Towards a personalized assessment of pancreatic function in diabetes

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ABSTRACT

Introduction: Type 2 diabetes (T2D) is a complex progressive disease that poses significant challenges to delivery of individualized patient-centered care. Despite tremendous efforts, the critical need for biomarkers which accurately predict or monitor disease in individuals beyond classical risk factors has not been realized in the clinic. Given the underlying role of pancreatic dysfunction to disease etiology, this review aims to survey the literature to evaluate the utility of the available biomarkers for a personalized assessment of pancreatic islet function in diabetes.

Areas covered: Literature survey and synopsis of genetic markers of monogenic and polygenic diabetes, imaging biomarkers, plasma metabolite and protein biomarkers, and multi-biomarker algorithms, in the context of personalized medicine. Arguments supporting the premise that the islet secretome is a logical place for discovery of the putative biomarkers with the required performance, supplemented with preliminary data for illustration purposes. Discussion of factors needed for successful adoption of biomarkers in the clinic.

Expert commentary: Speculation on what delivery of personalized medicine in diabetes could entail, with the expectation that it will be predicated on the discovery of easy-to-deploy biomarkers specifically reflective of pancreatic islet health, used in combination with traditional risk factors.

1. Introduction

Diabetes is a complex disease caused by genetic and environmental factors. The global prevalence of diabetes and associated societal and economic burden has been rising steadily, with clear links to lifestyle, inactivity, obesity, aging, and modernization [1,2]. In 2015, an estimated 415 million persons had diabetes, of which 75% of cases were in low- and middle-income countries [3].

There are a multitude of common and rare forms of diabetes which share clinical and genetic features [4]. Among these, type 2 diabetes (T2D) is the most prevalent, accounting for approximately 90% of cases. At the individual level, considerable variation is seen in both the progressive aspects of the disease and the pathophysiology, which can extend across nearly every major body system [4]. Diabetes thus represents a significant challenge for biomarker development as well as an ideal application for personalized medicine.

Pancreatic β cell dysfunction is widely considered to be the key requisite feature of T2D pathophysiology [5]. Development of overt diabetes is preceded by a prediabetes phase which can last several years and damage can start before development of overt disease [6]. Long-term exposure to hyperglycemia can lead to development of comorbidities in multiple other tissues [7]. Progression from prediabetes to diabetes, however, can be delayed or prevented through lifestyle modifications and pharmacological treatment [8,9], and β cell dysfunction may be reversible, particularly at early stages of T2D [10]. Aggressive early treatment to control glucose levels can lessen the long-term severity of complications and improve outcome in certain patient populations [11,12]. However, good metabolic control has not been achieved by a significant proportion of patients [13] in spite of the existing armamentarium of antihyperglycemic drugs and treatment guidelines.

Diagnosis and treatment monitoring of diabetes are currently based on testing of fasting plasma glucose (FPG), oral glucose tolerance tests (OGTT) and glycated hemoglobin (A1c) levels. Despite their proven utility as measures of blood glucose status, these tend to lack the sensitivity and performance needed for early disease detection and resolution of individual disease heterogeneity [14–17]. Tremendous efforts have been devoted toward the identification of biomarkers to accurately predict or monitor disease progression and associated complications, resulting in a significant body of literature describing combinations of risk factors, glycemic measures, and genomic, metabolite, or protein biomarkers [14–17]. With the increased emphasis on patient-centered care [5,18], the realization of individualized therapeutic strategies and treatment targets will likely require the integration of additional biomarker information reflective of particular stages of disease progression and possibly of specific tissue dysfunctions at those stages.

2. Review

This review aims to provide an assessment of the available diabetes biomarkers as direct indicators of pancreatic islet
function. Taken from the point of clinical utility, biomarkers considered in this review were evaluated on the available classification performance rather than their potential relevance to disease causation. The resulting synopses and discussion on the various classes of diabetes biomarkers follow, as viewed from their ability to classify disease status and based on their potential utility as direct indicators of islet function in personalized medicine. The rationale for using the islet secretome as a source for discovery of islet-specific biomarkers with the required performance is discussed, along with a brief consideration of factors needed for successful adoption of novel biomarkers in the clinic. This review concludes with the Expert Commentary and Five-year view sections, offering additional discussion and speculation on future developments toward the realization of personalized medicine in diabetes.

2.1. Genetic markers of monogenic diabetes

Monogenic diabetes is caused by rare, highly penetrant genetic defects with Mendelian inheritance. Linkage analysis and candidate gene studies have identified over 80 disease genes for monogenic diabetes, including multiple subtypes of maturity onset of diabetes in the young (MODY), neonatal diabetes mellitus, and various rare forms of atypical diabetes. Diagnosis of suspected cases of monogenic diabetes is performed via genetic testing, often using Sanger sequencing on a small number of candidate disease genes, selected according to the patients’ clinical, immunological, or biochemical phenotype [19,20]. However, a reasoned selection of gene candidates for sequencing may be difficult or impossible in cases where phenotypic information is lacking or otherwise unavailable [21]. Clinical diagnostic labs are thus increasingly shifting to use of next generation sequencing (NGS)-based tests, which can screen for multiple disease genes and defects in a single panel. The NGS-based tests are not yet considered stand-alone diagnostics, and findings are typically confirmed using microarray-based comparative genomic hybridization or Sanger sequencing [22,23].

The most notable and common form of monogenic diabetes is MODY, which is often reported to account for at least 1% to 2% of all cases of T2D, although epidemiological studies are lacking for many geographical areas and ethnicities [24]. There are currently 14 known MODY subtypes [25], and patients may present markedly different age of onset, disease trajectories, and responses to drug therapy [24]. The majority of diagnosed cases are caused by heterozygous mutations in GCK-MODY2, HNF1A-MODY3, and HNF4A [21]. GCK-MODY2 patients have mild fasting hyperglycemia which remains stable over the patients’ lifetime, and most are able to maintain A1c levels below 8% [26]. GCK-MODY2 patients usually do not require any pharmacotherapy and respond well to diet alone [27]. In contrast, patients with HNF1A-MODY3 are often normoglycemic in childhood and develop progressive β cell dysfunction and microvascular complications [28]. Age at diagnosis is usually between the second to fourth decades of life and has been shown to be related to the type and location of the mutation [29]. Affected individuals are extremely responsive to treatment with low-dose sulfonylureas (SU) [30,31], and consensus guidelines recommend low-dose SU as first line treatment [21]. Although good glycemic control may be maintained for many years, many patients eventually require combination therapy with insulin most often or the new class of dipeptidyl peptidase-4 inhibitors [32]. Patients with HNF4A-MODY1 present similarly to HNF1A-MODY3 and also respond well to low-dose SU treatment [31], whereas the extremely rare HNF1B mutations associated with MODY5 are insensitive to SU treatment and require early insulin therapy to prevent long-term complications [33].

General guidelines to help in MODY diagnosis and treatment selection are available [21,24,34]. However, population screening has not been widely implemented, leading to misdiagnoses particularly among children [35–37]. Nonetheless, accurate MODY diagnosis can inform on individual disease prognosis, guide treatment selection and clinical management, and result in improved patient care [38]. It is therefore an example of a specific but successful application of personalized medicine to diabetes.

2.2. Genetic markers of polygenic diabetes

Current understanding of inherited genetic variants predisposing to T2D is based largely on genome-wide association studies (GWAS) and meta-GWAS studies aimed at discovering single-nucleotide polymorphisms (SNPs) associated with T2D risk. Association analysis using sample sizes in excess of 100,000 and spanning multiple ethnicities have led to the identification of more than 80 robust association signals [39]. These variant loci are relatively common but modestly affect risk, with relative risks around 1.1–1.2 [40]. However, these markers appear to account only for a minority of observed T2D heritability [39].

The clinical value of GWAS-identified loci for T2D risk prediction has been investigated as part of numerous large studies [41–44], typically by generating a risk score based on a count of the number of risk alleles carried by each individual, and relating this score to individual rates of progression to T2D. Such genetic risk scores have failed to provide any additional discriminative power over risk prediction algorithms based on traditional clinical risk factors for disease, such as age, body mass index (BMI), and family history [45]. It is possible that several of the traditional risk factors already encapsulate much of the genetic risk represented by the GWAS-identified loci. GWAS-identified signals have provided limited insights with respect to disease biology and mechanism, as most variants map to noncoding regions of the genome. In time, those variants which have been found to be enriched in coding exons, transcription factor-binding sites, and enhancers active in pancreatic islets [46–49], as well as epigenetic modifications [50] may eventually lead to further insights into novel disease mechanisms and the development of new biomarkers to help guide treatment selection and assess efficacy.

2.3. Imaging biomarkers

Imaging has the advantage of being a direct method of assessing pancreatic β cell mass and thus may be able to introduce additional parameters for a personalized assessment of β cell status that are currently not available. Multiple approaches for imaging pancreatic β cells have been described, using a
variety of small molecule or antibody tracers [51–53]. However, significant challenges remain. Although, on average, β cell mass appears to drop with duration of clinical diabetes, substantial variability in β cell mass in both diabetic and healthy individuals has also been observed [54], suggesting that β cell mass alone may be too variable to use for a personalized assessment of β cell status. Multiple measurements over the course of a longitudinal study may be required to discern a significant change in β cell mass, and these results may need to be combined with indicators of β cell function to derive a full assessment of β cell status. Contrast agents, tracer molecules, as well as animal models are being currently developed or optimized, and full assessments of specificity, sensitivity, robustness, and toxicity remain to be completed [52]. Imaging biomarkers may thus not become available until these technical challenges have been overcome.

2.4. Plasma metabolite biomarkers

Diabetes is characterized by systemic metabolic alterations. Analysis of metabolites associated with these changes may, therefore, be expected to result in good candidate biomarkers. Indeed, multiple large-scale studies have shown that it is possible to identify metabolite biomarkers associated with and in some cases predictive of prediabetes, T2D, and long-term complications, using both targeted and non-targeted mass spectrometry [55]. Metabolites such as branched-chain and aromatic amino acids, gluconeogenesis intermediates, ketone bodies, and various fatty acids have been found to be associated with insulin resistance in a large northern European study [56] and a study of female twins [57]. A small number of amino acids that included isoleucine, leucine, valine, tyrosine, and phenylalanine [58] as well as combinations of glycine, lysophosphatidylcholine 18:2, and acetylcarnitine [59] have been shown to be able to predict T2D. However, branched-chain and aromatic amino acids may also predict cardiovascular disease (CVD) development either alone [60] or in combination with specific fatty acids [61]. Three metabolites that are products of liver metabolic pathways affected by insulin (oleic acid, α-hydroxybutyric acid, and 1-linoleoylglycerophosphocholine) have been developed into a commercial blood test for insulin resistance [62], which has been shown to predict progression from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) over 3 years with better performance than fasting insulin, FPG, homeostasis model assessment of insulin resistance (HOMA-IR), or BMI [62], and is also able to monitor the changes to insulin sensitivity following treatment [63]. A study in subjects with congenital lipodystrophy or loss-of-function insulin resistance mutations suggested that the increased concentrations of triacylglycerols with shorter saturated fatty acids that have been previously associated with insulin resistance were likely to be products of adipose tissue dysfunction [64]. Therefore, in addition to the commercialized liver-derived metabolite biomarkers of insulin resistance, additional metabolite biomarkers derived from other tissues involved in insulin resistance are also being developed.

Multiple recent studies have identified metabolites associated with newly diagnosed T2D, which tend to overlap with the insulin resistance-associated metabolite biomarkers [57, 65–67]. For instance, the metabolite glyoxylate was recently observed to become significantly elevated in plasma up to 3 years prior to diabetes diagnosis [68]. Although the link to β cell function remains uncertain, this reactive sugar-derived aldehyde is involved in the generation of advanced glycation end-products and shows some promise as an earlier indicator of T2D than current standard tests. In another example, a large study evaluated nine metabolites involved in cardiometabolic risk pathways either alone or in combination with 62 diabetes-related SNPs for their ability to predict T2D compared with conventional clinical predictors [69]. The metabolites handily outperformed the SNPs (area under the curve (AUC) 0.803 vs 0.641, respectively) and combining the metabolites with the SNPs only modestly improved overall performance (AUC 0.820). Performance was further improved, however, when the metabolites and the SNPs were used in combination with clinical traits (AUC 0.880). A similar conclusion was reached in another large-scale study [70] where 14 metabolites of carbohydrates, amino acids, and choline-containing phospholipids were able to significantly improve T2D prediction compared to conventional risk factors. The metabolites alone had predictive performance AUC 0.849, and when combined with the German Diabetes Risk Score [71] that combines anthropometric, dietary, and lifestyle factors into a predictive algorithm, T2D predictive performance improved to AUC 0.890. Addition of glucose and A1c only modestly further improved performance (AUC 0.912).

Changes in specific metabolite levels have also been associated with different T2D complications such as high blood pressure, nonalcoholic fatty liver disease, coronary heart disease, or various combinations thereof [72]. A recent study identified that changes to plasma histidine and butyroylcar- nitine levels as well as changes to urine hexose, glutamine, and tyrosine levels can be predictive of the development of nephropathy in type 2 diabetes [73]. Interestingly, however, metabolite profiling of urine was not able to identify differences in monogenic versus polygenic T2D [74]. Moreover, the same branched-chain amino acids associated with prediabetes and T2D were also elevated in the plasma of subjects with pancreatic adenocarcinomas, which are also associated with insulin resistance [75]. These results suggest that most metabolites may be better suited for early detection and monitoring of the overall metabolic dysfunction in diabetes rather than pinpointing the specific tissue defect from where the dysfunction originated.

2.5. Plasma protein biomarkers

Systemic inflammation has long been associated with diabetes, and diabetics have been repeatedly shown to express increased levels of circulating pro-inflammatory cytokines [76–79]. Significant increases in the ratio of neutrophils to lymphocytes have also been reported [80], as well as increased frequencies of senescent CD4+ T cells and reduced levels of CD4+ Treg cells [81]. Endothelial dysfunction has also been described and appears to be useful as a predictor of T2D independent of other risk factors [82]. Adipose tissue inflammation, which appears to be driven by tissue-resident
Chronic inflammation, however, is not a unique feature of pancreatic islets. The changes in the plasma concentration of these proteins are thus not likely to directly reflect the pathophysiological status of the pancreatic islets, but rather the effects of disease progression on those peripheral tissues. Chronic inflammation, however, is not a unique feature of diabetes as it has also been associated with other related conditions such metabolic syndrome as well as with an increased risk of CVD [89,90]. Therefore, similar to the plasma metabolites described earlier, the current plasma protein biomarkers may be better suited for monitoring the systemic dysfunctions in diabetes rather than assessing the physiological state of pancreatic islets.

2.6. Multi-biomarker algorithms

The high degree of variability in diabetes with respect to genetic and environmental risk and the involvement of multiple pathophysiological processes suggests that panels of biomarkers may be needed for optimal performance and disease discrimination. Indeed, although multiple potential biomarkers have been identified, it appears that individual biomarkers do not have sufficient resolution on their own and need to be combined into multi-analyte panels.

Multi-biomarker algorithms have been described for prediction of T2D based on combinations of noninvasive risk factors alone, as well as together with biochemical biomarkers [91–93]. Prediction models using noninvasive measures generally ranged from 0.7 to 0.8 AUC [91,93] though a few had higher performance [41,94,95]. Adding biochemical measures of glycemia modestly boosted overall performance (AUC 0.68–0.85), and genetic profiling appeared unable to improve the performance of the noninvasive metrics [91,93]. This suggests that the biochemical and genetic biomarkers used were largely unable to complement the noninvasive metrics and may indicate that a different type of biomarker, one that is not redundant to the noninvasive metrics, may be necessary to further improve predictive performance.

The limitations of the traditional risk factor metrics can be further illustrated from the results of a recent very large study (>1.1 million subjects) that generated a treatment selection algorithm for any given patient based on historical outcomes of similar patients [96]. Data available for the algorithm included date of birth, gender, ethnicity, height, weight, BMI, history of drug prescriptions, A1c, and creatinine levels. The algorithm had a modest effect, lowering mean A1c by 0.44% for approximately one-third of the patient visits, whereas for the remaining two-thirds of patient visits, the algorithms’ recommendations matched those of the standard of care (SoC). Thus, even with over a million patients to draw upon algorithms derived from the standard clinical information collected are unable to significantly improve treatment responsiveness. A multi-analyte assay that combined several biochemical measures such as the levels of adiponectin, C-reactive protein, ferritin, IL2RA, FPG, A1c, and insulin was used to develop a Diabetes Risk Score that had approximately 0.80 AUC in predicting diabetes over a 5-year period [97–100]. The assay was commercialized although it appears to have had issues with adoption, possibly since this assay’s performance was also comparable in predictive accuracy to the noninvasive risk factors, further underscoring the suggestion that prediction of T2D diabetes will require a different class of biomarkers that are not redundant with the traditional risk factors.

Multi-biomarker algorithms have also been described for the prediction of onset of complications such as retinopathy, neuropathy, and nephropathy. These typically combine analytes descriptive of the underlying diabetes such as glycemia, BMI, or waist circumference, with metrics tailored to advanced disease or to the specific comorbidity. For prediction of retinopathy, frequency of retinal hemorrhage, blood pressure, and urinary albumin and creatinine levels have been used [101,102]. For prediction of peripheral neuropathy, an algorithm was developed that combined metrics of diabetes disease severity such as length of disease duration, treatment with insulin and A1c levels, with metrics of foot issues such as sensory neuropathy, history of foot edema or ulcers, onychomyocysis, as well as vision issues [103]. This algorithm had 1-year predictive performance of AUC 0.81 and a 5-year predictive performance of AUC 0.78, which was confirmed by an
independent study [104]. For the prediction of diabetic nephropathy, the current standard used is the urinary albumin-to-creatinine ratio and the estimated glomerular filtration rate which are, however, not reliable indicators of early stage disease [105]. Recently, a predictive set of algorithms that used A1c and BMI, as well as occupational risks related to hypoglycemia, chronic renal failure, and frail elderly status, was developed to assess risk of diabetic nephropathy [106].

Although use of multi-biomarker algorithms appears to have promise, it is too early to make conclusive statements without additional clinical validation.

2.7. Pancreatic islet biomarkers

Pancreatic β cell status is central to the pathophysiology of diabetes. However, in current routine clinical practice, β cell functioning is only approximated and indirectly so. The prevailing gold standard is based on induced glycemia such as the 2-h OGTT and measurements of plasma insulin and C-peptide levels using a variety of indices [34]. Nonetheless, an elegant argument was recently made for a new classification schema of diabetes based on the status of β cells [107].

According to this new schema, unintended constraints on diabetes personalized medicine that are based on the current disease classification methods would be removed, and a more flexible choice of treatment, one that is more directly tailored to an individuals’ situation, can be implemented. Pancreatic β cells are thus not only key elements of the pathophysiology of diabetes but may also become key elements of a revised view of disease classification. For this vision to be realized, however, direct biomarkers of pancreatic β cell health will be required. These markers are currently lacking, and this has hampered the development of the higher-resolution tests that are necessary for the establishment of personalized assessments of pancreatic islet health.

Biomarkers directly derived from pancreatic islets may thus provide the additional resolution currently lacking in the clinical assessment and treatment selection algorithms described earlier as well as enable a β cell centric reclassification of disease. In furtherance of this argument, the case for biomarker discovery directly from pancreatic islets stems from their highly developed secretory capabilities. When faced with decreased host responsiveness to insulin, β cells can compensate by increasing insulin production [108,109], but chronic compensation can in turn lead to endoplasmic reticulum (ER) stress [110–112], with potential changes in the amount and quality of protein produced and exported. We have previously demonstrated that novel tissue-specific secretory biomarkers can be readily discovered via a comprehensive proteomic analysis of subcellular compartments involved in intracellular transport and protein secretion in the relevant tissues [113,114] and propose that a similar approach is also befitting of biomarker discovery from healthy and dysfunctional islets in diabetes.

To explore the possibility that biomarkers with improved performance [52,107,115] are perhaps more than just theoretical, some preliminary experimental data from a proteomic analysis of pancreatic islet cells has been included in this review for illustration purposes. Figure 1 shows the performance of small panels of three to five candidate biomarkers for classification of patient groups. The candidate biomarkers were identified from cultured primary pancreatic islets from healthy human donors under either normal or glucolipotoxic [116] conditions. Light density intracellular vesicles, which are part of the intracellular vesicle traffic network and the secretory apparatus and within which secreted proteins become highly concentrated, were isolated from the islets and analyzed by mass spectrometry to identify candidate islet-derived protein biomarkers. The specificity of the candidates was then evaluated by using the same experimental approach to identify secreted proteins from multiple organs and select the proteins secreted only by the pancreatic islets. The ability of candidate biomarkers to differentiate normal, prediabetic, and diabetic individuals using blood was assessed with a targeted, multiplexed multiple reaction monitoring mass spectrometry assay (MRM-MS) and sandwich ELISA assays for those candidates below the limit of detection of the MRM-MS assay. Human plasma samples were collected from healthy NGT subjects, subjects with IGT but not clinically diagnosed diabetes, and subjects diagnosed with T2D up to 1.5 years previously. All subjects were comprehensively characterized including by a 2-h OGTT. The biomarker candidates were assessed individually and as members of panels by regression analysis using multiple train and test sets. The small, early-stage data shown in Figure 1 shows that small panels of three to five candidate biomarkers were able to accurately classify the patient groups more effectively than the SoC, FPG, and A1c, and when used in combination with the SoC measurements, the biomarker panels were able to correctly classify all the individuals, suggesting that these islet-derived biomarkers were able to complement the information provided by the plasma glycemia metrics. Although as yet unvalidated, this example serves to illustrate that it should be possible to
combine islet-derived biomarkers with existing clinical measurements to produce tests with the higher resolution required for personalized medicine applications, and a full publication of these results is in preparation.

Although the literature traditionally refers to β cells as the central elements of diabetes pathophysiology, recent evidence has indicated significant cell lineage plasticity among islet cells [117–119]. In the endocrine pancreas, α cells have been shown to be able to differentiate into β cells [120,121], and β cells have been shown to be able to differentiate into α cells [122]. Even γ cells have been shown able to trans-differentiate into β cells [123]. Pancreatic α and β cells appear to have common origins and separate into their distinct lineages relatively late in development [124], and perhaps this relatedness might make the notion of trans-differentiation between these particular lineages relatively simpler to imagine. However, more distantly related exocrine pancreas cells such as duct epithelial cells and acinar cells have also been shown to be sources of β cell neogenesis [125–127]. Terminally differentiated β cells have also demonstrated proliferation capacity [128–130].

Most of this work has been done in rodent models, and the applicability of these results to human pancreatic islet regeneration has to be more fully established. However, an abundance of data suggests the presence of mechanisms that can dynamically alter cellular fate in response to environmental stimuli. Understanding these mechanisms may become important in the development of new islet-sparing or regenerative therapies, and thus, it will be critical for the development of these technologies to be able to identify biomarkers able to measure overall islet health as opposed to specifically β cell health. More practically, human and rodent islets also survive extraction much better than individual β cells, allowing ex vivo assays at the islet level that cannot be done with dissociated β cells. As such, the pancreatic islet may be the minimal biological unit whose health should be reflected by the novel biomarkers.

3. Adoption

While it has been argued that the realization of personalized medicine in diabetes is predicated on the discovery of biomarkers which accurately predict or monitor disease in individuals, the ultimate success of such markers in the clinical setting remains subject to a range of complex and disparate factors. Clinical utility, regulatory requirements, coverage and reimbursement, education, as well as access to the test and integration of health system data are all aspects which can have a great impact on clinical uptake. Studies by Lai-Goldman and Faruki [131,132] on the adoption of novel diagnostic tests have suggested that historically the completion of a high-profile pivotal clinical trial has been the key element impacting the incorporation of novel tests into routine clinical practice. The investigators formulated a model in which test adoption was characterized by three phases. The Early phase in which the clinical application becomes validated typically through multiple clinical studies that can lead to professional endorsement by inclusion in clinical practice guidelines and consensus statements, as well as payer coverage decisions that establish reimbursement.

Introduction of favorable reimbursement decisions and clinical practice guidelines recommending the test potentiates the Acceptance phase, which is also typically associated with a rapid increase in test orders. The test is said to have reached the Maturity phase once test orders reach a sustained and stable level. Timelines for adoption can be variable and may be lengthy. A widely cited study estimated that it takes 17 years for new scientific evidence to be put into practice [133], though the widespread adoption of A1c testing for diabetes appears to have required significantly longer [134].

Additional factors impacting adoption include outcomes research, assessment of reimbursement, and education of physicians and other stakeholders [135–141]. Lack of practitioner education may, for example, underlie the relatively sparse adoption of systematic testing for monogenic diabetes as summarized earlier. Ultimately however, tests which are robust and simple to use, with straightforward easy-to-interpret readouts that enable medical decision-making, should be more readily justifiable to payers. Consideration of such factors relatively early in the biomarker development process should increase the odds of success.

4. Expert commentary

Personalized medicine is expected to allow medical care to become more effective and thus more cost-efficient. Being able to form an accurate picture of a patients’ physiology by integrating each individuals’ risk factors, genetic polymorphisms, disease progression status, potential responsiveness to specific therapies, and systematically integrating this great array of data is expected to result in more accurate diagnoses, better targeted treatments, and thus fewer side effects and therapeutic failures as well as substantial improvements in treatment monitoring. This expansive, highly integrated definition of personalized medicine has yet to be implemented. However, more modest applications are being used today and have indeed resulted in clinical utility. Measurement of HER2 identifies the approximately 20% of breast cancer patients likely to respond to HER2-targeted therapies such as lapatinib and trastuzumab [142]. HIV-infected patients expressing HLA-B*5701, which are approximately 5% of the patient population, are more likely to experience a hypersensitivity reaction to abacavir, a nucleoside reverse-transcriptase inhibitor [143–145]. Colorectal cancer patients with mutations in codons 12 and 13 of k-ras, a G-protein located downstream of epidermal growth factor receptor (EGFR) and required for its signal transduction, are not likely to be responsive to EGFR inhibitor therapies such as cetuximab [146,147]. This list of examples is not exhaustive, but it is indicative of the type of personalized medicine applications currently available, which are based on the presence or absence of specific genes or gene alleles.

Currently, only monogenic diabetes can be served by this type of personalized medicine application. Understanding which specific mutations are present in the individual can significantly impact monogenic diabetes treatment selection and clinical management strategies. Monogenic diabetes, however, represents a small fraction of total diabetes cases, and a different type of personalization will be required to
address the common form of diabetes, which does not appear to be dependent on single gene mutations but on a complex multifactorial interaction of genes, gene products, and environment. Therefore, to produce personalized medicine solutions for the unmet medical needs of the common forms of diabetes, applications that integrate multiple analytes will be needed. This has already begun, and a number of multi-analyte algorithms have been described. Most combine traditional risk factors and metrics of systemic dysfunction to predict the onset of T2D or use these metrics in combination with tissue-specific damage indicators and related risk factors to predict the onset of specific T2D-associated complications. The performance of these algorithms, although better than that of any particular single metric, is however not yet optimal. We believe that continuing to include biomarkers descriptive of the specific tissue dysfunctions into the current algorithms would significantly boost their performance. In particular, inclusion of biomarkers specifically reflective of pancreatic islet health or β cell health in combination with the traditional risk factors should produce personalized medicine applications with clinically relevant performance.

To achieve the level of resolution necessary for these types of personalized medicine applications to be realized, it will become necessary to separate patients on increasingly finer physiological grounds. This cannot be done with the currently available tests. Therefore, a new class of higher-resolution biomarkers will be required. The biomarkers are not likely to be single analytes, but small panels of highly relevant and complementary analytes which in their combination will provide the necessary resolution. To successfully implement personalized medicine, in diabetes or other diseases, a number of structural changes are likely to be required since practitioners would be collecting and integrating far more data than ever before per patient. All this data would need to be all collected cheaply, integrated quickly, and used effectively in medical decision-making; otherwise the healthcare efficiencies envisioned will not materialize. Such wide and readily available data dissemination will most likely raise ethical issues, especially regarding tests that measure predispositions. Thus extensive education will be required by everyone involved in providing health care, including the physicians, insurers, administrators, as well as ethical practitioners and the patients themselves. However, as necessary as these factors may be, for the realization of personalized medicine, the development of this new, higher-resolution class of biomarkers will be the single most critical element and the one that would provide the momentum to drive the application of personalized medicine to diabetes.

5. Five-year view

In the main body of this review, we showed that all biomarkers evaluated through large-scale studies to date were found to have insufficient performance compared to traditional risk factors. Despite the development of very promising multi-parametric algorithms, as well as the frequent proposal of novel markers of islet function, none has been validated in large-scale studies, as yet. Given this current state of biomarker development, our experience with biomarker validation suggests that a 5-year time frame is too short to achieve adequate clinical validation. However, we are more optimistic about the next 10 years, wherein clinical validation of the yet-to-be identified biomarkers may be expected. Subsequent to a successful clinical validation, the various factors affecting uptake of novel biomarkers in the clinic, among them regulatory, reimbursement, and educational, to name a few, can run their course. As such, it may be well over a decade before personalized medicine in diabetes becomes a common clinical application.

Key issues

- T2D is a complex, progressive and potentially preventable disease for which the application of individualized patient care is particularly challenging.
- A number of studies have described attempts to combine clinical risk factors and genomic, metabolite, or protein biomarkers into predictive and monitoring algorithms.
- Algorithms based on combinations of biomarkers that reflect both tissue-specific and systemic dysfunctions at the different stages of disease are likely required for clinically relevant performance.
- Despite β cell dysfunction being a critical feature of T2D pathophysiology, blood based biomarkers directly descriptive of pancreatic islet β cell status are currently lacking.
- A rational, tissue-based biomarker discovery using secretory vesicles from human islets may identify the soluble biomarkers necessary for a personalized assessment of pancreatic islet β cell status.

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Declaration of interest

E Paramithiotis and C Sheu were both employees of Caprion Bisciences, Inc and the time of manuscript preparation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●) to readers.


85. Systematic meta-analysis of candidate diabetes biomarkers.


- **Example of multi-parametric algorithm application.**


- **Compelling argument for reclassifiication of diabetes according to beta cell function.**


- **Pancreatic islet cell plasticity.**


