

# Scientific models for diabetes mellitus health and social care essay



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## **Abstract**

Diabetes mellitus is one of the major clinical problems throughout the world. Previously most of the investigational studies for identification of disease and new therapies were based on animal studies; however, present research methods involve high throughput screening, molecular targeting, nanotechnology for recent discovery of drugs and disease identification to combat against hazardous diseases like diabetes. In this review, we have depicted an outlines enfolding various disease-specific animal modeling, sensing technologies, biomarker analysis, and novel scientific techniques that could be helpful in exploring the impending strategies for diabetes detection and treatment. To conclude, we believe that endorsement and upgrading of such novel high throughput screening assays and nanotechnology described herein may surely represent a significant improvement in the capability for screening and identifying the population at elevated risk of expected diabetes. Thereby in future, appreciation of such investigational techniques and technologies including metabolomics and genetic screening may help in early prediction of diabetes in patients at risk and may display a significant improvement over the researchers conducted after the declaration of the disease. Keywords: Biomarkers; biosensors; Diabetic animal models; High throughput screening.

## **Introduction**

To unearth the pathways associated with cellular injury due to hyperglycemia is one of a very crucial target for diabetes research which might lead to explore new therapeutic strategies to ameliorate diabetes associated cellular injuries. Pathogenesis of diabetes engrosses abnormally <https://assignbuster.com/scientific-models-for-diabetes-mellitus-health-and-social-care-essay/>

elevated levels of glucose and misbalanced levels of lipids (abnormally augmented levels of FFAs, TGs, LDL and VLDL while decreased levels of HDL) [1]. Both of these two metabolic disorders may act as nuclear signals and regulate transcriptional pathways (NF- $\kappa$ B, JNK and IKK $\beta$ ) of miscellaneous metabolic genes [2]. Abnormal activation of these pathways potentiates the glucolipotoxicity (combined term used for glucotoxicity and lipotoxicity) induced insulin resistance in peripheral tissues [3] and overt type 2 diabetes (T2DM). They also induce pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ ) in liver and adipose tissues. Glucolipotoxicity increases the chances of accepted risk factors that potentiate the incidence of diabetes associated complications like microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (atherosclerosis, cardiovascular complications) [4]. Altered life style and nutritional modifications modulate the diabetes and its associated complications [5, 6] that alter the pathophysiological changes inside the body. Therefore, it is much important to investigate the disease progression for its better treatment strategies. According to the FDA guidelines, it is virtually impracticable to pursue the initial stages of these studies on human beings and there is a need for alternate living organism in which these studies may perform the investigations and then the hypothesis originated from these animals must be correlated with human beings. To investigate the diabetes pathogenesis and therapeutic modalities for its treatment, rodents have been used for countless years as an animal model for diabetes, its complications and its possible treatment [7, 8]. The prevalence of T2DM is being increased day by day to staggering numbers and hurriedly becoming a leading cause of death and disability globally. This widespread prevalence of diabetes means that there is a critical need to

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investigate the pertinent causes and mechanism of disease progression. Previously most of the investigational studies were based on animal studies, however, present research methods utilize more enhanced techniques including genome mapping, imaging, target docking, spectrometry, metabolomics, nanosensing and various other novel HTS and nanotechnologies. The need of such novel therapeutic modalities for treatment cannot be neglected but these modalities may also require some specifically designed animal models to imitate all the prospective aspects of diabetes and its associated abnormalities along with the development of vulnerable metabolic pathways for the progression and dissemination of diabetes mellitus. Similarly, a proper understanding of the diabetic biomarkers is also important as it may act as chief platform for the functioning of modern technologies including multi-disciplinary bioassays, HTS, and nanotechnology that may finally help managing diabetes mellitus. Thereby, in this present review, we have focused on the animal models, diabetic biomarkers and their assays along with an overview of various novel HTS and nanotechnologies which are currently being used for the investigations of most susceptible diabetic metabolic pathways and new therapeutic modalities for its treatment.

## **Methods**

The data were collected by searching " PubMed", " Medline", " ISI web of Knowledge" and " Scopus". The key words used as search terms were " Diabetes Mellitus", " Diabetic Animal Models", " Biomarkers", " Bioassays", " Biosensing", " HTS", " Nanotechnologies", " Metabolomics" and " Genomics". 43 articles were retrieved on animal models used for the investigational

studies of diabetes mellitus, 6 articles were used to elucidate the biomarkers to predict the diabetes mellitus, 9 articles were used to describe the nanomaterials and nanotechnology for diabetes mellitus, 7 articles were used to describe the HTS assays for prediction of diabetes mellitus and 11 articles were used to discuss our results.

## **Animal-Modelling for T2DM investigation**

Among the genetic models for T2DM, mostly rodents have been used since many years due to their many advantages over the other animal models. Here, we have only considered the rodent animal models. Up till now, many genetically modified rodents have been developed according to the type of diabetes for the convenience of researchers and investigators. Among them, the rodent models for T2DM and obesity are Zucker diabetic fatty (ZDF or fa/fa) rats, db/db (C57BL/KsJ-db/db) mice, Otsuka Long-Evans Tokushima Fatty (OLETF) rats, ob/ob (C57BL/6J-ob/ob) mice. Goto-Kakizaki (GK) rats are the only rodents that behave as an animal model for nonobese diabetes. These animal models help the researchers to investigate the possible mechanisms involved in the development of diabetes and obesity. But still there are some limitations to use these rodents as animal models because of that both the genetic modifications and observations observed in these animals impersonate those observed in human [9]. In some of these rodent models, leptin gene has genetically mutated while such type of mutations are very rare recessive genetic disorders in human [10]. Similarly, cholecystekinin (CCK) plays its considerable role to control the signals for satiation [11] as it has been mutated in OLETF rats but only few studies reported CCK-1 receptor mutations in obese individuals [12, 13]. Zucker

Diabetic Fatty Rats: To elucidate the pathogenesis of T2DM, animal models are most commonly used by the researchers. Among them, the most usually used diabetic animal model is ZDF rats for investigation of T2DM [14]. In order to develop the early onset of obesity, these rats are specially inbred by mutating the leptin receptor gene [15]. The onset of diabetes usually appears at the age of 8-10 weeks [16] in association with other clinical symptoms of overt obesity, elevated serum levels of insulin, triglycerides and cholesterol [17], hyperphagia, polydipsia and polyuria [18] along with abnormal weight gain. Before the onset of diabetes and other metabolic disorders, the islet architecture and morphology is usually normal for up to 6 weeks of age but as the age increases,  $\beta$ -cell death starts that reveal the change of normoglycemia to hyperglycemia and at the age of 12 weeks, significant fibrosis occurs due to  $\beta$ -cell death [19]. At the age of 26 weeks, ZDF rats also develop inflammatory markers such as TNF- $\alpha$  and IL-1 $\beta$  [20].

db/db Mice: These mice are well known model of T2DM. These mice carry out the inheritance of leptin receptor gene mutation that is occurred at chromosome 4 [21]. Augmented levels of glucose usually arise after 8 weeks of age. The reason for hyperglycemia is due to the increased insulin resistance and consequential deficiency of  $\beta$ -cell mass. Hyperinsulinaemia and impaired glucose tolerance appear at the age of 12 weeks [22]. Plasma elevated levels of total cholesterol, triglycerides, LDL and FFAs whereas the decreased concentration of HDL is observed after 13 weeks of their age [23]. Due to these abnormal concentrations of lipids, these mice act as good model for the investigation of diabetic dyslipidemia.

OETF rats: These rats were discovered at Tokushima Research Institute in an out-bred colony of Long-Evans rats in 1984 with characteristics of obesity, onset of

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hyperglycemia, polyuria, polydipsia and chronic diabetes mellitus.

Furthermore, in response to development of spontaneous obesity in Long Evans rats, Otsuka Pharmaceuticals developed two groups of rats were by selective breeding. Due to this reason, these rats are known as obese Otsuka Long Evans Tokushima Fatty (OLETF) and control Long Evans Tokushima Otsuka (LETO) [24]. One of the main characteristics is that OLETF rats are hyperphagic and eat much more than that of LETO rats. The reason to consume more food by OLETF is that these OLETF rats are initially characterized by the absence of pancreatic acini cells that respond the brain and/or gut peptide cholecystokinin (CCK). CCK is key hormone that facilitates the digestion of food in small by the activation of CCK-1 receptors [25, 26]. These receptors are absent in OLETF rats. Due to the absence of CCK-1 receptors in OLETF rats, these rats are naturally occurring CCK-1 receptor knockout model for the investigation of obesity and T2DM. With the increase of their body weight, the degree of glucose intolerance increases and impaired glucose tolerance appears at the age of 5 weeks that leads to overt hyperglycemia and hyperinsulinaemia [27].

**ob/ob Mice:** These mice were discovered at Jackson laboratory in 1949. These mice were developed by the inheritance of monogenetic autosomal recessive mutation of leptin gene on chromosome 6 [28]. These mutant mice are phenotypically identical to their unmutated littermates at the time of birth but as the time passes, they gain their body weight more quickly throughout their life. Usually, they gain their body weight three times more than that of their littermates. The onset of obesity, hyperglycemia and hyperinsulinaemia usually develop at the age of 4 weeks [29] whereas the onset of impaired glucose tolerance appears at the age of 12 weeks [30].

**GK rats:** These rats were specifically established from <https://assignbuster.com/scientific-models-for-diabetes-mellitus-health-and-social-care-essay/>

the Wistar rats after their repetitive inbreeding [31]. These GK rats have the ability to reduce their pancreatic  $\beta$ -cell mass up to 60%, due to diminished  $\beta$ -cell replication [32]. This diminution of  $\beta$ -cell mass imitates the restrictions of  $\beta$ -cells regeneration during their initial stage after birth and afterward, these GK rats become unambiguously diabetic during their weaning period after 3-4 weeks of their birth [33, 34] but their body weight is usually less than their age-matched wistar rats [35]. Low-grade local and systemic inflammation is present in GK rats and this inflammation has been considered as a pathophysiological hallmark in GK diabetes [36, 37]. Damage of  $\beta$ -cells followed by insulin resistance developing soon after in their life is the main characteristic of GK rats [38]. It has been confirmed from the already published data that islet inflammation directly correlates with  $\beta$ -cell dysfunction in GK rats [36, 37, 39], and their pancreatic islets express augmented mRNA levels of various cytokines (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ), chemokines (KC, MCP-1 and MIP-1 $\alpha$ ) and cytokine signaling intermediates (MyD88 and NF- $\kappa$ B) that correlate with immune cell infiltration [39]. GK rats have the ability to develop increased levels of TG, FFAs, cholesterol/ HDL ratio along with escalated levels of chemokines [40].

Genetically Engineered Diabetic Mice models: Recently, instead of genetic animal models, genetically engineered mice models have also been developed to investigate the effect of abnormalities induced by diabetes. These mice are either transgenic and/or knockout. Different kind of proteins, hormones and signaling receptors that play their crucial role in diabetes are usually removed by modification in the genomic sequence of mice [9]. The most important proteins and receptors for the onset of diabetes are glucose transporter type 4 (GLUT4), insulin receptor substrate 1 (IRS-1) and insulin

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receptor substrate 2 (IRS-2). IRS knocked out mice cannot stay alive for more than 72 hours due to the development of acute ketoacidosis [41] along with hyperglycemia and hyperinsulinaemia [42]. Due to their short life span, these genetically engineered mice cannot be used in long term studies. In addition to this drawback, these mice are doubtful to impersonate human conditions because the mutation of IRS is extremely rare in human [43]. Although, these knockout mice provide significant information regarding the function of unambiguous proteins but they do not have the ability to mimic the diabetic symptoms in human. Chemically induced animal models of diabetes: Instead of genetic and genetically engineered rodent models for diabetes, some animal models are also developed that are induced by the sudden chemical induction to investigate role of antidiabetic agents. The chemicals that are most commonly used to induce the diabetes are alloxan and streptozotocin. These chemicals enter into the pancreatic  $\beta$ -cells via GLUT2 transporter due to the structure similarity with that of glucose [44]. Single dose of these chemicals may cause the selective necrosis of pancreatic  $\beta$  cells in rats and mice [44-47] as a model of diabetes. Although, these chemically induced diabetic rodents exhibit inflamed fatty liver [48] while in contrast to the patients with diabetic syndrome, these rodents are hypoinsulinaemic [49]. The signs and symptoms of chemically induced diabetes depend on the dose of these chemicals administered and the age of the rodents. For example, to produce moderate hyperglycemia and decreased HDL-cholesterol concentrations without any other lipid abnormalities and oxidative induced enzymatic changes, usually low dose of streptozotocin (70 mg/kg) on 5th day of life is required to induce type 2 diabetes [50]. Insulin resistance and abnormally high levels of CRP and TNF-

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$\alpha$  are produced after 14 weeks when a little bit high dose (90 mg/kg) of streptozotocin administered in 2 days old rat [51]. Although, these changes which are usually observed in chemically induced diabetic rats are sufficient to investigate the effect of antidiabetic agents but regrettably inadequate to define the sign and symptoms of diabetes associated complications and metabolic syndromes in human.

## **Biomarkers as diagnostic tools for T2DM**

These above mentioned diabetic animal models are being used to characterize and investigate the diabetes and its associated complications. Here in the following sentences, we have described various biomarkers that are helpful to diagnose the diabetes and its associated complications, and how these markers play their potential role in these diabetic animal models or how can they be used as diagnostic tools in human. These are the factors or feature that is independently deliberated and evaluated as a pointer of typical biological procedure, pathogenicity and/or pharmacological responses to therapeutic modalities [52]. The integration of biomarkers has clinical remuneration that act as a linkage in between screening, diagnosing and/or monitoring of disease progression and evaluating therapeutic comebacks. Due to their broad spectrum functional integrity, these biomarkers have gain considerable primacy in diabetology. Although, there is no single biomarker that can confirm onset of diabetes but following are some important biomarkers that may be helpful to investigate diabetes and therapeutic interventions to be used for its treatment. Inflammatory biomarkers: Diabetes mellitus is state of chronic low-grade inflammatory syndrome in which multifactorial metabolic pathways and inflammatory mechanisms [53]

are involved. It is usually characterized by glucolipotoxicity and insulin resistance [54-56]. Low-grade inflammation plays its crucial role in progression of diabetes and the most important inflammatory biomarkers are high sensitive C-reactive proteins (hs-CRP), Interleukin-6 (IL-6), CC-chemokine ligand 2 (CCL-2) hyaluronic acid (HA) and tumor necrosis factor alpha (TNF- $\alpha$ ). Biochemical markers: Although, these biomarkers are not used to predict the inflammation but they are the strongly used as an indicators for the prediction of diabetes mellitus. The most commonly used biomarkers are plasma glucose, insulin, cholesterol, glycated hemoglobin (HbA1c), triglycerides (TGs), high density lipoprotein (HDL), low density lipoprotein cholesterol (LDL), leptin, adiponectin, free fatty acids (FFAs). Oxidative stress biomarkers: Oxidative stress is one of the key reasons that may cause the pathogenesis of T2DM dissemination [1]. The most important biomarkers that may predict the oxidative stress are oxidized LDL, glutathione peroxidase (GSH-Px), Thioredoxin (TRX) and lipid peroxidation products. CVD biomarkers: The chronic onset of T2DM may cause cardiovascular diseases and the biomarkers that may use to predict and diagnose the disease symptoms and its severity are intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), endothelin-1 (ET-1) and von Willebrand factor (vWf). Taken together, the various biomarkers discussed till now in this review validates the importance of biomarker screening assay as an essential tool for the management of diabetic patients for the determination, identification and development of potential and efficient therapeutic strategies including advances in anti-diabetic agents for treating diabetes mellitus.

## **Nanomaterials and Nanotechnology in Diabetes**

Nanotechnology presents precise and appropriate diagnostic information regarding diseases. Moreover this technology is also recognized for providing an automatic treatment using sensing technologies and devices and thus may help prevent some uncomfortable tests which are thought to be mandatory for the sake of patient's health like evaluation of blood glucose level in diabetic patients. Thereby nanotechnology has made some diagnostic assessments and drug dosing more accurate and accessible for patients. Investigators have been using nanotechnology to improve the lifetime, precision, extent and utilization of sensors for diabetic treatments. Here we will correspond to recently made advances of nanotechnology, specifically, its impact on improving diabetic diagnosis and treatment.

Electrochemical biosensors: To measure small amounts of blood glucose levels and insulin via insulin-producing cells is one of the latest innovations that are leading towards improvements in human health. Additionally, various electrochemical biosensors have been recently utilized in clinical responses [57], recently, a multiwalled carbon nanotube sensor utilizing the islets in a microfluidic system has been developed for the electrochemical detection of insulin even at lowest concentration of 1  $\mu\text{M}$  in multianalyte microphysiometer [58]. Similarly, other than microphysiometer, advances in biosensors have been recognized as an essential tool of modern science incorporated for glucose sensing. Measurement of glucose level in vivo using biosensors has been a significant improvement. Sandwich-type and the miniaturized flow-through biosensor [59] have been developed by Leegsma-Vogt and colleges which requires connection to implanted microdialysis

probes. They further suggested that these types of biosensors which can <https://assignbuster.com/scientific-models-for-diabetes-mellitus-health-and-social-care-essay/>

electrochemically detect glucose oxidase or lactate oxidase may be effectively used via subcutaneous and intravenous route, however, may require safe intravenous devices. The inclusion of nanomaterials in biosensors achieves advantages, for instance efficient transfer of enzyme electron to electrode. Recently, nanotechnology has been implied for targeting diabetic markers like autoantibodies in type I diabetes [60]. All of the common applicable nanotechnology as diabetic sensor is the utilization of the nanomaterials for enzymatic electrochemical analysis of glucose [61].

**Fluorescent nanosensors** One recent nanosensor of this type is polymeric nanosensor known to contain polymer having lipophilic glucose identifying components and fluorescent corresponding reporters [62]. They follow the principle of optical interrogation of glucose level via skin without any implanted electrode and may illustrate fluorescent change with the change in glucose concentration [60]. Similarly, to identify glucose some polymeric nanosensor contains boronic acid derivatives as nanospheres attaching fluorophores [63]. Moreover, to recognize glucose level, some fluorescent molecules are coated over polyethylene glycol beads which are placed under skin and this system detects drop in glucose level and emit fluorescence on skin tattoos [64].

**High Throughput Screening assays for Diabetes:** From previous few years, various innovative high throughput assays relating to diabetic biomarkers and receptors have been a major focus for diabetes screening. These High throughput assays have represented to be a significant improvement in the ability for appropriate, precise and economical screening of population along with reorganization of patients with high risk of diabetes. Moreover, these assays may assist in the development of new and competent anti-diabetic agents. Radioimmune

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assays: Recently a multi-autoantigen radioimmunoassay has been successfully utilized to analyze the immunoreactivity for four autoantigens which are majorly recognized in autoimmune diabetes, in combination via a single Radioimmune assay [65]. Similarly, another assay, the protein A-membrane plate assay has been suggested to work as an efficient autoantibody screening for patients with risk of diabetes [66]. This assay follows the method of radiobinding utilizing 96-well microtiter plates, in addition, the investigators have also utilized a novel method for immune complex capture through membrane-bound protein A.

Metabolic figureprinting: Diabetes is one of a metabolic disorder and so far, several recent studies have focused to measure the metabolic figureprinting as the most recent, high throughput and impending strategy of metabolomics and can distinguish the samples on the basis of origin. Thereby, in this context, many studies have utilized infrared and Raman spectroscopies in connection to disease linked interpretation [67].

Genetic screening and profiling: Understanding of genetic etiology for a disease facilitates for improved disease diagnosis and progression along with more suitable and enhanced treatment. Like prediction of Type I diabetes via autoantibodies immune assays, prediction of Type II diabetes can be done via identification of genetic polymorphism. Various countries have made testing of diagnostic molecular genetics accessible and have attributed for improvement in diagnosis of different genetic-forms of disorders including diabetes [68]. Similarly, identification of susceptible loci for diabetes has been considered as a helpful tool for better prediction and appropriate treatment [69]. A largest study for genetic polymorphism is Welcome Trust Case Control Consortium (WTCCC) which has also assisted further research works in <https://assignbuster.com/scientific-models-for-diabetes-mellitus-health-and-social-care-essay/>

identifying some new genes like FTO, CDKAL1 and IGF2BP2 related to Type II diabetes mellitus [70]. Such type of studies may give a better outcome regarding disease management by recognizing the specific gene as a risk factor. Similarly, few researchers have keenly focused on high throughput and genomic screening for the recognition of new therapeutic strategies including single nucleotide polymorphism (SNP)-based Genome-Wide Screening [71].

## **Discussion**

It has been always a crucial step to detect insulin directly in diabetes mellitus which has been usually carried out via standard static and perfusion testing [72], enzyme linked immunosorbent assay and chromatography [73]. However, such types of testing are considered to require sample collection and insulin labeling [74]. On the other hand, detection of insulin by electrochemical technique has presented a more sensitive and concise analytical approach allowing a continuous evaluation of the target. A multiwalled carbon nanotube sensor utilizing the islets in a microfluidic system [58], sandwich-type and the miniaturized flow-through biosensor [58], redox mediators and electrocatalysts like ruthenium and iridium oxide, ruthenium metallodendrimer for amperometric insulin detection [75] are few exemplar of modified electrodes and efficient electrocatalysts. Moreover, Florescence sensors offer optical interrogation via skin allowing continuous monitoring of glucose, such sensors have also assumed to bypass the immune system of the body [61]. These florescence sensors require utilization of nanofabrication techniques and more investigative studies may absolutely provide advances in development of such sensors for glucose and

insulin detection. Similarly, high throughput assays have represented significant improvement for appropriate, precise and economical screening of population along with reorganization of patients with high risk of diabetes. Fourier transform infrared (FT-IR) spectroscopy has been long considered as a robust investigative system having significant prospect for better high-throughput analysis, recently infrared and Raman spectroscopies for metabolic disorder interpretation has been utilized as metabolic fingerprinting [67]. Thereby, promotion of such investigative researches like metabolic fingerprinting can provide new approaches for usual clinical practice assisting patient diagnosis for metabolic diseases like diabetes mellitus. Recently a high throughput assay involving fluorescent binding has been also developed to scrutinize the capability of compounds for restoring the binding of fatty acyl-CoA to PPAR  $\alpha$  in presence of elevated glucose levels [76]. Correspondingly, selecting new target sites for anti-diabetic agents may be of great importance in revolutionizing diabetic treatment strategy. Lately in 2003, via high throughput screening Allosteric glucokinase activators (GKAs) have been discovered which are known to initiate insulin release and enhance the liver metabolism of glucose, thereby maintaining plasma glucose level. Nowadays these GKAs are considered efficiently effective for type II diabetes mellitus [77]. Thereby, current and advanced high throughput screening assays may greatly facilitate the discovery of new anti-diabetic agents for the amelioration of diabetes mellitus along with assisting in screening patients with high risk of disorder. In addition, genetic screening and profiling programs and studies recently including identification of susceptible loci for diabetes [69], studies for genetic polymorphism for gene identification for development of proper diabetic treatment strategies <https://assignbuster.com/scientific-models-for-diabetes-mellitus-health-and-social-care-essay/>



and single nucleotide polymorphism (SNP)-based Genome-Wide Screening may pave a pathway towards better outcome regarding diagnosis, early prediction and appropriate management of diabetes mellitus. Nevertheless, to elucidate the effect of new drugs and to verify the working of various novel detectors, carrying basic research on animals seems to become a necessity for better progression of medical knowledge. Similarly, a proper understanding of diabetic biomarkers is also important for the implementation of modern technologies that may finally facilitate managing of diabetes mellitus.

## **Summary and Future Perspectives**

In this review, we have made an effort to present a comprehensive impression on the emerging technologies and bioassays involving target site determination via high throughput screening and nanotechnology. These multi-analytical expertise overviewed here may unlock many opportunities for moving ahead in ameliorating diabetes mellitus. In short, the advances in nanotechnology together with high throughput investigational studies involving utilization of biosensors, biomarker detection methodologies and targeting new receptor sites all in combination may perhaps pave a pathway for the development of multitude proposal of novel anti-diabetic treatment strategies. Though, further investigation into the current along with newly designed animal-models and biomarker analysis might also yield more relevant mechanistic information into the pathways involved in the genesis and progression of diabetes. To conclude, we believe that endorsement and upgrading of such novel high throughput screening assays and nanotechnology described herein may surely represent a significant

improvement in the capability for screening and identifying the population at elevated risk of expected diabetes. Thereby in future, appreciation of such investigational techniques and technologies including metabolomics and genetic screening may help in early prediction of diabetes in patients at risk and may display a significant improvement over the researchers conducted after the declaration of the disease.

### **Conflict of interest**

The authors declare no conflict of interest

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