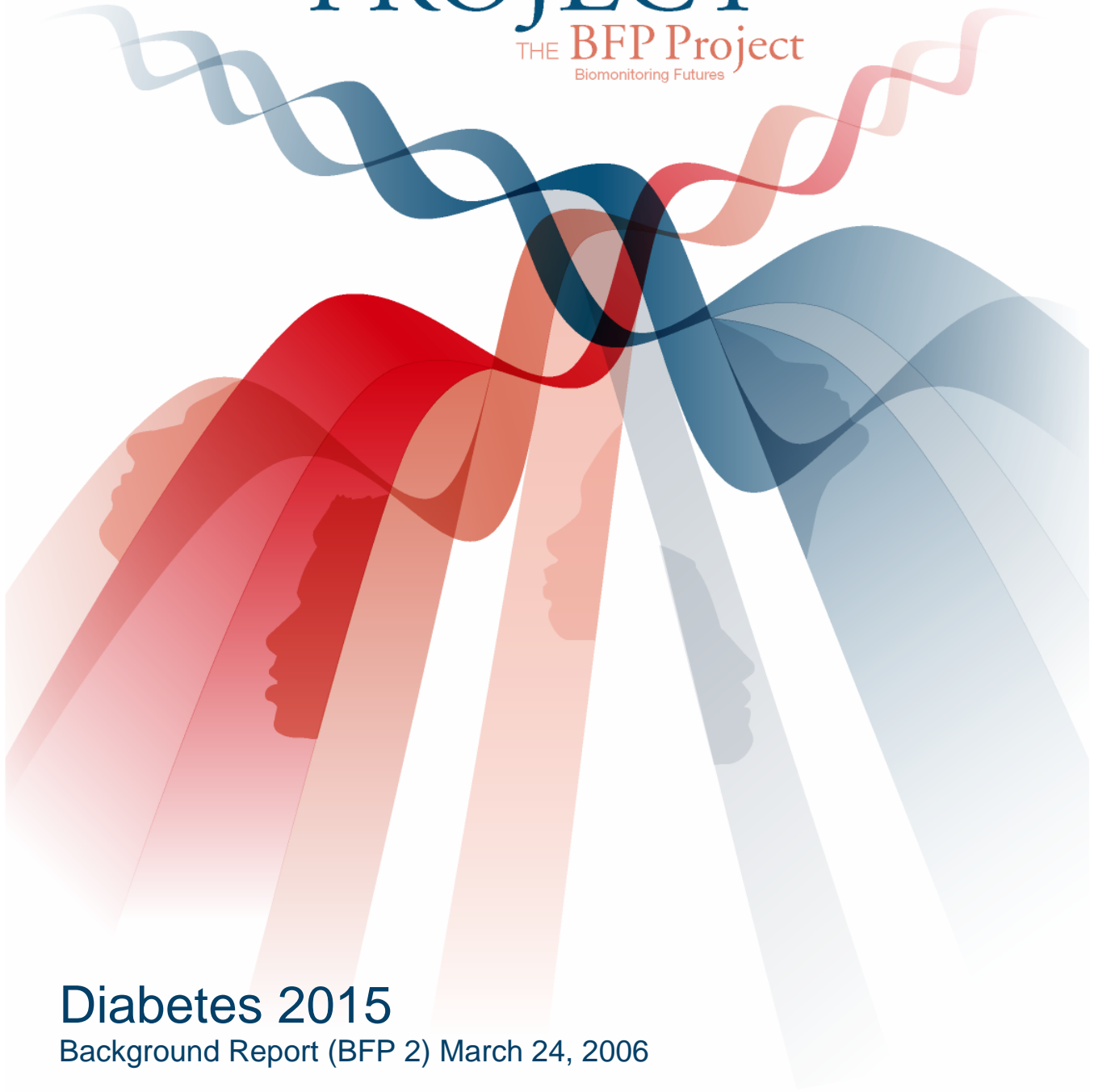


THE **DRA** Accelerating Disparity  
Reducing Advances  
**PROJECT**  
THE **BFP Project**  
Biomonitoring Futures



## Diabetes 2015

Background Report (BFP 2) March 24, 2006

## Diabetes 2015

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# DIABETES 2015

## A forecast of likely incidence and treatment advances

### Introduction

The Biomonitoring Futures Project (BFP) is exploring how biomonitoring related to diabetes and cancer might evolve over the next decade and its potential to reduce health disparities. The BFP, funded by the Robert Wood Johnson Foundation, is a component of IAF's larger effort to identify and accelerate the most significant disparity reducing advances – the DRA Project. This document summarizes recent forecasts for the increasing incidence of diabetes, then explores likely developments in the prevention and treatment of diabetes. A separate report will provide more detailed forecasts for developments in biomarkers and biomonitoring for diabetes and pre-diabetes. There is great potential for reducing diabetes related health disparities and enhancing health gains through the use of low cost, culturally appropriate and clinically efficient biomonitoring.

This report provides two types of forecasts for 2015. The first type is likely forecasts – given current trends or research they identify what will likely happen. The second type of forecasts is optimistic – they identify trends and potential changes which are desirable but are less certain. For example prevention will become far more possible for diabetes – that is highly likely. What is uncertain is whether and how health care payors and providers will pursue prevention.

### The Looming Crisis

The prevalence of diabetes increased 5% annually over the past five years with an estimated 1,500,000 new cases in 2005 for a total of 20.8 million patients with the disease (14.6 million diagnosed and 6.2 million undiagnosed).<sup>1</sup> If this trend continues there will be at least 30 million<sup>2</sup> and possibly even 35 million people<sup>3</sup> with diabetes in 2015. The risk of an American male getting diabetes in his life time is 1 in 3 whereas females have a 2 in 5 chance.<sup>4</sup> Minorities have an even higher lifetime risk: 53% for a Mexican American female and 49% for a Black female.<sup>5</sup>

The primary factor accelerating the incidence of diabetes appears to be the epidemic of obesity. Currently two-thirds of American adults are overweight with almost one-third reaching the obese level (greater than 30% body fat).<sup>6</sup> A new Framingham heart study concludes that 80% of White Americans

will become overweight during their lifetimes with 40-50% going on to obesity.<sup>7</sup> This is likely to be higher in minorities. Obesity is becoming a disease of the young with 15% of 6-19 years being overweight (23% for Blacks and Hispanics).<sup>8</sup> Type 2 (adult onset) diabetes was until recently unheard of in children, but now it makes up 40-50% of cases with the rest being type 1 diabetes. Children as young as four have been found with abnormally high insulin levels and 13% of all children have elevated cholesterol levels.<sup>9</sup> These trends portend rising numbers of young adults with diabetes and cardiovascular disease.

The disease burden is significant and will increase as more patients develop the disease at an earlier age. People with diabetes tend to have hypertension and dyslipidemia leading to cardiovascular disease, the cause of their death 65-75% of the time. Based on estimates from the American Diabetes Association and forecasts from the Centers for Disease Control, in 2015 at least 42,000 will develop blindness, 75,000 will go into renal failure and 144,000 will require a lower extremity amputation due to diabetic complications.<sup>10</sup> Depending upon age of onset, sex and race, people with diabetes lose between 15 and 30 quality-adjusted life years (QALY) and die 10 to 20 years prematurely.<sup>11</sup> Diabetes is now the 6<sup>th</sup> leading cause of death and will directly contribute to about 400,000 deaths in 2015.<sup>12</sup> The cost to society from diabetes will be over \$225 billion (in constant 2002 dollars).<sup>13</sup>

This is a realistic picture of the magnitude of the diabetes epidemic if American society and the healthcare system do not change. To dramatically reduce this disease burden of diabetes we must change our communities to promote more exercise and our food industry and lifestyles to prevent obesity. Our healthcare system must shift to aggressive prevention and effective early intervention with proven methodologies for managing multiple chronic diseases. Society must also find ways to ensure healthcare access for all Americans and to address inequities of the social determinates of health.

***By 2015, unless current trends change, the twin epidemics of obesity and diabetes will be the biggest challenge in public health and for the healthcare system. Minorities and the underserved will be impacted the most. Community health centers will devote a major portion of their resources and efforts in addressing the multiple comorbidities of these twin problems.***

## Advances in Type 2 Diabetes Prevention and Management

### Prevention

A large proportion of all ethnic groups carry genes permitting diabetes to develop if the environment and lifestyle are conducive, as we have recently seen. Society and the medical professions are becoming aware of the need for action using as a model the effective campaigns against smoking and encouraging seat belt usage. The most comprehensive approach for reducing the potential disease burden would be to address the major risk factors simultaneously – obesity, physical inactivity, smoking, hypertension, hyperglycemia, hyperlipidemia – that predict the development of several major chronic diseases – diabetes, cardiovascular disease, cancer and dementia.<sup>14</sup> Interventions must include ways to successfully modify behavior. Of course, a bigger challenge is for society to address the social determinants of health such as the elimination of poverty. An optimistic forecast would be:

***By 2015 effective measures are available to change behavior and randomized, controlled trials demonstrate efficacy. Efforts by health plans, community health centers, and state and federal agencies are beginning to reduce the incidence of diabetes and obesity. It is a work in progress that will take many years for a significant reduction in societal disease burden.***

### The Biggest Challenge: Screening with Early Intervention

In 2005 the ADA estimates there are 41 million adult Americans with “prediabetes” which will lead to clinical diabetes about 50% of the time within 10 years.<sup>15</sup> Modest weight loss and moderate daily activity have been shown to prevent this progression to diabetes in 58% for at least a few years.<sup>16</sup> Few people at risk are screened since test results are not immediately available, thus making follow-up visits necessary. There are not enough qualified health interventionists (nurses, dietitians, health educators, community health workers) with the required training to effectively intervene in changing lifestyles. Moreover, payors seldom reimburse treatment of “predisease.” In this context an optimistic forecast would be:

***By 2015 people with risk factors for diabetes are screened routinely. Aggressive primary prevention is undertaken when they are found to have prediabetes. Health care payors routinely pay for effective health/behavior intervention from a range of health care providers, including CHCs.***

Currently there is an estimated 9-12 year delay in diagnosis for those who have progressed to true diabetes so around 30% of all those with the disease are undiagnosed and therefore not under treatment. Given this current delay in diagnosis, it is likely that 20% of patients already are experiencing eye, nerve or kidney damage, and many have developing atherosclerosis by the time their diabetes is diagnosed.

An optimistic forecast for changing this situation is:

***By 2015 inexpensive noninvasive screening tests for glucose and lipids are available. Electronic health records make it easy to identify those at risk who have not been tested so “opportunistic screening” tests are given when a person checks into the clinic or ER for another problem. High risk patients who do not seek care are located through screening at church, work, soup kitchens, homeless shelters, and health fairs at malls and sporting events. Noninvasive testing is fast, pleasant and provides immediate feedback for timely intervention.***

## **Effective Management of Chronic Diseases<sup>17 18 19</sup>**

An estimated 125 million Americans live with chronic diseases and half of them have multiple chronic diseases, very often including diabetes. Unfortunately, American healthcare is still focused on acute care delivered episodically on-site by physicians without reimbursement for effective team management and continuity. There is recent emphasis on disease management, but it is not coordinated for effective management of multiple complex chronic diseases, and the focus is on controlling cost with little effort to improve quality of life.

Ninety percent of those with diabetes receive the majority of care in primary care practices. This is the perfect setting for multidisciplinary care teams directed by evidence-based guidelines and supported by electronic health records and performance feedback to practice coordinated continuous care. Attention goes beyond current diseases and addresses risk factors for future comorbidities. Emphasis is placed on patient education and coaching to support self-management goals and home self-care. This plays to the strengths of community health centers which have a culture of teamwork and caring, usually have access to a single paper record, and have the need to focus on simple evidence-based activities, rather than a financial incentive to focus on high-tech procedures. As a result many CHCs produce higher scores on performance measures compared to managed care plans.

The chart below summarizes the shifts that should be in place by 2015, again in an optimistic forecast, for effective management of chronic disease:

### Effective Management of Chronic Diseases

Current Practices	Effective Chronic Disease Care
Episodic testing	Extensive use of biomonitoring
Engage when symptomatic	Prospective prevention
Focus on current medical problem	Focus on all risks
Primary care physician	Cooperative team of providers
Care based on periodic visits	Continuous healing relationships
Short visits with little information	Emphasis on education and coaching
Decisions by clinical autonomy	Evidence-based decisions for team
Information restricted	Electronic information flows freely
One size fits all	Care customized to needs and values
Patient a passive participant	Patient/family active participants

### Biomonitoring<sup>20</sup>

*This section provides a brief glimpse of what is possible. Separate Biomonitoring Futures Project reports consider current best practices and future developments in diabetes biomonitoring.*

People with advanced diabetes must test their blood sugar several times a day requiring many finger sticks. Researchers have been trying for years to create effective noninvasive methods for determining blood glucose using infrared spectroscopy, iontophoresis and sonophoresis as ways to get serum to pass through the skin for sampling. The Glucowatch was such a device, but it was expensive and of limited clinical usefulness. It is realistic to expect that technical obstacles will be overcome with a suitable device likely available by 2015. Effective noninvasive testing devices with high accuracy will also dramatically improve screening for diabetes and hyperlipidemia.

Inexpensive home test kits are now available for hemoglobin A1c, LDL & HDL cholesterol and triglycerides. It is important for patients to receive periodic feedback about how well they are managing glucose, blood pressure or lipids as they are usually asymptomatic and stop taking medications after a few months because they can't tell that the drugs are making any difference.

A Korean company makes a cell phone that has an internal glucometer and motion sensor for monitoring daily exercise. The results are stored and can be sent to health providers. The cell phone (or personal computer or PDA) can be used to give the patient reminders about care, to provide information from the Web and to easily consult electronically with a nurse. With increasing artificial intelligence capabilities

the glucometer, cell phone or computer will assess lab trends and give the patient recommendations for better management of glucose or lipids. The “Glucoboy” is an example of a game that promotes effective management. It is a Gameboy attached to a glucometer. The patient gets access to higher levels of a game if her blood sugar is under better control from appropriate testing and insulin usage.

Again, these are simply an indication of the range of biomonitoring that is likely to be available by 2015. It leads to the optimistic forecast that:

**By 2015 noninvasive testing will be used for rapid screening, speedy clinic visits and by empowered patients for effective self-management of their diabetes and dyslipidemias.**

### Medicines for Controlling Glucose Metabolism<sup>21 22 23 24 25 26 27</sup>

In 2006, there are five major classes of oral diabetes agents on the market. They stimulate beta cells to produce more insulin, reduce the amount of glucose made in the liver, increase cellular sensitivity to insulin or slow intestinal conversion of ingested carbohydrates into glucose. Major drawbacks are that many cause weight gain and none of the current drugs modify the disease to slow down progression.

Under development are agents that:

- Improve or mimic metabolic actions of insulin to counter insulin resistance,
- Preserve beta-cell function and prevent loss of cell mass by either promoting neogenesis or preventing apoptosis,
- Stimulate insulin biosynthesis by beta-cells to support required increased secretion,
- Reduce the lipotoxic effects of chronically elevated triglycerides and fatty acids on beta-cell function and insulin action,
- Suppress gluconeogenesis and glucogenolysis eliminating glucotoxicity exacerbating insulin resistance and beta-cell failure,
- Address impaired glucose uptake and utilization by tissues,
- Reduce obesity leading to reduction of hyperglycemia as weight is lost.

New therapies based on these approaches are becoming available. Exendtide is an incretin mimetic drug similar to the body’s glucagon-like peptide-1 (GLP-1) hormone. It was recently approved as an adjunctive therapy given by injection twice a day to increase insulin secretion, lower plasma glucagon

(thereby reducing the amount of glucose produced by the liver), and bind to the hypothalamic appetite center telling the brain to stop eating. These effects result in appetite suppression, progressive weight loss and sustained glucose control. It also reduces inflammatory markers suggesting improvement in blood vessel endothelial function and it might preserve beta cells by stimulating regeneration and stopping cell death. Dipeptidyl peptidase IV inhibitors are another class of drugs that target the incretin pathway. They have similar effects, but can be given orally. Multiple compounds are in development or clinical trials.

Dual peroxisome proliferators-activated receptor (PPAR) alpha/gamma agonist drugs are in late clinical trials. They improve insulin sensitivity lowering blood glucose and hemoglobin A1c, and they also decrease triglycerides and raise HDL cholesterol – a two-in-one solution for diabetes and lipid disorders. However, the FDA is requesting additional studies because of concern with potential cardiac side effects. These drugs or modified candidates may be on the market within the next few years.

Given these and several related developments a likely forecast is that:

***By 2015 there will be new classes of effective drugs for treating both diabetes and comorbidities. The big question is whether the price will be too high to make them available for use by community health centers.***

### **New Insulins and New Delivery Methods<sup>28 29 30</sup>**

There are new short- and long-acting insulin analogues for better glucose control as a result of advances in recombinant DNA technology. Hepatoselective insulin that is selectively absorbed by the liver for delivery via the portal vein causes less build up in peripheral tissues and may cause fewer complications. An insulin substitute is under investigation that is a novel insulin-mimetic heterodimer peptide which attaches to each of the insulin receptor binding sites to activate the insulin pathway. Other research developments include the creation of uniform nanometer size insulin particles that may be more efficient, as well as exploration of heat-stable insulins for easier storage and distribution.

This leads to the likely forecast that:

***By 2015 there will be even more effective insulins on the market, especially for new delivery systems.***

New approaches to insulin delivery are under development to avoid the discomfort of injections, thereby improving compliance with better glucose control. Promising examples:

- **Inhaled insulin** is under development by several companies and a dry power form using a special controlled nebulizer has just been approved by the FDA. Currently inhaled insulin is short-acting for use just before meals, and longer-acting injectable insulin would have to be used at bedtime. Longer-acting forms are being developed. As the bioavailability of inhaled insulin is only about 10% of current injected forms, it will likely be expensive, and it is uncertain if payers will cover it.
- **Oral insulin** would be ideal, but has been a difficult challenge because it is broken down in the stomach and its large molecule is not easily absorbed into the bloodstream. Work is ongoing on a gel-polymer coated version. Another approach is oral spray insulin that is absorbed through the buccal mucosa. It is uncertain whether technical challenges will be overcome to produce oral insulin.
- **Transdermal insulin** is being considered using multiple “minimally invasive” methodologies such as microneedles, sound waves or electrical current to overcome the skin barrier. If successful a patch could deliver continuous low dose insulin through a pump mechanism. If the device had a glucose biomonitor and computer intelligence the dose could be continuously adjusted to automatically control blood sugar – a closed loop system.
- **Insulin pump** technology has been under development for a long time. External pumps now in use provide better control of hemoglobin A1c in those with juvenile diabetes. Implanted externally controlled pumps that infuse insulin directly into the peritoneal cavity are available in Europe and being considered by the FDA for use in the U.S. The pump reservoir is refilled percutaneously every 90 days. Work is progressing on a durable implanted glucose sensor, but an automatic closed-loop system using this implanted pump approach or a transdermal approach is still several years away.
- **Islet Cell Transplantation and the Bio-Artificial Pancreas are two** experimental approaches to implant cadaver, xenograft or stem cell islets. Islet cell transplantation done by injecting cadaver cells via the portal vein directly into the liver has been performed on more than 500 patients with about 80% remaining free of the need for insulin injections after one year. However, they must be maintained indefinitely on immunosuppressive drugs with significant costs and side effects. The bio-artificial pancreas is a microporous membrane containing islet cells that is inserted in the body. Nutrients enter the membrane to sustain the islet cells and insulin passes out, however larger immune system components cannot enter to destroy the foreign islet cells. Much more research is necessary before this technology could be approved for human use.
- **The “gene pill” is another novel idea in early animal research.** The gene for manufacturing insulin is inserted into a pill that is swallowed, permitting the gene to be taken up by the lining cells of the gut, which then produce insulin that is absorbed into the blood stream. As mucosal cells are continually sloughed off and replaced, a pill is needed every couple days. The gene stays out of the blood stream so cells elsewhere do not start producing uncontrollable insulin. Someday this process may be used to supplement the inadequate insulin production in many with type 2 diabetes.

The resulting likely forecast is that:

***It is reasonable to expect that noninvasive ways to administer insulin will be available by 2015. The big question is whether these will be effective and inexpensive enough for routine use, or only practical for special cases. Ease of use and avoidance of painful injections could dramatically improve compliance with better control and fewer long-term complications.***

## Drugs for Obesity<sup>31</sup>

Obesity is a strong risk factor with about 60% of new cases of diabetes being obese and an additional 30% being overweight. Weight reduction and exercise are superior to oral anti-diabetes drugs in preventing the development of diabetes in those with impaired glucose tolerance. Although there has been tremendous research on the metabolic and neurohumeral pathways controlling metabolism and weight, targets showing great promise in research animals have frustratingly little impact when used in humans. This will soon change.

The only currently approved long-term drug effective in reducing weight is orlistat. It is a lipase inhibitor that works in the intestine to block absorption of one-third of dietary fat. It has also been shown to prevent and reverse early type 2 diabetes.

Rimonabant is a selective CB<sub>1</sub> receptor endocannabinoid blocker that in phase III clinical trials is effective in producing sustained weight loss. It also reduces hemoglobin A1c, triglycerides and blood pressure while raising HDL. This is an example of a drug with multiple beneficial effects for reducing cardiovascular risk while treating diabetes and obesity. It is expected to be approved in 2006, but it will take time to clarify its proper use in community health centers as well as availability based on its cost.

Other drugs under development will control absorption, metabolism, energy expenditure and hunger. They will probably have to be used in combination to prevent the body from working around one action to maintain obesity.

This leads to the likely forecast that:

***By 2015 there will be more effective drugs for obesity, but they are likely to be expensive and continuous long-term use will be required to keep weight under control.***

The logical approach to the obesity epidemic is a serious societal commitment to effective prevention programs. New drugs would be better used for reversing established obesity when other measures have failed.

## Will We Find a Cure for Diabetes?

Our increasing understanding of diabetes at the genetic, molecular and cellular levels will result in many advances. Identification of phenotypes at higher risk will lead to screening and early intervention for affected subpopulations. The most effective therapies for the individual with diabetes will be selected based on the unique characteristics of the disease and the patient's pharmacogenomic profile. The approach may be genetic or biochemical manipulation, often as preventive measures. It is possible that someday we will understand the underlying biomolecular pathophysiology well enough to create therapeutics that block diabetes from occurring. The obvious lesson at present is that it is much easier to prevent the disease in the first place.

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