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National Horizon Scanning Unit Horizon scanning report

GlucoWatch[®] G2 Biographer for the non-invasive monitoring of glucose levels

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Introduction

The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the introduction and use of the Gluowatch® G2 Biographer for the non-invasive monitoring of glucose levels in children (Horizon Scanning Register number: 000063).

Cygnus Inc manufactures the Gluowatch® G2 Biographer with the aim of providing continuous glucose monitoring of individuals with diabetes. The Gluowatch® G2 Biographer has recently been given approval from the United States FDA (2002) for use in children and adolescents with Type-I insulin-dependent diabetes but it has not, as yet, received Australian Therapeutic Goods Administration approval. This technology is currently unavailable for purchase in Australia; however, it is in limited use within Australia as it is available from Europe or the United States on a prescription basis through licensed General Practitioners.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of Gluowatch® G2 Biographer, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with GlucoWatch® G2 Biographer for the non-invasive monitoring of glucose levels in children and adolescents.

Background

Description of the technology

The procedure

Iontophoresis is a process, which uses a small electrical current to drive charged and highly polar compounds across the skin at much higher rates than normally would be permitted by the natural passive permeability of the compound (Sieg et al 2003). Iontophoresis has been in clinical use since the 1950s when Gibson and Cooke (1959) used it to deliver pilocarpine transdermally, using an electrical current, to stimulate sweating in infants and children. Sweat was then collected and electrolyte concentrations determined for the diagnosis of cystic fibrosis (Chernick 1998). Iontophoresis utilises two mechanisms: electro-migration and electro-osmosis. Electro-migration is the movement of small ions across the skin in response to, or as a result of, an electrical current being applied. Electron fluxes are transformed into ionic fluxes and ionic transport occurs across the skin to maintain electro-neutrality.

Electro-osmosis is the main transport mechanism of uncharged molecules and high molecular weight cations. At physiological pH, the skin is negatively charged and will preferentially transport positive ions, usually sodium ions (Na^+), producing an electro-osmotic solvent flow, which carries neutral molecules in the anode (positive) to cathode (negative) direction.

Iontophoresis is non-specific and many ions and small, uncharged molecules other than the compound or molecule of interest are moved across the skin upon application of the current. In this manner, highly charged, ionic drugs may be placed on the skin with an electrode of the same charge, allowing direct current to drive the drug through the skin and into the interstitial tissue. Application of a positive current will drive positively charged drug molecules away from the electrode and into the tissues; similarly, a negative current will drive negatively charged ions into the tissues (Sieg et al 2003; Potts et al 2002).

The GlucoWatch[®] G2 Biographer is a small wristwatch-like device used for the non-invasive sampling of glucose by utilising *reverse iontophoresis*. The device contains sampling and detection devices (AutoSensor) and a digital display. The AutoSensor snaps into the back of the GlucoWatch[®] G2 Biographer housing and is a single-use, disposable component, needing to be replaced each time the device is worn. An adhesive backing is removed from the AutoSensor to enable it to adhere when in contact with the skin. A built-in alert system sounds an alarm if glucose readings are too high (hyperglycaemia), low (hypoglycaemia) or are declining rapidly (FDA 2001; Cygnus Inc 2003).

GlucoWatch[®] G2 Biographer sends a low-level electronic current (0.3 mA), produced by batteries contained in the watch housing, through the skin and then extracts fluid containing ions and associated glucose, across the skin by *reverse iontophoresis*. The extracted fluid is accumulated in the AutoSensor (Figure 1). The AutoSensor consists of three electrodes: a sensing (working) electrode, a counter/ iontophoresis and a reference electrode. Hydrogel discs are placed over the AutoSensor and are in contact with the skin.

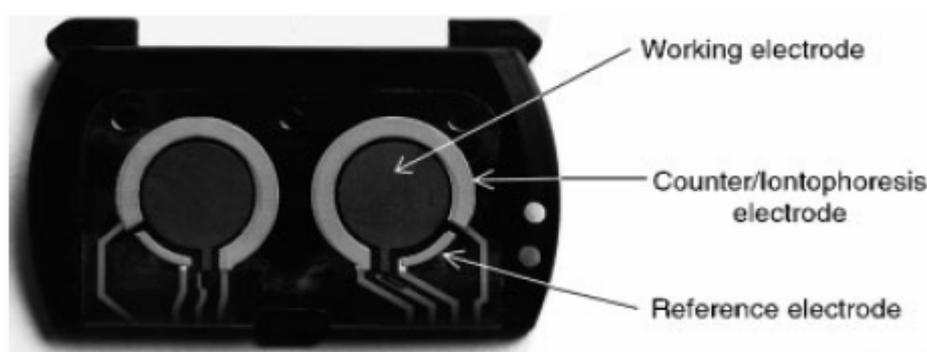


Figure 1 Biosensor electrode assembly (Potts et al 2002)

As glucose is an uncharged molecule, it is transported across the skin with Na^+ by electro-osmosis, towards the iontophoretic cathode. Glucose levels in the extracted fluid are then measured (Figure 2) (Potts et al 2002).

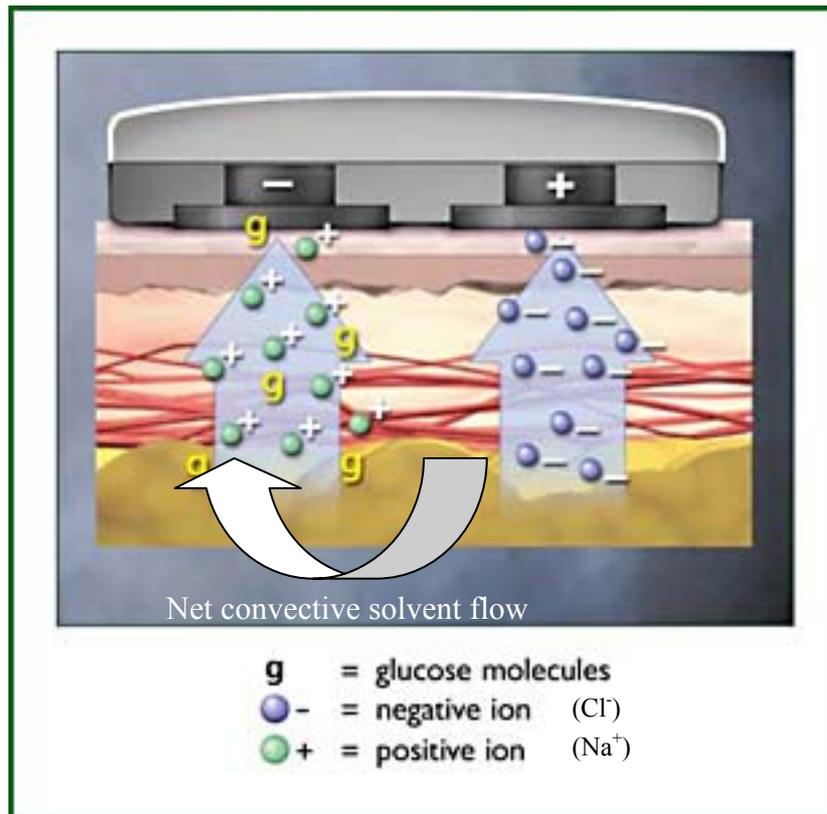


Figure 2 Reverse iontophoresis. Extraction of fluid through the skin. Neutral glucose molecules associated with positively charged sodium ions (Na⁺) are extracted from the skin into the GlucoWatch[®] G2 Biographer autosensor, where the level of glucose is measured (Copyright Cygnus Inc 2003, printed with permission).

Glucose oxidase is dissolved into the hydrogel discs and reacts with the accumulated glucose, oxidising it to form hydrogen peroxide, which is further oxidised to oxygen and hydrogen. The amount of hydrogen peroxide is measured and correlated, using an algorithm, to the amount of glucose in the original sample. The amount of glucose extracted across the skin correlates with blood glucose with an average lag time of 20 minutes. The sampling and detection process takes 10 minutes: three minutes to collect the glucose sample and seven minutes for the sensing mechanism to ensure that all the glucose, then the subsequent hydrogen peroxide, is consumed and broken down (Potts et al 2002).

The GlucoWatch[®] G2 Biographer device requires a three hour warm up period during which time it is calibrated against a blood glucose reading acquired from a traditional finger-prick test. The device is capable of conducting three glucose readings per hour for up to 12 hours of continuous monitoring, potentially giving a total of 36 readings (Figure 3). In addition, GlucoWatch[®] G2 Biographer is able to create an electronic diary of glucose readings, storing up to 8,500 readings in memory. The high and low glucose alarm levels may be set by the patient, under instruction from their health-care advisors. The GlucoWatch[®] G2 Biographer is designed to have an expected life time of at least four years when worn daily and stored and cared for according to the manufacturer's criteria. GlucoWatch[®] G2 Biographer can detect glucose levels over the range 2.2-22.2 mmol/L (FDA 2001; Cygnus Inc 2003).

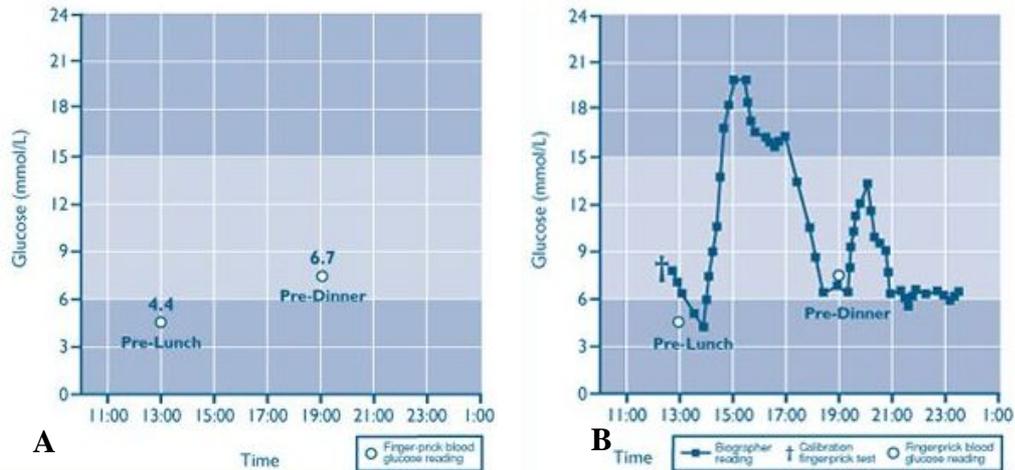


Figure 3 Finger-prick glucose monitoring (A) compared to continuous monitoring with GlucoWatch® G2 Biographer (B) (Copyright Cygnus Inc 2003, printed with permission)

Intended purpose

GlucoWatch® G2 Biographer is suitable for adults (aged over 18 years) and has recently gained Food and Drug Administration (USA) approval for use in children and adolescents (aged 7-17 years), who suffer from Type-I or Type-II diabetes requiring treatment with insulin (Formanek 2001; FDA 2001). The GlucoWatch® G2 Biographer may be particularly useful for night time monitoring of glucose levels, determining trends in blood glucose levels, preventing episodes of hypoglycaemia or managing patients with hypoglycaemia unawareness. GlucoWatch® G2 Biographer may also be of utility as a management tool for Type-I diabetes for both children and their families struggling to gain control over glucose levels (Cygnus Inc 2003).

Patients who are insulin dependent are required to monitor their blood glucose levels to ensure that appropriate levels of insulin are circulating. One of the primary treatment goals in patients with insulin-dependent diabetes is good glucose control, which may minimise microvascular and neurologic complications. Achieving tight glucose control as early as possible after diagnosis, in patients affected by diabetes, has great benefit for the reduction, or the slowing of progression, of microvascular complications such as diabetic retinopathy and nephropathy caused by hyperglycaemia (Bate & Jerums 2003). To achieve tight glucose control, patients may have to administer insulin by injection three or more times during the day, or have insulin delivered by an external or implanted pump. Increased glucose control may, however, lead to a three-fold increase in the risk of hypoglycaemia (American Diabetes Association 2000; The Diabetes Control and Complications Trial Research Group 1993). Serious hypoglycaemia may result in altered consciousness, coma, convulsions and organ damage.

Finger-prick testing is painful, inconvenient and messy, therefore a non-invasive method for measurement of blood glucose levels is being actively sought. Daily self-monitoring and missing insulin injections remain serious problems for many diabetic patients. The study by Altobelli et al (2000)

reported that although 49 per cent of diabetic adolescents (aged 15-18 years) followed their medical prescriptions regularly, the same group of patients “forgot” to conduct glycaemic tests 42 per cent of the time. This contrasted with children (aged 10-14 years), 30 per cent of whom followed medication prescriptions, but only “forgot” glycaemic testing 30 per cent of the time. Metabolic control of glycaemia in adolescents and children worsened with duration of disease. In addition, children may falsify glycaemic results in a desire to show improved results to their parents (Altobelli et al 2000).

The study by Perwien et al (2000) examined the accuracy of blood glucose monitoring skills amongst children and found that the accuracy of performance ranged between 15 to 100 per cent. Critical errors made in testing led to inaccurate blood glucose results, which may have serious consequences for diabetes management (Perwien et al 2000). Frequent, accurate monitoring of blood glucose levels through conventional finger-prick methods may reduce the risk of hypoglycaemia or hyperglycaemia. However, several studies have demonstrated that home glucose monitors may return inaccurate readings, emphasising the critical need for accurate calibration and maintenance of monitors (Alto et al 2002; Brunner et al 1998). The danger of hypoglycaemia is greater in infants and children due to less predictable food intake, activity and adherence to treatment schedules (American Diabetes Association 2000).

GlucoWatch® G2 Biographer is not designed to replace blood glucose finger-prick testing, which is the gold standard for glucose monitoring, but may reduce the number of times during a day that patients would need to use this method of glucose testing. Hypo- or hyperglycaemic episodes detected by GlucoWatch® G2 Biographer should be confirmed by a finger-prick test. Patients are advised to not change their treatment protocols based only on information attained from the GlucoWatch® G2 Biographer device, for example determining an insulin dose prior to a meal. GlucoWatch® G2 Biographer has no contraindications but the AutoSensor component may cause some skin irritation, therefore GlucoWatch® should not be placed on burned, injured or irritated skin. Excessive sweating caused by exercise, heat or low glucose levels will cause GlucoWatch® G2 Biographer to skip readings. Also, three compounds - acetaminophen, dopamine and tolazamide - have been shown to significantly induce errors in glucose measurements using GlucoWatch® G2 Biographer (FDA 2001).

Clinical need and burden of disease

Type-1 or juvenile diabetes sufferers have a near-total lack of insulin due to the auto-immune destruction of the insulin producing beta cells of the pancreas. Type-1 diabetes represents approximately 10-15 per cent of all diabetic patients, however 98 per cent of childhood diabetes is Type-1. Type-2 diabetes is characterised by reduced levels of insulin or insulin resistance and represents approximately 85-90 per cent of diabetic sufferers, most of whom are over the age of 40 years. Gestational diabetes is a temporary form of diabetes, which occurs during pregnancy in 3-8 per cent of females not previously diagnosed with diabetes (AIHW 2002).

It is estimated that approximately one million people suffer from the three types of diabetes (Type-1, Type-2 and gestational diabetes) in Australia.¹ In the year 2000, diabetes was the underlying cause of death of over 3,000 Australians, whilst over 10,000 deaths were recorded with diabetes as an underlying *or* associated cause. In 1999-2000, 12 per cent of patients aged over 25 years with diabetes suffered a heart attack and nine per cent a stroke. In addition, 15 per cent of people with diabetes had retinopathy, 6 per cent kidney disease, approximately 10 per cent had neuropathy, 19 per cent were at risk of foot ulcers and 2 per cent had amputated limbs. The number of public hospital separations in Australia associated with diabetes in 2001-02, was 25,277 (AIHW 2004).² In 1998 almost 64,000 Australians had a disability caused by diabetes (AIHW 2002).

There is currently a lack of reliable incidence and prevalence data for diabetes in Australia. Estimates for the age-standardised prevalence of Type-1 diabetes for 1999-2000 was 298 per 100,000 or approximately 37,000 individuals over the age of 25 years (AIHW 2002). Since 1999, the National Diabetes Register (NDR) has collected information on the number of new users of insulin. There were 4,548 new cases of Type-1 diabetes, aged 0-39 years, for the years 1999-2001, 50 per cent of these cases were children aged 0-14 years (Table 1). The most recent data on the incidence of childhood diabetes in Australia for the years 2000-2001 indicate an incidence of 20.3 and 18.9 per 100,000 for males and females, respectively (Table 2) (AIHW 2003).

Table 1 New insulin users with Type-1 diabetes, 1999-2001

Age at first use of insulin	Males		Females		Persons	
	Number	Per cent	Number	Per cent	Number	Per cent
0-14	1207	46.7	1092	55.7	2299	50.5
15-24	570	22	389	19.8	959	21.1
25-39	810	31.3	480	24.5	1290	28.4
Total	2587	100	1961	100	4548	100

Source: AIHW 2003

Table 2 New cases of Type-1 diabetes amongst 0-14 year olds, 2000-2001

Age at first use of insulin	Males	Females
0-4	14.2	11.4
5-9	20.1	21.2
10-14	26.4	23.6
Total	20.3	18.9

Source: AIHW 2003

¹ Total population in Australia was 20,122,416 as at June 16, 2004. Source: Australian Bureau of Statistics.

² 2,538, 5,418 and 17,321 for the Australian Refined- Diagnosis Related Group numbers K01Z, K60A and K60B, respectively.

Of the 21,346 new insulin users registered on the NDR for the years 1999-2001, 12,167 (57%) suffered from Type-2 diabetes. The majority (90%) of these patients were aged over 35 years (AIHW 2003). The prevalence of Type-2 diabetes is increasing and has been associated with obesity, poor nutrition and physical inactivity. The Australian population prevalence of Type-2 diabetes is approximately 7 per cent (Table 3). The prevalence of Type-2 diabetes is comparatively higher in the indigenous population (Table 4) (AIHW 2002).

Table 3 Prevalence of persons with Type-2 diabetes, 1999-2000

Age (years)	Males (%)	Females (%)	Persons (%)
25-34	0.1	0.1	0.1
35-44	2.4	1.9	2.1
45-54	6	5.2	5.6
55-64	16	9.9	13
65-74	21.2	15.5	18.1
75+	20.9	24.4	23
Total	7.6	6.7	7.2

Source: AIHW 2002

Table 4 Prevalence of self-reported diabetes in Indigenous vs Non-Indigenous persons^a

Age (years)	Indigenous (%)	Non-Indigenous (%)
15-24	14.2	11.4
25-44	20.1	21.2
45-54	26.4	23.6
55+	20.3	18.9

^a Includes both Type-1 and Type-2, but 98-99 % of diabetes is thought to be Type-2

Source: AIHW 2002

The burden of diabetes in New Zealand is similar to the Australian situation but proportional to the total population.³ The estimated incidence of Type-1 juvenile diabetes was 25.8 cases per 100,000 persons aged up to 19 years in 2001.⁴ The New Zealand National Health Survey estimated the prevalence of known diabetes (including gestational, Type-1 and Type-2 diabetes) in persons aged over 15 years in the year 2000 was 111,273. In this survey, the highest prevalence of diabetes occurred amongst Maori (8.3%) and Pacific Island (8.1%) New Zealanders, with Asians and Others (4%) and New Zealanders of European origin (3.1%) having comparatively lower rates.

There were 41,243 hospital admissions in 1998/99 for people with diabetes recorded as any diagnosis in the New Zealand national hospital database

³ Total population in New Zealand was 4,058,921 as at June 16, 2004. Source: Statistics New Zealand.

⁴ Lipid and Diabetes Research Group, Christchurch Hospital, New Zealand.

(NMDS). Diabetes may not have caused or contributed to many of these admissions, but there were 3,580 admissions with diabetes as the primary diagnosis. Utilisation studies suggest that about 5% of inpatient costs are the result of diabetes, and this equates to approximately \$80 million annually.⁵

Stage of development

GlucoWatch[®] G2 Biographer is currently unavailable in Australia or New Zealand and is only available overseas on a prescription basis. However some individuals in Australia have accessed this technology via overseas contacts and it is likely that demand from parent groups will see this technology introduced. The primary users of this technology would be children with Type-1 diabetes, however many adults may wish to use GlucoWatch[®] G2 Biographer as a management tool.

Treatment Alternatives

Existing comparators

The optimal method for assessing long-term glycaemic control is the measurement of blood glucose levels, which can be obtained by a general practitioner requesting, at least twice a year, a glycosylated haemoglobin test. Haemoglobin combines with blood glucose to form glycosylated haemoglobin or HbA1c. When plasma glucose is consistently elevated there is a corresponding increase in levels of HbA1c stored in erythrocytes. Due to the 120 day life span of erythrocytes, the levels of HbA1c will reflect the glycaemic history of the patient over the past 2-3 months. HbA1c levels determined by high-performance liquid chromatography (HPLC) is the standard reference for glycosylated haemoglobin measurements. Levels of HbA1c should mirror to a certain extent glucose levels determined by self-monitoring of blood glucose (SMBG). When measured by HPLC, a HbA1c level of 6 per cent approximates a plasma glucose level of 6.6 mmol/L or 120 mg/dL. A 1 per cent rise in the HbA1c level equates to a 1.7 mmol/L or 30 mg/dL increase in the mean glucose level (Braunwald et al 2001; FDA 2002). The normal average value for preprandial glucose is <5.5 mmol/L, with an ideal range of 4.4-6.7 mmol/L (Braunwald et al 2001). Glycaemic targets for children and adolescents are given in Table 5 (Pacaud et al 2003). Patient action should be taken for values <4.4 or >7.8 mmol/L. Similarly the normal average value for bedtime glucose is <6.1 mmol/L, with an ideal range of 5.5-7.8 mmol/L, with action required if values are <5.5 or >8.8 mmol/L. Hypoglycaemia and hyperglycaemia may be defined as plasma glucose levels of <2.5 mmol/L and 28 mmol/L, respectively. However these levels may vary with symptoms and physiologic responses (Braunwald et al 2001).

⁵ Source: From NZ Ministry of Health, Health Funding Authority (2000). Diabetes 2000. Wellington, New Zealand.

Table 5 Glycaemic targets for children and adolescents

Age (years)	HbA1c (%)	Pre-prandial plasma glucose (mmol/L)	Considerations
<5	≤ 9	6-12	Extreme caution is required to avoid severe hypoglycaemia due to the risk of cognitive impairment in this age group
5-12	≤ 8	4-10	Targets should be graduated to the child's age
13-18	≤ 7	4-7	Appropriate for most patients
	≤ 6	4-6	Consider for patients in whom these targets can be achieved safely

The current gold standard for SMBG for use by the patient in the home is the glucose meter, which is a small, portable battery operated device. There are currently more than 25 different brands of commercially available glucose meters, including Accu-Chek[®] Advantage[®] (Roche Diagnostic), One Touch[®] (LifeScan Inc) and Accutrend[®] DM (Boehringer Mannheim). SMBG is recommended for all people with diabetes, but especially for those treated with insulin. It is recommended that patients with Type-1 diabetes test glucose levels three or more times per day. SMBG plans may recommend testing glucose levels before all meals, two hours after meals and before retiring for the night. To test glucose levels patients should wash hands thoroughly to remove any trace of glucose and reduce risk of infection, prick the fingertip with a lancet and hold the finger until a large droplet of blood forms. The droplet of blood is placed onto a test strip, which is then inserted into the glucose meter. The test strip is coated with glucose oxidase, which then converts any glucose present in the blood to hydrogen peroxide. A dye impregnated into the test strip combines with the hydrogen peroxide and, when placed into the glucose meter, will reflect light according to the amount of glucose present. Higher glucose concentrations will reflect less light. Glucose meters should be calibrated regularly using a standard glucose solution (FDA 2002).

All portable blood glucose meters measure the amount of glucose in whole blood. Glucose levels in plasma are generally 10-15 per cent higher than glucose measurements in whole blood. The results are displayed on a digital readout approximately 1-2 minutes after the test strip is placed into the meter. Glucose meters can detect glucose over the range 0-34 mmol/L. Many SMBG meters now give results as "plasma equivalent", using a built in algorithm, allowing comparison of home glucose measurements to those determined from plasma by HPLC (FDA 2002).

In addition, in 1999 the FDA approved the Continuous Glucose Monitoring System (CGMS) manufactured by Medtronic MiniMed Incorporated. This system consists of a disposable glucose sensor, which is inserted under the skin of the abdomen and designed to be worn for up to 72 hours. The sensor continuously measures glucose levels every five minutes from the interstitial fluid, which lies between the skin and muscle (Medtronic 2004; FDA 1999). Glucose in the interstitial fluid reacts with glucose oxidase on the sensor needle, producing hydrogen peroxide. This chemical reaction produces a small

current proportional to the amount of glucose present in the sample (McGahan 2002). The sensor is connected to a monitor the size of a pager, which is worn externally by the patient. Glucose readings are stored in the monitor's memory, which may be downloaded at a later date. The monitor is designed to sound an alarm when glucose readings fall out of range of set hypo- and hyperglycaemic values. CGMS is not intended to replace finger-prick testing and is designed to supply information on trends in glucose levels, which may result in adjustment of therapy. The CGMS must be calibrated with a blood glucose reading from a conventional finger-prick test (Medtronic 2004; FDA 1999). The CGMS, which can detect glucose over the range 2.2-22.2 mmol/L, has a five year device life-expectancy (McGahan 2002).

Diagnostic Accuracy

GlucoWatch® G2 Biographer vs blood glucose monitoring

Eight studies compared GlucoWatch® G2 Biographer and blood glucose monitoring by standard means (Table 6). The majority of these studies reported findings on patients with Type-1 diabetes.

The study by Kulcu et al (2003) used data previously obtained by Tierney et al (2000 and 2001) to calculate the lag time between GlucoWatch® G2 Biographer and SBMG readings. The remaining seven studies (level 3b diagnostic evidence) reported on the agreement between blood glucose levels obtained by the gold standard of SBMG and glucose readings obtained by GlucoWatch® G2 Biographer. Two of these studies were conducted in a clinic setting, one in a home setting, one at a diabetic camp and two in both a clinic and home setting. In the clinic setting, the mean difference between glucose readings obtained by SBMG and GlucoWatch® G2 Biographer ranged from $-0.92 (\pm 2.48)$ to $0.23 (\pm 1.55)$ mmol/L, with the correlation coefficient ranging from $r=0.88 - 0.90$. In the home setting, the mean difference between glucose readings obtained by SBMG and GlucoWatch® G2 Biographer ranged from $-0.33 (\pm 2.06)$ to $0.26 (\pm 2.4)$ mmol/L, with the correlation coefficient ranging from $r=0.74 - 0.85$. This indicates a slightly greater variation in blood glucose readings for those patients using GlucoWatch® G2 Biographer at home. Lenzen et al (2002) reported no significant difference between glucose levels obtained with GlucoWatch® G2 Biographer and conventional blood glucose monitoring, however as this study was conducted on only five patients it is likely to be under powered.

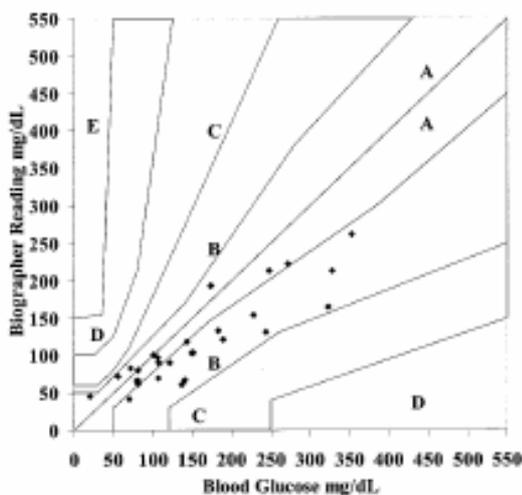


Figure 4 Consensus error grid (Gandrud et al 2004)

In addition, six of the studies utilised the Error Grid analysis method to evaluate the performance of the GlucoWatch® G2 Biographer (see Figure 4). Paired data points are placed in five categories, where regions A and B are considered clinically accurate or acceptable, regions C to E show increasing error and the possibility of adverse clinical outcomes (Clarke et al 1987). The number of paired data points falling into regions A+B for these six studies ranged from 94 to 97 per cent.

Table 6 GlucoWatch® G2 Biographer vs blood glucose monitoring

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Bozzetti et al (2003), Italy	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	74 Type-1 diabetic patients Mean age 18.5 years, range 7-25 years Study conducted in the home environment	Only 37/72 (51%) of patients were able to use GlucoWatch® G2 Biographer in the home environment successfully Median blood glucose levels 134 mg/dL (range 40-461 mg/dL) or 7.4 mmol/L (range 2.2 – 25.6 mmol/L) Median GlucoWatch® levels 112 mg/dL (range 37-437 mg/dL) or 6.2 mmol/L (range 2.0 – 24.3 mmol/L) Correlation coefficient ^a 0.74 Error grid analysis ^b Region (A+B) 95% Region (C+D) 5% Region E 0%
Eastman ^c et al (2002), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading ^d	66 Type-1 diabetic patients Mean age 11.9 ± 3 years, range 7-17 years Follow-up 12 hours Study conducted in a clinical environment	Biographer worn on Forearm (732 paired readings) Mean difference (mmol) -0.92 SD ^e 2.48 Mean relative difference (RD) -7.5% Mean absolute RD 21% Correlation coefficient 0.82 Upper arm (202 paired readings) Mean difference (mmol) -0.76 SD 2.52 Mean relative difference (RD) -5.4% Mean absolute RD 21.3% Correlation coefficient 0.76 Leg (229 paired readings) Mean difference (mmol) -0.87 SD 2.66 Mean relative difference (RD) -5.8% Mean absolute RD 21.8% Correlation coefficient 0.8 Torso (150 paired readings) Mean difference (mmol) -0.59 SD 2.54 Mean relative difference (RD) -4.3% Mean absolute RD 21.2% Correlation coefficient 0.82 Clarke error grid, % of paired readings in each region (1313 paired readings) Region A 58% Region B 36% Region C 0.4% Region D 5.6% Region E 0.1%

Gandrud et al (2004), USA	3b	Comparative study of controls vs GlucoWatch® G2 Biographer	<p>45 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer for a total of 45 nights</p> <p>Mean age 11.3 ± 2.2 years, range 7.1-17.2 years</p> <p>12 Type-1 diabetic controls</p> <p>Mean age 11.2 ± 3 years, range 7.4 -17.1 years</p> <p>Study conducted at a diabetic camp</p>	<p>Correlation between GlucoWatch® G2 Biographer readings taken</p> <p>10-20 mins after blood glucose meter readings, n=28</p> <p>Correlation coefficient 0.90</p> <p>20-30 mins after blood glucose meter readings</p> <p>Correlation coefficient 0.66</p> <p>0-10 mins before blood glucose meter readings</p> <p>Correlation coefficient 0.85</p>
Garg et al (1999), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	<p>28 Type-1 diabetic patients studied in a clinical environment, wearing 2 GlucoWatches®</p> <p>Mean age 30.9 ± 6.9 years, range 19-39 years</p> <p>12 Type-1 diabetic patients studied in the home environment,</p> <p>Mean age 32.2 ± 7.1 years, range 25-44 years</p>	<p>Clinic setting</p> <p>N=28, paired data points = 1,554</p> <p>Mean difference (mmol l⁻¹) 0.23</p> <p>SD (mmol l⁻¹) 1.55</p> <p>Mean absolute RD 14%</p> <p>Correlation coefficient 0.9</p> <p>Error grid analysis</p> <p>Region A 73.9%</p> <p>Region B 22.7%</p> <p>Region C 0.1%</p> <p>Region D 3.4%</p> <p>Region E 0%</p> <p>Home setting</p> <p>N=12, paired data points = 204</p> <p>Mean difference (mmol l⁻¹) -0.33</p> <p>SD (mmol l⁻¹) 2.06</p> <p>Mean absolute RD 19%</p> <p>Correlation coefficient 0.85</p> <p>Error grid analysis</p> <p>Region A 63%</p> <p>Region B 33%</p> <p>Region C 1.5%</p> <p>Region D 2.5%</p> <p>Region E 0%</p>
Kulcu ^f et al (2003), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	Same study populations as Tierney et al (2000) and (2001)	<p>Total lag time between GlucoWatch® G2 Biographer readings and blood glucose readings</p> <p>17.2 ± 7.2 minutes</p>

Lenzen et al (2002), United Kingdom	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	5 Type-1 diabetic patients studied in the home environment, Mean age 47 ± 7.8 years	No significant difference between SMBG and GlucoWatch® G2 Biographer readings (p< 0.44)																		
Tamada ^c et al (1999), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	92 patients with insulin dependent Type-1 or Type-2 diabetes Mean age 42.1 ±15.1 years Follow-up 15 hours Study conducted in a clinical environment	<table border="1"> <thead> <tr> <th>Glucose (mmol l⁻¹)</th> <th>ME ^g</th> <th>SD (mmol l⁻¹)</th> </tr> </thead> <tbody> <tr> <td>full range</td> <td>-0.07</td> <td>1.82</td> </tr> <tr> <td>≤ 3.9</td> <td>0.68</td> <td>0.97</td> </tr> <tr> <td>3.9-10</td> <td>-0.03</td> <td>1.36</td> </tr> <tr> <td>10-13.3</td> <td>-0.25</td> <td>2.42</td> </tr> <tr> <td>>13.3</td> <td>-0.35</td> <td>2.61</td> </tr> </tbody> </table> <p>MAE ^h 15.6% Correlation coefficient 0.88 Error grid analysis Region A 70% Region B 26.8% Region (C+D) 3.2% Region E 0% Total lag time between GlucoWatch® G2 Biographer readings and blood glucose readings 18 ± 10 minutes</p>	Glucose (mmol l ⁻¹)	ME ^g	SD (mmol l ⁻¹)	full range	-0.07	1.82	≤ 3.9	0.68	0.97	3.9-10	-0.03	1.36	10-13.3	-0.25	2.42	>13.3	-0.35	2.61
Glucose (mmol l ⁻¹)	ME ^g	SD (mmol l ⁻¹)																				
full range	-0.07	1.82																				
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10-13.3	-0.25	2.42																				
>13.3	-0.35	2.61																				
Tierney ^c et al (2001), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	<p>124 patients studied in the home environment, 74/124 (60%) were Type-1 and 50/124 (40%) were Type-2 diabetic, follow-up 5 days</p> <p>231 patients studied in a clinical environment, 151/231 (65%) Type-1 and 80/231 (35%) Type-2 diabetics, follow-up 1 day</p>	<p>Home environment N=124, paired data points = 2,996 Mean difference (mmol l⁻¹) 0.26 SD (mmol l⁻¹) 2.4 Mean relative difference (RD) 7% Mean absolute RD 21.3% Correlation coefficient 0.8 Error grid analysis Region (A+B) 94.2% Region (C+D) 5.7% Region E 0.1%</p> <p>Clinic environment N=213, paired data points = 6,909 Mean difference (mmol l⁻¹) -0.01 SD (mmol l⁻¹) 2.31 Mean relative difference (RD) 3.7% Mean absolute RD 19% Correlation coefficient 0.85 Error grid analysis Region (A+B) 95.3% Region (C+D) 4.7% Region E 0%</p>																		

^a correlation coefficient calculated using Deming regression, ^b Clarke and consensus error grids: regions A and B are considered clinically accurate or acceptable, regions C to E show increasing error with increasing possibility of adverse clinical outcomes, ^c Affiliated with Cygnus Inc., ^d blood glucose readings were obtained 20 ± 5 mins before GlucoWatch® G2 Biographer to adjust for 20 minute lag time, ^e SD = standard deviation, ^f study by Kulcu et al utilises data from the studies by Tierney 2000 and 2001, ^g ME = mean error, ^h MAE = mean absolute error

Hypoglycaemia

Two of the eleven studies reported on the diagnostic accuracy of the hypoglycaemic alarm function of the GlucoWatch® G2 Biographer device

(level 3b diagnostic evidence) (Table 7). Eastman et al (2002) reported a low positive predictive value of 26 per cent, which meant that for every 100 hypoglycaemic alerts, only 26 of the alerts were true hypoglycaemic events. Reassuringly, however, the negative predictive value was reported as 99 percent, meaning that for only one patient out of 100 who is actually hypoglycaemic, the alarm will fail to alert them. Tsalikian et al (2004) reported on 45 patients who underwent a controlled, induced hypoglycaemia test. Patients were infused with insulin and their blood glucose levels were monitored by GlucoWatch® G2 Biographer and conventional blood glucose monitoring. A false alarm rate for the device of 51 per cent and a sensitivity to detect hypoglycaemia of 23 per cent was reported under these clinical conditions.

Table 7 Hypoglycaemic alarm

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Eastman ^a et al (2002), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	66 Type-1 diabetic patients Mean age 11.9 ± 3 years, range 7-17 years Study conducted in a clinical environment Follow-up 12 hours	Detection of hypoglycaemia GlucoWatch® G2 Biographer worn on Forearm Diagnostic accuracy, area under the curve 0.92, 95%CI [0.89, 0.94] PPV ^b 26% NPV ^c 99% Alternative sites combined Diagnostic accuracy, area under the curve 0.89, 95%CI [0.86, 0.93] PPV 33% NPV 99%
Tsalikian et al (2004), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	89 Type-1 diabetic patients studied in a clinical environment, wearing 2 GlucoWatches® 45/89 (50%) took part in an induced hypoglycaemic test Mean age 9.9 years, range 3.5-17.7 years	Hypoglycaemic alarm set at ≤ 60mg/dL (3.3 mmol/L) 192/3672 (5%) of readings were ≤ 60mg/dL (3.3 mmol/L) Mean absolute difference 26 mg/dL (1.4 mmol/L) 31% of readings were within 15 mg/dL (0.8 mmol/L) of 60mg/dL (3.3 mmol/L) During induced hypoglycaemic test Sensitivity to detect hypoglycaemia = 23% False alarm rate = 51% Over night monitoring 16/89 (18%) reported 21 hypoglycaemic episodes ≤ 60mg/dL Hypoglycaemia was confirmed in 10/18 (56%) of cases 8/18 (44%) had glucose values between 75 – 108 mg/dL (4.2 – 6 mmol/L)

^a Affiliated with Cygnus Inc., ^b positive predictive value, ^c negative predictive value

Precision of GlucoWatch® G2 Biographer

Three of the eleven studies assessed the precision of GlucoWatch® G2 Biographer by comparing paired data readings from two synchronised biographers worn by patients simultaneously and calibrated against the same finger-prick blood glucose sample (Table 8). Results indicate that the coefficient of variation ranged from 8.4% to 10.3% for glucose values ≤ 5.56 mmol/L (100mg/dL) and from 5.2% to 6.3% for glucose levels above 13.3 mmol/L (240 mg/dL).

Table 8 Precision of GlucoWatch® G2 Biographer

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Garg et al (1999), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	28 Type-1 diabetic patients studied in a clinical environment, wearing 2 GlucoWatches® Mean age 30.9 ± 6.9 years, range 19-39 years 12 Type-1 diabetic patients studied in the home environment, Mean age 32.2 ± 7.1 years, range 25-44 years	n=36, wearing 2 biographers, number of paired readings = 1,063 Clinic setting Correlation coefficient ^a 0.94 Mean difference (SD ^b) between the 2 biographers 0.03 (1.16) mmol/L or 0.54 (20.9) mg/dL Glucose (mmol/L) CV% ^c ≤ 5.56 8.4 >13.33 5.2
Tamada ^d et al (1999), USA	3b	Patients own biological control, cross classification on GlucoWatch® G2 Biographer and blood glucose monitor reading	92 patients with insulin dependent Type-1 or Type-2 diabetes Mean age 42.1 ± 15.1 years Follow-up 15 hours Study conducted in a clinical environment	n=31, wearing 2 biographers Biographer 1 vs biographer 2 Correlation coefficient 0.93 Mean difference (SD) between the 2 biographers -0.04 (-1.34) mmol/L or -0.7 (24) mg/dL Glucose (mmol/L) CV% ≤ 5.56 8.4 >13.33 5.2

Tierney ^d et al (2001), USA	3b	Patients own biological control, cross classification on GlucoWatch [®] G2 Biographer and blood glucose monitor reading	124 patients studied in the home environment, 74/124 (60%) were Type-1 and 50/124 (40%) were Type-2 diabetic, follow-up 5 days	n=160, wearing 2 biographers number of paired readings = 3,531															
			231 patients studied in a clinical environment, 151/231 (65%) were Type-1 and 80/231 (35%) were Type-2 diabetic, follow-up 1 day																
				<table> <thead> <tr> <th>Glucose (mmol/L)</th> <th>CV%</th> <th>SD (mmol/L)</th> </tr> </thead> <tbody> <tr> <td>≤ 5.56</td> <td>10.3</td> <td>0.48</td> </tr> <tr> <td>5.56-10</td> <td>8.1</td> <td>0.63</td> </tr> <tr> <td>10-13.33</td> <td>7.4</td> <td>0.85</td> </tr> <tr> <td>>13.33</td> <td>6.3</td> <td>1.03</td> </tr> </tbody> </table>	Glucose (mmol/L)	CV%	SD (mmol/L)	≤ 5.56	10.3	0.48	5.56-10	8.1	0.63	10-13.33	7.4	0.85	>13.33	6.3	1.03
Glucose (mmol/L)	CV%	SD (mmol/L)																	
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10-13.33	7.4	0.85																	
>13.33	6.3	1.03																	

^a correlation coefficient calculated using Deming regression, ^b SD = standard deviation, ^c CV = coefficient of variation, ^d Affiliated with Cygnus Inc.

Utility of GlucoWatch[®] G2 Biographer

Seven of the eleven studies described the utility or ease of use of GlucoWatch[®] G2 Biographer (Table 9). Five of these studies reported on patients having difficulty, or being unable to successfully calibrate GlucoWatch[®] G2 Biographer, the critical step in the use of the device. The high quality study by Chase et al (2003) reported 954 unsuccessful GlucoWatch[®] G2 Biographer calibrations compared to 901 successful ones, over a three month intervention period in a home setting. Similarly, Bozetti et al (2003) reported in another home setting study, that 35/72 (49%) of patients were unable to use GlucoWatch[®] G2 Biographer. Two other studies reported that calibration was successful approximately 66 per cent of the occasions it was attempted.

Six of the studies reported on the number of missed data points. GlucoWatch[®] G2 Biographer is capable of recording 36 glucose readings in a 12 hour period. Each of the studies calculated the number of possible glucose readings and reported the number of missing data points. The high quality study by Chase et al (2003) reported 29 per cent of possible data points were skipped. Missed data points ranged from 10-46 per cent for studies conducted in a clinic setting and 35 per cent for home setting studies.

Common reasons for unsuccessful calibration or missed data points included excessive sweating, blood glucose level being out of range and changes in skin temperature. The study conducted in the diabetic camp for children (mean age 11 years) had a particularly poor success rate. Eighteen percent of biographers were removed prior to calibration, of those remaining only 66 per cent were successfully calibrated and of these only 37 and 19 per cent of females and males wore them for the entire night (mean length of wear 5.2 hours).

Table 9 Utility of GlucoWatch® G2 Biographer

Study	Population	Outcomes
Chase et al (2003), USA	20 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer. Mean age 11.9 ± 3.1 years, range 7-16 years Study conducted in the home environment	Difficulty with calibration During intervention phase there were 901 successful and 954 unsuccessful calibrations of the GlucoWatch® G2 Biographer 152/954 (16%) unsuccessful due to changes in skin temperature 76/954 (8%) unsuccessful due to blood glucose out of range 286/954 (30%) aborted calibrations were later successful Missed data points Average of 29% of readings were skipped in 3 months intervention phase
Bozzetti et al (2003), Italy	74 Type-1 diabetic patients Mean age 18.5 years, range 7-25 years Study conducted in the home environment	Difficulty with use 35/72 (49%) of patients were unable to use GlucoWatch® G2 Biographer in the home environment due to the following reasons: 13/35 (37%) experienced early shut off 4/35 (11%) suffered irritation 10/35 (29%) error in battery management 5/35 (14%) excessive sweating 3/35 (9%) difficulty with problem solving the device
Eastman ^a et al (2002), USA	66 Type-1 diabetic patients Mean age 11.9 ± 3 years, range 7-17 years Follow-up 12 hours Study conducted in a clinical environment	Missed data points GlucoWatch® G2 Biographer worn on Forearm 746/3132 (24%) of total possible 274/3132 (8.7%) due to early shut off 433/3132 (13.8%) skipped readings 39/3132 (1.2%) missing calibration value Alternative sites combined 1103/3060 (36%) of total possible 529/3060 (17%) due to early shut off 526/3060 (17%) skipped readings 48/3060 (1.6%) missing calibration value

<p>Gandrud et al (2004), USA</p>	<p>45 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer for a total of 45 nights</p> <p>Mean age 11.3 ± 2.2 years, range 7.1-17.2 years</p> <p>Study conducted at a diabetic camp</p>	<p>Difficulty with calibration</p> <p>18% (19% female, 17% male) of biographers were removed prior to calibration by user:</p> <p>9% of biographers worn by 7-9 years old were removed 22% of biographers worn by 10-11 years old were removed 44% of biographers worn by 12-14 years old were removed</p> <p>67% successful calibration in remaining wearers:</p> <p>67% for 7-9 years old 57% for 10-11 years old 70% for 12-14 years old</p> <p>Of those successfully calibrated, % of children that wore the biographer all night:</p> <p>37% of females 19% of males 38% of 7-9 years old 21% of 10-11 years old 0% of 12-14 years old</p> <p>Mean length of wear after calibration 5.2 hours</p> <p>Missed data points</p> <p>340/2507 (13.6%) of total possible 153/2507 (6%) due to early shut off 187/2507 (7.9%) skipped readings</p>
<p>Garg et al (1999), USA</p>	<p>28 Type-1 diabetic patients studied in a clinical environment</p> <p>Mean age 30.9 ± 6.9 years, range (19-39)</p> <p>12 Type-1 diabetic patients studied in the home environment,</p> <p>Mean age 32.2 ± 7.1 years, range 25-44 years</p>	<p>Clinic setting</p> <p>Missed data points</p> <p>174/1728 (10%) of total possible</p> <p>Home setting</p> <p>Missed data points</p> <p>104/308 (34%) of total possible</p>
<p>Lenzen et al (2002), United Kingdom</p>	<p>5 Type-1 diabetic patients studied in the home environment</p> <p>Mean age 47 ± 7.8 years</p>	<p>Difficulty with calibration</p> <p>Successful calibration 66%</p> <p>Of these, 49% were achieved at first attempt, 7% at second, 3% at third and 7% at fourth.</p> <p>Missed data points</p> <p>406/1168 (35%) of total possible 151/1168 (13%) due to error message 81/1168 (7%) due to unsatisfactory signal 81/1168 (7%) due to perspiration 70/1168 (6%) due to temperature change 23/1168 (2%) other</p>

<p>Tamada ^a et al (1999), USA</p>	<p>92 patients with insulin dependent Type-1 or Type-2 diabetes</p> <p>Mean age 42.1 ±15.1 years</p> <p>Follow-up 15 hours</p> <p>Study conducted in a clinical environment</p>	<p>Missed data points</p> <p>1263 total readings possible</p> <p>425/1263 (34%) skipped readings</p> <p>Of these skipped readings</p> <p>276/425 (65%) skipped due to data error caused by inconsistencies</p> <p>85/425 (20%) skipped due to excessive sweating</p> <p>68/425 (16%) skipped due to temperature change</p>
<p>Tierney ^a et al (2000), USA</p>	<p>18 Type-1 diabetic patients</p> <p>Mean age 30.4 years, range 19-42 years</p> <p>Study conducted in a clinical environment</p>	<p>Missed data points</p> <p>849/1836 (46%) of total possible</p> <p>32/1156 (2.8%) due to early shut off</p> <p>203/1156 (17.5%) skipped readings</p>

^a Affiliated with Cygnus Inc.

Effect of acetaminophen

The study by Tierney et al (2000) examined the effect of acetaminophen, or paracetamol, on glucose readings by GlucoWatch[®] G2 Biographer compared to standard blood glucose readings (Table 10). Acetaminophen may potentially interfere with the GlucoWatch[®] G2 Biographer biosensor due to its phenolic moiety, which is capable of being oxidised at the sensing electrode, producing an electrochemical signal other than that due to the glucose levels present. GlucoWatch[®] G2 Biographer and blood glucose readings were compared on day one. A 1,000 mg dose of acetaminophen (equivalent to two standard paracetamol tablets) was administered in Group 1 prior to calibration. Interference from acetaminophen would result in a faulty calibration of the GlucoWatch[®] G2 Biographer that would affect all subsequent readings. Group 2 were administered acetaminophen 2.5 hours after calibration. No effect of a therapeutic dose of acetaminophen was observed (Tierney et al 2000).

Table 10 Effect of acetaminophen ^a on glucose readings

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Tierney ^b et al (2000), USA	3b	Patients own biological control, cross classification on GlucoWatch [®] G2 Biographer and blood glucose monitor reading Effect of acetaminophen on the agreement between SMBG and GlucoWatch [®] G2 Biographer readings	18 Type-1 diabetic patients Mean age 30.4 years, range 19-42 years Study conducted in a clinical environment	<p>Day 1 (no acetaminophen) N=18, paired data points = 481</p> <p>Mean difference (mg/dL) 10.7 ^c Mean relative difference 12.5% Mean absolute RD 20.4% Correlation coefficient ^d 0.9 SD ^e (mg/dL) 25.6 ^c</p> <p>Error grid analysis Region (A+B) 93.1% Region (C+D) 6.9% Region E 0%</p> <p>Day 2 Group 1 (acetaminophen dose <i>pre-calibration</i> of GlucoWatch[®] G2 Biographer) N=9, paired data points = 264</p> <p>Mean difference (mg/dL) 11.8 ^c Mean relative difference 8.9% Mean absolute RD 16.3% Correlation coefficient 0.93 SD (mg/dL) 29.1 ^c</p> <p>Error grid analysis Region (A+B) 93.9% Region (C+D) 6.1% Region E 0%</p> <p>Day 2 Group 2 (acetaminophen dose 2.5 hours <i>post-calibration</i> of GlucoWatch[®] G2 Biographer) N=9, paired data points = 242</p> <p>Mean difference (mg/dL) 8.2 ^c Mean relative difference 10.5% Mean absolute RD 16.1% Correlation coefficient 0.93 SD (mg/dL) 22.7 ^c</p> <p>Error grid analysis Region (A+B) 95% Region (C+D) 5% Region E 0%</p>

^a acetaminophen = paracetamol, ^b Affiliated with Cygnus Inc., ^c values are in mg/dL, divide by 18 to get mmol/L equivalents, ^d correlation coefficient calculated using Deming regression, ^e SD = standard deviation, SMBG = self monitoring blood glucose

Effectiveness

Diabetic control

Only one study, a high quality randomised controlled trial by Chase et al (2003) (intervention level II evidence), monitored the HbA1c levels of 20 patients wearing a GlucoWatch® G2 Biographer for three months in the home setting (average wear 3.5 times per week) and 20 patients who experienced standard care alone (Table 11). This study reported that the HbA1c levels of the GlucoWatch® G2 Biographer patients were significantly lower (8.4%), which may indicate improved glycaemic control, than those patients using standard care alone (9.0%, $p < 0.05$), at the end of the three month intervention period.

Table 11 Diabetic control

Study	Level of evidence	Study design	Population	Outcomes
Chase et al (2003), USA	II	RCT	20 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer Mean age 11.9 ± 3.1 years, range (7-16) 20 Type-1 diabetic controls with standard care Mean age 11.9 ± 3.3 years, range (7-17) Study conducted in the home environment	Patients used biographer an average of 3.5 times per week Total readings 11,925 3.6% readings >300 mg/dL (16.7 mmol/L) 15.5% readings <70 mg/dL (3.9 mmol/L) HbA1c% (median) GlucoWatch® G2 Biographer Baseline 8.9 3 months 8.4 6 months 8.3 9 months 8.4 Control Baseline 8.6 3 months 9.0 6 months 8.5 9 months 8.6 At 3 months HbA1c was significantly lower in GlucoWatch® G2 Biographer compared to control $p < 0.05$, Wilcoxon Rank Sum test

RCT = randomised controlled trial

Quality of life

The high quality, level II study by Chase et al (2003) reported on the quality of life of patients wearing the GlucoWatch® G2 Biographer compared to those on standard care and found no difference between the two groups at the end of a three month intervention (Table 12).

Table 12 Quality of life

Study	Level of evidence	Study design	Population	Outcomes
Chase et al (2003), USA	II	RCT	<p>20 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer</p> <p>Mean age 11.9 ± 3.1 years, range (7-16)</p> <p>20 Type-1 diabetic controls with standard care</p> <p>Mean age 11.9 ± 3.3 years, range (7-17)</p> <p>Study conducted in the home environment</p>	<p>Fear of hypoglycaemia scores ^a at 3 months</p> <p>GlucoWatch® G2 Biographer 59.0 ± 14.3</p> <p>Control 56.4 ± 9.6</p> <p>DCCT ^b Quality of Life score ^a at 3 months</p> <p>GlucoWatch® G2 Biographer 81.3 ± 11.7</p> <p>Control 79.8 ± 15.5</p>

^a Both questionnaires are reliable and validated, ^b DCCT = Diabetes control and complications trial, RCT = randomised controlled trial

Safety

Hypoglycaemia

Two of the eleven studies reported on the hypoglycaemic alarm function of the GlucoWatch® G2 Biographer device compared to a control group (Table 13). However, Gandrud et al (2004) failed to report on the hypoglycaemic status of controls, reporting data only on patients wearing the GlucoWatch® G2 Biographer.

The high quality study by Chase et al (2003) (level II evidence), reported that hypoglycaemic events were detected significantly more often in the GlucoWatch® G2 Biographer intervention group than the control group ($p < 0.005$), and those patients wearing the GlucoWatch® G2 Biographer intermittently were able to detect hypoglycaemic events more easily even when not wearing the device ($p < 0.03$), which may reflect increased patient awareness of nocturnal hypoglycaemia resulting from the experience of wearing the GlucoWatch® G2 Biographer device. However, GlucoWatch® G2 Biographer was not able to detect all hypoglycaemic events, missing approximately 21 per cent of those events that actually occurred and were confirmed by conventional finger-prick testing. In addition, the proportion of readings below 70 mg/dL (3.9 mmol/L), and therefore in the hypoglycaemic range, increased over the course of the three month intervention, from 14.2 to 16.5 per cent of readings. The increase in hypoglycaemic readings may be due to a more aggressive approach to glycaemic management by the patients over the course of the intervention.

Gandrud et al (2004) reported 1/45 (2%) of children on a diabetic camp experienced the more serious safety concern of a non-arousable hypoglycaemic event, despite the hypoglycaemia alarm sounding (intervention level III-2 evidence). An unpublished study, not included in this assessment, reported in a letter to the Editor that the GlucoWatch® G2 Biographer hypoglycaemic alarm failed to alert the patient in the majority of cases, and 2/22 (9%) patients had severe hypoglycaemia with glucose values <30 mg/dL (1.7 mmol/L) (Iafusco et al 2004).

Table 13 Hypoglycaemic alarm

Study	Level of evidence	Study design	Population	Outcomes						
Chase et al (2003), USA	II	RCT	<p>20 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer</p> <p>Mean age 11.9 ± 3.1 years, range 7-16 years</p> <p>20 Type-1 diabetic controls with standard care</p> <p>Mean age 11.9 ± 3.3 years, range 7-17 years</p> <p>Study conducted in the home environment</p>	<p>Hypoglycaemia (≤70 mg/dL or 3.9 mmol/L)</p> <p>Detected more frequently in GlucoWatch® G2 Biographer compared to control group χ^2, p<0.0005</p> <p>There were 42 episodes of hypoglycaemia, 78.6% of these were registered by GlucoWatch® G2 Biographer</p> <p>Detected more frequently in GlucoWatch® G2 Biographer at night, compared to control group even when NOT wearing device χ^2, p<0.03</p> <p>Percent of GlucoWatch® G2 Biographer readings < 70mg/dL during intervention phase</p> <table border="0"> <tr> <td>Month 1</td> <td>14.2%</td> </tr> <tr> <td>Month 2</td> <td>16.6%</td> </tr> <tr> <td>Month 3</td> <td>16.5%</td> </tr> </table>	Month 1	14.2%	Month 2	16.6%	Month 3	16.5%
Month 1	14.2%									
Month 2	16.6%									
Month 3	16.5%									
Gandrud et al (2004), USA	III-2	Comparative study of controls vs GlucoWatch® G2 Biographer	<p>45 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer for a total of 45 nights</p> <p>Mean age 11.3 ± 2.2 years, range 7.1-17.2 years</p> <p>12 Type-1 diabetic controls</p> <p>Mean age 11.2 ± 3 years, range 7.4-17.1 years</p> <p>Study conducted at a diabetic camp</p>	<p>Hypoglycaemia alarm (set at 85 mg/dL or 4.7 mmol/L)</p> <p>188/1263 (15%) of readings recorded low glucose alarms</p> <p>20 of these low glucose alarms had corresponding low blood glucose readings</p> <p>10/20 (50%) were true positive alarms</p> <p>10/20 (50%) were false positive alarms</p> <p>1/45 (2%) children experienced a non-arousable hypoglycaemic attack (glucose 1.1 mmol/L) while GlucoWatch® G2 Biographer alarm was sounding</p>						

^a Affiliated with Cygnus Inc., ^b positive predictive value, ^c negative predictive value, RCT = randomised controlled trial

Erythema and oedema

The majority of studies reported that most patients experienced some degree of skin irritation, redness or oedema from wearing GlucoWatch® G2 Biographer, however only four studies recorded any significant reaction (intervention level IV evidence) (Table 14). The severity of erythema symptoms ranged from none or mild (85-99% of sites where GlucoWatch® G2 Biographer was placed) to severe (0.1% of sites). Rates for oedema were similar. In most cases symptoms were transient.

Table 14 Rates of erythema and oedema at GlucoWatch® G2 Biographer site

Study	Level of evidence	Study design	Population	Outcomes
Bozzetti et al (2003), Italy	IV	Case series	74 Type-1 diabetic patients Mean age 18.5 years, range 7-25 years Study conducted in the home environment	Of 44 patients who answered questionnaire, 34/44 (77%) reported skin irritation 4/35 (11%) of patients were unable to use GlucoWatch® G2 Biographer in the home environment due to irritation
Eastman ^a et al (2002), USA	IV	Case series	66 Type-1 diabetic patients Mean age 11.9 ± 3 years, range 7-17 years Follow-up 12 hours Study conducted in a clinical environment	Extraction site Erythema (redness of skin) None 34/102 (33%) of sites Mild 37/102 (66%) of sites Mod 1/102 (1%) of sites Oedema None 76/102 (75%) of sites Mild 34/102 (24%) of sites Mod 2/102 (2%) of sites Adhesive site Erythema (redness of skin) None 48/102 (47%) of sites Mild 48/102 (47%) of sites Mod 5/102 (5%) of sites Strong 1/102 (1%) Oedema None 81/102 (79%) of sites Mild 17/102 (17%) of sites Mod 4/102 (4%) of sites

Lenzen et al (2002), United Kingdom	IV	Case series	5 Type-1 diabetic patients studied in the home environment, Mean age 47 ± 7.8 years	<p>Erythema (redness of skin)</p> <p>Mild 1/5 (20%) Strong 3/5 (60%) Intense 1/5 (20%)</p> <p>Irritation</p> <p>None 1/5 (20%) Strong 3/5 (60%) Severe 1/5 (20%)</p> <p>Tingling</p> <p>None 1/5 (20%) Moderate 2/5 (40%) Strong 2/5 (40%)</p>
Tierney ^a et al (2001), USA	IV	Case series	<p>124 patients studied in the home environment, 74/124 (60%) were Type-1 and 50/124 (40%) were Type-2 diabetic, follow-up 5 days</p> <p>231 patients studied in a clinical environment, 151/231 (65%) were Type-1 and 80/231 (35%) were Type-2 diabetic, follow-up 1 day</p>	<p>Erythema (redness of skin)</p> <p>Score (0-4) ^b</p> <p>0 or 1 84.9% of sites 4 0.1% of sites</p> <p>Oedema</p> <p>0 or 1 83.4% of sites 3 1.2% of sites</p>

^a Affiliated with Cygnus Inc., ^b Draize skin scoring scale: 0 = none, 1 = mild, 3 = strong, 4 = intense. A score of 2 was not defined, and missing data were not supplied

Cost Analysis

Existing cost-effectiveness data

Eastman⁶ et al (2003) used a Monte Carlo simulation model to study the cost-effectiveness of the GlucoWatch[®] G2 Biographer based on patients enrolled in the randomised controlled trial described by Chase et al (2003) (Eastman et al 2003; Chase et al 2003). Patients (n=40, aged 7-17 years) were randomised to standard care (SMBG) or to wear GlucoWatch[®] G2 Biographer for four times per week. Follow-up was for three months, and subsequently all patients had access to GlucoWatch[®] G2 Biographer. This study was conducted in the United States so health costs to the patient will vary compared to those experienced by Australian patients. It was assumed that the same frequency of biographer usage would be required for the lifetime of the patient in order to achieve consistent lowering of HbA1c. The Monte Carlo model predicted that the use of GlucoWatch[®] G2 Biographer, if sustained for life, would delay the onset of the first serious complication of diabetes by 4.1 years. Treating 18 patients with GlucoWatch[®] G2 Biographer would prevent one case of blindness and 1.4 cases of renal failure. However, the validity of the model is questionable given that there are no long-term morbidity or mortality data reported in the study by Chase et al. The intervention costs US\$91,059 per year of life, US\$61,326 per quality adjust life year (QALY) and US\$9,930 per year free of major complication. If GlucoWatch[®] G2 Biographer ceased to be effective after 17 years of age, the cost per QALY would increase to US\$103,178 per QALY gained (Eastman et al 2003).

Simple costings

As stated previously, the GlucoWatch[®] G2 Biographer is not currently available in Australia. If purchased in either the United States or the United Kingdom the GlucoWatch[®] G2 Biographer would cost approximately A\$900 and a packet of 16 AutoSensors (one use only) is A\$130, or A\$8 each. A new AutoSensor is required for every 12 hours of monitoring (McGahan 2002). The GlucoWatch[®] G2 Biographer is designed to have an expected life time of at least four years when worn daily and stored and cared for according to the manufacturer's criteria (FDA 2001; Cygnus Inc 2003).

GlucoWatch[®] G2 Biographer may reduce the number of finger-prick blood glucose tests required but patients will still be required to purchase a blood glucose monitor and strips. A blood glucose monitor such as the Roche Diagnostic Accu-Chek Advantage 3 currently costs A\$70 and has a lifetime guarantee (Roche Diagnostics Australia Pty Limited). Newly diagnosed diabetic patients are issued with a National Diabetic Supply Scheme (NDSS) card. The NDSS is a Australian Government registration scheme, which provides a subsidy for blood glucose testing strips and free insulin syringes and free needles for insulin delivery pens. The NDSS does not provide a

⁶ Dr Richard Eastman is affiliated with Cygnus Incorporated

subsidy for blood glucose meters, lancets or lancet devices. By quoting their unique NDSS number, patients may order testing strips from their local diabetic association. Testing strips and lancets currently cost approximately A\$13 (packet 100) and A\$16 (packet of 200), respectively and would cost a total of approximately 64 cents per day if patients tested three times daily (personal communication, Diabetes South Australia).

Ethical Considerations

Informed Consent

Patients and the parents of patients offered GlucoWatch[®] G2 Biographer must be informed of the limitations of the device, in that GlucoWatch[®] G2 Biographer is *not* a replacement for conventional finger-prick testing, but would be offered as an adjunct to reduce the number of conventional tests required during the course of a day. GlucoWatch may be viewed as a de-medicalisation strategy, aimed at monitoring glucose levels in a less invasive manner and reducing the number of what may be stressful and painful invasive tests experienced by the patient. In addition patients must be informed of the potential harms associated with the device, such as gaining false reassurance from the hypoglycaemia alarm. The introduction of this technology would imply that follow-up strategies would be in place to monitor patients.

Access Issues

GlucoWatch[®] G2 Biographer may not be deemed necessary for glucose control by all patients, however many patients may find it an attractive option as part of their overall therapeutic management strategy. Due to the initial cost, the relatively short lifetime of the device and the ongoing costs of device replacement and AutoSensors for the life of the patient, it is unlikely to be available equitably to all Australians and differential access to GlucoWatch[®] G2 Biographer may occur.

GlucoWatch[®] G2 Biographer is currently unavailable in Australia, but may be purchased, on a prescription basis, from overseas. If introduced into the Australian health system, patients would be required to liaise with their current diabetic care provider, whether general practitioner, diabetic clinic, community nurse or the NDSS, to ensure that management of their diabetes is maintained at their current level. Currently in Australia, 6.6 per cent of people with diabetes live in large rural centres, 7.1 per cent in small rural centres, and 16.7 per cent in other rural areas and remote areas. Services for people with diabetes are limited in rural areas and the distribution of diabetes services products occurs through remote area pharmacy services rather than through the NDSS (AIHW 2002).

Training

Patients and/or parents of patients are required to be trained in the use of their GlucoWatch® G2 Biographer by their physicians. It should be emphasised to patients that GlucoWatch® G2 Biographer does not replace finger-prick glucose monitoring completely and is to be used only as an adjunct to standard care. Patients should be instructed to calibrate the GlucoWatch® G2 Biographer device correctly against a finger-prick glucose reading for each new sensor used. In addition, the low glucose alert should be set 1.1 to 1.7 mmol/L above the blood glucose level required to be detected (FDA 2001).

Clinical Guidelines

In Australia there are currently no clinical practice guidelines established for Type-1 diabetes. The Canadian Diabetes Association's clinical guidelines suggest that HbA1c levels should be tested every three months to ensure that glycaemic targets are being met and maintained. The frequency of SMBG should be determined individually based on the type of diabetes, the treatment prescribed and the individual's ability to use information from testing to modify medication or behaviour. For patients with Type-1 diabetes, performance of three or more tests per day is recommended. For patients with Type-2 diabetes the optimal frequency of SMBG remains unclear, however testing at least once per day is recommended. For people using insulin or oral anti-hyperglycaemic agents, SMBG before, during and, especially, for many hours after exercise is important for establishing response to exercise. This information should be used to make appropriate adjustments to exercise, medication or carbohydrate intake to avoid significant dysglycaemia (Brez 2003).

It is also recommended that patients with diabetes have access to timely and ongoing care from a diabetes team. This should include a doctor, nurse and dietitian with specific training and experience in the management of diabetes. Additional expertise, in podiatry, social work, behavioural psychology and counselling should be available as required, as should referral access to specialist services for the management of identified complications (Pacaud et al 2003).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological

advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of GlucoWatch® G2 Biographer, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The medical literature (Table 15) was searched utilising the search terms outlined in Table 16 to identify relevant studies and reviews, until April 2004. In addition, major international health assessment databases were searched.

Table 15 Literature sources utilised in assessment

Source	Location
<i>Electronic databases</i>	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsyInfo	University library
Web of Science – Science Citation Index Expanded	University library

<i>Internet</i>	
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hsat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html
Websites of Specialty Organisations	Dependent on technology topic area

Table 16 Search terms utilised

Search terms
MeSH Hypoglycemia, diabetes mellitus type I, blood glucose, blood glucose self- monitoring
Text words Hypoglycemia, hypoglycaemia, diabetes mellitus type I, blood glucose, blood glucose self- monitoring, glucowatch
Limits English

Availability and Level of Evidence

Eleven studies were included in this report to assess the safety, effectiveness and diagnostic accuracy of GlucoWatch® G2 Biographer for the non-invasive monitoring of glucose levels. Profiles of these studies are provided in Appendix A. Only one level II study reported on the effectiveness of GlucoWatch® G2 Biographer in terms of patient outcomes (Table 17). Six studies reported on safety outcomes of patients wearing GlucoWatch® G2 Biographer. Of these six studies, one study was level II, one was level III-2 and four were level IV evidence (Table 17). Ten of the eleven studies reported on diagnostic accuracy outcomes and provided level 3b diagnostic level of evidence (Table 18). Five of the eleven studies' authors were affiliated with Cygnus Incorporated, the company that manufactures GlucoWatch® G2 Biographer. Of the remaining six studies, two studies involved more than one co-author affiliated with Cygnus Inc. Of the eleven studies, only three were conducted in locations other than California, United States.

Table 17 Designations of levels of evidence ^a

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

^a Modified from (National Health and Medical Research Council 1999).

Table 18 Levels of evidence for assessing diagnostic accuracy ^a

Level of evidence	Study design
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Validating** cohort study with good† reference standards; or CDR tested within one clinical centre
1c	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of Level ≥2 diagnostic studies
2b	Exploratory** cohort study with good† reference standards; CDR after derivation, or validated only on split-sample§ or databases
2c	n/a
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

^a (Phillips et al 2001). SR = systematic review; CDR = clinical decision rule - these are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category; RCT = randomised controlled trial; n/a = not applicable. * Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a “-” at the end of their designated level. ** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. † Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. †† An “Absolute SpPin” is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An “Absolute SnNout” is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. § Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into “derivation” and “validation” samples.

Sources of Further Information

There are currently three randomised controlled trials involving GlucoWatch[®] G2 Biographer being conducted, two in the United Kingdom and one in the United States. The American study is a randomised controlled trial with 200 participants, aged 7-17 years. Equal numbers of participants have been randomised to either the GlucoWatch[®] G2 Biographer or standard care arm. Recruitment for the study began in July 2003 and participant numbers have been reached. Follow-up will be conducted at 3, 6, 9 and 12 months. The two British studies are both four arm randomised controlled trial, comparing GlucoWatch[®] G2 Biographer, standard care, increased clinical surveillance and the continuous glucose monitoring system, MiniMed. Both of these studies are currently recruiting participants and one is expected to end in late 2005. Outcome measures include changes in HbA1c, acceptability of the devices, number of hypoglycaemic events, adverse device events, change in quality of life and change in perception of diabetes.

Conclusions

GlucoWatch[®] G2 Biographer is a watch-like device, worn on the wrist, which is capable of sampling interstitial glucose levels continuously for 12 hours by a process called reverse iontophoresis. The amount of glucose extracted across the skin correlates with blood glucose levels with a lag time of approximately 20 minutes. GlucoWatch[®] G2 Biographer may be useful as a tool in the management of insulin dependent diabetes and night time monitoring of glucose levels, potentially preventing episodes of hypoglycaemia.

There are no long-term trials that assess the safety and effectiveness of GlucoWatch[®] G2 Biographer and the effect of continuous glucose monitoring on diabetes related morbidity or mortality. In addition, the numbers of patients enrolled in the studies included in this assessment are small considering the prevalence of insulin dependent Type-1 and Type-2 diabetes in Western populations, such as the United States. Of the studies included in this assessment, four were conducted in a clinical setting and two studies were conducted both in the clinic and home setting. Four studies were conducted either in a home or camp environment exclusively.

It appears that GlucoWatch[®] G2 Biographer is effective at lowering HbA1c levels, a marker for diabetic control, significantly when compared to patients on standard care alone (8.4% vs 9.0%, $p < 0.05$) (level II evidence). However, more long-term studies are required to ascertain if this effect is clinically significant. Level II evidence indicates that there was no effect on the quality of life of patients using GlucoWatch[®] G2 Biographer compared to those on standard care.

Level II evidence suggests that hypoglycaemic events were detected significantly more often in the GlucoWatch[®] G2 Biographer intervention group compared to the control group ($p < 0.005$). In addition, those patients wearing the GlucoWatch[®] G2 Biographer intermittently were able to detect

nocturnal hypoglycaemic events more easily even when *not* wearing the device, possibly due to increased awareness. However, GlucoWatch® G2 Biographer failed to achieve an improvement in glycaemic control as it did not detect approximately 21 per cent of all hypoglycaemic events that actually occurred. In addition, glycaemic control did not improve as the percent of readings below 70 mg/dL (3.9 mmol/L), and therefore in the hypoglycaemic range, increased over the course of the three month intervention from 14.2% to 16.5%. The increase in the number of hypoglycaemic readings may be due to a more aggressive approach to glycaemic control management by patients over the course of the intervention period.

The majority of available studies were concerned with the diagnostic accuracy of GlucoWatch® G2 Biographer (diagnostic level 3b evidence). These studies reported the correlation of GlucoWatch® G2 Biographer readings with blood glucose readings obtained from the same patient using conventional finger-prick blood glucose testing. Glucose readings obtained by conventional blood glucose testing and GlucoWatch® G2 Biographer correlated well in the clinical setting ($r= 0.88$ to 0.90) and the mean difference between readings ranged from $-0.92 (\pm 2.48)$ to $0.23 (\pm 1.55)$ mmol/L. One study conducted in the clinical setting reported the sensitivity for detecting hypoglycaemia was 23 per cent. Another study reported a positive predictive value of 26 per cent, indicating that for every 100 hypoglycaemic alerts, only 26 were true hypoglycaemic events. Readings obtained in the home setting did not correlate as well as those in the clinical setting ($r= 0.74 - 0.85$), however the mean difference between readings ranged from $-0.33 (\pm 2.06)$ to $0.26 (\pm 2.4)$ mmol/L.

Of concern are the number of unsuccessful calibration attempts, the critical step in the use of GlucoWatch® G2 Biographer, and the number of missed data points. Studies reported between 33 to 51 per cent of calibration attempts were unsuccessful. The number of missed data points ranged from 10 to 45 per cent of the number of potential data point readings possible. Common reasons for unsuccessful calibration and missed data points included excessive sweating, blood glucose reading being out of range and changes in the skin temperature, factors which are difficult to control.

The most serious safety concern is the one reported case of a child at a diabetic camp who experienced a non-arousable hypoglycaemic event, despite the hypoglycaemia alarm sounding (level III-2 evidence). Parents may reduce their vigilance and gain false reassurance from a device, which purports to have an alarm system.

A Monte Carlo simulation, conducted by an affiliate of Cygnus Incorporated, was used to model the cost effectiveness of GlucoWatch® G2 Biographer. The model predicted that the use of GlucoWatch® G2 Biographer, if sustained for life, would delay the onset of the first serious complication of diabetes by 4.1 years. Treating 18 patients with GlucoWatch® G2 Biographer would prevent one case of blindness and 1.4 cases of renal failure. However, the validity of the model used is questionable given that there are no long-term morbidity or mortality data reported in the study on which the model is based. The

intervention costs US\$91,059 per year of life, US\$61,326 per quality adjust life year (QALY) and US\$ 9,930 per year free of major complication. If GlucoWatch® G2 Biographer ceased to be effective after 17 years of age, the cost per QALY would increase to US\$103,178 per QALY gained.

Of serious concern is that five of the eleven studies' primary authors were affiliated directly with Cygnus Incorporated, the company that manufactures GlucoWatch® G2 Biographer and of the remaining six studies, two studies involved more than one co-author affiliated with Cygnus Inc. This may raise issues of conflict of interest.

In summary, GlucoWatch® G2 Biographer cannot replace conventional finger-prick blood glucose testing completely but may be a useful adjunct in the overall management of diabetes. GlucoWatch® G2 Biographer may be effective in the assessment of hypoglycaemic patterns, which may impact on long-term therapeutic decisions by a clinical management team.

Appendix A

Profiles of the studies included for assessment for the safety and effectiveness of GlucoWatch® G2 Biographer for the non-invasive monitoring of glucose levels in children.

Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
Chase, H.P. Roberts, M.D. Wightman, C. Klingensmith, G. Garg, S. ^a Van Wyhe, M.M. Desai, S. ^a Harper, W. ^a Lopatin, M. ^a Bartkowiak, M. ^a Tamada, J.A. ^a Eastman, R.C. ^a (2003)	California, USA	RCT	20 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer Mean age 11.9 ± 3.1 years, range (7-16) 20 Type-1 diabetic controls with standard care Mean age 11.9 ± 3.3 years, range (7 -17) Study conducted in the home environment	Median HbA1c Hypo- glycaemia Quality of life Missed data points	3 months intervention and 9 months follow-up
Bozzetti, V. Viscardi, M. Bonfanti, R. Azzinari, A. Meschi, F. Bognetti, E. Chiumello, G. (2003)	Milan, Italy	Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings	74 Type-1 diabetic patients Mean age 18.5 years, range 7-25 years Study conducted in the home environment	Agreement between SMBG and GlucoWatch® G2 Biographer readings Inability to use GlucoWatch® G2 Biographer	Did not state

<p>Eastman, R.C.^a Chase, H.P. Buckingham, B. et al (2002)</p>	<p>California, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>66 Type-1 diabetic patients Mean age 11.9 ± 3 years, range 7-17 years Study conducted in a clinical environment</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings Accuracy of hypoglycaemia alarm Number of missed data points Erythema and oedema</p>	<p>Follow-up 12 hours</p>
<p>Gandrud, L.M. Paguntalan, H.U. Van Wyhe, M.M.^a Kunselman, B.L. Leptien, A.D.^a Wilson, D.M. Eastman, R.C.^a Buckingham, B.A. (2004)</p>	<p>California, USA</p>	<p>Comparative study of controls vs GlucoWatch® G2 Biographer</p>	<p>45 Type-1 diabetic patients wearing GlucoWatch® G2 Biographer Mean age 11.3 ± 2.2 years, range (7.1-17.2) 12 Type-1 diabetic controls Mean age 11.2 ± 3 years, range (7.4 -17.1) Study conducted at a diabetic camp</p>	<p>Performance of GlucoWatch® G2 Biographer in the detection of hypoglycaemia Difficulty with device</p>	<p>45 campers wore the GlucoWatch® G2 Biographer for a total of 154 nights</p>
<p>Garg, S. Potts, R.O.^a Ackerman, N.R.^a Fermi, S.^a Tamada, J.A.^a Chase, H.P. (1999)</p>	<p>California, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>28 Type-1 diabetic patients studied in a clinical environment, wearing 2 GlucoWatch® G2 Biographers Mean age 30.9 ± 6.9 years, range (19-39) 12 Type-1 diabetic patients studied in the home environment, Mean age 32.2 ± 7.1 years, range (25-44)</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings Precision of GlucoWatch® G2 Biographer</p>	<p>Follow-up: multiple days Follow-up: 3 consecutive days</p>

<p>Kulcu, E.^{a,b} Tamada, J.A.^a Reach, G. Potts, R.O.^a Lesho, M.J.^a (2003)</p>	<p>California, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>Same study populations as Tierney et al (2000) and Tierney et al (2001)</p>	<p>Lag time between SMBG and GlucoWatch® G2 Biographer readings</p>	<p>Follow-up 1, 2 and 5 days</p>
<p>Lenzen, H. Barrow, B.A. White, S. Holman, R.R. (2002)</p>	<p>Oxford, United Kingdom</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>5 Type-1 diabetic patients studied in the home environment, Mean age 47 ± 7.8 years</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings Skin irritation Number of missed data points</p>	<p>Follow-up 3 weeks</p>
<p>Tamada, J.A.^a Garg, S. Jovanovic, L. Pitzer, K.R.^a Fermi, S.^a Potts, R.O.^a (1999)</p>	<p>California, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>92 patients with insulin dependent Type-1 or Type-2 diabetes Mean age 42.1 ±15.1 years Study conducted in a clinical environment</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings and lag time between readings Precision of GlucoWatch® G2 Biographer Number of missed data points</p>	<p>Follow-up 15 hours</p>
<p>Tierney, M.J.^a Garg, S. Ackerman, N.R. Fermi, S.J.^a Kennedy, J. Lopatin, M. Potts, R.O.^a Tamada, J.A.^a (2000)</p>	<p>California, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>18 Type-1 diabetic patients Mean age 30.4 years, range 19-42 years Study conducted in a clinical environment</p>	<p>Effect of acetaminophen^d on the agreement between SMBG and GlucoWatch® G2 Biographer readings Number of missed data points</p>	<p>Follow-up 2 days</p>

<p>Tierney, M.J.^a Tamada, J.A.^a Potts, R.O.^a Jovanovic, L. Garg, S. (Cygnus Research Team) (2001)</p>	<p>Multicentre, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and blood glucose monitor readings</p>	<p>124 patients studied in the home environment, 74/124 (60%) were Type-1 and 50/124 (40%) were Type-2 diabetic Mean age 46.5 ± 11.7 years</p> <p>231 patients studied in a clinical environment, 151/231 (65%) were Type-1 and 80/231 (35%) were Type-2 diabetic Mean age 48.2 ± 15 years</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings Precision of GlucoWatch® G2 Biographer Erythema and oedema</p>	<p>Follow-up 5 days</p> <p>Follow-up 1 day</p>
<p>Tsalikian, E. Beck, R.W. Tamborlane, W.V. Chase, H.P. Buckingham, B.A.^a Weinzimer, S.A. Mauras, N. Ruedy, K.J. Kollman, C. Xing, D. (2004)</p>	<p>Florida, USA</p>	<p>Cross classification of patients on GlucoWatch® G2 Biographer and CGMS^c and blood glucose monitor readings</p>	<p>89 Type-1 diabetic patients studied in a clinical environment, wearing 2 GlucoWatch® G2 Biographers 45/89 (50%) took part in an induced hypoglycaemic test Mean age 9.9 years, range 3.5-17.7 years</p>	<p>Agreement between SMBG and GlucoWatch® G2 Biographer readings before, during and after an induced hypoglycaemic test</p>	<p>Follow-up 24 hours</p>

^a Affiliated with Cygnus Inc., ^b study by Kulcu et al utilises data from the studies by Tierney 2000 and 2001, ^c CGMS = continuous glucose monitoring system, ^d acetaminophen = paracetamol, RCT = randomised controlled trial, SMBG = self monitored blood glucose, HbA1c = glycosylated haemoglobin

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