). A mid-infrared laser is used to detect glucose molecules in the ISF. The reflected wavelength is analyzed to gather data on the amount of glucose molecules. Data analysis involves a leave-one data set-out machine learning system. Technology similar to D-Band and D-Base. ¹⁰⁰	ISF ¹⁰⁰	No information available.	No information available.
12	GlucoBeam; ASP Systems	NIO-GM	This device uses Raman scattering spectroscopy to detect the amount of glucose in ISF. An excitation laser is shined into the finger and the Raman scatter from glucose molecules is analyzed. This technology used confocal methods to focus on a specific depth into the skin matrix. ¹⁰⁶	ISF ¹⁰⁶	medARD: 18.9%, consensus error grid: 93.1% in zones A + B. ²²⁹	Substances that have similar structures to glucose (such as ethanol) could interfere with the accuracy of the results.
13	GlucoFit; GlucoActive	NIO-GM	Using spectrophotometry to measure the scattering of light by molecules such as glucose. Irradiates the skin with wavelength of light to determine glucose concentration. Technology similar to GlucoStation and GlucoWear. ²³⁰	Skin ²³⁰	No information available.	No information available.
14	Gluco Quantum; Genki Vantage Ltd	NIO-GM	Uses metabolic heat (in the form of radiation, convection, and evaporation) from the finger's skin to detect blood flow velocity and make an extrapolation of glucose levels. Infrared light is shone onto the skin to measure the skin's temperature. ¹⁰⁹	Skin ¹⁰⁹	MARD: 13.12% ²³¹	No information available.
15	Glucosense; Glucosense Diagnostics Ltd.	NIO-GM	Application of fluorescence measurement after excitation with a low-energy laser. Photonic chip with fluorescent ions. Uses infrared light and measures level of ion fluorescence to determine glucose concentration. The fluorescence ions are embedded with a silica glass photonic chip. These ions fluoresce in the infrared region of the spectrum (this could be near infrared close to the visible spectral range). ²³²	Skin ²³²	No information available.	No information available.
16	GlucoStation; GlucoActive	NIO-GM	Using spectrophotometry to measure the scattering of light by molecules such as glucose. Irradiates the skin with wavelength of light to determine glucose concentration. Technology similar to GlucoFit and GlucoWear. ²³³	Skin ²³³	No information available.	No information available.
17	GlucoTrack; Integrity Applications Ltd	NIO-GM	Ultrasound, electromagnetic, and thermal parameters in earlobe tissue are measured to estimate blood glucose levels. ²³⁴	Skin ²³⁴	MARD: 17.5%- 19.7% consensus error grid: 62.4% in zone A, 37.6% in zone B ²³⁵	Device can operate in an environmental temperature of +15°C to +35°C/ +59°F to +95°F. However, if the ambient sensor detects an environmental temperature that is beyond these temperatures, the device will present an error message. ²⁶
18	GlucoWear; GlucoActive	NIO-GM	Using spectrophotometry to measure the scattering of light by molecules such as glucose. Irradiates the skin with wavelength of light to determine glucose concentration. Technology similar to GlucoFit and GlucoStation. ²³⁷	Skin ²³⁷	No information available.	No information available.

(continued)

Table 2. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
19	GlucoWise; MediWise	NIO-GM	Using low-power radio waves scattering. Radio waves (40 GHz) are transmitted through a thin layer of skin with adequate blood supply. Radiation passes through the skin layer (transflectance experiment). Uses a film technology that makes the skin transparent to the incident radiation, thereby giving consistent readings across different types of skin. ²³⁸	Blood ²³⁸	No information available.	No information available.
20	Glutrac; Add Care Ltd.	NIO-GM	Employs absorption spectroscopy, electrocardiography, photoplethysmography, and dynamic metabolic heat monitoring to collect data. Machine learning and artificial intelligence is then used to estimate the user's blood glucose. ¹¹⁹	Blood ¹¹⁹	No information available.	No information available.
21	HELO Extense; Wor(l) d Master Distributors	NIO-GM	Photoplethysmography to measure glucose concentrations. ²³⁹	Blood ^{122,239}	Instead of blood glucose numbers, the device provides a color coded scale for glucose. ¹²¹ No information on accuracy.	No information available.
22	HELO LX PRO; Wor(l) d Master Distributors	NIO-GM	Photoplethysmography to measure glucose concentrations. ¹²²	Blood ¹²²	No information available.	No information available.
23	LIFELEAF; LifePlus	NIO-GM	Optical Sensor using photoplethysmography (detection of the reflection of infrared light) to detect glucose. ²⁴⁰	Blood ²⁴⁰	No information available.	No information available.
24	Movano Wearable; CGM Movano	NIO-GM	Scattering of high-frequency radio waves (in mm range). One antenna transmits a radio frequency below the skin surface. The amplitude and phase data (impedance) of the reflected waves are then processed by processing circuits and outputs a relevant value for blood glucose levels in the wrist. The sensor uses a frequency of around 60 GHz to penetrate deeper past the skin and illuminate a wider range. Uses a 122-126 GHz spectral range for measurement of glucose, blood pressure, and heart rate. Also uses Doppler measurements to isolate signals corresponding to relative movements. ²⁴¹	Blood ²⁴¹	No information available.	No information available.
25	No product name; Omni Sciences, Inc	NIO-GM	Near infrared spectroscopy after excitation with fiber lasers. ²⁴²	No information available	No information available.	No information available.
26	Sanmina; Sanmina Corporation	NIO-GM	Optical measurement: detect several photoplethysmography signals (detection of the reflection of infrared light) in interstitial tissue ²⁴³	Blood volume and vascular wall ²⁴³	MARD: 8%. Consensus error grid: 98% in zone A, 1.9% in zone B ²⁴³	No information available.
27	Tensor Tip Combo Glucometer; Cnaga Medical Ltd	NIO-GM	Measurement of infra-red light (600-1000 nm) passing through the fingertip (after partial absorption in the finger). Real-time color images related to the blood glucose level in the capillaries are translated into a vector that can be used to identify patterns of glucose concentration ²⁴⁴	Blood/ISF ²⁴⁴	MARD: 14-18.1%. Consensus error grid: 91.1% in zone A and 7.8% in zone B ^{33,245}	The finger would have to be adequately warmed up to ensure blood flow to the capillaries. Results might also be affected if the skin or device screen is dirty. ²⁴⁴
28	Uband; Know Labs, Inc	NIO-GM	Spectroscopy techniques combined with radio waves are used to detect glucose concentrations in the body. ²⁴⁶	Blood ²⁴⁶	No information available.	No information available.
29	Bios; GraphWear Technologies Inc	NIFS-GM	Detection of biomolecules from the surface of skin: Nanotechnology to measure glucose that comes out of the skin surface through sweat ^{89,247}	Sweat ⁸⁹	No information available.	Tattoos or other skin alterations ²⁴⁸

(continued)

Table 2. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
30	gSense; Nutrix	NIFS-GM	Detection of biomolecules. Uses nanotechnology to detect glucose changes (concentration of molecules) in saliva. ²⁴⁹	Saliva ²⁴⁹	No information available.	No information available.
31	NextGen CGM; Echo Therapeutics	NIFS-GM	Uses technology that enhances skin permeation (using ultrasound) to measure analytes. Sensor includes a hydrogel component and electrodes. The hydrogel contains glucose oxidase to measure glucose. ²⁵⁰	ISF ²⁵⁰	MARD: 12.4%-20.4% Clarke error grid: 70.7%-89.6% in zone A, 9.6%-26.2% in zone B ²⁵⁰	No information available.
32	Saliva Glucose Biosensor; Gbs Inc.	NIFS-GM	Glucose oxidase is used to detect glucose in a saliva sample through an electrochemical method. ²⁵¹	Saliva ²⁵¹	No information available.	No information available.
33	sugarBEAT; Nemaura Medical	NIFS-GM	Reverse iontophoresis for sampling and electrochemical sensing with glucose oxidase. Adhesive skin patch. Electrochemical signal of ISF glucose via glucose oxidase reaction using reverse iontophoresis by stimulating the migration of glucose from the ISF through an electrical current. ²⁵²	ISF ²⁵²	MARD: 11.92%-12.4% ²⁵²	No information available.
34	Tear Glucose Sensor; NovioSense	NIFS-GM	Electrochemical sensing with glucose oxidase as a receptor for the biomarker, glucose. The amount of H ₂ O ₂ generated is an indicator for the amount of glucose in the lacrimal fluid. ^{36,253}	Lacrimal Fluid ^{36,253}	meMARD: 12.5% Consensus error grid: 90% in zones A + B ²⁵³	Ascorbic acid, acetaminophen, citric acid, lactic acid, pyruvic acid, and urea are all interfering substances ²⁵³
35	AiDex CGM; GlucoRx (Rebranding of MicroTech Medical) ^{146,147}	MI-GM	Electrochemical sensing with glucose oxidase. ²⁵⁴	ISF ²⁵⁴	Consensus error grid: 89.9% in zone A ²⁵⁵	No information available.
36	Bioling CGM; Bioling	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. Using patch with microneedles ¹⁴⁹	ISF ¹⁴⁹	No information available.	No information available.
37	Care Sense Air; i-SENS	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. ²⁵⁶	ISF ²⁵⁶	No information available.	No information available.
38	Cascade CGM System; Waveform	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. ²⁵⁷	ISF ²⁵⁷	MARD: 9.9%, MAD: 14.5 mg/dL Consensus error grid: 86.5% of the data pairs in zone A, greater than 98.6% in zones A + B ¹⁵²	Limited interference concerns. Does not interfere with acetaminophen. ¹⁵¹
39	CT-100; POC Tech X Ascensia	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. ²⁵⁸	ISF ²⁵⁸	MARD: 8.67%-10.22% Clarke error grid: 86.7%-91.6% in zone A, 8.4%-12.7% in zone B ^{259,260}	No information available.
40	Dexcom G6; Dexcom	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. GO + Perm-selective membrane coating. ²⁶¹	ISF ²⁶¹	MARD: 9% ¹⁵⁹	Hydroxyurea
41	Dexcom G7; Dexcom	MI-GM	No information available.	No information available.	No information available.	No information available.
42	Eclipse 3 iCGM; GlySens	Implanted MI-GM	Glucose oxidase and a potentiostatic oxygen sensor work together in the sensor to sense glucose and allow for long-term implanting of the sensor. ²⁶²	ISF ²⁶²	MARD: 8.2%-28.1%. Consensus error grid: 75.2% in zone A, 23.7% in zone B, 1.1% in zone C ²⁶²	No information available.

(continued)

Table 2. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
43	Eversense; Senseonics	Implanted MI-GM	Nonenzymatic electrochemical fluorescent-based polymer ²⁶³	ISF ²⁶³	MARD: 8.5%-9.6% ²⁶³	Mannitol, Tetracycline ²⁶⁴
44	FiberSense Technology CGM; EyeSense	MI-GM	Optical fiber fluorescence photometer measures concentration of glucose. Uses a receptor molecule that binds glucose and also binds a competitor molecule. ²⁶⁵	ISF ²⁶⁵	MARD: 8%-9% ²⁶⁵	No information available.
45	FreeStyle Libre 14 day; Abbott Diabetes Care	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase. GO + Redox sensing, use of a mediator of osmium oxide. ²⁶⁶	ISF ²⁶⁶	MARD: 9.4% ²⁶⁷	Ascorbic acid, salicylic acid ^{267,268}
46	FreeStyle Libre 2; Abbott Diabetes Care	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase. GO + Redox sensing, use of a mediator of osmium oxide ²⁶⁹	ISF ²⁶⁹	Adult MARD: 9.2%, pediatric MARD: 9.7% ²⁶⁹	Ascorbic acid ²⁶⁹
47	FreeStyle Libre 3; Abbott Diabetes Care	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase. GO + Redox sensing, use of a mediator of osmium oxide ²⁷⁰	ISF ²⁷⁰	Adult MARD: 9.2% ²⁷⁰	No information available.
48	Glucomen Day CGM; Menarini Diagnostics	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase. Electrochemical enzymatic sensor. ²⁷¹	ISF ²⁷¹	MARD: 9.7%. Consensus error grid: 84.9% in zone A, 12.9% in zone B ²⁷²	No information available.
49	Gluonovo i3 CGM; Infivivo Medical Co Ltd.	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase electrochemical sensor. ²⁷³	ISF ²⁷³	No information available.	No information available.
50	Glyde CGM; GluSense	Implanted MI-GM	Glucose detection is performed using a proprietary fluorescent. Biosensor protein. Biosensor uses the fluorescent resonant energy transfer effect. ¹⁸⁶ When glucose is bound to the biosensor, it changes its fluorescence emission.	ISF ¹⁸⁶	No information available.	No information available.
51	Indigo CGM; Indigo	Implanted MI-GM	Glucose measurement with near infrared spectroscopy in a small subcutaneously implanted spectrometer, measure glucose and ketones up to 2 years ²⁷⁴	ISF ²⁷⁴	(Measured in swine model) MARD: 6.4%-6.5%. Consensus error grid 99.3%-99.4% in zone A, 0.6% in zone B, 0%-0.1% in zone C ²⁷⁵	No information available.
52	No product name; Integrated Medical Sensors	Implanted MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction ¹⁹⁰	ISF ¹⁹⁰	(Measured in swine model) MARD: Better than 12%. Clarke error grid: 96% in Zones A + B ¹⁹⁰	No information available.
53	No product name; One Drop (acquired Sano Intelligence, Inc., which was developing patch biosensor glucose monitor) ¹⁹²	MI-GM	Biosensor patch with microneedles that measures ISF for glucose concentration. ^{192,194,276} Glucose forecast by using artificial intelligence.	ISF ¹⁹⁴	No information available.	No information available.
54	K'Watch; PKVitality	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. Measured through microneedles ^{277,278}	ISF ^{277,278}	No information available.	No information available.
55	Lumee; Profusa	Implanted MI-GM	Biosensor inserted into the body will have porous smart gel and will emit fluorescent signal in response to certain analytes like glucose ²⁷⁹	ISF ²⁷⁹	No information available.	No information available.

(continued)

Table 2. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Mechanism of glucose sensing	Matrix	Degree of accuracy	Interferences
56	Medtronic Guardian Connect (Powered by Medtronic Guardian Sensor 3); Medtronic MiniMed	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction ²⁸⁰	ISF ²⁸⁰	MARD: 8.7% ²⁸¹	Acetaminophen hydroxyurea ²⁸⁰
57	Medtronic Synergy; Medtronic MiniMed	MI-GM	No information available.	ISF ²⁸²	No information available.	No information available.
58	Medtronic Zeus; Medtronic MiniMed	MI-GM	No information available.	ISF ²⁸²	Pivotal results indicate possibility of iCGM standard ²	No information available.
59	No product name; Metronom Health	MI-GM	Electrochemical opto-enzymatic sensor. ²⁸³	ISF ²⁸³	No information available.	No interferences with commonly taken substances. ²⁸³
60	PercuSense CGM; PercuSense	MI-GM	Electrochemical enzymatic sensor combining measurement of glucose and ketone on a single sensor. Multi-analyte function. ²⁸⁴	ISF ²⁸⁴	No information available.	No information available.
61	Sanvita Medical, LLC and LifeScan	MI-GM	No information available.	ISF ²⁸⁵	No information available.	No information available.
62	Sencell; LifeCare AS	Implanted MI-GM	Implantable 3D printed nano-sensor with an osmotic pressure sensing core. Cantilever based glucose sensing. ²⁸⁶ Utilization of the reversible affinity sensing principle of ConA and dextran with glucose (change of binding in the presence of glucose and therefore change of osmotic pressure at a membrane).	ISF ²⁸⁶	No information available.	No information available.
63	SugarSenz; Glucovation	MI-GM	Electrochemical non-enzymatic sensor ²⁸⁷	ISF ²⁸⁷	No information available.	No information available.
64	SynerG; Pacific Diabetes Technologies	MI-GM	Insulin infusion set and CGM sensor combined into one integrated device. CGM sensor is hollow. Uses redox mediator technology. ²¹⁶	ISF ²¹⁶	MARD: 10-14% ^{216,217}	No information available.
65	TouchCare System A6; Medtrum	MI-GM	Electrochemical signal of ISF glucose via glucose oxidase reaction. ²¹⁹	ISF ²¹⁹	MARD: 9% ²⁸⁸	May be affected by strong radiation, such as MRI, X-ray, or CT scans. ¹¹⁸

Abbreviations: CGM, continuous glucose monitor; ConA, Concanavalin A; CT, computed tomography; ISF, interstitial fluid; MAD, mean absolute difference; MARD, mean absolute relative difference, medARD, median absolute relative difference; MI-GM, minimally invasive glucose monitor; MRI, magnetic resonance imaging; NIFS-GM, noninvasive fluid sensing glucose monitor; NIO-GM, noninvasive glucose monitor.

Table 3. Consumer features of NIO-GM, NIFS-GM, or MI-GM Identified Products (in Alphabetical Order Within Each Category of Invasiveness).

Entry number	Product and manufacturer	Degree of invasiveness	Measurement cycle	Pricing model	Size/Form factor
1	No product name; Afon Technology	NIO-GM	Continuous ⁸⁶	One purchase of a wristwatch ⁸⁶	Wearable wristwatch ⁸⁶
2	Alertgy-NI-GM; Alertgy	NIO-GM	Continuous ⁸⁸	One purchase of a wristwatch – no disposables announced ²⁸⁹	Wearable wristwatch ²⁸⁹
3	No product name; AnnNIGM	NIO-GMk	Continuous ²²³	One purchase of an earlobe clip. No disposables announced. ²²³	Earlobe clip with a wraparound wire. ²²³
4	Add on to the Apple Watch; Apple	NIO-GM	Continuous	Add on to the Apple Watch ⁹⁰	Wearable wristwatch ⁹⁰
5	BioMKR; Prediktor Medical	NIO-GM	Continuous ²²⁵	One purchase of a device – no disposables announced ²²⁵	Wearable wristwatch ²²⁵
6	Blood Analysis Sensor; Brolis Sensor Technology	NIO-GM	Continuous (based on sensor description that measurements are real-time and gathered in a fraction of a second) ²²⁷	No information available.	Working on a wearable on-the-chip system ²²⁷
7	CompanionCM; Socrates Health Solutions	NIO-GM	Continuous ²⁹⁰	Purchase of earpiece sensor as indicated in image on product website. ²⁹⁰ No other information available.	Earpiece ⁹⁸
8	CompanionSR; Socrates Health Solutions	NIO-GM	Intermittent ²⁹⁰	Purchase of a glucose monitor as indicated in image on product website. ²⁹⁰ No other information available.	Device image can be found on product website. ²⁹⁰ No other information available.
9	D-Band; DiaMonTech	NIO-GM	Continuous ¹⁰²	One purchase of a device – no disposables announced ¹⁰²	Wearable wristwatch ¹⁰²
10	D-Base; DiaMonTech	NIO-GM	Intermittent ¹⁰²	One purchase of a device – no disposables announced ¹⁰²	The D-Base is the size of a shoebox. ¹⁰²
11	D-Pocket; DiaMonTech	NIO-GM	Intermittent ¹⁰²	One purchase of a device – no disposables announced ¹⁰²	Handheld pocket-sized device. ¹⁰²
12	GlucoBeam; RSP Systems	NIO-GM	Intermittent ¹⁰⁴	One purchase of a device – no disposables announced ¹⁰⁴	Portable, handheld device ¹⁰⁴
13	GlucoFit; GlucoActive	NIO-GM	Intermittent ²⁹¹	One purchase of a device ²⁹¹	Wearable armband ²⁹¹
14	Gluco Quantum; Genki Vantage Ltd	NIO-GM	Intermittent ¹⁰⁹	One purchase of device- no disposables announced ¹⁰⁹	Portable, handheld device ¹⁰⁹
15	Glucosense; Glucosense Diagnostics Ltd	NIO-GM	Intermittent but working to make continuous wearable forms. ²⁹²	One purchase of device- no disposables announced ²³²	Portable, handheld device ²³²
16	GlucoStation; GlucoActive	NIO-GM	Intermittent ²⁹¹	One purchase of a device ²⁹¹	Stationary device, around the size of a lunchbox. ²⁹¹
17	GlucoTrack; Integrity Applications Ltd	NIO-GM	Intermittent ²⁹³	One purchase of a device. Each personal ear cuff must be replaced every 6 months. ²⁹⁴	Portable, handheld device, with cuff that clips onto earlobe. ²⁹³
18	GlucoWear; GlucoActive	NIO-GM	Intermittent ²⁹¹	One purchase of a device ²⁹¹	Wearable wristwatch ²⁹¹
19	GlucoWise; MediWise	NIO-GM	Intermittent ²³⁸	One purchase of a device – no disposables announced ²³⁸	Small, portable device that fits between the thumb and forefinger. ²³⁸
20	Glutrac; Add Care Ltd	NIO-GM	Continuous ¹¹⁹	One purchase of a device – no disposables announced ¹¹⁹	Wearable wristwatch ¹¹⁹

(continued)

Table 3. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Measurement cycle	Pricing model	Size/Form factor
21	HELO Extense; Wor(l)d Master Distributors	NIO-GM	Intermittent ²³⁹	Purchase of a HELO Extense glucose sensor and either HELO LX wristband (\$199 + USD) or HELO LX + (\$399 + USD). No disposables announced. ²⁹⁵ Manufacturer is described as using a multi-level marketing practice. ²⁹⁶ One purchase of a device, no disposables announced. ²⁹⁵ Manufacturer is described as using a multi-level marketing practice. ²⁹⁶	Fingertip clamp sensor ²³⁹
22	HELO LX PRO; Wor(l)d Master Distributors	NIO-GM	Continuous ²⁹⁵	One purchase of a device – no disposables announced ¹²⁶	Wearable wristband ²⁹⁵
23	LIFELEAF; LifePlus	NIO-GM	Intermittent ²⁹⁷	One purchase of a device- no disposables announced ²⁹⁷	Wearable wristwatch ²⁹⁷
24	Movano Wearable CGM; Movano	NIO-GM	Continuous ¹²⁶	One purchase of a device – no disposables announced ¹²⁶	Wearable wristwatch ¹²⁶
25	No product name; Omni Sciences, Inc	NIO-GM	No information available.	No information available.	Developing a wearable ²⁴²
26	Sammina; Sammina Corporation	NIO-GM	Intermittent	No information available.	Image provided by company representative presented in Table 5 shows form factor similar to a standard pulse oximeter. ²⁹⁸ 42.8 mm × 48 mm × 82 mm ²⁴⁵
27	Tensor Tip Combo Glucometer; Croga Medical Ltd	NIO-GM	Intermittent ²⁴⁵	A purchased device also comes with glucose test strips kit for calibration purposes ²⁴⁵	Wearable wristwatch ²⁴⁶ No information available.
28	Uband; Know Labs, Inc.	NIO-GM	Continuous ²⁴⁶	One purchase of a device – no disposables announced ²⁴⁶	Wearable wristwatch ²⁴⁶
29	Bios; GraphWear Technologies Inc.	NIFS-GM	Continuous ²⁴⁷	Patch sensor ⁸⁹	No information available.
30	gSense; Nutrix	NIFS-GM	Intermittent ²⁴⁹	One purchase of a sensor ²⁴⁹	Toothbrush-sized ²⁴⁹
31	NextGen; CGM Echo Therapeutics	NIFS-GM	Continuous ²⁵⁰	Includes self-use exfoliator, exfoliator tip, sensor, reusable transmitter, battery ⁴⁴	No information available.
32	Saliva Glucose Biosensor; Gbs Inc.	NIFS-GM	Intermittent ²⁹⁹	Disposable strips ¹⁴⁰	No dimensions mentioned on website. In images, looks to be a small one- to 2-inch-long thin strip ²⁹⁹
33	sugarBEAT; Nemauro Medical	NIFS-GM	Continuous ¹⁴¹	Non-insulin users: \$30/month annual subscription. 8 patches/month, transmitter, and recharger. ²⁵² Insulin users: \$55/month annual subscription. 16 patches/month, transmitter, and recharger. ²⁵²	No information available.
34	Tear Glucose Sensor; NovioSense	NIFS-GM	Continuous ¹⁴⁴	One purchase of a device – no information on whether or not the device needs to be replaced ¹⁴⁴	Very small, flexible coil that is placed in the bottom eyelid; 15 mm long and 1.3 mm in diameter ²⁵⁸
35	AiDex CGM; GlucoRx (Rebranding of MicroTech Medical)	MI-GM	Continuous	The sensor must be replaced every 14 days. The transmitter is designed to last 4 years. ²⁵⁵	No dimensions. The sensor is described as small and flexible. The transmitter is compact. ²⁵⁵
36	Biolinq CGM; Biolinq	MI-GM	Continuous ¹⁴⁹	Purchase of silicon enclosure with battery and sensor, replaceable adhesives ¹⁴⁹	1 mm length ¹⁴⁸
37	Care Sense Air; i-SENS	MI-GM	Continuous ⁸⁹	No information available.	No information available.

(continued)

Table 3. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Measurement cycle	Pricing model	Size/Form factor
38	Cascade CGM System; Waveform	MI-GM	Continuous ³⁰⁰	Purchase of disposable sensors ³⁰¹	Size of United States nickel, ³⁰² which is 21.21 mm in diameter. ³⁰³
39	CT-100; POC-Tech X Ascensia	MI-GM	Continuous ²⁵⁸	Purchase of disposable sensors ²⁵⁸	10 mm × 0.3 mm (L × W, approximate) ²⁵⁸
40	Dexcom G6; Dexcom	MI-GM	Continuous ¹⁵⁹	Transmitter: \$237 G6 receiver: \$365 Box of G6 sensors (3 pack); \$349 ³⁰⁴	Transmitter/sensor size: 1.8 in × 1.2 in × 0.6 in 0.42 oz. with sensor. Receiver size: 4.02 in × 2.44 in × 0.46 in. 3.3 oz. ³⁰⁵
41	Dexcom G7; Dexcom	MI-GM	Continuous	No information available.	Sensor size smaller than Dexcom G6 ³⁰⁶
42	Eclipse 3 iCGM; GlySens	Implanted MI-GM	Continuous ³⁰⁷	Sensor has expected 2-year life ³⁰⁷	3.4 cm diameter, 1.5 cm thick for previous prototype but making the implant smaller ²⁶²
43	Eversense; Senseonics	Implanted MI-GM	Continuous ⁵⁸	\$99 ³⁰⁸	Transmitter/sensor size: 1.48 in × 1.89 in × 0.35 in. 0.39 oz. ³⁰⁵
44	FiberSense Technology CGM; EyeSense	MI-GM	Continuous ²⁶⁵	Disposable sensors. No pricing information. ²⁶⁵	No information available.
45	FreeStyle Libre 14 day; Abbott Diabetes Care	MI-GM	Continuous ³⁰⁹	Most commercially insured patients pay between \$10 and \$75 per month for FreeStyle Libre 14 day sensors. One purchase of reader. ³⁰⁹	Transmitter/sensor size: 5 mm height 35 mm diameter ²⁶⁷
46	FreeStyle Libre 2; Abbott Diabetes Care	MI-GM	Continuous ³⁰⁹	Covered by Medicare in the USA. Considered to be 70% lower cost than most CGMs depending on insurance coverage. ³¹⁰	Transmitter/sensor size: 5 mm height, 35 mm diameter ²⁶⁹
47	FreeStyle Libre 3; Abbott Diabetes Care	MI-GM	Continuous ³¹¹	The FreeStyle Libre 3 will be the same price as previous FreeStyle Libre CGM systems, at \$109 per month. ³¹²	About the size of 2 United States pennies stacked. ³¹³
48	Glucomen Day CGM; Menarini Diagnostics	MI-GM	Continuous ²⁷¹	£139 per month if you subscribe. Rechargeable transmitter, disposable sensors. ¹⁸⁰	Sensor + transmitter size: 3.5 cm × 2.5 cm × 0.9 cm ²⁷¹
49	Glunovo i3 CGM; Infynovo	MI-GM	Continuous ²⁷³	- Starter Kit: 1 Glunovo Transmitter and 2 Glunovo Sensors. - Monthly Package: 2 Glunovo Sensors. - Annual Package: 25 Glunovo Sensors and 6 sensors shipped every 3 months. ³¹⁴	Transmitter size: 33 mm × 19 mm × 4 mm ²⁷³
50	Glyde CGM; GluSense	Implanted MI-GM	Continuous ¹⁸⁵	The sensor has to be replaced every year. ¹⁸⁶	No information available.
51	Indigo CGM; Indigo	Implanted MI-GM	Continuous ³¹⁵	No information available.	No information available.
52	No product name; Integrated Medical Sensors	Implanted MI-GM	Continuous ¹⁹⁰	It is estimated that the sensor must be replaced every 6 months. ¹⁸⁹	Smaller than a sesame seed. ¹⁹⁰

(continued)

Table 3. (continued)

Entry number	Product and manufacturer	Degree of invasiveness	Measurement cycle	Pricing model	Size/Form factor
53	No product name; One Drop (acquired Sano Intelligence, Inc, which was developing patch biosensor glucose monitor) ¹⁹²	MI-GM	Continuous ¹⁹²	Biosensor patch ^{192,194,276}	No information available.
54	K'Watch; PKVitality	MI-GM	Continuous ²⁷⁷	Expected to be set at \$199 for the K'Watch. K'apsul Sensor that is replaceable on the watch expected to be set at \$99 per month. ³¹⁶	Watch size. ²⁷⁷
55	Lumee; Profusa	Implanted MI-GM	Continuous ²⁷⁹	Will have a transmitter and sensor that is inserted under the skin. ²⁷⁹	Approx 5 mm in length and 500 microns in diameter. ²⁷⁹
56	Medtronic Guardian Connect (Powered by Medtronic Guardian Sensor 3); Medtronic MiniMed	MI-GM	Continuous ³¹⁷	Starts at \$50/month based on typical 20% copay with insurance ³¹⁸	1.41 in × 1.13 in × 0.38 in. 0.04 oz. with sensor. ³⁰⁵
57	Medtronic Synergy; Medtronic MiniMed	MI-GM	Continuous ²⁸²	No information available.	Sensor 50% smaller than Guardian Sensor 3. ³¹⁹
58	Medtronic Zeus; Medtronic MiniMed	MI-GM	Continuous ²⁸²	No information available.	Same size and shape as Guardian Sensor 3. ³²⁰
59	No product name; Metronom Health	MI-GM	Continuous ²⁸³	Transmitter with sensor. ²⁸³	As thin as 2 human hairs in width ³²¹
60	PercuSense CGM; PercuSense	MI-GM	Continuous ²⁸⁴	Transmitter with disposable sensor. ²⁸⁴	No information available.
61	Sanvita; Sanvita Medical, LLC and LifeScan	MI-GM	Continuous ²¹⁰	No information available.	No information available.
62	Sencell; LifeCare AS	Implanted MI-GM	Continuous ³²²	Implant sensor and wristwatch. No disposables announced. ³²³	Sensor size: 2 mm × 3 mm × 6 mm ³²³
63	SugarSenz; Glucovation	MI-GM	Continuous ²⁸⁷	The sensor must be replaced every 7-10 days. The transmitter is designed to last longer than a year. ²¹⁴	The sensor is a thin adhesive that sticks to the skin. The transmitter is the size of a smartphone. ²¹⁴
64	SynerG; Pacific Diabetes Technologies	MI-GM	Continuous ³²⁴	One purchase of a transmitter. Disposable sensors. ³²⁴	Dimensions unavailable. Sensor worn on the abdomen as indicated by manufacturer's website picture. ³²⁴
65	TouchCare System A6; Medtrum	MI-GM	Continuous ³²⁵	One purchase of a transmitter. Disposable sensors. ³²⁵	76.2 mm × 48.4 mm × 9.375 mm ³²⁵

Abbreviations: CGM, continuous glucose monitor; MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sensing glucose monitor; NIO-GM, noninvasive glucose monitor.

Table 4. Classification of Underlying Technologies of NIO-GM, NIFS-GM and MI-GM Identified Products.

Technology	Table entry
Noninvasive optical	
Short wavelength near infrared	27
Near infrared spectroscopy	4, 5, 6
Mid infrared spectroscopy	9, 10, 11, 14, 25
Raman scattering spectroscopy	12
Radio or microwave	1, 2, 19, 24, 28
Polarimetry	7, 8
Fluorescence	15
Scattering	13, 16, 18
Multiplex signals	17, 20
Photoplethysmography	21, 22, 23, 26
No information available	3
Noninvasive fluid sampling	
ISF extraction	31, 33
Tear fluid	34
Sweat	29
Saliva	30, 32
Minimally invasive	
Electrochemical glucose oxidase biosensor	35-40, 42, 45-49, 52-54, 56, 60, 64, 65
Non-enzymatic fluorescence	43, 44, 50, 55
Other	51, 59, 62, 63
No information available	41, 57, 58, 61

Table entry refers to the "Entry number" of the product specified in Tables 1–3. Abbreviation: ISF, interstitial fluid.

Underlying Glucose Sensing Technologies used in NIO-GM, NIFS-GM, or MI-GM Identified Products

Table 4 classifies the underlying glucose sensing technologies of the 65 identified products. Under NIO-GM, the glucose sensing technologies included: short wavelength near infrared, near infrared spectroscopy, mid infrared spectroscopy, Raman spectroscopy, radio or microwave devices, polarimetry, fluorescence, scattering, multiplex signals, and photoplethysmography. A few products were NIO-GM, but their exact glucose sensing technologies were not specified because this information was not available. Under NIFS-GM, the glucose sensing technologies included: saliva, tear fluid, sweat, and ISF extraction. Finally, under MI-GM, the glucose sensing technologies included: electrochemical glucose oxidase biosensor and non-enzymatic fluorescence sensors. Some MI-GM did not belong to either of these technologies, and some do not have publicly available information on what technology they use.

Images of Product Designs of Selected Identified Products

Table 5 presents images of product designs of identified products. We included images only if we were able to receive permission from manufacturer representatives. Images are

not to scale relative to each other. Table 5A is for products that are FDA cleared and/or CE marked, and Table 5B is for products that are neither FDA cleared nor CE marked.

Advantages and Disadvantages of Identified Products








Table 6 presents advantages and disadvantages of the identified products that were cleared by the FDA or CE marked. The features that we present in Table 6 for specific products are important highlights of each product, rather than a comprehensive list of advantages and disadvantages. In general, there are advantages and disadvantages for each of the three categories of glucose monitors employing bloodless sampling. All three categories of glucose monitors are less accurate than IGMs. (1) As a class, NIO-GM products are painless and do not generate biological waste, but they are less accurate than NIFS-GM, MI-GM, and IGM products. (2) As a class, NIFS-GM products require the sensor to be in direct contact with a body fluid that is not blood, and these systems generally produce less pain and less biological waste than IGMs. However, there can be a significant lag-time in their measurements, thereby rendering them less accurate than IGMs or MI-GMs. (3) As a class, MI-GM products have been studied the most of the three types of bloodless glucose monitors. More products in this category, compared to the other two categories, have received regulatory clearance. Currently, many MI-GMs are more accurate, more robust, and more conveniently calibrated than most NIO-GM and NIFS-GM products. The Abbott (Chicago, Illinois) and Dexcom (San Diego, California) MI-GMs are factory calibrated. All MI-GMs, however, require insertion or implantation of the glucose sensor and must be worn, which in rare cases creates an unpleasant sense of being tethered to a machine.³⁵² Many MI-GMs and some NIO-GMs and NIFS-GMs require adhesives for stabilization and allergic dermatitis has been reported with some adhesives.⁷³ The convenience, performance, and connectivity of MI-GMs have been advancing rapidly over the past few years and product manufacturers have predicted further advances in these areas.³⁵³ The worldwide market for CGMs was valued at \$1.8 billion in 2019 and with a projected compound annual growth rate of 22%, the market is expected to reach \$8.8 billion by 2027.³⁵⁴ This market has likely already surpassed four million CGM users.³⁵⁵

Discussion

Evolution of Bloodless Glucose Monitoring Products






In the past, one NIFS-GM³⁵⁶ and one NIO-GM³⁵⁷ were introduced to the market but were eventually discontinued, and two NIO-GMs^{358,359} were cleared but never introduced to the market.³⁵⁶⁻³⁵⁹ These products were all highly anticipated before their release but failed to live up to expectations. A particular problem was that such devices were touted in the lay press,

Table 5A. Designs of NIO-GM, NIFS-GM, and MI-GM Identified Products with Regulatory Clearance (in Alphabetical Order Within Each Category of Invasiveness).

Product and manufacturer	Degree of invasiveness	Product design
GlucoTrack; Integrity Applications Ltd	NIO-GM	 293
sugarBEAT; Nemauro Medical	NIFS-GM	 326
Cascade CGM System; Waveform	MI-GM	 327
Dexcom G6; Dexcom	MI-GM	 328
Eversense; Senseonics	Implanted MI-GM	 329
FreeStyle Libre 14 day; Abbott Diabetes Care	MI-GM	 330
FreeStyle Libre 2; Abbott Diabetes Care	MI-GM	 331
FreeStyle Libre 3; Abbott Diabetes Care	MI-GM	 332
Medtronic Guardian Connect (Powered by Medtronic Guardian Sensor 3); Medtronic MiniMed	MI-GM	 333
PercuSense CGM; PercuSense	MI-GM	 284
Sencell; Lifecare AS	MI-GM	 323

Abbreviations: MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sensing glucose monitor; NIO-GM, noninvasive glucose monitor.

Table 5B. Designs of NIO-GM, NIFS-GM, and MI-GM Identified Products without Regulatory Clearance (in Alphabetical Order Within Each Category of Invasiveness).

Product; <i>manufacturer</i>	Degree of invasiveness	Product design
No product name; <i>Afon Technology</i>	NIO-GM	 86 RCD No: 008213961-0001
D-Band; <i>DiaMonTech</i>	NIO-GM	 334
D-Base; <i>DiaMonTech</i>	NIO-GM	 335
D-Pocket; <i>DiaMonTech</i>	NIO-GM	 336
Glucobeam; <i>RSP Systems</i>	NIO-GM	 337
Glucofit; <i>GlucoActive</i>	ONI-GM	 230
Glucos Quantum; <i>Genki Vantage Ltd</i>	NIO-GM	 338
Glucostation; <i>GlucoActive</i>	NIO-GM	 233
Glucowear; <i>GlucoActive</i>	NIO-GM	 237
LifeLeaf; <i>LifePlus</i>	NIO-GM	 339
Movano Wearable; <i>CGM Movano</i>	NIO-GM	 340
Sanmina; <i>Sanmina Corporation</i>	NIO-GM	 298
Uband; <i>Know Labs, Inc.</i>	NIO-GM	 341
Tear Glucose; <i>Sensor NovioSense</i>	NIFS-GM	 144
K'Watch; <i>PKvitality</i>	MI-GM	 277
SynerG; <i>Pacific Diabetes Technologies</i>	MI-GM	 342

Abbreviations: MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sensing glucose monitor; NIO-GM, noninvasive glucose monitor.

Table 6. Advantages and Disadvantages of NIO-GM, NIFS-GM, or MI-GM Identified Products that were Cleared by the FDA or CE Marked (in Alphabetical Order Within Each Category of Invasiveness).

Product and manufacturer	Degree of invasiveness	Advantages	Disadvantages
GlucoTrack; Integrity Applications Ltd	NIO-GM	<ul style="list-style-type: none"> - Uses a blend of 3 optical technologies. 	<ul style="list-style-type: none"> - Ear measurement site can be inconvenient
TensorTip Combo Glucometer; Gnoga Medical Ltd	NIO-GM	<ul style="list-style-type: none"> - Portable 	<ul style="list-style-type: none"> - Not wearable - Requires regular recalibration
sugarBEAT; Nemaaura Medical	NIFS-GM	<ul style="list-style-type: none"> - Uses a well-tolerated adhesive - Skin ISF is measured without puncturing the skin. - You can wear the device on any single day and not have to wear it on multiple consecutive days. - There should be good correlation between glucose level in the ISF and in the blood under stable conditions. - Glucose measurement is based on the well-known enzymatic method. - Accurate¹⁵² - 14-day duration - Automatic data uploading - Inserts without a needle - Audible glucose alarms - Software identifies glucose patterns 	<ul style="list-style-type: none"> - No PubMed published data. - Reverse iontophoresis irritated the skin in a similar product from a different manufacturer: GlucoWatch - The accuracy has not been established if a patient is sweating, or if there are rapid changes in the blood glucose concentration.
Cascade CGM System; Waveform	MI-GM	<ul style="list-style-type: none"> - CT-100 features a 4-electrode system. In addition to a glucose sensing electrode, it features a dedicated blank electrode that monitors background and electrochemical interferences. It enables real time correction of any background drift and interference. - CT-100 sensor is built on a flexible polyimide matrix. It is one of the most flexible sensors available. This provides higher level comfort for 24/7 wearing. - CT-100 sensor features an all planar design and align electrodes on both sides of the matrix. It can fully utilize currently available industrial manufacturing techniques for mass production, and therefore provides a potential for a favorable cost effectiveness and easier quality control. 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation. - Sometimes allergic dermatitis due to adhesive
CT-100; POCTech X Ascensia	MI-GM	<ul style="list-style-type: none"> - CT-100 features a 4-electrode system. In addition to a glucose sensing electrode, it features a dedicated blank electrode that monitors background and electrochemical interferences. It enables real time correction of any background drift and interference. - CT-100 sensor is built on a flexible polyimide matrix. It is one of the most flexible sensors available. This provides higher level comfort for 24/7 wearing. - CT-100 sensor features an all planar design and align electrodes on both sides of the matrix. It can fully utilize currently available industrial manufacturing techniques for mass production, and therefore provides a potential for a favorable cost effectiveness and easier quality control. 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation.

(continued)

Table 6. (continued)

Product and manufacturer	Degree of invasiveness	Advantages	Disadvantages
Dexcom G6; Dexcom	MI-GM	<ul style="list-style-type: none"> - Accurate¹⁵⁹ - 10-day duration - Automatic data uploading with sharing feature - Factory calibration - Audible glucose alarms - Software identifies glucose patterns 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation. - Sometimes allergic dermatitis due to adhesive - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation. - Possible difficulty removing a chronically implanted sensor. - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix.
Eversense; Senseonics	Implanted (MI-GM)	<ul style="list-style-type: none"> - Accurate²⁶³ - 90-180 day duration - Automatic data uploading with sharing feature - Removable transmitter - Audible and vibratory glucose alarms - Software identifies glucose patterns 	<ul style="list-style-type: none"> - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation. - Possible difficulty removing a chronically implanted sensor. - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix.
FreeStyle Libre 14 day; Abbott Diabetes Care	MI-GM	<ul style="list-style-type: none"> - Accurate^{267,343,344} - 14-day duration³⁴³ - No separate transmitter; on demand data with sharing feature - Factory calibration - Software identifies glucose patterns 	<ul style="list-style-type: none"> - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - Patient must actively perform an action to determine glucose levels - System cannot be calibrated - no optional user calibration in cases of sensor inaccuracy - Sometimes allergic dermatitis due to adhesive - No hypoglycemia alarm - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - Patient must actively perform an action to determine glucose levels - System cannot be calibrated - no optional user calibration in cases of sensor inaccuracy - Sometimes allergic dermatitis due to adhesive
FreeStyle Libre 2; Abbott Diabetes Care	MI-GM	<ul style="list-style-type: none"> - Accurate²⁶⁹ - 14-day duration²⁶⁹ - No separate transmitter; on demand data with sharing feature - Factory calibration - Audible glucose alarms - Software identifies glucose patterns 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - Patient must actively perform an action to determine glucose levels - System cannot be calibrated - no optional user calibration in cases of sensor inaccuracy - Sometimes allergic dermatitis due to adhesive

(continued)

Table 6. (continued)

Product and manufacturer	Degree of invasiveness	Advantages	Disadvantages
FreeStyle Libre 3; Abbott Diabetes Care	MI-GM	<ul style="list-style-type: none"> - The FreeStyle Libre 3 system is designed to automatically deliver accurate real-time, up-to-the-minute glucose readings,³⁴⁵ and optional glucose alarms directly to smartphones - Designed to be the smallest and thinnest wearable glucose sensor. - Users can view their glucose levels anytime - Designed to have the same performance as the FreeStyle Libre 2 sensor, but with a new sensor design and at the same price as previous versions 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - System cannot be calibrated - no optional user calibration in cases of sensor inaccuracy - Sometimes allergic dermatitis due to adhesive
Glucomen Day CGM; Menarini Diagnostics	MI-GM	<ul style="list-style-type: none"> - Does not require any needles for insertion - Promoted as eco-friendly⁸⁰ - Transmitter can last 3 years³⁴⁶ 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation
Glunovo i3 CGM; Infinovo	MI-GM		<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation
Medtronic Guardian Connect (Powered by Medtronic Guardian Sensor 3); Medtronic MiniMed	MI-GM	<ul style="list-style-type: none"> - Accurate²⁸¹ - 7-day duration - Automatic data uploading - Audible glucose alarms - Software developed with IBM identifies glucose patterns 	<ul style="list-style-type: none"> - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - Point accuracy of MI-GMs that measure ISF is less than point accuracy of blood glucose monitors that use capillary blood as a comparator matrix. - Some patients do not want to carry an inserted or implanted device on their body at all times. - No CGM is labeled to allow for exposure to radiation - Sometimes allergic dermatitis due to adhesive - There is a need to calibrate twice a day with a blood glucose measurement - Wear time (7 days) shorter than some other products

Abbreviations: AID, automated insulin delivery; CGM, continuous glucose monitor; IBM, International Business Machines Corporation; iCGM, integrated continuous glucose monitor; ISF, interstitial fluid; MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sensing glucose monitor; NIO-GM, noninvasive glucose monitor.

raising expectations among people with diabetes and their families. Unfortunately, their performance repeatedly failed to meet these expectations. The NIFS-GM GlucoWatch Biographer from Cygnus Inc. was cleared by the FDA, marketed, and then discontinued.³⁶⁰ Three NIO-GM products were cleared with a CE Mark and then discontinued either soon after entering the market (Pendra Device from Pendragon Medical, Zürich, Switzerland), or without entering the market (NBM-200G from OrSense, Tel Aviv-Yafo, Israel and Optical Glucose Monitor from C8 MediSensors, San Jose, California). Two NIO-GM products that were cleared with a CE mark are currently on the market. They are the GlucoTrack (Integrity Applications Ltd, Ashdod, Israel) and TensorTip Combo Glucometer (Cnoga Medical Ltd, Caesarea, Israel).

The original GlucoWatch Biographer⁴¹ was an NIFS-GM device. This device was cleared by the FDA in 2001 and marketed.⁴⁰ An updated version (the GlucoWatch G2 Biographer⁴²) was also cleared in 2002 for use by individuals under 18 years of age.³⁵⁶ Because these devices used reverse iontophoresis, a low-level current was passed through the skin as part of the glucose sensing method. These products were discontinued after users complained of a burning sensation while using the device.³⁶⁰

The Pendra Device, which measured the change in the frequency-dependent resistance (impedance spectroscopy) in the interstitial flow when the glucose concentration changed,³⁶¹ was initially cleared with a CE Mark of Approval in 2003. However, this device was discontinued because it had readings that were considered dangerously inaccurate and it was incompatible with 30% of people considered for using the device. In 2005, Pendragon Medical went out of business.³⁵⁷

The NBM-200G, which used occlusion spectroscopy, received the CE Mark of Approval in 2007³⁵⁸ but was discontinued by OrSense for unspecified reasons. The C8 Optical Glucose Monitor received the CE Mark of Approval in 2012,³⁵⁹ but is no longer on the market officially because of a lack of funding.³⁶² Other NIO-GM products have been announced to be in development and then have subsequently disappeared from the public eye. These products include the ALIRA Infrared Biosensing sensor (Princeton University, Princeton, New Jersey), Glucoband (Calisto Medical, Plano, Texas), and a Glucose-Sensing Contact Lens (Novartis, Basel, Switzerland working with Verily, South San Francisco, California).

These shortcomings are discussed to emphasize the importance of recognizing, addressing, and avoiding past mistakes. These previous failures to create a usable product also highlight the barriers that must be overcome before a viable NIO-GM can be widely distributed, including (1) large device size, (2) potential skin reactions, (3) poor accuracy, (4) high power requirements, (5) interfering substances, and (6) the lack of a clear regulatory pathway. Although the majority of the NIO-GM products discovered in the search presented in the article are neither cleared nor publicly available, these products have potential, but one must guard against being overly optimistic for the sake of potential users.

Trends in Technology – A Path for Better Products

Many technologies are now being pursued to achieve the objective of noninvasive glucose measurements in people with diabetes. At this time, few NIO-GM or NIFS-GM systems are sufficiently mature for commercialization. The MI-GM market, however, is strong in many countries and growing worldwide. Many of these technologies not using IGM that are in development appear to have poor accuracy. Still, noninvasive approaches are attracting more attention by both researchers and investors owing to the tremendous need for managing diabetes optimally in an ever-growing number of patients and also because of commercial applications beyond medicine.

The commercial potential differs for the products identified in this article. The NIO-GMs are becoming more of a priority for medical device researchers. NIFS-GM sensors seem to be the least likely to satisfy user needs because of the requirement to harvest a representative fluid. Such approaches are prone to issues related to skin irritation as well as to the complexities of collecting, handling, and disposing of a representative clinical fluid. These issues render the noninvasive fluid sampling approach inconvenient in comparison to both the noninvasive optical and minimally invasive approaches. The former eliminates fluid handling and the latter provides continuous measurements. The commercial attractiveness of NIO-GM technologies is driven by the potential to achieve either continuous glucose measurements or repeated spot-measurements, both with minimal user interactions. Commercial success has already been realized for MI-GM technologies and will likely grow as future innovations lead to longer periods of operation and the quantitation of multiple analytes.

Success of NIO-GM, NIFS-GM, and MI-GM devices has started to decrease the market size of invasive blood glucose measurement systems considerably. Just as urine glucose testing was replaced by blood glucose testing, eventually these three bloodless technologies will replace blood glucose monitoring. This trend will continue within the next 10-20 years as new sensing strategies that do not require blood become increasingly accurate, practical, and affordable. Today many of the leading blood glucose monitor manufacturers are developing NIO-GM, NIFS-GM, or MI-GM technologies or partnering with companies with these types of products. The need for invasive blood glucose measurements will also decrease as factory-calibrated MI-GM devices become more accepted by people with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). A CE marked MI-GM was recently introduced for athletes without diabetes.³⁶³ As the accuracy and reliability of factory-calibrated MI-GM devices improve, the need to check an IGM reading will decrease.

Commercial success of any CGM system, regardless of whether it is noninvasive or minimally invasive, must recognize the demands placed on the user. Proper training is

paramount for CGM users, particularly as it relates to the continuous information provided by these devices.³⁶⁴ The users must gain confidence in viewing the large amount of data, interpreting the recorded glucose profiles, and using the data to guide therapeutic decisions. Trained users value the added analytical information provided by CGM and find that it benefits their therapy.³⁶⁵ However, improved data management software will be helpful for the users who are overwhelmed by the data output.

Noninvasive Technology for Diagnosing Diabetes

The current standard for diagnosing diabetes specifies invasive blood sampling, followed by measuring either plasma glucose concentration or hemoglobin A1c concentration.³⁶⁶ While several noninvasive and minimally invasive methods have been developed for monitoring glucose levels, as outlined throughout this paper, there have been few attempts to validate the use of such devices for making a diagnosis of diabetes. There is, however, an incipient technology using photoplethysmography that is intended to make this diagnosis.

Photoplethysmography measures the interaction of light with the vascular bed to determine the changes in blood volume with each heartbeat.³⁶⁷ This technique is currently used in four NIO-GM products under development, including Wor(l)d Global Network's (Miami, Florida) HELO Extense²³⁹ and HELO LX Pro,¹²² LifePlus' (San Jose, California) LifeLeaf,²⁴⁰ and Sanmina's (San Jose, California) NIO-GM.²⁴³ Furthermore, Avram et al. have reported using a smartphone-based photoplethysmography technology with a deep neural network scoring system to prospectively evaluate people with diabetes, by correlating the score with plasma glucose levels.³⁶⁸ This study's results suggest that this method could be potentially useful as a digital biomarker for diabetes diagnosis,³⁶⁸ but further work is needed.³⁶⁹

Miniaturization and Nanotechnology

Miniaturization is critical for future applications and user adoption of the glucose sensing technologies under development worldwide. Wearable devices demand small sensing packages that can be worn for prolonged periods with minimal user discomfort. Miniaturization will also facilitate comfortable systems that combine the sensing element with an insulin infusion system, perhaps in a single package, for novel AID systems.⁸² As the sensing technology advances to the stage of reliable, calibration-free operation for extended periods, miniature solid-state sensing systems will be necessary to serve as the glucose sensing element of an implantable autonomous AID systems.

Nanotechnology is a materials approach with the potential to facilitate device miniaturization while enhancing sensor performance.³⁷⁰ Nanostructures are capable of unique properties not available in bulk materials. The surface area to volume ratio is large for nano-dimensional materials which offers unique physical and chemical effects, such as novel interfacial

phenomena, altered reactivity, and charge carrier and quantum mechanical effects.³⁷¹ Such nanoscale properties can advance miniaturization and sensor operation through higher surface areas, thereby yielding larger sensitivity, quicker responses, and higher catalytic loadings. These enhancements promise superior overall analytical performance.

Nanofabrication techniques can also generate glucose sensors with small dimensions.³⁷² Such small dimensions can facilitate implantation or injection of glucose sensing "tattoos."^{373,374} Nanofabricated devices could potentially diminish or avoid troubling foreign body responses, resulting in simpler calibration processes and longer operational lifetimes. Solid-state photonic systems hold promise for miniaturizing spectroscopic sensors for application as NIO-GM devices. The system under development by Brolis (Vilnius, Lithuania), for example, uses a novel integrated photonic package for solid-state measurements of multiple analytes, including glucose, lactate, and ethanol. Finally, micro- and nano-electronic technologies offer the possibility of low-cost mass production, which can drive down user's costs and expand adoption.

Overcoming Technical Barriers to Widespread Adoption

Adoption of any bloodless glucose sensing technology will depend on a host of technical and nontechnical issues. First, and foremost, the technology must be accurate and robust in operation while adding value to the quality of life for the user. Advances in engineering, physics, clinical chemistry, and medicine will also be required to overcome the technical barriers that impede widespread adoption of NIO-GM, NIFS-GM, and MI-GM products.

From the engineering perspective, more sensitive sensing technologies are needed, particularly for *ex-vivo* NIO-GM and NIFS-GM devices. The ability to identify and detect a robust selective signature for glucose is paramount along with instrumentation able to collect such a signature reliably under non-laboratory conditions. Measurement accuracy in the low glucose range is critical to achieve tight glycemic control while avoiding potentially dangerous hypoglycemic episodes.

From the physics perspective, algorithms are needed to convert raw sensor signals into correct glucose concentration values. For NIO-GM technologies, a principal challenge is to effectively filter out variations in the measured signal, both the noise of the instrumentation as well as uncontrolled changes in the background matrix against which the glucose signature is determined. Success calls for understanding the source of such background variances and developing multivariate data analysis methods to overcome the adverse impact of the background variance. For NIFS-GM devices, the major barrier is to find a correlation between the concentration of glucose in blood and the sampled fluid. For MI-GM systems, reliable analytical measurements are needed for periods longer than 14 days.

From the clinical chemistry perspective, a better understanding is needed about how to assure the accuracy of

bloodless measurements by establishing traceability of their readings to a reference standard.³⁷⁵ This challenge is currently unresolved because of the difficulty of obtaining comparator ISF samples for testing against blood. Also, the controversy about whether capillary blood or venous blood is the best comparator matrix for ISF measurements must be resolved.³⁷⁵ Overall, a convenient and reliable method for collecting representative samples of ISF would have a large positive impact on the advancements of these and future NIO-GM, NIFS-GM, and MI-GM products.

From the medicine perspective, physicians need a better understanding of the clinical values of glucose measurements in fluids other than blood, that is, how to adjust the insulin dose of a patient in case of exercise, is the glucose signal from blood the more reliable signal or that from ISF? The utility of ISF glucose concentrations must be established and might actually be preferable over blood glucose concentrations for treatment decisions because the glucose concentration in ISF compared to that in blood might more closely track the glucose concentration in the brain.⁵⁴ Others have suggested that ISF glucose concentrations can be superior to blood glucose concentrations during periods of rapidly fluctuating glucose concentrations or hypoglycemia. Another clinical dimension for physicians to determine is the level of accuracy needed for various types of patients, such as those with: T1DM on multiple dose insulin therapy, T1DM on sensor augmented pump therapy, T1DM on AID therapy, T2DM using insulin, T2DM using other diabetes drugs known to cause hypoglycemia, T2DM using diabetes drugs not known to cause hypoglycemia, and T2DM using only diet and exercise for control.

Overcoming Non-Technical Barriers to Widespread Adoption

Overcoming nontechnical barriers will be required for the widespread adoption of bloodless glucose sensing technologies:

- (1) The cost of these products must be reduced to make adoption possible for large populations, especially in resource-poor regions of the world.
- (2) The interface between the user and instrumentation and the way in which the user interacts with the instrumentation must translate into an easily deployed wearable device that does not cause embarrassment or inconvenience, particularly in social settings.
- (3) Patients must accept the concept of wearing a continuously functioning device without concern that they are losing their humanity by being dependent on a mechanical device.³⁷⁶
- (4) A motivational factor for many potential users can be an understanding of the present and future environmental risks caused by the large amounts of medical and plastic waste generated by today's invasive blood glucose monitoring technologies.

The overall strategy is to provide a bloodless glucose sensing technology that simultaneously reduces waste, increases convenience, and saves money.

Regulatory agencies guided by solid clinical evidence will play an important role in determining the level of accuracy that each of these new bloodless devices must provide to achieve non-adjunctive status. This is the level of clearance whereby manufacturers can indicate on the product label that their glucose monitoring product can be used to make a treatment decision without the need for an accompanying blood glucose reading as a confirmatory test. Accuracy and robustness of the sensing product are required for non-adjunctive clearance, which will undoubtedly boost the appeal of these products. As shown in Table 3, four MI-GM products have a non-adjunctive indication per the FDA and it is likely that many future bloodless products will demonstrate adequate accuracy to also gain this distinction.

Conclusions

Commercial products for bloodless monitoring of glucose were identified and reviewed. These products are based on three categories of emerging technologies: (1) NIO-GM, (2) NIFS-GM, and (3) MI-GM. Many of these products are based on spectroscopic, electrochemical, and affinity sensing strategies for quantifying glucose molecules in ISF. A multiple database search was used to identify a total of 65 bloodless glucose monitoring products, of which 13 have received regulatory clearance and are currently on the market. The remaining products are under development. Further refinement of these technologies is anticipated over the upcoming decade to enhance both analytical performance and adoption of these products by people with diabetes. Future developments in bloodless glucose monitoring will require technical and nontechnical advances related to (1) superior analytical performance, (2) robust algorithm development, (3) traceability testing for glucose-containing matrices besides blood, such as ISF, and (4) appreciation of the clinical value of ISF glucose measurements. Bloodless glucose monitoring products, such as the ones discussed in this article, are expected to become key components of novel wearable digital health tools for monitoring glucose concentrations in the diabetes market and the fitness market.

Addendum

In May 2021, after this article was in press, Rockley Photonics disclosed a program to develop a chip size laser-based technology suitable for implementation in a smartwatch format. Health monitoring is its principal application and Apple is featured as a major partner in the development of this technology. Rockley stated that Apple is the largest of six customers with which it has entered into contracts with or engaged with, developing health and wellness devices. These companies are developing smartwatches and medical devices for biomarker detection.³⁷⁷ Rockley's sensors are designed to quantify glucose, alcohol, and oxygen levels non-invasively with infrared spectroscopy. Rockley will deliver its chipsets in 2022.³⁷⁸

Abbreviations

AID, Automated insulin delivery; AMBG, assisted monitoring of blood glucose; CE, Conformité Européenne; CGM, continuous glucose monitor; ConA, Concanavalin A; DF, fluorescently labeled dextran; FDA, United States Food and Drug Administration; GBP, glucose-binding protein; IGM, invasive glucose monitor; ISF, interstitial fluid; MARD, mean absolute relative difference; medARD, median absolute relative difference; MI-GM, minimally invasive glucose monitor; NIFS-GM, noninvasive fluid sampling glucose monitor; NIO-GM, noninvasive optical glucose monitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMBG, self-monitoring of blood glucose; SNR, signal-to-noise ratio; USA, United States of America

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