CONTINUOUS GLUCOSE MONITORING AND INSULIN DELIVERY FOR MANAGING DIABETES

Policy Number: DIABETIC 010.27 T2 **Effective Date**: October 1, 2018

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Related Policy

- Durable Medical Equipment, Orthotics, Ostomy Supplies, Medical Supplies and Repairs/ Replacements

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	Yes - Office No Outpatient, Home
Authorization Required (Precertification always required for inpatient admission)	Yes[1,2,3]
Precertification with Medical Director Review Required	Yes[2]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Home, Outpatient, Office

Special Considerations	[1]Long-term continuous glucose monitoring devices require precertification. [2]The following items require precertification with review by a Medical Director or their designee: • Implantable infusion pumps • Insulin infuser ports (e.g., I-port®) • External insulin pumps and continuous blood glucose monitors, combined into a single closed-loop system not requiring direct patient interaction [3]**Participating providers in the office setting**: Precertification is required for services performed in the office of a participating provider. **Non-participating/out-of-network providers in the office setting**: Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable. Many states require benefit coverage of services that diagnose or treat diabetes mellitus, including glucose monitors, test strips, syringes, medications and related supplies. Specific required coverage varies from state to state.

Repair and Replacement

The member specific benefit plan document includes information regarding repair and replacement of Durable Medical Equipment. Many benefit documents also include language governing the coverage of Durable Medical Equipment that meets the member's basic need. Further information can be found in the policy titled Durable Medical Equipment, Orthotics, Ostomy Supplies, Medical Supplies, and Repairs/Replacements. In all cases, the member specific benefit plan document must be used to determine coverage.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Insulin Delivery

External insulin pumps that deliver insulin by continuous subcutaneous infusion are proven and medically necessary for treating individuals with type 1 or insulin-requiring type 2 diabetes.
For medical necessity clinical coverage criteria, see MCG™ Care Guidelines, 22nd edition, 2018, Insulin Infusion Pump ACG: A-0339 (AC).

Note: Programmable disposable external insulin pumps (e.g., Omnipod) are considered clinically equivalent to standard insulin pumps.

Nonprogrammable transdermal insulin delivery systems (e.g., V-Go) are unproven and not medically necessary for treating individuals with diabetes.
There is insufficient evidence in the clinical literature demonstrating the safety and efficacy of transdermal insulin delivery in the management of individuals with diabetes.

Implantable insulin pumps are investigational, unproven, and not medically necessary for treating individuals with diabetes.
No implantable insulin pumps have received U.S. Food and Drug Administration (FDA) approval at this time. While some preliminary studies reported improved glycemic control and fewer episodes of hypoglycemia in carefully selected

individuals, complications such as catheter blockage and infection were observed. Larger, randomized controlled trials are needed to determine the long-term impact of implantable insulin pumps on diabetes management.

Insulin infuser ports are unproven and not medically necessary for insulin delivery in individuals with diabetes.
There is insufficient evidence demonstrating that the use of insulin infuser ports results in improved glycemic control beyond what can be achieved by using standard insulin delivery methods. In addition, an increase in complications, such as infection at the port site, has been reported when using these devices. Further well-designed, large-scale randomized controlled trials are needed to establish the safety and efficacy of these devices.

See the Description of Services section below for further details on the various types of insulin delivery systems.

Continuous Glucose Monitoring

Short-term (3-7 days) continuous glucose monitoring by a healthcare provider for diagnostic purposes is proven and medically necessary for managing individuals with diabetes.

Long-term continuous glucose monitoring for personal use at home is proven and medically necessary for managing individuals with type 1 diabetes who have demonstrated adherence to a physician ordered diabetic treatment plan and are on an intensive insulin regimen (3 or more insulin injections per day or insulin pump therapy).

Long-term continuous glucose monitoring for personal use at home is unproven and not medically necessary for managing individuals with type 2 diabetes or gestational diabetes.
There is insufficient evidence that the use of long-term continuous glucose monitoring leads to improvement of glycemic control in individuals with type 2 or gestational diabetes.

Continuous glucose monitoring using an implantable glucose sensor (e.g., Eversense) is unproven and not medically necessary for managing individuals with diabetes.
There is insufficient published clinical evidence to conclude that the use of continuous glucose monitoring using an implantable glucose sensor leads to an improvement in glycemic control. The small sample sized studies lack adequate controls, randomization and blinding.

Continuous glucose monitoring using a noninvasive device is investigational, unproven, and not medically necessary for managing individuals with diabetes due to lack of FDA approval.
There are no commercially available noninvasive systems at this time. There is insufficient published clinical evidence to assess the safety and efficacy of continuous glucose monitoring using a noninvasive device.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies may apply.

CPT Code	Description
0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation
95249	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording
95250	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording

CPT Code	Description
95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; analysis, interpretation and report

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Coding Clarification: E1399 is often misused when reporting the i-port device; however, the i-port device is not durable medical equipment (DME), nor does it have a listed code. E1399 can apply to other unspecified DME devices.

HCPCS Code	Description
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
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
E0784	External ambulatory infusion pump, insulin
E1399	Durable medical equipment, miscellaneous **Note**: The i-port device is not durable medical equipment (DME) nor does it have a listed code.
K0553	Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 Unit of Service
K0554	Receiver (monitor), dedicated, for use with therapeutic glucose continuous monitor system
S1030	Continuous noninvasive glucose monitoring device, purchase (for physician interpretation of data, use CPT code)
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use CPT code)
S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
S1036	Transmitter; external, for use with artificial pancreas device system
S1037	Receiver (monitor); external, for use with artificial pancreas device system

The following codes are unproven and not medically necessary for individuals with type 2 diabetes or gestational diabetes.

ICD-10 Diagnosis Code	Description
E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma
E11.10	Type 2 diabetes mellitus with ketoacidosis without coma
E11.11	Type 2 diabetes mellitus with ketoacidosis with coma
E11.21	Type 2 diabetes mellitus with diabetic nephropathy
E11.22	Type 2 diabetes mellitus with diabetic chronic kidney disease
E11.29	Type 2 diabetes mellitus with other diabetic kidney complication
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E11.3211	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E11.3212	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye

ICD-10 Diagnosis Code	Description
E11.3213	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.3291	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E11.3292	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E11.3293	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3299	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.3311	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E11.3312	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E11.3313	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.3391	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E11.3392	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E11.3393	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3399	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.3411	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E11.3412	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E11.3413	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.3491	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E11.3492	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E11.3493	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3499	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.3511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E11.3512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E11.3513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E11.3521	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye

ICD-10 Diagnosis Code	Description
E11.3522	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E11.3523	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E11.3529	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E11.3531	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E11.3532	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E11.3533	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E11.3539	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E11.3541	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E11.3542	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E11.3543	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E11.3549	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E11.3551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E11.3552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E11.3553	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E11.3559	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E11.3591	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E11.3592	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E11.3593	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E11.36	Type 2 diabetes mellitus with diabetic cataract
E11.37X1	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E11.37X2	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E11.37X3	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E11.37X9	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene

ICD-10 Diagnosis Code	Description
E11.52	Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E11.59	Type 2 diabetes mellitus with other circulatory complications
E11.610	Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E11.618	Type 2 diabetes mellitus with other diabetic arthropathy
E11.620	Type 2 diabetes mellitus with diabetic dermatitis
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer
E11.628	Type 2 diabetes mellitus with other skin complications
E11.630	Type 2 diabetes mellitus with periodontal disease
E11.638	Type 2 diabetes mellitus with other oral complications
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E11.65	Type 2 diabetes mellitus with hyperglycemia
E11.69	Type 2 diabetes mellitus with other specified complication
E11.8	Type 2 diabetes mellitus with unspecified complications
E11.9	Type 2 diabetes mellitus without complications
O24.111	Pre-existing type 2 diabetes mellitus, in pregnancy, first trimester
O24.112	Pre-existing type 2 diabetes mellitus, in pregnancy, second trimester
O24.113	Pre-existing type 2 diabetes mellitus, in pregnancy, third trimester
O24.119	Pre-existing type 2 diabetes mellitus, in pregnancy, unspecified trimester
O24.12	Pre-existing type 2 diabetes mellitus, in childbirth
O24.13	Pre-existing type 2 diabetes mellitus, in the puerperium
O24.410	Gestational diabetes mellitus in pregnancy, diet controlled
O24.414	Gestational diabetes mellitus in pregnancy, insulin controlled
O24.415	Gestational diabetes mellitus in pregnancy, controlled by oral hypoglycemic drugs
O24.419	Gestational diabetes mellitus in pregnancy, unspecified control
O24.430	Gestational diabetes mellitus in puerperium, diet controlled
O24.434	Gestational diabetes mellitus in puerperium, insulin controlled
O24.435	Gestational diabetes mellitus in puerperium, controlled by oral hypoglycemic drugs
O24.439	Gestational diabetes mellitus in puerperium, unspecified control

DESCRIPTION OF SERVICES

Diabetes mellitus is one of the leading causes of death in the United States and can be classified into the following general categories (American Diabetes Association guidelines):

- Type 1 diabetes (due to autoimmune beta-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of beta-cell insulin secretion frequently on the background of insulin resistance)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to pregnancy). GDM resembles type 2 diabetes and usually disappears after childbirth.
- Other subtypes of diabetes have been identified. The most common subtype is latent autoimmune diabetes in adults (LADA). LADA can be classified as a more slowly progressing variation of type 1 diabetes, yet it is often misdiagnosed as type 2.

If poorly controlled, diabetes can lead to complications such as heart disease, stroke, peripheral vascular disease, retinal damage, kidney disease, nerve damage and impotence. In gestational diabetes, fetal and maternal health can be compromised.

Improved glycemic control has been shown to slow the onset or progression of major complications. Management of diabetes involves efforts to maintain blood glucose levels near the normal range. Self-monitoring of blood glucose (SMBG) and laboratory testing of glycosylated hemoglobin (A1C) to measure longer term glycemic control are standard methods for glucose testing. (AACE, 2015; ADA, 2017)

Insulin Delivery

Standard external insulin pumps connect to flexible plastic tubing that ends with a needle inserted through the skin into the fatty tissue. Another type of insulin pump (OmniPod®) combines an insulin reservoir placed on the skin with a wireless device to manage dosing and perform SMBG. Both types of devices can be programmed to release small doses of insulin continuously (basal), or a bolus dose close to mealtime to control the rise in blood glucose after a meal. Newer patch devices (e.g., V-Go®) deliver preset dosages of insulin transdermally and lack programmability.

Implantable insulin pumps, with programmable infusion rates, provide continuous intraperitoneal insulin delivery. A blood glucose monitor is not an integral part of this type of system. (ADA website)

An insulin infuser port is a device used to reduce the number of needle injections for individuals with insulin-dependent diabetes. An insertion needle guides a soft cannula into the subcutaneous tissue. Once applied, the insertion needle is removed, leaving the soft cannula under the skin to act as a direct channel into the subcutaneous tissue. Insulin is then injected through the cannula using a standard needle and syringe or insulin pen. Devices, remain in place for up to 72 hours to accommodate multiple drug injections without additional needle sticks.

Continuous Glucose Monitors (CGM)

Continuous glucose monitoring (CGM) devices continuously monitor and record interstitial fluid glucose levels and have three components: a sensor, transmitter and receiver. Some CGM systems are designed for short-term diagnostic or professional use. These devices store retrospective information for review at a later time. Other CGM systems are designed for long-term personal use and display information in real-time allowing the individual to take action based on the data (AMA, 2009). For most devices, glucose measurements provided during continuous monitoring are not intended to replace standard self-monitoring of blood glucose (SMBG) obtained using fingerstick blood samples, but can alert individuals of the need to perform SMBG. These long-term devices are available with or without an integrated external insulin pump.

Implantable continuous glucose monitoring includes a small sensor, smart transmitter and mobile application. Based on fluorescence sensing technology, the sensor is designed to be inserted subcutaneously and communicate with the smart transmitter to wirelessly transmit glucose levels to a mobile device.

CLINICAL EVIDENCE

Insulin Delivery

A systematic review and meta-analysis conducted by the Agency for Healthcare Research and Quality (AHRQ) (Golden et al., 2012) compared insulin pumps with multiple daily injections (MDI) and found no differences in glycemic control or weight gain, as well as insufficient evidence on hypoglycemic events, mortality, and other clinical outcomes. Although recent trials have provided some evidence of clinical benefit, these have suffered from methodological concerns and use of nonstandard outcomes. Findings from the evidence base of eight RCTs suggests a moderate level of certainty that insulin pumps provide a comparable net health benefit to multiple daily injections in patient with type 2 diabetes. (ICER, 2014)

Karges et al. (2017) reported evidence for improved clinical outcomes associated with insulin pump therapy compared with insulin injection therapy in young patients with type 1 diabetes. In a population-based cohort study of 30,579 patients (mean age, 14.1 years; 53% male), 14,119 used pump therapy (median duration, 3.7 years) and 16,460 used insulin injections (median duration, 3.6 years). Pump therapy, compared with injection therapy, was associated with lower rates of severe hypoglycemia and diabetic ketoacidosis, and with better glycemic control during the most recent year of therapy. Total daily insulin doses were lower for pump therapy compared with injection therapy.

Reznik et al. (2014) conducted an international multicenter, randomized controlled trial comparing insulin pump treatment with multiple daily injections (MDI) for patients with poorly controlled type 2 diabetes. A total of 331 patients with an HbA1c of 8·0-12·0% were randomly assigned to pump treatment (n=168) or to continue with multiple daily injections (=163). Mean HbA1c at baseline was 9% in both groups. Neither patients nor investigators were masked to treatment allocation. The primary endpoint was change in mean HbA1c between baseline and end of the randomized phase. At 6 months, mean HbA1c had decreased by 1.1% in the pump treatment group and 0.4% in the MDI group. At the end of the study, the mean total daily insulin dose was 97 units with pump treatment versus 122 units for MDI with no significant difference in bodyweight change between the two groups. Two diabetes-related serious adverse events (hyperglycemia or ketosis without acidosis) resulting in hospitalization occurred in the pump treatment group compared with one in the MDI group. No ketoacidosis occurred in either group and one episode of severe hypoglycemia occurred in the MDI group. The authors concluded that in patients with poorly controlled type 2 diabetes, despite using multiple daily injections of insulin, pump treatment can be considered as a safe and valuable treatment option.

Bergenstal et al. (2010) conducted a multicenter, randomized, controlled trial comparing the efficacy of sensor-augmented pump therapy (pump therapy) to that of multiple daily insulin injections (injection therapy) in 329 adults and 156 children (ages 7 through 70 years) with inadequately controlled type 1 diabetes. The primary end point was the change from the baseline glycated hemoglobin level. At one year, the researchers found that the pump-therapy group had glycated hemoglobin levels that were significantly lower than the injection-therapy group. The baseline mean glycated hemoglobin level, which was 8.3% in the two study groups, had decreased to 7.5% in the pump therapy group, compared with 8.1% in the injection therapy group. The proportion of patients who reached the glycated hemoglobin target (<7%) was greater in the pump-therapy group than in the injection-therapy group. The rates of severe hypoglycemia and diabetic ketoacidosis in the pump-therapy group did not differ significantly from the injection-therapy group. The study concluded that sensor-augmented pump therapy resulted in significant improvement in glycated hemoglobin levels, as compared with injection therapy.

In a meta-analysis, Fatourechi et al. (2009) summarized the evidence on the effect of continuous insulin infusion (CSII) and multiple daily injections (MDIs) on glycemic control and hypoglycemia. Patients with type 1 diabetes using CSII had slightly lower HbA1c, with no significant difference in severe or nocturnal hypoglycemia. Adolescents and adults with type 1 diabetes enrolled in crossover trials had no significantly fewer minor hypoglycemia episodes per patient per week with CSII than MDI; children enrolled in parallel trials had significantly more episodes. Outcomes were not different in patients with type 2 diabetes. Contemporary evidence indicates that compared to MDI, CSII slightly reduced HbA1c in adults with type 1 diabetes, with unclear impact on hypoglycemia. In type 2 diabetes, CSII and MDI had similar outcomes. The authors stated that the effect in patients with hypoglycemia unawareness or recurrent severe hypoglycemia remains unclear because of lack of data.

Pickup and Sutton (2008) conducted a meta-analysis of 22 studies comparing severe hypoglycemia and glycemic control during continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI). The severe hypoglycemia rate in type 1 diabetes was markedly less during CSII than MDI, with the greatest reduction in those with most severe hypoglycemia on MDI and those with the longest duration of diabetes. The biggest improvement in HbA1c was in those with the highest HbA1c on MDI.

In a meta-analysis, Jeitler et al. (2008) compared the effects of continuous subcutaneous insulin infusion (CSII) with those of multiple daily insulin (MDI) injections on glycemic control, risk of hypoglycemic episodes, insulin requirements and adverse events in type 1 and type 2 diabetes mellitus. Twenty-two studies were included (17 on type 1 diabetes mellitus, two on type 2 diabetes mellitus, three on children). CSII therapy in adults and adolescents with type 1 diabetes resulted in a greater reduction of glycated hemoglobin. Total daily insulin requirements were lower with CSII than with MDI therapy. No beneficial effect of CSII therapy could be detected for patients with type 2 diabetes mellitus. No overall conclusions were possible for severe hypoglycemia and adverse events for any of the different patient groups due to rareness of such events, different definitions and insufficient reporting.

In a Cochrane review, Farrar et al. (2007) compared continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) of insulin for pregnant women with diabetes. The review found a lack of robust evidence to support the use of one particular form of insulin administration over another for pregnant women with diabetes. The data are limited because of the small number of trials appropriate for meta-analysis, small study sample size and questionable generalizability of the trial population. Conclusions cannot be made from the data available and therefore a robust randomized trial is needed. Assessed as up-to-date September 2011.

The Diabetes Control and Complications Trial (DCCT) demonstrated that tight glycemic control achieved with intensive insulin regimens significantly delayed the onset and slowed the progression of retinopathy, nephropathy or neuropathy in patients with type 1 or 2 diabetes. Elements of intensive therapy included testing blood glucose levels four or more times a day, injecting insulin at least three times daily or using an insulin pump, adjusting insulin doses according to food intake and exercise, following a diet and exercise plan and making monthly visits to a health care team. (DCCT, 1993)

Nonprogrammable Transdermal Insulin Delivery

Rosenfeld et al. (2012) performed an analysis of glycemic control in twenty-three patients who used the V-Go device. Clinical data was retrospectively collected before V-Go initiation, after 12 weeks of use, at the end of treatment and 12 weeks after discontinuation. Patient perceptions of device use were obtained through telephone surveys. The authors reported that glycemic control improved when patients were switched to the V-Go for insulin delivery and deteriorated when the V-Go was discontinued. No differences in hypoglycemic events were noted. Study limitations include retrospective design, small sample size and short-term follow-up. Further well-designed, prospective studies are needed to establish the safety and efficacy of this device in managing patients with diabetes.

Lajara et al. (2016) compared two methods of insulin delivery in patients with uncontrolled type 2 diabetes. Data were obtained using electronic medical records from a large multi-center system. Records were reviewed to identify patients transitioned to the V-Go device or insulin pen when A1c was >7% on basal insulin therapy. One hundred

sixteen patients were evaluated (56 V-Go, 60 insulin pen). Both groups experienced significant glycemic improvement from similar mean baselines. Progression to intensified insulin therapy resulted in significant glycemic improvement. Insulin delivery with V-Go was associated with a greater reduction in A1C and required less insulin than patients using an insulin pen. Study limitations include retrospective design and patient-reported outcomes.

Implantable Insulin Pumps

Implantable insulin pumps are a promising new technology for the treatment of insulin-dependent diabetes but at this time are only available in a clinical trial setting.

Insulin Infuser Ports

Blevins et al. (2008) conducted a prospective, randomized controlled cross-over trial comparing the outcomes of insulin-dependent diabetics (n=74) who used the i-port compared to standard multi-injection insulin therapy. Type 1 (n=56) and type 2 (n=18) diabetics were randomly assigned to one of four cohort groups. Cohort 1 (n=18) compared standard injections (SI) to single i-port, cohort 2 (n=20) compared single i-port to SI, cohort 3 (n=18) compared dual i-ports to single i-port and cohort 4 (n=18) compared single i-port to dual i-ports. At the end of the first three weeks, each group switched to the alternative method for an additional three weeks. Ten participants were lost to follow-up, six of which were due to device related issues (adhesive failure, discomfort, hyperglycemia, cannula bends and adverse events). Participant's glycosylated albumin was not significantly different between SI, single i-port and dual i-port treatment regiments. A1c levels were similar among all cohorts at the initiation and completion of the study. Adverse events included erythema, suppuration, skin irritation, itching, and bruising at the i-port insertion site. Three events of severe hyperglycemia were also reported.

Continuous Glucose Monitoring

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of glucose monitoring methods for diabetes. Studies suggested that real-time continuous glucose monitoring (rt-CGM) was superior to self-monitoring of blood glucose (SMBG) in lowering HbA1c in nonpregnant individuals with type 1 diabetes, particularly when compliance was high, without affecting the risk of severe hypoglycemia. rt-CGM/CSII in the form of sensor-augmented pumps was superior to MDI/SMBG in lowering HbA1c in the research studies analyzed in this review; however, other combinations of these insulin delivery and glucose monitoring modalities were not evaluated. (Golden et al., 2012)

In the multicenter, randomized controlled CONCEPTT trial, Feig et al. (2017) evaluated the effectiveness of CGM on maternal glucose control and obstetric and neonatal health outcomes in women with type 1 diabetes. Investigators ran two trials in parallel for pregnant participants and for participants planning pregnancy. A total of 325 women (215 pregnant, 110 planning pregnancy) were randomly assigned to capillary glucose monitoring with CGM (108 pregnant, 53 planning pregnancy) or without (107 pregnant, 57 planning pregnancy). Randomization was stratified by insulin delivery (pump or injections) and baseline HbA1c. The primary outcome was change in HbA1c from randomization to 34 weeks' gestation in pregnant women and to 24 weeks or conception in women planning pregnancy. Secondary outcomes included obstetric and neonatal health outcomes. The CGM group had a small but significant reduction in HbA1c levels at 34 weeks' gestation compared to the control group. Pregnant CGM users also spent more time in target glycemic control range and less time in the hyperglycemic range than did pregnant control participants. Neonatal health outcomes were significantly improved in the CGM group, with a lower proportion of infants who were large for their gestational age, fewer neonatal intensive care admissions lasting more than 24 hours, less neonatal hypoglycemia and shorter length of hospital stay. CGM offered no benefit to women planning pregnancy.

In a multicenter, open-label, crossover study, Lind et al. (2017) evaluated the effects of CGM in 161 adults with type 1 diabetes and HbA1c of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections. Participants were randomized to receive treatment using a CGM system or conventional treatment for 26 weeks, separated by a washout period of 17 weeks. Mean HbA1c was 7.92% (63 mmol/mol) during continuous glucose monitoring use and 8.35% (68 mmol/mol) during conventional treatment. Of 19 secondary end points comprising psychosocial and various glycemic measures, 6 met the hierarchical testing criteria of statistical significance, favoring continuous glucose monitoring compared with conventional treatment. Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of continuous glucose monitoring compared with conventional treatment for 26 weeks resulted in lower HbA1c.

In the multicenter, randomized controlled DIAMOND trial, Beck et al. (2017a) evaluated the effectiveness of CGM in 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9%. Participants were randomized 2:1 to CGM (n=105) or usual care (n=53). The use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks.

A separate cohort of 158 patients in the DIAMOND trial was used to evaluate the effectiveness of CGM in adults with type 2 diabetes who were using multiple daily insulin injections and had HbA1c levels of 7.5% to 9.9%. Individuals were randomly assigned to CGM (n=79) or standard care (n=79). In the short 6-month follow-up period, mean HbA1c

levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks. The groups did not differ meaningfully in CGM-measured hypoglycemia or quality-of-life outcomes. Studies with longer follow-up periods are needed to confirm these results. (Beck et al., 2017b)

In a subset of the DIAMOND trial, Ruedy et al. (2017) randomly assigned 116 adults ≥ 60 years of age with type 1 (n=34) or type 2 (n=82) diabetes using MDI to either CGM (n=63) or continued management with SMBG (n=53). CGM use was high and associated with improved HbA1c and reduced glycemic variability.

A meta-analysis of fourteen randomized controlled trials (n=1188) evaluated the use of continuous glucose monitoring (CGM) in patients with type 1 diabetes. Compared to self-monitoring of blood glucose (SMBG), the use of CGM was associated with a greater reduction in HbA1c. The number of hypoglycemic events was not significantly different between the two groups, but duration of hypoglycemia was shorter for the CGM group, with an incremental reduction of hypoglycemia duration. Continuous glucose monitoring also resulted in a shorter duration of hyperglycemia than SMBG. (Floyd et al., 2012)

In a randomized, controlled multicenter study, Battelino et al. (2011) assessed the impact of continuous glucose monitoring on hypoglycemia in patients with type 1 diabetes. A total of 120 children and adults on intensive therapy for type 1 diabetes and an A1c <7.5 were randomly assigned to a control group performing self-monitoring of blood glucose (SMBG) and wearing a masked continuous glucose monitor every second week for five days or to a group with real-time continuous glucose monitoring. Continuous glucose monitoring was associated with reduced time spent in hypoglycemia and a concomitant decrease in HbA1c in children and adults with type 1 diabetes.

The Juvenile Diabetes Research Foundation sponsored a multicenter, randomized controlled trial evaluating the use of continuous glucose monitoring in the management of type I diabetes mellitus. The investigators randomly assigned 322 adults and children who were already receiving intensive therapy for type 1 diabetes to a group with continuous glucose monitoring or to a control group performing home monitoring with a blood glucose meter. All the patients were stratified into three groups according to age and had a glycated hemoglobin level of 7.0 to 10.0%. The primary outcome was the change in the glycated hemoglobin level at 26 weeks. The changes in glycated hemoglobin levels in the two study groups varied markedly according to age group (P=0.003), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change, -0.53%; 95% confidence interval [CI], -0.71 to -0.35; P<0.001). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08; 95% CI, -0.17 to 0.33; P=0.52) or among those who were 8 to 14 years of age (mean difference, -0.13; 95% CI, -0.38 to 0.11; P=0.29). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The investigators concluded that continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes; however, further work is needed to identify barriers to effectiveness of continuous monitoring in children and adolescents. (Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group, 2008)

The same JDRF study group also evaluated factors associated with successful use of continuous glucose monitoring (CGM) among participants with intensively treated type 1 diabetes. 232 participants randomly assigned to the CGM group (165 with baseline A1C >or=7.0% and 67 with A1C <7.0%) were asked to use CGM on a daily basis. The associations of baseline factors and early CGM use with CGM use >or=6 days/week in the 6th month and with change in A1C from baseline to 6 months were evaluated. The only baseline factors found to be associated with greater CGM use in month 6 were age >or=25 years (P < 0.001) and more frequent self-reported prestudy blood glucose meter measurements per day (P < 0.001). CGM use and the percentage of CGM glucose values between 71 and 180 mg/dl during the 1st month were predictive of CGM use in month 6 (P < 0.001 and P = 0.002, respectively). More frequent CGM use was associated with a greater reduction in A1C from baseline to 6 months (P < 0.001), a finding present in all age-groups. After 6 months, near-daily CGM use is more frequent in intensively treated adults with type 1 diabetes than in children and adolescents, although in all age-groups near-daily CGM use is associated with a similar reduction in A1C. Frequency of blood glucose meter monitoring and initial CGM use may help predict the likelihood of long-term CGM benefit in intensively treated patients with type 1 diabetes of all ages. (JDRF, 2009a)

In a parallel study of 129 adults and children with intensively treated type 1 diabetes (age range 8-69 years), the JDRF study group reported that the evidence suggests that CGM is beneficial for individuals with type 1 diabetes who have already achieved excellent control with A1C <7.0%. (JDRF, 2009b)

In a 6-month extension to the JDRF trial, the study group evaluated the long-term effects of continuous glucose monitoring (CGM) in 83 intensively treated adults (≥ 25 years of age) with type 1 diabetes. The group found that most adults continued to use CGM on a daily or near daily basis and had sustained benefits for improved glucose control noted by A1c levels and the amount of time sensor glucose values were in the target range. These benefits persisted despite less intensive follow-up, designed to approximate usual clinical practice, than during the 6-month randomized phase of the study. (JDRF, 2009c)

In a Cochrane review, Langendam et al. (2012) assessed the effects of continuous glucose monitoring (CGM) systems compared to conventional self-monitoring of blood glucose (SMBG) in patients with Type 1 diabetes. Twenty-two randomized controlled trials (RCTs) comparing retrospective or real-time CGM with conventional self-monitoring of blood glucose levels or with another type of CGM system in patients with type 1 diabetes mellitus were included. The studies randomized 2883 patients with type 1 diabetes to receive a form of CGM or to use SMBG using fingerprick. The duration of follow-up varied between 3 and 18 months; most studies reported results for six months of CGM use. This review shows that CGM helps in lowering the HbA1c. In most studies the HbA1c value decreased in both the CGM and the SMBG users, but more in the CGM group. The difference in change in HbA1c levels between the groups was on average 0.7% for patients starting on an insulin pump with integrated CGM and 0.2% for patients starting with CGM alone. The most important adverse events, severe hypoglycemia and ketoacidosis did not occur frequently in the studies, and absolute numbers were low (9% of the patients, measured over six months). Diabetes complications, death from any cause and costs were not measured. There are no data on pregnant women with Type 1 diabetes and patients with diabetes who are not aware of hypoglycemia.

Mauras et al. (2012) assessed the benefit of continuous glucose monitoring (CGM) in young children aged 4 to 9 years with type 1 diabetes. A total of 146 children with type 1 diabetes (mean age 7.5 ± 1.7 years) were randomly assigned to CGM or to usual care. The primary outcome was reduction in HbA1c at 26 weeks by ≥0.5% without the occurrence of severe hypoglycemia. The primary outcome was achieved by 19% in the CGM group and 28% in the control group. Mean change in HbA1c was -0.1% in each group. Severe hypoglycemia rates were similarly low in both groups. CGM wear decreased over time, with only 41% averaging at least 6 days/week at 26 weeks. There was no correlation between CGM use and change in HbA1c. The authors concluded that CGM in 4- to 9-year-olds did not improve glycemic control despite a high degree of parental satisfaction with CGM. This finding may be related in part to limited use of the CGM glucose data in day-to-day management and to an unremitting fear of hypoglycemia.

Szypowska et al. (2012) conducted a systematic review and meta-analysis to explore the potential beneficial effects of real-time continuous glucose monitoring (RT-CGM) on diabetes management compared with self blood glucose measurement (SBGM) in patients with type 1 diabetes. Seven randomized controlled trials (n=948) were included. Combined data from all studies showed better HbA1c reduction in subjects using RT-CGM compared with those using SBGM. Patients treated with insulin pump and RT-CGM had a lower HbA1c level compared with subjects managed with insulin pump and SBGM (four RCTs, n=497) The benefits of applying RT-CGM were not associated with an increase in rate of major hypoglycemic episodes. The use of RT-CGM for over 60-70% of time was associated with a significant lowering of HbA1c. The authors concluded that RT-CGM is more beneficial than SBGM in reducing HbA1c in patients with type 1 diabetes. Further studies are needed to evaluate the efficacy of this system in the pediatric population, especially in very young children.

Vigersky et al. (2012) conducted a randomized controlled trial of 100 adults with type 2 diabetes, who were not on prandial insulin, to determine whether short-time, real-time continuous glucose monitoring (RT-CGM) had long-term glycemic effects. Intermittent RT-CGM over 12 weeks significantly improved glycemic control both during and for up to 1 year following the intervention. The authors concluded that additional studies are needed to confirm these results as well as determine the mechanism by which the improvement occurred, the minimum time for RT-CGM to be effective and the effect/timing of refresher courses of this intervention.

Hoeks et al. (2011) performed a systematic review of seven randomized controlled trials evaluating the effect of real-time continuous glucose monitoring systems in diabetes management. The analysis concluded that real-time continuous glucose monitoring has a beneficial effect on glycemic control in adult patients with diabetes, without an increase in the incidence of hypoglycemia. Studies in well-selected patient groups (pregnancy, history of severe hypoglycemia, type 2 diabetes) are lacking.

Chase et al. (2010) reported on the 12-month follow-up of 80 patients age 8–17 years who participated in the 6-month randomized JDRF study and the subsequent 6-month extension study. Outcomes included frequency of CGM use, HbA1c levels, rate of severe hypoglycemia and a CGM satisfaction scale. Seventy-six (95%) of 80 subjects were using CGM after 6 months (median use = 5.5 days/week) compared with 67 (84%) after 12 months (median use = 4.0 days/week). The 17 subjects using CGM >or=6 days/week in month 12 had substantially greater improvement from baseline in HbA1c than did the 63 subjects using CGM <6 days/week in month 12 (mean change - 0.8 +/- 0.6% vs. +0.1 +/- 0.7%). They also reported greater satisfaction with use of CGM. The incidence of severe hypoglycemic events was low during the 12 months of the study irrespective of the amount of CGM use. The study concluded that individuals who use CGM on a near-daily basis can have substantial improvement in glycemic control.

Chetty et al. (2008) performed a meta-analysis of randomized controlled trials comparing CGMS and SBGM in Type 1 diabetic patients. Seven studies with a total of 335 patients were included. Five studies were confined to the pediatric population (age<18 years). The authors concluded that while there was some indication of improved detection of

asymptomatic nocturnal hypoglycemia in the CGMS group, there was insufficient evidence to support the notion that CGMS provides a superior benefit over SBGM in terms of HBA1c reduction.

The Diabetes Research in Children Network (DirecNet) Study Group examined the feasibility of daily use of a continuous glucose monitor, the FreeStyle Navigator CGMS in children with type 1 diabetes using insulin pumps. Mean A1C improved from 7.1% at baseline to 6.8% at 13 weeks of unblinded sensor use, and the percentage of glucose values in the target range increased from 52% to 60%. There was a modest increase in the percentage of sensor values that were <70 mg/dL. (Buckingham 2007) The DirecNet Study Group also conducted a similar study in 27 children with type 1 diabetes using multiple daily injections of insulin. Mean A1C level fell from 7.9 at baseline to 7.3 at 13 weeks. (Weinzimer et al., 2008)

Gestational Diabetes

In a prospective, open label randomized controlled trial, Murphy et al. (2008) evaluated the effectiveness of continuous glucose monitoring during pregnancy on maternal glycemic control, infant birth weight and risk of macrosomia in women with type 1 and type 2 diabetes. 71 women with type 1 diabetes (n=46) or type 2 diabetes (n=25) were allocated to antenatal care plus continuous glucose monitoring (n=38) or to standard antenatal care (n=33). The primary outcome was maternal glycemic control during the second and third trimesters from measurements of HbA1c levels every four weeks. Secondary outcomes were birth weight and risk of macrosomia. Women randomized to continuous glucose monitoring had lower mean HbA1c levels from 32 to 36 weeks' gestation compared with women randomized to standard antenatal care. Compared with infants of mothers in the control arm those of mothers in the intervention arm had decreased mean birthweight, decreased median customized birthweight and a reduced risk of macrosomia. The authors acknowledged that, due to lack of blinding, they could not exclude the possibility of bias in clinical management. They also stated that because the number of women studied was small, larger multicentre trials are required to assess the impact of CGM during pregnancy.

Kestila et al. (2007) conducted a randomized controlled trial to compare CGMS (n=36) to SMBG (n=37) in detecting patients with GDM who needed antidiabetic drug treatment. In 11 out of 36 patients (31%) monitored with CGMS antihyperglycemic drug therapy was introduced whereas only 3/37 (8%) in the SMBG group were drug-treated. The authors concluded that further large-scale studies are needed to evaluate whether CGMS guided initiation of antihyperglycemic therapy results in less macrosomia and perinatal complications related to GDM.

Buhling et al. (2005) reported that CGMS detected more frequent and longer periods of hyperglycemia. Compared with SMBG, CGMS also offered more differentiation between nondiabetic pregnant women, patients with gestational diabetes and patients with impaired glucose tolerance.

A second small study found that when CGMS was used to adjust insulin treatment, there was a reduction in undetected hyperglycemia and nocturnal hypoglycemic events. However, the study did not indicate a clinical difference in perinatal outcomes between CGMS and SMBG. (Yogev, 2003)

National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and management of type 1 diabetes in adults make the following recommendations regarding CGM (August 2015; updated July 2016):

- Do not offer real-time CGM routinely to adults with type 1 diabetes.
- Consider real-time CGM for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring:
    - More than 1 episode a year of severe hypoglycemia with no obviously preventable precipitating cause.
    - Complete loss of awareness of hypoglycemia.
    - Frequent (more than 2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities.
    - Extreme fear of hypoglycemia.
    - Hyperglycemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time CGM only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.
- For adults with type 1 diabetes who are having real-time CGM, use the principles of flexible insulin therapy with either multiple daily injections or CSII.

NICE guidelines on the diagnosis and management of diabetes in children and young people make the following recommendations regarding CGM (August 2015; updated November 2016):

- Offer ongoing real-time CGM with alarms to children and young people with type 1 diabetes who have:
    - Frequent severe hypoglycemia or
    - Impaired awareness of hypoglycemia associated with adverse consequences (e.g., seizures or anxiety) or inability to recognize, or communicate about, symptoms of hypoglycemia (e.g., because of cognitive or neurological disabilities).

- Consider ongoing real-time CGM for:
  - Neonates, infants and pre-school children
  - Children and young people who undertake high levels of physical activity
  - Children and young people who have comorbidities or who are receiving treatments that can make blood glucose control difficult.
- Consider intermittent (real-time or retrospective) CGM to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support.

Implantable Glucose Sensor

In the prospective, multicenter PRECISE II trial, Christiansen et al. (2018) evaluated the accuracy and safety of the Eversense CGM system in 90 adult participants with type 1 and type 2 diabetes. The updated system included a modified algorithm and a new sensor configuration. The primary efficacy endpoint was the mean absolute relative difference (MARD) between Eversense and reference measurements through 90 days postinsertion for reference glucose values from 40 to 400 mg/dL. The primary safety endpoint was the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAEs) through 90 days postinsertion. The system was accurate, with an overall MARD value of 8.8% across the clinically relevant glucose range, with 93% of CGM values within 20% of reference values. The system correctly identified hypoglycemia (<70 mg/dL) 93% of the time and hyperglycemia (>180 mg/dL) 96% of the time. A limited but statistically significant reduction of accuracy occurred in the last month of use. 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 that the Eversense system provided accurate glucose readings through the intended 90-day sensor life with a favorable safety profile. Study limitations include lack of randomization and short-term follow-up. Long-term surveillance studies are required to ensure that the safety profile remains favorable with multiple sensor placements and removals.

In the PRECISE trial, Kropff et al. (2017) evaluated the accuracy and longevity of the Eversense (Senseonics, Inc.) implantable CGM sensor. Seventy-one participants, aged 18 years and older with type 1 and type 2 diabetes, participated in the 180-day prospective, multicenter pivotal trial. CGM accuracy was assessed during eight in-clinic visits with the MARD for venous reference glucose values >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 adverse events. The MARD value against reference glucose values >4.2 mmol/L was 11.1%. Clarke Error Grid Analysis showed 99.2% of samples in the clinically acceptable error zones. Eighty-one percent of hypoglycemic events were detected by the CGM system within 30 min. A limited but statistically significant reduction of CGM measurement accuracy occurred in the last month of use, possibly due to long-term degradation of the glucose indicating gel before end of sensor life was reached. No device-related serious adverse events occurred during the study. This study is limited by a lack of randomization and control, small patient population and short-term follow-up. Further studies are needed to assess the safety and efficacy of these devices.

Dehennis et al. (2015) performed a multisite study to assess the accuracy of glucose measurement by the Senseonics CGM system using matched paired measurements to those obtained by laboratory reference analyzer values from venous blood samples. The Senseonics CGM, composed of an implantable sensor, external smart transmitter, and smartphone app, uses a single sensor for continuous display of accurate glucose values for 3 months. Adults ≥18 and ≤65 years of age who had a clinically confirmed diagnosis of type 1 diabetes mellitus or type 2 diabetes and who were receiving insulin injection therapy were eligible to participant in this study. Ten men and 14 women with type 1 diabetes mellitus underwent subcutaneous implantation of sensors in the upper arm. Eight-hour clinic sessions were performed every 14 days (days 1, 15, 30, 45, 60, 75, and 90), during which sensor glucose values were compared against venous blood lab reference measurements using MARDs. The subjects maintained calibration of their CGM system twice daily by entering their self-monitored blood glucose (SMBG) measurement through the smartphone app. Twenty two of the twenty four (92%) sensors reported glucose continuously for 90 days, and the MARD for all 24 sensors was 11.4 ± 2.7% against venous reference glucose values. There was no significant difference in MARD throughout the 90-day study and no serious adverse events were noted. The authors concluded that the study showed successful in-clinic and home use of the Senseonics CGM system over 90 days in subjects with diabetes mellitus. Limitations of this study include non-randomization and small sample size.

Professional Societies

American Diabetes Association (ADA)

Insulin Delivery

The 2018 *Standards of Medical Care in Diabetes* state that most people with type 1 diabetes should be treated with MDI of prandial insulin and basal insulin or CSII. Although most studies of MDI versus CSII have been small and of short duration, a systematic review and meta-analysis concluded that there are minimal differences between the two forms of intensive insulin therapy in A1C and severe hypoglycemia rates in children and adults.

Continuous Glucose Monitoring

The 2018 *Standards of Medical Care in Diabetes* make the following recommendations:

- When used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lower A1c in selected adults with type 1 diabetes who are not meetig glycemic targets.
- CGM may be a useful tool in individuals with hypoglycemia unawareness and/or frequent hypoglycemic episodes.
- Given variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing.
- When prescribing CGM, robust diabetes education, training and support are required for optimal CGM implementation and ongoing use.

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)

Insulin Pumps

AACE/ACE clinical practice guidelines state that candidates for CSII include patients with type 1 diabetes and patients with type 2 diabetes who are insulin dependent. CSII should only be used in patients who are motivated and knowledgeable in diabetes self-care, including insulin adjustment. To ensure patient safety, prescribing physicians must have expertise in CSII therapy, and CSII users must be thoroughly educated and periodically reevaluated. Sensor-augmented CSII, including those with a threshold-suspend function, should be considered for patients who are at risk of hypoglycemia. (Handelsman et al., 2015)

Continuous Glucose Monitoring

AACE/ACE clinical practice guidelines state that CGM may be considered for patients with type 1 diabetes and type 2 diabetes on basal-bolus therapy to improve A1c levels and reduce hypoglycemia. Although data from small-scale randomized trials and retrospective or prospective observational studies suggest CGM may provide benefits in insulin-using patients with type 2 diabetes, additional research is needed before recommendations can be made regarding use in this patient population. (Handelsman et al., 2015)

Endocrine Society

Endocrine Society clinical practice guidelines address the use of CGM and CSII in adults with diabetes. (Peters et al., 2016)

Insulin Delivery

- Recommend CSII over analog-based basal-bolus MDI in patients with type 1 diabetes who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device. Strong recommendation based on moderate quality evidence.
- Recommend CSII over analog-based basal-bolus MDI in patients with type 1 diabetes who have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device. Strong recommendation based on low quality evidence.
- Suggest CSII in patients with type 1 diabetes who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device. Weak recommendation based on low quality evidence.
- Suggest CSII with good adherence to monitoring and dosing in patients with type 2 diabetes who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy and lifestyle modifications. Weak recommendation based on low quality evidence.

Continuous Glucose Monitoring

- Recommend real-time CGM devices for adult patients with type 1 diabetes who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis. Strong recommendation based on high quality evidence.
- Recommend real-time CGM devices for adult patients with well-controlled type 1 diabetes who are willing and able to use these devices on a nearly daily basis. Strong recommendation based on high quality evidence.
- Suggest short-term, intermittent real-time CGM use in adult patients with type2 diabetes (not on prandial insulin) who have A1C levels ≥7% and are willing and able to use the device. Weak recommendation based on low quality evidence.
- Suggest that adults with type 1 and type 2 diabetes who use CSII and CGM receive education, training and ongoing support to help achieve and maintain individualized glycemic goals. (Ungraded Good Practice Statement)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Insulin Delivery

For information on external insulin pumps, see the following website (use product code LZG): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 9, 2018)

For information on hybrid closed-loop insulin pumps (e.g., MiniMed 670G), see the following website (use product code OZP): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed May 9, 2018)

No implantable insulin pumps have received FDA approval at this time.

The i-port® Injection Port was approved by the FDA on September 9, 2005 (K052389). The injection port is indicated for use by people requiring multiple daily subcutaneous injections of physician prescribed medications, including insulin. The device is designed for use on adults and children for up to 72 hours. Additional information available at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K052389.pdf (Accessed May 9, 2018)

The i-port Advance® Injection Port was approved by the FDA on February 16, 2012 (K120337). This model has the same indications as the original device but includes an automatic insertion component. Additional information available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K120337.pdf (Accessed May 9, 2018)

The V-Go device (models V-Go20, V-Go30 and V-Go40) received FDA approval (K100504) on December 1, 2010. V-Go is a mechanical (no electronics), self-contained, sterile, patient fillable, single-use disposable insulin infusion device with an integrated stainless steel subcutaneous needle. The device is indicated for continuous subcutaneous infusion of insulin in one 24-hour time period and on-demand bolus dosing in 2-unit increments (up to 36 units per one 24-hour time period) in adult patients requiring insulin. Three models (20, 30 and 40 units/day) are available. The device is intended for use in patients with type 2 diabetes. Additional information available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K100504. (Accessed May 9, 2018)

A second FDA approval (K103825) came through on February 23, 2011. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K103825. (Accessed May 9, 2018)

Insulin Pump Models (this is not an exhaustive list):
- Insulet OmniPod
- Medtronic MiniMed 530G
- Medtronic MiniMed 630G
- Medtronic MiniMed 670G
- Medtronic MiniMed Paradigm Revel
- Sooil Dana Diabecare IIS
- Tandem T:flex
- Tandem T:slim X2

Continuous Glucose Monitors

For information on continuous glucose monitors, see the following web sites:
Product code LZG: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 9, 2018)
Product code MDS: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed May 9, 2018)

Continuous Glucose Monitor Models (this is not an exhaustive list):
- Abbott FreeStyle Libre Flash
- Dexcom G4
- Dexcom G5
- Dexcom G6
- Medtronic MiniMed 530G
- Medtronic MiniMed 630G
- Medtronic MiniMed 670G
- Medtronic MiniMed Guardian Connect
- Medtronic MiniMed Paradigm Revel
- Tandem T:slim X2

FreeStyle Libre Pro – stand-alone CGM approved for short-term professional diagnostic use only:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150021. (Accessed May 9, 2018)

iPro®2 Professional CGM
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150029. (Accessed May 9, 2018)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [*2018T0347Z]*

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	• Reformatted list of applicable ICD-10 diagnosis codes
10/01/2018	• Updated conditions of coverage/special considerations; modified notation to clarify: ○ For **participating providers in the office setting**: Precertification is

Date	Action/Description
	required for services performed in the office of a participating provider ○ For **non-participating/out-of-network providers in the office setting**: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review *for out-of-network benefits and* medical necessity after the service is rendered • Updated coverage rationale; modified language to clarify the listed services are: ○ Proven ***and*** medically necessary (as described); see the referenced MCG™ Care Guidelines for *medical necessity* clinical coverage criteria ○ Unproven ***and*** not medically necessary (as described) ○ Investigational, unproven, ***and*** not medically necessary (as described) • Archived previous policy version DIABETIC 010.26 T2