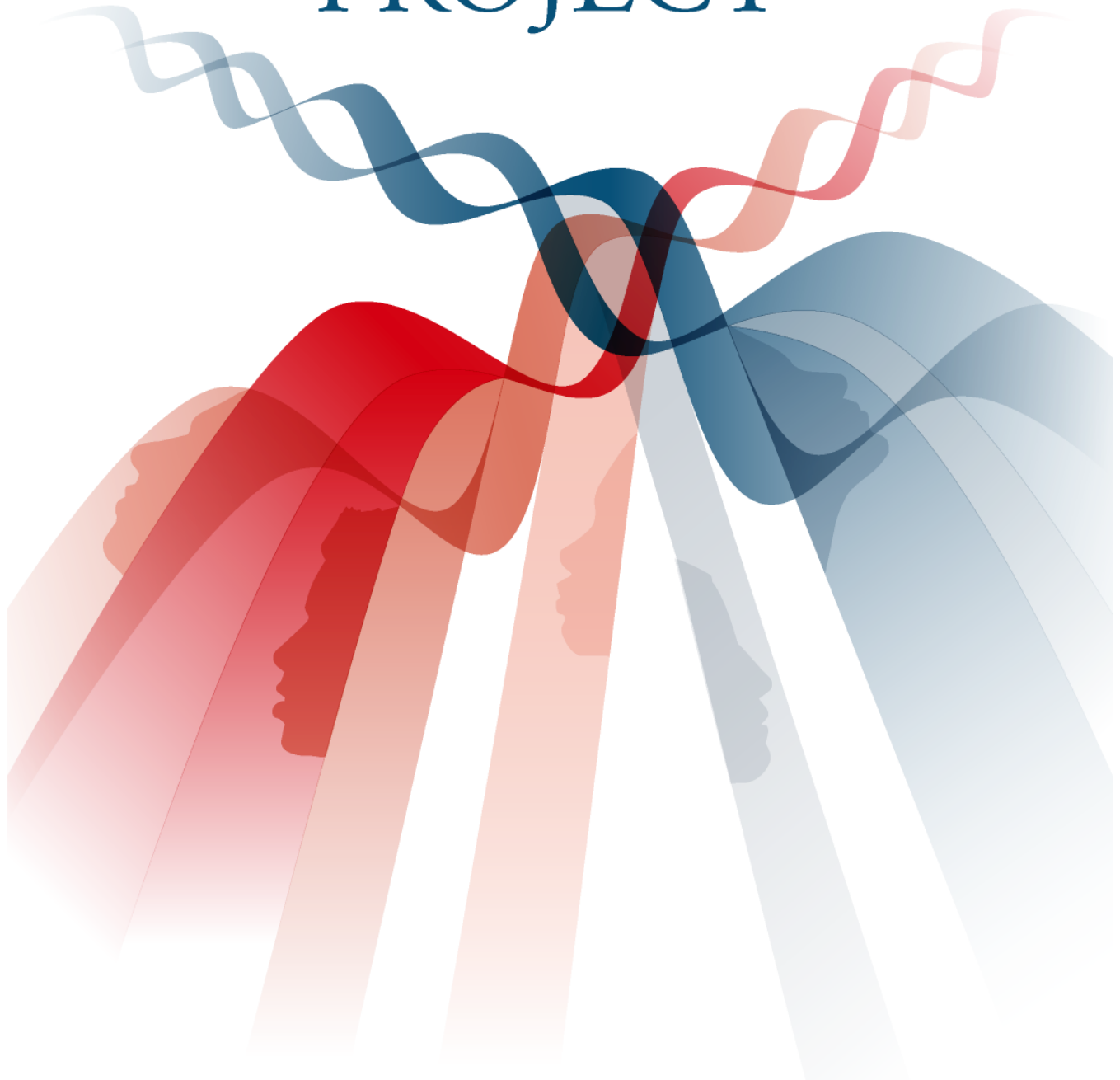


THE **DRA** Accelerating Disparity
Reducing Advances
PROJECT



**Report of the Automated Control of Insulin Levels
Committee**

September 2006 Report 06-05

Report of the Automated Control of Insulin Levels Committee

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Report of the Automated Control of Insulin Levels Committee

INTRODUCTION

The Biomonitoring Futures Project Advisory Committee at its April 2006 meeting identified the closed-loop insulin system as a promising area of focus as a Disparities Reducing Advance for further evaluation. A committee reviewed the current state of this technology and anticipated advances (see Appendix A, the background paper and Appendix B, the results of interviews, at the end of this report). Committee members and others provided input via telephone interviews. Their comments and subsequent review of the draft are the basis of this report.

NEED

There are an estimated 14.6 million Americans with diagnosed diabetes, of which almost 5.3 million are ethnic minorities. There are huge disparities in the treatment of those with diabetes. A key factor in reducing severe complications and resultant disability and death is aggressive management to keep blood glucose under control. For those with advanced disease on insulin this requires frequent finger sticks for blood glucose testing and possibly multiple insulin injections per day. A closed loop insulin delivery system (defined below) could facilitate better glucose control reducing the excess morbidity of poor, minority and underserved patients.

CONCEPT BACKGROUND

A closed-loop insulin delivery system has three major components. First there is a biomonitoring device that automatically checks the blood glucose level at appropriate intervals. This information is sent electronically to a small programmed computer that assesses the situation and determines when and how much insulin needs to be administered to keep blood sugar in good control. The third component is an insulin pump that is instructed to inject the right amount of insulin into the person's body.

External insulin pumps have been on the market for several years. The patient must insert a new special catheter under the skin in his abdomen about every three days and hook it to the pumping device that is usually worn on a belt. Pumps have become more sophisticated with a remote controller that can be programmed to give various doses of insulin at the users command. There are at least 400,000 people, almost all of them with type 1 diabetes, using these pumps rather than having to inject insulin multiple

times a day. Modern pumps cost over \$6,000 plus the consumable supplies, and most insurers reimburse most of the cost.

Continuous glucose monitoring systems have been recently approved for use. They require a catheter with an imbedded sensor to be inserted through the skin, which must be replaced every three days. The sensor wires are plugged into an external transmitter that is taped to the skin and wirelessly sends glucose data to a small computer data manager that displays and records the glucose readings. It also calculates the recommended dose of insulin to give. If the user consents, information is sent to the pump, which administers the precise amount of insulin to the patient. The sensor system with its consumable sensor, insertion and bandaging supplies are not covered by insurance and cost over \$4,000 a year.

This is a complicated system to use. The sensor and catheter sites must be kept sterile and bandaged. Finger stick blood glucose must be drawn at the time of new sensor insertion and 2-4 times a day while it is in place to calibrate the readings. Federal Food and Drug Administration has approved the system with the recommendation that the patient check a finger stick blood sugar before pushing a button approving the pump to administer the amount of insulin recommended by the data manager. Therefore, this is an “advise you” open loop system, not a fully automated “closed-loop” system.

There is a pump that can be surgically implanted (similar to a pacemaker) beneath the skin of the abdomen that contains a 3-month supply of insulin. A health professional can refill the reservoir by inserting a needle into the device. The batteries function up to 8 years. It is approved in Europe, but the special insulin for it is only approved in France so far. It is anticipated that the FDA will approve the implanted pump for use in the U.S. in 2-3 years. The pump is controlled wirelessly by an external controller, that could be combined with the external continuous glucose monitoring device mentioned above. The cost of the pump and surgical procedure for inserting it has not been determined, but is likely to be very expensive.

The eventual goal is to have a completely implanted “closed-loop” system that automatically checks glucose and administers the right amount of insulin so the patient does not have to think about managing his diabetes. This might be on the market within 10 years. The biggest hurdle is developing an implanted sensor that is durable and reliable. Safety is the other big issue – the software and total

system must be reliable with special controls so that a malfunction cannot over or under treat the patient with life-threatening consequences.

Reimbursement criteria of Medicare and other insurers for the current external insulin pump are strict. The appropriate patient almost always has type 1 diabetes requiring 4 or more finger sticks and 3 or more insulin injections a day. In spite of this amount of effort, the patient usually has a history of difficulty with control resulting in episodes of hypoglycemia. To successfully manage pump system complexity, the patient must be educated, understand diabetes well, be compulsive in controlling blood sugar levels, and be meticulous in details of sterility and checking device function.

Those who fit the above criteria tend to be satisfied with using the pump and find it gives them extra freedom in their lives while controlling their diabetes. Users have fewer episodes of hypoglycemia and manage to keep their glucose at a lower level. Clinical trials have not been done to determine long-term benefit in terms of reduced complications and premature deaths.

DIRECTION

With almost 200 million with diabetes world wide and about 400,000 patients currently on insulin pumps, there is sufficient market potential to spur further development, and at least 6 companies are selling devices in the U.S. Very short clinical trials have proven the concept of a closed-loop system, but the technology must catch up for long-term implantation. By 2015 there could well be an implanted closed-loop system on the market. It will likely take several years longer before it is clear when the device is a superior alternative to other advancing technologies.

OPPORTUNITIES

People interviewed saw the pump as useful for severe diabetics who were highly intelligent, well educated and committed. However, those who do not fit these criteria can be successfully managed by customary treatment. Most of the underserved population do not have the severity of disease, nor meet the educational level and compulsive meticulous management requirements for selection. In addition, there is the problem of high out-of-pocket expenses. The community health center internist on the committee could not think of any of his clinic's patients who would be appropriate candidates. Based on

the above, committee members did not see the current “advise you” open loop system as a worthy of a major DRA effort at this time.

Diabetes advocacy groups are working to get the continuous glucose monitoring system and its consumables covered by insurance. The cost of the devices and supplies is unlikely to drop in the foreseeable future because so much money is needed to improve the technology.

It is easy to imagine 10 – 20 years from now that patients will be implanted with a sophisticated device and then can forget about daily management of blood sugar. However, with all the other advances coming along it is unclear if there will be a big need for the closed-loop pump at that time.

- **RELATED IDEAS TO CONSIDER – mentioned in interviews**

1. All those with diabetes who have to monitor blood sugar would welcome non-invasive glucose monitoring devices that would not require a finger stick. Unfortunately, in spite of many researchers trying several different technologies, there does not appear to be a method likely to be ready for clinical trials anytime soon. Experts think it could well be 10 years before a successful device reaches the market.
2. Foster development of another kind of automated insulin control device with an intelligent digital manager directing an inhaled insulin device or recommending changes in dosage of oral medications or injected insulin.
3. Develop a CLIA-exempt, simple to use modular hemoglobin A1c device that could rapidly give the results of a finger stick or drawn blood sample at the point-of-care. Some of the machines available today can provide rapid (10 minute) results, but they still require venopuncture, and are time consuming. Community health centers and most other practice settings without a lab cannot get the A1c results in time to take action while the patient is being seen in clinic. It is harder than realized to track down some of these people to adjust their medications between visits. [Not researched to see if suitable devices are available now.]
4. Develop a polypill that contains genetic versions of 4 medications: (1) ACE inhibitor (protects kidneys and helps lower blood pressure), (2) statin (lowers cholesterol), (3) metformin (oral medicine lowering blood glucose) and (4) aspirin (beneficial for cardiovascular disease). Could such a pill be available for less than \$100 per year? Diabetics tend to have multiple chronic diseases and often take several pills a day. A polypill could improve compliance with better outcomes. However, individual patients require different dosages of each medicine to control their blood pressure, cholesterol and glucose so several standard formulations with different doses would likely be required.

RECOMMENDATIONS

5. Closed-loop insulin pump systems, non-invasive glucose monitors and other ideas of possible automated insulin control devices are not seen as realistic opportunities for accelerating advances for reducing disparities at this time. They are anticipated to take many years to reach the market and may not have an important role in the management of diabetes in the poor and underserved. There does not appear to be a way for DRA to significantly leverage their development in the near future, and there are much higher priority opportunities to pursue. Looking to the future, there is merit in periodically monitoring progress for reconsideration once a specific technology appears to be a winner.
6. Consider further committee research to evaluate the potential of a simple, fast point-of-care A1c testing device to see if a better model is needed for CHCs and doctors' offices.
7. Consider further committee research to evaluate whether a polypill for type 2 diabetes would be worthwhile in reducing disparities. If so what could DRA partners do to accelerate its development?
8. Consider further committee research to evaluate the status of noninvasive glucose monitoring device development to see if there are realistic opportunities for DRA to accelerate development for reducing disparities.
9. What are the true disparities in diabetes management and what are their magnitudes in relation to other disparities? What are the underlying root causes? What solutions to these disparities have been tried, and what has been their level of success? It would be valuable for the DRA project to have a better understanding of the answers to these questions. A literature review could uncover the data that exists and identify questions which need more research. This information could help DRA specifically focus its efforts on the most important disparities for diabetes and its comorbidities.

Appendix A

This background paper was developed to assist committee members in their deliberations.

Automated Control of Insulin Levels Committee Background Paper

Prepared by Bill Rowley, MD and Devin Fidler – July 2006

INTRODUCTION

The Biomonitoring Futures Project Advisory Committee recently recommended the closed-loop insulin system as a promising area of focus as a Disparities Reducing Advance. Given that certain minorities and the poor experience diabetes and its complications at higher rates, the capacity to control insulin levels more consistently could lower some diabetes related disparities. Big issues are (1) how often will a closed-loop system be clinically appropriate, (2) how often will cultural, life style and educational barriers limit its successful use and (3) what can be done to reduce the high initial and recurring costs to make it available to the underserved? For the DRA Project, the original concept has been broadened to “automated control of insulin levels” and a working group will consider the merits of this technological advance and the opportunities for accelerating its capacity to reduce health disparities. To aid the committee considering this issue, this background paper gathers the latest information of the current state of insulin pumps and monitoring systems, and integrates the preliminary findings from the DRA project’s focus group discussions of these advances with diabetic patients.

As discussed below, using rough estimates, potentially 650,000 type 1 patients and 200,000 type 2 patients in the US might benefit from automated insulin control. Among these there might be 212,000 type 1 and 79,000 type 2 patients who are members of minority and ethnic groups. These patients tend to have more severe disease and are more likely to experience healthcare disparities. There are important criteria for using automated insulin control that might disqualify poor or marginalized patients. These are reviewed below. The task of the DRA Project Committee on Automated Control of Insulin Levels is to consider whether the advances in this area are appropriate for reducing health disparities. If so, what aspects should be accelerated – from the perspectives of technology, usability, cultural appropriateness and reimbursement?

BACKGROUND

Almost all patients with type 1 and some with type 2 diabetes are totally dependent upon administered insulin. Due to dynamic changes in physical activity, nutrient intake, hepatic glucose output and insulin sensitivity, diabetics’ need for insulin continuously changes and adjustments in insulin dosing are necessary to minimize postprandial hyperglycemia and prevent episodes of hypoglycemia. There is considerable evidence showing that tight control of glucose reduces the microvascular-related complications of blindness, renal failure and lower extremity amputations. Also, tight glucose control combined with control of hypertension and dyslipidemias significantly reduces cardiovascular morbidity

and death. However, recent studies show patients, in reality, are euglycemic less than one-third of the time¹ and efforts at tight control result in many episodes of hypoglycemia.

The idea of an “artificial pancreas,” meaning a self-contained automatic glucose monitoring and insulin administration system is very appealing for these reasons. Conceived in the 1970s and available for patients since the 1990s, external insulin pumps are used by over 400,000 diabetics worldwide. Advantages of continuous subcutaneous insulin infusion (CSII) include better insulin pharmacokinetics, decreased variability in insulin absorption, reduced risk of nocturnal hypoglycemia, improved control of the dawn phenomenon, greater freedom in timing of meals, decreased risk of activity-induced hypoglycemia and convenience.²

However, insulin pumps are expensive, and their use requires good knowledge of diabetes, attention to detail and careful monitoring of activity and diet. They are best suited for those with severe type 1 diabetes requiring multiple insulin injections and many glucose checks daily. Successful insulin pump use resulting in high satisfaction is primarily confined to a group of knowledgeable, compulsive patients who meticulously attend to all aspects of diabetes management. The technology has reached the stage of an “advise you” open loop system with continuous glucose monitoring but still requiring user decision making for giving meal time boluses and adjusting baseline insulin. This is a challenging time for patients and healthcare providers because so much more information can be made available (e.g., glucose readings every 5 minutes) that proper dosing management must be refined through experience. The automatic closed-loop system is eagerly anticipated, but could take several more years before it is perfected and approved. A good all around reference on closed loop pumps is the article by Wayne L. Clark: “An Artificial Pancreas: How Close are we to Closing the Loop?”³

INFORMATION ON INSULIN PUMP SYSTEMS:

I. Appropriate Patients for Insulin Pump Use

Who are the appropriate patients in America for using the insulin pump? What are the numbers?

Prevalence of type 1 diabetes:

- A comprehensive study to estimate the number of patients with type 1 diabetes has not been done. Most experts feel about 5% of all those with diabetes are type 1 (5% of the total 14.6 million with diagnosed diabetes would be 730,000 patients). With the rapid growth in type 2 diabetes the actual percentage is likely lower.
- A low estimate is 1 in 800 or 340,000.⁴
- A high estimate is 3 million (over 20% of people with known diabetes).⁵
- These patients usually by the time they are discovered are totally dependent upon administered insulin

¹ Lewis J. Artificial pancreas: closer to an optimal treatment for diabetes? *Endocrine Today*, January 2006.

² Bode BW, Tamborlane WV, Davidson PC. Insulin pump therapy in the 21st century. *Postgraduate Medicine* 2002;111. http://postgradmed.com/issues/2002/05_02/bode3.htm (accessed 6/28/06).

³ Wayne L. Clark: An Artificial Pancreas: How Close are we to Closing the Loop?³ *JDRF Countdown Magazine*, Winter 2006. <http://www.jdrf.org/files/APP/Countdown%2006.pdf> (accessed 6/9/06).

⁴ Prevalence and Incidence of Type 1 Diabetes. <http://www.wrongdiagnosis.com/d/diab1/prevalence.htm> (accessed 6/15/06).

⁵ Insulin pump, glucose system is a significant step toward artificial pancreas technology. *Medical Devices & Surgical Technology Week*, May 16, 2006, p 355.

<http://www.jdrf.org/files/APP/MedicalDevicesweek%205%2016%2006.pdf> (accessed 6/28/06).

Prevalence of type 2 diabetes requiring insulin:

- Conventional wisdom is that at least 30% of those with type 2 diabetes will eventually require insulin.⁶
- 44% of the type 2 patients in the United Kingdom Prospective Diabetes Study (UKPDS) required insulin after 6 years.⁷
- About 10% - 20% of type 2 patients have Latent Autoimmune Diabetes of Adults (LADA) and 94% of them require insulin within 6 years versus 14% of patients without LADA⁸
- If 95% of the 14.6 million with known diabetes have type 2 there would be 13.87 million, and if 30% these were on insulin, then there would be 4.2 million insulin dependent people with type 2 diabetes.

Criteria for insulin pump use in type 2 diabetes:

- An article by Steven Wittlin⁹ recommends the following criteria of a successful pump candidate:
 - Monitor blood sugar at least 4 times daily
 - Learn to count carbohydrates
 - Have a “rescue algorithm” (how to respond to severe hypo or hyperglycemia)
 - Be sufficiently motivated
 - Have an appropriate support system
 - Possess problem-solving skills
- 2005 Criteria for Medicare insulin pump coverage (from Wittlin article):
 - Older patients must meet either criterion A or B and Medicare’s definition of diabetes (positive β -cell antibody test [evidence that they have LADA] or C-peptide criteria [gauge of how much insulin the body is producing])
 - Criterion A:
 - Require at least 3 injections of insulin a day
 - Make frequent self-adjustments of insulin for at least 6 months
 - Document need to self-monitor glucose at least 4 times a day for at least 2 months
 - Complete a diabetes education program
 - Meet one or more of following criteria:
 - Hemoglobin A1C > 7.0%
 - History of recurring hypoglycemic episodes
 - Wide fluctuations of blood glucose levels prior to meals
 - Experience the “dawn” phenomenon (fasting blood sugar > 200 mg/dL upon awakening in the morning)
 - History of severe glycemic excursions
 - Criterion B:
 - If using pump therapy prior to Medicare enrollment must document need to self-monitor glucose at least 4 times per day for month prior to enrollment

⁶ Margolis S. Insulin in Type 2 Diabetes. <http://healty-yahoo.com/experts/diabetes/13/insulin-in-type-2-diabetes> (accessed 6/9/2006).

⁷ UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

⁸ Wittlin SD. Treating the Spectrum of Type 2 Diabetes: Emphasis on Insulin Pump Therapy. *The Diabetes EDUCATOR* Jan/Feb 2006 Supplement, P39S-46S. <http://tde.sagepub.com/cgi/reprint/32/1/39S> (accessed 6/8/06).

⁹ Ibid.

- Have a positive β -cell antibody test

Candidates for pump use

- Using the criteria of at least 3 insulin injections a day, glucose monitoring about 4 times a day and challenges in controlling blood glucose, an estimated appropriate demand for the pump could be:
 - 80% of those with type 1 diabetes or about 650,000
 - 5% of those with type 2 diabetes on insulin or about 200,000
 - Total of about 850,000 with diabetes are candidates
- Considering the criteria for knowledge, problem-solving skills and motivation one might decide that 20% - 30% of potential users would not be ideal candidates at this time. Adding in the high cost and limited payer coverage would further reduce the candidate group. This could reduce the ideal candidate group to about 640,000.
- The industry estimates there are about 400,000 external pump users worldwide at this time. At least 200,000 are using one in the US with about 10,000 believed to be type 2 diabetes.¹⁰

Disparities considerations

- About 36% of the total number of people with diabetes is of a minority or ethnic group.¹¹ That would amount to almost 5.3 million with diagnosed diabetes. These patients tend to have more severe disease and are more likely to experience disparities. Possibly as many as 291,000 people with diabetes and disparities (212,000 with type 1 and 79,000 with type 2) might have disease severe enough to consider an insulin pump using back of the envelope calculations. Many of these would not be good candidates due to other factors mentioned above.

Components of the Closed Loop System:

II. Glucose Monitoring

What is the state of the current external system?

- ***Source of the sample?***

A sensor is implanted in the subcutaneous tissue using a specialized tool designed to minimize tissue damage. The tip of the sensor is made of a membrane selectively permeable to glucose. Once the glucose passes through the membrane, it is oxidized by the enzyme glucose oxidase. Reduced glucose oxidase can then be oxidized by reacting with molecular oxygen, forming hydrogen peroxide as a by-product. At the electrode surface, hydrogen peroxide is oxidized into water, generating a current which can be measured and correlated to the glucose concentration outside the membrane. This type of device requires at least 2 to 4 finger sticks per day for calibration because local inflammation can cause a drift of glucose levels surrounding the needle sensor.¹² However, with a lag time of approximately four minutes, it is more effective as a

¹⁰ Chait J. Insulin Pumps. 2006. <http://www.diabetesselfmanagement.com/article.cfm?aid=1844> (accessed 6/28/06).

¹¹ American Diabetes Association. Total Prevalence of Diabetes & Pre-diabetes. <http://www.diabetes.org/diabetes-statistics/prevalence.jsp> (accessed 6/15/06).

¹² Gabbay RA. New Developments in Home Glucose Monitoring: Minimizing the Pain. *Canadian Journal of Diabetes* 2003;27:271-276.

continuous glucose sensor than transcutaneous methodologies.¹³ The newest monitors give a glucose reading every 5 minutes and a new device must be inserted about every 3 days.¹⁴

The sensor is connected by wire to a pager-sized transmitter unit which records data that can later be downloaded onto a computer, and/or sent to the infusion pump. The transmitter can be used for about 9 months before its battery wears out, and then must be replaced.

- ***Emerging Technologies and Implanted Glucose Sensors?***

There are two thrusts to research into the further reduction of “biofouling” of the current subcutaneous glucose sensor. The first is the controlled release of drugs that prevent inflammation and inhibit fibrosis in favor of the growth of vascularized tissue that would not severely impair delivery of blood glucose to the sensor. The second technique has the same goal of promoting growth of vascularized tissue, but accomplishes this by modifying the sensor surface. These modifications can either involve adding certain functional groups to alter surface chemistry, or by controlling surface topography through processing in order to favor ingrowth of vascularized tissue.¹⁵ To date the implanted subcutaneous sensor is not satisfactory for long-term use as part of a closed-loop implanted system.

Although interstitial glucose levels are often an accurate indicator of blood glucose levels, the two can vary significantly at times, making the interpretation of such data difficult and potentially leading to insulin mismanagement. Because of this, there has been a recent movement toward intravenous continuous glucose sensing, employing free-floating enzymatic sensors placed in the blood stream. However, this requires a higher degree of biocompatibility because of the risk of thrombosis or embolism. This technology was incorporated into the Medtronic-MiniMed LTSS, a prototype artificial β -cell system used in the French clinical trials. The sensor itself was implanted into the superior vena cava via direct jugular access.¹⁶ This approach still is not perfected for complication-free long-term implantation.

Examples of other technologies being evaluated for implanted biosensors are a pill-shaped device that utilizes fluorescence and an infrared sensor device implanted across a small artery with emitting and receiving probes within the vessel.^{17 18}

- ***Continuous Readings?***

The MiniMed system takes measurements continuously and displays updated glucose values every five minutes.¹⁹ The sensor-transmitter wirelessly sends data to the continuous glucose

¹³ Muir A. New Technologies for Monitoring Metabolic Control of Diabetes in Children and Adolescents. Medscape July 17, 2003. <http://www.medscape.com/viewarticle/458390> (accessed 6/13/06).

¹⁴ About the Guardian RT Continuous Glucose Monitoring System. <http://www.minimed.com/professionals/guardianrt/index.html> (accessed 6/26/06).

¹⁵ Ibid

¹⁶ Renard E. Implantable closed-loop glucose-sensing and insulin delivery: the future for insulin pump therapy. Current Opinion in Pharmacology 2002;2:708 cited at http://biomed.brown.edu/Courses/BI108/BI108_2003_Groups/Diabetes_Technology/glucosesensing.htm (accessed 6/13/06).

¹⁷ Kretz AP, Styblo D. Toward Continuous Blood Glucose Monitoring. Medical Device & Diagnostic Industry 2003. <http://www.devicelink.com/mddi/archive/03/06/003.html> (accessed 6/21/06).

¹⁸ Animas Corporation: Implanted Infrared Sensor. http://www.diabetesnet.com/diabetes_technology/animas.php (accessed 6/21/06).

monitoring system which permits 24 hour monitoring and has automatic alarms warning the user if it detects serious hypo or hyperglycemia.

- ***Durability? –How often does it need to be reapplied?***

The MiniMed sensor system is worn for 3 consecutive days and cannot be reapplied should it malfunction or be removed prematurely. The sensor measures glucose in subcutaneous fluid every 10 seconds and stores the average of 30 measures obtained over 5 minutes. Continuous glucose monitoring system (CGMS) calibration requires that traditional blood glucose testing be performed at the time of application and throughout the test period. Four daily blood tests are recommended. Patients can improve the interpretation of their glucose trends by entering temporal markers for routine daily activities, e.g., eating, exercise, and insulin injection.²⁰

- ***Costs?***

The just released MiniMed Guardian CGMS glucose monitor component will cost about \$1,000 and includes 10 three-day sensors. Additional sensors cost \$35 each.²¹ Yearly costs for these components would be about \$4,300. Finger stick glucometer expenses would be additional.

III. Insulin Pumps

What is the status of the external insulin pump?

Manually controlled external insulin pumps have been on the market for several years. MiniMed's newest pump, the Paradigm Platform, has a list price of \$6,195 for the insulin pump components (without glucose monitoring component).²² The cost of the pump is usually covered by insurance (but not the cost of the disposable glucose sensors). There are a few other brands available (listed below).

What is the status of the implanted insulin pump?

- ***Has the FDA approved any implanted pump? Is it approved in Europe?***

The MiniMed 2007 implanted pump has received the CE mark for approval of sales in the European market, but commercialization is limited pending approval of the special U-400 insulin [already approved in France²³] used in the pump. It is controlled by an external hand held Personal Pump Communicator using RF telemetry. The user touches a few buttons to adjust continuous baseline insulin and give mealtime boluses. It is not a closed-loop system and the user makes decisions based on finger-stick or subcutaneous sensor glucose levels. The pump

¹⁹ Guardian RT Continuous Glucose Monitoring System.
<http://www.minimed.com/professionals/guardianrt/index.html> (accessed 6/26/06).

²⁰ Muir Op cit.

²¹ Manning A. Diabetics get high-tech help to track sugar. USA Today 5/21/2006.
http://www.usatoday.com/tech/news/techinnovations/2006-05-21-diabetes-monitoring_x.htm (accessed 6/13/06).

²² Frequently Asked Questions About the MiniMed Paradigm REAL-Time System.
<http://www.minimed.com/products/insulinpumps/faq.html> (accessed 6/28/06).

²³ D'Aquino R. Good Drug Therapy: It's Not Just the Molecule – IT's the Delivery. *Chemical Engineering Progress Magazine, Pharmaceutical Supplement*. Feb 2004:15S-17S.
<http://www.aiche.org/uploadedFiles/SBE/DepartmentUploads/GoodDrugTherapy.pdf> (accessed 6/13/06).

holds a 3 month supply of concentrated insulin and operates with a battery life up to 8 years.²⁴ Over 600 of the devices have been implanted worldwide.²⁵

- **Who is doing research and clinical trials of the implanted pump?**

[Dunn FL, Nathan DM, Scavini M, Selam JL, Wingrove TG.](#) Long-term therapy of IDDM with an implantable insulin pump. The Implantable Insulin Pump Trial Study Group. *Diabetes Care* 1997;20:59-63.

[Hanaire-Broutin H, Broussolle C, Jeandidier N, Renard E, Guerci B, Haardt MJ, Lassmann-Vague V.](#) Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM. A multicenter study. The EVADIAC Study Group. *Evaluation dans le Diabete du Traitement par Implants Actifs. Diabetes Care* 1995;18:388-92.

[Selam JL, Micossi P, Dunn FL, Nathan DM.](#) Clinical trial of programmable implantable insulin pump for type I diabetes. *Diabetes Care* 1992;15:877-85.

- **Any estimates of when implantable pumps will be available to the public in the US?**

Presently, MiniMed 2007 can be purchased only in France, the one country that has approved the use of U-400. Some expect FDA clearance for sale in America in the next 3-4 years²⁶

IV. Algorithms and automated decision system

- **What is a closed loop system or “artificial pancreas?”**

Future closed-loop systems are expected to continuously monitor glucose levels and automatically and continuously deliver the correct amount of insulin to the user to maintain blood glucose within an acceptable range. The ultimate goal is to mimic the human pancreas. In a closed-loop system, a continuous glucose monitor and an advanced mathematical algorithm are applied to an external or implantable insulin pump²⁷. The challenge is the lag time, particularly during meals. The system must first detect rising glucose and then respond by estimating and giving an appropriate amount of insulin. Since the insulin is injected subcutaneously, it takes time for it to be absorbed and act on the body. If the pump overshoots the needed insulin, there will be a period of hypoglycemia. A fully automatic system would require very sophisticated algorithms. To accomplish precise control the system may need the ability to administer both insulin and glucagon.²⁸ Future artificial pancreas systems may also incorporate physiological

²⁴ Patni P, Varghese D, Balekar N, Jain DK. Needle-free insulin drug delivery. *Indian J Pharm Sci* 2006;68:7-12. <http://www.ijpsonline.com/article.asp?issn=0250-474X;year=2006;volume=68;issue=1;spage=7;epage=12;aulast=Patni> (accessed 6/13/06).

²⁵ MiniMed Insulin Pump Therapy. <http://www.diabetic.com/MiniMed.htm> (accessed 6/13/06).

²⁶ D'Aquino. Op cit.

²⁷ Medtronic. Future Products.

http://wwwp.medtronic.com/Newsroom/LinkedItemDetails.do?itemId=1101850830145&itemType=backgrounder&lang=en_US (accessed 6/13/06).

²⁸ Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabetic Medicine* 2005;23:1-12.

sensors to determine onset of a meal, the level and duration of physical activity and the actual concentration of blood insulin to fine-tune decision-making.²⁹

- **Are any systems working as a closed loop now?**

No system is currently working as a closed loop outside of short-term research settings.

The newest external pumps can be attached to an **“advise you” open loop** automated decision system where the pump software calculates a recommended dose and the wearer must decide if it is appropriate and push a button for execution. FDA approval of the system requires that a finger stick glucose reading be done for confirmation before accepting the sensor glucose reading.

- **How are safety concerns addressed?**

As mentioned above, current automated open-loop decision systems require patient confirmation. Safety will be a major concern for future closed-loop systems and regulatory agencies will be very cautious in approving them. The glucose sensor system must have high reliability and likewise the pump must not malfunction and overdose the patient causing sudden severe hypoglycemia. There will be alarms and shut off mechanisms if any component is not functioning or if automatic dosing is outside selected parameters.

V. Evidence of Effectiveness

- **Is there evidence that patients using pumps are less likely to experience episodes of hypoglycemia?**

In a 1996 study, the incidence of severe hypoglycemia declined from 138 to 22 events per 100 patient-years during the 1st year of continuous subcutaneous insulin infusion (CSII) and remained significantly lower in years 2, 3, and 4 on CSII.³⁰ A meta-analysis of 52 studies covering 1,547 patients showed a decrease or similar number of hypoglycemic episodes using CSII versus multiple daily injections (MDI).³¹

Another article has opined that “one strategy for preventing hypoglycemia is to set a higher target blood glucose level. This is most easily accomplished with an insulin pump, using a lower basal insulin delivery rate and eliminating the wide glyceic swings that can occur with multiple daily injections. Blood glucose levels will be higher, and the patient will experience fewer episodes of hypoglycemia. For example, blood glucose levels can be targeted in the range of 120 to 180 mg/dl instead of 70 to 130 mg/dl. After six to eight weeks, the basal rate of the insulin pump can be increased, allowing the physician to lower the target blood glucose range so that it

²⁹ Lewis J. Op cit. <http://www.jdrf.org/files/APP/Endocrine%20Today%20AP%20Article%20Jan2006.pdf> (accessed 6/28/06).

³⁰ Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care*. 1996;19:324-237 Abstract. <http://care.diabetesjournals.org/cgi/content/abstract/19/4/324> (accessed 6/13/06).

³¹ Weissberg-Benchell J, Antisdel-Lomaglio J, Seshardi R. Insulin Pump Therapy. *Diabetes Care* 2003;26:1079-1087.

is closer to normal. However, hypoglycemic unawareness can recur in many patients using this technique.”³²

- ***Are long-term outcomes better with insulin pumps?***

The meta-analysis of 52 studies of adults, adolescents and children showed a decrease in HgA1c which improved over time, decreased hypoglycemia and diabetic ketoacidosis, decreased insulin given per day and weight loss in two-thirds of the studies reporting weight data.³³ Complications were minimal and patients were more satisfied with CSII than MDI. Multiple other studies have reported similar findings. It must be remembered that pump users are a subset of compulsive knowledgeable patients.

Better glucose control with lower HgA1c values should lead to reduced complications and premature deaths. However, longitudinal studies have not yet confirmed this. This longitudinal data will be important to convince payors of the cost effectiveness of covering consumables.

There is little data on the benefits of pump therapy for type 2 diabetes. Clear evidence of effectiveness in every day use for the average diabetic is essential before payors will consider expanding coverage to these patients.

- ***What is the market potential of insulin pumps?***

The annual worldwide market for conventional insulin pump products is approximately \$2.5 billion. In 2005 there were an estimated 400,000 insulin pump users and their number is growing by 12 - 14% per annum.³⁴

VI. Patient Costs?

- The external pump costs about \$6,000 with most insurers covering much of the cost under a Durable Medical Equipment clause.
 - The cost of an implanted pump will likely be much higher plus the cost of surgical implantation
- Monthly supplies include needle sets, insertion cannula, pump syringes, skin prep and sterile dressings, glucose sensors, insulin, etc. can cost \$250 - \$500+ per month depending upon the devices used. Continuous glucose sensors are not reimbursed by any health insurance at the present time.
- The Juvenile Diabetes Research Foundation (JDRF) and American Diabetes Association (ADA) are working to get reimbursement coverage from insurers, Medicare and Medicaid for devices and supplies.

VII. Who are the players?

- Continuous glucose monitor:
 - MiniMed – mentioned above

³² Unger J, Marcus AO. Insulin Pump Therapy: What You Need to Know. *Emergency Medicine* 2002;34:24-33. <http://mdchoice.com/emed/main.asp?template=0&page=detail&type=8&id=965> (accessed 6/13/06).

³³ Weissberg-Benchell J. Op cit.

³⁴ New generation of insulin pump. *Diabetes News* 19 Nov 2005. <http://www.medicalnewstoday.com/medicalnews.php?newsid=33847> (accessed 6/13/06).

- The DexCom STS Continuous Glucose Monitoring System – approved by the FDA in March. Retail price, \$800 (includes two sensors). Sensors and applicators come in bundles of five; each of the five sets provides up to three days of monitoring. Cost for five-pack: \$175.³⁵ Monthly cost would be \$350; yearly \$4200.
- Smiths Medical (under the brand Deltec CoZmonitor)
- Abbott's FreeStyle Navigator – awaiting FDA approval, will be waterproof, and the sensor patch can be worn five days. Pricing has not been announced.³⁶
- External insulin pump:
 - MiniMed – mentioned above
 - Disetronic Medical Systems ACCU-CHEK Spirit Insulin Pump System³⁷
 - Animas Corporation³⁸
 - Smiths Medical (under the brand Deltec Cozmo); pump and blood glucose module together are called the CozMore Insulin Technology System³⁹
 - Nipro Diabetes Systems
 - Insulet Corporation OmniPod is a small self-adhesive insulin pod that is worn directly on the body for 3 days, delivering insulin through a canula. It is controlled by the Personal Diabetes Manager (PDM) that wirelessly gives patient-controlled instructions to the pump. The PDM also incorporates a FreeStyle blood glucose meter for intermittent testing. The blood glucose results are integrated into the suggested bolus calculations. The PDM stores, displays and downloads glucose, insulin and entered carbohydrate history records.⁴⁰

OTHER OPTIONS TO CONSIDER:

I. Non-invasive glucose monitoring with wireless data collection and management software

At the present time essentially all diabetes patients being treated with insulin and many on oral therapy monitor their blood glucose with finger stick glucometers, often several times a day. Non-invasive glucose monitoring is another area of extensive research and development activity. Dozens of companies are trying several technologies hoping to create a successful commercial solution that avoids finger sticks. Within the next few years a technology is likely to succeed which is practical and accurate (but probably not inexpensive).

Non-invasive glucose monitoring will eliminate an important barrier to close monitoring and aggressive treatment of diabetes. This should dramatically improve compliance and reduce patients' HgA1c values with a marked reduction in long-term serious complications. For the 14.6 million with diagnosed diabetes in the US this will be a significant advance. (See IAF's paper – BFP #4 Biomonitoring Platform Assessment at www.alfutures.com/bfp for more details.)

What are examples of non-invasive glucose monitoring approaches and current efforts?

³⁵ Technology Overview: DexCom STS Continuous Glucose Monitoring System. http://www.dexcom.com/html/healthcare_professionals.html (accessed 6/28/06).

³⁶ Questions & Answers: FreeStyle Navigator Continuous Glucose Monitoring System. <http://abbottdiabetescare.com/freestylenavigator/qa.aspx> (accessed 6/28/06).

³⁷ Disetronic Infusion Systems. <http://disetronic.com/files/2.asp?menuId=2&languageId=2> (accessed 6/28/06).

³⁸ Animas Corporation IR 1250 Insulin Pump. http://animascorp.com/products/pr_ir1250_1.shtml (Accessed 6/28/06).

³⁹ CozMore Insulin Technology System. <http://www.cozmore.com> (accessed 6/28/06).

⁴⁰ The OmniPod System. <http://www.myomnipod.com/products/section/188> (accessed 6/28/06).

The only FDA approved non-invasive glucose monitoring device, the Gluowatch, was a market failure due to expense, inconvenience and limited clinical benefit.

Approaches currently being tested include:⁴¹

- Interstitial fluid drawn through the skin to a surface sensor patch. Iontophoresis, sonophoresis, infrared spectroscopy or a laser are used to create the porosity and draw the fluid to the sensor.
- Infrared analysis of glucose in eye scleral capillaries and near-infrared spectroscopy through the skin.
- Photonic crystal color shift sensing contact lens detecting level of glucose in eye tear fluid that changes color depending upon glucose concentration.
- A tattoo that changes color depending upon glucose concentration.
- Radiomolecular magnetics for measuring biochemistries.

It appears that all these technologies have a long way to go before they are ready for clinical trials and FDA approval. However, if a technology turns out to give reliable accurate results and can be packed into a practical device, it could come to the market quite fast.

Marrying the non-invasive sensor to management software

Some current glucometers have incorporated management software or wirelessly download their readings to a computer or special management device. This would be an expected capability of a non-invasive glucose sensor. The management device would track readings, provide trend graphs and if algorithm software were included, it could recommend insulin or pill management choices. For most type 2 patients this may be a more realistic option than an insulin pump.

II. Semi-closed loop system with other insulin administration devices

A non-invasive glucose monitoring system with intelligent software could be combined with an insulin injector or inhaled insulin system to control dose administered. This is an alternative to the external or implanted insulin pump that may be satisfactory for managing less severe type 2 patients.

PATIENT INPUT ON AUTOMATED SYSTEMS

The DRA Project through its Biomonitoring Futures component, conducted focus groups with patients and providers in Orlando, Galveston and Detroit. The participants were presented with forecasts for systems that took automated glucose readings, integrated into inhaled insulin with calibrated dosing; and for closed loop implantable pumps. Most would welcome advances that eliminated the need for needle sticks. Most also would welcome reliably automated insulin dosing. They raised concerns about reliability, cost of the equipment use and replacement issues. Some patients have difficulty affording current test strips. Others were not trusting in the relevance of using automated systems. Others live in situations where it would be difficult to meet the criteria set out above.

⁴¹ Mendosa D. Part 14: Blood Glucose Meters. <http://www.mendosa.com/meters.htm> (accessed 6/21/06).

SUMMARY

- There may be at least 640,000 who good candidates for the insulin pump. It is an especially useful advance for many type 1 patients whose glucose control is difficult to manage and require several injections of insulin and glucose checks a day. It is still unclear when the pump is beneficial for type 2 patients.
- The technology has come a long way with an integrated system that continuously monitors glucose, a management system with algorithms providing advice on amount of insulin required and an external pump injecting insulin through a subcutaneous canula. This “advise you” open loop system dramatically increases the complexity of management. It has beneficial for those dedicated to its use, but it is unclear when it should be used.
- Diabetes experts feel current pumps (with or without continuous glucose monitoring) are best used by those who are knowledgeable, very meticulous in their diabetes management and accept fact that the system requires a lot of attention. These people value the benefits of the pump. Others do not desire using a pump system and get about the same satisfactory results with multiple daily injections as they would by trying to manage a pump.
- Controlled studies on the benefits of insulin pumps and continuous glucose monitoring are still needed to demonstrate a clear benefit over other aggressive therapeutic options. This applies to both type 1 and type 2 patients.
- The current integrated system is very expensive – up to \$7,500 a year for the disposable sensors, canulas and insulin plus the cost of the pump. It requires insertion of new glucose sensors and insulin canulas every 3 days or more often and attention to detail in safely keeping all the components functioning properly. Focused attention is also required in adjusting and administering bolus insulin doses.
- Many insurers provide reimbursement for the pump. Diabetes advocacy groups (JDRF & ADA) are working hard to secure insurance and Medicaid coverage for the continuous glucose monitoring component with its expensive disposable components.
- Within the next 2-4 years, an implanted pump will be available that will allow more freedom, but at more expense and risk. It will work like the new external pumps and can be used with the independent subcutaneous glucose monitor. It will not be a closed-loop system.
- A completely “closed-loop” device is much more complicated and it remains to be seen how long it will take to develop a durable long-term implanted glucose monitor and acceptably precise and safe algorithm dosing system. It is possible that such a device could be on the market in 5-7 years if the technological barriers can be overcome, but most experts think 10 years or more is more realistic.
- With over 400,000 people worldwide currently using pumps and many more considering pump usage, there appear to be sufficient marketplace incentives to encourage technological advances. Our rough estimates suggest 650,000 in the US might benefit from these systems.
- With high volume use, the cost of the pump and disposable components could drop, but a lot of expensive research is still needed to refine glucose sensors, the closed-loop algorithms and

implantable systems. Competition and large payor negotiated purchases could eventually drive prices down.

- Studies showing that insulin pumps and continuous monitoring can be effective in better controlling HgA1c and preventing complications in a minority and underserved population might be valuable in making the case for improving access and reducing costs. At present there does not appear to be not much enthusiasm for using the pump in Community Health Clinics.
- Efforts at achieving a non-invasive glucose monitoring device are likely to be more valuable in improving diabetes care and outcomes than closed-loop pump technology at this time. A non-invasive monitor might dramatically reduce disparities for those with advanced diabetes. However, it appears that it could take 10 years before a successful noninvasive monitor is on the market.

Appendix B

Committee for Automated Control of Insulin Levels Results of Interviews

CLOSED LOOP INSULIN PUMP

- Current pumps with continuous glucose monitoring “advise you” open loop systems are expensive and complicated – There do not appear to be many appropriate candidates among the poor, ethnic minorities or underserved. Standard therapeutic approaches can adequately manage their diabetes.

Role for DRA?

- See little role for current insulin pumps in CHC setting – patients treated adequately without them (“not sure about all kids with type 1 diabetes, but we don’t see many”).
- The pump with continuous glucose monitoring is too complex and still requires multiple finger sticks. It is not suitable for the majority of poor, minorities and underserved. Also there is little data of long-term effectiveness, especially for type 2 diabetes.
- Do not see useful ways for the DRA project to leverage the development of closed-loop systems. The marketplace already has incentives to develop it, but the technology will likely take years to reach the marketplace.
- Maybe in distant future when implanted closed-loop pumps are well proven they will be of some value. However they are likely to be expensive and require a lot of expertise for some time after market introduction.

NONINVASIVE GLUCOSE TESTING

- There does not seem to be anything just around the corner. Ten years for something to reach the marketplace that is successful seems reasonable.
- Medical Automation Research Center of the University of Virginia is working on a noninvasive glucose monitor that wirelessly sends the data to a box that can store it or send it off via cell phone to health care providers. Won’t say much about it, but it may be implanted. Will take 5 or more likely 10 years to develop.

Role for DRA?

- Noninvasive glucose testing could have a role when it is available and inexpensive, but CHC patients rarely self-manage their diabetes. They come in with a log of glucose results and providers make the treatment decisions based on glucose trends plus the A1c.

POLYPILL

- Not sure if IP and large trials of effectiveness are barriers. The pills are all generic and efficacy well proven.
- Could an American generics company become interested or is this something for an Indian pharmaceutical company to develop?
- Would there need to be several doses? Standard doses of aspirin and statins are safe. However, people needed different doses to control their low density lipoprotein level. A low dose ACE

inhibitor helps prevent renal failure, but higher doses are needed for hypertension with some concern about side effects. Likewise, metformin dosage varies from 500 mg twice a day to up to a total of 2550 mg a day. Providing for all the combinations would defeat the purpose of a simple to use, once a day, inexpensive polypill.

- With the obesity and diabetes crises maybe CDC and NIH could get interested.
- The global TB drug collaboration with companies sharing some expertise and IP could be a model – they get some wins without too much effort (publicity, tax write offs, etc.)
- Working on genetic test to see if loop diuretic is appropriate for the patient

Role for DRA?

- Polypill has merit because many CHC patients are taking 10-15 pills a day. Based on combining 3 HIV pills into one, the cost did not go down. There would have to be different strengths of the medications for the pill to be tailored to the patient's needs.
- If further evaluation shows the polypill to be realistic in management of the average type 2 patient, DRA could play a role in helping encourage its development, trials and low cost availability.

ROLE FOR DRA – THINGS A COMMUNITY HEALTH CENTER COULD USE

- Electronic health records to remind us of all the evidence-based interventions that are required throughout the year on patients with multiple chronic diseases. Now we have a registry on one computer, but it would be nice if we could access the specific individual anytime anywhere with automatic prompts of actions to consider.
- Inexpensive handheld A1c testing device for use in clinics without a lab (point-of-care) and give quick results before the patient left the clinic. Need to make medication alterations then as it is hard to track these patients down if the result comes in a day later.