Diabetes Tests, Programs and Supplies

- Clinical Policy Bulletins
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Number: 0070

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses diabetes tests, programs and supplies.

Note: For Statement of Medical Necessity (SMN) precertification forms, see Specialty Pharmacy Precertification.

1. **Medical Necessity**

   Aetna considers the following medically necessary for members with diabetes:

   1. **Diabetes Self-Care Programs**

      Outpatient medical self-care programs when such programs meet the following criteria:

      1. The program consists of services of recognized healthcare professionals (e.g., physicians, registered dieticians, registered nurses, registered pharmacists); *and*
      2. The program is designed to educate the member about medically necessary diabetes self-care; *and*
      3. The program is ordered by the physician treating the member's diabetes and includes a statement signed by the physician that the service is needed.

   2. **Diabetic Supplies**

      The following diabetic supplies:

      1. Alcohol swabs;
      2. Blood glucose monitors;
      3. Blood glucose test strips;
      4. Control solutions;
      5. Insulin pens;
      6. Lancets;
      7. Needles and syringes for insulin administration; *and*
      8. Urine test tablets/strips.

   3. **Glutamic Acid Decarboxylase (GAD) Autoantibodies**

      1. Measurement of autoantibodies to GAD for distinguishing type 1 from type 2 diabetes when the clinical history is ambiguous and the results of testing will influence patient management;
      2. Measurement of anti-GAD antibodies in diagnosing stiff-person syndrome.

      Anti-GAD antibody measurement is considered experimental, investigational, or unproven for predicting the onset of diabetes and for all other indications.

   4. **Jet Injectors**

Jet injectors (e.g., Vita-Jet II, Advanta Jet, Freedom Jet, Medi-Jector EZ, Biojector 2000) as durable medical equipment (DME) when the member or the member's caregiver is physically unable to use a conventional needle-syringe.

The use of jet injectors for other reasons is considered a matter of preference and convenience.

5. **Continuous Glucose Monitoring (CGM) Devices**

    1. Short-term (72 hours to 1 week) *diagnostic use* of continuous glucose monitoring (CGM) devices for the following indications:

        1. For members with diabetes who have *either* of the following problems in controlling blood glucose level, unresponsive to conventional insulin dose adjustment:

            1. Hypoglycemia unawareness; *or*
            2. Repeated hypoglycemia (less than 50 mg/dL) and hyperglycemia (greater than 150 mg/dL) at the same time each day; *or*

        2. To diagnose primary islet cell hypertrophy (nesidioblastosis) or persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (congenital hypoglycemia) in members with symptoms suggestive of recurrent hypoglycemia. For short-term (72 hours to 1 week) diagnostic use, no more than 2 continuous glucose monitoring periods within a 12-month period;

    2. Long-term (greater than 1 week) therapeutic use of continuous glucose monitoring (CGM) devices (e.g., Dexcom, Eversense, Freestyle Libre, Guardian) for the following indications:

        1. **Criteria for Initial Approval**

            1. Member has a diagnosis of diabetes mellitus (type 1 or type 2) and meets *both* of the following:

                a. The member is using an intensive insulin regimen (defined as multiple daily injections [i.e., 3 or more injections per day] or insulin pump therapy); *and*
                b. The member meets *one* of the following criteria:

                    1. The member is less than 18 years of age; *or*
                    2. The member is not meeting glycemic targets; *or*
                    3. The member is experiencing hypoglycemia (including hypoglycemia unawareness); *or*

            2. Member has a diagnosis of glycogen storage disease;

        2. **Continuation of Therapy**

            1. The member has a diagnosis of diabetes mellitus and meets *all* of the following criteria:

                a. The member is using an intensive insulin regimen (defined as multiple daily injections [i.e., 3 or more injections per day] or insulin pump therapy); *and*
                b. The member meets *one* of the following:

                    1. The member has experienced improved glycemic control or decreased hypoglycemia episodes while using a CGM; *or*
                    2. The member is being assessed every 6 months by the prescriber for adherence to their CGM regimen and diabetes treatment plan; *or*

            2. All members (including new members) with diagnosis of glycogen storage disease meets all initial criteria.

    Long-term therapeutic use of a CGM device is considered experimental, investigational, or unproven for all other indications, including the following (not an all-inclusive list), because there is insufficient evidence of the clinical benefits of this approach for these indications:

    1. Gestational diabetes
    2. Member with type 2 diabetes not using intensive insulin regimens;
    3. Monitoring blood glucose in non-diabetic members following gastric bypass surgery
    4. Neonatal hypoglycemia
    5. Nesidioblastosis (primary islet cell hypertrophy).

3. **Artificial Pancreas Device Systems**

   For artificial pancreas device system that incorporate a continuous glucose monitor and insulin infusion pump, see CPB 0161 - Infusion Pumps

   For Trina Health artificial pancreas treatment, see CPB 0742 - Intermittent Intravenous Insulin Therapy.

4. **Blood Glucose Meters for Members with Visual Impairment**

   Reflectance meters with an electronic voice, automatic timers, and specially designed arrangements of supplies and materials to allow the visually impaired to use the equipment without assistance as DME only for legally blind (best corrected visual acuity less than 20/200) members with diabetes.

5. **Blood Glucose Monitors with Integrated Lancing/Blood Sample**

   Blood glucose monitors with integrated lancing/blood sample as DME in members with diabetes who meet *either* of the following criteria:

   1. Members who are legally blind (best corrected visual acuity less than 20/200); *or*
   2. Members with impairment of manual dexterity severe enough to require the use of this special monitoring system.

6. **Alternate Site Blood Glucose Monitors**

   Alternate site blood glucose monitors as DME for the following members with diabetes, when an alternate site blood glucose monitor is recommended by their physician:

   1. Children below age of 12 years; *or*
   2. Members who have used conventional blood glucose meters for at least 1 month (more than 30 days) and who have been non-compliant with blood glucose testing because of pain sensitivity or heavily callused fingertips.

   Alternate site blood glucose monitors have no proven value over standard blood glucose monitors for other indications.

7. **Disposable Blood Glucose Monitor**

   A disposable blood glucose monitor (e.g., the ReliOn NewTek (Hypoguard USA, Inc., Edina, MN)) is an acceptable alternative to a standard blood glucose monitor.

8. **Insulin Infusion Pumps**

   For insulin infusion pumps, please see CPB 0161 - Infusion Pumps.

9. **Flash Glucose Monitoring Systems**

   Intermittently scanned "flash" continuous glucose monitoring systems (FreeStyle Libre Flash Glucose Monitoring System) are an equally acceptable alternative to other continuous glucose monitoring systems for medically necessary indications.

10. **Implantable Glucose Sensors**

    Continuous glucose monitors with implantable glucose sensors (e.g., the Eversense E3 implantable CGM sensor) are an equally acceptable alternative to standard continuous glucose monitors for medically necessary indications.

11. **I-Port**

    Aetna considers the I-Port Injection Port (Patton Medical) a non-covered convenience item.

12. **Combinational Items**

Aetna considers combination devices that include a home blood glucose monitor combined with a blood pressure monitor, cholesterol screening analyzer, or other devices (e.g., cellular telephone) not specifically indicated for the management of diabetes mellitus as not medically necessary convenience items.

13. **Hypoglycemic Wristband Alarms**

    Aetna considers hypoglycemic wristband alarms (e.g., Sleep Sentry) a noncovered convenience item.

14. **Cellular Glucometry**

    Aetna considers a feature that allows wireless transmission of blood glucose test results (cellular-enabled glucometer) as an integral part of the glucometer and not separately reimbursed.

6. Experimental, Investigational, or Unproven

The following interventions are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

1. **Lasette™ Laser Blood Glucose Monitoring Device**

   The Lasette laser blood glucose monitoring device (Cell Robotics International Inc., Albuquerque, NM) uses a laser instead of a lancet to perforate the skin to obtain a blood sample for glucose measurement. There is insufficient evidence in the peer-reviewed medical literature that laser skin perforation offers clinically significant advantages over standard lancets.

2. **Glycated Serum Proteins (GSP)**

   The clinical utility of monitoring glycated serum proteins with devices to measure glycated serum proteins (fructosamine) (e.g., Duet™ Glucose Control System by LXN Corporation) has not been established.

3. **PreDX Test**

   The PreDx Test has inadequate evidence in the published peer-reviewed clinical literature regarding its effectiveness.

4. **GlucoWatch® Biographer Monitor**

   The GlucoWatch Biographer (Cygnus Inc, Redwood City, CA.), a glucose meter that is worn on the wrist.

5. **Home Glycated Hemoglobin Monitors**

   For home glycated hemoglobin (HbA1c or A1C) monitors (e.g., A1cNow Diabetes Monitor, Metrika Inc., Sunnyvale, CA) there are no prospective clinical studies demonstrating improvements in compliance or other clinically significant benefits of home A1C testing over laboratory A1C testing. Individual-case exceptions to this policy may be made upon medical review for members who are unable to access laboratory A1C testing.

6. **Diabetes Management Software**

   Aetna considers mobile application software (e.g., BlueStar, d-Nav) for self-management of diabetes experimental, investigational, or unproven because its effectiveness has not been established.

   Note: Aetna considers computer software for analyzing blood glucose monitor test results as an integral part of a blood glucose monitor and not separately reimbursed. In addition, software or hardware required for downloading data from a blood glucose monitor to a computer are considered an integral part of the blood glucose monitor and not separately reimbursed.

   For mobile application software for self-management of diabetes, see CPB 0999 - Prescription Digital Therapeutics.

7. **Personal Digital Assistant-Based Blood Glucose Monitor**

A personal digital assistant-based blood glucose monitoring device (e.g., TheraSense FreeStyle Tracker, Accu-Check Advantage Module) and module have not been shown in published clinical studies to improve clinical outcomes over standard blood glucose monitors. **Note:** A personal digital assistant (PDA) does not meet Aetna's definition of covered DME in that the PDA can be used in the absence of illness or injury.

8. **Infrared Thermometer Device**

   There is insufficient evidence for the effectiveness of an infrared thermometer device (e.g., TempTouch) for the intermittent measurement and monitoring of skin surface temperature in reducing the risk for diabetic foot ulceration.

9. **Measurement of Advanced Glycation End Products by Skin Autoflourescence**

   There is insufficient evidence of the effectiveness of measurement of advanced glycation end products by skin autofluorescence compared to the oral glucose tolerance test.

10. **Remote Glucose Monitoring**

    There is insufficient published evidence of the impact of remote glucose monitoring on clinical outcomes by remote wireless glucose monitoring devices (e.g., mySentry) for managing members with diabetes. Aetna does not cover an attachment to allow wireless transmission from a continuous glucose montor to a smart phone or computer (e.g., MiniMed Connect) because it is considered a convenience feature. Aetna provides no additional reimbursement for a wireless transmission feature that is integrated into a continuous glucose monitor (e.g., Dexcom SHARE) because it is considered a convenience feature.

11. **Cellular Activation Therapy**

    Cellular activation therapy by means of the Bionica Microdose infusion pump (Diabetic Innovations, Franklin lakes, NJ).

12. **Skin Microvascular Flow-Motion**

    Skin microvascular flow-motion for the management of diabetes mellitus.

7. Policy Limitations and Exclusions

Note: Except for Medicare plans and where coverage is mandated by state law, generally coverage for diabetic supplies would be provided under a pharmacy rider and not as part of medical coverage. Certain diabetic supplies may also be covered under the medical plan if no pharmacy or diabetic supplies rider is available. Please check plan benefits.

Note: Coverage of diabetic supplies varies by medical and pharmacy plan. Please check plan documents for details.

8. Related Policies

- CPB 0161 - Infusion Pumps
- CPB 0742 - Intermittent Intravenous Insulin Therapy.
- CPB 0999 - Prescription Digital Therapeutics

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
0403T	Preventive behavior change, intensive program of prevention of diabetes using a standardized diabetes prevention program curriculum, provided to individuals in a group setting, minimum 60 minutes, per day
82947	Glucose; quantitative, blood (except reagent strip)
82948	blood, reagent strip

Code	Code Description
82950	post glucose dose (includes glucose)
82962	Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use
83519	Immunoassay, analyte, quantitative; by radiopharmaceutical technique (eg, RIA)
86341	Islet cell antibody

CPT codes not covered for indications listed in the CPB:

0740T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; initial set-up and patient education
0741T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; provision of software, data collection, transmission, and storage, each 30 days
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adoponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score [PreDx Diabetes Risk Score]

Other CPT codes related to the CPB:

83036	Hemoglobin; glycosylated (A1C)
83037	glycosylated (A1C) by device cleared by FDA for home use
97802	Medical nutrition therapy; initial assessment and intervention, individual, face-to-face with the patient, each 15 minutes
97803	re-assessment and intervention, individual, face-to-face with the patient, each 15 minutes
97804	group (2 or more individual(s)), each 30 minutes

HCPCS codes covered if selection criteria are met:

A4206	Syringe with needle, sterile 1 cc or less, each
A4207	Syringe with needle, sterile 2 cc, each
A4208	Syringe with needle, sterile 3 cc, each
A4209	Syringe with needle, sterile 5 cc or greater, each
A4211	Supplies for self-administered injections
A4212	Non-coring needle or stylet with or without catheter
A4213	Syringe, sterile, 20 cc or greater, each
A4215	Needle, sterile, any size, each
A4221	Supplies for maintenance of drug infusion catheter, per week (list drug separately)
A4222	Infusion supplies for external drug infusion pump, per cassette or bag (list drugs separately)
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
A4233	Replacement battery, alkaline (other than J cell), for use with medically necessary home blood glucose monitor owned by patient, each
A4234	Replacement battery, alkaline, J cell, for use with medically necessary home blood glucose monitor owned by patient, each
A4235	Replacement battery, lithium, for use with medically necessary home blood glucose monitor owned by patient, each
A4236	Replacement battery, silver oxide, for use with medically necessary home blood glucose monitor owned by patient, each
A4238	Supply allowance for adjunctive continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A4244	Alcohol or peroxide, per pint
A4245	Alcohol wipes, per box
A4246	Betadine or pHisoHex solution, per pint
A4247	Betadine or iodine swabs/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
A4255	Platforms for home blood glucose monitor, 50 per box

Code	Code Description
A4256	Normal, low, and high calibrator solution/chips
A4258	Spring-powered device for lancet, each
A4259	Lancets, per box of 100
A4271	Integrated lancing and blood sample testing cartridges for home blood glucose monitor, per month
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
A9275	Home glucose disposable monitor, includes test strips
E0607	Home blood glucose monitor
E0784	External ambulatory infusion pump, insulin
E2101	Blood glucose monitor with integrated lancing/blood sample
E2102	Adjunctive continuous glucose monitor or receiver
E2104	Home blood glucose monitor for use with integrated lancing/blood sample testing cartridge
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
J1811	Insulin (fiasp) for administration through dme (i.e., insulin pump) per 50 units
J1812	Insulin (fiasp), per 5 units
J1813	Insulin (lyumjev) for administration through dme (i.e., insulin pump) per 50 units
J1814	Insulin (lyumjev), per 5 units
J1815	Injection, insulin, per 5 units
J1817	Insulin for administration through DME (i.e., insulin pump) per 50 units
S5550	Insulin, rapid onset, 5 units
S5551	Insulin, most rapid onset (Lispro or Aspart); 5 units
S5552	Insulin, intermediate acting (NPH or LENTE); 5 units
S5553	Insulin, long acting; 5 units
S5560	Insulin delivery device, reusable pen; 1.5 ml size
S5561	Insulin delivery device, reusable pen; 3 ml size
S5565	Insulin cartridge for use in insulin delivery device other than pump; 150 units
S5566	Insulin cartridge for use in insulin delivery device other than pump; 300 units
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)
S9140	Diabetic management program, follow-up visit to non-MD provider
S9141	Diabetic management program, follow-up visit to MD provider
S9145	Insulin pump initiation, instruction in initial use of pump (pump not included)
S9353	Home infusion therapy, continuous insulin infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9455	Diabetic management program, group session
S9460	Diabetic management program, nurse visit
S9465	Diabetic management program, dietician visit

HCPCS codes not covered for indications listed in the CPB:

***Remote Glucose monitor, MiniMed Connect, Skin microvascular flow-motion* - no specific code [e.g. Dexcom SHARE - no additional reimbursement provided] :**

A4210	Needle-free injection device, each
A4257	Replacement lens shield cartridge for use with laser skin piercing device, each
A9280	Alert or alarm device, not otherwise classified [hypoglycemic wristband alarm (e.g., Sleep Sentry)]
C1788	Port, indwelling (implantable)
E0620	Skin piercing device for collection of capillary blood, laser, each
E2100	Blood glucose monitor with integrated voice synthesizer

ICD-10 codes covered if selection criteria are met:

Code	Code Description
E08.00 - E13.9	Diabetes mellitus
G25.82	Stiff-man syndrome [indicated for GAD anitbodies]
O24.011 - O24.93	Diabetes mellitus in pregnancy, childbirth, and the puerperium
O99.810 - O99.815	Abnormal glucose complicating pregnancy, childbirth, and the puerperium

***Continuous Glucose Monitoring Devices (e.g., Dexcom, Eversense, Freestyle Libre, Guardian)*:**

***Short-term monitoring [72 hours to 1 week]* :**

CPT codes covered if selection criteria are met:

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; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251	analysis, interpretation and report

ICD-10 codes covered if selection criteria are met:

E08.00 - E13.9	Diabetes mellitus

***Long-term monitoring [greater than 1 week]*:**

CPT codes covered if selection criteria are met :

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
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; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251	analysis, interpretation and report

HCPCS codes covered if selection criteria are met:

***Eversense E3 implantable CGM sensor* - no specific code:**

A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, 1 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
E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver
G0564	Creation of subcutaneous pocket with insertion of 365 day implantable interstitial glucose sensor, including system activation and patient training
G0565	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new 365 day implantable sensor, including system activation
S1030	Continuous noninvasive glucose monitoring device, purchase
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor

Code	Code Description
ICD-10 codes covered if selection criteria are met :	
E10.10 - E10.9	Type 1 diabetes mellitus
E11.00 - E11.9	Type 2 diabetes mellitus [is considered experimental and investigational for persons not using intensive insulin regimens]
E74.00	Glycogen storage disease, unspecified
E74.01	Von Gierke disease [type 1a glycogen storage disease]
E74.02	Pompe disease
E74.03	Cori disease
E74.04	McArdle disease
E74.05	Lysosome-associated membrane protein 2 [LAMP2] deficiency
E74.09	Other glycogen storage disease
ICD-10 codes not covered for indications listed in the CPB:	
E16.9	Disorder of pancreatic internal secretion, unspecified [nesidioblastosis]
O24.410 - O24.439	Gestational diabetes mellitus
P70.3 - P70.4	Iatrogenic and other neonatal hypoglycemia

Background

Diabetes Test Strips and Meters

Diabetic test strips and meters are test strips and meters used for blood sugar testing. Once a blood sample has made it on to the glucose strip, a glucose meter device is used to measure the glucose in the blood. In each test strip, glucose oxidase reacts with the glucose in the blood sample to form gluconic acid. Diabetic test strips and meters are available in multiple brands. Examples of brand names include: Abbott Optium Plus; Abbott Freestyle; Accu-Chek Aviva; Accu-Chek Active; Accu-Chek Advantage; Accu Chek Compact; Bayer Contour; Bayer Contour NEXT; OneTouch Ultra; OneTouch VerioFlex; and OneTouch Verio.

Glycated Serum Proteins (Fructosamine)

The fructosamine test measures the average of continuous glucose levels over the prior 2- to 3-week period, and is being marketed as an indicator of overall glucose control in diabetics. The American Diabetes Association has determined that measurement of glycated serum protein (GSP) should not be considered the equivalent of measurement of glycated hemoglobin, and that the clinical utility of monitoring GSPs has yet to be established. A randomized clinical trial (Petitti et al, 2001) of 140 patients with diabetes found that patients randomized to home fructosamine monitoring had higher levels of glycated hemoglobin (HbA1c) after 3 and 6 months of follow-up. In a review of GSP and diabetes, Goldstein (1997) concluded that "further studies are recommended to determine whether the use of GSP to document short-term changes (e.g., 1 to 2 weeks) in glycemic status is clinically useful".

Glutamic Acid Decarboxylase (GAD-65) Antibodies

Glutamic acid decarboxylase (GAD) is an enzyme that is produced primarily by pancreatic islet cells. A number of recent studies indicate that patients with type 1 diabetes often have antibodies to GAD and several other islet cell antigens. This is consistent with the hypothesis that type 1 diabetes is an autoimmune disease and that autoantibody production is an early step in the development of type 1 diabetes. Autoantibodies can be detected in many cases prior to the onset of glucose intolerance. The presence of GAD autoantibodies has been shown to be a strong predictive marker for the eventual onset of type 1 diabetes.

Measurement of anti-GAD antibodies has been proposed for evaluating the risk of developing type 1 diabetes in persons at high risk. However, the value of such testing is unproven, as there are no measures that have been demonstrated to be effective in preventing the onset of type 1 diabetes. Guidelines from the Canadian Diabetes Association (Ur et al, 2003) explain that the loss of pancreatic beta cells in persons who subsequently develop type 1 diabetes passes through a subclinical prodrome that can be detected reliably in first- and second-degree relatives of persons with type 1 diabetes by the presence of anti-GAD antibodies and other pancreatic islet cell autoantibodies in their sera. While randomized trials testing prevention strategies have been completed or are now underway, safe and effective preventive strategies have not been identified. The guidelines concludde: "Therefore, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols."

Measurement of anti-GAD antibody can be of use in distinguishing type 1 from type 2 diabetes when the clinical history is ambiguous. Guidelines from the Royal Australian College of General Practitioners (RACGP, 2007) explained that measurement of GAD can be of particular use in diagnosing Late onset Autoimmune Diabetes in Adults (LADA), a form of late onset diabetes that is autoimmune and requires treatment with insulin within a relatively short period of time after diagnosis (often within the next 2 years). RACGP guidelines explained that persons with LADA tend to be young (30 to 40 years of age, lean, and have a personal and/or family history of other autoimmune diseases (e.g., hypo- or hyper-thyroidism). The guidelines stated that testing for GAD antibodies can confirm the diagnosis in ambiguous cases and prompt counseling the person about the likely time course of diabetes progression and the possibility of other autoimmune disease. In addition, the establishment of the LADA diagnosis may be useful in selecting therapy (Brophy et al, 2007)

Antibodies to GAD are often markedly elevated in patients with the stiff-person syndrome (also referred to as stiff-man syndrome), a condition that is associated with fluctuating stiffness and paroxysmal spasms of the trunk and legs.

PreDx Diabetes Risk Score

The PreDx® Diabetes Risk Score (DRS) test is a multiple-biomarker test to identify high-risk individuals who might develop diabetes within 5 years. Using a proprietary algorithm combines seven biomarkers to quantify the risk of developing diabetes within 5 years. The model also includes age and sex. A diabetes risk score between 1 and 10 is calculated, with a higher score indicating an increased likelihood of developing diabetes within 5 years. Since the biomarkers are a combination of proteins and metabolites, they are measured using several different methods: ion-exchange high-performance liquid chromatography (HbA1c), chemiluminescent immunoassay (ferritin and interleukin 2 receptor alpha [IL2-Rα]), enzymatic (glucose), immuno-turbidometric assay (C-reactive protein [CRP]), and an enzyme-linked immunosorbent assay (adiponectin and insulin). The PreDx DRS is used for patients who do not have type 2 diabetes (T2D) but are at increased risk for developing this condition. Patients to be considered include those with impaired fasting glucose, metabolic syndrome, or other risk factors, including family history, age > 45 years, presence of obesity, coronary artery disease, hypertension, low high-density lipoprotein cholesterol (HDL) (i.e., < 35 milligrams per deciliter), increased triglycerides, and belonging to an ethnic group with a higher prevalence of diabetes (for example, African American, Hispanic, Asian or Native American). Currently, two laboratories offer the PreDx DRS multibiomarker test. However, all testing is done at one of these facilities, Tethys Bioscience Inc.

Jet Injectors

Jet injectors offer an alternative method of hypodermic drug delivery from conventional needle-syringe. The main objective in using a jet injector as opposed to conventional needle-syringe is for increased patient comfort during injection. A review of the literature indicates some patients do prefer injection by jet injector while others may experience more discomfort. The Youth Task Force of the American Diabetes Association (Task Force on Jet Injections, 1998, 1991) reviewed the scientific literature on jet injection and could not make general recommendations for their use due to insufficient information. There are hypothetical risks and benefits associated with their use for insulin delivery which have not been clearly addressed in the literature. There is insufficient information on the frequency and significance of aversion to needles, therefore, the use of jet injectors because of a fear of needles is a matter of convenience and patient preference. A jet injector may be appropriate for some individuals with medical conditions that make it impossible for them to use a conventional needle-syringe. Which group of patients unable to use syringes and who are therefore candidates for jet injections based on medical necessity has not been defined in the literature, but reasonably includes individuals with severe arthritis, severe tremors, or blindness.

I-Port Injection Port

The I-Port Injection Port (Patton Medical, Austin, TX) is an insulin delivery port which is used to reduce the number of needle injections of insulin. The I-Port is applied using an insertion needle to guide a soft cannula into the subcutaneous tissue. Once applied, the insertion needle is removed, leaving the soft cannula under the skin, acting as the gateway into the subcutaneous tissue. To inject through the I-Port, the needle of a syringe or insulin pen is used. The needle remains above the surface of the skin, while the medication is delivered through the soft cannula into the subcutaneous tissue. According to the manufacturer, the I-Port can accommodate 75 injections, and be worn for up to 72 hours. The I-Port was cleared by the U.S. Food and Drug Administration (FDA) based upon a 510(k) application.

In a prospective, randomized study, Blevins et al (2008) compared the I-Port to standard multiple dose insulin administration in diabetic patients receiving insulin injections (n = 74). Patients were randomly assigned to 2 of 3 treatment regimens:

1. standard injections (SI),
2. a single I-Port device, or
3. 2 separate I-Port devices (Dual I-Port).

Each treatment regimen lasted 3 weeks and included 5 assessment visits. Patients in the single I-Port regimen injected both regular human or rapid-acting insulin and insulin glargine through the same device, whereas patients in the Dual I-Port regimen injected each type of insulin through 2 separate devices. Of the 74 patients who qualified to participate in the study, 64 (86 %) completed all 5 assessment visits. Six of the 10 patients (8.1 %) who did not complete the trial terminated for device-related reasons (e.g., adhesive failure, wear discomfort, high blood glucose levels, cannula bends) and 4 patients (5.4 %) terminated for

non-device-related reasons. The authors reported that 69.4 % of the patients found the I-Port useful and helpful in the management of their diabetes and there was no significant difference in patient's glycosylated albumin between SI, single I-Port, and Dual I-Port treatment regimens.

In a systematic review of adherence with medications for diabetes, Cramer (2004) found a lack of studies evaluating interventions to improve adherence in which adherence was measured using appropriate methods. Cramer stated, "Further research is needed to quantify the specific improvement in glycemic control that might be obtained from improved medication adherence. Such studies should demonstrate the health benefits that may be derived from more convenient therapeutic regimens that are being developed for diabetes."

There is a lack of studies demonstrating an improved health benefit of the I-Port over standard injection regimens. Clinical studies are necessary to evaluate the I-Port's impact on compliance and other clinical outcomes.

Continuous Glucose Monitors (CGMs)

Continuous glucose monitoring systems (CGMS) are devices that measure glucose levels in interstitial fluid at programmable intervals. These readings, used along with fingerstick results, help detect any patterns or trends with an individual’s glucose levels and are intended to assist in calculating the insulin dosage needed to manage glycemic control. CGMS readings are intended to supplement, not replace, fingersticks.

CGMS use sensors that are inserted under the skin in the abdomen and work by extracting glucose from the interstitial fluid, measuring and recording the glucose level and converting these measurements into equivalent blood glucose readings.

With certain CGMS (sometimes referred to as "professional CGM"), the patient receives no information while wearing the device. Results can be determined in a clinician's office and graphed to provide information about the frequency of unrecognized hypoglycemia and the extent of within-day and between-day variations in blood glucose.

Other devices (often referred to as "personal CGM") provide the patient with real-time results of glucose values on a continuous basis, which can be automatically and securely shared with a clinician via a mobile medical glucose-monitoring application downloaded on to a mobile device, such as a cell phone

Many sensors are designed to be worn three to seven days, depending on the product. Calibration is required whenever a new glucose sensor is inserted, which requires obtaining blood glucose from a traditional fingerstick sample.

MiniMed Continuous Subcutaneous Glucose Monitoring System is an example of a diagnostic continuous glucose monitor for short-term use. The FDA granted the MiniMed CGMS (Medtronic MiniMed, Minneapolis, MN) pre-market approval in June 1999 for use as an adjunct to finger-stick blood glucose testing. CGMS that uses a recorder and subcutaneously implanted glucose sensor to store data to be downloaded to a personal computer. The system provides continuous measurements of the interstitial glucose levels that range from 40 to 400 mg/dl. The glucose sensor signal is acquired every ten seconds. An average of the acquired signals is saved in memory every five minutes for up to 3 days. While in operation, the MiniMed CGMS monitor does not display glucose values, and individuals are still required to test their glucose levels several times a day by a standard method (finger sticks) and enter the glucose measurements into the monitor for calibration purposes. The system is used as a diagnostic tool to evaluate glucose levels over a three day period and is then returned to the physician for evaluation of results to potentially modify diabetes treatment regimens and is not intended for long-term use. According to the FDA, the MiniMed CGMS is not intended to replace standard finger-stick testing. The newest short-term CGMS version of the MiniMed is the iPRO2.

More recently, the FDA approved the Guardian Real-Time (RT) Continuous Glucose Monitoring System (Medtronic, Minneapolis, MN), which is described by the manufacturer as the first consumer continuous glucose monitoring device. The Guardian CGMS device uses a glucose sensor connected to a transmitter that sends glucose readings every five minutes to a monitor. The glucose sensor is typically discarded and replaced after three days. According to the manufacturer, the device provides up to 288 glucose readings per day or every 5 minutes. Unique features include predictive and rate of change alarms and expanded trend graphs. Graphs can show the effect of exercise, diet, and lifestyle, as well as medication on glucose values using 3, 6, 12 and 24-hour increments. Alarms that signal high and low glucose alerts warn individuals of any significant glucose changes. Data is downloaded using the Medtronic Carelink Therapy Management Software. According to the FDA-approved labeling, the Guardian RT is indicated to supplement blood glucose information from standard home blood glucose meters, for persons 7 years and older with type 1 or type 2 diabetes. A fingerstick measurement is required before taking action.

The DexCom STS Continuous Glucose Monitoring System (DexCom, Inc., San Diego, CA) gained FDA approval on March 24, 2006. It is a glucose sensor that reports glucose values every 5 minutes for up to 72 hours. These readings are used with fingerstick results to detect trends and patterns in glucose levels in adults with diabetes, aged 18 years and over. The DexCom STS is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices.

The Dexcom G4 PLATINUM (adult and pediatric) Systems with Share is a CGMS that incorporates a sensor, transmitter and receiver and allows glucose to be monitored every five minutes. The sensor reports glucose for seven days before a new sensor

replacement is necessary. A built-in alarm system can be programmed by the user when glucose falls below a pre-set low and a pre-set high level. A built-in hypoglycemia safety alarm alerts user when glucose hits 55 mg/dl. FDA approved for use in adults and children ages 2 years and older. Dexcom Share is an integrated wireless communication system that is built into the receiver, enabling remote monitoring capabilities and sharing of data through a compatible internet-accessible device application.

The Dexcom G5 Mobile CGM System is described as a complete, mobile CGMS with wireless technology that is built into the transmitter. Glucose information is sent wirelessly from the device transmitter to a compatible smart device or Dexcom G5 receiver. FDA approved for use in adults and children ages 2 years and older.

In 2018, the US Food and Drug Administration (FDA) approved the Dexcom G6 device to replace the Dexcom G5 system. The Dexcom G6 system can be integrated with an automated insulin dosing system, such that a rise in blood glucose would trigger release of insulin from an insulin pump without the need for confirmatory fingerstick glucose testing. Fingerstick glucose determinations are also not needed for calibration. In a study using an older version of the Dexcom device, use of CGM without confirmatory self-monitoring of blood glucose (SMBG) was as safe and effective as using CGM with SMBG. Older Dexcom CGMs and the Enlite CGM do not have a non-adjunctive claim, so fingerstick glucose readings are required both for calibration and as confirmation of glucose levels before making decisions on insulin dosing.

Combined external insulin pumps with CGMS are devices that integrate an insulin pump with real-time continuous glucose monitoring and is not intended to replace finger sticks. These systems incorporate features including predictive alerts that give early warnings so action can be taken to prevent dangerous high or low blood glucose events.

The Paradigm Real Time System (Medtronic MiniMed) is an open-loop insulin delivery system that combines an external insulin pump with continuous monitoring of interstitial glucose levels via a subcutaneous sensor. The sensor communicates glucose readings to the pump using a radio transmitter. The pump can also calculate recommended insulin doses, which the patient can accept or modify. Readings from the continuous glucose monitor (CGM) are not intended to be used to make therapy adjustments. A conventional blood glucose meter reading is needed before making adjustments because there is a lag of up to 10 minutes in glucose concentration in the interstitial fluid relative to the concentration in the blood (CADTH, 2007). Furthermore, readings from the sensor may be less accurate in the hypoglycemic range. An assessment of the Paradigm Real Time System by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2007) concluded: "Based on the limited amount of research published to date, the impact of the Paradigm Real-Time System on long-term glycemic control, prevention of diabetic complications, or quality of life is unclear." The assessment noted that open-loop systems such as the Paradigm Real Time System are an incremental step towards a fully closed-loop system, also known as an artificial pancreas, where insulin dosages would be automatically adjusted, rather than requiring patient input.

The MiniMed Paradigm REAL-Time Revel System is approved for use in adults and children ages 7 years and older and works with the my Sentry remote monitoring system. The mySentry remote monitoring system is an optional monitoring device for the MiniMed Paradigm REAL-Time Revel System. The mySentry consists of a remote outpost and monitor. Blood glucose levels collected by the CGM are sent to the remote (wireless) monitor, which also has alarms to alert the user of high or low blood glucose levels.

The Animas Vibe System combines a Dexcom G4 Platinum sensor and transmitter with the Animas Vibe insulin pump. It is FDA approved for use in adults and children, ages 2 years and older.

Guidelines from the National Institute for Health and Clinical Excellence (2004) recommended the use of CGM devices for the evaluation of persons with type 1 diabetes on insulin therapy who have repeated hypoglycemia and hyperglycemia at the same time each day, and hypoglycemia unawareness, unresponsive to conventional insulin dose adjustment.

A Cochrane systematic evidence review found limited evidence for the effectiveness of real-time continuous glucose monitoring (CGM) use in children, adults and patients with poorly controlled diabetes (Miranda, et al., 2012). The authors found that the risk of severe hypoglycemia or ketoacidosis was not significantly increased for CGM users, but as these events occurred infrequent these results have to be interpreted cautiously.

A multi-center randomized clinical study sponsored by the Juvenile Diabetes Research Foundation (JDRF, 2008) provided evidence of improved glycemic control over the intermediate term (6 months) with the use of CGMs in adults greater than 24 years of age. In this study, 322 adults and children who were already receiving intensive therapy for type 1 diabetes were randomly assigned to a group with continuous glucose monitoring or to a control group performing home monitoring with a blood glucose meter. All subjects were stratified into 3 groups according to age and had a glycated hemoglobin level of 7.0 to 10.0 %. The investigators found that the changes in glycated hemoglobin levels in the 2 study groups varied markedly according to age group, with a significant benefit in patients 25 years of age or older with continuous glucose monitoring (mean difference in change, – 0.53 %, $p < 0.001$). There was no significant benefit in glycated hemoglobin levels with continuous glucose monitoring in subjects who were 15 to 24 years of age (mean difference, 0.08; $p = 0.52$) or among those who were 8 to 14 years of age (mean difference, – 0.13; $p = 0.29$). The investigators posited that the disparate outcomes may be due to poorer compliance among younger age groups. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83 % of patients 25 years of age or older, 30 % of those 15 to 24 years of age, and 50 % of those 8 to 14 years of age. The study also found no significant difference in the rate of severe hypoglycemia among persons who were assigned to CGMs and those who

performed home monitoring with a blood glucose meter; however, the investigators noted that the trial was not powered to detect such a difference. Commenting on the JDRF study of continuous glucose monitoring, Brett (2008) noted that "although this method is appealing theoretically, the extent to which it will improve long-term clinical outcomes remains to be determined."

A controlled clinical study, the Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 trial, found that, in both adults and children with inadequately controlled type 1 diabetes, sensor-augmented pump therapy resulted in significant improvement in glycated hemoglobin levels, as compared with injection therapy (Bergenstal, et al., 2010). However, whether these results can be translated into community practice outside of the controlled clinical trial setting is unknown. A 1-year, multi-center, randomized, controlled trial, compared the efficacy of sensor-augmented pump therapy (pump therapy) with that of a regimen of multiple daily insulin injections (injection therapy) in 485 patients (329 adults and 156 children) with inadequately controlled type 1 diabetes. Patients received recombinant insulin analogs and were supervised by expert clinical teams. The primary end point was the change from the baseline glycated hemoglobin level. At 1 year, the baseline mean glycated hemoglobin level (8.3 % in the 2 study groups) had decreased to 7.5 % in the pump-therapy group, as compared with 8.1 % in the injection-therapy group ($p < 0.001$). The proportion of patients who reached the glycated hemoglobin target (less than 7 %) was greater in the pump-therapy group than in the injection-therapy group. The rate of severe hypoglycemia in the pump-therapy group (13.31 cases per 100 person-years) did not differ significantly from that in the injection-therapy group (13.48 per 100 person-years, $p = 0.58$). There was no significant weight gain in either group. A commentator noted that this is a manufacturer-sponsored study, and the investigators included employees of the firm. An editorialist (Wolpert, 2010) offered several caveats: These patients received intensive support and monitoring that are not available to many patients, were highly skilled at self-management before enrollment, and had to be adept at calibration and management of equipment failures and alarms. The editorialist warned that the "expert training and guidance [on the use of continuous glucose monitoring] received by patients in clinical trials cannot be readily duplicated in a busy clinical practice." A commentary (Schwenk, 2010) concluded: "This new and expensive technology must be tested in wider community-based trials before it will be ready for broad dissemination."

The editorialist (Wolpert, 2010) also compared the results of the STAR-3 trial with the JDRF trial, and stated that the differences in outcome may be due to diffences in the design of these trials. In the STAR 3 study, the patients in the pump-therapy group changed their mode of both insulin delivery and glucose monitoring at the time of randomization, whereas in the JDRF trial, patients who were assigned to receive continuous glucose monitoring did not change their mode of insulin delivery. The editorialist stated that the greater reduction in glycated hemoglobin levels among adult patients in the STAR 3 trial than in the JDRF study may reflect the additional effect of initiating pump therapy, as well as the increased baseline glycated hemoglobin levels in the STAR 3 study, as compared with the JDRF study (8.3% and 7.6%, respectively).

The editorialist (Wolpert, 2010) also noted that, in the STAR 3 study, the improved glycemic control among children in the pump-therapy group contrasted with the lack of apparent benefit for continuous glucose monitoring among children in the JDRF trial. The editorialist questioned whether the benefits that were seen in the pump-therapy group in the STAR 3 study were due primarily to the initiation of pump therapy rather than to continuous glucose monitoring. The editorialist explained that consistent with this possibility is the fact that patients in the STAR 3 study who had a relatively low frequency of sensor use had significant improvements in glycated hemoglobin levels. The editorialist noted that children in the injection-therapy group, who used intermittent capillary blood glucose monitoring, had lower rates of both severe and biochemical hypoglycemia than did patients in the JDRF trial who used continuous monitoring. The editorialist said that these results suggest that the selection of patients may also account for some of the differences in the outcomes of these two trials.

Whether the benefits of CGM in improving glycemic control extend beyond the intermediate-term (12 months) is unknown. A large clinical study of CGM, the Minimally Invasive Technology Role and Evaluation (MITRE) study, sponsored by the National Institute for Health Research Health Technology Assessment Program, found that continuous blood glucose monitoring had no durable effect on blood glucose control (Newman et a., 2007; Newman et al, 2009). The purpose of the MITRE study was to evaluate the efficacy of minimally invasive glucose monitoring devices in 400 patients with diabetes mellitus treated with insulin. The primary endpoint was long-term glucose control, as indicated by changes in glycosylated hemoglobin (HbA1c) levels for 18 months. A total fo 400 patients were randomly assigned to the CGMS by MiniMed, the Biographer by Animas, a standard control or to an attention control group. Mean baseline HbA1c ranged from 7.0 % to 15.5 % for participants. All groups demonstrated a decline in mean HbA1c, especially during the first few months of the study. However, by month 18, the percentage of patients that had a relative reduction of at least 12.5 % was 15 % in the Biographer group, 27 % in the CGMS group, 24 % in the standard control, and 27 % in the attention control group. The relative decline in HbA1c from baseline ranged from 1 % to 4.6 %. The results suggested that the use of the CGMS had a small benefit, but only in the short-term, and that the Biographer had less impact on HbA1c than either the CGMS or standard treatment. The assessment concluded: "Continuous glucose monitors as assessed in this study do not lead to improved clinical outcomes and are not cost-effective for improving HbA1c in unselected individuals with poorly controlled insulin-requiring diabetes" (Newman et al, 2009). Some commentators have posited that more advanced continuous glucose monitoring devices currently in use may provide more durable results than the monitors used in the MITRE study. The results from CGMs used in this study were downloaded and reviewed with the endocrinologist, but only the Glucowatch Biographer provided real-time display of glucose results to the patient (the MiniMed CGMS used in this study did not include a real-time display of glucose readings). Whether the more advanced CGMs with real-time display will provide more durable results than earlier models used in the MITRE study is a question for future long-term studies.

Norgaard et al (2013) reported on the largest and longest multicenter prospective observational study of continuous glucose monitoring with insulin infusion pumps, so called sensor-augmented pump therapy. The investigators reported on a 12-month observational study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII), upon the

introduction of continuous glucose monitoring (CGM). The study was conducted in 15 countries to document the real-life use of sensor-augmented pump therapy and assess which variables are associated with improvement in type 1 diabetes management. Data from 263 patients (38% male; mean age, 28.0±15.7 years [range, 1-69 years]; body mass index, 23.3±4.9 kg/m(2); diabetes duration, 13.9±10.7 years; CSII duration, 2.6±3 years) were collected. Baseline mean glycated hemoglobin A1c (HbA1c) was 8.1±1.4%; 82% had suboptimal HbA1c (≥7%). The investigators found that the average sensor use for 12 months was only 30% (range, 0-94%), and that sensor use decreased with time (first 3 months, 37%; last 3 months, 27%). The investigators found that there were significantly more patients with an HbA1c value of < 7.5% after 3 months of sensor-augmented pump therapy than at baseline (baseline, 29%; 3 months, 37%) However, the percentage of patients with an HbA1c value of < 7.5% decreased over the 12-month observation period, such that the percentage of patients with an HbA1c value of < 7.5% after 12 months was not statistically significantly higher than at baseline.

A published systematic evidence review and meta-analysis of the evidence for continuous glucose monitoring systems in children with type 1 diabetes reached the following conclusions (Golicki et al, 2008): "The Continuous Glucose Monitoring System is not better than self-monitoring of blood glucose with regard to improvement of metabolic control among type 1 diabetic children. However, due to the small number of participants and methodological limitations of the studies included, findings of this meta-analysis should be interpreted with caution."

Chetty et al (2008) of McMaster University performed a meta-analysis of randomized controlled trials comparing continuous glucose monitoring and self-blood fingerstick glucose monitoring in persons with type 1 diabetes. The investigators found insufficient evidence to support the notion that CGM provides a superior benefit over self-blood fingerstick glucose monitoring in terms of hemoglobin A1c reduction. The investigators, however, found some indication of improved detection of asymptomatic nocturnal hypoglycemia in the CGM group. The investigators identified 7 studies with a total of 335 patients fulfilled the inclusion criteria. Five studies were confined to the pediatric population (age less than 18 years). Study duration varied from 12 to 24 weeks. The investigators found that, compared with self-blood fingerstick glucose monitoring, CGM was associated with a non-significant reduction in hemoglobin A1c (0.22 %; 95 % confidence interval [CI]: -0.439 % to 0.004 %, p = 0.055).

Regarding the therapeutic use of continuous glucose monitoring devices for hypoglycemic unawareness, current evidence from randomized controlled clinical trials have focused on CGM' effect on shortening the duration of asymptomatic hypoglycemia, an intermediate endpoint, rather than clinical outcomes. The clinical significance of reductions in duration of asymptomatic hypoglycemia are unknown. In addition, current evidence indicates that continuous glucose monitoring devices are least accurate in the hypoglycemic range (CADTH, 2007; Melki et al, 2006).

Hypoglycemia unawareness is reversible. Meticulous avoidance of hypoglycemia for several weeks is sufficient to restore awareness of hypoglycemia (Cheng et al, 2000; Fanelli et al, 1993; Dagogo-Jack et al, 1994; Cranston et al, 1994). The return of awareness is accomplished with minimal compromise of glycemic control, but that required substantial involvement of health professionals. In addition, unlike CGM, HAATT/BGAT (Hypoglycemia Anticipation, Awareness and Treatment Training/ Blood Glucose Awareness Training) has been proven to reduce the occurrence of severe hypoglycemia (Cox et al, 2001; Cox et al, 2004).

There is limited evidence of the effectiveness of CGMs to improve outcomes in pregnant women with diabetes. Murphy et al (2008) reported on an open-label randomized controlled clinical trial where 71 pregnant women with type 1 diabetes (n = 46) or type 2 diabetes (n = 25) were randomly assigned to antenatal care plus continuous glucose monitoring (n = 38) or to standard antenatal care (n = 33). Continuous glucose monitoring was used as an educational tool to inform shared decision making and future therapeutic changes at intervals of 4 to 6 weeks during pregnancy. All other aspects of antenatal care were equal between the groups. Women randomized to continuous glucose monitoring had lower mean hemoglobin A1c levels (5.8 %) from 32 to 36 weeks' gestation compared with women randomized to standard antenatal care (6.4 %). Compared with infants of mothers in the control arm those of mothers in the intervention arm had decreased mean birthweight standard deviation scores (0.9 versus 1.6), decreased median customized birthweight centiles (69 % versus 93 %), and a reduced risk of macrosomia (odds ratio 0.36). The investigators noted a number of limitations to this study. Although efforts were made to standardize antenatal contacts between groups, health professionals were not blinded and therefore the possibility of bias in clinical management cannot be excluded. Differences in maternal characteristics, with longer duration of diabetes in the intervention group, may have contributed to some of the effect on infant outcomes. The investigators stated that the study included a small number of women and that larger multicenter trials are required to assess the impacts of continuous glucose monitoring in pregnancy.

Guidelines from the American Diabetes Association (2018) state that, when used properly, continuous glucose monitoring (CGM) 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 (A - recommendation based upon evidence from well conducted, generalizable, randomized controlled trials that are adequately powered). The guidelines state that CGM may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes (C - recommendation based upon evidence from poorly controlled or uncontrolled studies.) Given the variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing (E - recommendation based upon expert consensus or clinical experience.) When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use (E - based upon expert consensus or clinical experience.) People who have been successfully using CGM should have continued access after they turn 65 years of age (E - based upon expert consensus or clinical experience.)

A joint statement from the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group stated the first systems for continuous glucose monitoring (CGM) became available over 15 years ago. Many then believed CGM would revolutionize the use of intensive insulin therapy in diabetes; however, progress toward that vision has been gradual. Although increasing, the proportion of individuals using CGM rather than conventional systems for self-monitoring of blood glucose on a daily basis is still low in most parts of the world. Barriers to uptake include cost, measurement reliability (particularly with earlier-generation systems), human factors issues, lack of a standardized format for displaying results, and uncertainty on how best to use CGM data to make therapeutic decisions. This Scientific Statement makes recommendations for systemic improvements in clinical use and regulatory (pre- and postmarketing) handling of CGM devices. The aim is to improve safety and efficacy in order to support the advancement of the technology in achieving its potential to improve quality of life and health outcomes for more people with diabetes.

A structured review of the evidence conducted by the BlueCross BlueShield Association Technology Evaluation Center (2003) concluded that "use of intermittent or continuous interstitial fluid glucose monitoring in patients with diabetes mellitus does not meet Blue Cross and Blue Shield Association Technology Evaluation Center criteria." Similarly, a technology assessment conducted by the California Technology Assessment Forum (CTAF) concluded that continuous glucose monitoring does not meet CTAF's criteria (Tice, 2003). An updated assessment of continuous glucose monitoring by the California Technology Assessment Forum (Karliner, 2009) concluded that continuous glucose monitoring devices meet CTAF criteria for use in type 1 diabetes mellitus in non-pregnant adults requiring multiple (greater than or equal to 3) daily insulin injections and frequent (greater than or equal to 3) self-monitoring blood glucose checks. Continuous glucose monitoring devices did not meet CTAF criteria 3 for the management of type 1 diabetes mellitus in children, adolescents and pregnant women. The CTAF assessment explained that the largest randomized controlled clinical trial to date of continuous glucose monitoring devices for adults and children (citing JDRF, 2008) found conclusive benefit only for adults 25 years and older. The CTAF assessment explained that, while in this study, and in other smaller randomized controlled trials there is evidence that both children and adults spend less time in a hypoglycemic glucose range when using a continuous glucose monitoring device compared to usual care frequent SMBG, there is little evidence that use of a continuous glucose monitoring device confers an ultimate health benefit as measured by HbA1C as a marker of overall glycemic control. The CTAF assessment stated that it may be that for children and adolescents this is in large part due to difficulty with device adherence and not with the device itself. The CTAF assessment explained, however, that a health technology is only as good as its actual clinical application, and the evidence has not yet shown conclusive benefit for children, adolescents, and even young adults. Likewise, while the small studies that exist of pregnant women show the feasibility of continuous glucose monitoring device use during pregnancy, they do not yet demonstrate conclusive benefit in this population either. The CTAF assessment concluded that future study of these devices should incorporate more research on how the devices can be made more acceptable and user-friendly for children and adolescents with type 1 diabetes in order to optimize potential clinical benefit for this population. The CTAF assessment also stated that larger studies of pregnant women which are limited to those women requiring multiple insulin injections per day are needed in order to adequately assess potential benefit in this population.

There are fewer trials evaluating CGM in patients with type 2 diabetes. In one meta-analysis, there was a significant reduction in A1C with use of CGM versus SMBG in adults with type 2 diabetes (WMD -0.7 percent). In a subsequent trial, 158 adults treated with multiple daily injections of insulin (mean A1C 8.5 percent), were randomly assigned to CGM or usual care (SMBG at least four times daily). After 24 weeks, the reduction in A1C was greater with CGM (0.8 versus 0.5 percentage points, respectively; adjusted mean difference -0.3, 95% CI -0.5 to 0.0 percent). Patients in the CGM group performed a mean of 2.9 fingersticks daily, compared with 3.8 per day in the control group. There was no difference in hypoglycemia, which was infrequent in both groups, or in quality-of-life measures.

A technology assessment of self-monitoring of blood glucose in persons with type 2 diabetes prepared for the Centers for Medicare and Medicaid Services (Balk et al, 2006) commented that "currently, CGM [continuous glucose monitoring] has been studied primarily in children with type 1 diabetes. It is unclear whether CGM provides added value to traditional SMBG [self monitoring of blood glucose]."

Available evidence shows that, in contrast to type 1 diabetes, persons with type 2 diabetes do not benefit from tight glucose control. In 3 recent large randomized trials (ACCORD,2 ADVANCE,3 and VADT4), tight control in patients with long-standing type 2 diabetes did not lower overall mortality, cardiovascular-related mortality, stroke, amputations, or even clinical (as opposed to surrogate) microvascular endpoints (Gerstein et al, 2008; Patel et al, 2008; Duckworth et al, 2009). Some authorities suggested that the HbA1c goals for practice guidelines should not be less than 7 % and that, to encourage individualized treatment, performance measures should set an upper limit (e.g., 9 %) rather than a lower limit (e.g., less than 7 %) (Lehman and Krumholz, 2009).

A Cochrane systematic evidence review found that intensive glucose control significantly prevents the development of clinical neuropathy in type 1 diabetes mellitus (Callaghan, et al., 2012). However, in type 2 diabetes mellitus, the effect of intensive glucose control on the incidence of clinical neuropathy was not statistically significant. The systematic evidence review also found that intensive glucose control significantly increases the risk of severe hypoglycemic episodes, which needs to be taken into account when evaluating its risk/benefit ratio.

A systematic evidence review of continuous glucose monitoring by the Ontario Ministry of Health and Long-Term Care Medical Advisory Secretariat (MAS, 2011) found that there was moderate quality evidence that in diabetic individuals with an infusion

pump, continuous blood glucose monitoring plus self-monitoring was not more effective in reducing glycosylated hemoglobin, hypoglycemic events or severe hypoglycemic events than self-monitoring alone.

A systematic evidence review prepared for the Agency for Healthcare Research and Quality (Golden, et al., 2012) reported that randomized controlled trials showed no difference in the effect of CSII and MDI on HbA1c (moderate strength of evidence [SOE]) or severe hypoglycemia (low SOE) for children or adolescents with type 1 diabetes, or for adults with type 2 diabetes. In adults with type 1 diabetes, HbA1c decreased more with CSII than with MDI (low SOE), but results were heavily influenced by one study. The assessment found that there was no difference in severe hypoglycemia (low SOE). In children and adults with type 1 diabetes, CSII use was associated with improved quality of life compared with MDI (low SOE). There was insufficient evidence about quality of life for adults with type 2 diabetes. The SOE regarding pregnant women with pre-existing diabetes was either low or insufficient on all outcomes.

A systematic evidence review (Coca, et al., 2012) found that intensive glucose control reduced the risk for microalbuminuria and macroalbuminuria in persons with type 2 diabetes, but evidence was lacking that it reduced the risk of significant clinical renal outcomes, such as doubling of the serum creatinine level, end-stage renal disease or death from renal disease during the years of follow-up of the trials.

A review of continuous glucose monitors in type 2 diabetes by Meade (2012) stated that only five of the studies reviewed documented a reduction in HbA1c, and of these five, only three focused exclusively on patients with type 2 diabetes. The review stated that the majority of the studies evaluating CGM use in patients with type 2 diabetes were not designed to show a reduction in HbA1C. Studies of patients with type 2 diabetes mellitus had a smaller sample size than the studies reviewing continuous glucose monitoring in patients with type 1 diabetes.

Evidence to support the use of continuous glucose monitoring in persons with diabetes not on insulin is very limited. Vigersky, et al. (2011) reported on a randomized controlled trial of 100 adults with type 2 diabetes who were not on prandial insulin. This study compared the effects of 12 weeks of intermittent continuous glucose monitoring with self-monitoring of blood glucose (SMBG) on glycemic control over a 40-week follow-up period. Subjects received diabetes care from their regular provider without therapeutic intervention from the study team. The investigators reported that there was a significant difference in A1C at the end of the 3-month active intervention that was sustained during the follow-up period. The mean, unadjusted A1C decreased by 1.0, 1.2, 0.8, and 0.8% in the continuous glucose monitoring group vs. 0.5, 0.5, 0.5, and 0.2% in the SMBG group at 12, 24, 38, and 52 weeks, respectively ($p = 0.04$). There was a significantly greater decline in A1C over the course of the study for the continuous glucose monitoring group than for the SMBG group, after adjusting for covariates ($p < 0.0001$). The subjects who used continuous glucose monitoring per protocol (≥48 days) improved the most ($p < 0.0001$). The investigators reported that the improvement in the continuous glucose monitoring group occurred without a greater intensification of medication compared with those in the SMBG group.

Ehrhardt et al (2010) evaluated the utility of short-term use of continuous glucose monitoring in people with type 2 diabetes on a variety of treatment modalities except prandial insulin. The investigators conducted a prospective, 52-week, two-arm, randomized trial comparing real-time continuous glucose monitoring (RT-CGM) (n = 50) versus self-monitoring of blood glucose (SMBG) (n = 50) in people with type 2 diabetes not taking prandial insulin. Real-time continuous glucose monitoring was used for four 2-week cycles (2 weeks on/1 week off). All patients were managed by their usual provider. Mean (± standard deviation) decline in A1C at 12 weeks was 1.0% (± 1.1%) in the RT-CGM group and 0.5% (± 0.8%) in the SMBG group ($p = .006$). There were no group differences in the net change in number or dosage of hypoglycemic medications. Those who used the RT-CGM for ≥ 48 days (per protocol) reduced their A1C by 1.2% (± 1.1%) versus 0.6% (± 1.1%) in those who used it <48 days ($p = .003$). Multiple regression analyses statistically adjusting for baseline A1C, an indicator for usage, and known confounders confirmed the observed differences between treatment groups were robust ($p = .009$). There was no improvement in weight or blood pressure. Limitations of this study was the short duration (12 weeks) for the primary endpoint (52-week results were not reported), the atypical short-term use of CGM, the fact that person assigned to CGM tested their blood glucose more frequently than persons assigned to SMBG, and the lack of other self-care data that may explain difference between groups.

Beck et al (2017) noted that continuous glucose monitoring (CGM) has not been well-evaluated in those with type 2 diabetes receiving insulin. The investigators reported on a manufacturer-funded randomized controlled trial to determine the effectiveness of CGM in adults with type 2 diabetes receiving multiple daily injections of insulin. The study included 158 adults who had had type 2 diabetes for a median of 17 years (interquartile range, 11 to 23 years). Participants were aged 35 to 79 years (mean, 60 years [SD, 10]), were receiving multiple daily injections of insulin, and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9% (mean, 8.5%). Subjects were randomly assigned to CGM (n = 79) or usual care (control group, n = 79). The primary outcome was HbA1c reduction at 24 weeks. The investigators reported a small but statistically significant reduction in mean HbA1c levels in the CGM group compared to the control group. Mean HbA1c levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks (adjusted difference in mean change, -0.3% [95% CI, -0.5% to 0.0%]; P = 0.022). The authors reported that the groups did not differ meaningfully in CGM-measured hypoglycemia or quality-of-life outcomes. The CGM group averaged 6.7 days (SD, 0.9) of CGM use per week. Limitations of this study included the modest reduction in HbA1c levels and limited (6-month) follow-up. In an accompanying editorial, Arguello and Freeby (2017) concluded, "With these data, we should seek to further understand patient populations that will benefit most from CGM intervention, such as those with the skills to address glucose variability. Future RT-CGM studies must also assess whether this approach improves health care outcomes for T2DM; its financial effects on the health care system; and further generalizability in T2DM subgroups, such as those with higher risk for hypoglycemia." In a commentary, Soloway, et al. (2017) noted "This study suggests that, in some patients with type 2

diabetes, CGM might lower HbA1c levels compared with standard fingerstick monitoring. However, because the study did not specify a glycemic treatment target, it doesn't prove that information from CGM — as opposed to other differences in how treating physicians managed CGM and fingerstick-monitored patients — was responsible for the lower HbA1c values. Moreover, the trial was short and set in specialty practices, and the investigators didn't assess clinical outcomes or cost-effectiveness.

There is some evidence to support the short-term diagnostic use of CGMs by medical professionals to detect unrecognized hypoglycemia, particularly unrecognized nocturnal hypoglycemia, in persons with type 2 diabetes. Chico et al (2003) reported on the diagnostic yield of the professional CGMs in persons with type 1 (n = 40) and type 2 diabetes (n = 30). The investigators reported that continuous glucose monitoring detected unrecognized hypoglycemias in 62.5 % of the type 1 diabetic patients and in 46.6 % of the type 2 diabetic patients. The investigators noted that 73.7 % of all unrecognized hypoglycemic events occurred at night. Tanenberg et al (2004) reported on a randomized controlled trial evaluating the effect of continuous glucose monitoring in 128 subjects with insulin-treated diabetes; 10 subjects were diagnosed with type 2 diabetes. Subjects were randomly assigned to insulin therapy adjustments based on either professional continuous glucose monitoring or self-monitoring of blood glucose values. At the end of the study, patients in both groups used theCGM for 3 days; these values were used to calculate measures of hypoglycemia. Subjects assigned to continuous glucose monitoring had a significantly shorter duration of hypoglycemia (sensor glucose less than or equal to 60 mg/dL) at week 12 of the study (49.4 +/- 40.8 versus 81.0 +/- 61.1 minutes per event, p = 0.009). The small number of subjects with type 2 diabetes in this study do not allow reliable conclusions to be made about the impact of continuous glucose monitoring in this subgroup. Other limitations of the study include its short duration and the use of an outcome, duration of hypoglycemia, of uncertain clinical significance. It should be noted that, in both this study by Tannenberg et al (2004), and the study by Chico et al (2003) described above, continuous glucose monitoring was reported to have no significant effect on glycemic control as measured by hemoglobin A1c.

Hay et al (2003) reported on the incidence of hypoglycemia and hypoglycemia detected by short-term (72-hour) continuous glucose monitoring in 25 elderly persons (greater than 65-year old) with type 2 diabetes treated with a sulfonylurea who were well controlled (hemoglobin A1c less than 7.5 %). Elderly patients with type 2 diabetes were recruited if their glycosylated hemoglobin (HbA1c) was less than 7.5 % and if their oral hypoglycemic therapy included a sulfonylurea. Patients underwent 2 consecutive 72-hour periods of continuous glucose monitoring at baseline and then again at 1 month. Patients were asked to record 4 self-monitored capillary blood glucose levels each day for calibration of the monitor and also to record meal times, exercise, and symptoms of hypoglycemia. The number of hyperglycemic (greater than 144 mg/dL), hypoglycemic (less than 50 mg/dL), and borderline-hypoglycemic (50 to 65 mg/dL) events were determined (an event was defined as a glucose value that persisted for at least 15 mins with or without symptoms). Twenty-five patients (21 men, 4 women) 73.9 +/- 4.4 years old with an HbA1c of 6.2 +/- 0.8 % were each monitored for an average of 187.57 hrs. The mean glucose values were: fasting, 139 +/- 40 mg/dL; 2 hrs post-breakfast, 167 +/- 58 mg/dL; 2 hrs post-lunch, 157 +/- 53 mg/dL; and 2 hrs post-dinner, 149 +/- 49 mg/dL. Twenty patients (80 %) experienced a total of 103 hypoglycemic events (less than 50 mg/dL), and 14 of these patients experienced 54 events where the glucose levels were less than or equal to 40 mg/dL. Twenty-four patients (96 %) experienced borderline-hypoglycemia (50 to 65 mg/dL) (n = 229 events). Patients experienced a mean of 0.62 +/- 0.72 episodes of hypoglycemia (interstitial glucose less than 50 mg/dL) per day (4 to 5 episodes overall), 0.35 +/- 0.6 episodes per day where the interstitial glucose was less than or equal to 40 mg/dL (2 to 3 episodes overall), and 1.37 +/- 1.22 episodes of borderline-hypoglycemia (9 to 10 episodes overall). Each episode of hypoglycemia persisted for 78 +/- 73 mins, and borderline-hypoglycemia for 45 +/- 11 mins. Patients were hypoglycemic 3.3 % of the time and borderline-hypoglycemic 3.7 % of the time. No episode of hypoglycemia was recorded by any patient in his or her daily diary. High post-prandial glucose values (greater than 144 mg/dL 2 hrs post-prandial) were recorded after 57 % of all meals (breakfast 60 %, lunch 57.5 %, dinner 55.2 %). The CGM was generally well-tolerated, but 52 % of patients could not be studied for the full 12 days of monitoring. The investigators reported that hypoglycemia and excessive post-prandial glycemic excursions are common in well-controlled patients with type 2 diabetes treated with a sulfonylurea with or without metformin. Limitations of the study included the fact that it was limited to persons on oral hypoglycemics, and that the study did not evaluate the impact of continuous glucose monitoring on improvements in clinical outcomes.

Zick et al (2007) reported on the yield of 72-hr continuous glucose monitoring versus self-monitoring of blood glucose in detecting hypoglycemia (less than or equal to 60 mg/dL) in patients with type 2 diabetes on multiple daily injections of insulin. Study subjects received NPH insulin (2-week run-in) followed by insulin glargine (8-week treatment phase). Glucose levels were measured by continuous glucose monitoring and self-monitored blood glucose profiles over the 72-hour pre- and post-treatment phase. Of 367 patients in the data set, 209 patients (56.9 %) experienced hypoglycemia according to continuous glucose monitoring; 97 (26.4 %) recorded hypoglycemia by conventional methods. Continuous glucose monitoring and self-monitoring of blood glucose reported similar mean daytime glucose levels at baseline and end point; however, nocturnal glucose levels were significantly lower with continuous glucose monitoring versus self-monitoring of blood glucose at baseline (130.2 versus 145.0 mg/dL) and at end point (123.3 versus 137.3 mg/dL).

The American Diabetes Association (2007) concluded that there is insufficient evidence to support the use of CGM in the hospital setting: "The introduction of real-time blood glucose monitoring as a tool for outpatient diabetes management has potential benefit for the inpatient population. However, at this time, data are lacking examining this new technology in the acutely ill patient population. Until more studies are published, it is premature to use continuous blood glucose monitoring except in a research setting."

A major limitation of CGM is the durability and stability of the glucose sensors. Interstitial glucose concentrations, obtained with subcutaneous sensors, correlate with blood glucose concentrations. However, the sensors become progressively less accurate

over time, so they can not be used on a maintenance basis, and must be changed every 3 days. Another potential concern is the 6 to 10 minutes delay in interstitial glucose sensor response to changes in serum glucose levels. This delay appears to be most important when glucose levels are falling rapidly, since it might result in development of clinically significant hypoglycemia before it was reflected in the sensor reading.

The Dexcom G7 Continuous Glucose Monitoring System entails a small wearable that sends real-time glucose readings to the Dexcom G7 app or receiver every 5 mins; no finger sticks or scanning is needed. It has various features to facilitate better diabetes management decisions. The “Urgent low soon alert” setting provides a 20-min advance warning of when one’s glucose level will r each 55 mg/dL so that one can act quickly and avoid a potential hypoglycemic event. In the “Silence all” setting, all alerts will not sound or vibrate for up to 6 hours. Visual notifications will still appear on the lock screen. The “Delay 1st alert” setting allows one to delay one’s “First high alert” until one’s sensor reading is high for a while (user chooses how long). The “Quiet mode” setting allows all users’ G7 alerts will vibrate; users’ “Urgent low glucose and technical alerts” will still escalate to sound if not acknowledged.

Garg et al (2022) examined the safety and accuracy of a 7th generation (G7) Dexcom CGM during 10.5 days of use in adults with diabetes. Adults with either T1 or T2 DM (on intensive insulin therapy or not) participated at 12 investigational sites in the U.S. In-clinic visits were caried out on days 1 or 2, 4 or 7, and on the 2nd half of day 10 or the 1st half of day 11 for frequent comparisons with comparator blood glucose measurements obtained with the venous blood glucose measurements (YSI) 2300 Stat Plus glucose analyzer. Participants wore sensors concurrently on the upper arm and abdomen. Accuracy evaluation included the proportion of CGM values within 15 % of comparator glucose levels of greater than 100 mg/dL or within 15 mg/dL of comparator levels of 100 or less mg/dL (%15/15), along with the %20/20 and %30/30 agreement rates. The mean absolute relative difference (MARD) between temporally matched CGM and comparator values was also calculated. Data from 316 participants (619 sensors, 77,774 matched pairs) were analyzed. For arm- and abdomen-placed sensors, overall MARDs were 8.2 % and 9.1 %, respectively. Overall %15/15, %20/20, and %30/30 agreement rates were 89.6 %, 95.3 %, and 98.8 % for arm-placed sensors and were 85.5 %, 93.2 %, and 98.1 % for abdomen-placed sensors. Across days of wear, glucose concentration ranges, and rates of change, %20/20 agreement rates varied by no more than 9 % from the overall %20/20. No serious AEs were observed. The authors concluded that the G7 CGM provided accurate glucose readings with single-digit MARD with arm or abdomen placement in adults with DM.

Laffel et al (2023) examined the accuracy of a 7th-generation "G7" CGM system in children and adolescents with T1DM. Sensors were worn on the upper arm and abdomen. The CGM data were available from 127 of 132 participants, aged 7 to 17 years, across 10.5 days of use, various glucose concentration ranges, and various rates of glucose change for comparisons with temporally matched YSI. Data were also available from 28 of 32 participants, aged 2 to 6 years, for whom capillary (finger stick) blood provided comparator glucose values. Accuracy metrics included the MARD between CGM and comparator glucose pairs, the proportion of CGM values within 15 mg/dL or 15 % of comparator values of less than 100 or 100 or greater than mg/dL, respectively, and the analogous %20/20 and %30/30 agreement rates. For participants aged 7 to 17 years, a total of 15,437 matched pairs were obtained from 122 arm-placed and 118 abdomen-placed sensors. For arm-placed sensors, the overall MARD was 8.1 % and overall %15/15, %20/20, and %30/30 agreement rates were 88.8 %, 95.3 %, and 98.7 %, respectively. For abdomen-placed sensors, the overall MARD was 9.0 % and overall %15/15, %20/20, and %30/30 agreement rates were 86.0 %, 92.9 %, and 97.7 %, respectively. Good accuracy was maintained across wear days, glucose ranges, and rates of glucose change. Among those aged 2 to 6 years, a total of 343 matched pairs provided an overall MARD of 9.3 % and an overall %20/20 agreement rate of 91.5 %. The authors concluded that G7 CGM placed on the arm or abdomen was accurate in children and adolescents with T1DM.

A draft evidence review prepared by the Center for Evidence-Based Policy for the Washington State Health Care Authority Health Technology Assessment Program (Durbin, et al., 2025) found that CGM use in adults with type 2 diabetes on non-intensive insulin regimens resulted in small reductions in HbA1c from baseline that were statistically significant but did not meet the prespecified threshold for clinical significance. The evidence review identified 7 randomized controlled trials in 15 publications (N = 802; follow-up range, 12 to 52 weeks) that assessed CGM among adults with type 2 diabetes on non-intensive insulin regimens (1 to 3 injections per day). The investigators found that CGM use resulted in a small reduction in HbA1c from baseline that was statistically significant (moderate certainty of evidence, based on 7 RCTs). At final follow-up (range, 12 to 52 weeks), CGM use was associated with a significant reduction in HbA1c compared with no CGM (pooled mean difference, -0.27%; 95% CI, -0.46 to -0.08; p = .005). However, this difference did not meet the threshold for clinical significance (minimal clinically important difference, 0.5% change). There was no difference between CGM and self-monitoring of blood glucose (SMBG) groups in the proportion of participants who achieved target HbA1c levels (i.e., 7.0%, 7.5%) at 12 or 24 weeks (low certainty of evidence, based on 1 RCT). There was no clear association between CGM and improved diabetes-related quality of life (QoL) (low certainty of evidence, based on 4 RCTs). There was no clear association between CGM and improved general QoL (low certainty of evidence, based on 2 RCTs). The evidence review did not identify any eligible randomized controlled trials evaluating the effectiveness or safety of CGMs in children with type 2 diabetes on non-intensive insulin regimens,

The evidence review found, in adults with type 2 diabetes on oral hypoglycemic medications, there was no consistent difference in change in HbA1c from baseline with CGM versus other non-CGM monitoring methods (low certainty of evidence, based on 6 RCTs) (Durbin, et al., 2025). They did not identify any eligible randomized controlled trials evaluating CGMs in adults with type 2 diabetes not on insulin or oral hypoglycemic medication regimens. In adults with type 2 diabetes on mixed non-intensive hypoglycemic therapies, there was no consistent difference in change in HbA1c from baseline with CGM versus other non-CGM monitoring methods (very low certainty of evidence, based on 5 RCTs).

Continuous Blood Glucose Monitoring for Individuals with Type 1a Glycogen Storage Disease

Hershkovitz et al (2001) noted that glycogen storage disease type I (GSD I) is characterized by impaired production of glucose from glycogenolysis and gluconeogenesis resulting in severe fasting hypoglycemia. These investigators examined the efficacy of a CGMS (MiniMed) to determine the magnitude and significance of hypoglycemia in GSD I and assessed the efficacy of its dietary treatment. A total of 4 children with GSD I were studied over a 72-hour period. Results indicated that the values recorded with a subcutaneous CGMS were highly correlated with paired blood glucose values measured by glucometer. Significant periods of asymptomatic hypoglycemia were noted, especially during night-time. The authors concluded that the findings of this study suggested that repeated continuous subcutaneous glucose monitoring may serve as a useful tool for the assessment of the long-term management of GSD I patients.

Maran et al (2004) stated that the development of new systems for CGM has recently increased the interest for their potential applications among physicians involved in diabetes care. One of the most common applications of such devices is the identification of hypoglycemic events in insulin-treated diabetic patients (particularly during the night) and the evaluation of the full daily glucose excursions. Among commercially available glucose sensors, the Glucoday System has been used for practical clinical application in the last 2 years. One of the most important features of this device is the accuracy in monitoring interstitial glucose values, specifically in the hypoglycemic range. This feature is clinically relevant when applied in the clinical setting of patients with T1DM. The ability to monitor glucose continuously could be indeed a useful tool for the study of hypoglycemic conditions other than diabetes. In patients with hyper-insulinemic hypoglycemia, recurrent episodes of asymptomatic hypoglycemia are common, and in patients with GSDs, avoidance of recurrent and prolonged hypoglycemic episodes usually require frequent determinations by mean of home blood glucose monitoring. The authors concluded that experimental preliminary evidences suggested that this new technology could be applied in the clinical setting to help the physician to identify mainly nocturnal hypoglycemic events, otherwise not revealed by traditional self blood-glucose monitoring, even in those patients who are not treated by conventional insulin therapy.

White and Jones (2011) noted that CGMS are now in widespread use in diabetes management with an increasing evidence base; nevertheless, there are few reports of their use in GSD. Liver GSDs are most often managed by intensive dietary regimens; however, risks of over and under-treatment remain. These researchers described their use of CGMS in a cohort of GSD patients, the results obtained and the frequency of complications. Their experience was that CGM is a reliable, well accepted and valid tool in the monitoring of GSD patients and allows for assessment of blood sugar control in the "real-life" setting, unlike hospital admissions. Combining CGM with urine ketone and/or blood lactate measurements, again at home, improves the investigation yet further. It is possible to perform CGM for periods including both school days and weekends, and also to change the dietary regimen during the period of monitoring to reduce the frequency of assessments. Risks of decreased reliability in the low range of blood sugars may be out-weighed by the increased validity of the patient being in the home environment, with a normal diet and activity schedule.

Kasapkara et al (2014) noted that GSD I is an autosomal recessive metabolic disorder caused by defects in the glucose-6-phosphatase complex. Deficient activity in the glucose-6-phosphatase-α catalytic unit characterizes GSD Ia and defects in the glucose-6-phosphate transporter protein characterize GSD Ib. Type Ia involves the liver, kidney and intestine (and Ib also leukocytes), and the clinical manifestations are hepatomegaly, failure to thrive, severe fasting hypoglycemia within 3 to 4 hours after a meal, hyperlactatemia, hyperuricemia and hyperlipidemia. These researchers examined the safety and efficacy of a subcutaneous CGMS to determine the magnitude and significance of hypoglycemia in GSD I and evaluated the efficacy of the revised dietary treatment. A total of 16 children with GSD I were studied over a 72-hour period; CGM was repeated in all patients 3 to 6 months after the 1st monitoring to examine the effects of revised dietary instructions on glycemic control. All the patients completed the study without any major AEs. Significant periods of asymptomatic hypoglycemia (below 4 mmol/L, 70 mg/dL) were noted. There was a close correlation between CGM sensor and capillary blood glucose values measured by a glucometer. CGM indicated a considerable reduction in duration of hypoglycemia, liver size and improvements in secondary metabolic derangements such as hyperlacticacidemia and hyperlipidemia. The authors concluded that CGM could be applied in the clinical setting to help the physician to identify hypoglycemic events, and repeated CGM may serve as a safe and useful tool for the assessment of the long-term management of patients with GSD I; however, the long-term benefits on metabolic control remain to be determined.

Herbert et al (2018) stated that management of liver GSDs primarily involves maintaining normoglycemia through dietary modifications and regular glucose monitoring. Self-monitoring of blood glucose is typically done 3 to 6 times per day, and may not sufficiently capture periods of asymptomatic hypoglycemia, particularly during sleep; CGMS provide 24-hour continuous glucose data and have been used effectively in DM to monitor metabolic control and optimize treatment. This is a relatively new approach in GSDs with only a handful of studies examining this modality. In this study, these investigators used Dexcom CGMS to study the glycemic profile of 14 pediatric and 6 adult patients with GSD I, III, and IX. A total of 176 days of CGMS data were available. The CGMS was found to be a reliable tool in monitoring glucose levels and trends at all times of the day with good concordance with finger-stick glucose values. This study revealed that in addition to over-night hypoglycemia, CGMS could uncover previously undetected, subclinical, low glucose levels during daytime hours. Additionally, the CGMS detected daytime and over-night hyperglycemia, an often overlooked concern in liver GSDs. The CGMS with concurrent dietary adjustments made by a metabolic dietitian improved metabolic parameters and stabilized blood glucose levels. The authors concluded that CGMS was found to be a safe, effective, and reliable method for optimizing treatment in patients with GSD I, III, and IX. This was a small (n = 20) study; and it is unclear how many of the 6 adult participants had GSD I.

Alsaffar et al (2018) noted that the factory calibrated FreeStyle Libre (FSL) flash glucose monitoring system has recently been introduced for use in patients with diabetes mellitus. There are no reports available regarding its use in patients with congenital hyperinsulinism (CHI). These investigators examined the accuracy of FSL compared to the finger prick capillary blood glucose (CBG) over a 2-week period in patients with CHI and assessed parents' experience of using FSL. A total of 467 episodes of CBG along with corresponding swipe FSL readings were available from 11 children with CHI (0.5 to 5 years). A detailed questionnaire was completed by the parents. The mean variation between the 2 methods was 0.29 mmol/L (SD ± 1.07), higher readings by FSL compared to CBG. The FSL sensors stayed in-situ for an average period of 11.5 days. There was a positive correlation between the 2 methods (r = 0.7). The FSL tended to over-estimate compared to CBG (bias = 0.29 mmol/l; 95 % CI: 0.19 to 0.38). Only 70 % of values were within the reference standard (± 0.83 mmol/L) at glucose concentrations less than 5.6 mmol/l. The overall Mean Absolute Relative Difference (MARD) was 17.9 %; 42 episodes of hypoglycemia (CBG less than 3.5 mmol/L) were noted; but FSL identified only 52 % of these episodes. The Bland Altman analysis showed the 95 % limits of agreement between the 2 methods ranging from - 1.8 (95 % CI: -1.97 to - 1.64) to 2.37 (95 % CI: 2.21 to 2.54). The majority of the parents found the glucose trend on FSL to be useful to detect and prevent hypoglycemic episodes. All parents felt that FSL was a very easy and convenient method to measure the glucose especially during sleep. A significant proportion of parents felt that FSL readings were not accurate and 56 % of parents expressed interest to continue using FSL after the trial period. The authors concluded that noticeable variability between the 2 methods of measuring the glucose was noted. Despite the ease of using the FSL system, concerns related to accuracy, especially at low glucose values remained although parents found the glucose trend to be very useful. These researchers stated that further larger trials are needed in CHI patients before FSL is recommended as a routine alternative method for measuring glucose levels.

Dunn et al (2018) stated that RCTs showed that using flash glucose monitoring improved glycemic control; however, it is unclear if this applies outside trial conditions. These investigators examined glucose testing patterns in users worldwide under real life settings to establish testing frequency and association with glycemic parameters. Glucose results were de-identified and uploaded onto a dedicated database once readers were connected to an internet-ready computer. Data between September 2014 and May 2016, comprising 50,831 readers and 279,446 sensors worldwide, were analyzed. Scan rate per reader was determined and each reader was sorted into 20 equally-sized rank-ordered groups, categorized by scan frequency. Glucose parameters were calculated for each group, including estimated HbA1c, time above, below and within range identified as 3.9 to 10.0 mmol/L. Users performed a mean of 16.3 scans/day [median (inter-quartile range [IQR]): 14 (10 to 20)] with 86.4 million hours of readings and 63.8 million scans. Estimated HbA1c gradually reduced from 8.0 % to 6.7 % (64 to 50 mmol/mol) as scan rate increased from lowest to highest scan groups (4.4 and 48.1 scans/day, respectively; $p < 0.001$). Simultaneously, time below 3.9, 3.1 and 2.5 mmol/L decreased by 15 %, 40 % and 49 %, respectively (all $p < 0.001$). Time above 10.0 mmol/L decreased from 10.4 to 5.7 hours/day (44 %, $p < 0.001$) while time in range increased from 12.0 to 16.8 hours/day (40 %, $p < 0.001$). These patterns were consistent across different countries. The authors concluded that in real-world conditions, flash glucose monitoring allowed frequent glucose checks with higher rates of scanning linked to improved glycemic markers, including increased time in range and reduced time in hyper and hypoglycemia.

Massa et al (2018) stated that the FSL flash glucose monitoring System (FGM) measures glucose concentrations in the interstitial fluid for up to 14 days. It has been approved for use in children aged greater than 4 years in January 2016. Experience in children is still limited. These researchers examined the accuracy and usability of the FGM in children with type 1 diabetes mellitus (T1DM). A total of 67 children with T1 DM (35 girls), aged 4 to 18 years, were included in this trial. Subjects wore a sensor on the back of their upper arm. For the first 14 days, they regularly CBG with their usual BG meter (Accu-Chek Mobile [ACM], Roche [n = 24]; Contour Next Link [CNL], Bayer [n = 26]; OneTouch Verio IQ [OTV], LifeScan [n = 17]) followed by a sensor glucose (SG) scanning. SG readings were compared to BG measurements by consensus error grid (CEG) analysis; the mean difference (MD), the mean relative difference (MRD), the mean absolute difference (MAD), and the mean absolute relative difference (MARD) were calculated. After 14 days, subjects were asked to fill in a questionnaire on the usability of the FGM. A total of 2,626 SG readings were paired with BG results. FGM readings were highly correlated with BG ($r = 0.926$, $p < 0.001$). 80.3 % of the data pairs were in zone A (= no effect on clinical action) and 18.4 % were in zone B (= altered clinical action with little or no effect on the clinical outcome) of the CEG. Overall MD was +7.5 mg/dL; MD varied with the BG meter: ACM +10.4 mg/dL, CNL +14.2 mg/dL, OTV -3.6 mg/dL ($p < 0.001$). Overall, MARD was 16.7 %. These investigators observed a large inter-individual variability in the accuracy parameters. MD and MRD were inversely related to BMI ($r = -0.261$ [$p < 0.05$]; $r = -0.266$ [$p < 0.05$], respectively). MARD was inversely related to age ($r = -0.266$ [$p < 0.05$]); 29 patients (43.3%) reported sensor problems, mainly early detachment of the sensor. Nonetheless, the usability questionnaire indicated high levels of satisfaction. The authors concluded that the findings of this study showed a reasonable agreement between the FGM SG readings and CBG measurements in children. There was, however, a large inter-individual variability. The wearing of the sensor required special attention. These investigators stated that further studies in children are needed to document the accuracy and safety of the FGM in the pediatric population.

Furthermore, an UpToDate review on "Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease)" (Sun, 2020) does not mention continuous blood glucose monitor as a management tool.

Peeks et al (2021) noted that CGM systems have great potential for real-time assessment of glycemic variation in patients with hepatic glycogen storage disease (GSD); however, detailed descriptions and in-depth analysis of CGM data from hepatic GSD patients during interventions are scarce. These researchers carried out a retrospective in-depth analysis of CGM parameters, acquired in a continuous, real-time fashion describing glucose management in 15 individual GSD patients. CGM subsets were obtained both in-hospital and at home, upon nocturnal dietary intervention (n = 1), starch loads (n = 11) as well as treatment of

GSD Ib patients with empagliflozin (n = 3). Descriptive CGM parameters, and parameters reflecting glycemic variation and glycemic control were considered useful CGM outcome parameters. Furthermore, the combination of 1st and 2nd order derivatives, cumulative sum and Fourier analysis identified both subtle and sudden changes in glucose management; thus, helping in the evaluation of dietary and medical interventions. CGM data interpolation for nocturnal intervals reduced confounding by physical activity and diet. The authors concluded that in-depth CGM analysis could be a powerful tool to evaluate glucose management and optimize treatment in patients with hepatic GSD.

Parikh and Ahlawat (2021) stated that GSD I (also known as Von Gierke disease) is an inherited disorder caused by deficiencies of specific enzymes in the glycogen metabolism pathway. It was first described by Von Gierke in 1929 who reported excessive hepatic and renal glycogen in the autopsy reports of 2 children. It comprises 2 major subtypes, GSD Ia and GSD Ib. In GSD Ia, there is a deficiency of enzyme glucose-6-phosphatase (G6Pase) that cleaves glycogen to glucose; thus, leading to hypoglycemia and lactic acidosis. Patients with GSD 1b have normal G6Pase enzyme activity; but have a deficiency of the transporter enzyme, glucose-6-phosphate translocase (G6PT). Patients present with manifestations of hypoglycemia and metabolic acidosis typically around 3 to 4 months of age. In patients suspected of having the disease, genetic testing is the investigation of choice to confirm the diagnosis. Dietary treatment prevents hypoglycemia and improves the life expectancy of patients. However, to prevent long-term complications such as hepatic adenomas and renal failure, animal models of GSD I are being developed to study the disease more closely and develop new treatment strategies such as gene therapy. Monitoring of blood glucose along with the laboratory parameters should continue as with increasing growth, the child’s nutritional needs change. All patients with GSD I should wear a medical alert bracelet. Along with blood glucose monitoring, a lactate meter can be a good tool to alert the parents especially in times of emergency.

Continuous Blood Glucose Monitoring for Neonatal Hypoglycemia

An UpToDate review on "Pathogenesis, screening, and diagnosis of neonatal hypoglycemia" (Rozance, 2020) states that "Continuous glucose monitoring using a sensor that measures interstitial glucose concentration was reported to be reliable (when compared with blood glucose measurement), safe, and tolerable in neonates including very preterm infants. However, it is unclear how to interpret the clinical significance of low interstitial blood glucose levels and whether treatment should be initiated. Further studies are needed to determine whether continuous interstitial glucose monitoring has a useful role in the screening and management of neonatal hypoglycemia".

Furthermore, an UpToDate review on "Diagnostic approach to hypoglycemia in infants and children" (De Leon-Crutchlow and Lord, 2020) does not mention continuous glucose monitoring as a diagnostic option.

Artificial Pancreas or Bionic Endocrine Pancreas

An artificial pancreas is a closed-loop system with an insulin infusion pump, real-time continuous glucose monitor and a small computing device to coordinate glucose sensing and insulin administration.

Closed-loop glucose management systems with a continuous glucose monitor and an insulin pump programmed with a computer algorithm calculates insulin doses (or glucagon) from the CGM readings and tells the pump to deliver or temporarily suspend or reduce insulin based upon specified thresholds of measured glucose levels.

Artificial pancreas may also be referred to as an automated insulin-delivery system, closed-loop system, or bionic pancreas. For additional information on artificial pancreas system devices, see CPB 0161 - Infusion Pumps.

GlucoWatch Biographer

The GlucoWatch Biographer provides non-invasive continuous glucose measurements, and is intended to detect trends in glucose levels in persons with diabetes. GlucoWatch measures the concentration of glucose by iontophoresis; a constant low-level electrical current is conducted through the skin, which causes glucose to be transported across the skin where it can be measured. After a 3-hr warm-up period and calibration from a fingerstick blood measurement, the device can provide up to 3 non-invasive glucose measurements per hour for up to 12 hours. Readings can be stored for several months and can be down-loaded into a computer. Clinical studies (Garg et al, 1999; Tamada et al, 1999) have reported correlations between GlucoWatch readings and standard fingerstick blood glucose measurements.

Because clinical studies showed that the GlucoWatch is less accurate than fingerstick testing, the device does not eliminate the need for painful fingersticks. In studies submitted to the FDA, measurements differed from fingerstick results by more than 30 % up to 1/3 of the time. The GlucoWatch won't measure blood glucose levels if the person perspires excessively, and is less effective at detecting life-threatening low blood sugar than at spotting dangerously high glucose levels. According to the FDA-approved labeling, the GlucoWatch is intended to supplement, not replace, standard fingerstick testing. The product labeling states that users should never decide to use insulin based on a GlucoWatch measurement and that users should double-check the GlucoWatch reading with a fingerstick measurement before changing insulin dosages. In addition, the user must calibrate the GlucoWatch with a fingerstick reading each time the device is worn.

A structured evidence review conducted by the BlueCross BlueShield Association Technology Evaluation Center (TEC) (2002) concluded that the GlucoWatch Biographer does not meet the TEC criteria because the impact of this device on health outcomes is unknown.

A technology assessment conducted by CTAF concluded that the GlucoWatch Biographer does not meet CTAF's criteria (Tice, 2003). Furthermore, in a multi-center, randomized controlled study (n = 200), Chase et al (2005) concluded that use of the GlucoWatch G2 Biographer in addition to standard glucose monitoring did not improve glycemic control or reduce the frequency of severe hypoglycemia in children with type 1 diabetes.

Alternate Site Blood Glucose Monitors

Blood glucose monitors that permit "alternate site" testing allow persons to test blood samples obtained from sites other than their fingertips, such as the arm or thigh. The primary advantage of alternate site testing is that it may be less painful as there are fewer nerve endings at alternate sites than at the fingertips. However, people who draw blood frequently develop calluses which reduce the pain from fingerstick blood draws.

A Consumer Reports test of several alternate site meters concluded that alternate site testing is "slightly less painful" than fingertip testing. However, thigh samples were found to be "less convenient" than fingertip testing, and forearm samples were "harder to obtain and messier than finger pricks."

Although an alternative blood glucose monitor may be an appropriate choice for persons who can't use a conventional blood glucose monitor, there are a number of concerns about alternate site blood glucose monitors that argue against their routine prescription to all persons with diabetes. First, it is more difficult to start the bleeding at alternate sites, and it is more difficult to stop the bleeding once started. Blood draws from alternate sites may also induce bruising. Second, there is some concern about drawing blood from alternate sites because of diabetic persons' increased risk of infection. Risk of infection may be increased with alternate site testing because there is less blood flow at alternate sites than at fingertips.

A third concern is that alternate site testing may not reflect systemic glucose levels as accurately as finger-sticks, especially when blood glucose levels are rapidly changing, such as after a meal or exercise. This is because blood flow to alternate sites is slower than to the fingertips. Finally, there are no studies proving that alternate site testing improves compliance with blood glucose monitoring.

Home Glycated Hemoglobin Monitors

There are no prospective clinical studies demonstrating improvements in compliance or other clinically significant benefits of home A1C testing over laboratory A1C testing. Because A1C testing reflects a mean glycemia over 2 to 3 months, the ADA recommends repeat A1C testing no more frequently than quarterly. Thus, A1C testing can be performed during regularly scheduled office visits. In addition, with office-based testing, health care providers are available to properly interpret the test and to determine whether the person's treatment regimen needs to be modified. An assessment of home glycated hemoglobin monitors by the CTAF found that there is a paucity of data on home monitoring of HbA1c (Tice, 2003). One study (Rector et al, 2001) mailed free HbA1c kits to patients with diabetes reported that less than 50 % of the patients used the kits. The main reasons given for not performing the tests were that their physicians had already done the test or that they were too busy. The CTAF assessment (Tice, 2003) noted that "[d]ay to day clinical decisions about diabetes therapy are based on daily glucose testing, not HbA1c. HbA1c levels are usually used to make long-term changes in care in consultation between the patient and their doctor. It is unlikely that home HbA1c testing will improve clinical outcomes for patients with diabetes."

Personal Digital Assistant-Based Blood Glucose Monitors

The FreeStyle TrackerTM (TheraSense, Inc., Alameda, CA) and the Accu-Check Advantage Module (Roche Diagnostics Corp., Indianapolis, IN) combine a glucose meter with a PDA. Together, these create a glucose meter that also tracks and helps manage blood sugar (glucose) levels. Both the FreeStyle Tracker and the Accu-Check Advantage Module use a Handspring VisorTM PDA, which may be purchased separately. When a glucose module is inserted into its expansion slot, the PDA gives instructions for testing blood sugar and displays the results on its screen. The FreeStyle Tracker Diabetes Management System and the Accu-Check Advantage Module were cleared by the FDA through 510(k) applications in June 2002.

To use these systems, an individual inserts a test strip into the glucose module, pierces the skin with a lancet, and places a drop of blood on the test strip. In addition to showing current blood sugar levels, these systems store readings in an electronic database. This database can also include insulin usage, food intake, exercise, and medicine. These data can be graphed and displayed on the PDA, or they can be uploaded to a personal computer (PC).

In addition, there is an unanswered question about whether these computerized tracking programs improve clinical outcomes. The ADA guidelines (2003) concluded: "Although a number of SMBG [self-monitoring of blood glucose] methods store test results and with a computer interface can provide sophisticated analyses of blood glucose data, it is not known whether use of these data management systems yields better glucose control than patient review of results recorded in a logbook."

There is no published clinical literature demonstrating that proves that the use of PDA-based blood glucose monitors improves clinical outcomes over standard blood glucose monitors.

Sevick et al (2008) noted that ENHANCE is a randomized controlled trial to test an intervention designed to improve regimen adherence in adults with type 2 diabetes. The intervention, based on Social Cognitive Theory (SCT), is paired with PDA-based self-monitoring. The authors described

1. the manner in which PDA-based self-monitoring is integrated within the SCT-based intervention,
2. feasibility and acceptability of PDA-based dietary self-monitoring, and
3. issues encountered in teaching participants to self-monitor using a PDA.

During the first 30 months of this 5-year study, 232 subjects were screened and 151 were randomized. A total of 6 cohorts completed the study. The retention rate is 85 % (n = 129). Of those randomized to the intervention (n = 74) and completing the study (n = 61), 88 % reported understanding the usefulness of PDA-monitoring, 85 % reported ease in entering foods into the device, 70 % reported ease in interpreting feedback graphs, and 82 % indicated that they would continue to use the PDA for self-monitoring after the study concluded. Assuming 3 meals per day, subjects entered an average of 58 % of their meals in their PDA, and 43 % were entered assuming 4 meals per day. If the investigators eliminated from the analysis those individuals who entered less than 10 % of their expected meals (n = 12), the average rate of self-monitoring was 69 % assuming 3 meals per day, and 52 % assuming 4 meals per day. The authors concluded that PDA-based dietary monitoring is perceived by participants to be useful and acceptable, and PDA technology shows promise as a tool for assisting those with type 2 diabetes in their efforts to manage their disease.

Disposable Blood Glucose Monitors

The ReliOn NewTek has been cleared by the FDA for marketing under the 510(k) process for persons with diabetes when recommended by their physician. It includes a disposable meter containing 100 test strips plus control solution. The ReliOn NewTek (Express Blood Glucose Monitoring System) received FDA 510(k) marketing clearance in 2003. According to the FDA 510(k) summary letter submitted by the manufacturer to the FDA, testing demonstrated that its performance was substantially equivalent to the Hypoguard Advance Blood Glucose Monitoring System.

Infrared Thermometer Device

Foot ulcers develop in approximately 15 % of patients with diabetes. Ulceration is caused by several factors, but particularly by neuropathy. The annual incidence of foot ulceration is slightly more than 2 % among all patients with diabetes and between 5 and 7.5 % among diabetic patients with peripheral neuropathy. Peripheral neuropathy results in loss of the protective sensation of pain and in autonomic dysfunction, with sympathetic denervation, dry skin, and warm feet. Appropriate medical education regarding early assessment for lesions or warning signs of imminent ulceration in patients with sensory loss is essential. Other causes of ulceration include peripheral vascular disease, callus, edema, and deformity. The triad of neuropathy, deformity, and trauma is present in almost two-thirds of patients with foot ulcers. Inappropriate footwear is the most common source of trauma.

Neuropathy can be detected with a simple neurological examination of the lower extremities involving the use of a 10-g monofilament to test sensation, or a composite score such as the modified neuropathy disability score. Both are predictive of the risk of foot ulcers. The modified neuropathy disability score assigns a number to each of the following:

1. vibration threshold utilizing a tuning fork,
2. temperature (tuning fork placed in ice water or warm water),
3. pinprick, and
4. Achilles' reflex.

A score of 6 or greater is predictive of foot ulceration. The TempTouch (Diabetica Solutions Inc., San Antonio, TX) is an infrared hand-held, battery-operated thermometer intended for the intermittent measurement and monitoring of human skin surface temperature. It received 510(k) marketing clearance from the FDA in March, 2005 and is being marketed as an early warning device for the development of diabetic foot neuropathy. Individuals take temperatures on the bottom of both feet with the device and compare results from one day to the next. If there is a 4-degree Fahrenheit difference on the same spot (e.g., the heel of one foot versus the other) from one day to the next, the spot with the higher temperature is a 'hot spot' and may be predictive of an ulceration.

Lavery and colleagues (2004) evaluated the effectiveness of at-home infrared temperature monitoring as a preventative tool in individuals at high risk for diabetes-related lower-extremity ulceration and amputation in 85 patients who fit diabetic foot risk category 2 or 3 (neuropathy and foot deformity or previous history of ulceration or partial foot amputation). Patients were randomized into a standard therapy group (n = 41) or an enhanced therapy group (n = 44). Standard therapy consisted of therapeutic footwear, diabetic foot education, and regular foot evaluation by a podiatrist. Enhanced therapy included the addition of a handheld infrared skin thermometer to measure temperatures on the sole of the foot in the morning and evening. Elevated temperatures (greater than 4 degrees Fahrenheit compared with the opposite foot) were considered to be "at risk" of ulceration

due to inflammation at the site of measurement. When foot temperatures were elevated, subjects were instructed to reduce their activity and contact the study nurse. Study subjects were followed for 6 months and included a podiatry evaluation every 10 to 12 weeks. The enhanced therapy group had significantly fewer diabetic foot complications (enhanced therapy group 2 % versus standard therapy group 20 %, p = 0.01, odds ratio 10.3, 95 % CI: 1.2 to 85.3). There were 7 ulcers and 2 Charcot fractures among standard therapy patients and one ulcer in the enhanced therapy group. The authors concluded that these results suggest that at-home patient self-monitoring with daily foot temperatures may be an effective adjunctive tool to prevent foot complications in individuals at high-risk for lower-extremity ulceration and amputation. However, Parrella et al (2005) reviewed the study by Lavery and colleagues (2004) and stated, "[a]lthough these results suggest effectiveness, they may be influenced by patients changing activity levels in the TemPTouch and/or seeking a clinical evaluation by the study nurse when temperature differences were noted."

Lavery and colleagues (2007) conducted a further study with a follow-up period of 15 months. Diabetics with a previous history of diabetic foot ulceration (n = 173) were assigned to standard therapy, structured foot examination, or enhanced therapy groups. Each group received therapeutic footwear, diabetic foot education, and regular foot care. Subjects in the structured foot examination group performed a structured foot inspection daily and recorded their findings in a logbook. If standard therapy or structured foot examinations identified any foot abnormalities, subjects were instructed to contact the study nurse immediately. Subjects in the enhanced therapy group used an infrared skin thermometer to measure temperatures on 6 foot sites each day. Temperature differences greater than 4 degrees Fahrenheit (greater than 2.2 degrees Celsius) between left and right corresponding sites triggered patients to contact the study nurse and reduce activity until temperatures normalized. The enhanced therapy group had fewer foot ulcers than the standard therapy and structured foot examination groups (enhanced therapy 8.5 versus standard therapy 29.3 %, p = 0.0046 and enhanced therapy versus structured foot examination 30.4 %, p = 0.0029). Patients in the standard therapy and structured foot examination groups were 4.37 and 4.71 times more likely to develop ulcers than patients in the enhanced therapy group. The authors concluded that infrared temperature home monitoring, in serving as an "early warning sign," appears to be a simple and useful adjunct in the prevention of diabetic foot ulcerations.

Armstrong and colleagues (2007) evaluated the effectiveness of home temperature monitoring and the incidence of foot ulcers in high-risk patients with diabetes. Diabetics at high risk for ulceration (n = 225) were randomly assigned to standard therapy (standard therapy group) or dermal thermometry (dermal thermometry group) groups. Both groups received therapeutic footwear, diabetic foot education, regular foot care, and performed a structured foot inspection daily. The dermal thermometry group used an infrared skin thermometer to measure temperatures on 6 foot sites twice daily. Temperature differences greater than 4 degrees Fahrenheit between left and right corresponding sites triggered patients to contact the study nurse and reduce activity until temperatures normalized. A total of 8.4 % (n = 19) subjects ulcerated over the 18-month study period. Subjects were 1/3 as likely to ulcerate in the dermal thermometry group compared with the standard therapy group (12.2 % versus 4.7 %, odds ratio 3.0, 95 % CI: 1.0 to 8.5, p = 0.038). Proportional hazards regression analysis suggested that thermometry intervention was associated with a significantly longer time to ulceration (p = 0.04), adjusted for elevated foot ulcer classification (International Working Group Risk Factor 3), age, and minority status. Patients that ulcerated had a temperature difference that was 4.8 times greater at the site of ulceration in the week before ulceration than did a random 7 consecutive-day sample of 50 other subjects that did not ulcerate (3.50 +/- 1.0 versus 0.74 +/- 0.05, p = 0.001). The authors concluded that high temperature gradients between feet may predict the onset of neuropathic ulceration and self-monitoring may reduce the risk of ulceration.

In a clinical pilot study, Fierheller and Sibbald (2010) quantified the relationship between increased peri-wound skin temperature and wound infection, as well as validated use of a hand-held infrared thermometer for the wound care practitioner. Using a cross-sectional design, 2 groups of participants were recruited from a chronic wound clinic:

1. without wounds (n = 20) and
2. with chronic leg ulcers (n = 40).

Participants and wound characteristics were documented. All skin temperatures were documented using a hand-held infrared thermometer under consistent environmental conditions within the clinic. Data analysis was based on the difference (Delta) in skin temperature (in degrees Fahrenheit) between a target or wound site and an equivalent contralateral control site. Wound infection was identified using the combination of a validated assessment tool and clinical judgment. Supplemental semi-quantitative bacterial swabs were collected from all wounds. Descriptive statistics were analyzed using the chi-squared calculation. A Pearson r calculation of test-retest skin temperature data collected from non-wounded participants initially determined reliability of the infrared thermometer. Correlation of increased peri-wound skin temperature to wound infection was determined by calculation of a 1-way analysis of variance. The infrared thermometer was found to be reliable (r = 0.939, p = 0.000 at a 95 % CI). A statistically significant relationship between increased peri-wound skin temperature and wound infection was identified (F = 44.238, p = 0.000 at a 95 % CI). Neither patient nor wound characteristics were significantly different between the participants with non-infected or infected wounds. The authors concluded that these findings demonstrated that incorporating quantitative skin temperature measurement into routine wound assessment provides a timely and reliable method for a wound care practitioner to quantify the heat associated with deep and surrounding skin infection and to monitor ongoing wound status. Study limitations may reduce transferability of these findings to wound types other than chronic leg ulcers. They stated that further research is needed to support and strengthen these results.

The International Working Group on the Diabetic Foot practice guidelines (1999) recommended that all individuals with diabetes be examined at least annually for potential foot problems and that the risk of future ulceration can be determined with a 10-g

monofilament to test sensation. These guidelines are supported in part by data from clinical trials and in part by expert opinion.

The American College of Foot and Ankle Surgeons clinical practice guideline on diabetic foot disorders (2006) outlined a preventive treatment strategy for the diabetic foot and stated that home temperature assessment of the foot has been shown to reduce the incidence of foot ulcers 10-fold compared with standard preventive care (citing the 2004 study by Lavery and colleagues).

The ADA's clinical practice recommendations on preventive foot care for diabetics recommends a foot examination at least annually by a health care provider and patient education regarding preventive foot care (ADA, 2010).

There is insufficient evidence of the effectiveness of an infrared thermometer device versus standard foot care in reducing the risk for diabetic foot ulceration.

Measurement of Advanced Glycation End Products by Skin Autoflourescence

Skin autofluorescence is a non-invasive measurement of the level of tissue accumulation of advanced glycation end products (AGEs), representing cumulative glycemic and oxidative stress. Several studies have shown that AGEs accumulate in skin faster in individuals with poor blood sugar control and that measurement of AGEs by skin autofluorescence may be able to predict the risk of developing diabetes and related complications (Lutgers et al, 2006 and 2009; Meerwald et al, 2007; Gerrits et al, 2008; and Ediger et al, 2009).

The Scout DS system (Veralight, Inc., Albuquerque, NM) measures skin AGEs by autoflorescence spectroscopy. The device is a portable desktop system with an arm cradle. The subject places the palm side of their forearm into the cradle and the device shines multiple wavelengths of light into the skin causing the AGEs to fluoresce. The instrument optically calibrates for skin pigmentation, making the measurement impervious to variations in skin color. A specially designed fiber-optic probe sends excitation light to the subject and relays resulting skin fluorescence to the detection module. A value from 0 to 100 representing the likelihood of that subject having an abnormal glucose tolerance test is reported in about 60 seconds. The proposed benefits of the Scout DS system is that the patient would not need to fast or provide a blood sample and results are received much quicker. The system is not intended to replace an oral glucose tolerance test.

There is insufficient evidence of the effectiveness of the Scout DS system compared to fasting plasma glucose tolerance testing. The device is currently used for research purposes only. The manufacturer is conducting a prospective, multi-center clinical trial comparing the Scout DS system to the fasting plasma glucose tolerance test in subjects at risk for diabetes.

de Ranitz-Greven et al (2012) noted that AGEs are tissue proteins that accumulate with age and in DM. Advanced glycation end products can be measured by the AGE-Reader (DiagnOptics Technologies BV, Groningen, The Netherlands), which measures skin auto-fluorescence (SAF); SAF has been suggested as a measure to screen for undiagnosed DM or impaired glucose tolerance. Skin auto-fluorescence has never been investigated in GDM. Therefore, these researchers compared SAF at diagnosis in GDM patients with normal pregnancy. If SAF is elevated in GDM, future research could focus on the possible use of the AGE-Reader as a screening method for GDM. In this mono-center observational study, SAF was measured in 60 GDM patients at diagnosis and 44 pregnant women without diabetes. Skin auto-fluorescence did not differ between GDM at diagnosis (mean [SD], 1.74 [0.31] arbitrary units) and normal pregnancy (1.76 [0.32] arbitrary units); SAF was lower in white European patients than in patients with other ethnicity. The authors concluded that this first study of tissue AGE accumulation in pregnancy shows no differences in SAF between women with GDM at diagnosis and normal pregnancy. This was most likely due to mild severity and short duration of hyperglycemia in GDM at diagnosis, but it did not exclude potential differences in SAF later in pregnancy. However, the fact that no differences were detected at diagnosis made it unlikely that the AGE-Reader can be developed as a screening method for GDM in the future. Furthermore, these investigators found that ethnicity should be taken into account when measuring SAF.

Temma et al (2015) stated that AGEs are thought to play a major role in the pathogenesis of diabetic vascular complications. Skin autofluorescence was recently reported to represent tissue AGEs accumulation with a non-invasive method. These researchers evaluated association between AF value and diabetic vascular complications (e.g., retinopathy, nephropathy and cervical atherosclerosis) using the carotid intima-media thickness (IMT), an established marker of cardiovascular disease in patients with type 2 diabetes. A total of 68 patients with type 2 diabetes were enrolled in a cross-sectional manner; AGEs accumulation was measured with AF reader. Clinical parameters were collected at the time of AF and IMT measurement. Max-IMT was correlated with age and AF ($r = 0.407$, $p = 0.001$), but not with HbA1c, GA, and pentosidine. Also, AF was not correlated with HbA1c, GA and pentosidine, but was correlated with age ($r = 0.560$, $p < 0.001$), duration of diabetes ($r = 0.256$, $p < 0.05$). Multivariate regression analysis revealed that AF, but not age, was an independent determinant of max-IMT. The authors concluded that AF might be a beneficial surrogate marker for evaluating carotid atherosclerosis in patients with type 2 diabetes non-invasively.

Yamagishi et al (2015) noted that a non-enzymatic reaction between reducing sugars and the amino groups of proteins, lipids and nucleic acids is known as the "Maillard reaction". The reactions have progressed in a normal aging process and at an accelerated rate under hyperglycemic, inflammatory, and/or oxidative stress conditions, thus leading to the formation and accumulation of AGEs. Cross-linking modification of organic matrix proteins such as collagen by AGEs not only leads to an increase in vascular and myocardial stiffness, but also deteriorates structural integrity and physiological function of multiple

organ systems. Furthermore, there is a growing body of evidence that interaction of AGEs with a cell surface receptor RAGE elicits oxidative stress generation and subsequently evokes inflammatory, thrombogenic and fibrotic reactions, thereby being involved in the development and progression of various age- or diabetes-related disorders, including cardiovascular disease (CVD), Alzheimer's disease, osteoporosis, cancer growth and metastasis. Skin AGE levels measured in biopsy specimens are associated with the development and progression of diabetic microangiopathy. Recently, accumulation levels of AGEs in the skin can be measured non-invasively by autofluorescence. The authors concluded that accumulating evidence has suggested that SAF is correlated with the presence and severity of vascular complications of diabetes and could predict future cardiovascular events and death in patients with diabetes.

Continuous Glucose Monitoring in Gestational Diabetes

Yu et al (2019) noted that in the last 10 years, continuous glucose monitoring (CGM) has been proven to have similar accuracy to self-monitoring of blood glucose (SMBG) and yet provides better therapy optimization and detects trends in glucose values due to higher frequency of testing. Even though the feasibility and utility of CGM has been proven successfully in type 1 and 2 diabetes, there is a lack of knowledge of its application and effectiveness in pregnancy, especially in gestational diabetes mellitus (GDM). In a systematic review, these investigators examined the available evidence on the use of CGM in pregnancies complicated with GDM. They carried out search using keywords related to CGM and GDM on PubMed and articles were filtered based on full text, year of publication (January 1998 to December 2018), human subject studies, and written in English. Reviews and duplicate articles were excluded. A total of 29 articles were included in this review. In terms of maternal and fetal outcomes, inconsistent evidence was reported. Among GDM patients using CGM and SMBG, 2 randomized controlled trials (RCTs) found no significant differences in macrosomia, birth weight (BW), and gestational age (GA) at delivery between these 2 groups, while 1 prospective, cohort study found a lower incidence of cesarean section and macrosomia in CGM use subjects. In addition, CGM use was consistently found to have increased detection in dysglycemia, and glycemic variability compared to SMBG. In terms of clinical utility, CGM use resulted in more treatment adjustments and lower gestational weight gain (GWG). Finally, CGM use showed higher post-prandial glucose levels in GDM-complicated pregnancies than in normal pregnancies. The authors concluded that available evidence suggested that CGM is superior to SMBG among GDM pregnancies in terms of detecting hypoglycemic and hyperglycemic episodes, which might result in an improvement of maternal and fetal outcomes. Furthermore, CGM detected a wider glycemic variability in GDM mothers than non-GDM controls. Moreover, these researchers stated that further research with larger sample sizes and complete pregnancy coverage is needed to examine the clinical utility such as screening and predictive values of CGM for GDM.

In a systematic review and meta-analysis, García-Moreno et al (2022) examined the effect of CGM on maternal and neonatal outcomes in GDM. Two authors carried out a systematic search using PubMed, Embase, CENTRAL, CINAHL, Scopus, Web of Science, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. The inclusion criteria for the systematic review were randomized clinical trials that compared the effects of CGM and blood glucose monitoring (BGM) in women with GDM. A restricted maximum likelihood random-effects model was used for the meta-analysis. The measures of effect were risk ratios (RRs) for categorical data and mean differences (MDs) for continuous data. Of the 457 studies reviewed, 6 randomized clinical trials met the inclusion criteria. A total of 482 patients were included in the meta-analysis. The use of CGM was associated with lower hemoglobin A1c (HbA1c) levels at the end of pregnancy (MD: -0.22; 95 % CI: -0.42 to -0.03) compared to BGM. Women using CGM also had less gestational weight gain (MD: -1.17, 95 % CI: -2.15 to -0.19), and their children had lower birth-weight (MD: -116.26, 95 % CI: -224.70 to -7.81). No differences were observed in the other outcomes evaluated. The authors concluded that women with GDM using CGM may achieve lower average blood glucose levels, lower maternal weight gain and infant birth-weight than women using BGM. Nevertheless, current evidence is limited by the low number of studies and the small sample sizes of these studies. These researchers stated that larger clinical trials are needed to better understand the effects of CGM in GDM.

In a systematic review and meta-analysis, Chang et al (2022) examined the effects of CGM on maternal and neonatal outcomes in perinatal women with diabetes. A 3-step comprehensive search was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. Randomized controlled trials (RCTs) were retrieved from international databases of PubMed, Embase, Cochrane Library, CINAHL, PsycINFO and Scopus from their respective inception dates until January 5, 2021. Comprehensive Meta-Analysis Software Version 3 was used. The overall effect was determined using Hedges' g. Cochrane collaboration's tool version 1 and grading of recommendations, assessment, development, and evaluation criteria were used for quality assessment. A total of 1,215 records were identified and 10 RCTs involving a total of 1,358 perinatal women were selected. The meta-analysis revealed that CGM significantly improved HbA1c levels (g = -0.43, 95 % CI: -0.63 to -0.22), lowered cesarean section rate (g = -0.17, 95 % CI: -0.33 to -0.02) and neonatal birth-weight (g = -0.16, 95 % CI: -0.27 to -0.04) when compared to the comparator. The majority (86.67 %) has a low risk of biases and certainty of evidence ranged from very low to moderate. The authors concluded that CGM improves maternal and neonatal outcomes. Moreover, these researchers stated that future studies should use well-designed large-scale trials.

Majewska et al (2022) stated that GDM is one of the most common complications of pregnancy, affecting up to 14 % of pregnant women. The population of patients with risk factors of GDM is increasing; therefore, it is important to improve management of this condition. One of the key factors affecting perinatal outcomes in GDM is glycemic control. Until recently, glucose monitoring was only available with SMBG; however, to-date, there is a new method, CGM, which has been shown to be safe in pregnancy. Since proper glycemia assessment has been shown to affect perinatal outcomes, these investigators carried out a systematic review to examine the role of CGM in glycemic control in GDM. They performed a web search of the Medline, Embase,

Cochrane Library, Scopus, and Web of Science databases according to the PRISMA guidelines. The web search was carried out by 2 independent researchers and resulted in 14 articles included in the systematic review. The main outcome of the systematic review was determining that, when compared, CGM played an important role in better glycemic control than SMBG. In addition, glycemic control with CGM improved qualification for insulin therapy. However, most of the articles did not reveal CGM's role in improving neonatal outcomes. The authors concluded that more studies are needed to examine the role of CGM in affecting perinatal outcomes in GDM.

In an RCT, Lai et al (2023) examined the effect of CGM versus SMGB in GDM with HbA1c of less than 6 %. From January 2019 to February 2021, a total of 154 GDM patients with HbA1c of less than 6 % at 24 to 28 gestational weeks were recruited and assigned randomly to either SMBG only or CGM in addition to SMBG, with 77 participants in each group. CGM was used in combination with fingertip blood glucose monitoring every 4 weeks until antepartum in the CGM group, while in the SMBG group, fingertip blood glucose monitoring was applied. The CGM metrics were evaluated after 8 weeks, HbA1c levels before delivery, gestational weight gain (GWG), adverse pregnancy outcomes and CGM medical costs were compared between the 2 groups. Compared with patients in the SMBG group, the CGM group patients had similar times in range (TIRs) after 8 weeks (100.00 % (93.75 % to 100.00 %) versus 99.14 % (90.97 % to 100.00 %), p = 0.183) and HbA1c levels before delivery (5.31 % ± 0.06 % versus 5.35 % ± 0.06 %, p = 0.599). The proportion with GWG within recommendations was higher in the CGM group (59.7 % versus 40.3% , p = 0.046), and the newborn birth-weight was lower (3,123.79 ± 369.58 g versus 3,291.56 ± 386.59 g, p = 0.015). There were no significant differences in pre-natal or obstetric outcomes, e.g., cesarean delivery rate, hypertensive disorders, pre-term births, macrosomia, hyperbilirubinemia, neonatal hypoglycemia, respiratory distress, and neonatal intensive care unit (NICU) admission of greater than 24 hours, between the 2 groups. Considering glucose monitoring, SMBG group patients showed a lower cost than CGM group patients. The authors concluded that for GDM patients with HbA1c of less than 6 %, regular SMBG is a more economical blood glucose monitoring method and can achieve a similar performance in glycemic control as CGM, while CGM is beneficial for ideal GWG.

Davies et al (2023) stated that incidence of GDM is increasing and is associated with adverse perinatal outcomes including macrosomia, pre-eclampsia, and pre-term delivery. Optimum glycemic control can reduce these adverse perinatal outcomes. CGM informs users regarding interstitial glucose levels allowing early detection of glycemic excursions and pharmacological or behavioral intervention. Few adequately powered RCTs to examine the impact of using CGM in women with GDM on perinatal outcomes have been undertaken. These researchers aim to establish the feasibility of a multi-site RCT to assess the clinical- and cost-effectiveness of an intermittently scanned CGM (isCGM) compared with SMBG in women with GDM for reducing fetal macrosomia and improving maternal and fetal outcomes. They will evaluate recruitment and retention rates, adherence to device requirements, adequacy of data capture and acceptability of trial design and isCGM devices. This study is an open-label, randomised-controlled, multi-center, feasibility trial. Inclusion criteria are pregnant women, singleton pregnancy, recent diagnosis of GDM (within 14 days of commencing medication, up to 34 weeks gestation) prescribed metformin and/or insulin. Women will be consecutively recruited and randomised to isCGM (FreestyleLibre2) or SMBG. At every ante-natal visit, glucose measurements will be evaluated. The SMBG group will use blinded isCGM for 14 days at baseline (approximately 12 to 32 weeks) and approximately 34 to 36 weeks. The primary outcome is the recruitment rate and absolute number of women participating. Clinical assessments of maternal and fetal/infant health will be undertaken at baseline, birth, up to approximately 13 weeks post-natal. Psychological, behavioral and health economic measures will be assessed at baseline and approximately 34 to 36 weeks gestation. Qualitative interviews will be undertaken with study decliners, participants, and professionals to examine trial acceptability, of using isCGM and SMBG. The authors stated that GDM can be associated with adverse pregnancy outcomes. isCGM could offer a timely, easy-to-engage-with intervention, to improve glycemic control, potentially reducing adverse pregnancy, birth and long-term health outcomes for mother and child. This study will determine the feasibility of conducting a large-scale, multi-center RCT of isCGM in women with GDM.

An UpToDate review on “Gestational diabetes mellitus: Glucose management and maternal prognosis” (Durnwald, 2023a) states that “Continuous glucose monitoring (CGM) allows determination of peak postprandial glucose levels, mean glucose level, episodes of nocturnal hyperglycemia, and percent time in range for a 24-hour period. We do not routinely use CGM in patients with GDM because of cost and it has not been proven to improve maternal or fetal outcome, but few trials have been performed. When CGM was compared with frequent self-monitoring of blood glucose in a meta-analysis of two small, randomized trials, outcomes were similar for both approaches: cesarean birth (risk ratio [RR] 0.91, 95 % CI 0.68-1.20), large for gestational age newborn (RR 0.67, 95 % CI 0.43-1.05), neonatal hypoglycemia (RR 0.79, 95 % CI 0.35-1.78). There were no perinatal deaths. Larger trials may clarify whether the favorable trends that were observed are real”.

Furthermore, UpToDate reviews on “Gestational diabetes mellitus: Obstetric issues and management” (Caughey, 2023), and “Gestational diabetes mellitus: Screening, diagnosis, and prevention” (Durnwald, 2023b) do not mention continuous glucose monitoring as a management option.

A draft evidence review prepared by the Center for Evidence-Based Policy for the Washington State Health Care Authority Health Technology Assessment Program (Durbin, et al., 2025) found that, in pregnant women with gestational diabetes who are not using insulin, CGM use was not associated with a significantly lower HbA1c at the end of pregnancy (low certainty of evidence, based on 3 RCTs). They did not identify any eligible RCTs evaluating the effectiveness or safety of CGMs in pregnant women with type 2 diabetes who were not using insulin before or during pregnancy.

Post-Partum Screening for Diabetes

Dietz et al (2008) estimated trends in post-partum glucose testing in a cohort of women with gestational diabetes mellitus (GDM). A validated computerized algorithm using Kaiser Permanente Northwest automated data systems identified 36,251 live-births or still-births from 1999 through 2006. The annual percentage of pregnancies complicated by GDM with clinician orders for and completion of a fasting plasma glucose (FPG) test within 3 months of delivery was calculated. Logistic regression with generalized estimating equations was used to test for statistically significant trends. The percentages of pregnancies affected by GDM increased from 2.9 % in 1999 to 3.6 % in 2006 ($p < 0.01$). Clinician orders for post-partum tests increased from 15.9 % in 1999 to 79.3 % in 2004 ($p < 0.01$), and then remained stable through 2006. Completed FPG tests increased from 9.0 % in 1999 to 57.8 % in 2004 ($p < 0.01$), and then remained stable through 2006. No oral glucose tolerance tests were ordered. From 2004 to 2006, the practice site where women received care was the factor most strongly associated with the clinician order, but it was not predictive of test completion. Among women with clinician orders, those who were Asian or Hispanic or who attended the 6-week post-partum examination were more likely to complete the test than their counterparts. The authors concluded that post-partum glucose testing in women with GDM-affected pregnancies increased over time. However, even in recent years, 42 % of women with GDM-affected pregnancies failed to have a post-partum FPG test, and no test was ordered for 21 % of GDM-affected pregnancies.

The American College of Obstetricians and Gynecologists' Committee opinion on post-partum screening for abnormal glucose tolerance in women who had GDM (ACOG 2009) stated that establishing the diagnosis of GDM offers an opportunity not only to improve pregnancy outcome, but also to decrease risk factors associated with the subsequent development of type 2 diabetes. The ACOG's Committee on Obstetric Practice recommends that all women with GDM be screened at 6 to 12 weeks post-partum and managed appropriately.

Continuous Glucose Monitoring Following Gastric Bypass and for Nesidioblastosis (Primary Islet Cell Hypertrophy)

Hanaire et al (2010) stated that hypoglycemia is rare after a gastric bypass and can be taken for a dumping syndrome. There is no report in the literature of the contribution of continuous glucose monitoring (CGM) to the diagnosis of hypoglycemia in these circumstances. The present case report showed that CGM can be a useful tool for the diagnosis and the management of such episodes. Continuous glucose monitoring revealed hypoglycemic episodes in free living circumstances that were not present during 72-hr fasting. These episodes followed wide hyperglycemic swings. No such episode resumed over 8 months after specific dietary advices and treatment by 50 mg TID of acarbose. Because hypoglycemia can be difficult to diagnose from dumping syndrome, CGM is a very useful tool revealing the episodes in free-living circumstances and can be used to monitor the treatment success. The findings of this single-case study need to be validated by well-designed studies.

Hanaire et al (2011) evaluated glucose variability after gastric bypass CGM in a real-life setting. Continuous glucose monitoring was performed for 4.2 +/- 1.3 days in 3 groups of 10 subjects each:

1. patients who had undergone gastric bypass and who were referred for post-prandial symptoms compatible with mild hypoglycemia,
2. non-operated diabetes controls, and
3. healthy controls.

The maximum interstitial glucose (IG), SD of IG values, and mean amplitude of glucose excursions (MAGE) were significantly higher in operated patients and in diabetes controls than in healthy controls. The time to the post-prandial peak IG was significantly shorter in operated patients (42.8 +/- 6.0 mins) than in diabetes controls (82.2 +/- 11.1 mins, $p = 0.0002$), as were the rates of glucose increase to the peak (2.4 +/- 1.6 versus 1.2 +/- 0.3 mg/ml/min; $p = 0.041$). True hypoglycemia (glucose less than 60 mg/dL) was rare: the symptoms were probably more related to the speed of IG decrease than to the glucose level achieved. Half of the operated patients, mostly those with a diabetes background before surgery, had post-prandial glucose concentrations above 200 mg/dL (maximum IG, 306 +/- 59 mg/dL), in contrast to the normal glucose concentrations in the fasting state and 2 hrs post-meal. The authors concluded that glucose variability is exaggerated after gastric bypass, combining unusually high and early hyperglycemic peaks and rapid IG decreases. This might account for post-prandial symptoms mimicking hypoglycemia but often seen without true hypoglycemia. Early post-prandial hyperglycemia might be under-estimated if glucose measurements are done 2 hrs post-meal. This study reported on differences in glycemia in persons with diabetes who had undergone obesity surgery, persons with diabetes without obesity surgery, and normal controls. It did not report on the use of the CGM in clinical management

UpToDate reviews on "Medical management of patients after bariatric surgery" (Kushner and Cummings, 2012) and "Complications of bariatric surgery" (Adair and Ellsmere, 2012) do not mention the use of continuous glucose monitoring.

There is a lack of published studies on the use of continuous glucose monitors in nesidioblastosis. An UpToDate review on "Pathogenesis, clinical features, and diagnosis of persistent hyperinsulinemic hypoglycemia of infancy" (Sunehag and Haymond, 2013) states that "Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), also referred to as congenital hyperinsulinism, familial hyperinsulinemic hypoglycemia, and primary islet cell hypertrophy (nesidioblastosis), is the most common cause of persistent hypoglycemia in neonates and infants. PHHI is a genetic disorder with both familial and sporadic forms, characterized by dysregulation of insulin secretion. Early recognition, diagnosis, and treatment are necessary to prevent or minimize

neurologic damage from recurrent or prolonged episodes of hypoglycemia". However, this review does not mention the use of continuous glucose monitoring as a management tool.

Glucose Meters for Persons with Visual Impairment

There are blood glucose monitoring systems designed especially for use by those with visual impairments. The monitors used in such systems are identical in terms of reliability and sensitivity to standard blood glucose monitors. They differ by having such features as voice synthesizers, automatic timers, and specially designed arrangements of supplies and materials to enable the visually impaired to use the equipment without assistance.

Hypoglycemic Wristband Alarm (e.g., Sleep Sentry)

Hypoglycemic alarms are skin temperature/skin conductance devices for detecting nocturnal hypoglycemia. Through sensors on the back surface of the device, electronic information is sent to a built-in microprocessor. When there is deviation from pre-set levels for skin temperature and/or perspiration, an alarm will sound. The device may be worn on the ankle, forearm, or wrist. One of the disadvantages of these devices for alerting hypoglycemia 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. However, the clinical utility of these devices has not been proven.

Hansen and Duck (1983) examined the effectiveness of the Teledyne Sleep Sentry in detecting nocturnal hypoglycemia in pediatric patients. A total of 24 insulin-dependent diabetic pediatric subjects were studied for 1,444 nights for detection of nocturnal hypoglycemia with the Teledyne Sleep Sentry: a wristwatch-like unit that measures absolute changes in skin temperature and decreases in galvanic skin resistance, indicators of hypoglycemia. The device detected 42 of 46 recognized hypoglycemic episodes; 150 alarms were sounded without evidence of hypoglycemia, probably due to night sweating; 25 % of the subjects experienced unacceptable cutaneous reactions, presumably due to metallic iontophoresis.

Johansen and colleagues (1986) examined the effectiveness and credibility of a skin temperature/skin conductance meter (Teledyne Sleep Sentry) for detecting hypoglycemia during night-time in 22 adult insulin-treated diabetics. Capillary blood glucose concentration was measured 99 times (when the alarm sounded, in case of hypoglycemic symptoms, and at 3 a.m.). Hypoglycemia was defined as a capillary blood glucose concentration of less than or equal to 3 mmol/L. Blood glucose was measured 61 times in connection with sounding of the alarm and 38 times without the alarm sounding. At 3 a.m. the Sleep Sentry sounded the alarm 22 times, of which hypoglycemia was present 6 times giving a diagnostic specificity or diagnostic true positive rate of 0.27 (95 % CI: 0.11 to 0.50). In 35 of 38 cases of no alarm the blood glucose was greater than 3 mmol/L, giving a diagnostic sensitivity of 0.92 (95 % CI: 0.79 to 0.98). The Sleep Sentry sounded the alarm in 6 of 9 cases of hypoglycemia, giving a nosological sensitivity of 0.67 (95 % CI: 0.30 to 0.93). The Sleep Sentry did not sound the alarm in 35 of 51 cases of non-hypoglycemia, giving a nosological specificity of 0.69 (95 % CI: 0.54 to 0.81). The authors concluded that the Sleep Sentry detected about 2/3 of blood glucose values less than or equal to 3 mmol/L, but in addition it sounded a false alarm in 2/3 of the cases.

Clarke et al (1988) reported metabolic and cutaneous events associated with hypoglycemia detected by the Sleep Sentry. A total of 18 insulin-dependent diabetic subjects [age (mean +/- SD) 33.2 +/- 10.6 years] participated in a study designed to determine the metabolic and cutaneous parameters associated with activation of the nocturnal hypoglycemia monitor Sleep Sentry. Plasma glucose, glucagon, epinephrine, norepinephrine, and pancreatic polypeptide concentrations were determined every 10 minutes during a 2-hour constant intravenous insulin infusion (40 mU/kg/hour). In addition, skin temperature and electrical conductance were monitored at the same time intervals, and subjects were asked to rate the degree to which they felt cold and/or sweaty. Ten of the subjects (alarmers) activated the device with a mean plasma glucose nadir of 52.8 +/- 13.8 mg/dL, whereas 8 (non-alarmers) failed to do so despite a mean plasma glucose nadir of 50.5 +/- 8.2 mg/dL. There were no significant differences between alarmers and non-alarmers with respect to initial or nadir plasma glucose levels, rate of fall of plasma glucose, or changes in plasma epinephrine, norepinephrine, or pancreatic polypeptide concentrations. In addition, changes in skin temperature and conductance were similar in both groups as were descriptive variables including age, disease duration, gender, and level of glucose control. No subject reported an increase in coldness, whereas 80 % of both groups reported an increase in sweatiness; 3 subjects studied on more than one occasion over a year failed to exhibit consistent activation of the alarm. The authors concluded that the findings of this study suggested that it may not be possible to identify patients for whom the Sleep Sentry would be a reliable addition to their self-management regimen and that physicians should exercise caution in recommending its use.

Remote Glucose Monitoring (e.g., the Dexcom SHARE)

On October 20, 2014, Dexcom, Inc. (San Diego, CA) announced that it has received FDA approval for its CGM remote mobile communications device: Dexcom SHARE, which is an accessory to the Dexcom G4® PLATINUM Continuous Glucose Monitoring System. It uses a secure wireless connection to transmit the glucose levels of a person with diabetes to the smartphones of up to 5 designated recipients, or "followers". These followers can remotely monitor a patient’s glucose information and receive alert notifications from almost anywhere via their Apple® iPhone® or iPod® touch. With Dexcom SHARE, parents and personal caregivers can monitor a child’s or loved one’s glucose data from a remote location.

- The Dexcom SHARE consists of a small cradle device in which the Dexcom G4 PLATINUM is docked. The cradle also functions as a battery charger for the receiver and must be connected to an electrical outlet.
- The Dexcom SHARE cradle is equipped with Bluetooth technology, enabling the device to wirelessly transmit glucose levels from the Dexcom G4 PLATINUM receiver to the Dexcom SHARE App on the patient's Apple® iPhone® or iPod® touch.
- The Dexcom SHARE App uploads glucose data to a secure server. Personal caregivers or parents can then remotely receive notifications about glucose levels and trends on their Apple® iPhone® or iPod® touch.

However, there is a lack of evidence that the Dexcom SHARE would improve health outcomes of patients with diabetes.

In a systematic review, Mushcab et al (2015) evaluated evidence for viability and impact of Web-based tele-monitoring for managing type 2 diabetes mellitus. A review protocol included searching Medline, EMBASE, CINAHL, AMED, the Cochrane Library, and PubMed using the following terms: telemonitoring, type 2 diabetes mellitus, self-management, and web-based Internet solutions. The technology used, trial design, quality of life measures, and the HbA1c levels were extracted. This review identified 426 publications; of these, 19 met preset inclusion criteria. Ten quasi-experimental research designs were found, of which 7 were pre-posttest studies, 2 were cohort studies, and 1 was an interrupted time-series study; in addition, there were nine randomized controlled trials (RCTs). Web-based remote monitoring from home to hospital is a viable approach for healthcare delivery and enhances patients' quality of life. Six of these studies were conducted in South Korea, 5 in the United States, 3 in the United Kingdom, 2 in Taiwan, and 1 each in Spain, Poland, and India. The duration of the studies varied from 4 weeks to 18 months, and the participants were all adults. Fifteen studies showed positive improvement in HbA1c levels; 1 study showed high acceptance of the technology among participants. The authors concluded that it remains challenging to identify clear evidence of effectiveness in the rapidly changing area of remote monitoring in diabetes care. They stated that both the technology and its implementations are complex; the optimal design of a telemedicine system is still uncertain, and the value of the real-time blood glucose transmissions is still controversial.

Karhula and colleagues (2015) examined if a structured mobile phone-based health coaching program, which was supported by a remote monitoring system, could be used to improve the health-related quality of life (HRQL) and/or the clinical measures of type 2 diabetes and heart disease patients. A randomized controlled trial was conducted among type 2 diabetes patients and heart disease patients of the South Karelia Social and Health Care District. Patients were recruited by sending invitations to randomly selected patients using the electronic health records system. Health coaches called patients every 4 to 6 weeks and patients were encouraged to self-monitor their weight, blood pressure, blood glucose (diabetics), and steps (heart disease patients) once per week. The primary outcome was HRQL measured by the Short Form (36) Health Survey (SF-36) and HbA1c among diabetic patients. The clinical measures assessed were blood pressure, weight, waist circumference, and lipid levels. A total of 267 heart patients and 250 diabetes patients started in the trial, of which 246 and 225 patients concluded the end-point assessments, respectively. Withdrawal from the study was associated with the patients' unfamiliarity with mobile phones -- of the 41 drop-outs, 85 % (11/13) of the heart disease patients and 88 % (14/16) of the diabetes patients were familiar with mobile phones, whereas the corresponding percentages were 97.1 % (231/238) and 98.6 % (208/211), respectively, among the rest of the patients ($p = 0.02$ and $p = 0.004$). Withdrawal was also associated with heart disease patients' co-morbidities – 40 % (8/20) of the drop-outs had at least 1 comorbidity, whereas the corresponding percentage was 18.9 % (47/249) among the rest of the patients ($p = 0.02$). The intervention showed no statistically significant benefits over the current practice with regard to HRQL -- heart disease patients: beta = 0.730 ($p = 0.36$) for the physical component score and beta = -0.608 ($p = 0.62$) for the mental component score; diabetes patients: beta = 0.875 ($p = 0.85$) for the physical component score and beta = -0.770 ($p = 0.52$) for the mental component score. There was a significant difference in waist circumference in the type 2 diabetes group (beta = -1.711, $p = 0.01$). There were no differences in any other outcome variables. The authors concluded that a health coaching program supported with tele-monitoring did not improve heart disease patients' or diabetes patients' quality of life or their clinical condition. There were indications that the intervention had a differential effect on heart patients and diabetes patients. Diabetes patients may be more prone to benefit from this kind of intervention. This should not be neglected when developing new ways for self-management of chronic diseases.

Furthermore, an UpToDate review on "Blood glucose self-monitoring in management of adults with diabetes mellitus" (Mcculloch, 2015) does not mention remote glucose monitoring as a management tool.

Implantable Glucose Sensors

Wang and colleagues (2015) analyzed the overall nocturnal performance during home use of a long-term subcutaneous implantable CGM sensor. In this study, a total of 12 subjects with type 1 diabetes mellitus (T1DM) (mean ± SD age of 37 ± 8 years; mean ± SD disease duration of 11 ± 6 years) were implanted with an investigational continuous glucose sensor in the upper arm for up to 90 days. All subjects received full access to real-time glucose display and user programmable hypo- and hyper-glycemic alarms. Subjects calibrated the sensors with a SMBG meter and continued to rely on their regular SMBG measurements for their diabetes management. Accuracy of the sensors during the home-use study was calculated using SMBG as the reference. The nocturnal sensor attenuation (NSA) concept was tested. Sensitivity and specificity of the nocturnal hypoglycemic alarm were calculated. Mean ± SD glucose sensor life span was 87 ± 7 days. The mean ± SE absolute relative difference over the range of 40 to 400 mg/dL for the sensors in this home-use study was 12.3 ± 0.7 % using SMBG as the reference. The hypoglycemia alarms were set to be triggered when the glucose level went below 70 mg/dL. Percentage of nights with hypoglycemic alarms triggered for at least 10 mins was 13.6 %. Recovery into euglycemia within 30 mins from the

time-stamp of the immediate confirmatory SMBG testing was obtained in 74 % of all episodes (n = 20). The implanted continuous glucose sensor showed a hypoglycemia detection sensitivity and specificity of 77 % and 96 %, respectively. The NSA-associated high negative rate of change of at least -4 mg/dL/min was not encountered during night use of the system. The authors concluded that this home-use study of a fully implantable, long-term continuous glucose sensor showed excellent performance in nocturnal hypoglycemia detection in T1DM patients. The apparent lack of NSA affecting the implanted sensor and the high specificity of the hypoglycemic alarm expedited the recovery from night-time hypoglycemia.

Dehennis and co-workers (2016) noted that CGM, which enables real-time glucose display and trend information as well as real-time alarms, can improve glycemic control and quality of life in patients with diabetes mellitus. Previous reports have described strategies to extend the useable lifetime of a single sensor from 1 to 2 weeks to 28 days. These researchers described the characterization of a sensing platform achieving 90 days of continuous use for a single, fully implanted sensor. The Senseonics CGM system is composed of a long-term implantable glucose sensor and a wearable smart transmitter. Study subjects underwent subcutaneous implantation of sensors in the upper arm; 8-hour clinic sessions were performed every 14 days, during which sensor glucose values were compared against venous blood lab reference measurements collected every 15 mins using mean absolute relative differences (MARDs). All subjects (mean ± standard deviation age: 43.5 ± 11.0 years; with 10 sensors inserted in men and 14 in women) had T1DM. Most (22 of 24) sensors reported glucose values for the entire 90 days. The MARD value was 11.4 ± 2.7 % (range of 8.1 to 19.5 %) for reference glucose values between 40 to 400 mg/dl. There was no significant difference in MARD throughout the 90-day study (p = 0.31); no serious adverse events (AEs) were noted. The authors concluded that the Senseonics CGM, composed of an implantable sensor, external smart transmitter, and smart-phone application, is the first system that uses a single sensor for continuous display of accurate glucose values for 3 months.

In a prospective, multi-center trial, Kropff and colleagues (2017) studied the Eversense (Senseonics Inc.) implantable CGM sensor in 71 participants aged 18 years and older with T1DM and T2DM in a 180-day trial. Participants used the CGM system at home and in the clinic; CGM accuracy was assessed during 8 in-clinic visits with the MARD for venous reference glucose values greater than 4.2 mmol/L as the primary end-point. Secondary end-points included Clarke Error Grid Analysis and alarm performance. The primary safety outcome was device-related serious AEs. The MARD value against reference glucose values of greater than 4.2 mmol/L was 11.1 % (95 % CI: 10.5 to 11.7). Clarke Error Grid Analysis showed 99.2 % of samples in the clinically acceptable error zones A and B; 81 % of hypoglycemic events were detected by the CGM system within 30 mins. No device-related serious AEs occurred during the study. The authors concluded that these findings indicated the safety and accuracy of this new type of implantable CGM system and supported it as an alternative for transcutaneous CGM.

On June 21, 2018, the U.S. Food and Drug Administration approved the Eversense Continuous Glucose Monitoring (CGM) system for use in people 18 years of age and older with Type 1 and Type 2 diabetes. This is the first FDA-approved CGM system to include a fully implantable sensor to detect glucose, which can be worn for up to 90 days. The Eversense CGM system uses a small sensor that is implanted just under the skin by a qualified health care provider during an outpatient procedure. The implanted sensor works with a novel light-based technology to measure glucose levels and send information to a mobile app. The sensor is coated with a fluorescent chemical which, when exposed to blood sugar, produces a small amount of light that is measured by the sensor. Every five minutes, measurements are sent to a compatible mobile device (e.g., smart phone or tablet) that is running a device-specific mobile app.

The FDA evaluated clinical study data from 125 individuals aged 18 and older with diabetes and reviewed the device's effectiveness by comparing readings obtained by the Eversense CGM system to those obtained by a laboratory-based glucose analyzer. The safety of the Eversense CGM system's 90-day implantable sensor, and the procedure used to implant it, was also evaluated during the clinical studies. The FDA held an Advisory Committee meeting to provide an independent assessment of the safety and effectiveness of the Eversense CGM system. In an 8 to 0 vote, the committee recommended that the benefits of the Eversense CGM system outweigh the risks for patients with diabetes.

During these studies, the proportion of individuals experiencing a serious adverse event with the implanted sensor was less than 1 percent. Potential adverse effects related to insertion, removal and wear of the sensor include allergic reaction to adhesives, bleeding, bruising, infection, pain or discomfort, scarring or skin discoloration, sensor fracture during removal, skin inflammation, thinning, discoloration or redness. Other risks associated with use of the CGM system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate or where alerts are missed. The safety of this novel system will also be evaluated in a post-approval study.

Christiansen et al (2018) stated persistent use of real-time continuous glucose monitoring (CGM) improves diabetes control in individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D). PRECISE II was a nonrandomized, blinded, prospective, single-arm, multicenter study that evaluated the accuracy and safety of the implantable Eversense CGM system among adult participants with T1D and T2D (NCT02647905). The primary endpoint was the mean absolute relative difference (MARD) between paired Eversense and Yellow Springs Instrument (YSI) reference measurements through 90 days post insertion for reference glucose values from 40 to 400 mg/dL. Additional endpoints included Clarke Error Grid analysis and sensor longevity. The primary safety endpoint was the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAEs) through 90 days post insertion. Ninety participants received the CGM system. The overall MARD value against reference glucose values was 8.8% (95% confidence interval: 8.1%-9.3%), which was significantly lower than the prespecified 20% performance goal for accuracy ($P < 0.0001$). Ninety-three percent of CGM values were within 20/20% of reference values over the total glucose range of 40-400 mg/dL. Clarke Error Grid analysis showed 99.3% of samples in the clinically acceptable error zones A (92.8%) and B (6.5%). Ninety-one percent of sensors were functional through day 90. One related SAE (1.1%)

occurred during the study for removal of a sensor. The authors concluded the PRECISE II trial demonstrated that the Eversense CGM system provided accurate glucose readings through the intended 90-day sensor life with a favorable safety profile.

Currently, there is insufficient evidence to support that the use of implantable glucose sensor for improving glycemic control. The available evidence have small sample size, lack adequate controls, blinding and randomization.

Cellular Activation Therapy

Cellular activation therapy (CAT), also known as hepatic treatment , metabolic treatment, and pulsatile intravenous insulin therapy (PIVIT), was developed and owned by Cellular Activation Therapy Clinics (CATC) and Bionica Inc. Cellular activation therapy supposedly achieves better metabolism by stimulating the liver to naturally produce the enzymes needed for proper carbohydrate and lipid metabolism; CAT is delivered by the Bionica microdose infusion pump, an FDA-approved pump with special abilities and software. Cellular activation therapy employs pulses of insulin and oral glycemic stimulation, providing the 2 signals needed for the liver to perform its job of producing the enzymes that are deficient in diabetics. The improvement in resting metabolism is documented by standard metabolism measurement equipment. In fact, every cell uses insulin, and CAT activates proper functioning at the cellular level, hence the name cellular activation therapy.

However, there is a lack of evidence regarding the clinical effectiveness of CAT in the treatment of diabetes.

FreeStyle Libre Flash Glucose Monitoring System

The FreeStyle Libre Flash Glucose Monitoring System (Abbott Diabetes Care Inc.) is the 1st continuous glucose monitoring system that can be used by diabetic patients to make diabetes treatment decisions without calibration using a blood sample from the fingertip (often referred to as a "finger-stick". The system reduces the need for finger-stick testing by using a small sensor wire inserted below the skin’s surface (arm or abdomen) that continuously measures and monitors glucose levels; after a 12-hour start-up period, the FreeStyle Libre Flash Glucose Monitoring System can be worn for up to 10 days. Users can determine glucose levels by waving a dedicated, mobile reader above the sensor wire to determine if they are hyperglycemic or hypoglycemic, and how glucose levels are changing. On September 27, 2017, the Food and Drug Administration (FDA) approved the FreeStyle Libre Flash Glucose Monitoring System for use in individuals 18 years of age and older with diabetes.

The FDA evaluated data from a clinical study of individuals aged 18 and older with diabetes, and reviewed the device’s performance by comparing readings obtained by the FreeStyle Libre Glucose Monitoring System to those obtained by an established laboratory method used for analysis of blood glucose. Risks associated with use of the system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate and used to make treatment decisions, as well as mild skin irritations around the insertion site. It does not provide real-time alerts or alarms in the absence of a user-initiated action (e.g., it cannot alert users to low blood glucose levels while they are asleep).

While the FreeStyle Libre Flash Glucose Monitoring System has been approved by the FDA, it is unclear if this system can provide improved adherence and improved glycemic outcomes with continued use over time.

Guidelines from the American Diabetes Association (2018) state: "The intermittent or 'flash' CGM device, very recently approved for adult use only, differs from previous CGM devices. Specifically, it does not have alarms, does not require calibration with SMBG, and does not communicate continuously (only on demand). It is reported to have a lower cost than traditional systems. A study in adults with well-controlled type 1 diabetes found that flash CGM users spent less time in hypoglycemia than those using SMBG [citing Bolinder, et al., 2016). However, due to significant differences between flash CGM and other CGM devices, more discussion is needed on outcomes and regarding specific recommendations."

The American Diabetes Association (2018) stated that, "for most CGM systems, confirmatory SMBG is required to make treatment decisions, though a randomized controlled trial of 226 adults suggested that an enhanced CGM device could be used safely and effectively without regular confirmatory SMBG in patients with well-controlled type 1 diabetes at low risk of severe hypoglycemia [citing Aleppo, et al., 2017). Two CGM devices are now approved by the U.S. Food and Drug Administration (FDA) for making treatment decisions without SMBG confirmation, including the flash CGM device."

Bailey et al (2015) evaluated the performance and usability of the FreeStyle Libre Flash glucose monitoring system (Abbott Diabetes Care, Alameda, CA) for interstitial glucose results compared with capillary blood glucose results. A total of 72 study participants with type 1 or type 2 diabetes were enrolled by 4 U.S. clinical sites. A sensor was inserted on the back of each upper arm for up to 14 days; 3 factory-only calibrated sensor lots were used in the study. Sensor glucose measurements were compared with capillary blood glucose (BG) results (approximately 8 per day) obtained using the BG meter built into the reader (BG reference) and with the YSI analyzer (Yellow Springs Instrument, Yellow Springs, OH) reference tests at 3 clinic visits (32 samples per visit). Sensor readings were masked to the participants. The accuracy of the results was demonstrated against capillary BG reference values, with 86.7 % of sensor results within Consensus Error Grid Zone A. The percentage of readings within Consensus Error Grid Zone A on Days 2, 7, and 14 was 88.4 %, 89.2 %, and 85.2 %, respectively. The overall mean absolute relative difference was 11.4 %. The mean lag time between sensor and YSI reference values was 4.5 ± 4.8 mins. Sensor accuracy was not affected by factors such as body mass index (BMI), age, type of diabetes, clinical site, insulin administration, or hemoglobin A1c. The authors concluded that interstitial glucose measurements with the FreeStyle Libre

system were found to be accurate compared with capillary BG reference values, with accuracy remaining stable over 14 days of wear and unaffected by patient characteristics.

Ji et al (2017) stated that Flash glucose monitoring is a new glucose sensing technique that measures interstitial glucose levels for up to 14 days and does not require any calibration. These investigators evaluated the performance of the new system in Chinese patients with diabetes. A multi-center, prospective, masked study was performed in a total of 45 subjects with diabetes. Subjects wore 2 sensors at the same time, for up to 14 days. The accuracy was evaluated against capillary BG and venous YSI measurements. During all 14 days, subjects were asked to perform at least 8 capillary BG tests per day. Each subject attended 3 days of 8-hour clinic sessions to measure YSI and sensor readings every 15 minutes; 40 subjects had evaluable glucose readings, with 6,687 of 6,696 (99.9 %) sensor and capillary BG pairs within consensus error grid zones A and B, including 5,824 (87.0 %) in zone A. The 6,969 sensor and venous YSI pairs resulted in 6,965 (99.9 %) pairs within zones A and B, including 5,755 (82.6 %) in zone A. The sensor pairs with BG and YSI result in mean absolute relative difference (MARD) of 10.0 % and 10.7 %, respectively. Overall between-sensor coefficient of variation (CV) was 8.0 %, and the mean lag time was 3.1 (95 % confidence interval [CI]: 2.54 to 4.29) minutes. The authors concluded that the system worked well for people with diabetes in China, and it is easy to wear and use.

Edge et al (2017) determined accuracy, safety and acceptability of the FreeStyle Libre Flash Glucose Monitoring System in the pediatric population. A total of 89 study participants, aged 4 to 17 years, with type 1 diabetes were enrolled across 9 diabetes centers in the UK. A factory calibrated sensor was inserted on the back of the upper arm and used for up to 14 days. Sensor glucose measurements were compared with capillary BG measurements. Sensor results were masked to participants. Clinical accuracy of sensor results versus BG results was demonstrated, with 83.8 % of results in zone A and 99.4 % of results in zones A and B of the consensus error grid. Overall MARD was 13.9 %. Sensor accuracy was unaffected by patient factors such as age, body weight, sex, method of insulin administration or time of use (day versus night). Participants were in the target glucose range (3.9 to 10.0 mmol/L) approximately 50 % of the time (mean of 12.1 hours/day), with an average of 2.2 hours/day and 9.5 hours/day in hypoglycemia and hyperglycemia, respectively. Sensor application, wear/use of the device and comparison to self-monitoring of blood glucose were rated favorably by most participants/caregivers (84.3 to 100 %); 5 device related adverse events (AEs) were reported across a range of participant ages. The authors concluded that accuracy, safety and user acceptability of the FreeStyle Libre System were demonstrated for the pediatric population. Accuracy of the system was unaffected by subject characteristics, making it suitable for a broad range of children and young people with diabetes.

The authors stated that one drawback of this study was the single body site used. Moreover, they stated that additional studies are needed to determine suitability of additional body sites for sensor wear and longer-term studies are needed to examine if this system can provide improved adherence with sensor wear and improved glycemic outcomes with continued use over time. Exploring alternate reference methods and more detailed analysis of the glycemic variability data using subgroups (e.g., age) may be of interest.

Fokkert et al (2017) evaluated the performance of the FreeStyle Libre Flash continuous glucose monitoring (FSL-CGM) system against established central laboratory methods. A total of 20 subjects (8 type 1 diabetes mellitus, 12 type 2 diabetes mellitus) were analyzed. FSL-CGM sensor measurements (inserted in arm and abdomen) were compared with capillary BG results analyzed with StatStrip as semi-gold standard. The glucose response after a standardized oral glucose load was measured by FSL-CGM and capillary samples analyzed by perchloric acid hexokinase (PCA-HK) method, StatStrip and FSL test strip (FSLC), and a commonly used CGM system (iPro2). FSL-CGM arm sensor readings showed 85.5 % of paired readings falling within Clarke Error Grid (ISO 15197:2013) zone A when compared with StatStrip. For FSL-CGM abdomen and FSLC, these percentages were 64 % and 98 %, respectively. The overall correlation of FSL-CGM in the arm and the StatStrip indicates a performance with lower results with the FSL-CGM in the arm than expected based on the StatStrip in the lower glucose ranges, and higher results than expected in the higher ranges. Following a standardized glucose load, a slower rise in glucose level was observed for FSL-CGM arm as compared with PCA-HK, StatStrip, FSLC, and iPro2 during the first 45 to 60 mins after glucose load ingestion. The authors concluded that certain matters need attention while using the FSL-CGM in daily life including the observed lower values in the lower ranges, and the under-estimation of the effect of a meal on glucose response. These effects of such deviations can partly be overcome by optimizing the available user instructions. Moreover, they stated that further evaluation is needed to identify the proper target population most likely to benefit from the FSL-CGM.

The authors noted that this study had several drawbacks:

1. small sample size (n = 20). In particular, the relatively low number of readings below 80 mg/dL, due to the non-blinded nature of the study patients were able to act on low glucose concentrations, could be of importance with respect to our aforementioned concerns about the influence of low readings. The accuracy of the FSL in the lower ranges, and also in the higher ranges, should be subject of future studies that include an acceptable amount of readings and, ideally, data concerning clinical tests and symptoms, and
2. as this study was applied in a daily life setting, the accuracy of the FSL-CGM could not be established against the "real gold standard" to measure arterial blood glucose concentrations. Further study limitations included the risk of individual subject errors in the study procedures (e.g., use of the device, reporting of glucose results, intake study drugs, despite correct instructions).

Olafsdottir et al (2017) evaluated the accuracy and treatment experience of the FreeStyle Libre system. A total of 58 adults with type 1 diabetes used FreeStyle Libre for 10 to 14 days and measured capillary BG levels with the HemoCue blood glucose measurement system at least 6 times a day simultaneously. For the entire study period, the MARD was 13.2 % (95 % CI: 12.0 % to 14.4 %). MARD was 13.6 % (95 % CI: 12.1 % to 15.4 %) during week 1 and 12.7 % (95 % CI: 11.5 % to 13.9 %) during week 2. The mean absolute difference (MAD) for the whole study period was 19.8 mg/dL (1.1 mmol/L) (95 % CI: 17.8 to 21.8 mg/dL), including 20.5 mg/dL (1.14 mmol/L) during week 1 and 19.0 mg/dL (1.05 mmol/L) during week 2. The overall correlation coefficient was 0.96. For glucose values less than 72, 72 to 180, and greater than 180 mg/dL (less than 4, 4 to 10, and greater than 10 mmol/L), the MARD was 20.3 % (95 % CI: 17.7 % to 23.1 %), 14.7 % (95 % CI: 13.4 % to 16 %), and 9.6 % (95 % CI: 8.5 % to 10.8 %), respectively, and respective MAD values were 12.3, 17.8, and 23.6 mg/dL (0.69, 0.99, and 1.31 mmol/L). Using the 10-item visual analog scale (VAS), patients rated their experience with FreeStyle Libre as generally positive, with mean values ranging from 8.22 to 9.8. The authors concluded that the FreeStyle Libre system appeared to have an overall accuracy that is similar to CGM-systems with high accuracy. The treatment experience was high. A non-negligible proportion of glucose values, however, deviated more than 20 % and 30 %, which is of concern to be aware of in clinical practice when dosing insulin. The calibration of the FreeStyle Libre system could likely be improved because it had a negative bias compared with HemoCue capillary whole blood.

The authors stated that the main drawbacks of this study were:

1. its short study duration (2 weeks), *and*
2. glucose values were measured by patients themselves, thus testing procedures were not controlled, although all patients received careful instructions of these procedures.

The results of the questionnaire should be viewed with some cautions because it has not been structurally validated and treatment experience can be difficult to fully evaluate over a relative short time period.

Ancona et al (2017) evaluated the accuracy of a novel subcutaneous flash glucose monitor (FreeStyle Libre [Abbott Diabetes Care]) in critically ill patients with diabetes. These investigators applied the FreeStyle Libre sensor to the upper arm of 8 patients with diabetes in the intensive care unit (ICU) and obtained hourly flash glucose measurements. Duplicate recordings were obtained to assess test-retest reliability. The reference glucose level was measured in arterial or capillary blood. These researchers determined numerical accuracy using Bland-Altman methods, the MARD and whether the International Organization for Standardization (ISO) and Clinical and Laboratory Standards Institute Point of Care Testing (CLSI POCT) criteria were met. Clarke error grid (CEG) and surveillance error grid (SEG) analyses were used to determine clinical accuracy. These researchers compared 484 duplicate flash glucose measurements and observed a Pearson correlation coefficient of 0.97 and a coefficient of repeatability of 1.6 mmol/L. They studied 185 flash readings paired with arterial glucose levels, and 89 paired with capillary glucose levels. Using the arterial glucose level as the reference, these investigators found a mean bias of 1.4 mmol/L (limits of agreement, -1.7 to 4.5 mmol/L). The MARD was 14 % (95 % CI: 12 % to 16 %) and the proportion of measurements meeting ISO and CLSI POCT criteria was 64.3 % and 56.8 %, respectively. The proportions of values within a low-risk zone on CEG and SEG analyses were 97.8 % and 99.5 %, respectively. Using capillary glucose levels as the reference, these researchers found that numerical and clinical accuracy were lower. The authors concluded that subcutaneous FreeStyle Libre blood glucose measurement system showed high test-retest reliability and acceptable accuracy when compared with arterial BG measurement in critically ill patients with diabetes.

Sekido et al (2017) noted that the FreeStyle Libre Flash Glucose Monitoring System (FGM), which can continuously measure glucose concentration in the interstitial fluid glucose (FGM-ISFG), has been in clinical use worldwide. However, it is not clear how accurately FGM-ISFG reflects plasma glucose concentration (PG). These investigators examined the clinical utility of FGM by oral glucose tolerance test (OGTT). In 8 healthy volunteers (3 men; mean age of 41.8 years) wearing FGM sensors for 14 days, OGTT was performed during days 1 to 7 and days 8 to 14, and then both FGM-ISFG and PG were compared. Parkes error grid analysis indicated that all of 65 FGM-ISFG values were within Zone A (no effect on clinical action) and Zone B (little or no effect on clinical outcome). However, in OGTT, the mean FGM-ISFG was higher than the mean actual PG at 30, 60, and 90 minutes after loading (155.5 versus 139.2 mg/dL, 166.2 versus 139.2 mg/dL, 149.5 versus 138.2 mg/dL, respectively; $p < 0.05$). Moreover, the area under the curve of FGM-ISFG was also significantly larger than that of PG (17,626.2 versus 15,195.0 min·mg/dL; $p < 0.05$). In 4 of 8 subjects, FGM-ISFG tended to be higher than PG in both OGTTs, and the greatest difference between the 2 values was 58 mg/dL. The authors concluded that FGM is useful for glycemic control, whereas it is not appropriate to change therapeutic regimens based on the judgment of nocturnal hypoglycemia and postprandial hyperglycemia by FGM-ISFG; careful attention is required for proper application of FGM. They stated that the FGM system will have potential to become an alternative diagnostic tool for diabetes by improvement of over-estimation of IFSG-based glucose levels ISFGs after glucose loading.

The main drawbacks of this study were:

1. its small sample size (n = 8), and
2. it did not include diabetic patients (participants were healthy volunteers).

To confirm these findings and obtain more detailed information on which subjects exhibit large discrepancies in FGM-ISFG and PG, it is desirable to perform clinical experiments in large numbers of subjects, including those with diabetes mellitus.

Rayman et al (2018) examined if interstitial glucose measurements using flash glucose-sensing technology can provide additional information to augment safe driving. Sensor data from 2 European studies on the use of the FreeStyle Libre Glucose Monitoring System in insulin-treated Type 1 and Type 2 diabetes, 241 and 224 participants respectively, were used to determine the frequency of a low interstitial sensor glucose result (less than 3.9 mmol/L) up to 4 hours subsequent to a daytime (07:00 to 21:00 h) capillary BG result greater than or equal to 5 mmol/L. Within 4 hours of a capillary BG result of greater than or equal to 5 mmol/L a sensor glucose result of less than 3.9 mmol/L occurred on 22.0 % of occasions (2,573 of 11,706 blood glucose readings) for those with Type 1 diabetes, and 8.4 % of occasions (699/8,352) for those with Type 2 diabetes; 13.8 % (,1610/11,628) and 4.4 % (365/8,203) within 2 hours, and 10.0 % (1,160/11,601) and 3.1 % (254/8,152) within 1.5 hours. Analysis of sensor glucose results 5 to 7 mmol/L demonstrated the glucose trend arrow descending on 14.7 % (1,163/7,894, Type 1 diabetes) and 9.4 % (305/3,233, Type 2 diabetes) of occasions. The authors concluded that sensor-based glucose information with directional arrows has the potential to support assessment of safe glucose levels associated with driving and offers distinct advantages over BG testing for individuals with Type 1 and Type 2 diabetes to concord with driving safety standards.

Skin Microvascular Flow-Motion

Los-Stegienta et al (2022) noted that diabetic kidney disease (DKD) plays an important role in morbidity and mortality in patients with diabetes mellitus (DM). The pathogenesis of this microangiopathy is primarily due to impaired vascular endothelial function. The flow-mediated skin fluorescence (FMSF) method is an innovative, non-invasive tool for evaluating the microcirculation function (especially micro-circulatory response to hypoxia), also in patients with complications of DM. This study enrolled 84 volunteers including 30 patients with DKD, 33 patients with DM without complications, and 21 healthy controls (HCs) who underwent microvascular function assessments using FMSF. This technique measures changes in the intensity of nicotinamide adenine dinucleotide (NADH) fluorescence from the skin on the fore-arm as a function of time, in response to blocking and releasing blood flow in the fore-arm. These researchers examined 2 key parameters: reactive hyperemia response (RHR) and hypoxia sensitivity [log(HS)] to characterize vascular circulation in patients with DKD and their response to transient ischemia. The patients with low reactive hyperemic response (the RHR parameter) had a significantly higher serum creatinine (sCr) than patients with moderate and high RHR value ($p < 0.001$, $p < 0.05$, respectively), and a significantly lower estimated glomerular filtration rate (eGFR) than the patients with moderate and high RHR parameter ($p < 0.001$, $p < 0.01$, respectively). Subjects with very low and low log(HS) values had a significantly higher sCr than those with high log(HS) ($p < 0.001$, $p < 0.01$, respectively), and a significantly lower eGFR than subjects with high log(HS) parameter ($p < 0.001$, $p < 0.01$, respectively). Subjects with very low log(HS) had a significantly higher sCr and a significantly lower eGFR than those with moderate ($p < 0.05$, $p < 0.01$, respectively). The mean value of the RHR parameter was significantly lower in DKD patients (18.31 % ± 5.06 %) compared to both HCs (34.37 % ± 8.18 %, $p < 0.001$) and DM without complications subgroup (28.75 % ± 7.12 %, $p < 0.001$). Similar trends were noted with the mean value of log(HS) parameter in DKD subgroup (1.03 ± 0.5) versus HCs (1.59 ± 0.53, $p < 0.001$), and versus DM without complications subgroup (1.73 ± 0.52, $p < 0.001$). These investigators found a significant inverse correlation between the RHR parameter and sCr and a significant positive correlations with eGFR ($R = -0.3$; $p < 0.05$, $R = 0.61$; $p < 0.001$, respectively). They also observed a significant negative correlations of the log(HS) measure with sCr and a significant positive correlations with eGFR ($R = -0.33$; $p < 0.01$, $R = 0.55$; $p < 0.001$, respectively). Furthermore, these investigators found a significant inverse correlation between the RHR and log(HS) parameters and AGEs ($R = -0.6$; $p < 0.001$, $R = -0.32$; $p < 0.01$, respectively). The AGEs parameter was also significantly higher in patients with low RHR parameter than in patients with moderate ($p < 0.01$) and high ($p < 0.001$) RHR parameters. The authors concluded that the FMSF technique made it possible to identify impairments of the microvascular function in patients with DKD. This study confirmed that the simple 2-parametric approach diagnostic tool could characterize the state of the microvascular system in diabetic patients with impaired renal function. Moreover, these researchers stated that these preliminary findings require further validation in a larger patients cohort.

Zhao et al (2024) stated that DM can result in microvascular complications such as diabetic neuropathy, nephropathy, and retinopathy. Hyperglycemia may initiate microvascular function impairment early in the course of DM, even before its clinical establishment during the pre-diabetes (PreD) stage. Microvascular vasomotion (i.e., the rhythmic arteriolar constriction and dilation) is an important function that regulates oxygen and nutrient delivery within the tissue and regulates peripheral resistance. Using laser Doppler flowmetry (LDF), vasomotion in skin microcirculation can be measured as flow-motion (skin blood flow oscillation). Changes in flow-motion have been reported in individuals with obesity, and type 1 or type 2 DM (T1DM, or T2DM). However, no data are available on associations between hyperglycemia and flow-motion in the general population. These researchers examined if measures of hyperglycemia were associated with different components of skin microvascular flow-motion (SMF) in a population-based cohort (The Maastricht Study). Data from 7,293 subjects of The Maastricht Study were used; SMF was measured using LDF. Endothelial, neurogenic, and myogenic component SMF power were used as dependent variables. These investigators examined the associations of glucose metabolism status (normal glucose metabolism, PreD, and type 2 DM), measures of hyperglycemia (FPG, 2-hour post-load glucose [2h-PG], HbA1c, AGEs assessed as SAF), and indices of glucose variability (incremental glucose peak [IGP] and CGM -- assessed as standard deviation [SD]) with each component of SMF power. These researchers used linear regression analyses with adjustments for confounders, and trend analyses. They observed consistent negative associations between HbA1c levels and all 3 (endothelial, neurogenic, and myogenic) SMF powers in the additionally adjusted model. Similarly, in the conservative model, these investigators found that multiple hyperglycemia metrics such as GMS trend, PreD, T2DM, FPG, 2h-PG, and HbA1c were consistently negatively associated with all 3 SMF powers. The authors showed that skin microvascular flow-motion was reduced in individuals with PD. Furthermore, different measures of hyperglycemia were negatively associated with skin microvascular flow-motion.

Marcinek et al (2024) examined studies dedicated to the assessment of microvascular function based on micro-circulatory oscillations monitored by the FMSF technique; 2 approaches were presented. The 1st approach employed oscillatory parameters measured under normoxic conditions, expressed as flow-motion (FM), vasomotion (VM), and the normoxia oscillatory index (NOI). These parameters have been used for the identification of impaired micro-circulatory oscillations associated with intense physical exercise, post-COVID syndrome, psychological stress, and erectile dysfunction. The 2nd approach entailed characterization of the micro-circulatory response to hypoxia based on the measurement of HS. The HS parameter was used to characterize microvascular complications in DM, such as diabetic kidney disease and diabetic foot ulcers. Based on research carried out by the authors of this review, the FMSF parameter ranges characterizing microvascular function were presented. The diagnostic approach to evaluating microvascular function based on FM monitored by the FMSF technique has a wide range of applications and the potential to be integrated into wide-spread medical practice.

Appendix

Medically Necessary Quantities of Diabetic Supplies (Test Strips, Lancets)

Usual Utilization

- For members with diabetes who are not currently being treated with insulin injections, up to 100 test strips and up to 100 lancets every 3 months are considered medically necessary.
- For members with diabetes who are currently being treated with insulin injections, up to 300 test strips and up to 300 lancets every 3 months are considered medically necessary.

High Utilization

- For members with diabetes who are not currently being treated with insulin injections, more than 100 test strips and more than 100 lancets every 3 months are considered medically necessary if criteria (a) – (c) below are met.
- For members with diabetes who are currently being treated with insulin injections, more than 300 test strips and more than 300 lancets every 3 months are considered medically necessary if criteria (a) – (c) below are met.

    a. The member's physician has concluded that the member (or the member’s caregiver) has sufficient training using the particular device prescribed as evidenced by providing a prescription for the appropriate supplies and frequency of blood glucose testing; *and*
    b. The treating physician has seen the member, evaluated their diabetes control within 6 months prior to ordering quantities of strips and lancets that exceed the utilization guidelines and has documented in the member's medical record the specific reason for the additional materials for that particular member; *and*
    c. If refills of quantities of supplies that exceed the utilization guidelines are dispensed, there must be documentation in the physician's records (e.g., a specific narrative statement that adequately documents the frequency at which the member is actually testing or a copy of the member's log) that the member is actually testing at a frequency that corroborates the quantity of supplies that have been dispensed. If the member is regularly using quantities of supplies that exceed the utilization guidelines, new documentation must be present at least every six months.

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Policy History

- Last Review 03/19/2025

  Effective: 10/20/1995

  Next Review: 01/08/2026

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes