

# Subcutaneous Open-loop Insulin Delivery for Type 1 Diabetes: Paradigm<sup>®</sup> Real-Time System

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## Summary

- ✓ **An open-loop insulin delivery system combines an external insulin pump with continuous monitoring of glucose levels via a subcutaneous sensor. The sensor communicates glucose readings to the pump using a radio transmitter.**
- ✓ **In four small, comparative studies, adults and children with poorly controlled type 1 diabetes who were randomized to use the Paradigm<sup>®</sup> Real-Time System had clinically important improvements in A<sub>1c</sub> (a measure of average glycemic control over the previous three months) compared to baseline.**
- ✓ **Some studies found greater improvements in A<sub>1c</sub> and less hypoglycemia with the Paradigm Real-Time System compared to multiple daily insulin injections or pump therapy combined with conventional glucometer readings.**
- ✓ **Adverse events with the Paradigm Real-Time System include infection, itching, irritation, and redness at the site of the glucose sensor, and rare instances of insulin pump malfunction.**
- ✓ **Based on the limited amount of research published to date, the impact of the Paradigm Real-Time System on long-term glycemic control, prevention of diabetic complications, or quality of life is unclear.**

## Background

Diabetes mellitus is an endocrine disorder that affects more than 5% of the Canadian population.<sup>1</sup> It is characterized by hyperglycemia or high blood sugar. Type 1 diabetes accounts for about 10% of cases. In type 1 diabetes, the insulin-producing cells of the pancreas are destroyed.<sup>2</sup> As a result, individuals with type 1 diabetes need daily injections of insulin to survive. Without adequate control of blood glucose, symptoms of hyperglycemia (excessive thirst, excessive urination, and unexplained weight loss) are immediately

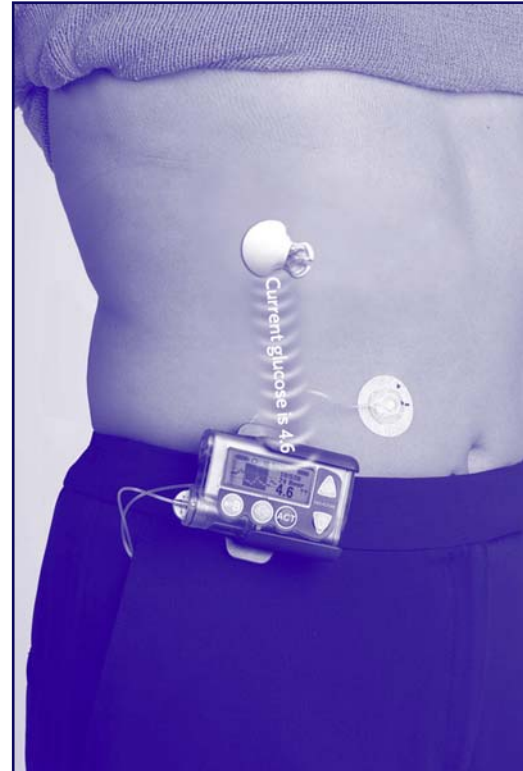


Image courtesy of Medtronic of Canada

*The Paradigm Real-Time System*

apparent. The long-term complications of chronic hyperglycemia include blindness, kidney disease, amputation, and cardiovascular disease.<sup>3</sup>

## The Technology

Open-loop insulin delivery systems combine insulin administration by continuous subcutaneous infusion and monitoring of glucose levels.<sup>4</sup> The Paradigm Real-Time System is an open-loop insulin delivery system that combines a Paradigm insulin pump with components of the Guardian<sup>®</sup> Real-Time Continuous Glucose Monitoring System.<sup>5</sup>

The insulin pump delivers basal infusion and meal-time bolus doses of insulin subcutaneously into the abdominal wall (continuous subcutaneous insulin infusion or CSII). The insulin is delivered using an infusion set (a flexible delivery cannula with a small needle on the end).<sup>6</sup> The insulin pump is about the size of a pager and can be worn on a belt. The continuous glucose monitoring system (CGMS) measures glucose in the interstitial fluid (the fluid that surrounds tissues) using a wire-like sensor

that is implanted subcutaneously into the abdomen.<sup>7</sup> The sensor tip reacts with the glucose in the interstitial fluid to generate an electrical current that is proportional to the glucose concentration. The current is converted to a glucose reading, based on external calibration from a blood glucose meter (glucometer).<sup>8</sup> The glucose concentration is measured every 10 seconds and averaged every five minutes. The sensor attaches to a wireless radio transmitter that communicates the average reading to the insulin pump unit up to 288 times per day.<sup>9</sup> The pump displays the reading, the direction of the glucose trend, and sounds alarms when high- or low-glucose values are detected. The pump can also calculate recommended insulin doses, which the patient can accept or modify.<sup>9</sup> Readings from the CGMS are not intended to be used to make therapy adjustments. A conventional glucometer reading is needed before making adjustments because there is a lag of up to 10 minutes in glucose concentration in the interstitial fluid relative to the concentration in the blood.<sup>7</sup> Furthermore, readings from the sensor may be less accurate in the hypoglycemic range.<sup>10</sup>

Combining continuous glucose readings with CSII has several advantages. An open-loop insulin delivery system could administer insulin in a manner more like that of a functioning pancreas.<sup>6</sup> This would allow tighter glycemic control, which has been shown to significantly reduce the risk of complications associated with diabetes.<sup>11</sup> Open-loop systems are an incremental step towards a fully closed-loop system, also known as an artificial pancreas, where insulin dosages would be automatically adjusted, rather than requiring patient input.<sup>7</sup>

## Regulatory Status

The Paradigm Real-Time System (Medtronic Minimed of Canada, Mississauga, ON) was licensed in Canada in July 2007.<sup>12</sup> Individual system components were already licensed here.<sup>12</sup> The Paradigm Real-Time System received US premarket approval in April 2006.<sup>5</sup> It is also available in Europe and Australia.

## Patient Group

It is estimated that less than 10% of all individuals with diabetes would benefit from pump therapy<sup>13,14</sup> and be candidates for open-loop insulin delivery. CSII is recommended for individuals with type 1 diabetes who fail to achieve adequate control of blood glucose using multiple doses of insulin and who have the motivation

and competence to use an insulin pump.<sup>13</sup> Continuous glucose monitoring may benefit those who have hypoglycemic unawareness, poor or variable control, or nocturnal hypoglycemia. Individuals who are pregnant, those with recurrent severe hypoglycemia, and individuals who adjust their medication dosages themselves may also benefit from using CGMS, with or without CSII.<sup>15</sup>

## Current Practice

The 2003 Canadian Diabetes Association (CDA) guidelines do not address the use of open-loop insulin delivery systems. They do, however, provide direction on the use of CSII and CGMS. The guidelines regard CSII as a safe and effective means of delivering intensive insulin therapy to adults and children, and state that CSII may have advantages over other means of intensive therapy.<sup>16</sup> Intensive insulin therapy with three to four daily injections or CSII should be considered to achieve glycemic targets in adults.<sup>16</sup> For children with type 1 diabetes, the guidelines state that consideration should be given to implementing CSII therapy for reasons relating to quality of life, or if two to three daily insulin injections fail to optimize metabolic control.<sup>16</sup>

The 2003 CDA guidelines for monitoring glycemic control state that there is insufficient evidence to support the widespread use of CGMS, but that it may provide useful clinical information. At that time, the available continuous glucose monitors did not provide real-time readings, but stored data that could be reviewed retrospectively. The guidelines recommend that individuals with type 1 diabetes test blood glucose at least three times daily when using conventional glucometers.<sup>16</sup> Furthermore, the guidelines state that testing before meals, at bedtime, and intermittently after meals and during the night can provide useful information for adjusting insulin dosages in intensive management with multiple daily injections of insulin (MDI) or CSII.<sup>16</sup> These guidelines are under review, and revised guidelines are expected in 2008.

## The Evidence

The Paradigm Real-Time System was evaluated in adults or children with poorly controlled type 1 diabetes and compared to MDI or CSII combined with conventional glucometer readings, also known as self-monitoring of blood glucose (SMBG) (Table 1).<sup>17-20</sup> Clinically important and statistically significant improvements in A<sub>1c</sub> from baseline were observed with the Paradigm Real-Time System. An improvement in A<sub>1c</sub> was also seen with either

MDI or CSII combined with SMBG. The magnitude of the change in  $A_{1c}$  from baseline to follow-up with the Paradigm Real-Time System was larger than that of the comparator in three of the four studies,<sup>17-19</sup> but one study did not report whether the difference was statistically significant.<sup>19</sup> Compliance with the use of the sensor appeared to be important in reaching the target<sup>20</sup> or in achieving a clinically significant decrease in  $A_{1c}$ .<sup>18</sup> Patient-reported outcomes with the Paradigm Real-Time System were also favourable.<sup>19</sup>

The generalizability of conclusions from the studies in Table 1 may be limited by small sample sizes, inclusion of inexperienced pump users, and selection of patients who had poor glycemic control at baseline. Furthermore, two studies may be reporting results from the same group of adolescents.<sup>18,20</sup> Achieving  $A_{1c}$  targets in diabetes requires motivation and strict adherence to self-care regimens, regardless of the technology used. The studies<sup>17-20</sup> did not evaluate whether the Paradigm Real-Time System improved adherence or increased the likelihood of reaching glycemic targets. Two larger phase IV randomized controlled trials are underway to compare the Paradigm Real-Time System to MDI in terms of change in  $A_{1c}$ , incidence and frequency of hypoglycemia, glucose variability, quality of life, and economic outcomes over six and 12 months.<sup>21,22</sup>

The Paradigm Real-Time System has also been evaluated in uncontrolled studies where improvements in glycemic control<sup>23</sup> and reductions in the number of symptomatic hypoglycemic episodes<sup>24</sup> compared to baseline were observed. The system was rated favourably for acceptability and ease of use.<sup>25</sup>

## Adverse Effects

The risks associated with CSII include hypoglycemia, diabetic ketoacidosis, rare instances of pump malfunction, needle or catheter occlusion, and infection.<sup>32</sup> The frequency of hypoglycemia and diabetic ketoacidosis with CSII is similar to that of MDI.<sup>32,33</sup> The most frequently reported adverse events with CGMS include itching or skin irritation, redness, bleeding, bruising, and discomfort at the site of sensor insertion.<sup>7,28</sup> Infections occur in approximately 1% of individuals.<sup>28</sup>

## Administration and Cost

Regular or fast-acting insulin is administered using a pump to maintain a basal level of insulin and deliver bolus doses when required.<sup>33</sup> Depending on the amount

of insulin needed, the pump's reservoir can hold up to six days' supply.<sup>33</sup> The infusion set for the insulin pump and the sensor for the CGMS must be replaced every three days, as indicated in the product labelling.<sup>4,7,33</sup>

The Paradigm Real-Time System, which costs approximately C\$7,500, is similar in price to the Paradigm 522 and 722 insulin pumps alone.<sup>9</sup> In addition, the pump accessories cost approximately C\$2,400 to \$3,000 annually.<sup>33</sup> This excludes the cost of the CGMS sensors and SMBG to calibrate the sensors. If sensors were worn daily and changed every three days,<sup>34</sup> 10 sensors would be used each month. This would make the cost of sensors about C\$5,700 annually. The use of sensors for a longer period (six days rather than three) is being investigated<sup>35</sup> and would reduce the annual cost of CGMS sensors by about one-half.

## Concurrent Developments

External subcutaneous closed-loop and implantable closed-loop systems are under development.<sup>36</sup> An implantable system would deliver insulin into the peritoneum. This is advantageous because rapid absorption and direct delivery to the hepatic circulation could occur.<sup>37</sup> Although less invasive, there is a delay in insulin absorption and action with the subcutaneous closed-loop system, which may limit its use.<sup>38</sup> The results from initial studies of subcutaneous and fully implantable closed-loop insulin delivery systems are promising.<sup>39-41</sup> The insulin pump component of the implantable closed-loop system is available in Europe.<sup>42</sup>

Islet cell transplantation, which replaces the non-functioning insulin-producing cells of the pancreas, has had initial success in achieving insulin independence for patients with type 1 diabetes, but insulin independence has not been sustained in the long term. This treatment is further limited by the availability of islet cells for transplant and by the requirement for lifelong immunosuppressive therapy after the procedure.<sup>43</sup> Islet cell neogenesis is also under investigation.<sup>14</sup>

## Rate of Technology Diffusion

Although open-loop insulin delivery systems may offer advantages over other approaches to insulin delivery and glucose monitoring, the uptake of this technology may be limited by several factors. First, unless public funding is available, the cost of the Paradigm Real-Time System and supplies may be prohibitive for most individuals.

**Table 1: Randomized studies of the Paradigm Real-Time System\***

Authors	Participants	Study Design	Outcomes
Lee <i>et al</i> , 2007 <sup>17</sup>	16 insulin pump-naïve adults with type 1 DM	15-week randomized study comparing the Paradigm Real-Time system (n=8) to MDI with SMBG (n=8)  All participants received an educational intervention	<b>Change in A<sub>1c</sub> from baseline:</b> Paradigm Real-Time System: 9.45 ± 0.55 at baseline to 7.4 ± 0.66 (p<0.001)  MDI with SMBG: 8.58 ± 1.30 at baseline to 7.5 ± 1.01 (p=0.04)  p-value for between-groups comparison: 0.02
Peyrot and Rubin, 2007 <sup>19</sup> (Abstract)	28 insulin pump-naïve adults with poorly controlled type 1 DM	16-week randomized study comparing an integrated Real-Time CGMS and CSII with the Paradigm 722 insulin pump (n=14) to MDI with SMBG (n=14)	<b>Change in A<sub>1c</sub> from baseline:</b> CSII and CGMS: -1.8% MDI with SMBG: -1.0% p-value for between-groups comparison: not reported  <b>Patient-reported outcomes:</b> CGMS and CSII group had greater improvements in ratings of satisfaction and more positive attitudes towards blood glucose monitoring and insulin delivery than with the MDI with SMBG group (p<0.05)
Buckingham <i>et al</i> , 2007 <sup>18</sup> (Abstract)	40 adolescents with poorly controlled type 1 DM who were experienced pump users	6-month randomized study comparing an integrated Real-Time CGMS and CSII with the Paradigm 722 insulin pump (n=20) to CSII with SMBG (n=20)	<b>Change in A<sub>1c</sub> from baseline:</b> CSII and CGMS: 8.8% at baseline to 8.0% (p=NS)  CSII and SMBG: 8.6% at baseline to 8.2% (p=NS)  p-value for between groups comparison: 0.01  <b>Hypoglycemia:</b> The difference in the number of severe hypoglycemic events was not statistically significant between groups  The CSII and CGMS group spent significantly less time in the hypoglycemic range at follow-up relative to the CSII and SMBG group (p<0.001)  <b>Hyperglycemia:</b> Differences between groups were not statistically significant at follow-up
Hirsch <i>et al</i> , 2007 <sup>20</sup> (Abstract)	98 adults and 40 adolescents with poorly controlled type 1 DM	6-month randomized study comparing an integrated Real-Time CGMS and CSII with the Paradigm 722 insulin pump to CSII with SMBG.†	<b>Change in A<sub>1c</sub> from baseline:</b> CSII and CGMS: 8.5% at baseline to 7.8% (p<0.001)  CSII and SMBG: 8.4% at baseline to 7.8% (p<0.001)  p-value for between groups comparison: NS  <b>Percent reaching A<sub>1c</sub>&lt;7.0%:</b> CSII and CGMS: 28% CSII and SMBG: 19% (p=0.02)  <b>Hypoglycemia:</b> The difference in the number of severe hypoglycemic events was not statistically significant between groups  CSII and CGMS group spent significantly less time in the hypoglycemic range at follow-up relative to the CSII and SMBG group (p<0.001)

CGMS=continuous glucose monitoring system; CSII= continuous subcutaneous insulin infusion; DM=diabetes mellitus; MDI= multiple daily injections; NS=not significant; SMBG=self-monitoring of blood glucose

\*Other studies were identified that used both CGMS and CSII, but the two technologies were not combined as an open-loop system because the CGMS sensor did not communicate with the insulin pump or the pump did not display real-time blood glucose readings<sup>26-31</sup>

† The sample size of each group was not reported

The Paradigm Real-Time System does not reduce or eliminate the need for SMBG, because metered blood glucose measurements must be used to calibrate the system at the time of insertion of a new sensor, as well as three to four times daily, and for insulin dose adjustment.<sup>7</sup> Thus, the CGMS creates additional monitoring costs, rather than substituting for SMBG. Evidence is still needed to show that open-loop insulin delivery can reduce other health care costs, such as those arising from emergency room visits, hospitalizations, and diabetic complications.

## Implementation Issues

To use open-loop systems effectively, individuals must be highly motivated to control their blood sugar, willing to assume control of daily care, understand how to use the pump, self-monitor appropriately, and know what to do with the data.<sup>44</sup> For some individuals, an open-loop insulin delivery system may be too demanding. It is recommended that CSII be prescribed, implemented, and followed by a team of health care providers who are skilled in this area and who can provide support to the user.<sup>44</sup> Such health care professionals are unavailable in some jurisdictions or health regions, although diabetes care delivered via telehealth could overcome this inequity in access to services. Recently available software allows patients to upload monitoring data for health care providers to access and analyze over the Internet. This innovation could provide a mechanism for remote monitoring of individuals who use continuous glucose monitoring systems.

## References

1. Health Canada. *Responding to the challenge of diabetes in Canada. First report of the National Diabetes Surveillance System (NDSS), 2003*. Ottawa: National Diabetes Surveillance System, Public Health Agency of Canada; 2003. Cat no H39-4/21-2003E. Available: [http://www.phac-aspc.gc.ca/ccdpc-cpcmc/ndss-snsd/english/pubs\\_reports/pdf/WEB\\_NDSS\\_English\\_Report-nocover.pdf](http://www.phac-aspc.gc.ca/ccdpc-cpcmc/ndss-snsd/english/pubs_reports/pdf/WEB_NDSS_English_Report-nocover.pdf)
2. Health Canada. *Diabetes in Canada*. 2nd ed. Ottawa: Health Canada; 2002. Available: [http://www.phac-aspc.gc.ca/publicat/dic-dac2/english/01cover\\_e.html](http://www.phac-aspc.gc.ca/publicat/dic-dac2/english/01cover_e.html)
3. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003;27(Suppl 2):ii-S152. Definition, classification and diagnosis of diabetes and other dysglycemic categories; p. S7-S10.
4. Combined insulin pump and continuous glucose monitoring system for diabetes management. In: *HTIAS Hotline Service* [database online]. Plymouth Meeting (PA): ECRI; 2006.
5. Paradigm real time system. In: *Premarket approval (PMA) database*. [database online]. Rockville (MD): U.S. Food and Drug Administration; 2007. Available: [http://www.accessdata.fda.gov/scripts/cdrh/cfdoc\\_s/cf/PMA/PMA.cfm?ID=9058](http://www.accessdata.fda.gov/scripts/cdrh/cfdoc_s/cf/PMA/PMA.cfm?ID=9058)
6. Pickup JC. Open- and closed-loop insulin delivery systems and glucose sensors. In: Sperling MA, editor. *Type 1 diabetes : etiology and treatment*. [Contemporary endocrinology]. 2003. p.233-47.
7. *Real-time continuous glucose monitoring*. [Target report 896]. Plymouth Meeting (PA): ECRI; 2007.
8. Weinzimer SA, et al. *Curr Diab Rep* 2004;4(2):95-100.
9. *The MiniMed Paradigm® REAL-Time insulin pump and continuous glucose monitoring system*. [brochure]. Mississauga (ON): Medtronic MiniMed of Canada; 2007.
10. Melki V, et al. *Diabetes Metab* 2006;32(2):123-9.
11. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329(14):977-86.
12. *Medical devices active license listing* [database online]. Ottawa: Medical Devices Bureau, Therapeutic Products Directorate, Health Canada; 2007. Available: <http://www.mdall.ca/>
13. Hammond P, et al. *Pract Diabetes Int* 2006;23(9):395-400.
14. *Closed-loop glucose management and insulin pump therapy for diabetes management*. [Health technology forecast]. Plymouth Meeting (PA): ECRI; 2005.
15. Wilson DM, et al. *Diabetes Technol Ther* 2005;7(5):788-91.
16. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003;27(Suppl 2):ii-S152.
17. Lee SW, et al. *Journal of Diabetes Science and Technology* 2007;1(3):400-4.
18. Buckingham B, et al. Presentation at American Diabetes Association 67 Scientific Sessions, 22-27 June 2007; 2007; Chicago. Available: [http://professional.diabetes.org/Abstracts\\_Display.aspx?TYP=1&CID=53936](http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=53936)
19. Peyrot P, Rubin, R.R. Presentation at American diabetes Association 67th Scientific Sessions 2007 June 22-26; 2007; Chicago. Available:

- [http://professional.diabetes.org/Abstracts\\_Display.aspx?TYP=1&CID=54169](http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=54169)
20. Hirsch IB, et al. Presentation at American Diabetes Association 67th Scientific Sessions 2007 June 22-26; 2007; Chicago. Available: [http://professional.diabetes.org/Abstracts\\_Display.aspx?TYP=1&CID=54079](http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=54079)
  21. Obtain a good blood glucose control with the Paradigm Real Time System (RTD). In: *Clinical trials*. [database online]. Bethesda (MD): U.S. National Library of Medicine; 2007. Available: <http://clinicaltrials.gov/show/NCT00441129>
  22. Study to compare the efficacy of the MiniMed Paradigm REAL-Time System vs. multiple daily injections in subjects naive to insulin pump therapy. In: *Clinical trials*. [database online]. Bethesda (MD): U.S. National Library of Medicine; 2007. Available: <http://clinicaltrials.gov/show/NCT00417989>
  23. Halvorson M, et al. *J Pediatr* 2007;150(1):103-5.
  24. Broz J, et al. *Diabetologia* 2006;49(Suppl 1):591-2.
  25. Danne T, et al. *Diabetes* 2006;55(Suppl 1):A194-A195.
  26. Guerci B, et al. *Diabetes Care* 2003;26(3):582-9.
  27. Deiss D, et al. *Pediatr Diabetes* 2004;5(3):117-21.
  28. Mastrototaro JJ, et al. *Adv Ther* 2006;23(5):725-32.
  29. Yates K, et al. *Diabetes Care* 2006;29(7):1512-7.
  30. Mastrototaro JJ, et al. *Diabetes Res Clin Pract* 2006;74(Suppl 2):S156-S159.
  31. Deiss D, et al. *Diabetes Care* 2006;29(12):2730-2.
  32. Weissberg-Benchell J, et al. *Diabetes Care* 2003;26(4):1079-87.
  33. Côté B, et al. *Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes*. Montreal: Agence d'évaluation des technologies et des modes d'intervention en santé; 2005.
  34. Transmitter supplies. *Medtronic MiniMed* 2004. Available: <http://www.minimed.ca/CanadaCategory.aspx?uid=165&CategoryLevel=2>
  35. Wong LG, et al. *Diabetes Technol Ther* 2006;8(2):139-145.
  36. Chia CW, et al. *Endocrinol Metab Clin North Am* 2004;33(1):175-95.
  37. Taylor MJ, et al. *Am J Drug Delivery* 2004;2(1):1-13.
  38. Hovorka R. *Diabet Med* 2006;23(1):1-12.
  39. Chee F, et al. *IEEE Trans Inf Technol Biomed* 2003;7(1):43-53.
  40. Steil GM, et al. *Diabetes* 2006;55(12):3344-50.
  41. Renard E, et al. *Diabetes Res Clin Pract* 2006;74(Suppl 2):S173-S177.
  42. Renard E, et al. *Diabetes Metab* 2007;33(2):158-66.
  43. Blue Cross and Blue Shield Association. *Islet transplantation in patients with Type 1 diabetes mellitus* [Evidence Report/Technology Assessment]. Rockville (MD): Agency for Healthcare Research and Quality; 2004. AHRQ Publication No. 04-E017-2. Available: <http://www.ahrq.gov/downloads/pub/evidence/pdf/islet/islet.pdf>
  44. Continuous subcutaneous insulin infusion. *Diabetes Care* 2003;26(Suppl 1):S125.

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