Medical Coverage Policy

Effective Date..... 2/15/2019
Next Review Date..... 2/15/2020
Coverage Policy Number 0106

Diabetes Equipment and Self-Management

Table of Contents

Coverage Policy 1
Overview..... 5
General Background 6
Coding/Billing Information 35
References 37

Related Coverage Resources

Afrezza
Implantable Infusion Pumps for Non-Musculoskeletal Conditions
Insulin Glargine

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Coverage for Durable Medical Equipment including home blood glucose monitors, external insulin pumps, needle-free insulin injection systems, consumable medical supplies (e.g., insulin pens, needle-free injections systems) and diabetes self-management education varies across plans. Coverage for home blood glucose monitors, therapeutic continuous glucose monitors and sensors, and diabetic supplies may be available under the medical benefit or the pharmacy benefit. Please refer to the customer's benefit plan document for coverage details.

Coverage for diabetes self-management education may be governed by state and/or federal mandates.

If coverage is available for a home blood glucose monitor, external insulin pump, specific diabetic supplies and diabetes self-management education the following conditions of coverage apply.

Home Blood Glucose Monitors

A home blood glucose monitor is considered medically necessary for EITHER of the following when used for the management of diabetes mellitus:

- standard home blood glucose monitor (HCPCS Code E0607)

- enhanced feature glucose monitor (e.g., large readout, audio monitor, integrated lancing/blood sample) for an individual who is able to both self-monitor and self-administer insulin, but has a visual or physical impairment that precludes the successful use of a standard home blood glucose monitor (HCPCS Code E2100, E2101)

Continuous Glucose Monitoring System (CGMS)

A minimally invasive, continuous glucose monitoring system (CGMS) is considered medically necessary for the management of difficult to control insulin-treated diabetes mellitus (e.g., hypo- or hyperglycemic episodes unresponsive to adjustments in therapy, asymptomatic nocturnal hypoglycemia) for up to 14 days under the core medical benefits of the plan, for up to six separate sessions in any given 12-month period (CPT® code 95250, 95251).

EITHER of the following minimally invasive, therapeutic continuous glucose monitoring systems (CGMS) (HCPCS K0553, K0554), which may include sensors (HCPCS A9276), transmitters (HCPCS A9277) and reader/receiver (HCPCS A9278), is considered medically necessary for the management of type 1 or type 2 diabetes mellitus:

- Freestyle Libre for an individual age 18 years and older
- Dexcom G6® for an individual age 2 years and older

WHEN the individual is on EITHER of the following treatment programs:

- insulin regimen which includes long-acting (basal) insulin and rapid-acting (prandial/mealtime) insulin OR multiple daily injections of U500 insulin
- continuous subcutaneous external insulin pump

When the above criteria for a minimally invasive, therapeutic continuous glucose monitoring system are met, the following quantities for sensors (HCPCS A9276) apply:

- Freestyle Libre 10-day system: three sensors every 30 days
- Freestyle Libre 14-day system: two sensors every 28 days
- Dexcom G6: three sensors every 30 days

A minimally invasive non-therapeutic continuous glucose monitoring system (CGMS) used with a fingerstick blood glucose monitor (e.g., Guardian® REAL-Time HCPCS code A9277, A9278) is considered medically necessary for the management of type 1 or type 2 diabetes mellitus when used according to the U.S. Food and Drug Administration (FDA) approved indications and ALL of the following criteria have been met:

- completion of a diabetes self-management education program
- EITHER of the following:
  - treatment program including at least three insulin injections per day with frequent self-adjustments of insulin dose for at least three months
  - documented blood glucose self-testing an average of at least four times per day during the two months prior to initiation of an insulin pump

- **ANY** of the following while on the multiple daily injection regimen:

  - glycated hemoglobin level (HbA1c) > 7.0%
  - history of recurring hypoglycemia
  - wide fluctuations in blood glucose before mealtime
  - dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL
  - history of severe glycemic excursions

A continuous glucose monitoring system with an implantable interstitial glucose sensor (e.g., Eversense®) (CPT® codes 0446T, 0447T, 0448T) is considered experimental, investigational or unproven.

Replacement of a Continuous Glucose Monitoring System and Components

Replacement of an existing continuous glucose monitoring system or component is considered medically necessary for an individual managing type 1 or type 2 diabetes mellitus on a continuous glucose monitor when BOTH of the following criteria are met:

- documentation confirming that the monitor/component is malfunctioning, is no longer under warranty and cannot be repaired
- evidence of an evaluation by the health care provider managing the diabetes within the last six months that includes a recommendation supporting continued use of a continuous glucose monitor

Not Covered

Each of the following has not demonstrated an improvement to health outcomes and is therefore, considered not medically necessary and/or a convenience item.

- additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus
- combination devices that include a home blood glucose monitor combined with a cellular telephone or other device not specifically indicated for the management of diabetes mellitus (e.g., blood pressure monitor, cholesterol screening analyzer)
- remote glucose monitoring device (e.g., mySentry)
- hypoglycemic wristband alarm (e.g., Diabetes Sentry™)

External Insulin Pumps

ANY of the following external insulin pumps* is considered medically necessary for the management of type 1 and type 2 diabetes mellitus:

- an external insulin pump* (HCPCS code E0784) (e.g., t:slim), including a combined or integrated continuous subcutaneous insulin infusion pump and standard finger-stick blood glucose monitoring (CSII-BGM) system (e.g., Omnipod® and Personal Diabetes Manager) when used according to the U.S. Food and Drug Administration (FDA) approved indications
- a combined or integrated continuous subcutaneous insulin infusion and blood glucose monitoring system, that includes a continuous blood glucose monitor (HCPCS code E0784) with or without wireless capabilities
- a combined or integrated continuous subcutaneous insulin infusion and blood glucose monitoring system that includes a continuous blood glucose monitor with automated insulin suspension when used according to the U.S. Food and Drug Administration (FDA) approved indication (i.e., MiniMed 530G with Enlite™ Insulin Pump; 630G System, 670G System)

When ALL of the following have been met:

- completion of a diabetes self-management education program
- treatment program including at least three insulin injections per day with frequent self-adjustments of insulin dose for at least three months
- documented blood glucose self-testing an average of at least four times per day or documented use of a therapeutic factory calibrated CGM during the two months prior to initiation of an insulin pump
- **ANY** of the following while on the multiple daily injection regimen:
    - glycated hemoglobin level (HbA1c) > 7.0%
    - history of recurring hypoglycemia

- wide fluctuations in blood glucose before mealtime
- dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL
- history of severe glycemic excursions

***Note: A transdermal insulin delivery system (e.g., V-Go) does not require Physician supervision, is considered self-use and therefore, may be excluded from coverage under standard medical benefit plans. Some transdermal insulin delivery systems may be covered under a Cigna pharmacy benefit plan.**

Enhanced Features

An external insulin pump with enhanced features is considered medically necessary when the criteria for a standard external insulin pump are met and there is a documented special need, such as a hearing impairment, that requires an additional or enhanced feature for successful use of an insulin pump.

Replacement of External Insulin Pump or System Component

The replacement of an existing external insulin pump or an insulin pump system component required for the delivery of insulin is considered medically necessary for an individual with successfully managed type 1 or type 2 diabetes mellitus when BOTH of the following criteria are met:

- documentation that the pump/component is malfunctioning, no longer under warranty and cannot be repaired
- evidence of an evaluation by the health care provider managing the diabetes within the last six months that includes a recommendation supporting continued use of a replacement device

Supplies

The supplies required for the proper use of a medically necessary external insulin pump including custom-designed batteries and power supplies are considered medically necessary DME. However, off-the-shelf batteries that can also be used to power non-medical equipment are considered not medically necessary.

Not Covered

EACH of the following is considered a convenience item and not medically necessary:

- replacement of a currently functioning insulin pump for the sole purpose of receiving the most recent insulin pump technology (i.e., “upgrading” for improved technology)
- additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus

Diabetic Supplies

A needle-free insulin injection system or a jet injector is considered medically necessary when EITHER of the following criteria is met:

- The individual has needle phobia.
- The individual/caregiver is unable to use standard syringes.

Each of the following diabetic supplies is considered medically necessary under the pharmacy benefit (copayment may apply):

- alcohol wipes
- blood test strips (glucose/ketone)

- insulin pens (medical necessity criteria may apply)
- needles and syringes for insulin administration
- standard lancets
- urine test tablets/strips (glucose/ketone)

Glucose sensors for EITHER of the following minimally invasive, therapeutic continuous glucose monitoring systems (CGMS) for the management of type 1 or type 2 diabetes mellitus are considered medically necessary under the pharmacy benefit (copayment may apply):

- Freestyle Libre for an individual age 18 years and older
- Dexcom G6® for an individual age 2 years and older

WHEN the individual is on EITHER of the following treatment programs:

- insulin regimen which includes long-acting (basal) insulin and rapid-acting (prandial/mealtime) insulin OR multiple daily injections of U500 insulin
- continuous subcutaneous external insulin pump

When the above criteria for a minimally invasive, therapeutic continuous glucose monitoring system are met, the following quantities for sensors (HCPCS A9276) apply:

- Freestyle Libre 10-day system: three sensors every 30 days
- Freestyle Libre 14-day system: two sensors every 28 days
- Dexcom G6: three sensors every 30 days

A home glycated serum protein (GSP) monitor is considered experimental, investigational or unproven.

Each of the following is considered a convenience item and not medically necessary:

- home glycated hemoglobin (A1C) monitor
- hypoglycemic wristband alarm (e.g., Sleep Sentry)
- insulin infuser (e.g., i-port®)
- laser lancet

Diabetes Self-Management Education

Diabetes self-management education is considered medically necessary when ALL of the following criteria are met:

- The individual has a diagnosis of diabetes mellitus.
- The services have been prescribed by a physician.
- The services are provided by a licensed healthcare professional (e.g., registered dietician, registered nurse or other health professional) who is a certified diabetes educator (CDE).

Note: The scope of this Medical Coverage Policy is limited to diabetes self-management education and does not address coverage of medical nutrition therapy.

Overview

This Coverage Policy addresses various types of diabetic equipment and supplies, including home glucose monitors, continuous glucose monitoring systems, external insulin pumps, jet injectors and insulin pens, and diabetes self-management.

General Background

Diabetes Mellitus

Diabetes mellitus (DM) is a disease characterized by hyperglycemia resulting from abnormal insulin secretion and/or abnormal insulin action within the body. Chronic hyperglycemia, resulting from poorly controlled diabetes, may result in serious and life-threatening damage, including dysfunction and failure of the eyes, kidneys, nervous system and cardiovascular system. The presence of insulin, a hormone, is essential for the body to convert sugar, starches and other foods into energy.

There are three major types of diabetes mellitus: type 1, type 2 and gestational diabetes mellitus (GDM). Type 1 diabetes, insulin-dependent diabetes, or juvenile-onset diabetes, is an autoimmune disease in which the pancreas produces very little or no insulin due to autoimmune β-Cell destruction. Type 1 diabetes occurs in 5–10% of cases and typically occurs in patients less than age 20-30 years. Type 1 diabetics require insulin therapy for life. Type 2 diabetes is typically adult-onset diabetes and includes those individuals who are insulin resistant (i.e., the body fails to use insulin properly) due to a progressive loss of β-cell insulin secretion. Type 2 diabetics normally do not require insulin therapy and are typically controlled with diet and exercise. In some cases, oral hypoglycemic agents are indicated in the treatment of type 2 diabetics. GDM develops is typically diagnosed in the second or third trimester of pregnancy and was not clearly overt prior to gestation, GDM involves a degree of glucose intolerance and generally subsides following delivery (American Diabetes Association [ADA], 2019).

Diabetes is diagnosed and monitored by routine testing of blood glucose levels, glycosylated hemoglobin (HbA1c or A1C), plasma insulin levels and glycosuria. As a guide to adjustments in therapy (i.e., diet, exercise and medication), monitoring of blood glucose levels is a cornerstone of diabetes care.

Insulin is a naturally occurring hormone secreted by the pancreas. Individuals with diabetes may require insulin therapy because the pancreas does not produce insulin (type 1 diabetes) or the body does not use insulin properly (type 2 diabetes). Insulin is the mainstay of therapy for individuals with type 1 diabetes. Basal insulin refers to insulin that is long acting and used to keep blood sugar stable in between meals and during the night. “Bolus” refers to insulin that is fast acting and is given following a meal or to treat abnormally high blood glucose levels. There are different types of insulin depending on how quickly they work, when they peak, and how long they last. The types of insulin include rapid-acting, short-acting, intermediate-acting, long-acting, and pre-mixed.

Type of Insulins	Onset	Peak	Duration	Compounds/Brands
Rapid-acting insulin (Bolus)	10–30 minutes	30 minutes to 3 hours	3–5 hours	Glulisine (Apidra®), Lispro (Humalog®) Aspart (NovoLog®, Fiasp®; Ademelog®) Inhaled (Afrezza®)
Short-acting	30 minutes to 1 hour	1–5 hours	Up to 12 hours	Humulin Regular® Novolin Regular®
Intermediate-acting	1–4 hours	4–12 hours	12–24 hours	Humulin NPH Novolin NPH
Long-acting insulin (basal analogs)	1–2 hours	Minimal peak	Up to 42 hours	Detemir (Levemir®) Degludec (Tresiba®) Glargine (Lantus®, Toujeo®) Glargine biosimilar (Basaglar®)

Premixed insulin (intermediate-acting and short-acting insulin) is available for individuals who have trouble drawing up insulin from two separate bottles. Humulin 70/30®, Novolin 70/30®, Novolog 70/30®, Humulin 50/50®, and Humalog mix 75/25® are premixed insulins. Most insulin comes dissolved or suspended in liquids. The standard and most commonly used is U-100, which means it has 100 units of insulin per milliliter of fluid. U-500 insulin is available for patients who are extremely insulin resistant (ADA 2019; ADA, 2015). Afrezza (insulin human) is a rapid acting inhaled insulin used at the beginning of a meal. Afrezza is available in 4 unit, 8 unit and 12 unit single use cartridges (See Cigna Drug and Biologic Coverage Policy on Afrezza).

Self-management of diabetes is essential for the control of the disease and curtailing irreversible dysfunction and possible failure of multiple body systems. To assist diabetics in self-management of their care, diabetic supplies such as needles, syringes, needle-free insulin injection devices, insulin pens, test strips (i.e., glucose and ketone), lancets and alcohol wipes may be indicated. A subpopulation of diabetics may use a glucose meter, continuous glucose monitor and/or a continuous insulin infusion pump.

Home Blood Glucose Monitors

Blood glucose monitors (BGMs) measure blood glucose concentration using a reagent strip, cartridge or cuvette and a drop of capillary blood from a finger puncture. Some devices measure glucose level in the interstitial space on a continuous basis. Used at home, portable glucose monitors allow diabetics to detect and treat fluctuations in blood glucose levels. The normal fasting blood glucose concentration ranges from 70–100 milligrams (mg) per deciliter (dL) in blood serum or plasma, although capillary blood glucose concentrations may be higher (e.g., by 10–15%). A person with diabetes can adjust insulin dosage, food intake, and exercise in response to the monitor's readings of the blood glucose level to achieve normoglycemia. Frequent blood glucose monitoring to maintain normoglycemia facilitates treatment designed to reduce the incidence and severity of diabetes-related microvascular and neurological complications.

Standard Fingerstick Home Blood Glucose Monitor
The American Diabetes Association (ADA) recommends fingerstick self-monitoring of blood glucose (SMBG) as an integral component of diabetes therapy for type 1 and type 2 diabetics, as well as diabetes during pregnancy (maternal diabetes) or diabetes that develops during pregnancy (i.e., gestational diabetes). ADA stresses that the patient/caregiver should receive instructions in, and routine follow-up of, SMBG technique and their capability to use the data to adjust therapy. The ADA reports that clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved.

The ADA's 2019 recommendations for home blood glucose testing include:

- Most patients using intensive regimens (multiple-dose insulin or insulin pump therapy) should assess glucose levels using self-monitoring of blood glucose (SMBG) (or continuous glucose monitoring) prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.
- When prescribed as part of a broader educational program SMBG may help to guide treatment decisions and/or self-management for patients using less frequent insulin injections.
- When prescribing SMBG, ensure that patient is receive ongoing instruction and regular evaluation of technique, results, and their ability to use SMBG data to adjust therapy. Similarly, continuous glucose monitoring use requires robust and ongoing diabetes education, training, and support.

Features that may be considered when purchasing a home glucose monitor include: analytical ranges; reproducibility of test results; performance reliability; ease of use; size of displays and buttons; safety features; memory and data management capabilities; warnings and alarms; type of batteries needed; and durability.

U.S. Food and Drug Administration (FDA): The standard glucose monitor and test strips are approved under the Class II, 510(k) process for the purpose of providing quantitative measurement of glucose in whole blood by people with diabetes at home. Examples of home blood glucose meters approved by the FDA include: Accu-Chek® (Roche Diagnostics, Indianapolis, IN), Freestyle® (Therasense, Inc., Alameda, CA), Ascensia® (Bayer HealthCare, Mishawaka, IN), CONTOUR® NEXT ONE Blood Glucose Meter (Ascensia Diabetes Care, Mishawake, IN) and One Touch® (LifeScan, Inc., Milpitas, CA). The Sidekick blood glucose test system (Home Diagnostics, Inc., Fort Lauderdale, FLA) is a disposable system in which the meter is attached to the cap of the vial of strips. Being disposable, calibration of the meter is not required. Several new 2018 devices were FDA approved as substantially equivalent to existing devices. These devices include: Accu-Chek Guide Me Blood

Glucose Monitoring System (Roche Diabetes Care, Indianapolis, IN); POPS! One Blood Glucose Monitoring System (TaiDoc Technology Corporation, New Taipei City, TW); and Rightest Blood Glucose Monitoring System Wiz and Wiz Plus (Dynamic Biotech Inc., San Juan Capistrano, CA). The Wiz and Wiz Plus are identical with the exception that the Wiz Plus has a Bluetooth function which allows for wireless information transfer (FDA, 2018).

Some of the more recently approved glucose meters have the ability to transmit data from the glucose meter to an on-line account. An example is the Genesis Health Technologies (GHT) Blood Glucose Monitoring system, model TD-4123 (TaiDoc Technology Corp., New Taipei City, Taiwan), originally FDA 510(k) approved in 2012. The Genesis Health Record System (GHRS), an optional accessory, is an internet browser-based software system that receives test results from the glucose meter (Genesis BGM) by secure cellular transmission over the Verizon wireless network and stores the results in a secured database. After the glucose reading is measured, the cellular transmission technology automatically uploads the tests results to the patient's account on the Verizon cellular network. Patients and physicians can access the stored data from a computer. The data management system is 510(k) approved for use by adult diabetic patients in the home and healthcare professionals in the professional setting (FDA, 2013; FDA, 2012).

Literature Review: As recommended by the ADA, the use of SMBG is an established, primary technique available for diabetic patients to assess blood glucose levels. The evidence in the published peer-reviewed scientific literature including meta-analysis, systematic reviews, randomized controlled trials and case series reported statistically significant decreases in hemoglobin A1c (HbA1c) in SMBG subjects, increased regularity of medication usage, improved glucose control and better metabolic control in type 1 and type 2, insulin and non-insulin treated diabetics (Schutt, et al., 2006; Sarol, et al., 2005; Welschen, et al., 2005; Soumerai, et al., 2004).

Enhanced Feature Glucose Monitors
Audio monitors are available for the patient who has severe visual impairment. The monitor gives instructions and results verbally, allowing the patient to use the equipment without assistance. Monitors are also available with large readouts for those with impaired vision. BGMs may have various other features, such as speaking in Spanish and data management systems. The Prodigy Voice™ Glucose Meter (Diagnostic Devices, Inc., Deerfield, IL) is an example of an FDA-approved audio blood glucose monitor.

Home Continuous Glucose Self-Monitoring (CGM)
A proposed alternative to intermittent SMBG is continuous glucose monitoring (CGM). CGM devices provide ongoing, real-time monitoring and recording of blood glucose levels by continuous measurement of interstitial fluid which generally lags from three to 20 minutes behind finger-stick values. There are three primary types of CGM systems: short-term, non-therapeutic and therapeutic. Short-term CGM systems can be used by a healthcare provider for up to 14 days for diagnostic purposes. Non-therapeutic and therapeutic CGMs are used on an ongoing basis by a subgroup of diabetics who are on an intensive insulin treatment plan. Non-therapeutic CGMs must be used with a fingerstick blood glucose monitoring device. Therapeutic CGMs are a standalone device that can be used to make treatment decisions without adjunctive fingerstick monitoring.

Short-term CGM may be used by the treating physicians as a one-time evaluation tool for up to fourteen days for type 1 and type 2 insulin-treated individuals who are experiencing hypo- or hyperglycemic episodes unresponsive to adjustments in therapy (e.g., insulin administration and nutrition). CGM may also be used to detect asymptomatic nocturnal hypoglycemia and for lowering A1c levels without risking severe hypoglycemia The recording can identify fluctuations in blood glucose levels that were not detected by intermittent fingersticks. This data allows adjustments to be made in the therapeutic regimen (e.g., oral medication, insulin therapy, diet, exercise) to minimize glucose excursion. Repeat short-term assessments may be needed periodically until the individual stabilizes and achieves ideal treatment targets (Inzucchi and Sherwin, 2007; Behrman, 2004).).

Non-therapeutic CGM systems are used with finger-stick blood glucose monitoring and should never be used alone. The continuous glucose monitoring system (CGMS) consists of a sensor, transmitter and receiver. Some monitors provide real-time information, while others require that data be downloaded and reviewed retrospectively. Depending on the device, a sensor may be worn for 3–7 days before it must be changed. CGM may be used on a long-term basis for the treatment of a subtype of type 1 or type 2 diabetics. The Medtronic Guardian REAL-time CGMS is an example of the non-therapeutic CGM.

A new class of CGM systems, called therapeutic CGMs, has been developed as a proposed replacement for the current non-therapeutic CGMs that must be used as an adjunct to finger-stick glucose monitoring. Therapeutic CGMS are defined as a CGM system approved by the US Food and Drug Administration (FDA) to replace other blood glucose monitoring testing and to be used to make diabetes treatment decisions without adjunctive finger-sticks. The Abbott FreeStyle Libre (Abbott Diabetes Care Inc., Alameda, CA) and the Dexcom G5 and G6 are examples of FDA approved therapeutic CGMs.

The FreeStyle Libre therapeutic CGM is a sensor-based continuous glucose monitoring system that uses an ambulatory glucose profile (AGP) to assess glycemic levels on a 24-hour basis through a minimally invasive method called flash glucose monitoring. Unlike the FreeStyle Libre Pro used for a short period of time by the healthcare professional, the FreeStyle Libre Flash is used by the patient for continuous glucose monitoring. The System includes a Sensor kit, Reader Kit and software. The Sensor kit includes the sensor and the sensor applicator. The glucose sensor is worn under the skin and connected to a plastic patch worn on the back of the upper arm for up to 10 days. About one hour after insertion, the sensor begins reading glucose levels and stores data every fifteen minutes, trending the information. The Reader is used to obtain glucose readings from the Sensor. Data are transferred by radiofrequency identification to the reader when it is brought into close proximity to the sensor. The Reader displays the current sensor glucose level, a glucose trend arrow, and glucose readings over the preceding eight hours at fifteen minute intervals. Scanning can be done as often as is needed for current glucose concentration. The Reader can store up to 90 days of glucose history data and has a built-in meter that can be used to test blood glucose and blood ketone levels. Notes can be entered into the Reader by the user. The data in the reader memory can be uploaded using the device software to generate summary glucose reports (including an ambulatory glucose profile). The Libre is proposed for use instead of fingerstick glucose measurements except when the user is hypoglycemic, experiencing rapid changes in glucose readings and/or when symptoms do not match the Libre's readings. There are no alarms on the system and it is calibrated at the point of manufacture (i.e., factory-calibrated) and does not require or accept any user-entered calibration (Abbott Laboratories, 2018; CMS 2017; Haak, et al., 2017; Bolinder, et al., 2016; Edge, et al., 2016; Bailey, et al., 2015; Karla and Gupta, 2015).

The Dexcom G5 is another example of a therapeutic CGM and was also designed to replace fingerstick blood glucose testing. The G5 could be used to make treatment decisions in diabetics age ≥ 2 years. The G5 has subsequently been replaced with the Dexcom G6. The Dexcom G6 is different from the Dexcom G5 because it is an integrated device to be used alone or with any compatible devices, is factory calibrated and does not require users to calibrate the sensor with fingerstick blood glucose measurements. The G6 has an updated sensor probe that minimizes interference with acetaminophen. Users are informed by Dexcom that if the glucose alerts and readings from the G6 do not match symptoms or expectations, to perform a fingerstick and use a blood glucose meter to make diabetes treatment decisions (FDA, 2018; Dexcom, 2018).

U.S. Food and Drug Administration (FDA): U.S. Food and Drug Administration (FDA): Some continuous glucose monitors provide a sensor that records data for a limited period of time and are intended for occasional use by the health care profession rather than everyday use by the patient. The Medtronic's iPro2™ Professional CGM (Medtronic MiniMed, Inc., Northridge, CA) and the Freestyle Libre Pro Flash Glucose Monitoring System (Abbott Diabetes Care, Inc., Alameda, CA) are examples of CGM systems for professional use only. The Medtronic iPro2 system received FDA approval for use with the Elite sensor which records data for up to six days (FDA, 2016). The Freestyle LibrePro is indicated for use in persons age 18 years and older and records data for up to 14 days. The data in the FreeStyle LibrePro cannot be viewed by the patient.

Non-therapeutic CGMS are used only as an adjunct to SMBG and should never replace or be used instead of SMBG. Examples of FDA approved adjunctive CGMs include the DexCom™ G4 Platinum Continuous Glucose Monitoring System (DexCom, Inc., San Diego, CA), DexCom G4 Platinum (Pediatric) Continuous Glucose Monitoring System (ages 2–7 years), and the Medtronic Guardian® REAL-Time Continuous Glucose Monitoring System. These systems provide data for up to five to seven days.

The Freestyle Libre continuous glucose monitoring system (Abbott Diabetes Care Inc., Alameda, CA) and the Dexcom G6 (Dexcom Inc., San Diego, CA) are examples of therapeutic monitoring systems that do not require adjunctive fingersticks. The Freestyle Libre continuous glucose monitoring system is FDA PMA approved "for the management of diabetes in persons age 18 years and older. It is designed to replace blood glucose testing for

diabetes treatment decisions" (FDA, 2017). It is a sensor-based continuous glucose monitoring system that uses an ambulatory glucose profile (AGP) that assesses glycemic levels on a 24-hour basis through a minimally invasive method called flash glucose monitoring. This device is factory-calibrated and is never calibrated by the patient. The first FDA approved device includes a sensor that can be worn for up to 10 days. The most recent Freestyle Libre system has a 14-day sensor.

The Dexcom G6 was FDA approved for marketing on March 27, 2018 for determining blood glucose levels in diabetics age two years and older. The G6 is the first type of continuous glucose monitoring (CGM) system permitted by the FDA to be used as part of an integrated system with other compatible medical devices and electronic interfaces including automated insulin dosing systems, insulin pumps, blood glucose meters or other electronic devices used for diabetes management. With approval of the G6, the FDA reduced the regulatory burden of integrated CGMs and classified them as moderate risk Class II devices with special controls. The G6 has three key parts: the applicator with built-in sensor, the transmitter that sends the glucose information from the sensor to the display device and the display device (receiver and/or smart device).

Literature Review – Non-therapeutic CGM used in conjunction with a standard home blood glucose monitor: The evidence in the published peer-reviewed literature supports the use of a CGM when used in conjunction with SMBG to aid in the management of insulin dependent diabetics who are difficult to control and not achieving treatment targets. Studies including type 1 and type 2 adult and child diabetics have been in the form of systematic reviews and meta-analysis, randomized controlled trials and case series (Beck, et al., 2017a; Beck, et al., 2017b; Lind, et al., 2017, Poolsup, et al., 2013; Langendam, et al., 2012; Battelino, et al, 2011; Hoeks, et al., 2011; Gandhi, et al., 2011; Chase et al., 2010; Juvenile Diabetes Research Foundation [JDRF], 2009a; JDRF, 2009b; Newman, et al., 2009; Rodbard, et al., 2009; JDRF, 2008; Mazze, et al., 2008; Weinzimer, et al., 2008b; Chetty, et al., 2008; Golicki, et al., 2008; Yoo, et al., 2008; Weber, et al., 2007; Zisser, et al., 2007; Wilson, et al., 2007; Bailey, et al., 2007; Diabetes Research in Children Network [DirecNet] Study Group, 2007; Garg, et al., 2007; Deiss, et al., 2006a; Garg, et al., 2006; Lagarde, et al., 2006; Chico, et al., 2003; Ludvigsson, et al., 2003; Chase, et al., 2001).

Literature Review – Therapeutic CGM: Randomized controlled trials and case series have reported a significant reduction in mean time spent in hypoglycemia, nocturnal hypoglycemia, daytime hypoglycemia, reduction in the number of hypoglycemic events, and/or improvement in perceived frequency of hyperglycemia and patient satisfaction when using a therapeutic CGM. Some studies also reported an improvement in A1C levels (Boscari, et al., 2018a; Boscari, et al., 2018b; Aleppo, et al., 2017; Bolinder, et al., 2016; Haak, et al., 2017a; Haak, et al., 2017b).

Professional Societies/Organizations: The ADA's 2019 clinical practice recommendations for the treatment and management of diabetes mellitus states that continuous glucose monitoring (CGM) has an important role in assessing the effectiveness and safety of treatment in subgroups of patients with type 1 diabetes and in selected patients with type 2 diabetes. ADA recommendations for CGM include:

- "Sensor-augmented pump therapy may be considered for children, adolescents, and adults to improve glycemic control without an increase in hypoglycemia or severe hypoglycemia. Benefits correlate with adherence to ongoing use of the device".
- "When prescribing continuous glucose monitoring, robust diabetes education, training, and support are required for optimal continuous glucose monitor implementation and ongoing use".
- "Real-time continuous glucose monitoring use in youth: Real-time continuous glucose monitoring should be considered in children and adolescents with type 1 diabetes, whether using multiple daily injections or continuous subcutaneous insulin infusion, as an additional tool to help improve glucose control and reduce the risk of hypoglycemia. Benefits of continuous glucose monitoring correlate with adherence to ongoing use of the device".
- Real-time continuous glucose monitoring use in adults:
  - "When used properly, real-time continuous glucose monitoring in conjunction with intensive insulin regimens is a useful tool to lower A1c in adults with type 1 diabetes who are not meeting glycemic targets."
  - "Real-time continuous glucose monitoring may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes."

    - "Real-time continuous glucose monitoring should be used as close to daily as possible for maximal benefit."
    - "Real-time continuous glucose monitoring may be used effectively to improve A1C levels and neonatal outcomes in pregnant women with type 1 diabetes."
    - "Sensor-augmented pump therapy with automatic low-glucose suspend may be considered for adults with type 1 diabetes at high risk of hypoglycemia to prevent episodes of hypoglycemia and reduce their severity."
- "Intermittently scanned continuous glucose monitor use may be considered as a substitute for self-monitoring of blood glucose in adults with diabetes requiring frequent glucose testing".

Regarding continuous glucose monitoring (CGM) in adults, the 2016 Endocrine Society guidelines for CGM include the following:

- Recommend real-time continuous glucose monitoring (RT-CGM) devices for adult type 1 diabetics who have A1C levels above target and are willing and able to use the devices on a nearly daily basis (strong recommendation; high level of evidence).
- Recommend RT-CGM for well-controlled adult type 1 diabetics who are willing and able to use these devices on a nearly daily basis (strong recommendation; high level of evidence).
- Suggest short-term real-time continuous glucose monitoring (RT-CGM) use in adult type 2 diabetics not on prandial insulin who have A1C levels ≥ 7% and are willing and able to use the device (weak recommendation; weak level of evidence). Although the number of studies is limited, results showed a significant improvement in A1C compared to baseline with CGM.

In a 2017 Choosing Wisely statement, the Society of General Internal Medicine did not recommend daily home finger glucose testing in Type 2 diabetics who are not on hypoglycemic medications or insulin. According to the Society, there is no benefit to SMBG in this subpopulation and potential negative clinical impact is possible. SMBG should be reserved for use during titration of medication doses or periods of change in diet and exercise routines. The Endocrine Society and American Association of Clinical Endocrinologists (2017) recommended avoiding routine SMBG in adults with stable type 2 diabetes on hypoglycemic agents when target control is achieved. Exceptions include acute illness, change in medication, significant change in weight, A1c drifts off course and any other time when SMBG is needed to maintain targets and/or needed for learning.

In the 2016 consensus statement on outpatient glucose monitoring, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) made the following recommendations for CGM in diabetics:

- Type I adults: CGM is recommended, particularly for patients with history of severe hypoglycemia, hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM users must know basics of sensor insertion, calibration, and real-time data interpretation.
- Type 1 pediatric patients: Recommendation same as for type 1 adults. However, the authors noted that prevalence and persistent use of CGM is lower in children and more in-depth training and follow up is recommended to ensure successful use of this technology.
- Type 2 diabetics using insulin/ sulfonylureas, glinides: Data on CGM for this population are limited and trials are ongoing.
- Type 2 diabetics with low risk of hypoglycemia: No recommendation was made.
- Gestational diabetics: Based on current data, the benefit of CGM in pregnant women with preexisting diabetes is unclear. CGM can be used during pregnancy as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing. CGM can also supplement blood glucose monitoring, especially for monitoring nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.

In their consensus statement on glycemic control for type 2 diabetics, the AACE and ACE (Rodbard, et al., 2009) stated that CGM may be considered for the management of type 2 diabetics who are receiving insulin and the disease is otherwise difficult to control. CGM may help to "educate the patient regarding the glycemic effects of various foods, help the patient titrate insulin, and provide warnings when the patient is experiencing hyperglycemia or hypoglycemia.

Continuous Glucose Monitoring System with an Implantable Interstitial Glucose Sensor (e.g., Eversense®)
The Eversense (Senseonics™ Inc., Germantown, MD) is a continuous glucose monitoring (CGM) system with an implantable sensor. The system includes 1) the sensor, which is inserted subcutaneously by a health care provider, 2) a removable smart transmitter worn over the sensor, and 3) a mobile medical application (MMA) which displays the glucose readings. A 24-hour warm-up phase is required prior to initial calibration and calibration is required twice per day.

The sensor is 18.3 millimeters (mm) long and 3.5 mm in diameter. It has a silicone collar impregnated with 1.75 mg of dexamethasone acetate (DXA) (an anti-inflammatory steroid drug) that elutes an average of 3 micrograms (µg) per day over the life of the sensor to attenuate the body's local inflammatory response and prolong the sensor life. The sensor is inserted, by the health care provider, under the skin in the upper arm using local anesthesia. An approximately 5 mm incision is made at the insertion location to create a subcutaneous pocket approximately 3-5 mm below the skin surface. A suture or adhesive skin closure (e.g., Steri-Strip™) is used to close the incision. The device can be worn for up to 90 days and is activated to measure the glucose level every five minutes when it receives radio frequency power from the transmitter. The removable smart transmitter is worn externally over the sensor and powers the sensor. The transmitter calculates the glucose levels and wirelessly sends the data via Bluetooth to the mobile device app. At the end of the 90-day wear period, the sensor is removed by the healthcare provider (Christiansen, et al., 2018; Senseonics, 2017).

The smart transmitter provides on-body vibration alerts (e.g., low blood glucose, high blood glucose) and the mobile device sends alerts based on the glucose settings that the user chooses. It has a rechargeable battery, requires recharging every other day for about 15 minutes and is reusable for up to one year. The manufacturer notes that if the vibration is not felt by the user and the mobile device is not available, then the alerts will not be effective. Fingerstick blood glucose levels are indicated to validate hyperglycemia, hypoglycemia and to make treatment decisions. The Eversense App is a software application that runs on a mobile device (e.g., smartphone or tablet) and displays glucose data in a variety of ways. It also provides the user with an option to upload the data to the Senseonics Data Management System (DMS) for historic viewing and storing of glucose data (Senseonics, 2017).

U.S. Food and Drug Administration (FDA): FDA PMA notice of approval was issued June 21, 2018 for the Eversense® continuous glucose monitoring system (Senseonics™ Inc., Germantown, MD). Eversense is approved for "measuring glucose levels in adults (age 18 and older) with diabetes for up to 90 days". The system is intended to: provide real-time glucose readings, glucose trend information, and alerts for the detection and prediction of episodes of low and high blood glucose levels. Historical data from the system can be interpreted to aid in providing therapy adjustments on patterns seen over time. The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices. During sensor removal procedures in the earlier clinical study (PRECISE) there were several instances where the end cap of the sensor was broken off or missing after sensor removal. In some cases, the broken end caps were located, and in other cases the end caps were not located. A root-cause analysis into this failure concluded that the cause was most likely physicians grasping the end cap with the forceps during removal, instead of grabbing the sensor body. To reduce the potential for this failure, Senseonics redesigned the sensor end cap to be flush with the end of the sensor and changes were also made to the algorithm used in the FDA preapproval study (FDA, 2018; FDA, 2017).

Literature Review: There is insufficient evidence in the published, peer-reviewed published literature to support the safety and effectiveness of the Eversense CGM. Studies have primarily been in the form of case series with small patient populations and short-term follow-ups (Christiansen, et al., 2018; Kropff, et al., 2017; DeHennis, et al., 2015; Wang et al., 2015; Mortellaro and DeHennis, 2014).

Christiansen et al. (2018) conducted a non-randomized, blinded, prospective, single-arm, eight-center study (PREISE II) (n=90) to assess the safety and accuracy of the Eversense CGM system including the updated sensor and algorithm. Subjects were age ≥ 18 years with a clinically confirmed diagnosis of type 1 (n=61) or type 2 (n=29) diabetes mellitus for ≥ 1 year and an HbA1c of 7.6% ± 1.2. Exclusion criteria included subjects with a history of severe hypoglycemia or diabetic ketoacidosis, requiring an emergency room visit or hospitalization

during the previous six months; a condition that might interfere with sensor placement, operation, or removal; symptomatic coronary artery disease, unstable angina, myocardial infarction or stroke in the six months prior to the study; uncontrolled hypertension; hematocrit < 30% or > 50%; and lactation, pregnancy or intent to become pregnant during the study. The study included a screening visit, sensor insertion visit, four accuracy assessment visits and a postsensor removal follow-up visit. With the exception of 15 subjects, a single sensor was inserted. Subjects and investigators were blinded to the CGM values and all glucose-related alerts. The accuracy of the system was evaluated in the clinic following insertion at days 1, 30, 60 and 90 by comparing Sensor glucose values to plasma glucose values drawn every 5–15 minutes for 4.5–12.5 hours. Individuals on insulin and without gastroparesis underwent hyperglycemia and hypoglycemia challenges on days 30, 60, and 90. The intent of the challenges was to safely manipulate the participant's blood glucose level using fasting and insulin dosing or meals of known carbohydrate content so that sensor performance could be evaluated over a wider range than might otherwise not be observed. After the accuracy assessment at the day 90 clinic visit, venous blood samples were obtained for HbA1c and dexamethasone levels, and the sensors were removed. Ten days after removal (day 100), participants returned for follow-up and the insertion site was inspected. The primary outcome measure was the mean absolute relative difference (MARD) for paired sensor and venous reference glucose measurements, using the Yellow Springs Instrument (YSI), collected during the clinic visits across a glucose range of 40–400 mg/dL. The primary effectiveness endpoint was evaluated against a prespecified 20% performance goal. The primary safety endpoint was the incidence of device-related or sensor insertion/removal procedure-related serious adverse events. Additional endpoints included Clarke Error Grid analysis and sensor longevity. Subjects performed calibration twice a day. All diabetes care decisions were based on blood glucose meter values and clinical standards of care. The first participant at each clinical site (n = 8) was considered a training participant. Eighty-two participants (91%) completed the study with day 90 data collection. Five participants experienced a sensor replacement alert before day 90, which ended glucose data collection. The primary effectiveness endpoint of MARD over the glucose range of 40–400 mg/dL was 8.8% for the prespecified analysis population and 16,653 matched glucose measurements. This percentage was significantly lower than the prespecified 20% performance goal for accuracy ($p<0.0001$). Analysis showed that 93.3% of CGM values were within –20 mg/dL or 20% of YSI reference values (20/20%) over the total YSI glucose range of 40–400 mg/dL. Post hoc analysis of all 90 participants (18,261 matched glucose measurements) showed a MARD of 8.9% and a total of 93% of CGM values within 20/20% of reference values. Clarke Error Grid analysis showed 99.3% of samples in clinically acceptable error zones A (92.8%) [values within 20% of reference sensor] and B (6.5%) [points that are outside of 20% but would not lead to inappropriate treatment]. A subset of 15 subjects at one clinical site had two Sensors inserted to test the impact of intrapatient variability and the effect of compression of the system that would occur during sleep. There was no significant difference in the percentage of CGM readings within 20/20% of the reference values for readings taken during compression (92.3%) or no compression (93.4%) conditions ($p=0.88$). No significant differences were seen in values with exercise and nonexercise ($p=0.35$). A total of 91% of sensors were functional through day 90. Hypo- (93%) and hyperglycemic (96%) events were identified with YSE. When a hypoglycemic or hyperglycemic event was detected by the device, the system determination was in agreement with YSI in 86% and 94% of cases, respectively. Median device wear time of the transmitter was 23.4 hours/day with no reported skin reactions to the adhesive patch. A 0.5% point reduction in HbA1c from a baseline of 7.6% was observed at 90 days postinsertion ($p<0.0001$). The plasma dexamethasone levels were undetectable (<2 ng/mL) for all participants before insertion and at day 90. Adverse events included: nine cases of bruising, erythema, or pain/discomfort; one syncopal episode after insertion; and one episode of paresthesia or tingling. There were two events in which it could not be assured that a small element of the sensor encasement was removed and one event of an inability to remove the sensor on first attempt. Author-noted limitations of the study were the inability to assess the full utility of the device by the users due to the blinding of subjects to the real-time CGM display and device alerts; under-representation of non-Caucasian subjects; and the short-term follow-up. Long-term studies are needed to validate the safety profile following multiple sensor placements and removals and to determine if subjects choose to continue use of the implant every ninety days.

A Hayes Technology Brief (2018) evaluating the safety and efficacy of the Eversense continuous glucose monitor concluded that the "very-low-quality" of evidence suggested that the Eversense is highly correlated with and moderately accurate in the measurement of glucose levels compared with venous or finger stick glucose reference values. However, substantial uncertainty remains pertaining to the accuracy of the device across a range of glucose values. In addition, the evidence is limited by the "fair- to poor-quality" of the studies, small number of patients, inconsistencies and variability in the clinical validity outcomes, and insufficient evidence to

evaluate the clinical utility of the Eversense. Five studies met the inclusion criteria and evaluated the clinical validity, clinical utility, and safety of the Eversense CGM for the management of type 1 and type 2 diabetes mellitus. The effect of the long-term use of the Eversense sensors has not been evaluated. Therefore, it is unknown whether repeated implantation and removal of the sensor would cause scar tissue formation or other complications that might alter the sensor accuracy. Overall, due to the very-low quality of evidence conclusions could not be made regarding the clinical utility of the Eversense.

Continuous Glucose Monitoring in Pregnancy
Management of diabetes during pregnancy (maternal diabetes) is essential for healthy outcomes for the mother and the infant. An individual with preexisting type 1 or type 2 diabetes mellitus may become pregnant or a woman can develop diabetes during the pregnancy (i.e., gestational diabetes). Gestational diabetes typically subsides following delivery. Uncontrolled diabetes during pregnancy can be associated with miscarriage, pre-eclampsia, preterm labor, stillbirth, congenital malformations and other complications. Both 72-hour and long-term CGM have been proposed for use during pregnancy (Kitzmiller, et al., 2008; NICE, 2015).

Literature Review: Feig et al. (2017) conducted a multicenter, open-label randomized controlled trial (n=325) to evaluate the effectiveness of CGM on maternal glucose control and obstetrical and neonatal health outcomes when used before pregnancy and from early pregnancy. The study included two parallel trials, a pregnancy trial with 215 subjects (n=108 CGM; n=117 controls without CGM) and a planning pregnancy trial with 110 subjects (n=53 CGM; n=57 controls). Subjects were included if they were age 18-40 years, type 1 diabetics ≥ 12 months, receiving intensive insulin therapy via multiple daily injections or insulin pump, ≤ 13 weeks and 6 days' gestation, with an HBA1C 6.5%-10.0% or planning pregnancy with an HBA1C 7.0%-10.0%. Regular CGM users or medical conditions requiring hospitalization that could prevent a subject from completing the trial were excluded. The primary outcome in the pregnancy group was the change in HBA1C from randomization to 34 weeks gestation and the change in HBA1C from randomization to 24 weeks or conception in the planning pregnancy group. Secondary outcomes for all subjects were percentage of time spent in, above, and below the recommended glucose control target range (3·5–7·8 mmol/L); area under the curve for glucose levels; episodes of hypoglycemia; and glucose variability measures derived from CGM measures. Secondary outcomes for the pregnancy group included: gestational weight gain, gestational hypertension, preeclampsia, mode of delivery, length of hospital stay, insulin dose, and questionnaires relating to fear of hypoglycemia, coping with diabetes, quality of life, and satisfaction with monitoring device. Neonatal secondary outcomes included: preterm delivery, hypoglycemia requiring intravenous dextrose, intensive care unit admission requiring a duration of at least 24 hours, cord blood gas pH, total length of hospital stay, birthweight, and macrosomia (birthweight ≥4 kg). Pregnancy group follow-up visits occurred at 8, 12, 16, 20, 24, 28, 32, 34, and 36 weeks gestation. Planning pregnancy group follow-ups occurred at 4, 8, 12, 16, 20, and 24 weeks after randomization. Women who conceived during the trial continued in their same randomized group and followed the pregnancy study visit schedule. Outcomes included the following:

- Significantly more pregnant CGM user than controls (p=0.0171) completed scheduled follow-up visits due to sensor issues (p<0.001) and sensor-related diabetes management issues (p<0.001).
- There was no difference in number of visits completed between the planning pregnancy groups.
- Frequency of CGM use was comparable in the pregnancy and pregnancy planning groups with highest sensor use in later gestation and earlier time (median 6.7 days) in pregnancy planning women.
- There was a significant between-group difference in improvement in HBA1C from baseline to 34 weeks' gestation, favoring CGM use (p=0.0207). There was no significant difference in planning pregnancy groups.
- Pregnant CGM users spent significantly more time in target (p=0.0034) and less time hyperglycemic (p=0·0279) compared to pregnant controls.
- There was no significant difference in the pregnancy group vs. the control group in severe hypoglycemic episodes and time spent hypoglycemic (p=0.10).
- Neonatal health outcomes were significantly improved, with lower incidence of large for gestational age (p=0.0210), fewer neonatal intensive care admissions lasting more than 24 h (p=0.0157), fewer incidences of hypoglycemia (p=0.0250), and 1-day shorter length of hospital stay (p=0.0091).
- There was no apparent reported benefit of CGM in women planning pregnancy.

The most common adverse events were skin reactions occurring in 49/103 CGM subjects and 8/104 control subjects in the pregnancy groups and in 23/52 CGM subjects and 5/57 controls planning pregnancy. The most

common serious adverse events were nausea and vomiting in four pregnancy subjects and three planning pregnancy subjects. Author-noted limitations included: the planning pregnancy trial did not have sufficient power to detect the magnitude of differences that were significant in the pregnancy trial; HBA1C data and CGM data sets were missing due to dropouts, missing or lost samples, unavailable participants, pregnancy losses or delivery before 34 weeks; potential differences between the CGM data collected using real-time sensors in the CGM group and masked sensors in the control group; and there were no data on the frequency of capillary glucose monitoring and its relationship to glucose control or on the use of insulin suspension. The authors noted that this was the first study to indicate potential for improvements in non-glycemic outcomes for CGM users.

Wei et al. (2016) conducted a prospective, observational, open-label, randomized controlled trial (n=106) to investigate the effects of glucose monitoring (CGM) on maternal and neonatal outcomes. Subjects were randomized to antenatal care plus CGM vs. antenatal care plus fingerstick self-monitoring blood glucose (SMBG) following a gestational diabetes mellitus (GDM) diagnosis. The CGM group was subdivided into early (24-28 weeks) and late (28-36 weeks). Subjects were included who were 24-28 weeks' gestation with a singleton pregnancy. Exclusion criteria were: diagnoses of diabetes mellitus, previous treatment for GDM, presence of infection or other severe metabolic, endocrine, medical or psychological comorbidities. Obstetrical and neonatal outcomes included: caesarean section, birthweight, standard deviation of weight for gestational weeks and Apgar score at five minutes. HBA1C and glycemic control were also recorded. Follow-ups occurred every 2-4 weeks until 28 gestational weeks, every two weeks until 32 gestational weeks and weekly thereafter. Four subjects in the CGM group and seven in the SMBG group were lost to follow-up. Thus, outcomes were reported for 51 CGM users and 55 SMBG subjects. Outcomes included the following:

- Caesarean delivery rate was greater in the SMBG group than in the CGMS group but was not statistically significant (p=0.37).
- No births occurred before 35th gestational week.
- No perinatal deaths occurred.
- There was no significant difference in Apgar scores at five minutes, macrosomia, neonatal hypoglycemia, extreme large-for-gestational age (LGA) (≥ 97th percentile) and small-for-gestational age (SGA) (≤ 10th percentile).
- Fewer LGAs were born in CGM group but the difference was not statistically significant (p=0.071).
- HbA1C levels were lower in the CGMS group but were not significantly different throughout the last two trimesters.
- Similar reductions in HbA1C levels were observed in the CGMS and SMBG groups (p=0.089) in later pregnancy (32 to 36 weeks gestation).
- Mean amplitude of glucose excursions (MAGE) was significantly higher in CGM group in the third trimester than among those wearing the CGMS in the second trimester (p=0.046).
- Significantly more insulin (p=0.02) and more regular insulin (p=0.027) were used in CGM group.
- Significantly more NPH insulin was used in the SMBG group (p=0.066).
- By the last visit there was no significant difference in required insulin doses between the groups (p=0.45).
- CGM users gained significantly less weight (p=0.004), had a lower proportion of subjects who experienced excess gestational weight gain and more subjects with appropriate weight gain.
- Significantly fewer CGM users gained an inadequate amount of gestational weight (p=0.039).
- Subjects who used CGM in the early stage gained significantly less weight than SMBG users (p=0.003).

There were no significant differences in adverse events or glycemic control between the two groups. The CGM group experienced mild erythema, itching, and inflammation. Author-noted limitations of the study included: the small patient population and the few perinatal complications possibly limited the generation of statistically significant results; education management was not blinded possibly creating the Hawthorne effect (altering behavior); some clinical data (e.g., sensor data on instrument failure, instrument error, pain, and discomfort) were unavailable and follow-up data at six weeks postpartum were deficient. The study showed that CGM, especially when initiated early, plus professional antenatal care helped to reduce maternal weight gain and glycemic variability. Additional studies are needed to assess the effectiveness of CGM on maternal weight gain in reducing perinatal problems, especially fetal macrosomia.

Raman et al. (2017) conducted a Cochrane systematic review to compare various glucose monitoring methods for women with gestational diabetes and the monitoring effects on maternal and fetal, neonatal, child and adult

outcomes. Two randomized controlled trials that investigated CGM vs. self-monitoring of blood glucose reported no significant difference in caesarean section rates (n=179), large-for gestational age infants (n=106) and neonatal hypoglycemia (n=179). There were no perinatal deaths (n=179). The evidence was considered of very low quality.

Secher et al. (2013) conducted a randomized controlled trial including 123 type 1 and 31 type 2 women with pregestational diabetes. Patients were randomized to CGM (n=79) for six days at 8, 12, 21, 27, and 33 weeks in addition to routine care or routine care only (n=75). Routine care included self-monitored blood glucose seven times per day. Twenty-seven type 1 diabetics were on insulin pump therapy, most initiated prior to pregnancy. Forty-nine women used real-time CGM per protocol. At 33 weeks, there was no significant difference in HbA1c (p=0.64), episodes of severe hypoglycemia (p=0.91) and prevalence of large-for-gestational-age infants (p=0.19) between the groups. Other perinatal outcomes were also comparable. Intermittent use of CGM did not improve outcomes in this patient population. A limitation of the study is the low number of CGM users who followed protocol.

Murphy et al. (2008) conducted a randomized controlled trial to compare the outcomes of type 1 (n=46) and type 2 (n=25) diabetic women, age range 16–45 years, who used CGMS (n=38) compared to SMBG (n=33) during pregnancy. CGM was performed for up to seven days at 4–6 week intervals, between 8–32 weeks' gestation. Data were downloaded and reviewed during follow-up visits and, in correlation with SMBG values, adjustments were made to diet, exercise and insulin therapy as indicated. The CGMS was used 0–8 times, mean 4.2 times, with 80% of the women wearing the monitor at least once per trimester. No significant differences were found in the mean A1c level between the two groups prior to week 32, but the CGM group had a consistently lower A1c level. A significant difference in A1c was seen between 32–36 weeks' gestation with the CGMS group having a lower mean A1c (p=0.007). Although not statistically significant, the CGMS group had a trend toward reduced emergency caesareans (p=0.08). There was no significant difference in infant morbidity between the two groups. Compared with healthy singletons of women in the SMBG group (n=30), women in the CGMS group (n=32) had significantly decreased mean birth weight standard deviation scores (p=0.05) and median birth weight centiles (p=0.02). Thirteen infants in the CGMS group compared to 18 infants in the SMBG group were macrosomic (p=0.05). The study suggested that the use of CGMS during pregnancy was associated with third-trimester improved glycemic control, lower birth weights and reduced risk of macrosomia. Author-noted limitations of the study included: the health professionals were not blinded, the small patient population, women were predominantly of white European ethnicity, and differences in the maternal characteristics with longer duration of diabetes in the intervention group.

Kestilä et al. (2007) conducted a randomized controlled trial to compare CGM (n=36) to SMBG (n=37) in detecting patients with gestational diabetes mellitus (GDM) who needed antidiabetic drug treatment. High-risk pregnant women at 22–34 gestational weeks who had at least two abnormally high glucose values on oral glucose tolerance testing were included in the study. The mean CGM period was 47.4 ± 2.5 hours. SMBG was performed at least five times per day. Treatment modalities were offered within five days of monitoring. As a result of CGMS, 11 women were treated with either oral agents or insulin compared to three patients in the SMBG group (p=0.0149). Within the CGM group, SMBG values were compared to the CGM values, and five SMBG patients were identified with indications for antihyperglycemic treatment compared to 16 CGM patients.

Professional Societies/Organizations: The 2019 ADA Standards of Care Guidelines state that Real-time continuous glucose monitoring may be used effectively to improve A1C levels and neonatal outcomes in pregnant women with type 1 diabetes. One well-designed RCT (Feig, et al., 2017) showed a reduction in A1C levels in adult women with type 1 diabetes on multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) who were pregnant and neonatal outcomes were better when the mother used CGM. However, two studies in which subjects used intermittent CGM showed no difference in neonatal outcomes in women with type 1 diabetes or gestational diabetes.

The 2013 Endocrine Society's practice guideline on diabetes and pregnancy recommended SMBG testing in all pregnant women with gestation or overt diabetes prior to meals and 1–2 hours after the start of each meal. The Society suggested that CGM be used during pregnancy with overt or gestational diabetes when SMBG levels or HbA1cs are not sufficient to assess glycemic control.

Replacement of a Continuous Glucose Monitoring System and Components
Replacement of a Continuous Glucose Monitoring System (CGM) and/or components is indicated when the device malfunctions, cannot be repaired and is no longer under warranty. Warranties for continuous glucose monitor and various components range from six months to three years. There is a lack of evidence to support improved outcomes due to advanced technology for CGM. Diabetics should be routinely followed by a health care provider and seen by their provider within six months of a request for a replacement monitor to ensure compliance to the management of their diabetes and the continued need for CGM.

Data Management Systems
Although data management systems offer convenience in tracking test results and glucose levels, disadvantages of some of the management systems include the complexity, time and labor intensiveness of downloading the data. There is insufficient evidence in the peer-reviewed literature to support that data management systems improve diabetic management. Due to the limitations of the available studies (e.g., lack of randomization, heterogeneous patient populations, various outcome measures, participant attrition) the benefits of data management systems in overall health outcomes in the treatment of diabetes mellitus is unknown (Costa, et al., 2009; Russell-Minda, 2009). Additional software or hardware for downloading data to computers, iPhones®, iPad® or iPods® for data management are not medically indicated.

U.S. Food and Drug Administration (FDA): Data management systems are approved as an FDA 510(k) Class II device. An example is the Telserve Data Management System (Telcare, Inc., Bethesda, MD). The System serves as an accessory to blood glucose meters to assist in the review and evaluation of blood glucose test results and related information to aid in diabetes management. The software system consists of two different levels of functionality, one for home use and one for professional use.

Literature Review: Laffel et al. (2007) conducted a randomized controlled trial (n=205) to evaluate glycemic control in insulin-treated patients who utilized an integrated glucose meter and electronic logbook compared to patients who used a conventional glucose meter and paper logbook. Type 1 and type 2 adult and pediatric patients (n=70) were recruited from seven centers to participate in the study. Participants were either using continuous insulin infusion or multiple daily injections of insulin, performing SMBG two or more times a day, and had an A1c ≥ 8% with stable glycemic control. During the first four weeks, all patients used their glucose monitor and written logbooks. At week four, patients were randomized to either a glucose monitor and written logs (i.e., paper group) (n=92) or to an integrated glucose meter/logbook (i.e., electronic group) (n=113). Follow-up visits occurred at four, eight, 12, 16 and 20 weeks. Upon completion of the study, mean A1c decreased -0.27% in the paper group compared to -0.35% in the electronic group (p=0.022). Pediatric patients also demonstrated similar results (p=0.024). The electronic group reported performing more average daily SMBG checks than the paper group (p=0.03). There was no significant difference in the mean amplitude of glycemic excursion between the two groups, but the rate of reported hypoglycemic events was lower in the paper group (p<0.0001). A total of 104 patients were available for a follow-up visit at 66 weeks, and patients were identified by four subgroups (i.e., group 1a had continued with meter/paper log since the 20-week visit; group 1b switched to integrated meter/electronic log; group 2a continued with integrated meter/electronic log; and group 2b switched to meter/paper log). Between the four-week follow-up visit and the 66-week follow-up visit, mean A1c decreased significantly in those who continued using the electronic logbook (p=0.008) compared to the other three subgroups who experienced an increase. A1c levels returned to the pre-trial level in these three groups. There was a statistically significant difference in mean A1c in those who used paper logbooks the entire time compared to those who used the electronic logbooks (p=0.006). The same trend was seen among the pediatric patients (p=0.053). From the last study visit to the 66-week visit, A1c increased in all groups. Limitations noted by the authors included short-term follow-up, neither patients or providers could be fully blinded, the “greater reduction in A1c in the electronic group may have yielded a greater number of measured hypoglycemic episodes,” the increased recognition of hypoglycemic episodes in the electronic users may have resulted from more frequent monitoring and detection of events, and the choice of switching was made by the patient and provider. The authors noted that, although statistically significant, the differences between the two study groups from the end of the RCT and the absolute reductions in A1c were modest and stated that additional studies were needed to confirm the outcomes of this study.

Remote Glucose Monitoring Device

mySentry (Medtronic MiniMed, Inc., Northridge, CA) is a remote glucose monitor that can be placed at the bedside of a parent or guardian to allow monitoring of glucose information throughout the night. The system consists of a monitor, power source and radio-frequency operated Outpost that transmits information from a Medtronic MiniMed Paradigm REAL-Time Revel insulin pump. The Outpost allows monitoring from 50 feet away or greater. The monitor displays the same information and sounds the same alarms as the pump itself if the alarm silence option is off. The device is not used for making therapy adjustments nor does it control the insulin pump in any way (Medtronic, 2018). Remote glucose monitoring devices purely for the intent of surveillance of the original device, like the mySentry, are considered a convenience item and not medically necessary in the treatment of diabetes mellitus.

mySentry was FDA approved as a supplement to the original premarket agreement (PMA) for the Medtronic continuous glucose monitoring system. The approval order included a monitor and a remote outpost for use with the paradigm real-time system (FDA, 2011).

Hypoglycemic Alarm Wristband
Alarm devices that can be worn on the wrist or ankle have been proposed for use by a diabetic to detect changes in skin conditions as an alert for hypoglycemia. The FDA approved Diabetes Sentry (Diabetes Sentry Products, LLC. Fort Worth, TX) is an example of a hypoglycemic alarm that can be worn on the wrist, ankle or bicep. The device is proposed to detect an increase in perspiration and/or drop in skin temperature and alert the wearer. The Sentry does not measure glucose levels (Diabetes Sentry, 2017). This type of device is not used for making decision regarding treatment and is considered a convenience item and not medically necessary.

GlucoWatch® G2™ Biographer
The GlucoWatch® G2™ Biographer (Cygnus, Inc., Redwood, CA) was an FDA, PMA CGMS that was worn on the wrist like a watch and took noninvasive glucose measurements through the skin every 10 minutes for up to 13 hours at a time. It was approved for use in patients seven years and older. After a two-hour warm-up period and calibration, the GlucoWatch began monitoring by producing an electrical current that pulled fluid from the skin and measured the glucose in the fluid. It has a high/low glucose alarm feature. This device is no longer available.

Literature Review: The overall evidence in the published peer-reviewed literature in the form of randomized controlled trials (Newman, et al., 2010; Chase, et al., 2005; Chase, et al., 2003) indicated that the use of the GlucoWatch resulted in minimal or no significant improvements in glycemic control or in a reduction in the occurrence of hypoglycemic attacks. Use of the device was associated with skin irritation, edema, erythema, skipped readings, false alarms, and inaccurate results (Weinzimer, et al. 2008a; Ellis, et al., 2007).

Other Home Blood Glucose Monitors
Some monitors combine a standard finger-stick blood glucose meter with non-medical devices and/or non-diabetic testing capabilities. Examples of these monitors include a finger-stick meter combined with a cellular telephone (glucophone), (e.g., GlucoPack™, HealthPia America Corp., Newark, NJ), a blood pressure monitor (e.g., Advocate DUO, Diabetic Supply of Suncoast, Taipei County, Taiwan), and a cholesterol screening analyzer (e.g., CardioChek PA Analyzer, Polymer Technology Systems, Inc. Indianapolis, IN). These devices are considered convenience items for the individual and not medically necessary in the treatment of diabetes mellitus.

Use Outside of the US
Different systems for standard and continuous glucose monitoring (CGM) are available outside of the United States. Examples of standard finger-stick blood glucose monitors offered in various countries throughout the world include the Accu-Chek and the One Touch. The Navigator Continuous Glucose Monitor (Abbott Diabetes Care, Alameda, CA) is available in Europe and other countries such as Israel and Australia. The Optical Glucose Monitor CGM system (C8 MediSensors, Inc., San Jose, CA) is Conformité Européenne (CE) Mark approved for marketing in Europe.

GlucoTrack® (Integrity Applications, Ashdod, Israel) is a CE Mark approved, non-invasive device for measuring glucose levels of persons with Type 2 diabetes or at risk of developing diabetes. The device is clipped on the earlobe when the user wants to measure the glucose level. The principle of operation is based on tracking the

physiological effects of glucose variations in the earlobe tissue. GlucoTrack measures ultrasonic, electromagnetic and thermal parameters of the tissue which occur due to glucose-related shifts in ion concentration, density, compressibility, and hydration of both cellular and extracellular compartments of the tissue (Bahartan et al., 2017; Harman-Boehm, et al., 2009). The intended use of GlucoTrack Model DF-F is for non-invasive intermittent glucose monitoring for home-use for adults 18 years and older with type 2 diabetes or pre-diabetes (Integrity Applications, 2019).

Two Eversense CGM systems (Senseonics Holdings, Inc., Germantown, MD) have been approved in Europe, the 90-day Eversense and the 180-day Eversense XL. The FreeStyle Libre™ Flash CGM (Abbott Diabetes Care, Alameda, CA) for individual use is currently available in Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden and the United Kingdom. Outside the US, the FreeStyle is approved for use by children and teens with diabetes aged 4-17 years old as well as adults.

Literature Review – Eversense XL: Kropff et al. (2017) conducted a prospective, multicenter, observational study (n=71) to evaluate the safety and accuracy of the 180-Eversense CGM system (Eversense XL device, not FDA approved). Subjects were age ≥ 18 years with type 1 and type 2 diabetes and used insulin therapy. Exclusion criteria included: history of severe hypoglycemia, diabetic ketoacidosis; known severe microvascular complications, diabetic retinopathy, macular edema, and other comorbidities. The primary outcome was mean absolute relative difference (MARD) for venous reference glucose values > 4.2 mmol/L (75 mg/dL), defined as the average of the absolute difference of paired CGM system and Yellow Springs Instrument (YSI) readings (reference) divided by the YSI reading multiplied by 100. Secondary outcomes included Clarke Error Grid Analysis and alarm performance which was defined as confirmed and missed event detection rates and true and false alarm rates given for low and high glucose alarm (<3.9 mmol/L and >10 mmol/L or < 70 mg/dL and >180 mg/dL, respectively).The MARD value against reference glucose values > 4.2 mmol/L was 11.1%. Performance of the system in the hypoglycemic range was less than the overall performance 21.7% vs.11.6% MARD (p<0.0.001). Analysis for sensors survival estimated that 100%, 82% and 40% of sensors were functional through day 45, day 90, and day 180 respectively (median sensor life 149 days). Twelve sensors were lost to the study due to subjects withdrawing or electronic or mechanical failure. Five sensors were replaced due to electronic or mechanical failure within three months of initiation of the study. There was a significant improvement (p<0.001) in the HbA1c from baseline (7.54%) to study end (7.19%). Subjects with a baseline HbA1c < 7.5% did not significantly change during the study (p=0.669). Clarke Error Grid Analysis showed 99.2% of samples in the clinically acceptable error zones, A and B. Eighty-one percent of hypoglycemic events were detected by the CGM system within 30 minutes. The in-clinic alarm performance for hypoglycemia and hyperglycemia showed detection rates of 81% and 88%, and an event true rate of 67% and 90%, respectively. Short-Form (SF-36) quality of life scores were unchanged from baseline to end of study. A statistically significant reduction of CGM measurement accuracy was seen in the last month of use. Fourteen device or procedure-related nonsevere adverse events occurred in 11 patients. A total of 147 sensors were implanted, used and removed. Adverse events included skin rashes (n=5) and incision site infection (n=2). Limitations of the study include the uncontrolled observational study design, lack of a comparator, small patient population and short-term follow-up.

Literature Review – Freestyle Libre CGM in Pediatric Patients: Edge et al. (2016) conducted a single center, prospective case series (n=89) to determine the safety and accuracy of the FreeStyle Libre Flash in pediatric patients. Subjects were age 4–17 years with type 1 diabetes, who were being treated with multiple daily injections (MDI) of insulin or continuous subcutaneous insulin infusion (CSII), and testing capillary blood glucose levels (BG) at least two times per day. Baseline A1Cs were 5.6%–10.4%. The device was used for 14 days and the Freestyle results were compared to capillary blood glucose measurements. Sensor results were masked to the patients. Subjects attended clinic three times during the 14 day period. A FreeStyle Sensor was worn on the back of the upper arm. Subjects were asked to perform four capillary BG tests daily using the BG strip-port on the FreeStyle Libre (FreeStyle Optium test strips, Abbott Diabetes Care), immediately followed by an interstitial fluid (ISF) glucose sensor measurement (data masked to participants) to allow comparison of results between the sensor and BG. Consensus error grid (CEG) analysis demonstrated 83.8% of Freestyle results in Zone A and 99.4% of results in Zones A and B (considered clinically accurate). Sensor results were in good agreement with BG results. Lag effect (sensor results higher/lower than BG when glucose was decreasing/increasing) was not evident with the FreeStyle. The sensor detected hypoglycemia (when capillary BG <3.9 mmol/L) on 70% (438/622) of occasions, increasing to 84% when pending alerts (i.e., sensor results within ± 10% of the

hypoglycemic threshold) were included. For the 30% of subjects when hypoglycemia measured in capillary testing was not detected by the FreeStyle sensor, further analysis showed that 164 of the results were in Zones A and B (clinically acceptable) and 20 were in Zone C (altered clinical action was likely to affect clinical outcome). The sensor detected hyperglycemia (when BG >13.3 mmol/L) on 85% of occasions, increasing to 94% when pending alerts were included (n=999). User experience with sensor application and sensor wear was favorable compared to SMBG. Adverse events included: allergic reaction, blister, pink mark/scabbing and abrasion on sensor removal. All were resolved at study completion. Limitations of the study include: single-center study; small patient population; and short-term follow-up.

Professional Societies/Organizations: Based on a review of the evidence-based literature, the Working Group Diabetes Technology of the German Diabetes Association published a consensus statement (Liebl, et al., 2013) that included the following indications for CGM for type 1 diabetics:

- hypoglycemia, i.e., frequent, severe hypoglycemic episodes (requiring assistance from third parties), severe nocturnal hypoglycemia, and/or proven hypoglycemia unawareness;
- unsatisfactory metabolic control if, despite the use of all available forms of treatment (including also CSII), good compliance and the exclusion of severe psychological/psychiatric problems, the target HbA1c level cannot be achieved;
- before/during pregnancy with inadequate metabolic control using conventional forms of treatment; and
- the need to perform more than 10 blood glucose measurements per day to achieve the target HbA1c level.

The Scottish Intercollegiate Guidelines Network (SIGN) recommendations on the management of diabetes (2010; updated 2017) stated that CGM may be a useful adjuvant to conventional self-monitoring in selected adults with type 1 diabetes who have persistent problems with glycemic control. However, further research is required to identify individuals who will gain the most benefit. CGM should not be used routinely in people with diabetes. Although there is limited evidence that continuous glucose monitoring may be of benefit to women during pregnancy, CGM may be considered for type 1 and type 2 diabetics in pregnancy.

The National Institute for Clinical Excellence (NICE) (United Kingdom) (2015; updated 2016) recommended self-monitoring of blood glucose levels for all adults with type 1 diabetes at least four times a day, including before each meal and before bed. Testing may be performed up to ten times per day in various situations including the following: A1C isn't achieved; the frequency of hypoglycemic episodes increases; before, during and after sports; when planning pregnancy, during pregnancy and while breastfeeding; or during illness. NICE stated that CGM could be considered for adults with type 1 diabetes who commit to using CGM at least 70% of the time and who have any of the following despite optimized insulin therapy and conventional blood glucose monitoring:

- More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycemia.
- Frequent asymptomatic hypoglycemia (more than two episodes a week) that is causing problems with daily activities.
- Extreme fear of hypoglycemia.
- Hyperglycemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.

Regarding pregnancy, NICE (2015) recommended that CGM not be routinely offered to pregnant women with diabetes. CGM may be considered for pregnant women on insulin therapy who have problematic severe hypoglycemia or have unstable blood glucose levels or to gain information about variability in blood glucose levels. The role of CGM in helping women achieve blood glucose targets before pregnancy needs further research.

External Insulin Pumps

External insulin pumps are designed to provide continuous subcutaneous insulin infusion (CSII) in patients with diabetes mellitus. The external insulin pump is a programmable battery-powered mechanical syringe/reservoir regulated by a miniature computer that delivers a steady, continuous ("basal") amount of insulin and releases a bolus dose at meals or smaller amounts at programmed times. Frequent monitoring of the blood glucose (e.g., four times per day) is essential to ensure appropriate delivery of insulin dosage.

CSII candidates include a diabetic whose hyper- and/or hypoglycemia cannot be controlled with daily injections of insulin. Individuals with wide fluctuations in blood glucose before mealtime, a marked increase in fasting blood glucose levels at dawn (i.e., exceeding 200 milligrams/deciliter [mg/dL]), unpredictable hypoglycemia, persistent glycated hemoglobin levels greater than 7.0%, and patients unable to administer multiple daily injections (MDI) may also be candidates for CSII (Primary Care Education Consortium, 2009; White, 2007).

Standard External Insulin Pumps
An external insulin pump is a battery-powered device worn and programmed by the user to deliver a continuous subcutaneous insulin infusion (CSII). Most conventional insulin pumps deliver insulin by applying pressure from behind the contents of the reservoir. Some newer pumps, like the t-slim®, draw insulin from the reservoir into a micro-delivery chamber allowing the insulin to be delivered in smaller increments from 0.001 units per hour (u/hr) to above 0.1 u/hr. Other pumps may be combined or integrated with standard finger-stick glucose monitoring system (CSII-BGM).

U.S. Food and Drug Administration (FDA): Most external insulin pumps are approved by the FDA as 510(k) Class II devices for the continuous infusion of insulin. Examples of FDA approved devices include:

- Animas® OneTouch® Ping™ (Animas Corp., Frazer, PA) insulin pump with a OneTouch® Ping™ Meter Remote for diabetics requiring continuous subcutaneous insulin delivery and measurement of glucose and Animas® Vibe® Insulin Pump intended for the continuous subcutaneous infusion of insulin for the management of insulin-requiring diabetes. Animas Corporation has announced that they intend to exit the insulin pump business and discontinue the manufacturing and sale of Animas Vibe and OneTouch Ping insulin pumps. Animas' goal is to transition all patients to another insulin delivery system and exit the market by September 2019.
- Dana Diabecare® II Insulin Pump (Sooil Development Co., Ltd., North Attleboro, MA) for subcutaneous delivery of insulin
- Minimed Paradigm® Real-Time Insulin Pump (Medtronic Minimed, Northridge, CA) for the management of diabetes mellitus in persons requiring continuous delivery of insulin (MMT-523/723 for adults and MMT-523K/723K for ages 7–17 years).
- MiniMed Paradigm Revel™ Insulin Pump (Medtronic MiniMed, Inc. Northridge, CA) used in conjunction with the Contour® Next Link glucose meter (Bayer HealthCare, Tarrytown, NY) for the continuous delivery of insulin in persons requiring insulin and the quantitative measurement of glucose in fresh capillary whole blood. This pump was discontinued by Medtronic in October 2018.
- OmniPod™ Insulin Management System (Insulet Corporation, Billerica, MA) is a wireless insulin pump that consists of a disposable insulin pod and Personal Diabetes Manager that includes a built-in FreeStyle® glucose meter. The pod is filled with insulin by the patient and replaced every 72 hours. Per the manufacturer the OmniPod is for children of all ages and adults.
- Omnipod DASH™ Insulin Management System (Insulet Corporation, Billerica, MA) is intended for subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus and is interoperable with Contour® NEXT ONE Blood Glucose Meter (Ascensia Diabetes Care, Mishawake, IN) for wireless transfer of blood glucose readings to the DASH™ Personal Diabetes Manager (PDM). The pod is replaced every 72 hours.
- Solo™ MicroPump Delivery System (Medingo, Ltd., Yoqneam, Israel) for the management of diabetes mellitus in persons requiring insulin
- t:slim® micro-delivery insulin pump (Tandem Diabetes Care, Inc., San Diego CA) for the subcutaneous delivery of insulin for the management of diabetes mellitus in persons requiring insulin, for individuals 12 years of age and greater
- t:flex™ Insulin Delivery System (Tandem Diabetes Care, Inc., San Diego CA) is a t:slim predicate device intended for the subcutaneous delivery of insulin for individuals 12 years of age and greater. The t:flex includes a 4.8 mL cartridge vs. 3.0 mL cartridge in the t:slim.

- T:slim X2™ (Tandem Diabetes Care, Inc., San Diego CA) is a t:slim predicate device approved for the subcutaneous deliver of insulin for individuals age ≥ 6 years. The device is indicated for use with NovoLog or Humalog U-100 insulin.

Literature Review
Type 1 Diabetic Adults: As evidenced by systematic reviews, meta-analysis (n=12–52 studies), randomized controlled trials, comparative studies and prospective longitudinal observational studies (n=100–1441), the use of external insulin pumps for the management of type 1 diabetes mellitus is a well-established, safe and effective treatment modality (Cummins, et al., 2010; Misso, et al., 2010; Monami, et al., 2010; Fatourechi, et al., 2009; Raccah, et al., 2009; Jeitler, et al., 2008; Giménez, et al., 2007; Hirsch, et al., 2005; Weissberg-Benchell, et al., 2003; Pickup, et al., 2002).

Type 1 Diabetic Children: CSII is an accepted treatment alternative for type 1 diabetic children. Overall, results from systematic reviews, randomized controlled trials, case series and comparative studies reported a significant initial improvement in glycated hemoglobin (HbA1c or A1c) and a decrease in the severity of hypoglycemic events. Additional outcomes included lower fasting blood glucose levels, less severe lipohypertrophy, less blood glucose variability, absence of diabetic ketoacidosis (DKA), and fewer sick-day calls. Outcomes varied based on age and the number of years the subject had been a diabetic (Overgaard, et al., 2015; Cummins, et al., 2010; Churchill, et al., 2009; Naghan, et al., 2009; Skogsberg, et al., 2008; Opipari-Arrigan, et al. 2007; Alemzadeh, et al., 2007; Kapellen, et al., 2007; McVean, et al., 2007; Pańkowska, et al., 2007; Berhe, et al., 2006; Kordonouri, et al., 2006; Wood, et al., 2006; Fox, et al., 2005; DiMeglio, et al., 2004; Plotnick, et al., 2003).

Type 2 Diabetics: In general, insulin pump usage in type 2 diabetics is not an established treatment modality. However, insulin pumps are a treatment option for a subgroup of type 2 diabetics who are not being controlled (e.g., A1C >7.0%, recurring hypo- and/or hyperglycemic episodes) despite frequent adjustments in therapy and adherence to treatment regimens including daily self-management of blood glucose levels and three or more daily injections of insulin for three or more months. There are relatively few published clinical trials regarding the safety and efficacy of CSII in type 2 diabetics. Available randomized controlled trials and case series have reported an improvement in HbA1c, reduction in fasting plasma glucose and postprandial plasma glucose levels, reduction in the glucose area under the curve values, and/or decreased insulin demand following use of CSII while other studies reported no significant difference in MDI and insulin pump outcomes. Overall, complications were not greater with CSII (Reznik, et al., 2014; Bode, 2010; Johnson, et al., 2010; Noh, et al., 2008; Parkner, et al., 2008; Pickup and Renard, 2008; Berthe, et al., 2007; Wainstein, et al., 2005; Raskin, et al., 2003).

Pregnancy: Because pregnancy causes an increase in insulin resistance, there may be a need for increased insulin dosage during pregnancy in type 1 diabetics. In type 2 diabetics, oral hypoglycemics are discontinued during pregnancy. If the type 2 diabetic and the gestational diabetic (i.e., diabetes that occurs only during pregnancy) are unable to maintain glycemic control with diet, exercise, and self-monitoring blood glucose (SMBG), insulin injections may be required. Poor blood sugar control during pregnancy can lead to congenital abnormalities, miscarriages, stillborns, and unusually large babies. In a carefully selected subset of pregnant diabetics, an insulin pump may be considered when intensive insulin therapy is required for glycemic control. One concern regarding the use of an insulin pump during pregnancy is the potential for ketoacidosis due to interruption in the flow of insulin secondary to pump malfunction. Ketoacidosis may occur more rapidly in the pregnant diabetic and can result in fetal loss (ADA, 2019; Trujillo, 2008; Mukhopadhyay, et al., 2007; American College of Obstetricians and Gynecologists [ACOG], 2005; reaffirmed 2014; Rodbard, et al., 2007).

Farrar et al. (2016) conducted a Cochrane systematic review of randomized controlled trials comparing CSII to MDI in pregnant women with diabetes, preexisting and gestational. Five studies (n=154 pregnancies) were found that met inclusion criteria. No significant differences were reported in caesarean section rates, large-for-gestational age, maternal weight gain during pregnancy, maternal hypoglycemia or hyperglycemia, mean HbA1c, perinatal mortality, fetal anomaly and fetal birthweight. The authors concluded that there was no evidence to support the use of one form of insulin administration over another for pregnant women with diabetes. Due to the small number of trials and subjects generalizability of the results to all pregnant women was questionable.

González-Romero et al. (2010) conducted a comparative prospective study to evaluate the outcome of type 1 pregnant diabetic women treated with CSII (n=35 pregnancies/26 women) compared to MDI (n=64

pregnancies/53 women) (control group). CSII was implemented during prepregnancy for women who did not reach A1c <7.5%, had dawn phenomenon not responsive to a change in bedtime insulin dosage, had uncontrolled hypoglycemic episodes or an unfavorable obstetrical history. CSII was started on two women during pregnancy. The control group was treated with 3–6 insulin injections per day. The A1c was significantly lower ($p<0.05$) before pregnancy in the CSII group and also significantly improved ($p<0.001$) in 3–6 months following CSII. CSII had lower insulin requirements ($p<0.05$) during the first trimester. There were no significant differences between severity and frequency of hypoglycemic events in the two groups. One CSII and one control group patient experienced ketoacidosis. Women in the CSII group weighed more than MDI women, but the increase in weight between the first and third trimesters was lower in the CSII group. No significant differences were reported between the groups regarding hypertension or progression of retinopathy or nephropathy. There were no significant differences between the groups in miscarriages, perinatal mortality, congenital anomalies, or birth weight. The study did not show an advantage of CSII over MDI in metabolic control or obstetrical or perinatal outcomes.

Mukhopadhyay et al. (2007) conducted a systematic review and meta-analysis of published and unpublished randomized controlled trials comparing MDI to CSII in pregnant diabetic women. Six studies (n=213) met inclusion criteria with only two studies being truly randomized. Pregnancy outcomes and glycemic control were not significantly different between the study groups. Although ketoacidotic episodes and diabetic retinopathy were reported more often in the CSII groups, the differences were not statistically significant. There were no reported advantages for the use of CSII over MDI. The authors noted that the small number of trials and subjects which could contribute to a lack of statistical power were limitations of the study. The outcomes of the study did not demonstrate a “clear-cut” benefit of using CSII over MDI. They suggested that the use of CSII in pregnant diabetics might be reserved for women requiring very high doses of insulin or cases in which normoglycemia is not achieved by conventional therapy.

Professional Societies/Organizations: In the 2018 American College of Obstetricians and Gynecologists (ACOG) practice bulletin on pregestational diabetes mellitus, ACOG stated that in those women without good control, conversion to a subcutaneous insulin pump before pregnancy may improve glycemic control, particularly in those with type 1 diabetes. ACOG went on to explain that patients who use continuous subcutaneous insulin infusion must be highly motivated and compliant. Advantages of the insulin pump may include a decrease in episodes of severe hypoglycemia, better control of hyperglycemia, and a more flexible lifestyle. In addition to the disadvantage of the increased cost of the pump and pump supplies, adverse events with the pump have been reported to occur approximately three times per year of use and of these events approximately 38% are pump malfunctions. If the delivery of insulin is interrupted or impaired by battery failure or infection at the infusion site, diabetic ketoacidosis (DKA) may develop rapidly with 9.8% of pump adverse events leading to high ketones or DKA. Despite potential advantages and modest evidence that glycemic control may be improved, a meta-analysis of five small randomized trials evaluating insulin pump versus injectable insulin, reported that there were no statistically significant differences in outcomes. Thus, women who have euglycemia with multiple dose injectable insulin can be maintained on that insulin dosage approach.

The 2014 consensus statement on insulin pump management by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) (Grunberger, et al., 2014) included recommendation for the use of continuous subcutaneous insulin infusion (CSII). Ideal CSII candidates include type 1 diabetics or intensively managed insulin-dependent type 2 diabetics who meet the following:

- currently performing ≥ 4 insulin injections and ≥ 4 self-monitored blood glucose (SMBG) measurements daily
- motivated to achieve optimal blood glucose control
- willing and able to carry out the tasks that are required to use this complex and time consuming therapy safely and effectively
- willing to maintain frequent contact with their health care team

Recommendations for pediatric patients included an individual with elevated HbA1c levels on injection therapy with frequent, severe hypoglycemic events and widely fluctuation glucose levels. Families should be motivated to monitoring blood glucose ≥ 4 times/day and have a working understanding of basic diabetes management. The patient’s age and duration of diabetes should not be factors in determining the transition from injections to CSII (Grunberger, et al., 2014).

Regarding pregnant women with type I diabetes, AACE/AAC stated that the literature does not provide clear evidence that CSII is necessary for optimal treatment. For gestational and type 2 diabetics, insulin pump therapy seems to be safe and effective for maintaining glycemic control in women requiring large insulin doses (Grunberger, et al., 2014).

In a clinical practice guideline for diabetes and pregnancy, the Endocrine Society (Blumer, et al., 2013) recommended the use of continuous insulin infusion during pregnancy if the pump was started or used prior to the pregnancy. The Society does not recommend initiation of pump therapy during pregnancy unless other strategies such as multiple daily doses of insulin have proven unsuccessful.

A 2007 consensus statement endorsed by the ADA and the European Association for the Study of Diabetes, the European Society for Pediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, International Society for Pediatric and Adolescent Diabetes (Phillip, et al., 2007) listed the following considerations for CSII therapy in all pediatric patients with type 1 diabetes, regardless of age:

- "recurrent severe hypoglycemia
- wide fluctuations in blood glucose levels, regardless of A1c
- suboptimal diabetes control (i.e., A1c exceeds target range for age)
- microvascular complications and/or risk factors for macrovascular complications
- good metabolic control but insulin regimen that compromises lifestyle"

Other circumstances in which CSII may be beneficial include:

- "young children and especially infants and neonates
- adolescents with eating disorders
- children and adolescents with a pronounced dawn phenomenon
- children with needle phobia
- pregnant adolescents, ideally preconception
- ketosis-prone individuals
- competitive athletes"

The guidelines included a discussion regarding the importance of the involvement and support of a multidisciplinary team and family members in the initiation and ongoing pump management and glucose monitoring of CSII in children.

Standard Features for External Insulin Pumps
A number of factors should be taken into consideration when deciding what insulin pump is best suited for each individual patient. Attention should be given to the ease of use and reading of the screens; reservoir size; type of insulin used by the pump; basal capabilities; bolus capabilities; dosing increments (especially for children); alarms and settings; compatibility with standard glucose monitor and/or continuous glucose monitor; type of battery needed; data management capabilities; device size and weight; and patient and/or caregivers ability to operate the pump. Standards for external insulin pumps in pediatric patients may differ from those in adults. Children may require additional features to accommodate their unique needs. The following features may be compared when selecting an insulin pump for a child: size, weight, battery life, infusion sets, number of basal rates available, basal range, smallest basal possible, obstruction alarm, over-delivery alarm, near-empty alarm, and warranty and special features.

Enhanced Features
A number of technological advances have been made in insulin infusion pumps over the past several years, including decrease in size and weight, improved safety features, voice synthesizers, larger digital displays, and more sophisticated programming options. New models are introduced periodically, and patients who are undergoing CSII may wish to upgrade to these newer devices as they become commercially available. There is limited information available in the peer-reviewed literature regarding replacing pumps with newer models, features that might provide additional health benefits and features that are primarily for convenience or ease of

use. However, in certain situations such as hearing or visual impairment, or when glycemic control with a standard external pump has not been achieved and an integrated bolus wizard feature for an individual less than age 18 years is medically necessary.

Data Management Systems
Although data management systems offer convenience in tracking test results and glucose levels, there is insufficient evidence in the peer-reviewed literature to demonstrate that data management systems improve diabetic management. Due to the limitations of the studies (e.g., lack of randomization, heterogeneous patient populations, various outcome measures, participant attrition) the benefit of data management systems in overall health outcomes in diabetics is unknown (Costa, et al., 2009; Russell-Minda, et al., 2009). Additional software or hardware for downloading data to computers, iPhones®, iPad® or iPods® for data management are not medically indicated.

Replacement of External Insulin Pump
The average warranty on an insulin pump is four years. Warranties for other components of a pump or combined or integrated systems (e.g., remote control, reservoirs, transmitters) range from six months to two years. Some components may have no warranty (e.g., sensors) (Medtronic, 2018; Omnipod, 2016). There is a lack of evidence to support improved outcomes (e.g., A1C) because of insulin pump enhanced technology. Diabetics should be routinely followed by a physician and seen by their physician within six months of a request for a replacement pump to ensure compliance to the management of their diabetes.

Combined or Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Blood Glucose Monitoring System That Includes a Continuous Blood Glucose Monitor (CBGM) System
A CSII used in conjunction with a CBGM (CSII-CBGM) is also referred to as sensor-augmented pump therapy. These systems include an insulin pump and continuous glucose monitor and may or may not include software for tracking and trending glucose readings. Some systems connect the insulin pump to the CGM using wired technology while others are wireless. Newer models are offering wireless technology to allow transmission of data to mobile phones. All wireless capabilities are considered an integral part of the system. The MiniMed Paradigm® REAL-Time Revel™ System (Medtronic MiniMed, Northridge, CA) is an example of a device that includes a continuous glucose monitor as opposed to the standard finger-stick glucose monitor. The glucose sensor inserts under the skin and connects to the MiniLink® transmitter that sends data to the insulin pump using wireless radiofrequency technology. The system also includes CareLink™ Therapy Management Software, a free online tool. A combined system with a CSII and a CBGM may be used on a long-term basis for the treatment of type 1 diabetes mellitus.

U.S. Food and Drug Administration (FDA): Combination systems are FDA approved under the premarket approval (PMA) process. Examples of approved devices include:

- Paradigm REAL-Time Revel System includes an insulin pump, continuous glucose monitor and management software. The continuous glucose monitor is intended to continuously record interstitial glucose levels. The sensor was approved by the FDA for use by individuals age 18 years and older and can be worn for up to 72 hours. The insulin pump is indicated for the continuous delivery of insulin at set and variable rates for the management of diabetes.
- Animas® Vibe™ System consists of the Animas Vibe Insulin Pump paired with the Dexcom G4 PLATINUM Sensor and Transmitter. The Animas Vibe insulin pump is indicated for continuous subcutaneous insulin infusion for the management of insulin-requiring diabetes. In December 2015, the FDA approval of the Animas Vibe System included the Dexcom® G4 Platinum Sensor and Transmitter continuous glucose monitor (CGM) for ages two years and older. The system if indicated for detecting trends and tracking patterns in persons with diabetes. CGM is intended to complement, not replace, information obtained from standard home glucose monitoring devices. The insulin pump can be used with or without the CGM. Animas Corporation has announced that they intend to exit the insulin pump business and discontinue the manufacturing and sale of Animas Vibe and OneTouch Ping insulin pumps. Animas' goal is to transition all patients to another insulin delivery system and exit the market by September 2019.
- t:slim G4 Insulin Pump with Dexcom G4 Platinum CGM includes the t:slim G4 Insulin Pump intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons age 12 or older who require insulin. The CGM is indicated for detecting trends and tracking

patterns in persons with diabetes for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices. The insulin pump can be used alone without the CGM.
- T:slim X2™ can be paired with the Dexcom G6 CGM. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin and can be used solely for continuous insulin delivery or as part of the t:slim X2 System to receive and display continuous glucose measurements from the Dexcom G6 Mobile Sensor and Transmitter. The t:slim X2 System is indicated for use in individuals 6 years of age and older.

Literature Review: CSII with CBGM has become an accepted method for monitoring diabetes in a subgroup of type 1 and type 2 diabetics. Although a limited number of randomized controlled trials and case series with short-term follow-ups are lacking in strong, definitive conclusions, the evidence is suggestive of improved clinical outcomes including normalization of A1c levels and a reduction in the number of hypoglycemic episodes (Bergenstal, et al., 2010; Kordonouri, et al., 2010; Raccah, et al., 2009; Halvorson, et al., 2007; Mastrototaro, et al., 2006).

Schaeffer et al. conducted a randomized controlled trial (n=72) to compare usability and training needs for the t:slim insulin pump and the Medtronic MiniMed Paradigm Revel insulin pump. Subjects were 18 years of age or older, used multiple daily insulin injections to manage their diabetes, had a basic understanding of insulin pumps, and had correct or corrected vision and hearing. Subjects attended a 90-minute training session on pump use. At the second visit, subjects completed a usability evaluation for their pump and were unknowingly observed as they performed pump tasks. The t:slim group took statistically significant less amount of time (27%) for training than the Revel group (p=0.025) and were more satisfied with the length of training (p=0.46). The t-slim subjects also took statistically significant less time to complete the task of delivering an extended bolus with correction (p-0.034) and time to complete the task of resuming therapy (p<0.001) and had fewer failure rates (p<0.001). The results of questionnaires on ease of use and global usability were higher in the t:slim group.

Professional Societies/Organizations: The 2019 ADA Standards of Care include the following recommendations for insulin pumps:
- “Most adults, children, and adolescents with type 1 diabetes should be treated with intensive insulin therapy with either multiple daily injections or an insulin pump.”
- “Insulin pump therapy may be considered as an option for all children and adolescents, especially in children under 7 years of age.”
- Automated insulin delivery systems may be considered in children more than 7 years of age and adults with type 1 diabetes to improve glycemic control.

ADA notes that there is no consensus to guide choosing which form of insulin administration is best for a given patient. The choice of multiple daily injections (MDIs) or an insulin pump should be based on the individual characteristics of the patient. Pump therapy can be successfully started at the time of diagnosis. Practical aspects of pump therapy initiation include: assessment of patient and family readiness, selection of pump type, initial pump settings, patient/family education of potential pump complications (e.g., diabetic ketoacidosis with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates, extended/square/dual wave bolus). Regarding automated insulin delivery systems, ADA states that with these systems, insulin delivery cannot only be suspended but also increased or decreased based on sensor glucose values. Emerging evidence suggests such systems may lower the risk of exercise related hypoglycemia and may have psychosocial benefits.

The 2016 Endocrine Society guidelines on continuous subcutaneous insulin infusion (CSII) therapy in adults included the following:

- Recommend CSII over analog-based basal-bolus multiple daily injections (MDI) in type 1 diabetics who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device (strong recommendation; moderate quality of evidence)
- Recommend CSII over analog-based basal-bolus MDI in type 1 diabetics who have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device (strong recommendation; low level of evidence)

- Suggest CSII in type 1 diabetics who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device (weak recommendation; low level of evidence)
- Suggest CSII for type 2 diabetics with good adherence to monitoring and dosing who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications (weak recommendation; low level of evidence). The Society noted that randomized controlled trials (RCTs) have shown mixed results, and subsequent meta-analyses have failed to show significant reductions of A1C or reductions in hypoglycemia for type 2 diabetics on CSI. However, one RCT with a defined subset of patients reported a statistically superior reduction in A1C of 1.1% from the baseline mean of 9.0% in the CSII group and a 0.4% reduction in the MDI. The study (Reznik, et al., 2014) included insulin resistant type 2 diabetics with an A1C between 8.0%–10%.

Combined or Integrated Continuous Subcutaneous Insulin Infusion and Blood Glucose Monitoring System with Automatic Insulin Suspension

The MiniMed 530G, called The MiniMed Paradigm® Veo™ in Europe, is an insulin delivery system that consists of an insulin pump integrated with a continuous glucose monitor and advanced software algorithms. The System included the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink Personal Therapy Management Software for Diabetes. There are two models, the MMT-551 and the MMT-751. The only difference is the size of the reservoir. The pump was designed for adults and children (Medtronic, 2017, FDA, 2013). The Threshold Suspend automation component automatically stops the delivery of insulin if the glucose level reaches a preset threshold between 60–90mg/dL. An alarm alerts the user who can take appropriate action. If the user is unable to respond, insulin delivery will be suspended for up to two hours or sooner if reset by the user. Sale of the Minimed 530G was discontinued by Medtronic in October 2018.

More recent MiniMed pump models include the 630G and the 670G systems. The 630G is combined with the Enlite® sensor, and SmartGuard™ technology. This system also includes the one-press serter (helps to insert the sensor), Guardian® Link Transmitter, CareLink® USB, Bayer's Contour® Next Link 2.4 wireless meter, and Bayer's Contour® Next test strips. Similar to the 530G, the system automatically pauses insulin delivery for up to two hours if the glucose values go below a preset level and the user does not respond (Medtronic, 2017, FDA, 2016).

The 670G system includes the Guardian® Sensor-3 (7-day wear), Guardian Link-3, one press serter (helps to insert the sensor) and the Contour® Next Link 2.4 glucose meter. The Guardian Link-3 Transmitter powers the glucose sensor, collects and calculates sensor data, and wirelessly sends the data to the 670G insulin pump. The Guardian Sensor-3 is used as an adjunctive device to a standard blood glucose meter. The SmartGuard technology is available in a manual mode and an auto mode. In the manual mode the suspend before low feature stops insulin delivery 30 minutes before the pre-selected low limit is reached and resumes after sensor glucose levels recover. The auto mode automatically adjusts basal insulin delivery using continuous glucose monitor data and can automatically increase or decrease the amount of insulin delivered based on sensor values. The auto mode uses a target of 120mg/dL (Medtronic, 2017, FDA, 2016).

U.S. Food and Drug Administration (FDA): The MiniMed 530G received FDA premarket approval (PMA) in 2013 as an artificial pancreas device system with threshold suspend. The 530G is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes mellitus in persons, sixteen years of age and older, requiring insulin as well as, for the continuous monitoring and trending of glucose levels in the fluid under the skin.

In August 2016, the MiniMed 630G System with SmartGuard™ technology was FDA PMA approved "for continuous delivery of basal insulin (at user selected rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes mellitus in persons, sixteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin" (FDA, 2016).

The 670G was FDA PMA approved in 2016 "intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes

mellitus in persons, fourteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin". The Guardian Sensor is indicated for seven days of continuous use (FDA, 2016). June 21, 2018 the FDA expanded the indications of the 670G to include patients age 7 to 13 years (FDA, 2018).

Literature Review: The European equivalent of the MiniMed 530G is the MiniMed Paradigm® Veo. The Veo has a wider glucose range to trigger suspension (40–110 mg/dL), a higher maximum bolus capacity (75 units vs. 25 units) and automatically recalibrates following suspension whereas the 530G asks the user if they want to recalibrate. The differences are due to FDA requirements. Therefore, studies evaluating the Veo are applicable to the 530G. Randomized controlled trials have shown that threshold suspend pump therapy significantly reduced nocturnal hypoglycemic events without increasing glycated hemoglobin levels, reduced the occurrence of severe and moderate hypoglycemic events and reduced the duration and severity of induced hypoglycemia without rebound hyperglycemia (Garg, et al., 2017; Bergenstal et al., 2013; Ly et al., 2013; Garg, et al., 2012).

Use Outside of the US
The European equivalent of the MiniMed 530G is the Paradigm® Real Time Veo™ System (Medtronic MiniMed, United Kingdom). The software for the Threshold Suspend tool is the same for the 530G System and the Veo. Although the sensors for the two pumps are not identical, they operate using similar principles and fundamental scientific technology. The Veo received Conformite Europeenne (CE) mark approval in 2009 for marketing in Europe. Medtronic's MiniMed 640G with insulin suspension was launched in Australia and is also available in the United Kingdom and Denmark. Studies including randomized controlled trials and prospective case series have reported that the 640G resulted in a significant reduction in hypoglycemic events without adverse effects from rebound hyperglycemia (Battelino, et al., 2017; Biester, et al., 2017; Buckingham, et al., 2017).

The OmniPod System was launched in the United States in 2005 and subsequently became available in Latin America and Israel. In 2010, Ypsomed AG, an independent diabetes specialist and technology provider, began distributing OmniPod in a number of countries with a primary focus on Europe.

The Scottish Intercollegiate Guidelines Network (SIGN) recommendations on the management of diabetes (2017) stated that insulin pump therapy is associated with modest improvements in glycemic control and should be considered for patients unable to achieve their glycemic targets. CSII therapy should be considered in patients who experience recurring episodes of severe hypoglycemia.

The National Institute for Clinical Excellence (NICE) (United Kingdom) 2015 (updated 2016) guideline on the diagnosis and management of diabetes in children recommends that children be offered an insulin pump if a multiple daily injection regimen is not appropriate for the child with type 1 diabetes. In a 2015 guideline on the management of diabetes and its complications in pregnancy, NICE stated that women with insulin-treated diabetes could be offered continuous subcutaneous insulin infusion during pregnancy if adequate blood glucose control is not obtained by multiple daily injections of insulin without significant disabling hypoglycemia.

In a Rapid Response Report (2015) on insulin pumps for adults, the Canadian Agency for Drugs and Technologies in Health (CADTH) concluded that the clinical effectiveness of CSII versus multiple daily injections in adult patients or pregnant women remains uncertain. However, an insulin pump integrated with a continuous glucose monitor, including a sensor-augmented pump, appeared to result in better glycemic control without an increase in hypoglycemia. Two systematic reviews, three randomized controlled trials, one economic evaluation study and two guidelines met inclusion criteria.

Diabetic Supplies

Needle-Free Insulin Injection Systems/Jet Injectors
Alternatives to needles and syringes for insulin administration are needle-free insulin injection systems, also called jet injectors. These devices eject a high speed, narrow stream of insulin through a fine-holed nozzle that forces the insulin to penetrate the skin subcutaneously. The devices deliver 0.5–100 units of insulin with force produced by a powerful spring mechanism or by compressed carbon dioxide. Some injectors are single-dose (i.e., disposable cartridge jet injectors [DCJIs]) and may be totally disposable, while others have a disposable reservoir and nondisposable actuation mechanism. Use of jet injectors has been associated with consistently

lower blood glucose levels, shortened peak action of regular insulin, reduced insulin requirements, more rapid absorption of short-acting insulin, and reduced occurrence of hyperglycemia. These injectors offer an advantage for patients unable to use syringes or those with needle phobias. The limitations of the devices include bruising and/or bleeding at the injection site. Jet injectors are not suitable for every patient with diabetes. Many patients are deterred by the noise the injector makes on delivery, the bulky size, the need to carry a vial, and the frequent maintenance and cleaning that the jet injectors require (Heinemann, 2013; Baxter and Mitragotri, 2006; ADA, 2004a).

Jet injectors are Class II, 510(k) U.S. Food and Drug Administration (FDA)-approved devices, described as nonelectrically powered fluid injectors. Examples of jet injectors approved by the FDA include the Pharmjet® Needle-free Injection System (Pharmjet, Inc. Golden, CO) and the Biojector® 2000 (Bioject, Inc., Portland, OR).

The ADA stated that jet injection of insulin may be an appropriate alternative to conventional needle injection for carefully selected patients in the following situations:

- patients with needle phobia, since jet injectors may reduce their anxiety by making them more willing to self-administer multiple daily injections of insulin in order to maintain glycemic control and reduce the risk of long-term complications
- patients or caretakers who are unable to perform insulin injection by standard syringe (e.g., those who may be neurologically impaired)

Per the ADA the use of jet injectors may result in more rapid absorption of short-acting insulin, and may cause trauma/bruising to the skin (ADA, 2004a).

Blood and Urine Glucose Testing
Self-monitoring of blood glucose (SMBG) has replaced urine glucose testing for most patients because urine glucose testing provides only a rough estimate of prevailing blood glucose levels. Urine glucose testing in the home setting consists of semi-quantitative measurements based on single voiding or, less often, by more quantitative blocks collected over 4–24 hours. The rationale for its use is that urinary glucose values reflect mean blood glucose during the period of urine collection. Urine testing is less accurate than blood glucose monitoring and does not provide a complete picture of diabetes. A urine test does not depict the presence of glucose until the blood glucose level is above 180 milligrams per deciliter (mg/dl), making the test useless in monitoring for hyperglycemia. For these reasons, SMBG is the preferred method of monitoring glycemic status on a daily basis The 2019 ADA standards of medical care for diabetes state that patients on multiple-dose insulin or insulin pump therapy should perform SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose. SMBG results may help to guide self-management for patients using less frequent insulin injections or noninsulin therapies. The need for SMBG may vary with type 2 diabetics on insulin, but before a meal and two hours after a meal are common times. In type 2 diabetics not on insulin, routine SMBG monitoring may be of limited additional clinical benefit. According to the Society of General Internal Medicine's (2017) Choosing Wisely recommendation, SMBG is an integral part of patient self-management in maintaining safe and target-driven glucose control in type 1 diabetics. However, daily finger glucose testing is not indicated for type 2 diabetics who are not on insulin or medications associated with hypoglycemia.

Blood glucose test strips are typically unique to the glucose meter being used by the diabetic. For example the FreeStyle glucose test strips are used with a FreeStyle blood glucose monitor (Therasense, Inc., Alameda, CA) and a OneTouch® (LifeScan, Inc., Milpitas, CA) glucose monitor uses the corresponding OneTouch glucose strip.

Insulin Pens
Insulin pens are another alternative to the standard needle and syringe. Several pen-like needle devices and insulin cartridges are available for the administration of subcutaneous insulin. They may be used by patients on a multidose regime, and can also be helpful for the visually impaired, active individuals, and patients with a lack of coordination and/or dexterity issues. In many patients, the pens have been demonstrated to improve accuracy in insulin administration and/or adherence. The devices, resembling a large pen, have a fine needle under the cap

and a plunger at the other end. They are prefilled with insulin or have disposable or reusable insulin cartridges. Different pens are compatible with different types of insulin so the patient needs to ensure that they have the correct pen. Pens also differ in their dosing increments and the maximum amount of insulin that can be dispensed at a single time. Some pens have dials that assist the patient in selecting accurate dosage. Disposable pens come prefilled with a cartridge of insulin, are stored in the refrigerator, kept at room temperature after opening and then discarded when all of the insulin is used (ADA, 2019; ADA, 2017b; Stockl, et al., 2007; Salsali and Nathan, 2006).

Insulin pen are approved by the FDA 510(k) process. Examples of disposable pens include the Original Prefilled Pen (Eli Lilly, Indianapolis, IN) that uses Humulin® N and Humulin 70/30, the Flexpen® (Novo Nordisk, Inc., Princeton, NJ) that uses Levemir®, Novolog® Flexpen and Novolog Mix 70/30 insulin and the Lantus® Solostar® (Sanofi-Vantis, Bridgewater, NJ) which uses Apidra® or Lantus® insulin. Eli Lilly also makes the Basaglar Kwikpen, Humalog Kwikpen and Humulin Kwikpen disposable pens. Examples of reusable pens include the HumaPen Savvio, and Humapen Luxura™ HD by Eli Lilly for the administration of Humalog® insulin and the Novopen Echo by Novo Nordis for Novolog insulin. Eli Lilly's HumanPen Ergo® II allows for injection of 1–60 units of Humulin or any Humalog 3 mL cartridge (100 IU/ml). The NovoPen Echo (Novodish Inc. Plainsboro, NJ) is a reusable pen that uses the PenFill® 3 mL cartridge of NovoLog® 100 units/mL (U-100) and a single use detachable and disposable pen needle. The pen allows the user to dial the desired dose from 0.5 to 30 units in 0.5 unit increments and has a memory feature that remembers the last dose injected. The InPen (Companion Medical, Inc. San Diego, CA) is a reusable pen for diabetics age 12 and older. The pen injector is compatible with Lilly Humalog® U-100 3.0 mL cartridges. The pen injector allows the user to dial the desired dose from 0.5 to 30 units (FDA, 2017b).

Blood and Urine Ketone Testing

Ketone bodies, by-products of the burning of fat in the absence of insulin, can build up and cause serious complications, including diabetic ketoacidosis (DKA), a condition that requires immediate medical attention. Three types of ketone bodies develop during DKA: ß-hydroxybutyrate (ß-HB), acetoacetate and acetone. The two methods of assessing and monitoring for ketone bodies are the semi-quantitative estimation of acetoacetate and acetone levels in the urine which are based on a nitroprusside reaction on urine dip sticks and the measurement of ß-HB in capillary blood based on an enzymatic reaction on a ketone finger-stick blood strip. Ketones will be present in the urine when the blood level of ketones surpasses a certain threshold and can be detected by ketone urine test strips. Acetoacetic and ß-HB are reabsorbed by the renal tubules and their final concentration in the urine exceeds that in the blood. The presence of urine ketones may be present long after blood levels have normalized. Ketone testing is indicated in the following situations: type 1 diabetics with a blood glucose greater than 240 mg/dl; all diabetics who are ill, under stress or have a blood glucose over 300 mg/dl; any diabetic exhibiting signs of ketoacidosis, such as nausea, vomiting, or abdominal pain; when blood glucose levels are consistently elevated; and in pre-existing pregnancy diabetes and gestational diabetes mellitus. In a 2004 position statement on the tests of glycemia, ADA stated that blood ketone testing methods that quantify ß-hydroxybutyric acid, the predominant ketone body, are available and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for ß-hydroxybutyric acid are available. In their discussions of ketone testing, the ADA indicates that either blood or urine ketone testing are appropriate when ketone testing is indicated. Urine ketone testing may be indicated when the blood sugar is over 300 mg/dl; when experiencing symptoms of hypoglycemia, hyperglycemia, or vomiting; when the breath smells fruity and/or during illness (e.g., cold, flu, infection). Women with type 1 diabetes who are pregnant should be offered ketone testing strips and advised to test for ketones in urine (ketonuria) or ketones in blood (ketonaemia) if they become hyperglycemic or unwell (ADA; 2019; ADA, 2013; Weber, et al., 2009; Kitabchi, et al., 2009; Laffel and Wood, 2008; Laffel, et al., 2006; ADA, 2004b).

Home Glycated Hemoglobin (A1C) Monitors

Glycated hemoglobin (GHb) (also referred to as glycohemoglobin, glycosylated hemoglobin, HbA1c, HbA1, or A1C) is a term used to describe a series of stable minor hemoglobin components formed from a combination of hemoglobin and glucose. It is used primarily to identify the plasma glucose concentration over time. The normal life span of the red blood cell (RBC) is 120 days. Once hemoglobin is glycated, it remains that way. During the life cycle of the RBC, there is a build-up of glycated hemoglobin, reflecting the glycemic history of the previous 120 days. The A1C test has been shown to predict the risk for development of many of the chronic complications in diabetes and is performed routinely in patients with diabetes (e.g., twice a year in patients who are meeting

goals, and quarterly in patients whose therapy has changed or who are not meeting goals). Based on the evidence, the ADA recommends that the goal of therapy for nonpregnant adults to reduce microvascular and neuropathic complication, in general, should be an A1C < 7%. Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin (ADA, 2019; NICE, 2016a). Home glycated hemoglobin monitors are not medically necessary because A1C testing can be performed during regularly scheduled office visits, where health care providers can properly interpret the test and modify the treatment plan as necessary.

Home glycated hemoglobin tests include FDA 510(k) approved products, such as the A1c Now® Self Check (Bayer HealthCare LLC, Tarrytown, NY), AccuBase A1c Glycohemoglobin Test Kit™ (Diabetes Technologies, Inc., Thomasville, GA) and the Home Access® A1C (Home Access Health Corp., Marlborough, MA) which the patient mails to the lab for analysis (FDA, 2017).

Hypoglycemic Wrist Band Alarm
A hypoglycemic alarm that looks like a wristband or watch has been proposed to alert diabetics to hypoglycemic episodes. Through sensors on the back surface of the device, electronic information is sent to a built-in microprocessor. When there is deviation from preset levels for skin temperature and/or perspiration, an alarm will sound. The device may be worn on the forearm, wrist or ankle. One of the disadvantages of the device is that activities that cause changes in skin temperature and/or perspiration can set off false alarms. An example of this device is the Sleep Sentry® (Diabetes Sentry Products, Inc., Bellingham, WA). The product is FDA approved by the premarket approval process (PMA) as a temperature and skin resistance measuring device. The clinical utility of these devices has not been proven. Therefore, these devices are considered convenience items and are not considered medically necessary.

Insulin Infusers
An insulin infuser is a device in which a cannula is inserted under the skin creating a portal that remains in place for 3–4 days. The presence of the cannula allows the patient to insert insulin into the subcutaneous tissue without subsequent injections. To apply an infuser an insertion needle guides a cannula under the skin, the insertion needle is removed and the cannula remains in the subcutaneous tissue. The insulin is then injected through the cannula. One of the concerns with this device is the development of an infection at the site of entry.

One example of an infuser is the i-port® (Patton Medical Devices, Austin, TX) which is FDA 510(k) approved as "a sterile, single use, low profile injection port through which physician prescribed medications can be injected subcutaneously from a standard syringe and needle, pen or alternative manual injection device. The device is designed to reduce the hardships of multiple daily subcutaneous injections by allowing users to receive physician prescribed medication, including insulin, without repeated needle punctures of the skin." It is intended for home and health care facility use (FDA, 2005). Other infusion devices include the insuflon™ (IntraPump Infusion Systems, Grapevine, TX), Inset 3® Infusion Set (Animas Corp., West Chester, PA) and the Medtronic Minimed® mio™ infusion set.

Blevins et al. (2008) conducted a randomized controlled cross-over trial to compare the outcomes of insulin-dependent diabetics (n=74) who used the i-port compared to standard multiple dose insulin injections. The patients, type 1 and type 2 diabetics, were randomly assigned to one of four cohorts. Cohort 1 (n=18) compared standard injections (SI) to single i-port, cohort 2 (n=20) compared single i-port to SI, cohort 3 (n=18) compared dual I-Ports (i.e., one for regular human and rapid-acting insulin and one for glargine), to single i-Port, and cohort 4 (n=18) compared single i-port to dual i-ports. At the end of the first three weeks, each group switched to the alternative method for an additional three weeks. Sixty-four participants completed all five follow-up visits. The ten who did not complete the trial terminated for device related issues (i.e., adhesive failure, discomfort, hyperglycemia, cannula bends and adverse events). For the SI and single i-port patients, the glycosylated albumin were within normal limits (98.9% and 107.3%, respectively) (p=0.99). The results for the single i-port vs. the dual i-port were also within normal limits (99.5% vs. 110.99%, respectively) (p=0.97). The A1C levels were similar among all subjects initially and at the completion of the study. Via questionnaire, patients reported that it was significantly more difficult to control their diabetes during the SI phase (p=0.16) and that their overall health

was very good or excellent using the i-port compared to SI ($p<0.001$). I-port adverse events included: erythema, suppuration, skin irritation, itching, bruising at the i-port insertion site and five events of severe hyperglycemia.

There is a lack of evidence demonstrating the clinical utility of insulin infusers. They are not considered medically necessary and are used primarily for the convenience of the patient.

Laser Lancets
An alternative to the standard lancet used for skin perforation to obtain a capillary blood sample for glucose measurement is the use of a laser lancet. The device emits a single shot laser beam that produces a small hole in the finger. The laser may be used by individuals who prefer not to use a needle/blade. It is proposed that the laser reduces tissue trauma and is less painful than a standard lancet. The laser lancet requires 510(k) FDA approval. An example of the laser lancet is the Lasette® Plus (Cell Robotics International, Inc., Albuquerque, NM). Laser lancets are not considered medically necessary because they have no proven clinical utility and are used primarily for the individual's convenience.

Glycated Serum Protein (GSP)
Measurements of total glycated serum proteins (GSPs) have been suggested as alternative methods for routine monitoring of glycemic control in patients with diabetes. GSP (e.g., fructosamine assay) provides an index of glycemia over the preceding 1–2 weeks as opposed to a 2–3 month period as seen with A1C levels. GSP is proposed to be useful in situations where A1C cannot be measured or may not be useful (e.g., hemolytic anemia). It is also proposed for use in pregnant diabetics or after major changes in therapy. However, the evidence is lacking as to the usefulness of GSP in these situations. According to Goldstein et al. (2004), "GSP is not equivalent to A1C and has not been shown to be related to the risk of the development or progression of chronic complications of diabetes." There is no conclusive evidence that correlates GSP concentration to the chronic complications of diabetes. Further studies are needed to determine whether these assays provide clinical information equivalent to A1C for routine management of patients with diabetes and, if so, whether they offer any significant advantages over A1C. Unlike the A1C test, GSP has not been shown to be related to the risk of development or progression of chronic complications of diabetes. The GSP is not considered equivalent to the A1C test, and the clinical utility of monitoring glycated serum protein has not been established (ADA, 2004b).

The first available home GSP device was the Duet™ Glucose Control System (LXN Corporation, San Diego, CA), which received FDA 510(k) approval in 1999. This device was discontinued due to concerns that the test strips were producing false-high results. The Duet System was replaced by the InCharge™ Diabetes Control System (LXN Corp., San Diego, CA). The InCharge has also been discontinued. Both of these devices measured blood glucose and glycated protein (Lindsey, et al., 2004).

Lindsey et al. (2004) conducted a prospective, three-center, randomized controlled study to "(1) compare the annual A1C results of subjects monitoring weekly fructosamine with those receiving usual care, (2) identify the number of subjects achieving goal A1C, and (3) determine if the addition of a weekly fructosamine test changed a subject's quality of life (i.e., concerns re diabetes control, anxiety and worry, social burden, sexual functioning, energy and mobility)." The study group performed weekly fructosamine and daily glucose tests (n=42), while the control group performed daily glucose testing (n=30). The majority of subjects were middle-aged, type 2 diabetics. Follow-up visits occurred at three-month intervals for a year, baseline and quarterly A1C tests were conducted, and quality of life assessments were measured at baseline and at the final study visit. Quality of life remained constant in both groups; seven subjects in each group attained an A1C < 7%. At the end of one year, blood glucose alone testing was shown to be superior to blood glucose plus fructosamine testing. However, weekly fructosamine testing resulted in a decrease in A1C values earlier and more consistently than blood glucose monitoring.

Petitti et al. (2001) conducted a randomized trial which compared weekly fructosamine monitoring and daily glucose monitoring (n=70) to a control group of daily glucose only (n=70). Patients were type 2 diabetics, age 18 years or older, had an A1C of ≥ 8%, not pregnant, disease-free, and able to self-administer the tests. Both groups exhibited significant improvements in glycemic control during the course of the study. The authors concluded that the addition of fructosamine testing to glucose testing did not improve glycemic control and, initially, control was poor with the study group. Author-noted limitations of the study included: lack of guidelines

regarding changes in diet, drugs, or medical follow-up based upon fructosamine test results; and patients were not instructed to reduce the frequency of glucose monitoring based upon fructosamine results.

Use Outside of the US
The National Institute for Health and Clinical Excellence (2016a), United Kingdom, guidance for diabetes management in children and young people who have type 1 diabetes included a recommendation for the diabetic to routinely perform at least five capillary blood glucose tests per day. A second recommendation stated that children and young people with type 1 diabetes should have blood ketone testing strips and a meter to test for ketonemia if they are ill or have hyperglycemia. Regarding diabetes and pregnancy (2015) NICE stated that if a woman with diabetes is planning to become pregnant she may need to increase the frequency of self-monitoring of blood glucose to include fasting levels and a mixture of pre-meal and post-meal levels if intensification of blood glucose-lowering therapy is needed. SMBG should be done in type 1 diabetic women planning to become pregnant or who are pregnant and type 2 diabetics or gestational diabetics who are on insulin. Ketone testing is recommended if they are ill or have hyperglycemia. For adults (2017a; 2017b) on insulin, various options for insulin injections should be offered including a pen injector or disposable pen. Special devices should be offered to individuals with manual or visual disabilities. Ketone monitoring (blood or urine) should be available to facilitate self-management of an episode of hyperglycemia or illness. Routine SMBG for type 2 diabetics is not recommended unless the person is on insulin, experiencing hypoglycemic episodes, is on oral medication that may increase their risk of hypoglycemia while driving or operating machinery, or is pregnant, or planning to become pregnant. Consider short-term SMBG in adults with type 2 diabetes when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycemia.

Diabetes Self-Management Education

Diabetes self-management education (DSME), also referred to as diabetes self-management training (DSMT), is the process of facilitating the knowledge, skill, and ability necessary for diabetes self-care (Powers, et al., 2015). In order to maintain optimal control of this condition, individuals or caregivers of individuals with diabetes must be directly involved in the day-to-day management of the disease. As such, diabetes is considered a self-managed disease. The national standards for DSME state diabetes self-management education and support (DSMES) is a critical element of care for all people with diabetes and those at risk for developing the condition. DSMES is the ongoing process of facilitating the knowledge, skills, and ability necessary for prediabetes and diabetes self-care, as well as activities that assist a person in implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis, beyond or outside of formal self-management training (Beck, et al., 2017).

The national standards include the following core content areas that demonstrate successful outcomes and must be reviewed to determine which are applicable to the participant (Beck, et al., 2017):

- Diabetes pathophysiology and treatment options
- Healthy eating
- Physical activity
- Medication usage
- Monitoring and using patient-generated health data (PGHD)
- Preventing, detecting, and treating acute and chronic complications
- Healthy coping with psychosocial issues and concerns
- Problem solving

The national standards note that while the content areas listed above provide a solid outline for a diabetes education and support curriculum, it is crucial that the content be tailored to match each individual's needs and be adapted as necessary for age, type of diabetes, cultural factors, health literacy and numeracy, and comorbidities (Beck, et al., 2017).

The instructor should be a skilled and experienced healthcare professional with recent education in diabetes, educational principles and behavior change strategies. The American Association of Diabetes Educators (AADE) noted that at least one of the instructors responsible for designing and planning DSME and Diabetes self-management support (DSMS) should be a registered nurse, registered dietitian, or pharmacist with training and

experience pertinent to DSME, or another professional with certification in diabetes care and education, such as a certified diabetes educator (CDE) or health care professional with Board Certified-Advanced Diabetes Management (BC-ADM) certification. Other health workers can contribute to DSME and provide DSMS with appropriate training in diabetes and with supervision and support (Powers, et al., 2016).

Literature Review
Several systematic reviews have been published regarding diabetes self-management education (Klein,et al., 2013; Loveman, et al., 2008; Ellis, et al., 2004; Norris, et al., 2002; Norris, et al., 2001). Overall it was noted in the reviews that although there was heterogeneity between studies there is evidence to support the effectiveness of diabetes self-management training. In 2007, Kulzer et al. (2007) conducted a randomized, prospective trial to test the efficacy of three education programs for type 2 diabetes. The conclusion was that self-management training had a significantly higher medium-term efficacy than the didactic diabetes education and that the group sessions were more effective than a more individualized approach. Wattana et al. (2007) conducted a randomized, controlled study of 147 patients to determine the effects of a diabetes self-management program on glycemic control, coronary heart disease (CHD) risk, and quality of life. The experimental group received the diabetes self-management program and the control group received the usual nursing care. The results of this trial indicated that the experimental group demonstrated a significant decrease in the glycosylated hemoglobin (HbA1c or A1C) level and CHD risk, with an increase in quality of life as compared to the control group.

Professional Societies/Organizations
Several specialty organizations have included DSME in their guidelines for management of diabetes.

The American Diabetes Association's (ADA) Standards of Medical Care in Diabetes (2019) include the following recommendations for DSME:

- In accordance with the national standards for diabetes self-management education and support, all people with diabetes should participate in diabetes self-management education to facilitate the knowledge, skills, and ability necessary for diabetes self-care Diabetes self-management support is additionally recommended to assist with implementing and sustaining skills and behaviors needed for ongoing self-management.
- There are four critical times to evaluate the need for diabetes self-management education and support: at diagnosis, annually, when complicating factors arise, and when transitions in care occur.
- Clinical outcomes, health status, and quality of life are key goals of diabetes self-management education and support to be measured and monitored as part of routine care.
- Diabetes self-management education and support should be patient centered, may be given in group or individual settings or using technology, and should be communicated with the entire diabetes care team.
- Because diabetes self-management education and support can improve outcomes and reduce costs , adequate reimbursement by third-party payers is recommended.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a consensus statement on management of type 2 diabetes (Handelsman, et al., 2015; Garber et al, 2017). The guidelines recommended that, persons with DM receive comprehensive DM self-management education at the time of DM diagnosis and subsequently as appropriate.

The Institute for Clinical Systems Improvement (ICSI) notes in their guidelines for management of type 2 diabetes, people with diabetes should receive DSME according to national standards and diabetes self-management support when their diabetes is first diagnosed and as needed thereafter. The treatment and management of diabetes should include patient education for self-management, including disease process, prevention of complications, risk reduction, medical compliance, foot care and available community resources (2014).

Use Outside of the US
The National Institute for Clinical Excellence (NICE) (United Kingdom) published guidance on management of Type 2 diabetes. The guidelines include the following recommendations for diabetes education (NICE, 2017):

- Offer structured education to adults with type 2 diabetes and/or their family members or carers (as appropriate) at and around the time of diagnosis, with annual reinforcement and review. Explain to people and their carers that structured education is an integral part of diabetes care.
- Ensure that any structured education program for adults with type 2 diabetes includes the following components:

    - It is evidence-based, and suits the needs of the person.
    - It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.
    - It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down.
    - It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the program.
    - It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.
    - The outcomes are audited regularly.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Home Blood Glucose Monitor

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
E0607	Home blood glucose monitor
E2100	Blood glucose monitor with integrated voice synthesizer
E2101	Blood glucose monitor with integrated lancing/blood sample

Continuous Glucose Monitoring System (CGMS)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
95249	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording
95250	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum 72 hours; analysis, interpretation and report

HCPCS Codes	Description
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, one unit = 1 day supply
A9277	Transmitter; external, for use with interstitial continuous glucose monitoring system
A9278	Receiver (monitor); external, for use with interstitial continuous glucose monitoring system
K0553	Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 unit of service

K0554	Receiver (monitor), dedicated, for use with therapeutic glucose continuous monitor system

Considered Experimental/Investigational/Unproven

CPT®* Codes	Description
0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation

Considered Convenience Item/Not Medically Necessary when used to report the use of additional software or hardware required for downloading data to a device, combination devices, remote glucose monitoring devices and/or hypoglycemic wristband alarm:

HCPCS Codes	Description
A9279	Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified
A9280	Alert or alarm device, not otherwise classified
E1399	Durable medical equipment, miscellaneous

External Insulin Pumps

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
A4224	Supplies for maintenance of insulin infusion catheter, per week
A4225	Supplies for external insulin infusion pump, syringe type cartridge, sterile, each
A4230	Infusion set for external insulin pump, non needle cannula type
A4231	Infusion set for external insulin pump, needle type
A4232	Syringe with needle for external insulin pump, sterile, 3cc
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
E0784	External ambulatory infusion pump, insulin
S1034	Artificial pancreas device system (e.g., low glucose suspend (LGS) feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
S1036	Transmitter; external, for use with artificial pancreas device system
S1037	Receiver (monitor); external, for use with artificial pancreas device system
S9145	Insulin pump initiation, instruction in initial use of pump (pump not included)

Diabetic Supplies

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
A4206	Syringe with needle, sterile, 1 cc or less, each
A4210	Needle-free injection device, each
A4211	Supplies for self-administered injections

A4215	Needle, sterile, any size, each
A4245	Alcohol wipes, per box
A4250	Urine test or reagent strips or tablets (100 tablets or strips)
A4252	Blood ketone test or reagent strip, each
A4253	Blood glucose test or reagent strips for home blood glucose monitor, per 50 strips
A4258	Spring-powered device for lancet, each
A4259	Lancets, per box of 100
S5560	Insulin delivery device, reusable pen; 1.5 ml size
S5561	Insulin delivery device, reusable pen; 3 ml size
S5570	Insulin delivery device, disposable pen (including insulin); 1.5 ml size
S5571	Insulin delivery device, disposable pen (including insulin); 3 ml size
S8490	Insulin syringes (100 syringes, any size)

Considered Experimental/Investigational/Unproven when used to report a home glycated serum protein (GSP) monitor:

HCPCS Codes	Description
E1399	Durable medical equipment, miscellaneous

Considered Not Medically Necessary/Convenience Item when used to report home glycated hemoglobin (A1C) monitors, hypoglycemic wristband alarm (e.g., Sleep Sentry), laser lancet and/or insulin infusers (e.g., i-port®):

HCPCS Codes	Description
A4257	Replacement lens shield cartridge for use with laser skin piercing device, each
E0620	Skin piercing device for collection of capillary blood, laser, each
E1399	Durable medical equipment, miscellaneous

Diabetes Self-Management Education

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
G0108	Diabetes outpatient self-management training services, individual, per 30 minutes
G0109	Diabetes outpatient self-management training services, group session (2 or more), per 30 minutes

References

1. Abbott Laboratories. FreeStyle Libre Flash Glucose Monitoring System. 2018. Accessed Dec 19, 2018. Available at URL address: https://www.freestylelibre.us/

2. Agrawal P, Welsh JB, Kannard B, Askari S, Yang Q, Kaufman FR. Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump. J Diabetes Sci Technol. 2011 Sep 1;5(5):1137-41.

3. Alemzadeh R, Palma-Sisto P, Holzum M, Parton E, Kicher J. Continuous subcutaneous insulin infusion attenuated glycemic instability in preschool children with type 1 diabetes mellitus. Diabetes Technol Ther. 2007 Aug;9(4):339-47.

4. Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, Bergenstal RM, Toschi E, Ahmann AJ, Shah VN0, Rickels MR, Bode BW, Philis-Tsimikas A, Pop-Busui R, Rodriguez H, Eyth E,

Bhargava A, Kollman C, Beck RW; REPLACE-BG Study Group. REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes. Diabetes Care. 2017 Apr;40(4):538-545.

5. American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology. 2016 Outpatient Glucose Monitoring Consensus Statement. Accessed Dec 13, 2018. Available at URL address: https://www.aace.com/publications/position-statements

6. American College of Obstetricians and Gynecologists (ACOG). 201 Pregestational Diabetes Mellitus (November 20, 2018) (Replaces Practice Bulletin Number 60, March 2005). Accessed Dec 19. 2018. Available at URL address: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins-List

7. American College of Obstetricians and Gynecologists (ACOG). Pregestational diabetes mellitus. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2005 Mar. Reaffirmed 2016. 11 p. (ACOG practice bulletin; no. 60). Accessed Dec 19, 2018. Available at URL address: https://www.acog.org/-/media/List-of-Titles/PBListOfTitles.pdf?dmc=1&ts=20170210T1620592463

8. American Diabetes Association (ADA). Checking for ketones. 2013. Accessed Dec 19, 2018. Available at URL address: http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/checking-for-ketones.html

9. American Diabetes Association (ADA). Continuous subcutaneous insulin infusion. Jan, 2004. Accessed Dec 19, 2018. Available at URL address: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s110

10. American Diabetes Association (ADA). Consumer guide. All about infusion sets. 2018. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesforecast.org/2018/02-mar-apr/all-about-infusion-sets.html

11. American Diabetes Association (ADA). Consumer guide. Insulin pens. 2018. Accessed Dec 19, 2018. Available at URL address: http://main.diabetes.org/dforg/pdfs/2016/2016-cg-insulin-pens.pdf

12. American Diabetes Association (ADA). Diabetes Forecast. Consumer guide. Accessed Dec 13, 2018. Available at URL address: http://www.diabetesforecast.org/landing-pages/lp-consumer-guide.html

13. American Diabetes Association (ADA). Diabetes Forecast. Insulin pumps 2009-2018. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesforecast.org/landing-pages/dt-page.html?blood_glucose=cg-pumps

14. American Diabetes Association (ADA). Diabetes Forecast. Everything you need to know about infusion sets. Mar 2017a. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesforecast.org/2017/mar-apr/infusion-sets-101.html

15. American Diabetes Association (ADA). Diabetes Forecast. Everything you need to know about insulin pens. Mar 2017b. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesforecast.org/2017/mar-apr/insulin-pens-101.html

16. American Diabetes Association (ADA). Insulin administration. Position statement. Diabetes Care. 2004a;27:S106-7. Accessed Dec 20, 2018. Available at URL address: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106

17. American Diabetes Association (ADA) Insulin basics. 2015. Accessed Dec 20, 2019. Available at URL address: http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html

18. American Diabetes Association (ADA). Position statement. Tests of glycemia in diabetes. Diabetes Care. 2004b;27:S91-3. Accessed Dec 20, 2018. Available at URL address: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s91?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&andorexactfulltext=and&searchid=1105956189473_1074&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=27&firstpage=s91&resourcetype=1&journalcode=diaca

19. American Diabetes Association (ADA). Standards of medical care in diabetes (previously called clinical practice recommendations) 2019. Accessed Dec 21, 2018. Available at URL address: http://care.diabetesjournals.org/content/42/Supplement_1/S1

20. Anhalt H, Bohannon NJ. Insulin patch pumps: their development and future in closed-loop systems. Diabetes Technol Ther. 2010 Jun;12 Suppl 1:S51-8.

21. ASTS Enterprises. Jet injector comparison table. 2017. Accessed Dec 20, 2018. Available at URL address: https://www.injectneedlefree.com/compare-jet-injectors/

22. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. Diabetes Technol Ther. 2015 Nov;17(11):787-94.

23. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. Diabetes Technol Ther. 2015 Nov;17(11):787-94.

24. Bahartan K, Horman K, Gal A, Drexler A, Mayzel Y, Lin T. Assessing the Performance of a Noninvasive Glucose Monitor in People with Type 2 Diabetes with Different Demographic Profiles. J Diabetes Res. 2017;2017:4393497.

25. Bailey TS, Ahmann A, Brazg R, Christiansen M, Garg S, Watkins E, Welsh JB, Lee SW. Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor. Diabetes Technol Ther. 2014 May;16(5):277-83.

26. Bailey TS, Zisser HC, Garg SK. Reduction in hemoglobin A1C with real-time continuous glucose monitoring: results from a 12-week observational study. Diabetes Technol Ther. 2007 Jun;9(3):203-10.

27. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011 Apr;34(4):795-800.

28. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of Hypoglycemia With Predictive Low Glucose Insulin Suspension in Children With Type 1 Diabetes: A Randomized Controlled Trial. Diabetes Care. 2017 Jun;40(6):764-770.

29. Baxter J, Mitragotri S. Needle-free liquid jet injections: mechanisms and applications. Expert Rev Med Devices. 2006 Sep;3(5):565-74.

30. Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE; 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care. 2017 Jul 28.

31. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D; DIAMOND Study Group. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA. 2017a Jan 24;317(4):371-378.

32. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, McGill JB, Polonsky W, Price D, Aronoff S, Aronson R, Toschi E, Kollman C, Bergenstal R; DIAMOND Study Group. Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. Ann Intern Med. 2017b Sep 19;167(6):365-374.

33. Behrman RE, Kliegman RM, Jenson HB. 583.2 Type 1 diabetes mellitus (immune mediated) monitoring. In: Behrman: Nelson Textbook of Pediatrics, 17th ed. Philadelphia: Saunders: 2004.

34. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013 Jul 18;369(3):224-32.

35. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA; STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010 Jul 22;363(4):311-20.

36. Berhe T, Postellon D, Wilson B, Stone R. Feasibility and safety of insulin pump therapy in children aged 2 to 7 years with type 1 diabetes: a retrospective study. Pediatrics. 2006 Jun;117(6):2132-7.

37. Berikai P, Meyer PM, Kazlauskaite R, Savoy B, Kozik K, Fogelfeld L. Gain in patients' knowledge of diabetes management targets is associated with better glycemic control. Diabetes Care. 2007 Jun;30(6):1587-9.

38. Berthe E, Lireux B, Coffin C, Goulet-Salmon B, Houlbert D, Boutreux S, Fradin S, Reznik Y. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm Metab Res. 2007 Mar;39(3):224-9.

39. Biester T, Kordonouri O, Holder M, Remus K, Kieninger-Baum D, Wadien T, Danne T. "Let the Algorithm Do the Work": Reduction of Hypoglycemia Using Sensor-Augmented Pump Therapy with Predictive Insulin Suspension (SmartGuard) in Pediatric Type 1 Diabetes Patients. Diabetes Technol Ther. 2017 Mar;19(3):173-182.

40. Blackman SM, Raghinaru D, Adi S, Simmons JH, Ebner-Lyon L, Chase HP, Tamborlane WV, Schatz DA, Block JM, Litton JC, Raman V, Foster NC, Kollman CR, DuBose SN, Miller KM, Beck RW, DiMeglio LA. Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. Pediatr Diabetes. 2014 Dec;15(8):564-72.

41. Blevins T, Schwartz SL, Bode B, et al. A Study assessing an injection port for administration of insulin. Diabetes Spectr. 2008;21:197-202.

42. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, Yogev Y. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013 Nov;98(11):4227-49. Accessed Dec 19, 2018. Available at URL address: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines

43. Bode BW. Insulin pump use in type 2 diabetes. Diabetes Technol Ther. 2010 Jun;12 Suppl 1:S17-21.

44. Bohannon N, Bergenstal R, Cuddihy R, Kruger D, List S, Massaro E, Molitch M, Raskin P, Remtema H, Strowig S, Whitehouse F, Brunelle RL, Dreon D, Tan M. Comparison of a novel insulin bolus-patch with pen/syringe injection to deliver mealtime insulin for efficacy, preference, and quality of life in adults with diabetes: a randomized, crossover, multicenter study. Diabetes Technol Ther. 2011 Oct;13(10):1031-7.

45. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. *2016;* 388:2254-63.

46. Bonora B, Maran A, Ciciliot S, Avogaro A, Fadini GP. Head-to-head comparison between flash and continuous glucose monitoring systems in outpatients with type 1 diabetes. J Endocrinol Invest. 2016 Dec;39(12):1391-1399.

47. Boscari F, Galasso S, Acciaroli G, Facchinetti A, Marescotti MC, Avogaro A, Bruttomesso D. Head-to-head comparison of the accuracy of Abbott FreeStyle Libre and Dexcom G5 mobile. Nutr Metab Cardiovasc Dis. 2018a Jan 31. pii: S0939-4753(18)30020-6. [Epub ahead of print]

48. Boscari F, Galasso S, Facchinetti A, Marescotti MC, Vallone V, Amato AML, Avogaro A, Bruttomesso D. FreeStyle Libre and Dexcom G4 Platinum sensors: Accuracy comparisons during two weeks of home use and use during experimentally induced glucose excursions. Nutr Metab Cardiovasc Dis. 2018b Feb;28(2):180-186. doi: 10.1016/j.numecd.2017.10.023. Epub 2017 Nov 11.

49. Brazg RL, Bailey TS, Garg S, Buckingham BA, Slover RH, Klonoff DC, Nguyen X, Shin J, Welsh JB, Lee SW. The ASPIRE study: design and methods of an in-clinic crossover trial on the efficacy of automatic insulin pump suspension in exercise-induced hypoglycemia. J Diabetes Sci Technol. 2011 Nov 1;5(6):1466-71.

50. Brown SA, Breton MD, Anderson SM, Kollar L, Keith-Hynes P, Levy CJ, Lam DW, Levister C, Baysal N, Kudva YC, Basu A, Dadlani V, Hinshaw L, McCrady-Spitzer S, Bruttomesso D, Visentin R, Galasso S, Del Favero S, Leal Y, Boscari F, Avogaro A, Cobelli C, Kovatchev B1. Overnight Closed-Loop Control Improves Glycemic Control in a Multicenter Study of Adults With Type 1 Diabetes. J Clin Endocrinol Metab. 2017 Oct 1;102(10):3674-3682.

51. Buckingham BA, Bailey TS, Christiansen M, Garg S, Weinzimer S, Bode B, Anderson SM, Brazg R, Ly TT, Kaufman FR. Evaluation of a Predictive Low-Glucose Management System In-Clinic. Diabetes Technol Ther. 2017 May;19(5):288-292.

52. Canadian Agency for Drugs and Technologies in Health. Rapid Response Report. Insulin Pumps for Adults with Type 1 Diabetes: A Review of Clinical Effectiveness, Cost-effectiveness and Guidelines. Dec 10, 2015. Accessed Dec 19, 2018. Available at URL address: https://www.cadth.ca/insulin-pumps-adults-type-1-diabetes-review-clinical-effectiveness-cost-effectiveness-and-guidelines

53. Centers for Medicare and Medicaid [CMS]. Continuous glucose monitors – frequently asked questions. May 2017. Accessed Dec 19, 2018. Available at URL address: https://www.cgsmedicare.com/jc/pubs/news/2017/0517/cope3049.html

54. Centers for Medicare and Medicaid [CMS]. Two new K codes for therapeutic continuous glucose monitors. Jul 3, 2017. Accessed Dec 19, 2018. Available at URL address: https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM10013.pdf

55. Chase HP, Beck R, Tamborlane W, Buckingham B, Mauras N, Tsalikian E, et al. the diabetes research in children (DirectNet) study group. A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. Diabetes Care. 2005 May;28(5):1101-6.

56. Chase HP, Beck RW, Xing D, Tamborlane WV, Coffey J, Fox LA, Ives B, Keady J, Kollman C, Laffel L, Ruedy KJ. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther. 2010 Jul;12(7):507-15.

57. Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, Garg SK Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics. 2001; 107:222-6.

58. Chase HP, Roberts MD, Wightman C, Klingensmith G, Garg SK, Van Wyhe M, et al. Use of the GlucoWatch biographer in children with type 1 diabetes. Pediatrics. 2003 Apr;111(4 Pt 1):790-4.

59. Chetty VT, Almulla A, Odueyungbo A, Thabane L. The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: a systematic review. Diabetes Res Clin Pract. 2008 Jul;81(1):79-87.

60. Chico A, Saigi I, García-Patterson A, Santos MD, Adelantado JM, Ginovart G, de Leiva A, Corcoy R. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: influence of continuous subcutaneous insulin infusion and lispro insulin. Diabetes Technol Ther. 2010 Dec;12(12):937-45.

61. Chico A, Vida K, Rios P, Sutra M, No vials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia inpatients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements fir improving metabolic control. Dia Care. 2003 Apr;26(4):1153-7.

62. Choosing Wisely. 2017. Accessed Dec 13, 2018. Available at URL address: http://www.choosingwisely.org/

63. Chico A, Saigi I, García-Patterson A, Santos MD, Adelantado JM, Ginovart G, de Leiva A, Corcoy R. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: influence of continuous subcutaneous insulin infusion and lispro insulin. Diabetes Technol Ther. 2010 Dec;12(12):937-45.

64. Choudhary P, Shin J, Wang Y, Evans ML, Hammond PJ, Kerr D, Shaw JA, Pickup JC, Amiel SA.Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. Diabetes Care. 2011 Sep;34(9):2023-5.

65. Christiansen MP, Klaff LJ, Brazg R, Chang AR, Levy CJ, Lam D, Denham DS, Atiee G, Bode BW, Walters SJ, Kelley L, Bailey TS. A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor: PRECISE II. Diabetes Technol Ther. 2018 Mar;20(3):197-206.

66. Churchill JN, Ruppe RL, Smaldone A. Use of continuous insulin infusion pumps in young children with type 1 diabetes: a systematic review. J Pediatr Health Care. 2009 May-Jun;23(3):173-9.

67. Conget I, Battelino T, Giménez M, Gough H, Castañeda J, Bolinder J; SWITCH Study Group. The SWITCH study (sensing with insulin pump therapy to control HbA(1c): design and methods of a randomized controlled crossover trial on sensor-augmented insulin pump efficacy in type 1 diabetes suboptimally controlled with pump therapy. Diabetes Technol Ther. 2011 Jan;13(1):49-54.

68. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of insulin and patient-controlled analgesia pump technology: a 10-year Food and Drug Administration retrospective study of adverse events. Pediatrics. 2008 May;121(5):e1133-8.

69. Costa BM, Fitzgerald KJ, Jones KM, Dunning Am T. Effectiveness of IT-based diabetes management interventions: a review of the literature. BMC Fam Pract. 2009 Nov 17;10:72.

70. Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess 2010;14(11). iii-iv, xi-xvi, 1-181.

71. Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, Bläsig S, Wadien T, Zierow S, Hartmann R, Thomas A. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. Diabetes Technol Ther. 2011 Nov;13(11):1129-34. doi: 10.1089/dia.2011.0084.

72. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, et. al.. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017 Dec;40(12):1631-1640. doi: 10.2337/dc17-1600.

73. Davis SN, Horton ES, Battelino T, Rubin RR, Schulman KA, Tamborlane WV. STAR 3 randomized controlled trial to compare sensor-augmented insulin pump therapy with multiple daily injections in the treatment of type 1 diabetes: research design, methods, and baseline characteristics of enrolled subjects. Diabetes Technol Ther. 2010 Apr;12(4):249-55.

74. DeHennis A, Mortellaro MA, Ioacara S. Multisite Study of an Implanted Continuous Glucose Sensor Over 90 Days in Patients With Diabetes Mellitus. J Diabetes Sci Technol. 2015 Jul 29;9(5):951-6.

75. Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care. 2006b Dec;29(12):2730-2.

76. Deiss D, Hartmann R, Schmidt J, Kordonouri O. Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes. Exp Clin Endocrinol Diabetes. 2006a Feb;114(2):63-7.

77. Dexcom Inc. G6 continuous glucose monitor. 2018. Accessed Dec 19, 2018. Available at URL address: https://www.dexcom.com/faq/g6

78. Dexcom Inc. Product guides. Dexcom G5. 2018. Accessed Dec 19, 2018. Available at URL address: https://www.dexcom.com/guides

79. Diabetes Forecast. Consumer guide. Continuous glucose monitors. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesforecast.org/landing-pages/lp-consumer-guide.html

80. Diabetes Health. Product reference guide 2012-2018. Accessed Dec 19, 2018. Available at URL address: https://www.diabeteshealth.com/charts/

81. Diabetes Net. Diabetes Technology. 2014. Accessed Dec 19, 2018. Available at URL address: http://www.diabetesnet.com/diabetes-technology

82. Diabetes Research in Children Network (DirecNet) Study Group. The accuracy of the Guardian RT continuous glucose monitor in children with type 1 diabetes. Diabetes Technol Ther. 2008 Aug;10(4):266-72.

83. Diabetes Research in Children Network (DirecNet) Study Group, Buckingham B, Beck RW, Tamborlane WV, Xing D, Kollman C, Fiallo-Scharer R, Mauras N, Ruedy KJ, Tansey M, Weinzimer SA, Wysocki T. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr. 2007 Oct;151(4):388-93, 393.e1-2.

84. Diabetes Sentry. Product overview. 2013. Accessed Dec 19, 2018. Available at URL address: http://www.diabetessentry.com/product.htm

85. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. J Pediatr. 2004 Sep;145(3):380-4.

86. Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, Randell T, Smith A, Trevelyan N. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child. 2017 Jan 30. pii: archdischild-2016-311530. doi: 10.1136/archdischild-2016-311530. [Epub ahead of print])

87. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA. Diabetes patient education: a meta-analysis and meta-regression. Patient Educ Couns. 2004 Jan;52(1):97-105.

88. Endocrine Society. Clinical practice guidelines. Diabetes technology—Continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults. 2016. Accessed Dec 17, 2018. Available at URL address: https://www.endocrine.org/education-and-practice-management/clinical-practice-guidelines

89. Endocrine Society. Clinical practice guideline. Diabetes and Pregnancy. 2013. Accessed Dec 17, 2018. Available at URL address: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines

90. Eugster EA, Francis G; Lawson-Wilkins Drug and Therapeutics Committee. Position statement: Continuous subcutaneous insulin infusion in very young children with type 1 diabetes. Pediatrics. 2006 Oct;118(4):e1244-9.

91. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD005542. DOI: 10.1002/14651858.CD005542.pub3.

92. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy. A systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab. 2009 Mar;94(3):729-40.

93. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, Asztalos E, Barrett JFR, Sanchez JJ, de Leiva A, Hod M, Jovanovic L, Keely E, McManus R, Hutton EK, Meek CL, Stewart ZA, Wysocki T, O'Brien R, Ruedy K, Kollman C, Tomlinson G, Murphy HR; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017 Nov 25;390(10110):2347-2359. Accessed Jan 4, 2019. Available at URL address: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32400-5/fulltext#relatedClinic

94. Fonda SJ, Salkind SJ, Walker MS, Chellappa M, Ehrhardt N, Vigersky RA. Heterogeneity of responses to real-time continuous glucose monitoring (RT-CGM) in patients with type 2 diabetes and its implications for application. Diabetes Care. 2013 Apr;36(4):786-92.

95. Fonseca VA, Grunberger G, Anhalt H, Bailey TS, Blevins T, Garg SK, Handelsman Y, Hirsch IB, Orzeck EA, Roberts VL, Tamborlane W; Consensus Conference Writing Committee. Continuous Glucose Monitoring: A Consensus Conference Of The American Association Of Clinical Endocrinologists And American College Of Endocrinology. Endocr Pract. 2016 Aug;22(8):1008-21.

96. Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. Diabetes Care. 2005 Jun;28(6):1277-81.

97. Galderisi A, Schlissel E, Cengiz E. Keeping Up with the Diabetes Technology: 2016 Endocrine Society Guidelines of Insulin Pump Therapy and Continuous Glucose Monitor Management of Diabetes. Curr Diab Rep. 2017 Sep 23;17(11):111.

98. Gandhi GY, Kovalaske M, Kudva Y, Walsh K, Elamin MB, Beers M, Coyle C, Goalen M, Murad MS, Erwin PJ, Corpus J, Montori VM, Murad MH. Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. J Diabetes Sci Technol. 2011 Jul 1;5(4):952-65.

99. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm-2017 Executive

Summary. Endocr Pract. 2017 Feb;23(2):207-238. Accessed Dec 21, 2018. Available at URL address: https://www.aace.com/sites/all/files/diabetes-algorithm-executive-summary.pdf

100. Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. Diabetes Technol Ther. 2012 Mar;14(3):205-9.

101. Garg S, Jovanovic L. Relationship of fasting and hourly blood glucose levels to HbA1c values: safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor. Diabetes Care. 2006 Dec;29(12):2644-9.

102. Garg SK, Kelly WC, Voelmle MK, Ritchie PJ, Gottlieb PA, McFann KK, Ellis SL. Continuous home monitoring of glucose: improved glycemic control with real-life use of continuous glucose sensors in adult subjects with type 1 diabetes. Diabetes Care. 2007 Dec;30(12):3023-5.

103. Giménez M, Conget I, Jansà M, Vidal M, Chiganer G, Levy I. Efficacy of continuous subcutaneous insulin infusion in Type 1 diabetes: a 2-year perspective using the established criteria for funding from a National Health Service. Diabet Med. 2007 Nov 26;24(12):1419-1423.

104. Goldstein D, Little R, Lorenz R, Malone J, Nathan D, Peterson C, et al. American Diabetes Association (ADA) Tests of glycemia in diabetes. Diabetes Care. 2004 Jul;27(7):1761-73.

105. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetologia. 2008 Feb;51(2):233-40.

106. González-Romero S, González-Molero I, Fernández-Abellán M, Domínguez-López ME, Ruiz-de-Adana S, Olveira G, Soriguer F. Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with type 1 diabetes. Diabetes Technol Ther. 2010 Apr;12(4):263-9.

107. Grunberger G, Abelseth JM, Bailey TS, Bode BW, Handelsman Y, Hellman R, Jovanovič L, Lane WS, Raskin P, Tamborlane WV, Rothermel C. C. Consensus statement by the American Association Of Clinical Endocrinologists/American College Of Endocrinology Insulin Pump Management Task Force. Endocr Pract. 2014 May;20(5):463-89. Accessed Dec 19, 2018. Available at URL address: https://www.aace.com/publications/position-statements

108. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. Diabetes Ther. 2017a Feb;8(1):55-73.

109. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Ther. 2017b Jun;8(3):573-586.

110. Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, et al.; 2012 Standards Revision Task Force. National standards for diabetes self-management education and support. Diabetes Care. 2013 Jan;36 Suppl 1:S100-8.

111. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A Pilot Trial in Pediatrics with the Sensor-Augmented Pump: Combining Real-Time Continuous Glucose Monitoring with the Insulin Pump. J Pediatr. 2007 Jan;150(1):103-105.

112. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al.. American association of clinical endocrinologists and American college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87. Accessed Dec 21, 2018. Available at URL address: https://www.aace.com/publications/guidelines

113. Harman-Boehm I, Gal A, Raykhman AM, Zahn JD, Naidis E, Mayzel Y. Noninvasive glucose monitoring: a novel approach. J Diabetes Sci Technol. 2009 Mar 1;3(2):253-60.

114. Hayes Inc. Technology brief. Eversense continuous glucose monitor for maintaining glycemic control in adults with diabetes mellitus. Landsdale, PA: Hayes, Inc. Sept 14, 2018.

115. Heinemann L. Insulin pens and new ways of insulin delivery. Diabetes Technol Ther. 2013 Feb;15 Suppl 1:S48-59.

116. Heinemann L, Franc S, Phillip M, Battelino T, Ampudia-Blasco FJ, Bolinder J, Diem P, Pickup J, Hans Devries J. Reimbursement for continuous glucose monitoring: a European view. J Diabetes Sci Technol. 2012 Nov 1;6(6):1498-502.

117. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care. 2005 Jul;28(7):1568-73.

118. Hirsch IB, Armstrong D, Bergenstal RM, Buckingham B, Childs BP, Clarke WL, Peters A, Wolpert H. Clinical application of emerging sensor technologies in diabetes management: Consensus guidelines for continuous glucose monitoring (CGM).Diabetes Technol Ther. August 2008, 10(4): 232-246.

119. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, Santiago OM, Kolaczynski JW; Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care. 2005 Mar;28(3):533-8.

120. Hoeks LB, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med. 2011 Apr;28(4):386-94. doi: 10.1111/j.1464-5491.2010.03177.x.

121. Inker LA, Perrone RD. Assessment of kidney function. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA. Aug 27, 2014.

122. Institute for Clinical Systems Improvement (ICSI). Diabetes Mellitus in Adults, Type 2; Diagnosis and Management of (Guideline). 7/2010; updated July 2014. Accessed Dec 21, 2018. Available at URL address: https://www.icsi.org/

123. Integrity Applications. GlucoTrack. 2019. Accessed Jan 2, 2019. Available at URL address: http://www.integrity-app.com/the-glucotrack/the-products/

124. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, Siebenhofer A. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008 Jun;51(6):941-51.

125. Ji L, Guo X, Guo L, Ren Q, Yu N, Zhang J. A Multicenter Evaluation of the Performance and Usability of a Novel Glucose Monitoring System in Chinese Adults With Diabetes. J Diabetes Sci Technol. 2016 Aug 23. pii: 1932296816662884. [Epub ahead of print]

126. Johnson SL, McEwen LN, Newton CA, Martin CL, Raskin P, Halter JB, Herman WH. The impact of continuous subcutaneous insulin infusion and multiple daily injections of insulin on glucose variability in older adults with type 2 diabetes. Diabetes Complications. 2010 Nov 8. [Epub ahead of print].

127. Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N,

O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76.

128. Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group, Bode B, Beck RW, Xing D, Gilliam L, Hirsch I, Kollman C, Laffel L, Ruedy KJ, Tamborlane WV, Weinzimer S, Wolpert H. Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care. 2009a Nov;32(11):2047-9.

129. Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009b Aug;32(8):1378-83.

130. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Fiallo-Scharer R, Cheng J, Beck RW, Buckingham BA, Chase HP, Kollman C, Laffel L, Lawrence JM, Mauras N, Tamborlane WV, Wilson DM, Wolpert H. Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Foundation continuous glucose monitoring randomized control trial dataset. Diabetes Research Diabetes Care. 2011 Mar;34(3):586-90.

131. Kalra S, Gupta Y. Ambulatory glucose profile: Flash glucose monitoring. J Pak Med Assoc. 2015 Dec;65(12):1360-2.

132. Kapellen TM, Heidtmann B, Bachmann J, Ziegler R, Grabert M, Holl RW. Indications for insulin pump therapy in different age groups: an analysis of 1,567 children and adolescents. Diabet Med. 2007 Aug;24(8):836-42.

133. Keenan DB, Cartaya R, Mastrototaro JJ. Accuracy of a new real-time continuous glucose monitoring algorithm. J Diabetes Sci Technol. 2010 Jan 1;4(1):111-8.

134. Keenan DB, Mastrototaro JJ, Zisser H, Cooper KA, Raghavendhar G, Lee SW, Yusi J, Bailey TS, Brazg RL, Shah RV. Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther. 2012 Mar;14(3):225-31. doi: 10.1089/dia.2011.0199.

135. Kestilä KK, Ekblad UU, Rönnemaa T. Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. Diabetes Res Clin Pract. 2007 Aug;77(2): 174-9.

136. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–1343

137. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM; American Diabetes Association (ADA). Hyperglycemic crises in diabetes. Diabetes Care. 2004 Jan;27 Suppl 1:S94-102.

138. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, Gunderson EP, Herman WH, Hoffman LD, Inturrisi M, Jovanovic LB, Kjos SI, Knopp RH, Montoro MN, Ogata ES, Paramsothy P, Reader DM, Rosenn BM, Thomas AM, Kirkman MS. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care. 2008 May;31(5):1060-79.

139. Klein HA, Jackson SM, Street K, Whitacre JC, Klein G. Diabetes self-management education: miles to go. Nurs Res Pract. 2013;2013:581012.

140. Kordonouri O, Hartmann R, Lauterborn R, Barnekow C, Hoeffe J, Deiss D. Age-specific advantages of continuous subcutaneous insulin infusion as compared with multiple daily injections in pediatric patients: one-year follow-up comparison by matched-pair analysis. Diabetes Care. 2006 Jan;29(1):133-4.

141. Kordonouri O, Pankowska E, Rami B, Kapellen T, Coutant R, Hartmann R, Lange K, Knip M, Danne T. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. Diabetologia. 2010 Dec;53(12):2487-95.

142. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Mize LB, Farret A, Place J, Bruttomesso D, Del Favero S, Boscari F, Galasso S, Avogaro A, Magni L, Di Palma F, Toffanin C, Messori M, Dassau E, Doyle FJ 3rd. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care. 2014 Jul;37(7):1789-96.

143. Kropff J, Choudhary P, Neupane S, Barnard K, Bain SC, Kapitza C, Forst T, Link M, Dehennis A, DeVries JH0. Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial. Diabetes Care. 2017 Jan;40(1):63-68.

144. Kulzer B, Hermanns N, Reinecker H, Haak T. Effects of self-management training in Type 2 diabetes: a randomized, prospective trial. Diabet Med. 2007 Apr;24(4):415-23.

145. Laffel LM, Hsu WC, McGill JB, Meneghini L, Volkening LK. Continued use of an integrated meter with electronic logbook maintains improvements in glycemic control beyond a randomized, controlled trial.Diabetes Technol Ther. 2007 Jun;9(3):254-64.

146. Laffel LM, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. Diabet Med. 2006 Mar;23(3):278-84.

147. Laffel LMB, Wood JRS. Ch 143 – diabetes mellitus in children and adolescents. In: Rakel & Bope: Conn't Current Therapy 2008, 60th ed. W.B. Saunders, St. Louis, 2008.

148. Lagarde WH, Barrows FP, Davenport ML, Kang M, Guess HA, Calikoglu AS. Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial. Pediatr Diabetes. 2006 Jun;7(3):159-64.

149. Langendam MW., Luijf YM, Hooft L, DeVries JH, Mudde AH, Scholten RJPM. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD008101. DOI: 10.1002/14651858.CD008101.pub2.

150. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

151. Levy JC, Davies MJ, Holman RR; 4-T Study Group. Continuous glucose monitoring detected hypoglycaemia in the Treating to Target in Type 2 Diabetes Trial (4-T). Diabetes Res Clin Pract. 2017 Sep;131:161-168.

152. Liebl A, Henrichs HR, Heinemann L, Freckmann G, Biermann E, Thomas A; Continuous Glucose Monitoring Working Group of the Working Group Diabetes Technology of the German Diabetes Association. Continuous glucose monitoring: evidence and consensus statement for clinical use. J Diabetes Sci Technol. 2013 Mar 1;7(2):500-19.

153. Lin T, Mayzel Y, Bahartan K. The accuracy of a non-invasive glucose monitoring device does not depend on clinical characteristics of people with type 2 diabetes mellitus. J Drug Assess. 2018 Jan 11;7(1):1-7.

154. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Ólafsdóttir AF, Frid A, Wedel H, Ahlén E, Nyström T, Hellman J. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA. 2017 Jan 24;317(4):379-387.

155. Lindsey CC, Carter AW, Mangum S, Greene D, Richardson A, Brown SJ, Essary JL, McCandless B. A prospective, randomized, multicentered controlled trial to compare the annual glycemic and quality outcomes of patients with diabetes mellitus monitored with weekly fructosamine testing versus usual care. Diabetes Technol Ther. 2004 Jun;6(3):370-7.

156. Lorenz C, Sandoval W, Mortellaro M. Interference Assessment of Various Endogenous and Exogenous Substances on the Performance of the Eversense Long-Term Implantable Continuous Glucose Monitoring System. Diabetes Technol Ther. 2018 May;20(5):344-352.

157. Loveman E, Frampton GK, Clegg AJ. The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review. Health Technol Assess. 2008 Apr;12(9):1-116, iii.

158. Lucidarme N, Alberti C, Zaccaria I, Claude E, Tubiana-Rufi N. Alternate-site testing is reliable in children and adolescents with type 1 diabetes, except at the forearm for hypoglycemia detection. Diabetes Care. 2005 Mar;28(3):710-1.

159. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics. 2003 May;111(5 Pt 1):933-8.

160. Ly TT, Nicholas JA, Retterath A, Davis EA, Jones TW. Analysis of glucose responses to automated insulin suspension with sensor-augmented pump therapy. Diabetes Care. 2012 Jul;35(7):1462-5. doi: 10.2337/dc12-0052.

161. Ly TT, Nicholas JA, Retterath A, et al. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2013;310(12):1240-1247.

162. Malanda UL, Welschen LMC, Riphagen II, Dekker JM, Nijpels G, Bot SDM. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD005060. DOI: 10.1002/14651858.CD005060.pub3

163. Mastrototaro JJ, Cooper KW, Soundararajan G, Sanders JB, Shah RV. Clinical experience with an integrated continuous glucose sensor/insulin pump platform: a feasibility study. Adv Ther. 2006 Sep-Oct;23(5):725-32.

164. Mastrototaro J, Shin J, Marcus A, Sulur G; STAR 1 Clinical Trial Investigators. The accuracy and efficacy of real-time continuous glucose monitoring sensor in patients with type 1 diabetes. Diabetes Technol Ther. 2008 Oct;10(5):385-90.

165. Mazze RS, Strock E, Wesley D, Borgman S, Morgan B, Bergenstal R, Cuddihy R. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. Diabetes Technol Ther. 2008 Jun;10(3):149-59.

166. McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. Aust N Z J Obstet Gynaecol. 2007 Jun;47(3):186-90.

167. McVean JJ, Eickhoff JC, MacDonald MJ. Factors correlating with improved A1C in children using continuous subcutaneous insulin infusion. Diabetes Care. 2007 Oct;30(10):2499-500.

168. Meas T, Taboulet P, Sobngwi E, Gautier JF. Is capillary ketone determination useful in clinical practice? In which circumstances? Diabetes Metab. 2005 Jun;31(3 Pt 1):299-303.

169. Medtronic MiniMed Inc. mySentry. 2018. Accessed Dec 19, 2018. Available at URL address: http://www.medtronicdiabetes.com/customer-support/device-settings-and-features/mysentry-settings/setting-up-your-mysentry

170. Medtronic MiniMed Inc. Products. 2018. Accessed Dec 19, 2018. Available at URL address: https://www.medtronicdiabetes.com/products/minimed-630g-insulin-pump-system

171. Medtronic MiniMed Inc. Warranties. 2018. Accessed Dec 19, 2018. Available at URL address; http://www.medtronicdiabetes.com/customer-support/tool-download-library/warranties

172. Meneghini L. Why and how to use insulin therapy earlier in the management of type 2 diabetes. South Med J. 2007 Feb;100(2):164-74.

173. Meneghini L, Kennedy L, Koff R, Kuritzky L, Leal S, Peterson K, Zamudio V. Appropriate advancement of type 2 diabetes therapy. J Fam Pract. 2007 Oct;56(10 Suppl A):19A-29A.

174. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD005103. DOI: 10.1002/14651858.CD005103.pub2.

175. Mitragotri. Current status and future prospects of needle-free liquid jet injectors. Nat Rev Drug Discov. 2006 Jun 23.

176. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol. 2010 Dec;47(Suppl 1):77-81.

177. Mortellaro M, DeHennis A. Performance characterization of an abiotic and fluorescent-based continuous glucose monitoring system in patients with type 1 diabetes. Biosens Bioelectron. 2014 Nov 15;61:227-31.

178. Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. Am J Obstet Gynecol. 2007 Nov;197(5):447-56.

179. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, Fowler D, Temple RC. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care. 2007 Nov;30(11):2785-91.

180. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, Fowler D, Campbell PJ, Temple RC. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008 Sep 25;337:a1680.

181. Nabhan ZM, Kreher NC, Greene DM, Eugster EA, Kronenberger W, DiMeglio LA. A randomized prospective study of insulin pump vs. insulin injection therapy in very young children with type 1 diabetes: 12-month glycemic, BMI, and neurocognitive outcomes. Pediatr Diabetes. 2009 May;10(3):202-8.

182. Nahata L. Insulin therapy in pediatric patients with type I diabetes: continuous subcutaneous insulin infusion versus multiple daily injections. Clin Pediatr (Phila). 2006 Jul;45(6):503-8.

183. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of

hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009 Jan;32(1):193-203.

184. National Institute for Health and Clinical Excellence (NICE). Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. NICE technology appraisal guidance (TA151), Jul 2008. Accessed Dec 13, 2018. Available at URL address: http://www.nice.org.uk/guidance/ta151

185. National Institute for Health and Clinical Excellence (NICE). Diabetes (type 1 and type 2) in children and young people: diagnosis and management. Nice guidelines (NG18). Aug 2015; updated 2016a. Accessed Dec 13, 2018. Available at URL address: http://www.nice.org.uk/guidance/ng18

186. National Institute for Health and Clinical Excellence (NICE). Type 1 diabetes in adults: diagnosis and management. Nice guidelines (NG17). Aug 2015; updated 2016a. Accessed Dec 13, 2018. Available at URL address: http://www.nice.org.uk/guidance/ng17

187. National Institute for Health and Clinical Excellence (NICE). Type 2 diabetes in adults: management. Nice guidelines (NG28). Dec 2015b; updated 2017b. Accessed Dec 13, 2018. Available at URL address: https://www.nice.org.uk/guidance/ng28

188. National Institute for Clinical Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline (NG 3). Feb 2015. Accessed Dec 13, 2018. Available at URL address: http://www.nice.org.uk/guidance/ng3

189. National Institute for Clinical Excellence (NICE). Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. Technology appraisal guidance (TA151). Jul 2008. Accessed Dec 13, 2018. Available at URL address: http://www.nice.org.uk/guidance/ta151

190. National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Education Program (NDEP). Guiding Principles for the Care of People With or at Risk for Diabetes. Updated Aug 2018. Accessed Dec 21, 2018. Available at URL address: https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/health-care-professionals/guiding-principles/Pages/index.aspx

191. Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, et al. A randomized controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol Assess 2009;13(28).

192. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care. 2001 Mar;24(3):561-87.

193. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes Care. 2002 Jul;25(7):1159-71.

194. Noh YH, Lee SM, Kim EJ, Kim DY, Lee H, Lee JH, Lee JH, Park SY, Koo JH, Wang JH, Lim IJ, Choi SB. Improvement of cardiovascular risk factors in patients with type 2 diabetes after long-term continuous subcutaneous insulin infusion. Diabetes Metab Res Rev. 2008 Jul-Aug;24(5):384-91.

195. Omnipod. PDM warranty. 2016. Accessed Dec 19, 2018. Available at URL address: https://www.myomnipod.com/sites/default/files/inline-files/17845-5A%20Guide%2C%20Eros%20US%20User%20Guide%20Rev%20B.pdf

196. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. Pediatr Diabetes. 2007 Dec;8(6):377-83.

197. Overgaard Ingeholm I, Svensson J, Olsen B, Lyngsøe L, Thomsen J, Johannesen J; DSBD. Characterization of metabolic responders on CSII treatment amongst children and adolescents in Denmark from 2007 to 2013. Diabetes Res Clin Pract. 2015 Aug;109(2):279-86.

198. Pańkowska E, Szypowska A, Lipka M, Skórka A. Sustained metabolic control and low rates of severe hypoglycaemic episodes in preschool diabetic children treated with continuous subcutaneous insulin infusion. Acta Paediatr. 2007 Jun;96(6):881-4.

199. Parkner T, Laursen T, Vestergaard ET, Hartvig H, Smedegaard JS, Lauritzen T, Christiansen JS. Insulin and glucose profiles during continuous subcutaneous insulin infusion compared with injection of a long-acting insulin in Type 2 diabetes. Diabet Med. 2008 May;25(5):585-91.

200. Patton Medical Devices, LP. I-Port Injection Port. 2015. Accessed Dec 20, 2018. Available at URL address: http://www.i-port.com/

201. Petitti DB, Contreras R, Dudl J. Randomized trial of fructosamine home monitoring in patients with diabetes. Eff Clin Pract. 2001 Jan-Feb;4(1):18-23.

202. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations : A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetologia. 2017 Dec;60(12):2319-2328.

203. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F; European Society for Paediatric Endocrinology; Lawson Wilkins Pediatric Endocrine Society; International Society for Pediatric and Adolescent Diabetes; American Diabetes Association; European Association for the Study of Diabetes. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2007 Jun;30(6):1653-62.

204. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years. Diabetes Care. 2002;25(3);593-8.

205. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care. 2008 Feb;31 Suppl 2:S140-5.

206. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008 Jul;25(7):765-74.

207. Pohar SL. Subcutaneous open-loop insulin delivery for type 1 diabetes: Paradigm Real-Time System. Issues Emerg Health Technol. 2007 Oct;(105):1-6.

208. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. Diabetol Metab Syndr. 2013 Jul 23;5(1):39. [Epub ahead of print]

209. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F; European Society for Paediatric Endocrinology; Lawson Wilkins Pediatric Endocrine Society; International Society for Pediatric and Adolescent Diabetes; American Diabetes Association; European Association for the Study of Diabetes. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2007 Jun;30(6):1653-62.

210. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years. Diabetes Care. 2002;25(3);593-8.

211. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care. 2008 Feb;31 Suppl 2:S140-5.

212. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008 Jul;25(7):765-74.

213. Pohar SL. Subcutaneous open-loop insulin delivery for type 1 diabetes: Paradigm Real-Time System. Issues Emerg Health Technol. 2007 Oct;(105):1-6.

214. Powers MA, Bardsley J, Cypress M, Duker P, Funnell MM, Fischl AH, et al. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. Clin Diabetes. 2016 Apr;34(2):70-80.

215. Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, Jeandidier N, Nicolino M. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care. 2009 Dec;32(12):2245-50.

216. Rai S, Hulse A, Kumar P. Feasibility and acceptability of ambulatory glucose profile in children with Type 1 diabetes mellitus: A pilot study. Indian J Endocrinol Metab. 2016 Nov-Dec;20(6):790-794.

217. Raman P, Shepherd E, Dowswell T, Middleton P, Crowther CA. Different methods and settings for glucose monitoring for gestational diabetes during pregnancy. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD011069. DOI:10.1002/14651858.CD011069.pub2.

218. Ramchandani N, Heptulla RA. New technologies for diabetes: a review of the present and the future. Int J Pediatr Endocrinol. 2012 Oct 26;2012(1):28.

219. Raskin P, Bode BW, Marks JB, Hirsch IB, Weinstein RL, McGill JB, Peterson GE, Mudaliar SR, Reinhardt RR. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. Diabetes Care. 2003 Sep;26(9):2598-603.

220. Reznik Y, Cohen O, Aronson R, Conget I, Runzis S, Castaneda J, Lee SW; OpT2mise Study Group.. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet. 2014 Oct 4;384(9950):1265-72.

221. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, Hellman R, Jellinger PS, Jovanovic LG, Levy P, Mechanick JI, Zangeneh F; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007 May-Jun;13 Suppl 1:1-68.

222. Rodbard D, Jovanovic, L, and Garg, SK. Responses to continuous glucose monitoring in subjects with type 1 diabetes using continuous subcutaneous insulin infusion or multiple daily injections. Diabetes Technol Ther. 2009;11(12):757-765.

223. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsman Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009 Sep-Oct;15(6):540-59. Erratum in: Endocr Pract. 2009 Nov-Dec;15(7):768-70.

224. Russell-Minda E, Jutai J, Speechley M, Bradley K, Chudyk A, Petrella R. Health technologies for monitoring and managing diabetes: a systematic review. J Diabetes Sci Technol. 2009 Nov 1;3(6):1460-71.

225. Salsali A, Nathan M. A review of types 1 and 2 diabetes mellitus and their treatment with insulin. Am J Ther. 2006 Jul-Aug;13(4):349-61.

226. Sarol JN Jr, Nicodemus NA Jr, Tan KM, Grava MB. Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin requiring type 2 diabetes patients: a meta-analysis (1966-2004). Curr Med Res Opin. 2005 Feb;21(2):173-84.

227. Schaeffer NE. The role of human factors in the design and development of an insulin pump. J Diabetes Sci Technol. 2012 Mar 1;6(2):260-4.

228. Schaeffer NE, Parks LJ, Verhoef ET, Bailey TS, Schorr AB, Davis T, Halford J, Sulik B. Usability and training differences between two personal insulin pumps. J Diabetes Sci Technol. 2015 Mar;9(2):221-30.

229. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013 May;36(5):1384-95.

230. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care. 2013 Jul;36(7):1877-83.

231. Schutt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R, Mayer I, Rosenbauer J, Wagner C, Zimmermann A, Kerner W, Holl RW; DPV Initiative. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp Clin Endocrinol Diabetes. 2006 Jul;114(7):384-8.

232. Scottish Intercollegiate Guidelines Network (SIGN). 116 Management of diabetes. A national clinical guideline. 2010. Updated Nov 2017. Accessed Dec 13, 2018. Available at URL address: https://www.sign.ac.uk/sign-116-and-154-diabetes.html

233. Secher AL, Stage E, Ringholm L, Barfred C, Damm P, Mathiesen ER. Real-time continuous glucose monitoring as a tool to prevent severe hypoglycaemia in selected pregnant women with Type 1 diabetes - an observational study. Diabet Med. 2014 Mar;31(3):352-6.

234. Senseonics™ Inc., Eversense®. User guides. 2017. Accessed Dec 13, 2018. Available at URL address: https://www.eversensediabetes.com/user-guides/

235. Senseonics. Eversense® CGM system. 2016. Accessed Dec 13, 2018. Available at URL address: https://eversensediabetes.com/products/

236. Skladany MJ, Miller M, Guthermann JS, Ludwig CR. Patch-pump technology to manage type 2 diabetes mellitus: hurdles to market acceptance. J Diabetes Sci Technol. 2008 Nov;2(6):1147-50.

237. Skogsberg L, Fors H, Hanas R, Chaplin JE, Lindman E, Skogsberg J.Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. Pediatr Diabetes. 2008 Oct;9(5):472-9.

238. Society of General Internal Medicine. Choosing Wisely recommendations. Accessed Dec 20, 2018. Available at URL address: http://www.choosingwisely.org/societies/society-of-general-internal-medicine/

239. Soliman AT, Omar M, Rizk MM, El Awwa A, AlGhobashy FM. Glycaemic control with modified intensive insulin injections (MII) using insulin pens and premixed insulin in children with type-1 diabetes: a randomized controlled trial. J Trop Pediatr. 2006 Aug;52(4):276-81.

240. Soumerai S, Mah C, Zhang F, Adams A, Barton M, Fajitova V, Ross-Degnan D. Effects of health maintenance organization coverage of self-monitoring devices on diabetes self-care and glycemic control. Arch Intern Med. 2004 Mar;164(6):645-52.

241. Šoupal J, Petruželková L, Flekač M, Pelcl T, Matoulek M, Daňková M, Škrha J, Svačina Š, Prázný M. Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: A COMISAIR Study. Diabetes Technol Ther. 2016 Sep;18(9):532-8.

242. Spaic T, Driscoll M, Raghinaru D, Buckingham BA, Wilson DM, Clinton P, Chase HP, Maahs DM, Forlenza GP, Jost E, Hramiak I, Paul T, Bequette BW, Cameron F, Beck RW, Kollman C, Lum JW, Ly TT; In-Home Closed-Loop (IHCL) Study Group. Predictive Hyperglycemia and Hypoglycemia Minimization: In-Home Evaluation of Safety, Feasibility, and Efficacy in Overnight Glucose Control in Type 1 Diabetes. Diabetes Care. 2017 Mar;40(3):359-366.

243. Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D, Chang E. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Curr Med Res Opin. 2007 Jan;23(1):133-46.

244. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab. 2008 Mar;93(3):666-73.

245. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Eur J Endocrinol. 2012 Apr;166(4):567-74.

246. Tandem Diabetes Care. Insulin pump. 2018. Accessed Dec 19, 2018. Available at URL address: https://www.tandemdiabetes.com/products

247. Thomas LE, Kane MP, Bakst G, Busch RS, Hamilton RA, Abelseth JM. A glucose meter accuracy and precision comparison: the FreeStyle Flash Versus the Accu-Chek Advantage, Accu-Chek Compact Plus, Ascensia Contour, and the BD Logic. Diabetes Technol Ther. 2008 Apr;10(2):102-10.

248. U.S. Food and Drug Administration (FDA). 510(k) premarket notification. Product code NBW; glucose meters. Product code LZG insulin pumps. 2018. Accessed Dec 17, 2018. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

249. U.S. Food and Drug Administration (FDA). FDA-approved home and lab tests. Updated Dec 17, 2018. Accessed Dec 20, 2018. Available at URL address: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LabTest/ucm126079.htm

250. U.S. Food and Drug Administration. Dexcom G6 continuous glucose monitoring system. DEN170088. Accessed Dec 19, 2018. https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170088.pdf

251. US Food and Drug Administration (FDA). Eversense continuous glucose monitoring system. P160048. Jun 21, 2018. Accessed Dec 19, 2018. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160048

252. US Food and Drug Administration (FDA). FDA executive summary. P160048. Eversense Continuous Glucose Monitoring System. Accessed Sept 18, 2018. Available at URL address: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ClinicalChemistryandClinicalToxicologyDevicesPanel/UCM602657.pdf

253. U.S. Food and Drug Administration. FDA news release. FDA authorizes first fully interoperable continuous glucose monitoring system, streamlines review pathway for similar devices. March 27, 2018. Accessed Dec 17, 2018. Available at URL address: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm602870.htm?elqtrackid=72abb2ce738544889abbfaf48712175b

254. U.S. Food and Drug Administration (FDA). Home A1C devices. 510(k) premarket notification. Product code LCP. Accessed Dec 20, 2018. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?start_search=1&Center=&Panel=&ProductCode=lcp&KNumber=&Applicant=&DeviceName=&Type=&ThirdPartyReviewed=&ClinicalTrials=&Decision=&DecisionDateFrom=&DecisionDateTo=07%2F11%2F2017&IVDProducts=&Redact510K=&CombinationProducts=&ZNumber=&PAGENUM=500

255. U.S. Food and Drug Administration (FDA). Insulin pens. 510(k) premarket notification. Product code FMF. Accessed Dec 20, 2018. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

256. U.S. Food and Drug Administration (FDA). I-Port Injection Port. 510(k) premarket notification. K052389. Sep 9, 2005. Accessed Dec 20, 2018. Available at URL address: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K052389.pdf

257. U.S. Food and Drug Administration (FDA). March 29-30, 2018: Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Meeting Announcement. [Eversense]. Accessed Dec 19, 2018. Available at URL address: https://www.fda.gov/advisorycommittees/calendar/ucm598537.htm

258. U.S. Food and Drug Administration (FDA). mySentry. P980022/S075. Dec 20, 2011. Accessed Dec 19, 2018. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

259. U.S. Food and Drug Administration (FDA). Needle-free injection systems/Jet injectors. 510(k) premarket notification. Product code KZE. Accessed Dec 20, 2018. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

260. U.S. Food and Drug Administration (FDA). Premarket approval (PMA) data base. Product codes MDS, PQF, QCD. Continuous glucose monitors. Feb 2017. Accessed Dec 19, 2018. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

261. U.S. Food and Drug Administration. Premarket approval (PMA) data base. Product code OZO. Insulin pumps. Accessed Dec 19, 2018. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

262. U.S. Food and Drug Administration. What is the pancreas? What is an artificial pancreas device system? Dec 17, 2017. Accessed Dec 19, 2018. Available at URL address: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259548.htm

263. Vaddiraju S, Burgess DJ, Tomazos I, Jain FC, Papadimitrakopoulos F. Technologies for continuous glucose monitoring: current problems and future promises. J Diabetes Sci Technol. 2010 Nov 1;4(6):1540-62.

264. Varshosaz J. Insulin Delivery Systems for Controlling Diabetes. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery 2007, 1, 25-40.

265. Vigersky RA, Huang S, Cordero TL, Shin J, Lee SW, Chhabra H, Kaufman FR, Cohen O; OpT2mise Study Group. Improved HBA1C, total daily insulin dose, and treatment satisfaction with insulin pump therapy compared to multiple daily insulin injections in patients with type 2 diabetes irrespective of baseline c-peptide levels. Endocr Pract. 2018 May;24(5):446-452.

266. Voormolen DN, DeVries JH, Evers IM, Mol BW, Franx A. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. Obstet Gynecol Surv. 2013 Nov;68(11):753-63.

267. Wainstein J, Metzger M, Boaz M, Minuchin O, Cohen Y, Yaffe A, Yerushalmy Y, Raz I, Harman-Boehm I. Insulin pump therapy vs. multiple daily injections in obese Type 2 diabetic patients. Diabet Med. 2005 Aug;22(8):1037-46.

268. Wang X, Ioacara S, DeHennis A. Long-Term Home Study on Nocturnal Hypoglycemic Alarms Using a New Fully Implantable Continuous Glucose Monitoring System in Type 1 Diabetes. Diabetes Technol Ther. 2015 Nov;17(11):780-6.

269. Wattana C, Srisuphan W, Pothiban L, Upchurch SL. Effects of a diabetes self-management program on glycemic control, coronary heart disease risk, and quality of life among Thai patients with type 2 diabetes. Nurs Health Sci. 2007 Jun;9(2):135-41.

270. Weber C, Kocher S, Neeser K, Joshi SR. Prevention of diabetic ketoacidosis and self-monitoring of ketone bodies: an overview. Curr Med Res Opin. 2009 May;25(5):1197-207.

271. Weber KK, Lohmann T, Busch K, Donati-Hirsch I, Riel R. High frequency of unrecognized hypoglycaemias in patients with Type 2 diabetes is discovered by continuous glucose monitoring. Exp Clin Endocrinol Diabetes. 2007 Sep;115(8):491-4.

272. Wei Q, Sun Z, Yang Y, Yu H, Ding H, Wang S. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. Sci Rep 2016;6:19920.

273. Weinzimer S, Xing D, Tansey M, Fiallo-Scharer R, Mauras N, Wysocki T, Beck R, Tamborlane W, Ruedy K; Diabetes Research in Children Network (DirecNet) Study Group. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. Diabetes Care. 2008b Mar;31(3):525-7.

274. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshandri R. Insulin pump therapy. Diabetes Care. 2003;26:1079-87.

275. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care. 2005 Jun;28(6):1510-7.

276. White RD. Insulin pump therapy (continuous subcutaneous insulin infusion). Prim Care. 2007 Dec;34(4):845-71.

277. Wilson DM, Beck RW, Tamborlane WV, Dontchev MJ, Kollman C, Chase P, Fox LA, Ruedy KJ, Tsalikian E, Weinzimer SA; DirecNet Study Group. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. Diabetes Care. 2007 Jan;30(1):59-64.

278. Wolpert HA. The nuts and bolts of achieving end points with real-time continuous glucose monitoring. Diabetes Care. 2008 Feb;31 Suppl 2:S146-9.

279. Wood JR, Moreland EC, Volkening LK, Svoren BM, Butler DA, Laffel LM. Durability of insulin pump use in pediatric patients with type 1 diabetes. Diabetes Care. 2006 Nov;29(11):2355-60.

280. Yoo HJ, An HG, Park SY, Ryu OH, Kim HY, Seo JA, Hong EG, Shin DH, Kim YH, Kim SG, Choi KM, Park IB, Yu JM, Baik SH. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract. 2008 Oct;82(1):73-9.

281. Zisser HC, Bevier WC, Jovanovic L. Restoring euglycemia in the Basal state using continuous glucose monitoring in subjects with type 1 diabetes mellitus. Diabetes Technol Ther. 2007 Dec;9(6):509-16.