Metabolic profiling in personalized medicine: bridging the gap between knowledge and clinical practice in Type 2 diabetes

Type 2 diabetes mellitus (DM2) is the most commonly diagnosed metabolic disease and its prevalence is expected to increase. Epidemiological studies clearly show excess mortality associated with DM2, as well as an increased risk of DM2-related complications. Advances in personalized medicine would greatly improve patient care in the field of diabetes and other metabolic diseases. Prediction of the disease in asymptomatic patients as well as its harsh complications in patients already diagnosed is becoming a necessity, with the considerable increase in the cost of the treatment. In the current article, we review the known clinical, molecular metabolic and genetic biomarkers that should be integrated in a future bioinformatic platform to be used at the point-of-care, and discuss the challenges we face in applying this vision of personalized medicine for diabetes into reality.

KEYWORDS: biomarkers ■ decision support system ■ diabetes ■ metabolic profiling ■ personalized medicine ■ prediction

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Scope of the problem

The overflow of scientific information has transformed the field of medicine. We are now facing an era in which in addition to the traditional medical training, medical information is readily available to professionals and to the public. Easily searched databases provide original research articles and focused reviews in seconds, and the flow of new information is constant as databases are updated as soon as new information is published. These databases hold key information that may lead to significant progress in clinical medicine. This includes clinical and biological markers as well as genetic markers indicating the variability between one individual to another. These advances in medical research may be used to shed light on the individual's potential medical course, attempting to predict personal risk of developing a disease state, the course of a known illness, the response to therapy and potential side effects. The new challenge for the healthcare system is therefore to be able to translate the success obtained in molecular, genomic, informatic research into readily available tools that can be used in clinical practice for an individual patient, that is, personalized medicine. Indeed, this trend toward personalized medicine is revolutionizing the medical world. Understanding and integrating genetic information with traditional clinical knowledge is the hallmark of this transformation. Physicians should be able to extract the relevant information for an individual patient during an office visit, and use a decision support system to drive personalized medical care. Such a system could be especially useful for physicians treating subjects suffering from metabolic diseases such as obesity, Type 2 diabetes mellitus (DM2) and hypertension. In this patient population personalized medicine can assist in identifying risk factors for prevention and prediction of chronic complications such as cardiovascular disease, as well as tailoring a treatment plan for an individual patient. Since these chronic diseases affect a large portion of the population worldwide, require daily treatment for many years, lead to significant deterioration in the quality of life, decrease life expectancy and increase health costs, such a system has obvious clinical significance. To best illustrate how personalized medicine can be utilized to improve diagnoses and patient outcomes, this article will focus on the future possibilities in employing personalized medicine for improving the management of DM2, thus bridging the gap between the advances in research and technology, and medical practice in the physician's office.

Background

Type 2 diabetes mellitus is the most commonly diagnosed metabolic disease. In 2009, approximately 23.7 million people, including approximately 10.7% of the adult population in the USA, were afflicted with DM2. Unfortunately, its prevalence is expected to increase to 44.1 million people by 2034 [1]. As a result, annual diabetes-related spending during this time period is expected to triple from

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US $113 billion in 2007 to an annual cost of approximately $339 billion. The importance of DM2 is further emphasized by epidemiological studies that clearly show excess mortality associated with DM2, as well as an increased risk of DM2 related complications, including heart disease, stroke, renal failure, peripheral sensory neuropathy and diabetic retinopathy [101].

According to the American Diabetes Association (ADA), diabetes is diagnosed owing to one of the four following criteria:

- Fasting plasma glucose (FPG) above 126 mg% (7 mmol/l)
- Random plasma glucose above 200 mg% (11.1 mmol/l) with classic symptoms of diabetes
- Plasma glucose above 200 mg% (11.1 mmol/l) 2 h after a 75 g oral glucose tolerance test
- Glycosylated hemoglobin (HbA1c) above 6.5% [2].

All diabetic patients share the same treatment goals of early diagnosis and tight control of glucose levels. In an attempt to decrease the chance of developing DM2 related-complications, the maintenance protocol is aimed at lowering HbA1c below 7%.

Treatment of DM2 is often very problematic. DM2 is diagnosed late in many patients and controlling glucose levels can be extremely difficult, which often leads to devastating complications that cause a significant decrease in quality of life. According to the WHO, 50% of people with DM2 die of cardiovascular disease (primarily heart disease and stroke). Of those patients who have lived with DM2 for 15 years or more, approximately 10% develop severe visual impairment and 2% become blind. Between 10–20% of people with DM2 die of kidney failure. The overall risk of dying at least doubles for patients with DM2, with life expectancy in uncontrolled diabetic patients reduced by approximately 8 years [3,4]. On the other hand, some advocate that in well-controlled DM2 patients, life expectancy is similar to that of nondiabetic patients [5]. As is mentioned above, in addition to personal health impairments, DM2 complications have a significant economic impact on the heath system worldwide [102].

Fortunately, not all the patients with DM2 develop all possible diabetes-related complications. As a result, an integrated medical platform in which clinical, biological and genetic markers that are most predictive of the development and appropriate treatment of the disease would be most beneficial for both the physician and the patient. This approach would allow the physician to more accurately identify an individual's risk for various complications, more easily identify patients who require more aggressive medical care and provide the tools a physician can use to create a personally tailored treatment regimen that minimizes the potential for negative side effects. Ideally, this process could be conducted during a 10–15 min office visit, providing quick, inexpensive, up-to-date and readily available diagnosis and treatment regimens that fully support clinical guidelines and scientific advancement of the field. The significance of this challenge clearly demonstrates the critical need for narrowing the gap between knowledge and clinical practice.

Identifying asymptomatic subjects at risk of developing DM2

Type 2 diabetes mellitus is a complex polygenic disorder in which common genetic variants interact with environmental factors to unmask the disease. Early identification of an individual's risk for developing DM2 may aid in the prevention of DM2 and diabetes-related comorbidities [6]. The use of personalized medicine can improve a physician's ability to more accurately identify a patient's risk for the onset of DM2. It is well established that certain populations are at increased risk for developing DM2. The 2011 ADA professional standards of medical care in DM2 recommend screening asymptomatic patients for diabetes if they are overweight or obese, and have additional risk factors such as physical inactivity, family history of DM2, membership in a high-risk ethnic group (African–American, Hispanic origin, Native American, Asian American and Pacific Islander) and women who have delivered a baby weighing more the 4 kg (9 lbs). Other individuals who should be screened include patients that have cardiovascular disease or risk factors for cardiovascular disease such as hypertension, dyslipidemia or conditions suggesting insulin resistance such as polycystic ovary syndrome and acanthosis nigricans [2]. In addition to clinical manifestations, several laboratory markers have been implicated in predicting increased risk for the development of DM2. These include metabolic markers, plasma proteins, markers for endothelial dysfunction recommendations and genetic predisposition.

Fasting glucose is frequently used for screening for diabetes. Current ADA standards of care indicate that impaired fasting glucose measurements

between 100 to 125 mg/dl identify individuals who are at increased risk for the development of DM2 [7,8]. However, even lower levels of impaired fasting glucose can be predictive of an increased risk. For young men who otherwise appear to be healthy, FPG levels as low as of 87 mg/dl have been found to represent an independent risk factor for DM2. It has been suggested that this criteria could be used in addition to traditional factors to identify apparently healthy men at increased risk for DM2 [9]. An additional biomarker that can assist in predicting increased risk for developing DM2 in apparently healthy young men involves taking two measurements of triglyceride levels over a 5-year period of time [10]. Indeed, the risk of developing DM2 was higher in men who progressed from lower triglyceride levels (30–66 mg/dl) to higher levels (164–299 mg/dl) as compared with men whose levels remained in the lower triglyceride range at both time points or men whose triglyceride levels decreased from the high range in the first measurement and the low range in the second measurement.

Sex hormone-binding globulin (SHBG) may also play a role in increased risk of DM2. SHBG is primarily considered a binding protein of circulating hormones, regulating the bioavailable fraction and sequestering circulating androgens and estrogens. Studies since the mid-1990s have suggested that SHBG may have biologic functions beyond simply the regulation of the levels of free sex hormones [11]. Research has found that sex hormone bound to SHBG may directly mediate biological functions such as cell-surface signaling and cellular delivery. Recent clinical studies have associated low circulating levels of SHBG with impaired glucose control, implicating the globulin in the maintenance of glucose homeostasis [12]. Furthermore, circulating levels of SHBG may be influenced by genetic variation. In a study aimed at investigating the relationship between SHBG plasma levels and *SHBG* polymorphisms, it was found that among postmenopausal women and men, higher plasma levels of SHBG were prospectively associated with a lower risk of DM2. Importantly, this finding suggests that *SHBG* may have a causal role in increased risk of DM2 [13].

Cross-sectional studies have consistently found that patients with DM2 [14] and individuals who are at increased risk for DM2 tend to have elevated levels of inflammatory mediators, such as cellular adhesion molecules (CAMs) including intercellular adhesion molecules 1 (ICAM-1), E-selectin, and vascular cell adhesion molecules 1 (VCAM-1), and that these mediators contribute to systemic endothelial dysfunction. A prospective study was performed to determine whether elevated plasma levels of these biomarkers could predict the development of DM2 in women who were initially nondiabetic. It was found that for women who later developed DM2, baseline median levels of these biomarkers were significantly higher than among control subjects. It was concluded that endothelial dysfunction predicts DM2 in women independent of other known risk factors, including obesity and subclinical inflammation [15].

In addition to biomarkers, multiple genetic variants have been associated with the risk of DM2. Recent genetic association studies have provided convincing evidence that several novel loci are associated with increased risk of diabetes [16]. Two studies have recently tested whether the knowledge of these loci provides improved prediction of the risk for development of DM2 over clinical predictors such as phenotypic measurements [17,18]. In these studies, SNPs at loci associated with DM2 were genotyped and analyzed to evaluate the risk of developing DM2. Researchers looked at the predictive value of these SNPs alone and in conjunction with other known DM2-related risk factors. Their findings suggest that a family history of diabetes, increased BMI, elevated liver-enzyme levels, current smoking status and reduced measures of insulin secretion and action are predictors for the development of DM2. Similarly, in a study that focused on the Finnish population, clinical data such as age, BMI, waist circumference, history of antihypertensive drug treatment and high-blood glucose, lack of physical activity and low daily consumption of fruits and vegetables were shown as variables predicting diabetes risk (*FINDRISC*) [19]. Independent of clinical risk factors, variants in several genes, such as *TCF7L2*, *PPARγ*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, *HNF1B*, *CDK2NA/B* and *HHEX*, were also found to be associated with increased risk of developing diabetes. Based on current research, when compared with the predictive value of clinical risk factors alone, common genetic variants that are associated with DM2 have been found to slightly improve the ability to predict future onset of DM2 [17,18,20]. Recent findings by Laakso and colleagues support this concept [21]. When investigating improved identification of previously undiagnosed DM2 individuals, these investigators found that adding measures of total triglycerides, high-density lipoprotein

cholesterol, adiponectin and alanine transaminase (ALT) to the FINDRISC model only slightly increased its predictive value (from 0.727 to 0.772). Adding DM2 risk alleles to the model did not further improve its predictive value [21]. The 40 known SNP variants only improved the predictive value for DM2 risk in patients younger than 50 years of age. Specifically, applying our knowledge of SNPs to DM2 risk appropriately reclassifies patients under the age of 50, but not older patients [22,23]. In addition, it is also strikingly evident that environmental factors affect gene expression and function. Inducing gene promoter methylation has been shown to repress gene expression and modulating key mitochondrial components results in impairment of essential metabolic function of cells. For example, altered metabolite patterns related to lipid pathways may reflect changes in insulin sensitivity [24].

Overall, these studies indicate that while genetic information measured in adulthood does not seem to improve the ability to predict DM2 risk, there is support for the supposition that heterogeneous metabolite fingerprints and phenotypic characteristics better identify individuals who are in a prediabetic state and improve the ability to predict the risk of DM2 onset. The potential use of DNA variants influencing DM2 predisposition and obesity lies in three main areas: the characterization of disease mechanisms that provide new targets for treatment and prevention; improved risk prediction and differential diagnosis; and personalized treatment of DM2 and obesity. To date, the use of molecular diagnostic tools is limited to screening of known causal genes for mutations that are often specific to a given family enabling a more precise diagnosis [23]. Thus, data mining of clinical digital records from large populations will be helpful in improving the ability to discover more accurate biomarkers of diabetes subtypes and additional risk factors. These new discoveries, when introduced into sophisticated algorithms, would improve our decision support system(s), providing physicians with a greater ability to identify patients with potential risks for developing diabetes and its complications.

Predictors of cardiovascular complications in DM2 patients

An additional challenge in personalized medicine is identifying individuals prone to suffer from DM2-related complications using diagnostic tests, whether looking at biological markers or genetic based assays. Once identified, physicians may use available measures in an attempt to prevent the development of these conditions. One example of using metabolic profiling in personalized medicine is the prediction of cardiovascular complications in DM2 patients. An association between metabolic disorders such as DM2 and cardiovascular disease has been known since the 1940s, but it wasn't until the 1980s that this association became more clearly defined, and well accepted, and the term metabolic syndrome (also known as syndrome X or the dysmetabolic syndrome) was coined. Metabolic syndrome describes a cluster of metabolic risk factors that, when present in a single individual, increases this individual's risk of developing cardiovascular disease. The main features of metabolic syndrome include abdominal adiposity, dyslipidemia (elevated levels of serum triglycerides and decreased levels of serum high-density lipoproteins), high fasting blood glucose levels and hypertension [25]. In addition to these clinical factors, there are several other factors that influence the prediction of cardiovascular complications in individuals diagnosed with DM2. These include metabolic factors such as glucose control, lipoprotein (a; Lp[a]) levels and microalbuminuria, in addition to genetic variance-related factors such as variations in the adiponectin gene and its receptor.

To evaluate disease management in DM2, physicians rely on fasting glucose levels as well as HbA1c levels, a marker for average glucose levels over the previous 3 months. Target levels of HbA1c were evaluated in several studies in an attempt to determine whether the rate of diabetes-related cardiovascular complications could be further decreased when levels of HbA1C in subjects with diabetes mellitus Type 1 (DM1) are kept closer to the levels observed in healthy individuals. In several studies, it was found that lowering HbA1c to 6–6.5% slightly increased, rather than decreased, cardiac-related mortality [26,27]. Other intervention studies have found that the incidence of new cardiovascular events is in fact reduced if postprandial hyperglycemia is well managed [28]. However, in patients with poorly controlled DM2, intensive glucose control had no significant effect on the rates of major cardiovascular events, death or microvascular complications [27]. On the other hand, follow-up studies to the UK Prospective Diabetes Study (UKPDS) showed a nonsignificant trend toward improvement in the rate of myocardial infarction in patients who are newly diagnosed with DM2 [14]. The Diabetes

Control and Complications Trial (DCCT) did not show a significant reduction in cardiovascular events with intensive control in young patients with DM1, but a follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, found a delayed benefit for these patients [29]. In a follow-up study conducted 10 years after both groups (intensive or conventional treatment) reached similar HbA1c levels, the patients in the original intensive-therapy group had significantly fewer cardiovascular events than those in the standard-therapy group. Similar results were seen in a 10-year follow-up of the UKPDS. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [30] reported no significant decrease in cardiovascular events with intensive glucose control. Furthermore, the trial ended its intensive therapy early, after only 3.5 years, because of a significant increase in deaths in the intensive-therapy group. The Study to Prevent NIDDM (STOP-NIDDM) found that treating individuals with impaired glucose tolerance using postprandial hyperglycemia medication reduces cardiovascular events by 49% [31]. These data support the hypothesis that glycemic episodes play a role in the development of cardiovascular complications in DM2 patients.

It has also been suggested that measuring Lp(a) levels might aid in predicting the risk of cardiovascular events in DM2 patients. Lp(a) is a nontraditional biochemical marker that has been found to be predictive of cardiovascular events [32,33]. Danesh *et al.* found a clear association between cardiovascular events and levels of Lp(a) in the general population [34]. Normal Lp(a) values are considered any levels below 30 mg/dl. Higher than normal values of Lp(a) have been found to be associated with a high risk for atherosclerosis, stroke and heart attack. In addition, a study that followed DM2 patients over a period of 10 years revealed that patients with low levels of Lp(a) (20 mg/dl) were at a higher risk for cardiovascular complications [32]. However, these studies primarily focused on high-risk individuals. Hence, extrapolating these results to the entire diabetic population is problematic and more research is thus required. For patients who have been diagnosed with diabetes for less than 10 years, several studies have found no clear-cut evidence of cardiovascular complications [35,36]. Previous research has also found that the ability to predict cardiovascular risk is less accurate as a patient's age progresses over 55 years [36]. In conclusion, relying solely on measures of Lp(a) levels when attempting to predict cardiovascular risk in diabetic patients is still not sufficiently accurate and further research in this area is needed.

Microalbuminuria (albumin excretion of 20–200 µg/min over a period of 24 h, or albumin/creatinine ration >30 mg/g in first morning midstream sample) has been found to be strongly associated with cardiovascular risk in DM2 [37]. Albuminuria reduction may improve cardiovascular outcomes: a 50% decrease in albuminuria has been found to be associated with an 18 and 27% reduction in cardiovascular and heart failure risks, respectively [38]. In patients diagnosed with DM1, microalbuminurea might serve as an independent predictor for cardiovascular complications after 10 years or more after the diagnosis of DM1 [39]. However, not all studies support the relationship between microalbuminuria and cardiovascular risk. Some studies have found that microalbuminuria is not a good predictor of cardiovascular risk in nondiabetic patients [40]. Thus, suppressing albuminuria should be evaluated further as a potential way of achieving optimal cardiovascular protection in patients with both types of diabetes.

Genetic variation in diabetic-related genes is another area of research being pursued whose main focus is on identifying individuals at risk for developing cardiovascular complications. For example, the *eNOS* gene was reported to be of clinical relevance to cardiovascular disease as well as nephropathy in DM2 [41]. Recently, a mutation or polymorphism in *eNOS* (rs1799983 GG-genotype) was found to be significantly and inversely associated with cardiovascular disease in DM1 [41]. The mechanism by which such a polymorphism affects the phenotype is as yet unclear, and further studies are needed to confirm these findings. In addition, adiponectin, an adipocyte-derived hormone, has been found to be involved in insulin action, while obtaining anti-inflammatory and antiatherogenic effects. However, its plasma level is reduced in obesity patients, which is likely contributing, at least in part, to impaired insulin resistance. The association between variants in the adiponectin gene (*ADIPOQ*) with circulating adiponectin levels and cardiovascular risk among women with DM2 has recently been examined [42]. The study found that promoter polymorphism 11365C3G was significantly associated with lower plasma adiponectin levels. Furthermore, the patients' homozygous for allele 4034C was found to be significantly associated with a 60% increase in cardiovascular risk. Controlling for

age, BMI and other covariants did not appreciably change this association. In addition, a common haplotype possessing allele 276T (CAATT) was associated with a significantly lower cardiovascular risk than the most common haplotype (CAATG). Another polymorphism in the adiponectin gene (276G3T) was significantly associated with a 45% decrease in cardiovascular risk under a recessive mode of inheritance in diabetic patients [42]. Genetic variability and presence of polymorphisms, though hypothesized to be a key predictor of illness and complications among diabetic patients, still needs further investigation, particularly when trying to determine the potential mechanisms that could be used as effective tools for both diagnostics and treatment.

Personalized medicine for the treatment of DM2 & its related complications

A variety of treatment options exist for individuals with DM2. In addition to dietary and physical activity, DM2 patients are currently treated pharmacologically with nine major classes of approved drugs. These medications include biguanides, sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors, amylin analogues, incretin-mimetics, dipeptidyl peptidase 4 (DPP4) inhibitors and insulin and its analogues [43]. In addition, patients with DM2 are often treated with medications for DM2-related complications such as statins to treat hyperlipidemia, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers , β-adrenergic blockers, calcium channel blockers and diuretics for hypertension, and antiplatelet agents. Initial therapy for DM2 focuses on lifestyle changes and administration of metformin (a biguanide). The rapid addition of other medications and transition to new regimens follow when target glycemic goals are not achieved or sustained, and insulin therapy is added for patients who do not meet target goals [44]. It is recommended that all patients achieve near normoglycemia and HbA1C levels below 7% [45]. Often the response to a specific medication varies between patients, and the physician may need to make several adjustments before finding the most appropriate treatment regimen for an individual patient. A primary focus of personalized medicine is to provide the physician with tools that aid in selecting the most effective treatment regimen for a patient, while decreasing the possibility for adverse events and complications related to the recommended medical care.

There are two major known components of drug response: the concentration of active drug available at its site(s) of action; and the ability of the drug to elicit an effect at its site of action. Drugs are often transported and activated (from inactive to active state), or metabolized to an inactive form, before excretion from the body. Variation of metabolizing enzymes or transporters might therefore have an impact on drug response. Furthermore, drug efficiency is affected mainly by its ability to bind to a receptor, the function of that receptor, and the function of the downstream pathways (direct factors). In addition factors that are different from the effector pathway, such as disease etiology and drug combinations, may contribute to the effect of the drug potency (indirect factors) [46]. Such interaction may inhibit the metabolism of the drug or prevent activation of certain medications, and should be further evaluated [47].

Several studies investigating variation in response to DM2 medications have been performed. For example, studies of the transport mechanism of metformin, a medication commonly administered to diabetes patients, have recently identified organic cation transporters that play a role in metformin disposition. Plasma membrane monoamine transporter (SLC29A4) has been found to be involved in gut absorption [48], OCT1's (SLC22A1) primarily involvement in hepatic uptake, and OCT2 (SLC22A2) in tubular secretion [49,50]. Further studies in humans have demonstrated higher serum metformin concentrations in individuals carrying the reduced function polymorphisms of *OCT1*. This indicates that this transporter is important for metformin's therapeutic action and that genetic variation in *OCT1* may contribute to variation in response to the drug [51]. Metformin acts by activating adenosine monophosphate-activated protein kinase (AMPK), which leads to suppression of glucose production via gluconeogenesis and slightly increased peripheral glucose uptake [52]. Inhibition of hepatic gluconeogenesis by metformin occurs through AMPK-dependent regulation of the orphan nuclear receptor small heterodimer partner [53]. Protein-threonine kinase (LKB1), which phosphorylates and activates AMPK, is critical for the glucose-lowering effects of metformin in the liver [54]. In a recent study involving participants from the DPP study, common variations in 40 candidate genes previously associated with DM2 were analyzed to study their impact on diabetes incidence and their interaction with response to metformin and lifestyle interventions [6]. The genes encoding the AMPK kinase

STK11 and the *AMPK* subunit genes *PRKAA1*, *PRKAA2* and *PRKAB2* were found to be associated with the response to metformin. This promising finding warrants further investigation [55]. In addition to these effects, metformin may also exert a direct effect on pancreatic β-cells. In humans, metformin causes increased insulin release in response to glucose [56] and may help to preserve β-cell function [57]. In addition, it was recently shown in mice that metformin modulates multiple components of the incretin axis, mainly by enhancing the expression of the GLP-1 receptor and related insulinotropic islet receptors through a mechanism requiring PPAR-α [58].

Sulfonylureas (SU) are metabolized primarily by the cytochrome P450 2C9 enzyme. Variations in the common allele for *CYP2C9* affect the catalytic function of the enzyme. These variations, (Arg144Cys *2C9*2*; allele frequency 11% and Ile359Leu *2C9*3*; allele frequency 7%) may change the effect of these medications by changing their concentration in the serum. Most studies have found that individuals carrying the **2/*3* or **3/*3* genotype show reduced drug-metabolizing activities, with a lower dose requirement, as compared with individuals having the wild-type Arg144/Ile359 (*CYP2C9*1*) allele. In healthy volunteers receiving glimepiride, *CYP2C9* genotype altered the pharmacokinetic profile of the drug significantly, with a much slower elimination of glimepiride in individuals carrying the **3* allele compared with those who carry the **1/*1* genotype. When drug elimination is delayed, lower doses of the medication can be prescribed to patients to achieve the desired effect without increasing the risk for side effects such as severe hypoglycemia [43]. SUs act by binding to the SUR1 moiety of the pancreatic β-cell KATP channel, causing the channel to close and trigger insulin secretion. Genetic variation in this pathway was identified in subjects with a mutation in the *TCF1* gene encoding hepatocyte nuclear factor-1 α (*HNF-1α*), causing altered SU response. In a randomized trial involving patients with DM2 due to *TCF1* mutations, a treatment of SUs and metformin showed that the decrease in FPG in response to SU medication such as gliclazide was 3.9-fold greater than their response to metformin. In subjects with DM2, no differences in response to gliclazide or metformin were apparent [59,60]. Several studies have been performed in an attempt to identify polymorphisms in the *KATP* channel and downstream pathways that influence SU response. When 25 SNPs in 11 candidate genes were examined in a prospective trial of patients treated with gliclazide, Ser1369Ala of the *ABCC8* gene and rs5210 of the *CNJ11* gene were identified as significantly associated with reduction in FPG. Compared with subjects with the Ser/Ser genotype, subjects with the Ala/Ala genotype were found to have a 7.7% greater decrease in FPG and an 11.9% reduction in 2-h plasma glucose. No difference in HbA1c was found [59].

In addition to varied responses to DM2 medications, individual differences are commonly found in the levels of risk for DM2-related complications. Individuals with both DM2 and the haptoglobin (Hp) 2–2 genotype are at increased risk of cardiovascular disease. The antioxidant function of the Hp 2–2 protein is often impaired. As a result, several studies have focused on the effect of antioxidant vitamin E supplementation on cardiovascular events (stroke, myocardial infarction and cardiovascular death) in Hp 2–2 DM individuals. These studies found a significant overall reduction in cardiovascular events [61]. Although in clinical studies vitamin E supplementation did not provide any measure of cardiovascular protection in unselected populations with DM2 [62], individuals with Hp 2–2 may benefit from this treatment. In subpopulations derived from these trial cohorts, Hp 2–2 diabetic patients who were administered vitamin E appeared to benefit from this treatment by demonstrating decreased rates of cardiovascular events along with increased life expectancy. This finding further emphasizes the importance and advantages of engaging in personalized medicine over traditional clinical practices.

Prospective tools for personalizing early diagnosis & treatment of diabetes

New innovative tools that were originally developed to study diabetes may also be found to be advantageous for future use in personalized medical care. Examples of such tools include common laboratory markers not currently associated with diabetes or insulin resistance, new technologies for comprehensive analysis, such as 'metabolomics', and employing methods for metabolic profiling of discrete small molecule metabolites using nuclear magnetic resonance and mass spectrometry. In the past, molecules such as uric acid have been shown to be associated with insulin response to a glucose load in both men and women [63]. Recent studies of small molecule metabolites, such as amino acids and fatty acids, represent the net result of genomic, transcriptomic and proteomic variability, providing an integrated biological status

profile. In addition to studies of the mechanisms leading to the development of metabolic diseases, these molecules could also be used to study the action mechanisms of commonly used medications, responses to treatment and adverse event profiles [64]. Measurements of amino acids, acylcarnitines, free fatty acids and conventional metabolites such as glucose, lactate, uric acid, total ketones, hydroxybutyrate and nonesterified free fatty acids in sedentary, overweight to obese, dyslipidemic individuals have found that elevated concentrations of large, neutral amino acids were independently associated with insulin resistance, and that large neutral amino acids and fatty acids were related to appropriate pancreatic responses [65]. In a study aimed to elucidate the effect of exercise training on insulin sensitivity, leptin, adiponectin, D-dimer, paraoxonase activity cytokines, inflammatory markers and metabolic intermediaries were measured at baseline and after 6 months of aerobic training. Four factors were found to be independently associated with change in insulin sensitivity: free fatty acids and by-products of fatty acid oxidation, glycine and proline, acylcarnitine and C18:1-OH acylcarnitine. Modeling indicated that improvements in insulin sensitivity were retained 15 days after cessation of exercise training and, interestingly, greater sustained levels were seen in men than in women [65]. Further research into the role of these factors in the prevention and treatment of DM2, with concomitant development of tools for personalized medicine, are required before this information could be used in clinical settings.

In order to more effectively identify, accurately diagnose and successfully treat individuals at risk for DM2 and related complications, physicians must have access to readily available, reasonably priced and reliable tools. Once this is accomplished, physicians would be able to use these tools to tailor individualized treatment regimens by helping to reveal which patients would benefit from specific treatments while, at the same time, limiting negative side effects. Moreover, discovering which gene mutations or their products could affect treatment quality would also contribute to improved patient health.

Several government organizations (e.g., US FDA and NIH) are currently developing a regulatory platform for evaluating tools that can connect a range of diagnostic and treatment steps, from the identification of a potential therapeutic target by academic researchers to the approval of a therapy for clinical use [66]. As direct-to-consumer genome-wide profiling is readily available (although not yet approved by FDA), and given the complexity of available data we believe that in the near future, during physician–patient encounter a specific platform will be applied whereby from a single blood test/tissue sample, physicians could analyze DNA profile, proteins and metabolites, as well as clinical data to find potential therapeutic options suitable for the individual patient. Developing the regulatory aspect of such an undertaking is of great importance, particularly as it involves the use of genomic, proteomic and metabolomic information in drug and biomedical device development as well as clinical decision-making. Regulation of such requirements must be very strict, should include data protection, confidentiality requirements and quality control of genomic or proteomic databases. Furthermore, patients should be able to expect to receive the right diagnostics and treatment based on tests carried out during a single visit to the hospital, clinic or a physician's office. They should be able to be certain that the diagnostic tests administered to them will give precise and correct results, and that the treatment decisions made by physicians based on those test results are a result of appropriate analyses. Regulation should also include more accurate methods of DNA/protein/drug analysis, further ensuring that results are correct the first time. The clinical benefits of such an approach will increase as new products and approaches are incorporated into daily clinical practice. As the field further develops, it is expected that more efficient clinical trials will be developed based on better understanding of the genetic basis of disease.

Conclusion & future perspective

Advances in personalized medicine would greatly improve patient care in the field of diabetes and other metabolic diseases. Several challenges have to be met before this possibility progresses from theory to practice, and the vision of providing individualized medical care for metabolic diseases as standard practice advances towards realization. Physicians and scientists are working toward the time when, based on clinical and molecular data, patients suffering from a metabolic disease such as DM2 can be stratified according to disease risk, and their risk of developing disease-related complications. Clinical information obtained during an office visit and molecular data derived from on site analysis of various domains such as genomics, proteomics, epigenetics and metabolomics and specific biomarkers, will be combined with information obtained from analysis of large population databases and pertinent clinical guidelines and integrated into a decision support system that

would be used by physicians at the point-of-care to provide the best possible outcomes for their patients (Figure 1). Specifically, this increased use of personalized medicine will provide physicians with the ability to plan the most effective therapy protocol for their patients, while minimizing possible adverse drug events. To achieve these goals, several advances should be made:

- In the field of biology, biomarkers for disease course and management need to be identified. These include establishing a set of predictive biomarkers that would accurately identify patients at risk for developing diabetes and the risk for developing diabetes-related complications.
- In the field of biomedical informatics, data collection for the identification and validation of proposed biomarkers needs to be improved. This includes the development and accessibility of well organized, large scale, multiuser databases that contain clinical, laboratory and molecular information from large samples of individual patients.
- Tools that can provide more robust analysis of the data contained in these large-scale databases are needed. Importantly, the results of these analyses should include identification of a set of biomarkers that indicate the expected disease course in an individual patient, as well as that patient's potential response to various treatment options.
- Medical devices that could be used by physicians in their office during a scheduled visit need to be developed. These devices should be reliable and provide clinically relevant output, in a timely manner, and at an acceptable cost. The technology used in these devices should be able to integrate the individual's clinical, laboratory and genetic information, analyze known biomarkers and provide guidance for physicians that could be used in an individual patient's treatment. In addition, the technology behind these devices should be able to assess the response of a particular patient to a specific medical treatment, recommending dose adjustments and avoiding medications

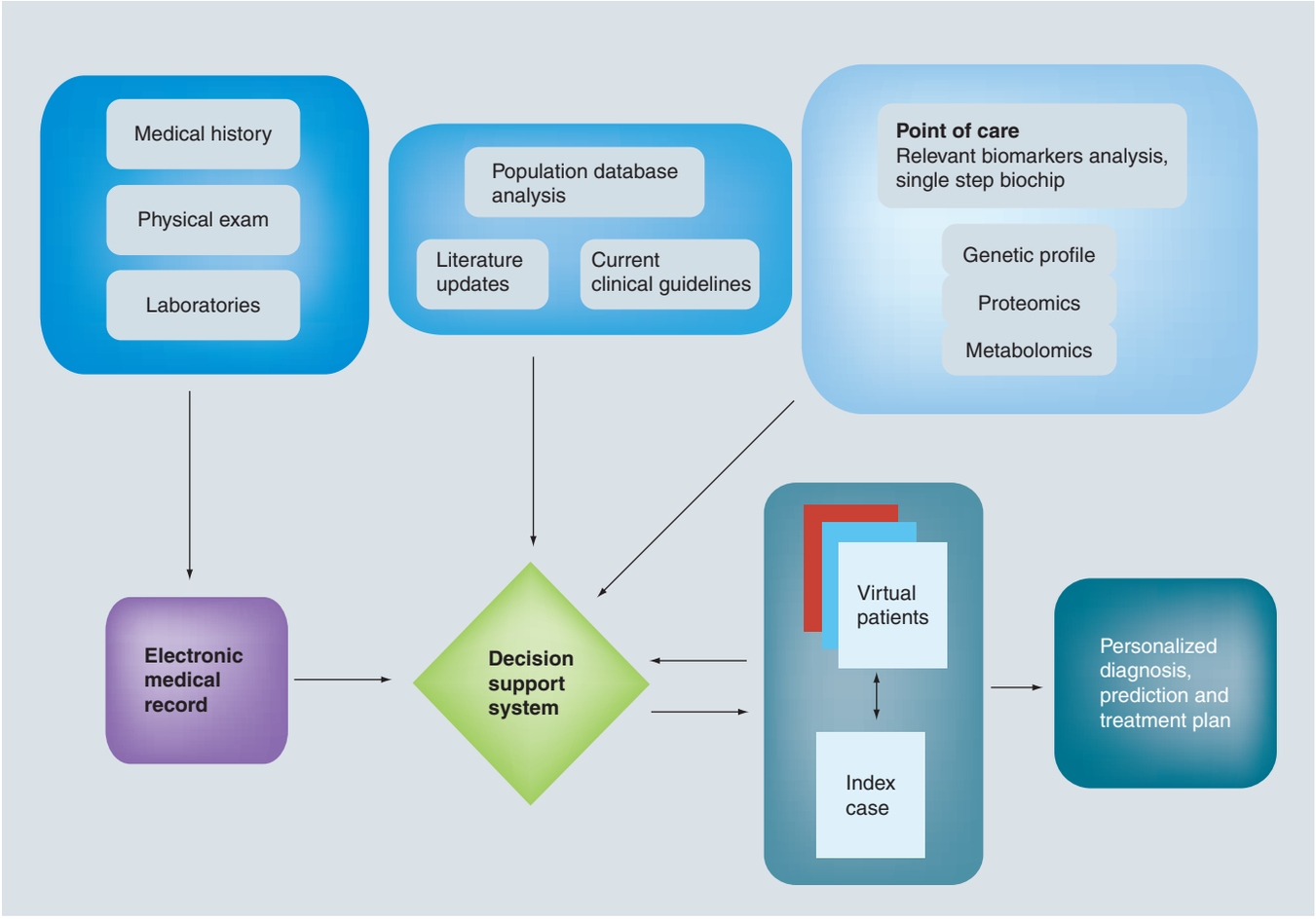

Figure 1. The decision process of tailoring individualized medical care in complex diseases.

that could potentially lead to negative outcomes. This technology would need to be made available in a cost-effective manner to primary care physicians and specialists serving the general population.

Accomplishment of these goals would greatly impact the prediction, prevention and treatment of diabetes, as well as provide substantial advances in personalized medicine. Furthermore, it would greatly improve the quality of medical care while, at the same time, reducing costs.

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Executive summary

Scope of the problem

- Currently available scientific information holds the key to progress in clinical medicine.
- The information could be used to predict the individual's potential medical course.
- Tools to extract information and support clinical decisions are not available in clinical practice.
- The focus of this article is on future possibilities in employing personalized medicine for improving the management of Type 2 diabetes mellitus (DM2).

Background

- Diabetes is the most common metabolic disease, expected to affect 44.1 million in the USA by 2034.
- Diabetes complications have a significant economic impact on the health system worldwide.
- There is a need to identify an individual at risk for various diabetes-related complications.
- Tailoring of medical treatment to the individual characteristics of each patient will minimize diabetes complications and the potential for adverse side effects.

Identifying asymptomatic subjects at risk of developing DM2

- Clinical factors such as obesity, physical inactivity, family history can predict the development of DM2.
- Laboratory factors such as fasting glucose, sex hormone-binding globulin, inflammatory mediators are associated with increased risk for developing DM2.
- Common genetic variants associated with DM2 have slightly improved the ability to predict future onset of DM2.

Predictors of cardiovascular complications in DM2 patients

- Potential predictors of cardiovascular complications in DM2 patients are glucose control, lipoprotein (a) levels, microalbuminuria and genetic variance.
- Subject with haptoglobin 2–2 genotype are at increased risk of cardiovascular disease and may benefit from treatment with vitamin E.

Prospective tools for personalizing early diagnosis & treatment of diabetes

- Metabolic profiling of discrete small molecule metabolites using nuclear magnetic resonance and mass spectrometry such as amino acids and fatty acids.
- Development of a regulatory platform for evaluating tools that can connect a range of diagnostic and treatment steps.

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