Diabetes is perceived as a “simple disease” and manifested in the form of inadequate blood glucose regulation. Paradoxically, it is now also recognized as a global, pandemic disease, with ~415 million patients reported to be suffering from diabetes. The disease is projected to impact ~642 million people worldwide by 2040. This appears to be the tip of a diabetic iceberg, since one-in-two adults are actually undiagnosed diabetics, an additional ~318 million people have impaired glucose tolerance, and are usually described as “pre-diabetic,” and 20-25 % of adults have metabolic syndrome. The limitations of modern healthcare have been ascribed as causative agents in the diabetes crisis. The current healthcare system tends to provide a reactive response to patient symptoms, with a subsequent diagnosis and corresponding treatment of the specific disease. More recently a rapid improvement in OMIC analyses, bioinformatics and knowledge management tools, as well as the emergence of big data analytics, and systems biology have led to a better understanding of the profound, dynamic complexity and variability of individuals and human populations as they undertake their daily activities. These developments in conjunction with escalating healthcare costs and relatively poor disease treatment efficacies have fermented a rethink in how we execute current medical practice. This has led to the emergence of “P-Medicine” which includes personalized and precision medicine. P-medicine is still in a fledgling and evolutionary phase and there has been considerable debate over its current status and future trajectory, as well as its ability to affect the runaway crises of pandemic diabetes. Some have argued that as personalized medicine has morphed into precision medicine (PM) we are just realizing the tip of the PM iceberg. In this paper we evaluate such claims and address the impact of PM on the diagnosis, treatment and prognosis of diabetes and the complementarity of the diabetic iceberg tip of despair and the PM iceberg tip of potential and hope.

Introduction

There appears to be a chronic lack of confidence in global healthcare systems'. Stakeholder expectations have been fueled by repetitive media reports of spectacular advances in the diagnosis and treatment of the major diseases that afflict patients. However, those same patients perceive a lack of delivered value from their healthcare provider. In part this is predicated on the transition of patients into consumers, and their accompanying expectations, particularly in the developed world. Many of these patient complaints involve diagnostic and prognostic inaccuracies, poor treatment efficacies for a specific disease indication, and lack of timely access to patient care. The general dissatisfaction is apparent regardless of the specific healthcare delivery system. The patient could be participating in a single payer, socialized medicine system like the National Health Service of the UK, or a market-driven, predominantly privatized model, such as the patchwork system in the USA'. How did we get to such a critical, and, some might argue, dysfunctional point in the practice of medicine?
The current modus operandi of modern medicine is based on the determination of an individual’s symptoms, along with an associated diagnosis and subsequent response to a specific treatment. These data for the individual are compared to a statistically similar and disease-relevant patient population dataset. There is also a focus on a specific disease indication as it pertains to compartmentalized tissue and/or organs involving, in many cases, a highly specialized clinician. The current healthcare system tends to be reactive, providing treatment post-onset of the disease, with limited efforts focused on prediction and prevention. This reliance on the comparative analysis of an individual compared to a defined population tends to neglect and disregard human individuality, complexity and variability. It also fails to recognize the systems level interconnectedness of human molecular biology, biochemistry, metabolism and physiology in the form of systems, network and pathway biology.

The current medical system has facilitated the escalation of healthcare costs, but has had limited impact on the prediction, prevention, accurate diagnosis, and effective treatment of acute and chronic disease. This lack of progress in concert with a growing awareness of the complexity and variability of individual patients as well as our limited understanding of causal mechanisms of most diseases has necessitated a growing need for change. The clamor for innovation led to the emergent growth of “P-Medicine”. The P-Medicine initiatives that have been implemented over the past decade include Personalized, Precision, Preventive, Predictive, Pharmacotherapeutic, Portable and Patient Participatory medicine. Historically, the first roots of the P-Medicine revolution took hold in the early 2000s. The Personalized Medicine Coalition was founded in 2004. This organization represented the interests of the medical community, and they defined personalized medicine as “…an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from these tests with an individual’s medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans.”

In a surprising development, a report published by the National Research Council (USA- NRC) in 2011 suggested that much of personalized medicine had been predicated on single, anecdotal stories involving lone individuals. The report suggested that such a premise makes for a weak foundation on which to make a diagnosis, treatment and prognosis recommendation to a patient by a clinician. Another common complaint noted was that the term “personalized medicine” implies the prospect of creating a unique treatment for each individual. Whilst the actual practitioners of personalized medicine have not suggested any such thing, the premise took hold and fueled the disappointment and disillusionment with it and the ascendancy of PM. The NRC report attempted to define and differentiate PM from personalized medicine. The report stated that “Precision medicine is the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment.”

P-medicine in the form of personalized and precision medicine is -twelve years old, and continues to be accompanied by enormous hope, hype, enthusiasm and expectation. Therefore, it is useful to evaluate the impact of personalized/precision medicine on a specific disease indication such as diabetes. Diabetes is often described and perceived as a “simple disease” of mis-regulated blood glucose. One might assume that armed with the powerful new personalized/precision medicine toolkit of OMIC analytics, and -OMIC bioinformatics/knowledge management/big data analytics, such a “simple disease” should be both preventable and curable! In 2003, the global estimate for adults (20-79 years of age) suffering from diabetes was -194 million, constituting 5.1% of the worldwide adult population. However, in the intervening twelve year life-span of personalized/precision medicine, the estimated adult population with diabetes has risen to a staggering ~415 million people in 2015, which represents 8.8% of the global adult population. This appears to be the tip of an iceberg, since one-in-two adults actually have undiagnosed diabetes, and an additional ~318 million people have impaired glucose tolerance, and are frequently described as “pre-diabetic” and individuals with metabolic syndrome have a five-fold enhanced probability of becoming diabetic.

Based on the statistics the initial tentative conclusion is that to date, the impact of personalized and precision medicine on diabetes has been minimal. Diabetic onset rates have increased significantly. In this work we consider the mismatched expectations of personalized/precision medicine advocates versus that of the global adult population as the latter struggles with rampant diabetes. We discuss the concept of diabetes as a “simple disease,” and the future role of PM in the diagnosis and treatment of diabetes. Finally, we consider the complementary icebergs of diabetes and PM. We regard the former as the tip of despair and the latter the tip of hope and potential.

**Diabetes - the Simple Disease?**

Diabetes is ostensibly a simple and well characterized disease state. An individual with diabetes manifests elevated blood glucose levels. This is primarily caused either by the individual’s body not producing enough insulin or because the cell/tissue/organ level insulin transport of glucose is compromised. The resulting chronic hyperglycemia can result in systemic damage to the body leading to possible disability and life-threatening complications. In 2015 it was estimated that ~5 million people worldwide died because of diabetes and the global cost was “between $673 billion and $1.197 trillion in healthcare spending.” It is also important to consider that for such a “simple disease,” most countries spend 5-20% of their total annual healthcare expenditures on the diagnosis, treatment and care of diabetic patients.
**Diabetic Types**

Diabetes manifests ultimately as elevated blood glucose levels with concomitant excessive thirst, frequent urination and blurred vision. However, causal onset can be due to a number of factors and this has resulted in the definition of three main types of diabetes as summarized in Figure 1.

**Type 1 diabetes (T1D)** - afflicts 4.73% of the population and is caused by a poorly understood auto-immune response of the body. This results in damage to the beta cells of the pancreas, which are responsible for the body’s insulin production. The disease is diagnosed in individuals of all age groups, but predominantly affects children or young adults, and was previously known as “juvenile diabetes.”

**Type 2 diabetes (T2D)** - this is the most common type of diabetes occurring in 93.5% of all estimated cases of adults. Causal onset is predominantly due to lifestyle choices, and risk factors include physical inactivity, poor nutrition and excessive body weight in the form of adipose tissue. This type of diabetes often goes unrecognized and it is estimated that one-in-two people are actually undiagnosed. According to the World Health Organization (WHO), diabetes should be diagnosed if fasting plasma glucose (fpg) is >126mg/dL, or two-hour plasma glucose (2-hpg) is >200mg/dL following a 75gram bolus of glucose.

**Gestational diabetes (GD)** - an elevated blood glucose level detected in a pregnant mother is classified as either i) gestational diabetes mellitus where fpg levels are 92-125mg/dL; or ii) diabetes mellitus in pregnancy, where fpg levels are >126mg/dL. The number of expectant mothers who are diagnosed with gestational diabetes is relatively small representing only 1.52% of the diabetic population. Gestational diabetes normally disappears after birth (60%), but some women can develop T2D (36%), or less commonly T1D (4%) as highlighted in Figure 1. It is interesting to note that babies born to mothers, who develop post-partum T2D, also have a higher probability of developing T2D themselves.

**Pre-diabetic conditions** - a normal, healthy individual has an fpg level within a 70-100 mg/dL range. However, individuals with elevated fpg levels of 100-126 mg/dL plus a 2-hpg of <140-200 mg/dL are diagnosed with Impaired Glucose Tolerance (IGT). Similarly, patients with an fpg of 110-125 mg/dL and 2-hpg of 140 mg/dL are classified as Impaired Fasting Glucose (IFG) individuals. The fundamental difference is that IGT is defined as a high blood glucose level after eating; whereas IFG is defined as high blood glucose after a period of fasting. People with IGT face a significant probability of developing diabetes. Approximately 5-10% of such individuals become diabetic on an annual basis and overall, up to 70% will eventually develop diabetes. However, this trajectory is not inevitable, and there are numerous reports that lifestyle change in the form of healthy diet and physical exercise and/or medication can prevent the progression to diabetes.

**Metabolic syndrome** - is the current term used for a group of risk factors that considerably raise the risk for developing T2D, as well as heart disease and stroke. In order for a patient to be diagnosed with metabolic syndrome he/she must have at least three of the following five risk factors:

- Abdominal obesity (35 inch waist for women and 40 inch waist for men)
- Elevated blood triglyceride levels (>150 mg/dL)
- Low HDL cholesterol (<40 mg/dL - women and <50 mg/dL - men)
- High blood pressure (>130/85 mm of mercury)
- High fasting blood sugar (>100mg/dL)

It is estimated that 20-25% of the global adult population has metabolic syndrome and 85% of Type 2 diabetics also have metabolic syndrome. Conversely, individuals with metabolic syndrome have a fivefold enhanced probability of developing T2D. This is yet another significant component of the diabetic iceberg scenario!
Diabetes Pandemic

In 1994 the International Diabetes Federation (IDF) estimated that the “global burden” of individual adults with diabetes was ~100 million adults, constituting ~2.9% of the world adult population. The diabetic population had increased to ~194 million (5.1%) adults by 2003, and up again to ~415 million (8.8%) individuals by 2015. Over that same ~20 year period conventional medicine had also been confronted with the advent of personalized/precision medicine (2001-2003). The latter developed under a cloud of scrutiny and the withering refrain “personalized medicine - technological innovation and patient empowerment or exuberant hyperbole?” To date based on the data showing an approximate doubling of diabetic adults every 10 years both conventional medicine and personalized/precision medicine have failed to limit the impact of this “simple disease.” Indeed, the IDF described diabetes as “one of the largest global health emergencies of the 21st century” in their report published last year. The WHO added that, high blood glucose is the third highest global risk factor for premature mortality, after high blood pressure and tobacco use.

The escalating pandemic of diabetes appears to continue unabated. The IDF has noted and tabulated this phenomenon by continuously gathering data from 220 countries/territories around the globe. In addition, they have described the global presence of diabetes by grouping the world into seven IDF regions: Africa (AFR), Europe (EUR), Middle East and North Africa (MENA), North America and Caribbean (NAC), South and Central America (SACA), South-East Asia (SEA) and Western Pacific/China (WPC). The IDF noted that in 2015 ~415 million people worldwide or 8.8% of adults aged 20-79, were estimated to have diabetes, and that ~75% live in low- and middle-income countries. They went on to state that if these trends continue, by 2040 one adult in ten, will have diabetes. The largest increases will take place in the regions where economies are moving from low-income to middle-income levels. Worryingly enough, this is already reflected in the current statistics for 2015, where 7 of the top 10 countries/territories for adults with diabetes were developing economies. They are in descending order China (109 million, ranked 1st); India (69.2 million, 2nd); Brazil (14.3 million, 4th); Mexico (11.5 million, 6th); Indonesia (10.0 million, 7th); Egypt (7.8 million, 8th); and Bangladesh (7.1 million, 10th). The data showing the global incidence of diabetes and the projections for 2040 in Figure 2 are ominous. However, we have noted above

![FIGURE 2: Global estimates of the number of adults (20-79 years old) with Type 1, Type 2 and Gestational diabetes. The estimates are delineated by regions as defined by the IDF and are Africa (AFR), Europe (EUR), Middle East and North Africa (MENA), North America and Caribbean (NAC), South and Central America (SACA), South-East Asia (SEA) and Western Pacific/China (WPC). Note for each region the top number is for the year 2003, the middle number is for 2015 and the bottom number is a projected estimate for 2040, as shown in the black world bubble at the bottom of the figure. All data were derived from either the 2nd or 7th IDF Diabetes Atlas editions. This composite figure was Adapted with Permission from the International Diabetes Federation in Brussels, Belgium.](image-url)
one-in-two adults were unaware of their diabetic condition and this constitutes ~193 million potential patients. The vast majority of these cases are Type 2 diabetics, and globally ~80% of them live in low-to middle income developing economies. Whilst a person with T2D can live quiescently for a protracted period of time, the elevated blood glucose is silently causing extensive and systemic damage to the body. The consequences of this non-diagnosis add considerably to future individual human suffering as well as contribute to escalating healthcare costs.

A different and equally problematic situation is the staggering number of adults estimated to have IGT. Not surprisingly, individuals that have IGT share many of the same characteristics as Type 2 diabetics. IGT afflicts adults of advancing age, who are overweight and possess insulin regulatory problems. The disease has been identified as a significant risk-factor for cardiovascular disease, but also, in many cases remains undetected. In addition, people with IGT have a 70% probability of developing diabetes, and the condition is still popularly referred to as “pre-diabetes.” In 2003, it was estimated that ~314 million people worldwide, (8.2%) of adults in the age group 20-79 years of age, had IGT. Ominously the developing economies of the SEA region had the highest number of people with IGT at ~93 million people as well as the highest prevalence rate of 13.2%. The WPC region that includes China was the next highest with an estimated ~78 million IGT patients representing 5.7% of the population. By 2015, some ~318 million people worldwide, representing 6.7% of adults, were estimated to have IGT.

The socioeconomic trend has continued and the vast majority (69.2%) of those people lived in low- and middle-income countries. However, in an interesting reversal of trends the NAC region was observed to have the highest prevalence of IGT with ~51.8 million adults afflicted, representing 13.9% of the adult population. Another disturbing facet of the data was that approximately half of adults with IGT were under the age of 50 (~159 million), reversing the temporal trend observed for T2D. Where onset is more likely to occur after 50 years of age. In addition, the IDF noted that “it is important to note that nearly one-third (29.8%) of all those who currently have IGT are in the 20 to 39 age group and are therefore likely to spend many years at high risk.” By 2040, the number of people with IGT is projected to increase to ~482 million, or 7.8% of the adult population. Much of this data is summarized in Figure 3 and represents a global pictogram of the estimated IGT adult populations dating from the period 2003-2040. The combination of undiagnosed diabetes, the incidence of IGT, and manifestation in younger adults combined with the growing envelopment of metabolic syndrome represents the hidden underbody of the diabetic iceberg, and must be a cause of concern for all of us.

Figure 3: Global estimates of adults (20-79 years old) with Impaired Glucose Tolerance. The estimates represent the same seven regions described in Figure 2, and the three different estimates per region represent 2003, 2015 and 2040. All data were derived from either the 2nd or 7th IDF Diabetes Atlas editions. This composite figure was Adapted with Permission from the International Diabetes Federation in Brussels, Belgium.
Diabetic Complications

The regulation of blood glucose levels is rigorously controlled in a healthy individual. However, when the process goes awry, the immediate consequence of elevated blood glucose appears to be somewhat inconsequential. Unfortunately, if this condition is left untreated it can lead to life-threatening secondary diseases affecting eyes, heart, kidneys, nerves and the peripheral circulatory system. Long term sufferers of diabetes can be afflicted with:

Retinopathy – the network of blood vessels to the retina of your eye can become blocked resulting in blurred vision and ultimately blindness.

Cardiovascular Disease – is the most common cause of death for individuals suffering from diabetes. This includes congestive heart failure, angina, myocardial infarction and peripheral artery disease.

Nephropathy – caused by damage to the blood vessels in the kidney leading to impairment and loss of function.

Neuropathy – this can lead to systemic malfunction throughout the body leading to problems with urination, digestion, and erectile dysfunction in men. In particular, peripheral neuropathy of the feet leads to infection, ulceration, and “diabetic foot” which can result in extreme cases to amputation.

Gingivitis – leads to a variety of oral health inflammation issues and increased risk of tooth loss and cardiovascular problems.

Sleep Apnea – it is estimated that 40% of individuals with sleep apnea also have diabetes.

Such a simple elevation of blood glucose leads to systemic, serious and often times life-threatening complications for patients with diabetes. This is all captured and summarized in Figure 4.

Diabetes – Carbohydrates and Lipids Intertwined

The regulation of blood glucose in a healthy individual involves the complex interplay of the hormones insulin and glucagon, as well as glucose. The primary tissue/organs involved are the pancreas, liver, skeletal muscle and adipose tissue. This complex series of interactions is summarized in Figure 5. In the case of diabetes, we have noted above it is perceived as a “simple disease” involving dysregulation of blood glucose levels. In reality it is more appropriate to consider the disease as a heterogeneous amalgam of syndromes, where causal onset and progression are still poorly understood. The disease is ultimately characterized by elevated blood glucose caused by a relative or absolute deficiency of the hormone insulin.

The causal onset of diabetes is different for T1D versus T2D. In the case of T1D there is ultimately an absolute deficiency of insulin. This is caused by a poorly understood autoimmune response resulting in damage to the beta cells of the pancreas. Over a period of years, depletion of the beta cell population occurs and when this reaches 80-90% then symptoms of diabetes begin to manifest in the individual. At this point the pancreas fails to respond to the ingestion of glucose, negligible amounts of insulin are produced, and this leads to elevation of blood glucose. If the patient...
does not receive exogenous insulin, death can occur due to ketoacidosis\textsuperscript{11-13}.

Type 2 diabetes is the most common form of the disease (see Figure 1) and is associated with imperceptible onset and poor diagnostic rates. Manifestation of T2D can occur through insulin resistance and/or dysfunctional beta cells of the pancreas\textsuperscript{11-13}. In the case of insulin resistance, target tissues such as liver, adipose and muscle inefficiently respond towards circulating insulin. This is followed by uncontrolled glucose production in the liver and decreased uptake of glucose by muscle and adipose tissue (see Figure 5). A primary cause of insulin resistance is obesity\textsuperscript{22}, although some authors postulate that insulin resistance causes obesity for many individuals. However, it is noteworthy that a significant percentage of obese individuals with insulin resistance do not become diabetic, since the presence of a functional pancreas compensates by producing increased levels of insulin. Type 2 diabetes actually develops in insulin resistant patients when beta cell function becomes impaired.

The cause of insulin resistance is also controversial. However, compelling arguments have been advanced suggesting that fat accumulation is important to facilitate insulin resistance onset. This adds a layer of additional complexity since adipose tissue should not simply be regarded as an energy store, but also is active in secreting a variety of hormones such as leptin, resistin and adiponectin\textsuperscript{22}. Finally, it should be noted that T2D beta cell dysfunction is also different than for T1D. In the former case the pancreas retains some beta cell function, but does not secrete enough insulin to modulate elevated blood glucose levels.
Elevation of blood glucose levels that occurs as a result of either Type 1 or Type 2 diabetes results in a slow, tsunami-like cascade effect. The resultant impact is a series of metabolic changes that occur primarily in the liver, muscle, adipose tissue and the circulatory system. They include:

**Hyperglycemia** – caused by the increased liver production of glucose in concert with diminished use of peripheral circulating glucose. This is driven by the inability of muscle and adipose tissue to take up glucose (see Figure 6).

**Hypertriacylglycerolemia** – after food ingestion not all the fatty acids flooding the liver can be readily disposed of via oxidation. These excess fatty acids are converted to triacylglycerol which is then packaged and secreted as very-low-density-lipoproteins ((VLDL). Ultimately this leads to elevated plasma chylomicrons and VLDL levels (Figure 6).

**Insulin levels** – these levels are either non-existent (Type 1) or extremely low (Type 2) which results in glucagon dominating the glucose cycle shown in figure 5.

**Ketoacidosis** – this typically occurs only in Type 1 diabetics. It results from an increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic synthesis of the two organic acids, 3-hydroxybutyrate and acetoacetate which build up in the circulatory system.

---

**FIGURE 6: Overview of insulin action on glucose, glycogen and lipid flux.**

- **A.** Healthy individual after food ingestion
- **B.** Healthy individual after several hours without food
- **C.** Type 2 diabetic after food ingestion
- **D.** Type 2 diabetic after several hours without food.

These figures were taken from Samuel and Shulman’s work and were Adapted with Permission.
Role of Lipids — We have discussed above the poorly understood causality of pancreatic beta cell dysfunction. Recently, however Taylor and colleagues from Newcastle University demonstrated that fat accumulation in the pancreas is a major causative factor of the under-production of insulin by the beta cells. In a small, but pivotal clinical trial, nine obese people diagnosed with T2D and a nine person control cohort were measured for weight, triglyceride levels in the pancreas (using functional NMR), and insulin response. These measurements were determined eight weeks before and eight weeks post bariatric surgery. Prior to surgery all T2D patients had significantly higher triglycerides in their pancreas compared to controls. After surgery both the T2D and control groups had lost similar amounts of weight, as well as comparable losses of systemic adipose tissue. However, pancreatic triacylglycerol normalized in the T2D cohort, whilst it did not change in the control cohort. In addition, insulin production by pancreatic beta cells also normalized (i.e. increased) in the T2D group but remained unchanged in the control group. This clinical trial was small, but nevertheless provided some compelling evidence that “fatty pancreas” is a major causative factor in beta cell dysfunction and limited insulin production.

In the case of insulin resistance Shulman has argued that “Insulin resistance is a complex metabolic disorder that defies a single etiological pathway. Accumulation of ectopic lipid metabolites, activation of the unfolded protein response pathway and innate immune pathways have all been implicated in the pathogenesis of insulin resistance. However, these pathways are also closely linked to changes in fatty acid uptake, lipogenesis, and energy expenditure that can impact ectopic lipid deposition. Ultimately, accumulation of specific lipid metabolites (diacylglycerols and/or ceramides) in liver and skeletal muscle may be a common pathway leading to impaired insulin signaling and insulin resistance.” This is all highlighted and summarized in Figure 6 A-D.

Lipids are insidiously associated with insulin resistance. It has however been unclear whether circulating lipids or tissue specific lipids result in insulin resistance. After food ingestion dietary carbohydrate (CHO) increases plasma glucose and results in insulin secretion from the pancreatic beta cells (Figure 6A). In the skeletal muscle, insulin increases glucose transport, facilitating glucose entry and glycogen synthesis. In the liver, insulin promotes glycogen synthesis as well as de novo lipogenesis and also inhibits gluconeogenesis. In the adipose tissue, insulin suppresses lipolysis and promotes lipogenesis.

In individuals who are fasting, insulin production and release is decreased. The loss of insulin mediation leads to an increase of hepatic gluconeogenesis and promotes glycogenolysis. Hepatic lipid production diminishes while adipose lipolysis increases (Figure 6B). In contrast for T2D patients ectopic lipid accumulation impairs insulin signaling. With accumulation of intracellular lipid, insulin mediated skeletal muscle glucose uptake is also impaired. As a result, glucose is diverted to the liver. In the liver, increased liver lipids also impair the ability of insulin to regulate gluconeogenesis and activate glycogen synthesis. In contrast, initial lipogenesis in the liver remains unaffected, but together with the incremental delivery of dietary glucose, leads to increased fatty liver. Impaired insulin action in the adipose tissue allows for increased lipolysis which promotes re-esterification of lipids in other tissues (e.g. liver) and further exacerbates insulin resistance. This is coupled with a decline in pancreatic beta cells, and hyperglycemia develops (Figures 6C and 6D). It is evident from Shulman’s work and others that lipid deposition in specific organs and tissue plays a critical role in inducing insulin resistance and appears to be organ/tissue specific.

Role of Carbohydrates — We have inferred above that elevated blood glucose levels are an effect of diabetes. However, it is unclear as to the role of carbohydrates in the mechanistic causal onset of the disease. In part this is due to the misunderstanding of the intimate relationship of glucose with insulin and their combined roles in insulin resistance. The concept of “insulin dependent” glucose uptake by muscle and other tissue has been propagated since the 1950s. Indeed, insulin does stimulate the translocation of the glucose transporter Glut-4 from the cell cytoplasm of muscle tissue to the cell membrane. This facilitates glucose uptake in an insulin dependent mechanism as compared to the basal state of the cell without insulin present. However, there are numerous other glucose transporters such as Glut-1, which is responsible for basal glucose uptake in muscle by an insulin-independent mechanism.

A study in 1983 indicated that in post-absorptive human subjects 75-85% of glucose uptake is noninsulin-mediated and provided additional evidence that insulin may modestly increase glucose uptake merely by providing additional transport sites. A subsequent study in 2001 concluded that there is a sufficient population of glucose transporters in cell membranes at all times to ensure enough glucose uptake to satisfy the cell’s respiration, even in the absence of insulin. Insulin can and does increase the number of these transporters in some cells but glucose uptake is never truly insulin dependent – in fact, even in uncontrolled diabetic hyperglycemia, whole body glucose uptake is inevitably increased.

The same author also addressed the issue of insulin and glucose transport in diabetics. He concluded that when insulin is administered to people with diabetes who are fasting, blood glucose concentration falls. It is generally assumed that this is because insulin increases glucose uptake into tissues, particularly muscle. In fact, this is not the case. It has been shown that insulin concentrations that are within the normal physiological range lowers blood glucose through inhibiting hepatic glucose production without stimulating peripheral glucose uptake.
Contrary to most textbooks and previous teaching, glucose uptake is actually increased in uncontrolled diabetes and decreased by insulin administration! The explanation for this is that because, even in the face of insulin deficiency, there are plenty of glucose transporters in the cell membranes. The factor determining glucose uptake under these conditions is the concentration gradient across the cell membrane; this is highest in uncontrolled diabetes and falls as insulin lowers blood glucose concentration primarily (at physiological insulin concentrations) through reducing hepatic glucose production. In other words, glycogen release of glucose by the liver is the causative reason that blood glucose rises, and insulin when present, mediates this action by inhibiting glucose release by the liver.

It is often believed that experimental and observational studies suggest that dietary glucose intake is associated with the development of T2D. However, when one considers this issue in isolation and independent of obesity related issues, it is unclear whether alterations in glucose intake can account for differences in diabetes prevalence among populations. In that light, Sabu and colleagues recently investigated this very matter and noted that numerous countries had high diabetes prevalence but low obesity rates. The list included a diverse range of socioeconomic and culturally different countries that included France, Romania, Bangladesh, Philippines and Georgia. They also noted that these trends were also dys-synchronous within countries. For example, in Sri Lanka the diabetes prevalence rate rose from 3% in the year 2000 to 11% in 2010, while its obesity rate remained at 0.1% during that time period. Conversely, diabetes prevalence in New Zealand declined from 8% in 2000 to 5% in 2010 while obesity rates in the country rose from 23% to 34% during that decade.

The authors ultimately concluded that every 150 kcal/person/day increase in sugar availability (in the form of both glucose and fructose) was associated with increased diabetes prevalence after testing for potential selection biases and controlling for all other variables. The impact of glucose/fructose on diabetes was independent of sedentary behavior and alcohol use, and the effect was modified but not confounded by obesity or overweight. Duration and degree of sugar exposure correlated significantly with diabetes prevalence in a dose-dependent manner, while declines in sugar exposure correlated with significant subsequent declines in diabetes rates independently of other socioeconomic, dietary and obesity prevalence changes. This is one of the first studies to indicate a direct correlation between carbohydrate intake and diabetes onset.

**Human Microbiome Twist**

The discussions so far clearly indicate that our understanding of the “simple disease” of diabetes is far from complete. The complex intertwining of carbohydrate and lipid metabolism is just now being unraveled. However, a new factor has recently been interjected in the form of the intestinal human microbiome. The microbiome refers to ~100-300 trillion microbes, composed of ~10,000 different species that constitute 1-3% of our body weight and contain an estimated 8 million protein-coding genes. These microorganisms play an intimate and undetermined role in the health and pathobiology of the human host. Recently our knowledge of the microbiome in relation to the function of the human digestive system has increased immensely due to the development of new analytical methods such as high-throughput metagenomic sequencing. This has enabled researchers to identify possible effects of the microbiome on human metabolism, including its potential role in metabolic disorders like obesity and T2D.

Recently the potential role of the gut microbiome in these metabolic disorders has been identified. For example, obesity is associated with changes in the composition of the intestinal microbiota, and the obese microbiome seems to be more efficient in harnessing energy from the diet. There is hope that such differences in gut microbiota composition might function as early diagnostic markers for the development of T2D in high-risk patients. However, for the present time, it is unclear as to the exact role our ~100-300 trillion microbial tenants play in modulating the biochemical elements associated with diabetes. Do they hold the key to innovative new diagnostic and therapeutic protocols, or are these microbes an exponential additive to the indeterminate nature of diabetes?

Recent studies suggest that the human microbiome will add several new dimensions of complexity to consider in the management and treatment of diabetes and related disorders. For example, non-caloric artificial sweeteners (NCAS) have been in use for over a century. They have provided a vehicle for ingestion of “sweet” foods without the accompanying high caloric content of the sugar/carbohydrate. In the past 20 years NCAS have been introduced into a wide variety of cereals, sodas and desserts and marketed as alternative food and beverage sources for individuals suffering from IGT and diabetes. Most NCAS pass through the human gastrointestinal tract without being digested and thus encounter the human microbiome, with a surprising and confounding outcome for diabetic patients!

In a recently widely reported study, Segal and Elinav found that the NCAS saccharin (brand name- Sweet’N Low), sucralose (brand name- Splenda) and aspartame (brand names- NutraSweet and Equal) raised blood sugar levels by dramatically changing the composition of gut microorganisms. They added saccharin, sucralose, or aspartame to the drinking water of mice and found that their blood sugar levels were higher than those of mice who drank sugar water -- no matter...
whether the animals were on a normal diet or a high-fat diet. Although saccharin, sucralose, and aspartame are three different compounds, "the effects were quite similar to each other". When the sweetener-fed mice were given antibiotics to clear their gut of bacteria, their blood sugar levels dropped back down to normal. To gather more evidence of the relationship between artificial sweeteners, gut bacteria, and blood sugar levels, the researchers transferred feces from mice that drank artificially sweetened water into mice that never had. Somewhat surprisingly, blood sugar levels rose in the recipients.

The study was extended to include 400 human subjects where it was determined that the bacteria in the guts of those who ate and drank artificial sweeteners were different from those who did not. People who used artificial sweeteners also tended to have higher fpg levels and IGT. Finally, the researchers recruited seven volunteers, five men and two women, who normally didn’t eat or drink products with artificial sweeteners and followed them for a week, tracking their blood sugar levels. The volunteers were given the FDA’s maximum acceptable daily intake of saccharin from day two through day seven. By the end of the week, blood sugar levels had risen in four of the seven people. Transfers of feces from people whose blood sugar rose increased blood sugar in mice, more evidence that the artificial sweetener had changed the gut bacteria. The sugar in mice, more evidence that the artificial sweetener had changed the gut bacteria. The researchers suggested that the primary focus has been on the treatment of the effect of elevated blood glucose levels, and not a therapeutic paradigm that considers human systems level complexity, variability and causality of diabetes. Recall that Pm “...is the tailoring of medical treatment to the individual characteristics of each patient”. Does a reconsideration of the causal mechanisms of diabetes and a move away from “one size fits all” provide a foundation for the application of the PM toolkit now available in the clinicians’ tool bag?

Diabetes Complexity and Precision Medicine

We have suggested elsewhere that the perception of diabetes as a “simple disease” has led to misunderstanding, poor diagnosis, inefficient treatments and a global prognosis of the disease that is now the “diabetic iceberg tip of despair.” The primary focus has been on the treatment of the effect of elevated blood glucose levels, and not a therapeutic paradigm that considers human systems level complexity, variability and causality of diabetes. Recall that PM “…is the tailoring of medical treatment to the individual characteristics of each patient”. Does a reconsideration of the causal mechanisms of diabetes and a move away from “one size fits all” provide a foundation for the application of the PM toolkit now available in the clinicians’ tool bag?

Earlier, diabetes was described as a heterogeneous mix of syndromes, each having a characteristic and differentiating polygenic etiology. The cardinal features are chronic hyperglycemia along with disturbances in the metabolism of carbohydrates, lipids and proteins (Figures 5 and 6). These disturbances are linked to deficiencies in insulin production and/or insulin resistance. This globally impaired metabolism, attended by varying degrees of hyperglycemia and lack of glycemic balance, is linked to inflammation and wide-ranging impact on all body systems. This systemic impact on the diabetic patient leads to significant disease variability within individuals. However, it is also important to consider the individual susceptibility to diabetes. For example more than 50 loci have been implicated as determinants of T1D risk using the genome wide association studies (GWAS) approach. However, it is likely that only the HLA genes, INS and PTPN22 loci have significant effects on disease risk. It is not clear whether these 3 loci have any equivalency relationship to the 3 clinical subtypes of type I, namely autoimmune, non-autoimmune non-fulminant and non-autoimmune fulminant.

In T2D GWAS studies across diverse populations 70 loci associated with T2D have been identified, although it is not known how many of these loci have a significant effect on the risk or expression of the disease. Significant association of single nucleotide polymorphisms (SNPs) in the CDKAL1, CDKN2A/B, KCNQ1, HHEX, SLC30A8, HLA-B, INS-IGF, TCF7L2 and CAPN10 genes might be associated with equivalent clinical subtypes. If this were the case, it might explain why subpopulations of individuals with T2D responded differentially to drug monotherapy across different categories of anti-diabetic drugs.

From retrospective analysis of electronic medical records, support for at least 3 distinct subtypes from a clinical population of T2D exists. The first subtype was associated with diabetic nephropathy and diabetic retinopathy, while subtype 2 was associated with cancer malignancy and cardiovascular diseases. The third subtype was also associated with cardiovascular diseases, plus HIV infections, allergies and neurological diseases. Genetic association analysis of the subtypes found 1279 SNPs that mapped to 425 unique genes. In the second subtype 1227 SNPs mapped to 322 genes and the third showed 1338 SNPs mapping to 437 genes. These 3 subtypes may substantiate the lower end of the range of subtypes for T2D (Figure 1). We suggest a speculative upper range of ~15 for both T1D and T2D as being about 20% of the gene loci in either case (one might argue that this is reasonable based on genetic association analysis of oncologic diseases). This would represent a reasonable estimate of the proportion of specific gene loci likely to have significant (detectable) impact on either risk or expression of disease components. As genomic studies gain sensitivity it may be necessary to identify and link more subtypes.

Across all of diabetes, it seems that there are subtypes that may respond differentially to various single and combined therapies. In GD, there are clearly, at least 3 subtypes, whereas...
in T1D and T2D there are grounds to suggest somewhere between 3 and 15 subtypes of treatment significance\textsuperscript{33-35}. This means that in approaching the treatment of diabetes, there could be anywhere from 9-33 or more treatable subtypes, where each subtype had treatment-sensitive characteristics. The existence of these subtypes could explain much of the variance in contemporary treatment outcomes, since each subtype might be sensitive only to specific single or combined therapies. One of the goals of precision medicine is to be able to determine the exact subtype sensitivity to therapies. This idea will be further developed below.

Treatment, in all cases, has the targets of glycemic control, both in the acute and long term sense, and the prevention and reduction of complications, including disturbances in lipid and protein metabolism and pathology in other body systems. Contemporary practitioners have a wide array of evidence-based treatment options and clinical decision support systems for choosing among these options. These options include:

- Drug mono-therapy
- Combination drug therapies
- Non drug therapies
- Combination therapy of drug therapies and non-drug therapies
- Lifestyle factor modifications
- Nutritional adjustment - addition or removal of nutrients
- Microbiome adjustments

Along with clinical experience, there are a variety of available PM tools that one can apply, for example clinical decision support systems for option management in the treatment of diabetes. These include CureHunter Inc. (www.curehunter.com), Therametrics (www.therametrics.com) and BioVista’s (www.biovista.com) platforms. For illustration, we will highlight how CureHunter provides PM decision support at a treatment level and how easy it is to use the platfrom to provide cost-effectiveness support too. Pharmacoeconomics are pivotal to the involvement and decision making of the diabetic patient in joint patient-caregiver dyads.

**Drug Therapy Treatment**

We have argued the current therapies are focused on only the effect of diabetes. In order to highlight that point we have assembled the marketed therapeutic agents used to lower systemic glucose levels. The following categories of common glucose lowering agents have a variety of mechanisms and actions and include direct insulin administration, and the popular SGLT2 proximal nephrion inhibitors and this information is all captured and summarized in Table 1.

We have suggested that T2D involves disturbances not just in carbohydrate metabolism but also in lipid and protein metabolism, inflammatory pathways, and microbiome and gut nutrient composition Therefore it would appear prudent to evaluate other types of therapies that may have mechanisms and actions very different from glucose lowering. In the search for further subtypes, it may be helpful to recognize that drug class therapy failure may help to characterize subtype-sensitivity profiles. For example, in GD the commonest management includes prenatal care, nutrition therapy and occasional use of insulin and other drug therapies. Prenatal care and nutrition therapy are highly effective therapies for glycemic control in gestational diabetes.

In the era of PM how can such tools be utilized to address such complex issues. As one example CureHunter Inc. utilizes an Integrated Systems Biology platform which effectively synthesizes all the data and knowledge available from literature sources and clinical trials to produce a clinical outcome database. This database is structured for autonomous prediction of new disease indications for any given drug, biomarker, or active biological agent. The platform consists of five modules:

1. **Controlled Source Knowledge Module** - US National Library of Medicine archive (USNLM) from 1809-current
2. **Data Acquisition Module** - high precision clinical efficacy variable text mining capability using a purpose built semantically intelligent Natural Language Processor
3. **Array Module** - all data is arrayed into a drug-disease-outcome relationships database where each relation is an empirically weighted contributor to clinical efficacy
4. **Analysis Module** - using Network Graph Theory and a suite of algorithms to determine the most centric and similar components of clinical efficacy for all diseases
5. **Prediction Module** - Answer System analytics automation layer with graphic user interface (GUI) for real time output of new indications with high probability of clinical success prediction

The CureHunter platform facilities the capture and automated analysis of all of published biomedical knowledge (in the USNLM) demonstrating a functional role in the clinical efficacy potential of over 250,000 active biological molecules, markers, mechanisms, and drugs operating in over 11,600 disease states. The following table (Table 2) illustrates the typical output for a query about T2D using the CureHunter engine. It shows the top ranked drug monotherapies for the treatment of T2D based upon an analysis of all relevant articles indexed by PubMed (USNLM). Article relevance is determined using an artificial intelligence approach that combines and weights each article based upon its level of evidence and the numbers of articles containing outcome statements, clinical trial or study statements.
<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism(s)</th>
<th>Primary action(s)</th>
<th>CureHunter Effectiveness Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Acarbose</td>
<td>inhibits intestinal α-glucosidase</td>
<td>slows carbohydrate digestion/ absorption</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>Pramlintide</td>
<td>activates amylin receptors</td>
<td>decreases glucagon secretion</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>slows gastric emptying</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>increases satiety feelings</td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>activates AMP-kinase</td>
<td>decreases hepatic glucose production</td>
<td>4.5</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>binds intestinal bile acids, increasing hepatic bile acid production</td>
<td>may decrease hepatic glucose production; may increase incretin levels</td>
<td>1*</td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>Bromocriptine</td>
<td>activates dopaminergic receptors</td>
<td>modulates hypothalamic regulation of metabolism</td>
<td>1*</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations</td>
<td>increases insulin secretion decreases glucagon secretion</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins</td>
<td>Rapid-acting</td>
<td>activates insulin receptors</td>
<td>increases glucose disposal decreases hepatic glucose production</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>shuts ATP$_K$ channels on β-cell plasma membranes</td>
<td>increases insulin secretion</td>
<td>4*</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Canagliflozin</td>
<td>inhibits SGLT2 in the proximal nephron</td>
<td>Blocks glucose reabsorption by the kidney, increasing glucosuria</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide/glibenclamide</td>
<td>shunts ATP$_K$ channels on -cell plasma membranes</td>
<td>increases insulin secretion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>Pioglitazone</td>
<td>activates nuclear transcription factor PPAR-β</td>
<td>increases insulin sensitivity</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1:

Classes of marketed therapeutic drugs used for treatment of diabetic patients, showing examples of each class, mechanisms of action, principal actions, and CureHunter effectiveness index. Based upon Inzucchi et al. 2015 and CureHunter output.

* Denotes Effectiveness Index value based on much more limited data and therefore lower confidence level scores.
and articles with clear context of study statements. The engine provides an effectiveness index on a scale of 1-10, with 10 being the most effective. The indices shown in the table have been rounded for ease of comparison. The importance of this real time computed meta-analysis output to the point of care (POC) provider is to support decision making about drug and related therapies with a higher net benefit to the patient populations being served. Any provider is able to drill down into the articles behind any effectiveness index for any drug or related therapy with one click access in order to satisfy themselves about the provenance of the engine’s recommendations.

In the subsequent table (Table 3) the typical output is shown for a query about T2D using the CureHunter engine. It shows the top ranked related therapies for treatment based upon an analysis of all relevant articles. Just as with drug therapies, the engine provides an effectiveness index on a scale of 1-10, with 10 being the most effective. The indices shown in the table have been rounded for ease of comparison.

The CureHunter recommendations for the treatment of T2D cover drug monotherapy, and comparison between CureHunter output measured in milliseconds with the recommendations of typical national agencies for diabetes. For example, the recent (NICE, 2015 http://www.nice.org.uk/guidance/ng28/evidence/full-guideline-2185320349) for the treatment of T2DM took 6 years to develop. The recent 2015 updated guidelines from the Canadian Diabetes Association (http://guidelines.diabetes.ca/executivesummary) and the January 2016 Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive T2D management algorithm: 2016 executive summary compare favorably with CureHunter recommendations.

<table>
<thead>
<tr>
<th>Related Diseases: 602</th>
<th>Related Drugs/ Bio-Agents: 2408</th>
<th>Related Therapies: 227</th>
<th>CureHunter Effectiveness Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related/Drug/ Important Bio-Agent (IBA)</td>
<td>Outcome Statements</td>
<td>Trial/Study Statements</td>
<td>All Context Statements</td>
</tr>
<tr>
<td>Insulin</td>
<td>273</td>
<td>795</td>
<td>5426</td>
</tr>
<tr>
<td>Metformin</td>
<td>106</td>
<td>244</td>
<td>938</td>
</tr>
<tr>
<td>Acarbose</td>
<td>34</td>
<td>78</td>
<td>179</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>32</td>
<td>108</td>
<td>326</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>29</td>
<td>45</td>
<td>157</td>
</tr>
<tr>
<td>Glyburide</td>
<td>27</td>
<td>56</td>
<td>239</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>26</td>
<td>61</td>
<td>256</td>
</tr>
<tr>
<td>Glucagon-like peptide 1</td>
<td>25</td>
<td>34</td>
<td>357</td>
</tr>
<tr>
<td>Exenatide</td>
<td>18</td>
<td>38</td>
<td>182</td>
</tr>
<tr>
<td>Glargine</td>
<td>16</td>
<td>48</td>
<td>136</td>
</tr>
<tr>
<td>Glipizide</td>
<td>14</td>
<td>27</td>
<td>95</td>
</tr>
<tr>
<td>Alpha-glucosidases</td>
<td>14</td>
<td>23</td>
<td>82</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>14</td>
<td>12</td>
<td>192</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>13</td>
<td>27</td>
<td>109</td>
</tr>
<tr>
<td>Miglitol</td>
<td>5</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>1</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Covasevalam</td>
<td>7</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>1</td>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 2: Type 2 Diabetes mellitus drug therapy

The first column indicates the related drug or bio-agent. The second column shows the number of supporting studies that contain outcome statements. The third column shows the number of supporting studies with clinical trial or study statements, the fourth column shows the number of supporting studies that contain context statements, and the fifth column shows the CureHunter effectiveness index. Users are able to scrutinize all or any of the studies that support a recommended therapy. Studies that are included must meet stringent evidentiary standards that are encoded in the data model and software that parses all articles published by the US National Library of Medicine by a given date. This table shows the capture for a late December, 2015 update.
### Table 3: Type 2 Diabetes mellitus related therapies

The first column indicates the related therapy or procedure. The second column shows the number of supporting studies that contain outcome statements. The third column shows the number of supporting studies with clinical trial or study statements. The fourth column shows the number of supporting studies that contain context statements, and the fifth column shows the CureHunter effectiveness index. Users are able to scrutinize all or any of the studies that support a recommended therapy. Studies that are included must meet stringent evidentiary standards that are encoded in the data model and software that parses all articles published by the US National Library of Medicine by a given date. This table shows the capture for a late December, 2015 update.

<table>
<thead>
<tr>
<th>Related/Diagnosis</th>
<th>Related Therapy</th>
<th>Outcome Statements</th>
<th>Trial/Study Statements</th>
<th>All Context Statements</th>
<th>CureHunter Effectiveness Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric bypass</td>
<td>53</td>
<td>24</td>
<td>147</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>53</td>
<td>16</td>
<td>157</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>15</td>
<td>19</td>
<td>83</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Caloric restriction</td>
<td>7</td>
<td>6</td>
<td>45</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Diet therapy</td>
<td>5</td>
<td>7</td>
<td>41</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aftercare</td>
<td>3</td>
<td>13</td>
<td>40</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Resistance training</td>
<td>3</td>
<td>8</td>
<td>32</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>2</td>
<td>14</td>
<td>68</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Angioplasty</td>
<td>2</td>
<td>14</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Transplants</td>
<td>2</td>
<td>5</td>
<td>50</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate restricted diet</td>
<td>2</td>
<td>4</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Root planning</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Biliopancreatic diversion</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Electroacupuncture</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Since it launched in 2013, the Center for Personalized Diagnostics at the University of Pennsylvania Health System has sequenced more than 4,000 clinical tumor samples to help provide actionable genomic data for the treatment of a variety of cancers. In this session, participants will learn from UPHS leaders of the program how other research centers and health systems can build from the ground up a genomic testing, and data collection function into their clinical operation to provide more precise, individualized care of cancer patients. Learn how to build the IT infrastructure needed to capture, store and analyze genomic data and how to “break down the walls” that exist between research and clinical care to deliver that genomic and diagnostic data across the care continuum, including directly to clinicians via the patient’s electronic health record (EHR).

Register at www.thejournalofprecisionmedicine.com

Sponsored by

[Oracle Logo]

Organized by

[The Journal of Precision Medicine Logo]
Real time meta-analyses of combination therapies linked to specific patient subpopulations are also available from CureHunter online to support further evidence-based steps toward personalized medicine. Combination therapies may consist of drug combinations or drug with non-drug therapies. For example, the POC provider can access instant decision support for choosing combination therapies where specific patients are not responding to prior treatment with monotherapy alone. The example that follows (Table 4) shows a small subset of the articles selected and analyzed for a query about a combination approach to T2D.

### Treatment Failure

When people are diagnosed with T2D, the normative practitioner response is to try drug monotherapy with metformin, unless it is contraindicated. If the response is not adequate, other ﬁrst line agents may be used singly or in combination. Outcome failure on any of these approaches may be viewed as a consequence of combinations of phenotype and genotype, representing subtypes that do not respond to specific single or combination approaches.

If we consider the main categories of anti-diabetic agents, it may be that specific categories do not have effective mechanisms and receptor interactions for people in a given speciﬁc subtype. It will be rewarding to start mapping categories of agents that are effective or non-effective for speciﬁc known subtypes. This would constitute a reasonable and rational approach to precision treatment. An example of a two pronged approach to this would be the convergence of a network biology approach looking to determine subtypes based upon theoretically supported responses to speciﬁc therapies combined with retrospective analysis of large populations with known subtypes looking for the most successful treatment outcomes in known subtype groups. This would allow a mapping of speciﬁc subtype-sensitive therapies to speciﬁc subtypes, one of the essential features of precision treatments.

### Selected Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chobit’ko VG, Zakharova NB, Rubin VI. [Relation between the changes in thiamine metabolism and energy processes in erythrocytes of patients with diabetes mellitus and approaches to their correction with drugs]. Vopr Med Khim. 1986;32(3):118-121.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4:

The first column shows a subset of CureHunter selected studies for a specific combination therapy and the second column shows a brief description for that combination.
There are numerous studies supporting the use of combination therapies both for drug combinations and combinations of drug therapy with non drug approaches. In some cases, positive treatment outcomes may not be directly attributable to specific components of the combination therapy, across or within subtypes. For treatment failure, however, it is possible to assert that the specific combination was ineffective across or within subtypes.

**Alternative Approach**

Earlier, we suggested that approaches of precision medicine (treatment) to diabetes need to be reasonable and rational, where reasonable includes the practical and the pragmatic. Tricorder technology refers to a form of precision nanomedicine using microfluidics with a lab-on-a-chip, where small samples of a person’s body fluid can be analyzed at low cost within a few minutes. Tricorder technology is able to diagnose at least 15 conditions and monitor vital signs for 72 hours. As tricorder technology evolves, it will be applied to the problem of identifying subtypes that are sensitive to specific treatment approaches.

If tricorder technology is combined with a network biology approach plus retrospective analysis of large populations with known subtypes looking for the most successful treatment outcomes, the resulting trivalent convergence should become a powerful strategy for reducing the global burden of diabetes, particularly for T2D. As trivalent convergence methodology identifies and characterizes new T2D subtypes, we see precision treatments evolving along the following lines:

- Drug mono-therapy
- Combination drug therapies
- Non drug therapies
- Combination therapy of drug therapies and non-drug therapies
- Lifestyle factor modifications
- Nutritional adjustment - addition or removal of nutrients
- Microbiome adjustments

Compelling evidence exists to support the existence of T2D subtypes of differential sensitivity to different drug monotherapies, varying combination drug therapies and several related therapies. This points to T2D being a constellation of subtypes where differentiating characteristics include single or combined dysfunctions of many aspects of metabolism, not just limited to carbohydrate metabolism.

It would seem that achieving the goals of PM for T2D could be accelerated by using a combination of clinical decision support systems along with trivalent convergence methodology and using a broad spectrum approach to treatment that included drug monotherapy, combination drug therapies, related non drug therapies, combination therapy of drug therapies and non-drug therapies, lifestyle factor modifications, nutritional adjustment, and microbiome adjustment. Beyond T2D we argue that this multi-pronged approach would satisfy the goals of PM for many other chronic conditions and diseases and simultaneously involve patients in the decision-making process, affording them more autonomy and responsibility for self-care along with choices in cost-effective treatments. This path will, by its very nature, make significant inroads to the huge proportion of national GDP currently spent on treatments in health care.

**Conclusions**

What have we learned from this journey across the current bleak iceberg terrain of diabetes and PM? The concept and perception that diabetes is a “simple disease” has fueled and driven much of our limited understanding of disease onset and therapeutic treatment over the past half century. The impact that conventional medicine, and fledgling “P-Medicine” in the form of PM, has had on diabetes has been exceedingly limited and disappointing. The resultant outcome has been a global pandemic that is staggering in its proportion, and yet reflects just the tip of the iceberg of diabetic despair. It is clear that diabetes results from a complex interplay of both carbohydrate and lipid metabolism mediated by a suite of hormones such as insulin and glucagon. But the clandestine role of lipids manifested in the form of fatty liver and fatty pancreas in diabetes onset and progression is just now being spotlighted.

Does this new insight afford innovative and novel approaches to augment the current tired and somewhat one-dimensional treatment regimes that provide a palliative to elevated blood sugar? At this time, it is unclear. There is a dire human health and socioeconomic need for innovation and creation of new approaches to the prevention, diagnosis, treatment and improved prognosis of this insidious disease. The advent of PM has been accompanied by the usual hyperbole and enthusiastic promise of a “brave new world” in human healthcare, with the past failures of personalized medicine conveniently forgotten. Do the spectra of the twin icebergs of diabetes and PM afford a complementary opportunity? The old cliché “only time will tell” is sorely overused, and woefully inadequate given the current crises of pandemic diabetes, and massive under-diagnosis, accompanied by IGT and metabolic syndrome. It is imperative that PM affords new insights and paradigms into the diagnosis, management and treatment of diabetes predicated on prediction and prevention as part of the vanguard approach to stave off the next engulfing wave of global diabetic patients. In a world where we love to dumb things down, it may be worthwhile to consider that such an approach has gotten us here. Recall that Precision Medicine “is the tailoring of medical treatment to the individual characteristics of each patient and/...classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment.” Maybe this is just what we need and what the doctor should order!
Acknowledgements
We would like to thank Mr. Andrew Jackson (flaircreative.com) and Mr. Damian Doherty (Editor-Journal of Precision Medicine) for their considerable help and input on the figures and content contained in this article. In addition, we express grateful appreciation to Mr. Judge Schonfeld, Founder and CEO of CureHunter Inc, for access to the CHI software and his unflagging support of our efforts.

References
39. Jack Yensen, RN, PhD, is an educator, writer and consultant in e-health and e-learning. He has held many academic and advisory positions throughout North America in universities and corporations in the fields of health informatics (former Director of Education, Canadian Nursing Informatics Association), pathopharmacology, pharmacology, research methodology and advanced nursing. His particular interest in diabetes was stimulated by serving as a National Publications Committee member, Canadian Diabetes Association.
40. Stephen Naylor, Ph.D., is the current Founder, Chairman and CEO of MaileHealth Inc, a systems/network biology level diagnostics company in the health/wellness and precision medicine sector. He was also the Founder, CEO and Chairman of Predictive Physiology & Medicine (PPM) Inc, one of the world’s first personalized medicine companies. He serves as an Advisory Board Member of CureHunter Inc. In the past he has held professorial chairs in Biochemistry & Molecular Biology, Pharmacology, Clinical Pharmacology and Biomedical Engineering, all at Mayo Clinic (Rochester, MN USA) from 1990-2001.

134-153-50