Scientia Advisors Spotlight

THE DIABETES PARADOX OCTOBER ISSUE

# INTRODUCTION

Harry Glorikian

*Diabetes is a paradox. The healthcare industry knows how to control the disease, yet the number of cases continues to explode. Today, over 150 million people are suffering from diabetes worldwide, and up to 1.7 billion people are at increased risk. To our dismay, diabetes is poised to become one of the defining diseases of the 21st Century.*

*In this issue of the Scientia Newsletter, our consulting teams have taken a multiple-angle view into diabetes. We have identified some new opportunities, and we offer helpful insights for players across the healthcare value chain.*

*Our scientific understanding is rapidly increasing, already establishing new linkages between diabetes and the gut microbiome, the internal and external chemical environment, and genetic factors. This is leading us to an entirely new diagnostic approach that detects diabetes, identifies new surrogate endpoints, delineates possible stages of disease progression, predicts age of onset, provides a dietary regime, and paves the way to new tailored treatment protocols.*

*In the crowded, but tantalizingly profitable therapeutic arena, winners will have to demonstrate cost-effectiveness and improved patient convenience versus the prevailing standard of care. If that were not challenging enough, the makers of new diabetes therapeutics will ultimately have to contend with a new power-broker in the management of diabetes: the pharmacist. That's right, your local pharmacist and not your primary care physician (PCP) may hold the key to the diabetes patient.*

*In the medical device space, companies are furiously attempting to perfect closed-loop insulin pumps - the "holy grail" of T1DM disease management.*

*And in the health and nutrition sector – the one industry that can have the biggest impact on slowing, even reversing, the tide of diabetes – is marked by in-action. As we explain, there is simply a tremendous growth opportunity for the food companies who can learn how to translate scientific diabetes jargon into consumer friendly marketing.*

*To round out the issue, we invited Arturo Rolla, MD, an endocrinologist at the Beth Israel Deaconess Medical Center, an acknowledged luminary on the topic of diabetes, to share his views with us. His perspective as a practicing physician offers an added dimension to the diabetes paradox. Don't miss the Q&A session of his talk in the featured video.*

*We at Scientia look forward to help you navigate the opportunities and challenges of the diabetes healthcare market. Together we can help solve the frustrating diabetes paradox.*

CONTENT





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# MANAGING THE DIABETES EPIDEMIC

Patrick Terry

As global populations gain affluence, the incidence rates of diabetes have soared. The disease is segmented into two types. Type 1 diabetes mellitus is an organ-specific autoimmune disease that destroys insulin-secreting beta cells by immune-mediated inflammation. Type 2 diabetes mellitus is a metabolic disease. Both are characterized by insufficient insulin production.

People with type 2 diabetes are at high risk of developing a plethora of additional diseases, including cardiovascular disease, renal disease, peripheral vascular disease, nerve disease, neuropathic pain, erectile dysfunction, skin ulceration, cataracts and cirrhosis, as well as increased risks from falls, bone fractures and cognitive decline[i]. Currently, more than 170 million people throughout the world have developed diabetes (type 1 and 2 combined), and that number is expected to more than double by 2030.[ii] In the U.S., the cost of treatment was estimated at $174 billion in 2007. As the burden grows, existing models of the disease and management assumptions are being challenged.

New scientific studies are finding links beyond the well-established models of diet and exercise to include studies of human nutrition, the gut microbiome, the internal and external chemical environment and genetic factors. This expanding understanding of the onset and progression of diabetes is leading to an entirely new diagnostic development opportunity to detect diabetes, identify new surrogate endpoints, delineate possible stages of disease progression, predict age of onset, guide a dietary regime, and to potentially drive new tailored treatment protocols. Although exercise and dietary modification remain key elements in preventing or delaying onset and severity, emerging approaches may include administering new classes of therapeutics, controlling the chemical exposure, altering dietary composition rather than quantity of food and, in the morbidly obese, implantable devices and even radical surgical interventions.

## SCARY FACTS

- Of the 81 million American Baby Boomers (born between 1946 and 1964), a third are obese and an additional 36 percent are overweight. *Source: Associated Press-LifeGoesStrong.com poll August 30, 2011*

- Today, over 150 million people are suffering from diabetes worldwide while over 300 million people are estimated to be obese. As a result, up to 1.7 billion of the world's population is at increased risk. *Source: World Health Organization 2011*

- A new study predicts that if the current "obesity epidemic" continues unchecked, by 2030 50 percent of the US adult population will be clinically obese. *Source: Lancet, 378, Issue 9793, August 2011*



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## Incidence increases

Diabetes often is considered a disease of affluence because its progression throughout the world can be correlated with the increasing wealth of nations. China is a prime example. Researchers at the China-Japan Friendship Hospital in Beijing tested some 46,000 people and concluded that 92.4 million people -- nearly 10 percent of the population of the Peoples' Republic of China -- have type 2 diabetes. That same study suggested that 148.2 million people have pre-diabetes, defined as abnormally high blood sugar levels that develop before the actual disease manifests itself. The onset of diabetes, as well as heart disease and obesity, is linked to the richer diets and reduced physical activity that accompanied China's economic gains.

In the United States, in contrast, diabetes is generally associated with low incomes and educational levels. Recent data from the Centers for Disease Control indicates that diabetes is more prevalent among self-reporting Hispanics and blacks (12 and 13 percent respectively,) than among whites (7 percent).[iii] Furthermore, the rate is inversely proportional to household income,[iv] often because of this population's higher exposure to synthetic chemicals in their environment, as well as predisposing risk factors and a possible susceptibility to metabolic disruption. Obesity rates in the U.S. have risen dramatically, with more than one-third of the adult population considered to be obese.[v]

## Causes

Studies of the onset of diabetes traditionally have been closely linked to the theory of energy balance – essentially, over-eating and under-exercising – which leads to fat cell weight gain. That weight gain leads to metabolic stress and fatness, which leads to the insulin resistance that is the predisposing factor in the onset of type 2 diabetes. Likewise, in type 1 diabetes, the inflammatory stress of obesity amplifies the immune response, triggering disease onset[vi].

The energy balance approach, however, minimizes the role of specific dietary components in energy metabolism and fuel oxidation, and overstates other environmental factors. For example, an analysis of data from more than 630,000 children revealed that 89 percent of the children who slept less than 10

### TEN INTERESTING DYNAMICS IN DIABETES

1. The theory that diabetes is triggered by energy imbalance is giving way to a more nuanced understanding of the multiple trigger points of a complex condition.
2. The exposome – the sum of all internal and external chemical exposure – plays a significant role in diabetes onset.
3. Rapid weight gain, coupled with the inability to shed stored fat, is closely linked to the preponderance of environmental chemical exposures.
4. 24 genomic loci are linked to diabetes, but none are powerfully predictive.
5. High levels of certain amino acids are associated with increased risk (60-100%).
6. Poor nutrition during pregnancy may increase the number of adipocyte precursor cells, re-set insulin signaling pathways in the neonate, thus increasing risk of obesity/diabetes later.
7. Lowering glucose level, though not aggressively, is most effective in delaying/preventing the onset of cardiovascular disease when achieved soon after onset of the disease.
8. SGLT2 inhibitors appear to have a positive impact on blood glucose concentration, weight loss, blood pressure, pancreatic function, high blood triglycerides and cholesterol.
9. Anti-CD3 therapy preserves β-cell function, enabling nearly insulin-independent diabetics.
10. For some, gastric surgery may be required to achieve balanced -energy intake and glycemic control.



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hours per night were obese[vii], while those sleeping 10 hours or more tended not to be obese.

Current research, therefore, points toward metabolic perturbation, which considers the composition, rather than the quantity of food consumed.[viii] Poor understanding of the relative merits of various types of foods, including the differences between processed and non-processed foods, appears to be a contributory factor in obesity and the onset of diabetes. For example, although foods labels prominently list fat content, carbohydrates are given lesser emphasis on the label despite significantly contributing to the glycemic load. Or in other words, the food stuffs that cause a biological inflammation response and a metabolic disturbance are not adequately presented on processed foods.

Changes in the Finnish diet since 1972 corroborate the effect of dietary changes upon disease. The Finnish Heart Association and the Finnish Diabetes Association, working together, have launched a Heart Symbol, which appears on packaging of heart-healthy foods, and the government launched a campaign in the early 1970s to change food consumption patterns. Since those studies began, Finns have replaced whole milk with skim or low fat milk and use low-fat margarine or oils instead of butter. Vegetable consumption has tripled.[ix] Consequently, fatty acid composition has changed so that the share of saturated fatty acid has decreased from 20 to 13 percent and the intake of fat has decreased from 38 to 33 percent, resulting in a 60 percent reduction in coronary mortality.

Recent research also points to a link between advanced glycation end-products (AGEs) that are used to enhance flavors in processed foods and onset of diabetes. AGEs suppress host defenses and intracellular reactive oxygen species, leading to inflammation and obesity and can contribute to beta cell dysfunction, impaired insulin secretion and insulin resistance.[x] Results indicate that restricting AGEs is a promising, cost-effective intervention that is broadly applicable.

Subsequent research has addressed the interactions between diet and genomics. Research now shows that fatty acids can modulate visceral fat deposition and thereby affect an individual's predisposition for obesity and obesity-related inflammation. This knowledge may help researchers understand the variability within the obese population in response to weight gain, weight retention, diabetes onset and response to treatment. That, however, is only part of the picture. Research suggests that the many classes of fatty acids probably do not act via a single pathway.[xi] There is data to suggest that many different pathways may be involved.

Environmental triggers also are causative. The speed of weight gain and the inability of patients to lose weight led researchers to suspect other factors, such as chemical exposure. As researchers learn more about disease onset, their definition of environmental factors is changing. Realizing that approximately 90 percent of human disease is attributed to environmental factors[xii], yet only 7 to 10 percent is attributed to occupational exposure,[xiii] they began considering the internal chemical environment (aka, the organism in and on our bodies, the gut, and the individual's microbiomes).

This exposome incorporates all exposures from conception onward, including not only exposure to air and water pollution, but also to chemicals ingested through the diet, smoking, drug use, radiation, inflammation, infections, peroxidation, the gut



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microbiome, bacteria and pre-existing diseases, etc. Although measuring all chemical exposures currently not accessible or reduced to practice, the Centers for Disease Control and Prevention have developed assays to detect approximately 300 exposures in blood or urine. Strong associations were reported between the risk of type 2 diabetes and exposure to polychlorinated biphenal, heptachlor epoxide and other substances[xiv]. Exposure to a wide variety of pollutants, whether internally or externally, causes epigenomic alterations that become heritable.[xv] Epigenetic modifications also are caused by transient exposure to hyperglycemia, resulting in long-term changes in the chromatin structure and in gene expression, immune response, which mediate persistent metabolic characteristics.[xvi]

So far, most research regarding environmental triggers of disease has concentrated upon external exposure, often to chemicals regulated by the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA). A long list of pollutants and their effects upon disease onset has been developed. Many of these are endocrine disrupters that interfere with the action of normal hormones and, therefore, promote the development of metabolic diseases, such as type 2 diabetes. Many of the modulation pathways affected by endocrine disruption chemicals are important in energy regulation and glucose homeostasis.[xvii] They also appear to interfere with xenobiotic signaling, which affects drug, lipid and glucose metabolism, as well as inflammatory response. There is speculation that these xenobiotic receptors are now overwhelmed in their attempts to adjust to environmental stressors and, therefore, contribute to the onset of diabetes.

A body of research suggests that endocrine disrupting compounds also may affect adipose tissue and that additional mechanisms of regulation also may be affected, thus providing additional approaches for diabetes therapeutics or exposure interference technologies.

## Neonatal factors

Many of the roots of adult onset diabetes are established before birth and during infancy. Changes in the mother's diet during pregnancy help program the neonate's predisposition to metabolic syndrome.[xviii] In other words, what the mother eats during critical periods of the pregnancy may modify the epigenome and thus re-set the baby's cellular energy homeostasis, fat cell production, and alter several key regulatory pathways. For example, poor nutrition during the first half of a pregnancy may increase the number of adipocyte precursor cells and thus re-set insulin signaling pathways. This, however, becomes a key component of metabolic syndrome only if it is followed by the child's accelerated growth rate soon after birth or if the child becomes obese. It appears that if the child is nutritionally challenged early in life, the risk of developing diabetes is dramatically increased.

## Prediction capabilities

Given the myriad causes of diabetes, developing risk profiles to more accurately predict the likelihood of disease onset can become extremely complicated. Although some 24 different genomic loci have been linked to type 2 diabetes, none improves the ability to predict onset of the disease.[xix] This leads to the conclusion that, although the understanding of the genetic and molecular networks underlying metabolic disease is incomplete, it plays an important role in obesity and, therefore diabetes.



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High throughput metabolic profiling, however, is revealing some promising biomarker(s) and candidate classifiers to stratify sub-groups. Metabolic diseases often are present years before they are clinically apparent as a defined phenotype. Therefore, it appears possible to identify changes in plasma metabolite concentrations, using the changes as clinical biomarkers to predict disease. In a multi-center longitudinal study[xx] of 6,000 individuals who were followed for decades, researchers used mass spectrometry to identify a panel of amino acids that, based upon their concentrations during fasting, predicted the development of diabetes in otherwise healthy individuals. High concentrations of five branched-chain and aromatic amino acids, in fact, elevated the risk of developing diabetes four-fold, and were detectable up to 12 years before any changes in insulin were evident. Earlier research supports the concept, noting that circulating amino acids may directly promote insulin resistance[xxi] and that many different amino acids modulate insulin secretion.[xxii]

Although assessing the potential for the onset of diabetes through monitoring genetic polymorphisms has indicated a risk increase of 5 to 37 percent, elevated levels of amino acids are associated with a risk increase of 60 to 100 percent. Hyperaminoacidemia, therefore, appears to be a very early indicator of insulin resistance in certain sub-groups.

## Treatment options

Lifestyle modifications are strongly recommended to curb obesity, delay diabetes onset and, after onset, mitigate its effects. To be most effective, these modifications typically result in the loss of 7 to 10 percent of a patient's initial weight.[xxiii] This weight loss, combined with exercise, reduces the risk of developing type 2 diabetes. Pharmacotherapy also often is recommended as an adjunctive treatment.

For the morbidly obese, however, implantable devices or gastric surgical options may be required for them to achieve their target glycemic control.[xxiv] In these individuals, substantial weight loss markedly improves hyperglycemia and sometimes results in a remission of type 2 diabetes. It also improves obesity-related cardiovascular risk factors. Some researchers suggest that because the risk reductions are seen soon after surgery, even before the patients lose weight, the metabolic changes that occur after gastric bypass surgery are triggered by a lower insulin baseline.[xxv]

Glycemic control is the standard treatment for diabetics, with long-term benefit of reducing the risk of developing diabetes-related diseases. Glycemic control, however, is not ideal. Although the degree of glucose elevation among type 2 diabetics is a key indicator of risk, lowering glucose levels is most effective in delaying or preventing the onset of cardiovascular and other diabetic-related disease for recent-onset diabetes. For those with established, long-duration diabetes, the benefits of glycemic control upon related diseases were inconclusive[1].

Food supplements have been advocated as a way of reducing obesity, and are generally welcomed by patients who view them as natural or as easier than changing their diet or exercising. Their effectiveness, however, remains questionable. A recent review of clinical trials studying the effectiveness of food supplements reported insufficient evidence of clinically significant weight loss without undue risks[xxvi]. But the open question remains, is it an issue of study design or ineffectiveness of the food supplements approach?



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One promising preclinical research program suggests that a particular lipid may mitigate the effects of a high-fat diet and thereby lower incidence rates for diabetes. The phospholipid dilauroyl phosphatidylcholine (DLPC), when administered to metabolically challenged mice, reverses the metabolic problems typically associated with high-fat diets, substantially improving glucose homeostasis and insulin signaling[xxvii].

Nearer-term, new measurement and monitoring technologies looks promising, such as continuous glucose monitoring, and the eventual adoption of artificial pancreas for individuals able to deal with the technological capability. Clinical use of advanced closed-loop insulin delivery systems, however, will most likely be very gradual. The likely early applications include overnight closed-loop control to prevent nocturnal hypoglycemia, and then eventually full-time use of such systems. Their current challenges include imperfect accuracy and reliability of their continuous glucose monitoring components, the slow absorption of subcutaneously administered rapid-acting insulin analogues and inadequate control algorithms to adjust performance to account for individual variability among patients.[xxviii]

## Type 1 and 2 therapies

Several new drugs that are in trials now address both type 1 and type 2 diabetes and, unlike earlier therapies, target novel pathways. Dapagliflozin, being developed by Bristol-Myers Squibb and Astra Zeneca, canagliflozin by Johnson & Johnson, and a similar compound jointly developed by Boehringer Ingelheim and Lexicon Pharmaceuticals, all target the sodium-dependent glucose co-transporter 1 (SGLT2), preventing it from reabsorbing glucose in the kidney. These SGLT2 inhibitors lower blood glucose concentrations by excreting simple sugar through the urine. They also trigger weight loss, lower blood pressure, improve pancreatic function, reduce high blood triglycerides and lower cholesterol.[xxix] They are in clinical trials now. But the community remains very concerned about the likelihood of achieving regulatory approval with those intended use claims. Failure seems likely to some observers.

### *Type 1 therapies*

The therapeutic objective for type 1 diabetes has evolved from preserving the functional capacity of the remaining beta cells to restoring the immune tolerance to target autoantigens.[xxx] Although the much heralded immune suppression strategies and autoantigen therapies have, so far, proved disappointing, an alternative approach seems to have some promise.

After watching the effectiveness of anti-CD3 monoclonal antibodies in oncology work, researchers theorized that some of the autoantigens within the host at disease onset remained, and could help restore self-tolerance. Therapeutic trials of two humanized Fc-engineering monoclonal anti-CD3 antibodies, teplizumab[xxxi] and otelixizumab[xxxii], were launched. European double-blind multi-center Phase II trials indicated that the antibody preserved beta cell function, even 48 months after therapy, resulting in a significant decrease in the need to administer insulin[xxxiii] so that patients neared insulin independence.


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This anti-CD3 approach was unique in terms both of potency and mechanism of action. Study results showed a long-lasting, single-dose effectiveness that enabled the full reconstitution of the immune responses to unrelated antigens within two to three weeks of treatment's end. The rapid remission is attributed to a mechanism of action that targets both pathogenic T cells and $T_{REG}$, making it most effective with a primed, ongoing immune response.

Although anti-CD3 therapy appears to be best-in-class, at least five other Phase II and Phase III trials indicate that it reduces insulin requirements but generally does not trigger long term disease remission.[xxxiv]. In mice, it is most effective immediately at diagnosis. Therefore, there is speculation that a multi-pronged approach will be most effective, involving combination therapies to maintain the balance of pathogenic and regulatory pathways, drugs that target co-stimulatory pathways and consideration of the state of the pancreatic beta cell when designing therapy - thus begging the question, who and how such combinatorial approaches will

## WHAT'S NEXT

**Medical Devices** Further technological innovation will have an incalculable influence on the future of obesity and diabetes epidemic including advances in miniaturization (micro and nano scale), alternative materials, novel delivery approaches, wireless communication, digital data transfer from various ubiquitous intelligent devices, as well as the human/machine interface all aligned to monitor, manage, treat, alleviate, and actually delay disease onset. Even fashion will have an impact on diabetes-related product development.

We predict that the social phenomenon of chic medical device fashion will be here soon enough, including designer monitor watches, functional jewelry, skin tattoos to interface with implantables, and other clothing accessories for a new age of "functional fashion." Companies such as PositiveID, Medtronic (with their MiniMed Infusion Systems), and larger firms like Abbott, Bayer, BD, and J&J are developing such technology, acquiring novel intellectual property and compelling device prototypes, like the G-Tone watch concept.

**Diagnostics** New developments will include: permanent on-skin rapid diagnostics to monitor and alert a person of out-of-range blood chemistry levels or metabolic aberrations with new age blood sensors; targeted personalized disease diagnostics that will stratify patient populations into metabolic sub-classifications, re-characterize the clinical phenotype, and alter the clinical trials and treatment of diabetes; and theranostic tests to identify pre-diabetes, predict disease trajectories for early aggressive intervention strategies, and target generic drugs over expensive biological agents. Companies advancing new diagnostics include Seventh Sense Biosystems, SecondGenome, Tethys Bioscience, Medco Health Solutions, Quidel, and all of the next generation sequencing companies.

**Study Focus and Study Designs:** The continued and inevitable product development failures for therapeutics in the areas of obesity and diabetes control will necessitate alternative pathways forward because the economic and social burden of the epidemic will remain untenable for society and financially troubled economies. As such, a renewed focus on the primacy of economics, clinical utility, patient adherence, and demonstrated durable behavioral change will be extremely important for commercial success of products, services, and informational medicine. The enabling technology platform for this enterprise will require collaboration from diverse stakeholders, direct lay public engagement, social network media, and creative circumnavigation of the traditional regulatory pre-market hurdles to commercialization. Industry will need to figure out how to engage and leverage these new types of circumstances. For example:

- Population-based disease registries and biocollections: Both public and private collections.
- Clinical observational studies: With linked longitudinal outcomes data and self-reported data.
- Adaptive clinical designs: Real time diagnostic and device interventions with tracked outcomes data.
- Self-organization patient social networks and research protocols: Community directed studies



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be performed and brought to market.

## Conclusion

Advances in understanding the many causes and contributing factors of type 1 and type 2 diabetes are resulting in promising approaches that include pharmacologic interventions, new diagnostics, new drug targets and new options in diet and lifestyle modification. For most, ongoing research is called for, but these many studies provide insights into new, evolving approaches to help clinicians treat new and established cases in ways that promote desirable results in the here and now.

Because of the burden of disease, the acute economic drag placed on populations, and the overall productivity shock wave caused by this epidemic, there is a demand for new solutions and innovative life science products, socio-behavioral interventions, health literacy programs, food consumption consciousness efforts and epidemiologically driven behavior tactics to alter the trajectory of diabetes globally.

Scientia Advisors believes that the convergence of food products, drugs, devices, diagnostics, measurement science, electronic medical information, and social network theory delivered to resolve some of these immediate dilemmas described above will become a new engine of compelling life science solutions in diabetes management.

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# ACHIEVING THE HOLY GRAIL OF T1DM TREATMENT

John McNamara

Whereas T2DM patients have a multitude of treatments (e.g., metformin, dipeptidyl peptidase-4 (DPP-IV) inhibitors, glucagon-like peptide (GLP)-1 agonists) available to them to assist in the management of their disease, those with T1DM are primarily reliant on insulin and insulin analogs to control their blood glucose levels. Though great strides have been made in developing short-, long-, and intermediate-acting insulins to optimize glucose control, T1DM patients have long been subject to hyperglycemia (post-meal) and hypoglycemia (overnight). These events can have numerous adverse effects on their health, which, in severe cases, can include diabetic neuropathy, blindness, and kidney disease. While the maintenance of optimal glucose levels (4-8 mmol/L (72 and 144 mg/dL) is largely predicated on the discipline of the patient, the emergence of patient-assisting devices have provided greater convenience and improved blood glucose control. These devices include continuous glucose monitors (CGMs), which alarm the patient if glucose levels become too high or too low, and insulin infusion pumps, which utilize complex algorithms to provide an appropriate dose of insulin to respond to vacillating glucose levels. Neither of these technologies is new (insulin pumps, for example, have existed for almost 30 years), but they have improved significantly over time with regard to clinical accuracy, patient convenience, and aesthetic attractiveness. More importantly, using CGMs and insulin infusion pumps in concert creates an "artificial pancreas" of sorts, through which blood glucose is monitored in real-time and appropriate levels of insulin are delivered accordingly with minimal conscious effort required from the patient (especially following meals). These systems promise both clinical and lifestyle benefits over manual management methods, but they are far from becoming the standard of care for T1DM patients given their relative nascency in the market. Nevertheless, many clinicians and researchers agree that perfecting this closed-loop paradigm represents the "holy grail" of T1DM disease management.

THE CLOSED-LOOP SYSTEM PROMISES BOTH CLINICAL AND LIFESTYLE BENEFITS, BUT IT IS FAR FROM BECOMING THE STANDARD OF CARE.

## Hurdles to CGMs and insulin pumps adoption

Key obstacles to adoption of CGMs include the following:

- CGMs are not widely reimbursed across Europe, preventing widespread adoption as monthly costs for sensors can cost upwards of $400; broadened incorporation into reimbursement schedules is occurring overseas, but it remains a significant hindrance to wider acceptance.
- Reported discrepancies between CGM readings and those obtained through traditional fingerstick testing have fueled cynicism from the endocrinologist community; as such, CGM use is only approved as an adjunctive use in the US and must be used in conjunction with traditional fingerstick testing.
- Patient compliance remains an issue with CGM systems, primarily with regard to the sensors. The sensors for many CGM systems require a constant source of power, so the transmitter must be continuously attached; additionally, the adhesives sticking the sensor to the skin can cause irritation in some patients and/or may not hold up during certain activities including exercising or showering. Implantable sensors would circumvent some of these issues and could be easily masked. However, this much more invasive approach may not appeal to a number of patients.



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Insulin infusion pumps also come with a similar set of limitations. These systems, which generally sit on a patient's hip, can be difficult to mask underneath clothing, and may be dislocated during physical activity. Furthermore, patients are concerned about the failure of programmed infusion or improper dosing, particularly older patients who have become very familiar with self-injected insulin management and are reluctant to switch to automated dosing through infusion pumps.

### Technological advances and change in reimbursement offer hope for wider adoption

Despite these hurdles, significant technological advances have boosted adoption of these systems in recent years. Medtronic, the global market leader in continuous glucose monitoring, offers the MiniMed Paradigm® REAL-Time REVEL™ system, which serves as their hallmark CGM + insulin pump product and is one of the most highly regarded products on the market. In an effort to provide a "closed-loop" solution to T1DM management, the CGM transmitter automatically submits a signal to the insulin pump based on the glucose data collected to deliver the appropriate dose of insulin to the patient. The CGM component allows customizable alerts to warn the patient of oncoming highs and lows, and provides trend data to help the patient better understand how their body responds to various activities (e.g., exercise, and eating) to further optimize control. The system remains the #1 prescribed insulin infusion pump in the United States and was the first to be approved with a built-in CGM component. The system, however, is not without its limitations. Patients have long complained about the tubing elements of the insulin pump, which are difficult to hide and can often become caught on stray clothing or other objects. To respond to this need, Insulet recently launched the OmniPod® patch pump, the world's first tube-free pump, which is becoming one of the fastest growing pumps on the market today. The pump is wireless and waterproof, allowing for significantly improved flexibility, and can communicate wirelessly with numerous CGM devices on the market, including the FreeStyle Navigator® (Abbott) or SEVEN™ PLUS (Dexcom).

In addition to device improvements, the reimbursement landscape has improved as well, with many providers agreeing to cover CGMs and pumps as long as patients have demonstrated proficiency in properly using the devices through the provider's specific training program.

So which hurdles remain? To date, insulin infusion pumps in combination with CGM devices cannot completely ''close the loop'' as current systems still possess inherent delays in glucose monitoring and subsequent insulin delivery, putting these devices at a disadvantage to self-monitoring using fingerstick methods and self-injected insulin thereafter – hence the discrepancies in glucose readings between the two methods. Currently available pumps are sufficient for most situations, though self-induced injections may still be necessary for post-prandial dosing or for insulin delivery after strenuous exercise. Lastly, combination patch pumps with CGM systems remain a desired product for patients as it allows for an all-in-one solution that is light, easily masked, and flexible. Though the concept of a fully hands-off "artificial pancreas" has yet to be developed and no cure exists for T1DM, the industry has made enormous strides in recent years to make medical devices

THOUGH THE CONCEPT OF A FULLY HANDS-OFF "ARTIFICIAL PANCREAS" HAS YET TO BE DEVELOPED AND NO CURE EXISTS FOR T1DM, THE MEDICAL DEVICES INDUSTRY HAS MADE ENORMOUS STRIDES IN RECENT YEARS.



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more attractive to diabetes patients and physicians alike.

The key moving forward is to focus on patient *convenience*, which inherently will lead to improved patient compliance and better clinical outcomes. Consider, for example, the patch infusion pump, pioneered by Insulet, which has abandoned the tubing associated with earlier models in favor of a lightweight, all-contained pump that sits at the hip, resembling a pager attached to the body. Despite Insulet's relatively small share of the overall insulin pump market, leading providers like Medtronic are on the innovator's toes. These players have recognized the potential of the OmniPod®'s emerging technology and are developing similar systems of their own. Furthermore, simplification of the pumps will be paramount to building acceptance and ultimately patient/clinician adoption. Having too many parts and components that need to be replaced, moved, or recalibrated will not only confuse and inconvenience the patient, but have the potential to complicate reimbursement as well. At least in the near-term, the successful attempts at closed-loop systems will not only offer improved outcomes for diabetics – it will make living with diabetes *easier*.

THE KEY MOVING FORWARD IS TO FOCUS ON PATIENT CONVENIENCE, WHICH INHERENTLY WILL LEAD TO IMPROVED PATIENT COMPLIANCE AND BETTER CLINICAL OUTCOMES.

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# THE DIABETES CARE PROVIDER SHIFT: FROM CLINIC TO PHARMACY

Jonathan Pan

Posted on Scientia Advisors Blog on October 3, 2011

*Understanding this new paradigm is key for market stakeholders*

The healthcare market is experiencing a rapid decentralization of diabetes care from the primary care physician (PCP) and endocrinologist to the pharmacist. The pharmacist is becoming an integral part in the management of diabetes from counseling on diet, checking blood glucose and HbA1c levels and assessing the types of medications a diabetic is taking, to other initiatives. The pharmacy is the place diabetic patients visit the most, with an average annual spend of about $4,500, to gain advice and services to best manage their disease. Along with the pharmacy becoming the best venue to dispense diabetes care, the pharmacist is emerging as a powerbroker in the battle against diabetes. In this blog post, we show how the basic components of effective diabetes care can easily be addressed by the pharmacist, and question how this shift in the diabetes management paradigm impact marketers, manufacturers and payers of diabetes-related products and services.

In fact, six of the seven key behaviors recommended by the American Association of Diabetes Educators (AADE) could be easily facilitated through pharmacists.

Healthy Eating*
Being Active
Problem Solving*
Healthy Coping*
Reducing Risks*
Taking Medications ("Adherence")*
Blood Glucose Monitoring*

*Directly Addressable by the Pharmacist

Healthy eating: Nutrition and diabetes are closely related as stated in an article published in our fall newsletter about the diabetes. Pharmacists can assist in managing diet through counseling events and individualized medical nutrition therapy, such as educating on portion size and understanding food labels, to enable patients to reach key goals.

Problem solving: Pharmacists traditionally troubleshoot therapy administrations by initially working with the patient to determine drug-interactions, dosing and the most effective way of using a medication. Pharmacists also can work with the physician to determine the best appropriate therapy, behavior changes and path forward to improved outcomes. This can be done through routine conversations with the patient's physician, reducing the time the patient needs to be with the PCP and thereby reducing costs.



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Healthy coping: Healthy coping can provide great benefits to the patient from routine vaccinations to support in working through the overall challenges of managing diabetes. The pharmacist can play a great role through routine interaction or by organizing local vaccination events for diabetic patients who are more likely to die from vaccine-preventable diseases. Positive reinforcement of the value of up-to-date vaccination can also contribute to lowering costs in the long-term.

Reducing risks, taking medications and monitoring blood glucose: Adherence to medication and the reduction of risky behaviors, such as smoking, are critical elements of diabetes management. These tasks can be easily performed by the pharmacist as opposed to the PCP. Checking refill rates and pill levels in the vial can help ensure the patient is taking their medication. Compliance is an easy way for pharmacists to help manage the care for a diabetic patient. Holding smoking cessation sessions specifically geared to diabetics can provide great opportunities for large groups of patients to work toward a healthier life with diabetes and diminish the occurrence of risky behaviors. Targeted health events also enable pharmacists to work with patients to help them understand the proper way to monitor their blood glucose, when to monitor it, and what the numbers mean. Having the right information delivered to diabetics about their disease by a trusted advisor in the community – the pharmacist – is critical to diabetes care.

The diabetes management paradigm is shifting from the PCP to the pharmacist, and market stakeholders should take notice. Marketers must be aware that their diabetes management practices and drug adherence programs are best targeted to pharmacists, since they are now playing a more important role in diabetic patient care. Manufacturers of diabetes-related products, from glucose monitors to diabetic therapeutic interventions, can benefit from the understanding of this new undercurrent by providing additional resources to pharmacists to further educate them on the changes in diabetes management Insurance companies can realize the cost effectiveness of using the pharmacist as an interventional intermediary to the physician, which not only reduces costly physician payments, but also diminishes the patients' waiting time for physician care. The diabetic market landscape is changing with the decision-making process moving from physicians to other emerging stakeholders.

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# THE NEW BATTLEGROUND FOR NOVEL DIABETIC AGENTS: INCREMENTAL COST-EFFECTIVENESS RATIO

Jeff Stoll, PhD

Diabetes remains one of the hottest R&D areas for the pharmaceutical industry. Physicians now have numerous therapeutic options, beyond insulin and glucagon, to choose from and the research pipeline suggests that the selection may become more diverse. Nine classes of therapeutics are available on the market including insulins, secretogogues, biguanides, insulin sensitizers, carbohydrate blockers, incretin mimetics, neuroendocrine hormones, DPP-IV inhibitors, and dopamine agonists. There is also a seemingly endless pipeline of novel mechanisms of action (MOAs) attempting to provide better HbA1c control and preserve β-cell functioning. As more novel therapeutics and me-too competitors enter the diabetes market, the treatment algorithm will become even more inundated, which will pressure pharmaceutical players to develop marketing strategies and clinical programs that will highlight the unique value of their branded therapeutic. Over the next decade, clinical trials will increasingly focus on the superiority of competing medication regimens, and on the fact that the patient population will likely become more segmented as different MOAs demonstrate unique advantages for different patient sub-types. Additionally, the current market dynamics require new therapeutics to demonstrate cost effectiveness. Cost effectiveness, or more specifically incremental cost-effectiveness ratio (ICER), is creating a higher hurdle for new therapeutics, especially new biologic agents. The efficacy and safety requirements for new agents are higher than for cheaper small molecules, and the only way a biologic agent will have a place in the treatment algorithm is if they demonstrate a dramatic improvement in long-term outcomes, while also demonstrating an acceptable ICER.

> DRUG DEVELOPERS MAY NEED TO REEVALUATE MARKET INTEREST AND INCREMENTAL COST EFFECTIVENESS FOR NEW EXPENSIVE DIABETIC THERAPIES.

## Cost effectiveness has changed the value proposition of agents in development

The pharmaceutical industry is investing heavily in diabetic therapies despite the general rule that therapeutics must be extremely affordable given the success of metformin, an inexpensive first-line diabetic drug. The market is likely to become even more price sensitive as thiazolidinediones (TZDs) head toward patent expiry and cheap generics flood the market. In fact, it will be interesting to see if DPP-IV inhibitors, the current gold-standard second-line therapeutic, are pressured into more third-line utilization as payors favor cheaper therapeutic options. There is already a precedent for payors requiring physicians to utilize less effective and safe drugs due to cost effectiveness, namely in the case of sulfonylureas. Given this cost pressure dynamic, it is a calculated risk for companies to invest in the development of expensive biological agents. On the one hand, if short-term use of a biologic agent significantly delays the onset of disease progression or provides a significant remission, then the cost justification is easy. On the other hand, a trend toward multimodal treatment is developing, which involves the combination of *good-enough* (cheap) drug therapy, plus incentives for diabetes education and behavioral change (i.e., improving dietary and exercise



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habits). If this multimodal regimen fails, then more expensive, newer therapies may be considered. If this multimodal approach to diabetic care (see our blog post on the decentralization of diabetes care) takes root, then drug developers need to reevaluate the market interest and ICER for new expensive drug therapies.

## Potential clinical value of immunomodulators

Two upcoming market events could eventually help determine how viable new expensive therapies are for the diabetes market. First, genotyping and phenotyping diabetes may lead to sub-types of diabetes beyond type 1 and type 2, and may allow for identifying more rigid criteria for metabolic syndrome or pre-diabetes. Second, new clinical data on immunomodulators suggest biological agents could have a significant impact on the diabetes space, particularly if the benefits of these therapies provide significant leaps with regard to the time-to-diabetic-complication. Several novel immunomodulating MOAs have been developed to treat type 1 diabetes; however, there have been several notable failures. For example, the attempts by GSK and Tolerx to develop otelixizumab, a humanized anti-CD3 monoclonal antibody, failed in a large Phase III trial earlier this year. While GSK and Tolerx have not publicly announced the termination of the otelixizumab program and plan to analyze the results of a second suspended Phase III trial, uncertainty about this class of drug exists. Teplizumab, a similar agent co-developed by Lilly and MacroGenics, also failed to meet its primary endpoints and was terminated in 2010. However, despite these two notable failures, there remain promising agents, such as DiaPep277, Kineret, and anti-CD40s targeted drugs, among others. In addition, one of the more reassuring signs demonstrating the potential clinical value of immunomodulators for type 1 diabetes came from a National Institutes of Health (NIH)-funded study of abatacept (brand name Orencia). The initial results from the abatacept trial suggest that preserving endogenous beta-cell function and delaying the onset of diabetes can significantly delay complications and lead to less hyperglycemia. Specifically, fewer patients on abatacept (32%) had C-peptide levels, a protein that shows how much insulin the body is producing, below 0.2nmol/L at 24 months than patients receiving placebo infusions (43%). Hemoglobin A1c remained under better control at 24 months with abatacept despite similar insulin doses. The proportion under an A1c of 7% was 47% compared with 26% for patients receiving placebo infusions (P=0.0071 over 24 months). While researchers have remained skeptical about the cost effectiveness of abatacept as a therapy for type 1 diabetes, the cost effectiveness bar which abatacept has to overcome may be facilitated with the recent FDA approval of the subcutaneous formulation on August 2, 2011. The ICER for abatacept is still unclear for diabetes; however, the ICER in rheumatology became notorious when the National Institute for Health and Clinical Excellence (NICE) rejected Orencia. NICE reported the ICER for Orencia plus methotrexate (i.e., the standard therapeutic regimen), compared with conventional DMARDs, represented a gain of $47,878 per quality-adjusted life year (QALY).

While further research is needed to determine if there are safe and effective therapies for preserving endogenous beta-cell functioning, other hurdles exist for new therapeutics. Demonstrating a clinically meaningful impact on preservation of endogenous beta-cells is an important advancement for diabetes; however, the field has moved beyond merely accepting scientifically important advances as the gateway for viable therapeutics. Diabetes is equally driven



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by economic dynamics. New agents will have to demonstrate acceptable ICER versus the standard of care and superiority to other new therapeutic regimens. ICER evaluations are becoming a central battleground not only between new branded drugs and generic alternatives, but also among new branded therapeutics.

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# GROWTH OPPORTUNITIES: MANAGING DIABETES VIA NUTRITION

Bob Jones

If you add up these three statements, what do you get?

- Many food companies are struggling to find areas of growth
- Diabetes is a huge national health problem, growing at an epidemic rate
- Proper nutrition can play a major role in successfully managing diabetes

The one-word answer: Opportunity

Many of us would conclude that food companies could realize a major growth opportunity by turning their focus toward managing diabetes. But they haven't pursued that opportunity.

In this article, we discuss the growth opportunity, the major roadblock to success, some of the roles that nutrition can play in managing diabetes, and some tantalizing possibilities that are just over the horizon. We also consider several unorthodox possibilities for pursuing success. Finally, we make an assertion: *This opportunity should catch fire in the food industry and expensive for our health care system.*

## The importance of diabetes management

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. Sustained high blood sugar typically produces symptoms such as frequent urination, increased thirst and increased hunger.

Improperly managed diabetes can lead to severe complications, including blindness, kidney failure and amputation of the extremities. Short-term complications can include hypoglycemic seizures.

> THERE ARE ANOTHER 79 MILLION PEOPLE IN THE U.S. WHO ARE PRE-DIABETIC. IF ALL OF THEM DEVELOP DIABETES, THE NUMBER OF PEOPLE WITH DIABETES WILL QUADRUPLE.

*In short, diabetes can be catastrophic for the patient,*

## The growth opportunity

Diabetes is a ticking time bomb for our nation. According to the American Diabetes Association, there are 17 million people in the United States who have been diagnosed, and another six million people who have diabetes but have not yet been diagnosed. The American Diabetes Association further states that the total cost of diagnosed diabetes in the U.S. was $174 billion in 2007, which is a heavy burden on our healthcare system. That burden motivates every health insurer in the country to pay attention to the lifestyle behavior modifications that can dramatically reduce the cost of care for people with diabetes. Proper diet and nutrition will be part of that behavior modification.

The American Diabetes Association also says that there are another 79 million people in the U.S. who are pre-diabetic. If all of them develop diabetes, the number of people with diabetes will quadruple. Globally, the



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International Diabetes Federation now estimates that there will be a total of 366 billion people with diabetes worldwide by 2030.
Many food executives have long avoided nutrition-related medical opportunities (for example, gluten allergies), viewing them as niche markets that simply weren't big enough. Diabetes is no longer a niche market – it is a substantial mainstream market and a significant growth opportunity for food companies.

## The major roadblock: Consumer education

Most consumers don't understand the vocabulary of managing diabetes. Clinicians talk about "fat exchanges" and "carbohydrate exchanges," and while that terminology is technically correct, most consumers remain baffled as to what they should eat to help them manage (or prevent) diabetes. And when the talk turns to "glycemic index" and "metabolic syndrome," there is literally not enough room on a food label to explain these concepts to a consumer.

Finally, most consumers don't realize how much they can reduce their risk of diabetes, just with exercise and proper diet. This is a real opportunity for food marketers. Food companies employ sophisticated marketing techniques and utilize persuasive advertising. Turning their focus to communicating the role that nutrition/diet can play in preventing or managing diabetes will open a huge opportunity for growth in the food industry.

## Opportunities: Where nutrition can help with diabetes management

The goals of successful diabetes management include:

- Maintaining normal blood glucose levels and minimizing large fluctuations in glucose levels
- Reducing blood pressure
- Improving blood lipid profiles (cholesterol, triglycerides, etc.)

So how can nutrition help achieve those goals? Here are a few options:

### *Fiber and glucose management*

There is considerable research that suggests that increased fiber may be helpful to a person with Type 2 diabetes (the most common form). Certain fibers delay the emptying of the gut and slow the absorption of glucose. This can help prevent the large spikes in blood glucose that often follow eating a meal, and can help with the regulation of blood glucose.

### *Omega 3s, sterols and blood lipids*

There is a wealth of elegant clinical data showing that certain omega 3 fatty acids (primarily EPA and DHA) can lower the levels of circulating triglycerides. Omega 3 fatty acids, commonly known as fish oils, can also come from vegetarian sources such as algae.

Similarly, there is considerable clinical evidence that shows that plant sterols will lower cholesterol.

These bio-active ingredients are now commonly available and easily purchased from a number of well-regarded companies.

### *Micro-nutrients and oxidative stress*

Oxidative stress is reported to be one of the key drivers of insulin resistance. Oxidative stress may damage mitochondria, which could induce apoptosis (cell death) of the pancreatic beta cells. This could blunt the secretion of insulin and dramatically interfere with proper blood glucose regulation. According to the *Journal of Biochemical and Molecular Toxicology*, pancreatic cells are particularly vulnerable to reactive oxygen species.



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This suggests that diets that are high in antioxidants could be particularly helpful to people with diabetes. Some antioxidants include traditional sources such as vitamins A, C and E, as well as more exotic sources such as EGCG (epigallocatechin gallate), a potent antioxidant found in green tea.

## On the horizon

In addition to these well-established areas where nutrition can play a role in managing diabetes, there are some exciting possibilities that are coming.

> EVERY COMPANY THAT PROVIDES PRODUCTS THAT COULD BE SUCCESSFUL DELIVERY VEHICLES FOR PROBIOTICS SHOULD BE WATCHING RESEARCH ON GUT VERY CAREFULLY.

***Probiotics and the microbiota***

There are preliminary data from Denmark that suggest that the bacteria in the gut of people who have diabetes are different from the bacteria in the gut of people who do not have diabetes. It's not yet clear which is cause and which is effect, but the potential is quite provocative: it could be possible to take probiotics that could address or even reverse diabetes. Every company that provides products that could be successful delivery vehicles for probiotics should be watching this very carefully.

***Reversing diabetes with very low calorie diets***

It has long been thought that diabetes was manageable but not reversible. That is, once you have it, you have it for life. A study recently published in *Diabetologia* challenges that thinking. The study authors found that an extremely low-calorie diet (600 calories/day) could reverse diabetes in just eight weeks. The authors found evidence that this extremely low calorie diet removed excess fat deposits that clog the pancreas, allowing normal insulin secretion to be restored.

This was only one study, which is far from conclusive. And living on 600 calories/day would be extraordinarily difficult for many people in the US, where 1,000 calorie lunches are not uncom-mon. Still, these findings are quite provocative.

> "MAKING IT EASY" WILL BE A NON-NEGOTIABLE REQUIREMENT FOR SUCCESSFUL ENTRY INTO THE DIABETES MARKET.

## What if…?

Let's consider a few unconventional possibilities.

Suppose we didn't try to market diabetes products as "for diabetes," but rather as "glucose healthy," much the way we now say, "heart healthy" rather than "will lower circulating triglycerides." In fact, products that contained certain fibers as well as, for example, sterols could have two insignia on their labels: "glucose healthy" and "heart healthy."

Suppose we didn't require consumers to understand carbohydrate exchanges and fat exchanges and didn't require them to calculate those exchanges in order to determine what they could eat. Suppose that we did that work for them and developed products that were certified by a recognized agency to be "glucose healthy."

Going further, suppose we suggested suites of these "glucose healthy" and



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"heart healthy" products that could go together well to create entire meals, much the way some restaurants recommend certain wines and desserts with specific entrees.

There are lessons to be learned from successful food products that embody a specific functionality. When consumers were concerned about inadequate calcium in their diet and Tropicana launched their orange juice fortified with calcium, it was a great success. The orange juice tasted great and it provided a painless way to add additional calcium to their diets.

"Making it easy" will be a non-negotiable requirement for successful entry into the diabetes market.

## Conclusion

Addressing the nutritional aspects of diabetes is a substantial opportunity for food companies:

- The market is large and it is growing rapidly
- The costs of not managing diabetes are very high
- Nutrition can clearly help manage – and potentially prevent – diabetes
- There are no major competitors who are aggressively pursuing this opportunity

The biggest single roadblock is consumer education/awareness, and the food industry has the means and the talent to clear that hurdle.

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# LUMINARY INSIGHT ON DIABETES

## Arturo Rolla, MD

Dr. Rolla answers Scientia's questions about diabetes therapeutics, diabetes prevention & healthcare cost, and insulin & beta cell functions.




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