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(54) Title: DIABETES-ASSOCIATED MARKERS AND METHODS OF USE THEREOF

Class	Subclass	Symbol	Text
G01N	33/53		Methods of identifying subjects with Diabetes or a pre-diabetic condition, methods of identifying subjects at risk for developing Diabetes or a pre-diabetic condition, methods of differentially diagnosing diseases associated with Diabetes or a pre-diabetic condition from other diseases or within sub-classifications of Diabetes, methods of evaluating the risk of progression to Diabetes or a pre-diabetic condition in patients, methods of evaluating the effectiveness of treatments in subjects with Diabetes or a pre-diabetic condition, and methods of selecting therapies for treating Diabetes or a pre-diabetic condition, using biomarkers.
G01N	33/567		Methods of identifying subjects with Diabetes or a pre-diabetic condition, methods of identifying subjects at risk for developing Diabetes or a pre-diabetic condition, methods of differentially diagnosing diseases associated with Diabetes or a pre-diabetic condition from other diseases or within sub-classifications of Diabetes, methods of evaluating the risk of progression to Diabetes or a pre-diabetic condition in patients, methods of evaluating the effectiveness of treatments in subjects with Diabetes or a pre-diabetic condition, and methods of selecting therapies for treating Diabetes or a pre-diabetic condition, using biomarkers.

(57) Abstract: Disclosed are methods of identifying subjects with Diabetes or a pre-diabetic condition, methods of identifying subjects at risk for developing Diabetes or a pre-diabetic condition, methods of differentially diagnosing diseases associated with Diabetes or a pre-diabetic condition from other diseases or within sub-classifications of Diabetes, methods of evaluating the risk of progression to Diabetes or a pre-diabetic condition in patients, methods of evaluating the effectiveness of treatments in subjects with Diabetes or a pre-diabetic condition, and methods of selecting therapies for treating Diabetes or a pre-diabetic condition, using biomarkers.

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DIABETES-ASSOCIATED MARKERS AND METHODS OF USE THEREOF

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INCORPORATION BY REFERENCE

This application claims priority from U.S. Provisional Application Serial No. 60/725,462, filed on October 11, 2005.

Each of the applications and patents cited in this text, as well as each document or reference cited in each of the applications and patents (including during the prosecution of each issued patent; "application cited documents"), and each of the U.S. and foreign applications or patents corresponding to and/or claiming priority from any of these applications and patents, and each of the documents cited or referenced in each of the application cited documents, are hereby expressly incorporated herein by reference. More generally, documents or references are cited in this text, either in a Reference List before the claims, or in the text itself; and, each of these documents or references ("herein-cited references"), as well as each document or reference cited in each of the herein-cited references (including any manufacturer's specifications, instructions, etc.), is hereby expressly incorporated herein by reference. Documents incorporated by reference into this text may be employed in the practice of the invention.

20

FIELD OF THE INVENTION

The present invention relates generally to the identification of biological markers associated with an increased risk of developing Diabetes, as well as methods of using such biological markers in diagnosis and prognosis of Diabetes.

25

BACKGROUND OF THE INVENTION

Diabetes Mellitus describes a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism that result from defects in insulin secretion, insulin action, or both. The effects of Diabetes Mellitus include long-term damage, dysfunction and failure of various organs. Diabetes may be present with characteristic symptoms such as thirst, polyuria, blurring of vision, chronic infections, slow wound healing, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in the absence of effective

treatment, death. Often symptoms are not severe, not recognized, or may be absent. Consequently, hyperglycemia sufficient to cause pathological and functional changes may be present for a long time, occasionally up to ten years, before a diagnosis is made, usually by the detection of high levels of glucose in urine after overnight fasting during a routine medical work-up. The long-term effects of Diabetes Mellitus include progressive development of complications such as retinopathy with potential blindness, nephropathy that may lead to renal failure, neuropathy, microvascular changes, and autonomic dysfunction. People with Diabetes are also at increased risk of cardiovascular, peripheral vascular, and cerebrovascular disease (together, "arteriovascular" disease). There is also an increased risk of cancer. Several pathogenetic processes are involved in the development of Diabetes. These include processes which destroy the insulin-secreting beta cells of the pancreas with consequent insulin deficiency, and changes in liver and smooth muscle cells that result in the resistance to insulin uptake. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity to insulin or lack of insulin.

Regardless of the underlying cause, Diabetes Mellitus is subdivided into Type 1 Diabetes and Type 2 Diabetes. Type 1 Diabetes results from autoimmune mediated destruction of the beta cells of the pancreas. The rate of destruction is variable, and the rapidly progressive form is commonly observed in children, but may also occur in adults. The slowly progressive form of Type 1 Diabetes generally occurs in adults and is sometimes referred to as latent autoimmune Diabetes in adults (LADA). Some patients, particularly children and adolescents, may exhibit ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual beta cell function sufficient to prevent ketoacidosis for many years. Individuals with this form of Type 1 Diabetes often become dependent on insulin for survival and are at risk for ketoacidosis. Patients with Type 1 Diabetes exhibit little or no insulin secretion as manifested by low or undetectable levels of plasma C-peptide. However, there are some forms of Type 1 Diabetes which have no known etiology, and some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. These patients are referred to as "Type 1 idiopathic."

Type 2 Diabetes is the most common form of Diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant

feature. Both are usually present at the time that this form of Diabetes is clinically manifested. Type 2 Diabetes patients are characterized with a relative, rather than absolute, insulin deficiency and are resistant to the action of insulin. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. Type 2
5 Diabetes accounts for 90-95% of all cases of Diabetes. This form of Diabetes can go undiagnosed for many years because the hyperglycemia is often not severe enough to provoke noticeable symptoms of Diabetes or symptoms are simply not recognized. The majority of patients with Type 2 Diabetes are obese, and obesity itself may cause or aggravate insulin resistance. Many of those who are not obese by traditional weight criteria
10 may have an increased percentage of body fat distributed predominantly in the abdominal region (visceral fat). Ketoacidosis is infrequent in this type of Diabetes and usually arises in association with the stress of another illness. Whereas patients with this form of Diabetes may have insulin levels that appear normal or elevated, the high blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their beta cell
15 function been normal. Thus, insulin secretion is often defective and insufficient to compensate for the insulin resistance. On the other hand, some hyperglycemic individuals have essentially normal insulin action, but markedly impaired insulin secretion.

Diabetic hyperglycemia may be decreased by weight reduction, increased physical activity, and/or pharmacological treatment. There are several biological mechanisms that are
20 associated with hyperglycemia such as insulin resistance, insulin secretion, and gluconeogenesis, and there are orally active drugs available that act on one or more of these mechanisms. With lifestyle and/or drug intervention, glucose levels can return to near-normal levels, but this is usually temporary. With time, additional second-tier drugs are often required additions to the treatment approach. Often with time, even these multi-drug
25 approaches fail, at which point insulin injections are instituted.

Over 18 million people in the United States have Type 2 Diabetes, and of these, about 5 million do not know they have the disease. These persons who do not know they have the disease and who do not exhibit the classic symptoms of Diabetes present a major diagnostic and therapeutic challenge.

30 There is a large group in the United States, nearly 41 million persons, who are at significant risk of developing Type 2 Diabetes. They are broadly referred to in the literature as "pre-diabetics." A "pre-diabetic" or a subject with pre-Diabetes represents any person or population with a greater risk than the broad population for conversion to Type 2 Diabetes in

a given period of time. The risk of developing Type 2 Diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior gestational Diabetes, and in individuals with hypertension and/or dyslipidemia. Its frequency varies in different ethnic subgroups. Type 2 Diabetes is often associated with strong familial, likely genetic, predisposition, however the genetics of this form of Diabetes are complex and not clearly defined.

Pre-diabetics often have fasting glucose levels between normal and frank diabetic levels. Occasionally in research, these persons are tested for their tolerance to glucose. Abnormal glucose tolerance, or "impaired glucose tolerance" can be an indication that an individual is on the path toward Diabetes; it requires the use of a 2-hour oral glucose tolerance test for its detection. However, it has been shown that impaired glucose tolerance is by itself entirely asymptomatic and unassociated with any functional disability. Indeed, insulin secretion is typically greater in response to a mixed meal than in response to a pure glucose load; as a result, most persons with impaired glucose tolerance are rarely, if ever, hyperglycemic in their daily lives, except when they undergo diagnostic glucose tolerance tests. Thus, the importance of impaired glucose tolerance resides exclusively in its ability to identify persons at increased risk of future disease (Stern et al, 2002). In studies conducted by Stern and others, the sensitivity and false-positive rates of impaired glucose tolerance as a predictor of future conversion to Type 2 Diabetes was 50.9% and 10.2%, respectively, representing an area under the Receiver-Operating Characteristic Curve of 77.5% and a *p*-value of 0.20. Because of its cost, reliability, and inconvenience, the oral glucose tolerance test is seldom used in routine clinical practice. Moreover, patients whose Diabetes is diagnosed solely on the basis of an oral glucose tolerance test have a high rate of reversion to normal on follow-up and may in fact represent false-positive diagnoses. Stern and others reported that such cases were almost 5 times more likely to revert to non-diabetic status after 7 to 8 years of follow-up compared with persons meeting conventional fasting or clinical diagnostic criteria. Clearly, there is a need for improved methods of assessing the risk of future Diabetes.

Often a person with impaired glucose tolerance will be found to have at least one or more of the common arteriovascular disease risk factors. This clustering has been termed "Syndrome X," or "Metabolic Syndrome" by some researchers and can be indicative of a pre-diabetic state. Alone, each component of the cluster conveys increased arteriovascular and diabetic disease risk, but together as a combination they become much more significant. This

means that the management of persons with hyperglycemia and other features of Metabolic Syndrome should focus not only on blood glucose control but also include strategies for reduction of other arteriovascular disease risk factors. Furthermore, such risk factors are non-specific for Diabetes or pre-Diabetes and are not in themselves a basis for a diagnosis of
5 Diabetes, or of diabetic status.

It should furthermore be noted that an increased risk of conversion to Diabetes implies an increased risk of converting to arteriovascular disease and events. Diabetes itself is one of the most significant single risk factors for arteriovascular disease, and is in fact often termed a "coronary heart disease equivalent" by itself, indicating a greater than 20
10 percent ten-year risk of an arteriovascular event, in a similar range with stable angina and just below the most significant independent risk factors, such as survivorship of a previous arteriovascular event. The same is true of other arteriovascular disease, such as peripheral artery disease or cerebrovascular disease.

It is well documented that pre-Diabetes can be present for ten or more years before
15 the detection of glycemic disorders like Diabetes. Treatment of pre-diabetics with drugs such as acarbose, metformin, troglitazone and rosiglitazone can postpone or prevent Diabetes; yet few pre-diabetics are treated. A major reason, as indicated above, is that no simple laboratory test exists to determine the actual risk of an individual to develop Diabetes. Thus, there remains a need in the art for methods of identifying and diagnosing these
20 individuals who are not yet diabetics, but who are at significant risk of developing Diabetes.

SUMMARY OF THE INVENTION

The present invention relates in part to the discovery that certain biological markers, such as proteins, nucleic acids, polymorphisms, metabolites, and other analytes, as well as
25 certain physiological conditions and states, are present in subjects with an increased risk of developing Diabetes Mellitus or a pre-diabetic condition such as, but not limited to, Metabolic Syndrome (Syndrome X), conditions characterized by impaired glucose regulation and/or insulin resistance, such as Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycemia (IFG), but where such subjects do not exhibit some or all of the conventional risk
30 factors of these conditions, or subjects who are asymptomatic for these conditions.

Accordingly, the invention provides biological markers of Diabetes or pre-diabetic conditions that can be used to monitor or assess the risk of subjects experiencing such diabetic or pre-diabetic conditions, to diagnose or identify subjects with a diabetic or pre-

diabetic condition, to monitor the risk for development of a diabetic or pre-diabetic condition, to monitor subjects that are undergoing therapies for Diabetes or a pre-diabetic condition, to differentially diagnose disease states associated with Diabetes or a pre-diabetic condition from other diseases, or within sub-classifications of Diabetes or pre-diabetic conditions, to
5 evaluate changes in the risk of Diabetes or pre-diabetic conditions, and to select therapies for use in treating subjects with Diabetes or a pre-diabetic condition, or for use in treating subjects who are at risk for developing Diabetes or a pre-diabetic condition. Preferably, the present invention provides use of biological markers, some of which are unrelated to Diabetes or have not heretofore been identified as related to Diabetes, but are related to early
10 biological changes that can lead to the development of Diabetes or a pre-diabetic condition, to detect and identify subjects who exhibit none of the symptoms for Diabetes, i.e., who are asymptomatic for Diabetes or pre-diabetic conditions or have only non-specific indicators of potential pre-diabetic conditions, such as arteriovascular risk factors, or who exhibit none or few of the conventional risk factor of Diabetes. Significantly, many of the biomarkers
15 disclosed herein have shown little individual significance in the diagnosis of Diabetes, but when used in combination (in "panels") with other disclosed markers and combined with the herein disclosed mathematical classification algorithms, becomes significant discriminates of the pre-Diabetes patient or population from one who is not pre-diabetic.

Accordingly, in one aspect, the present invention provides a method with a
20 predetermined level of predictability for assessing a risk of development of Diabetes Mellitus or a pre-diabetic condition in a subject comprising: measuring the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and measuring a clinically significant alteration in the level of the one or more, preferably two or more
25 DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.

In one embodiment, the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes. In other embodiments, the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.

30 The level of DBRISKMARKERS can be measured electrophoretically or immunochemically. Where the detection is immunochemical, the detection can be by radioimmunoassay, immunofluorescence assay or by an enzyme-linked immunosorbent assay. The detection can also be achieved by specific oligonucleotide hybridization.

In some embodiments, the subject has not been previously diagnosed or identified as having the Diabetes Mellitus or the pre-diabetic condition. In other embodiments, the subject is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.

5 The sample as defined by the present invention can be serum, blood plasma, blood cells, endothelial cells, tissue biopsies, ascites fluid, bone marrow, interstitial fluid, sputum, or urine.

In one embodiment of the present invention, the level of expression of five or more DBRISKMARKERS is measured, but can also encompass measurement of ten or more, twenty-five or more, or fifty or more DBRISKMARKERS.

10 In another aspect, a method with a predetermined level of predictability for diagnosing or identifying a subject having Diabetes Mellitus or a pre-diabetic condition is provided, comprising measuring the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and comparing the level of the effective amount of the
15 one or more (or two or more) DBRISKMARKERS to a reference value.

In one embodiment, the reference value is an index value. The reference value can also be derived from one or more risk prediction algorithms or computed indices for the Diabetes or pre-diabetic condition.

20 Another aspect of the present invention provides a method with a predetermined level of predictability for assessing a risk of impaired glucose tolerance in a subject comprising measuring the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and measuring a clinically significant alteration in the level of the one or more (or two or more) DBRISKMARKERS in the sample, wherein the alteration
25 indicates an increased risk of impaired glucose tolerance in the subject.

In one embodiment, the subject has not been previously diagnosed as having impaired glucose tolerance. In another embodiment, the subject is asymptomatic for the impaired glucose tolerance.

30 In another aspect, a method with a predetermined level of predictability for diagnosing or identifying a subject having impaired glucose tolerance is provided, comprising measuring the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and comparing the level of the effective amount of the one or more

(preferably two or more) DBRISKMARKERS to a reference value. The reference value can be an index value.

Alternatively, the reference value can be derived from one or more risk prediction algorithms or computed indices for impaired glucose tolerance.

5 Another aspect of the invention provides a method with a predetermined level of predictability for assessing the progression of Diabetes Mellitus or a pre-diabetic condition in a subject, comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time; detecting the level of an
10 effective amount of one or more, preferably two or more DBRISKMARKERS in a second sample from the subject at a second period of time; and comparing the level of the effective amount of the one or more (or two or more) DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value.

In one embodiment, the subject has previously been diagnosed or identified as
15 suffering from the Diabetes Mellitus or the pre-diabetic condition. In another embodiment, the subject has previously been treated for the Diabetes Mellitus or the pre-diabetic condition. In yet another embodiment, the subject has not been previously diagnosed or identified as suffering from the Diabetes Mellitus or the pre-diabetic condition. In other embodiments, the subject is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.

20 In the context of the invention, the first sample can be taken from the subject prior to being treated for the Diabetes Mellitus or the pre-diabetic condition. The second sample can be taken from the subject after being treated for the Diabetes Mellitus or the pre-diabetic condition. The reference value can be derived from one or more subjects who have suffered from Diabetes Mellitus or a pre-diabetic condition.

25 In another aspect of the present invention, a method with a predetermined level of predictability for assessing the progression of impaired glucose tolerance associated with Diabetes Mellitus or a pre-diabetic condition in a subject is provided, comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the
30 subject at a first period of time; detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS in a second sample from the subject at a second period of time; and comparing the level of the effective amount of the one or more (or two or

more) DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value.

The subject can be one who has previously been treated for the Diabetes Mellitus or the pre-diabetic condition. The subject can also be one who has not been previously
5 diagnosed or identified as having impaired glucose tolerance or suffering from the Diabetes Mellitus or the pre-diabetic condition. Alternatively, the subject can be asymptomatic for the impaired glucose tolerance, or is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.

In yet another aspect, a method with a predetermined level of predictability for
10 monitoring the effectiveness of treatment for Diabetes Mellitus or a pre-diabetic condition is provided, comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time; detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS in a second
15 sample from the subject at a second period of time; and comparing the level of the effective amount of the one or more (or two or more) DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value, wherein the effectiveness of treatment is monitored by a change in the level of the effective amount of one or more, preferably two or more DBRISKMARKERS from the subject.

20 In one embodiment, the treatment for the Diabetes Mellitus or the pre-diabetic condition comprises exercise regimens, dietary supplements, therapeutic agents, surgical intervention, and prophylactic agents. In another embodiment, the reference value is derived from one or more subjects who show an improvement in Diabetes risk factors as a result of one or more treatments for the Diabetes Mellitus or the pre-diabetic condition.

25 The effectiveness of treatment can be additionally monitored by detecting changes in body mass index (BMI), insulin levels, blood glucose levels, HDL levels, systolic and/or diastolic blood pressure, or combinations thereof. Changes in blood glucose levels can be detected by an oral glucose tolerance test.

Another aspect of the present invention provides a method with a predetermined level
30 of predictability for selecting a treatment regimen for a subject diagnosed with or at risk for Diabetes Mellitus or a pre-diabetic condition comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of

time; optionally detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS in a second sample from the subject at a second period of time; and comparing the level of the effective amount of the one or more (or two or more) DBRISKMARKERS detected in step (a) to a reference value, or optionally, to the amount
5 detected in step (b).

The present invention also provides a Diabetes Mellitus reference expression profile, comprising a pattern of marker levels of an effective amount of one or more, preferably two or more markers selected from the group consisting of DBRISKMARKERS 1-260, taken from one or more subjects who do not have the Diabetes Mellitus.

10 An impaired glucose tolerance reference expression profile is also provided by the invention, comprising a pattern of marker levels of an effective amount of one or more, preferably two or more markers selected from the group consisting of DBRISKMARKERS 1-260, taken from one or more subjects who do not have impaired glucose tolerance.

In another aspect, a Diabetes Mellitus subject expression profile is provided,
15 comprising a pattern of marker levels of an effective amount of one or more, preferably two or more markers selected from the group consisting of DBRISKMARKERS 1-260 taken from one or more subjects who have the Diabetes Mellitus, are at risk for developing the Diabetes Mellitus, or are being treated for the Diabetes Mellitus.

In another aspect, an impaired glucose tolerance subject expression profile is
20 provided, comprising a pattern of marker levels of an effective amount of one or more, preferably two or more markers selected from the group consisting of DBRISKMARKERS 1-260 taken from one or more subjects who have impaired glucose tolerance, are at risk for developing impaired glucose tolerance, or are being treated for impaired glucose tolerance.

The present invention also provides a kit comprising a plurality of
25 DBRISKMARKER detection reagents that detect the corresponding DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260, sufficient to generate the profiles of the invention. The detection reagent can comprise one or more antibodies or fragments thereof. Alternatively, or additionally, the detection reagent can comprise one or more oligonucleotides or one or more aptamers.

30 The present invention also provides, in another aspect, a machine readable media containing one or more Diabetes Mellitus reference expression profiles according to the invention, or one or more Diabetes Mellitus subject expression profiles according to the invention, and optionally, additional test results and subject information.

A machine readable media containing one or more impaired glucose tolerance reference expression profiles according to invention is also contemplated, or one or more impaired glucose tolerance subject expression profiles according to the invention, and optionally, additional test results and subject information.

5 In another aspect, a DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of a physiological and/or biochemical pathway associated with Diabetes Mellitus or a pre-diabetic condition is provided. In one embodiment, the physiological and biochemical pathways comprise autoimmune regulation, inflammation and endothelial function (including cytokine-cytokine receptor interactions, cell
10 adhesion molecules (CAMs), focal adhesions, leukocyte transendothelial migration, natural killer cell mediated cytotoxicity, regulation of the actin cytoskeleton, adherens/tight/gap junctions, and extracellular matrix (ECM)-receptor interaction), adipocyte development and maintenance (including adipocytokines, cell cycle, apoptosis, and neuroactive ligand-receptor interaction) as well as hematopoietic cell lineage, complement and coagulation cascades,
15 intra- and extracellular cell signaling pathways (including the mTOR, TGF- β , MAPK, insulin, GnRH, Toll-like receptor, Jak-STAT, PPAR, T-cell receptor, B-cell receptor, Fc ϵ RI, calcium, Wnt, and VEGF signaling pathways and other cell communication mechanisms), in addition to those pathways that are commonly associated with Type 1 and Type 2 Diabetes Mellitus.

20 A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of a site associated with Diabetes Mellitus or a pre-diabetic condition is also provided, wherein the site can comprise beta cells, endothelial cells, skeletal and smooth muscle, or peripheral, cardiovascular, or cerebrovascular arteries.

In other aspects, a DBRISKMARKER panel comprising one or more
25 DBRISKMARKERS that are indicative of the progression of Diabetes Mellitus or a pre-diabetic condition is provided.

The present invention further provides a DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of the speed of progression of Diabetes Mellitus or a pre-diabetic condition. The invention also concerns a DBRISKMARKER panel
30 comprising one or more DBRISKMARKERS that are specific to one or more types of Diabetes Mellitus and a DBRISKMARKER panel comprising one or more DBRISKMARKERS that are specific to a pre-diabetic condition.

A DBRISKMARKER panel comprising one or more DBRISKMARKERS selected from mathematical classification algorithms and factor analysis approach is provided, utilizing a relevant past cohort of subjects, or calculated indices which were developed in such past cohorts. In particular, a DBRISKMARKER panel of one or more, preferably two
5 or more DBRISKMARKERS selected from a subset of the disclosed DBRISKMARKERS comprising Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (ILGFBP3), Resistin (RETN), Matrix Metalloproteinase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (Rogers blood
10 group)(C4A), CD14 molecule (CD14), selectin E (endothelial adhesion molecule)(SELE), colony stimulating factor 1 (macrophage) (CSF1), and vascular endothelial growth factor (VEGF), c-reactive protein, pentraxin-related (CRP), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), CD26 (dipeptidyl peptidase 4; DPP4), and their statistical and/or
15 functional equivalents within mathematical classification algorithms using one or more of these DBRISKMARKERS.

A method for treating one or more subjects at risk for developing Diabetes Mellitus or a pre-diabetic condition is also contemplated by the present invention, comprising detecting the presence of increased levels of at least one, preferably two different DBRISKMARKERS present in a sample from the one or more subjects; and treating the one or more subjects with
20 one or more Diabetes-modulating drugs until altered levels of the at least one, preferably two different DBRISKMARKERS return to a baseline value measured in one or more subjects at low risk for developing the Diabetes Mellitus or the pre-diabetic condition, or a baseline value measured in one or more subjects who show improvements in Diabetes risk markers as a result of treatment with one or more Diabetes-modulating drugs.

25 The Diabetes-modulating drugs can comprise sulfonylureas; biguanides; insulin, insulin analogs; peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists; dual-acting PPAR agonists; insulin secretagogues; analogs of glucagon-like peptide-1 (GLP-1); inhibitors of dipeptidyl peptidase IV (DPP4); pancreatic lipase inhibitors; α -glucosidase inhibitors; and combinations thereof. In one embodiment, the improvements in Diabetes risk
30 markers as a result of treatment with one or more Diabetes-modulating drugs comprise a reduction in body mass index (BMI), a reduction in blood glucose levels, an increase in insulin levels, an increase in HDL levels, a reduction in systolic and/or diastolic blood pressure, or combinations thereof.

In another aspect, a method of evaluating changes in the risk of impaired glucose tolerance in a subject diagnosed with or at risk for developing a pre-diabetic condition is provided, comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time; optionally detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS in a second sample from the subject at a second period of time; and comparing the level of the effective amount of the one or more (or two or more) DBRISKMARKERS detected in step (a) to a reference value, or optionally, the amount in step (b).

The present invention further provides a method of differentially diagnosing disease states associated with Diabetes Mellitus or a pre-diabetic condition in a subject comprising detecting the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject; and comparing the level of the effective amount of the one or more (or two or more) DBRISKMARKERS detected in step (a) to the Diabetes Mellitus disease subject expression profile of the invention, to the impaired glucose tolerance subject expression profile of the invention, or to a reference value.

Further, in a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the present invention provides an improvement comprising measuring the level of an effective amount of one or more, preferably two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and measuring a clinically significant alteration in the level of the one or more (or two or more) DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.

In yet another aspect of the present invention, in a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the present invention provides an improvement comprising: measuring the level of an effective amount of one or more DBRISKMARKERS selected from the group consisting of: Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (ILGFBP3), Resistin (RETN), Matrix Metalloproteinase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (C4A), CD14 molecule (CD14), selectin E (SELE), colony stimulating factor 1 (macrophage; CSF1), and

vascular endothelial growth factor (VEGF), c-reactive protein, pentraxin-related (CRP), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), and CD26 (dipeptidyl peptidase 4; DPP4), and measuring a clinically significant alteration in the level of the one or more
5 DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.

In a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the present invention provides an improvement comprising: measuring the level of an effective amount of two or more
10 DBRISKMARKERS selected from the group consisting of: Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (ILGF3), Resistin (RETN), Matrix Metalloproteinase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (C4A), CD14 molecule (CD14), selectin E (SELE), colony stimulating factor 1 (macrophage; CSF1), and vascular endothelial growth factor
15 (VEGF), c-reactive protein, pentraxin-related (CRP), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), and CD26 (dipeptidyl peptidase 4; DPP4), and measuring a clinically significant alteration in the level of the two or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or
20 a pre-diabetic condition in the subject.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and materials are described
25 below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from and are
30 encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following Detailed Description, given by way of example, but not intended to limit the invention to specific embodiments described, may be understood in conjunction with the accompanying Figures, incorporated herein by reference, in which:

Figure 1 is a flow chart depicting DBRISKMARKER physiological and biological pathways and categories in the context of the disease progression from Normal to Pre-Diabetes to Diabetes.

Figure 2 is an illustration depicting classes and desirable characteristics of DBRISKMARKERS, and illustrating several differing illustrative patterns of markers that are useful in the diagnosis of subjects having Pre-Diabetes, and Diabetes as compared to normal.

Figures 3A - 3RR are graphic illustrations of the KEGG pathways highlighting three or more DBRISKMARKERS in each disclosed pathway.

Figure 3A depicts neuroactive ligand-receptor interactions.

Figure 3B depicts cytokine-cytokine receptor interactions.

Figure 3C depicts the adipocytokine signaling pathway.

Figure 3D shows the mitogen-activated protein kinase (MAPK) signaling pathway.

Figure 3E shows the insulin signaling pathway.

Figure 3F shows the Type II Diabetes Mellitus pathway.

Figure 3G depicts the apoptosis signaling pathway.

Figure 3H depicts the complement and coagulation cascades.

Figure 3I depicts the Jak-STAT signaling pathway.

Figure 3J is a representation of the hematopoietic cell lineage.

Figure 3K shows the PPAR signaling pathway.

Figure 3L is the Toll-like receptor signaling pathway.

Figure 3M shows the T-cell receptor signaling pathway.

Figure 3N depicts the focal adhesion signaling pathway.

Figure 3O shows the Type I Diabetes Mellitus pathway.

Figure 3P is the pancreatic cancer signaling pathway.

Figure 3Q depicts the mTOR signaling pathway.

Figure 3R shows the TGF- β signaling pathway.

Figure 3S is the calcium signaling pathway.

Figure 3T shows the natural killer cell-mediated cytotoxicity pathway.

Figure 3U shows the B-cell receptor signaling pathway.

Figure 3V shows the Fc ϵ RI signaling pathway.

- Figure 3W depicts the pathway of leukocyte transendothelial migration.
- Figure 3X depicts the arachidonic acid metabolic pathway.
- Figure 3Y depicts the Wnt signaling pathway.
- Figure 3Z shows the VEGF signaling pathway.
- 5 Figure 3AA depicts cell adhesion molecule interactions.
- Figure 3BB is a schematic showing regulation of the actin cytoskeleton.
- Figure 3CC depicts interactions relating to glioma.
- Figure 3DD depicts nicotinate and nicotinamide metabolism.
- Figure 3EE shows the signaling pathway of adherens junctions.
- 10 Figure 3FF is a schematic showing the signaling pathway of tight junctions.
- Figure 3GG depicts interactions relating to antigen processing and presentation.
- Figure 3HH shows interactions relating to long-term potentiation.
- Figure 3II shows the GnRH signaling pathway.
- Figure 3JJ shows the interactions relating to colorectal cancer.
- 15 Figure 3KK shows the interactions at cell junctions.
- Figure 3LL is a schematic showing the pathways involved in neurodegenerative disorders.
- Figure 3MM depicts the cell cycle signaling pathway.
- Figure 3NN shows ECM-receptor interactions.
- 20 Figure 3OO shows the interactions involved in circadian rhythms.
- Figure 3PP is a schematic showing the interactions involved in long-term depression.
- Figure 3QQ depicts the interactions relating to Huntington's Disease.
- Figure 3RR shows the signaling pathways involved in *Helicobacter pylori* infection.
- Figures 4A - 4F are listings of KEGG pathways with only one or two
- 25 DBRISKMARKERS each within them.
- Figures 5A - 5E are examples of Pre-Diabetes classification performance characteristics of selected individual DBRISKMARKERS as shown in ANOVA analysis of said markers between patient samples from Normal, Pre-Diabetes, and Diabetes cohorts.
- Figure 6 is a tabular example depicting the additive ROC performance characteristics
- 30 of pairs of DBRISKMARKERS in classification of pre-Diabetes from normal cohorts absent a mathematical algorithm indicating the tradeoff of increased sensitivity at the cost of reduced specificity.

Figure 7 is a graph depicting the change in classification algorithm performance, as measured by R^2 versus the Reference Diabetes Conversion Risk with the addition of multiple DBRISKMARKERS utilizing a forward selection algorithm.

Figure 8 is a graph depicting a three-dimensional rendering of the performance characteristics of the entire set of possible three marker combinations of a group of 50 DBRISKMARKERS, highlighting the highest performing combinations.

Figure 9 is a histogram depicting the distribution of the performance across the entire set of possible three marker combinations shown in Figure 6,

Figure 10 is a mathematical clustering and classification tree showing the Euclidean standardized distance the DBRISKMARKERS shown in Figure 6.

Figure 11 presents tables of selected DBRISKMARKERS by eight Position Categories useful for the construction of panels selecting DBRISKMARKERS according to the method disclosed herein.

Figure 12 is a listing of 25 high performing DBRISKMARKER panels using three DBRISKMARKERS selected from Position Categories according to the method disclosed herein. Logistic regression algorithms using said panels had calculated R^2 values ranging from 0.300 to 0.329 when employed on samples in the described example and non-diabetic patient cohort.

Figure 13 is a listing of 25 high performing DBRISKMAKER panels using eight DBRISKMARKERS selected from Position Categories according to the method disclosed herein. Logistic regression algorithms using said panels had calculated R^2 values ranging from 0.310 to 0.475 when employed on samples in the described example and non-diabetic patient cohort.

Figure 14 is a listing of 25 high performing DBRISKMAKER panels using eighteen DBRISKMARKERS selected from Position Categories according to the method disclosed herein. Logistic regression algorithms using said panels had calculated R^2 values ranging from 0.523 to 0.6105 when employed on samples in the described example and non-diabetic patient cohort.

Figure 15 is a graph ROC curve and AUC statistics for the highest performing three, eight, and eighteen DBRISKMARKER panels respectively when employed on samples in the described example and non-diabetic patient cohort.

Figure 16 is an ROC curve and AUC statistics indicating the three relative highest performing individual DBRISKMARKERS markers when employed on samples in the described example and non-diabetic patient cohort.

Figure 17 is a standard curve demonstrating a typical result from the methods of the present invention. Once a working standard curve is demonstrated, the assay is typically applied to 24 serum samples to determine the normal distribution of the target analyte across clinical samples.

Figure 18 depicts a graph exemplifying single molecule detection data across 92 samples for 25 biomarkers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the identification of biomarkers associated with subjects having Diabetes or a pre-diabetic condition, or who are pre-disposed to developing Diabetes or a pre-diabetic condition. Accordingly, the present invention features methods for identifying subjects who are pre-disposed to developing Diabetes or a pre-diabetic condition, including those subjects who are asymptomatic for Diabetes or a pre-diabetic condition by detection of the biomarkers disclosed herein. These biomarkers are also useful for monitoring subjects undergoing treatments and therapies for Diabetes or pre-diabetic conditions, and for selecting therapies and treatments that would be efficacious in subjects having Diabetes or a pre-diabetic condition, wherein selection and use of such treatments and therapies slow the progression of Diabetes or pre-diabetic conditions, or substantially delay or prevent its onset.

“Diabetes Mellitus” in the context of the present invention encompasses Type 1 Diabetes, both autoimmune and idiopathic and Type 2 Diabetes (together, “Diabetes”). The World Health Organization defines the diagnostic value of fasting plasma glucose concentration to 7.0 mmol/l (126 mg/dl) and above for Diabetes Mellitus (whole blood 6.1 mmol/l or 110 mg/dl), or 2-hour glucose level ≥ 11.1 mmol/L (≥ 200 mg/dL). Other values suggestive of or indicating high risk for Diabetes Mellitus include elevated arterial pressure $\geq 140/90$ mm Hg; elevated plasma triglycerides (≥ 1.7 mmol/L; 150 mg/dL) and/or low HDL-cholesterol (< 0.9 mmol/L, 35 mg/dl for men; < 1.0 mmol/L, 39 mg/dL women); central obesity (males: waist to hip ratio > 0.90 ; females: waist to hip ratio > 0.85) and/or body mass index exceeding 30 kg/m^2 ; microalbuminuria, where the urinary albumin excretion rate $\geq 20 \mu\text{g/min}$ or albumin:creatinine ratio $\geq 30 \text{ mg/g}$.

“Pre-diabetic condition” refers to a metabolic state that is intermediate between normal glucose homeostasis and metabolism and states seen in frank Diabetes Mellitus. Pre-diabetic conditions include, without limitation, Metabolic Syndrome (“Syndrome X”), Impaired Glucose Tolerance (IGT), and Impaired Fasting Glycemia (IFG). IGT refers to post-prandial abnormalities of glucose regulation, while IFG refers to abnormalities that are measured in a fasting state. The World Health Organization defines values for IFG as a fasting plasma glucose concentration of 6.1 mmol/L (100 mg/dL) or greater (whole blood 5.6 mmol/L; 100 mg/dL), but less than 7.0 mmol/L (126 mg/dL)(whole blood 6.1 mmol/L; 110 mg/dL). Metabolic syndrome according to the National Cholesterol Education Program (NCEP) criteria are defined as having at least three of the following: blood pressure $\geq 130/85$ mm Hg; fasting plasma glucose ≥ 6.1 mmol/L; waist circumference >102 cm (men) or >88 cm (women); triglycerides ≥ 1.7 mmol/L; and HDL cholesterol <1.0 mmol/L (men) or 1.3 mmol/L (women).

“Pre-Diabetes” in the context of the present invention indicates the physiological state, in an individual or in a population, of having a higher than normal expected rate of disease conversion to frank Type 2 diabetes mellitus. Such absolute expected rate of conversion to frank Type 2 diabetes in Pre-Diabetes populations may be up to 1 percent or more per annum, and preferably 2 percent per annum or more. It may also be stated in terms of a relative risk from normal between quartiles of risk or as a likelihood ratio between differing biomarker and index scores, including those coming from the invention. Unless otherwise noted, and without limitation, when a categorical positive diagnosis of Pre-Diabetes is stated here, it is defined experimentally by the group of patients with an expected conversion rate to Type 2 Diabetes of two percent (2%) per annum over the coming 7.5 years, or fifteen percent (15%) of those testing at a given threshold value (the selected Pre-Diabetes clinical cutoff). When a continuous measure of Pre-Diabetes conversion risk is produced, having a “pre-diabetic condition” encompasses any expected annual rate of conversion above that seen in a normal reference or general unselected normal prevalence population.

“Impaired glucose tolerance” (IGT) is defined as having a blood glucose level that is higher than normal, but not high enough to be classified as Diabetes Mellitus. A subject with IGT will have two-hour glucose levels of 140 to 199 mg/dL (7.8 to 11.0 mmol) on the 75-g oral glucose tolerance test. These glucose levels are above normal but below the level that is diagnostic for Diabetes. Subjects with impaired glucose tolerance or impaired fasting glucose

have a significant risk of developing Diabetes and thus are an important target group for primary prevention.

“Insulin resistance” refers to a condition in which the cells of the body become resistant to the effects of insulin, that is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed in order for insulin to exert its effects.

“Normal glucose levels” is used interchangeably with the term “normoglycemic” and refers to a fasting venous plasma glucose concentration of less than 6.1 mmol/L (110 mg/dL). Although this amount is arbitrary, such values have been observed in subjects with proven normal glucose tolerance, although some may have IGT as measured by oral glucose tolerance test (OGTT).

Two hundred and sixty biomarkers have been identified as being found to have altered or modified presence or concentration levels in subjects who have Diabetes, or who exhibit symptoms characteristic of a pre-diabetic condition, or have Pre-Diabetes (as defined herein) such as those subjects who are insulin resistant, have altered beta cell function or at risk of developing Diabetes based upon known clinical parameters or risk factors, such as family history of Diabetes, low activity level, poor diet, excess body weight (especially around the waist), age greater than 45 years, high blood pressure, high levels of triglycerides, HDL cholesterol of less than 35, previously identified impaired glucose tolerance, previous Diabetes during pregnancy (“gestational Diabetes Mellitus”) or giving birth to a baby weighing more than nine pounds, and ethnicity.

The biomarkers and methods of the present invention allow one of skill in the art to identify, diagnose, or otherwise assess those subjects who do not exhibit any symptoms of Diabetes or a pre-diabetic condition, but who nonetheless may be at risk for developing Diabetes or experiencing symptoms characteristic of a pre-diabetic condition.

The term “biomarker” in the context of the present invention encompasses, without limitation, proteins, nucleic acids, polymorphisms of proteins and nucleic acids, elements, metabolites, and other analytes. Biomarkers can also include mutated proteins or mutated nucleic acids. The term “analyte” as used herein can mean any substance to be measured and can encompass electrolytes and elements, such as calcium. Finally, biomarkers can also refer to non-analyte physiological markers of health status encompassing other clinical characteristics such as, without limitation, age, ethnicity, diastolic and systolic blood pressure, body-mass index, and resting heart rate.

Proteins, nucleic acids, polymorphisms, and metabolites whose levels are changed in subjects who have Diabetes or a pre-diabetic condition, or are predisposed to developing Diabetes or a pre-diabetic condition are summarized in Table 1 and are collectively referred to herein as, *inter alia*, “Diabetes risk-associated proteins”, “DBRISKMARKER polypeptides”, or “DBRISKMARKER proteins”. The corresponding nucleic acids encoding the polypeptides are referred to as “Diabetes risk-associated nucleic acids”, “Diabetes risk-associated genes”, “DBRISKMARKER nucleic acids”, or “DBRISKMARKER genes”. Unless indicated otherwise, “DBRISKMARKER”, “Diabetes risk-associated proteins”, “Diabetes risk-associated nucleic acids” are meant to refer to any of the sequences disclosed herein. The corresponding metabolites of the DBRISKMARKER proteins or nucleic acids can also be measured, as well as any of the aforementioned conventional risk marker metabolites previously disclosed, including, without limitation, such metabolites as dehydroepiandrosterone sulfate (DHEAS); c-peptide; cortisol; vitamin D3; 5-hydroxytryptamine (5-HT; serotonin); oxyntomodulin; estrogen; estradiol; and digitalis-like factor, herein referred to as “DBRISKMARKER metabolites”. Non-analyte physiological markers of health status (e.g., such as age, ethnicity, diastolic or systolic blood pressure, body-mass index, and other non-analyte measurements commonly used as conventional risk factors) are referred to as “DBRISKMARKER physiology”. Calculated indices created from mathematically combining measurements of one or more, preferably two or more of the aforementioned classes of DBRISKMARKERS are referred to as “DBRISKMARKER indices”. Proteins, nucleic acids, polymorphisms, mutated proteins and mutated nucleic acids, metabolites, and other analytes are, as well as common physiological measurements and indices constructed from any of the preceding entities, are included in the broad category of “DBRISKMARKERS”.

A “subject” in the context of the present invention is preferably a mammal. The mammal can be a human, non-human primate, mouse, rat, dog, cat, horse, or cow, but are not limited to these examples. Mammals other than humans can be advantageously used as subjects that represent animal models of Diabetes Mellitus or pre-Diabetes conditions. A subject can be male or female. A subject can be one who has been previously diagnosed or identified as having Diabetes or a pre-diabetic condition, and optionally has already undergone treatment for the Diabetes or pre-diabetic condition. Alternatively, a subject can also be one who has not been previously diagnosed as having Diabetes or a pre-diabetic condition. For example, a subject can be one who exhibits one or more risk factors for

Diabetes or a pre-diabetic condition, or a subject who does not exhibit Diabetes risk factors, or a subject who is asymptomatic for Diabetes or pre-Diabetes. A subject can also be one who is suffering from or at risk of developing Diabetes or a pre-diabetic condition.

5 A "sample" in the context of the present invention is a biological sample isolated from a subject and can include, for example, serum, blood plasma, blood cells, endothelial cells, tissue biopsies, lymphatic fluid, ascites fluid, interstitial fluid (also known as "extracellular fluid" and encompasses the fluid found in spaces between cells, including, *inter alia*, gingival crevicular fluid), bone marrow, sputum, or urine.

10 One or more, preferably two or more DBRISKMARKERS can be detected in the practice of the present invention. For example, two (2), five (5), ten (10), fifteen (15), twenty (20), forty (40), fifty (50), seventy-five (75), one hundred (100), one hundred and twenty five (125), one hundred and fifty (150), one hundred and seventy-five (175), two hundred (200), two hundred and ten (210), two hundred and twenty (220), two hundred and thirty (230), two hundred and forty (240), two hundred and fifty (250) or more DBRISKMARKERS can be
15 detected. In some aspects, all 260 DBRISKMARKERS disclosed herein can be detected. Preferred ranges from which the number of DBRISKMARKERS can be detected include ranges bounded by any minimum selected from between one and 260, particularly two, five, ten, twenty, fifty, seventy-five, one hundred, one hundred and twenty five, one hundred and fifty, one hundred and seventy-five, two hundred, two hundred and ten, two hundred and
20 twenty, two hundred and thirty, two hundred and forty, two hundred and fifty, paired with any maximum up to the total known DBRISKMARKERS, particularly five, ten, twenty, fifty, and seventy-five. Particularly preferred ranges include two to five (2-5), two to ten (2-10), two to fifty (2-50), two to seventy-five (2-75), two to one hundred (2-100), five to ten (5-10), five to twenty (5-20), five to fifty (5-50), five to seventy-five (5-75), five to one hundred (5-
25 100), ten to twenty (10-20), ten to fifty (10-50), ten to seventy-five (10-75), ten to one hundred (10-100), twenty to fifty (20-50), twenty to seventy-five (20-75), twenty to one hundred (20-100), fifty to seventy-five (50-75), fifty to one hundred (50-100), one hundred to one hundred and twenty-five (100-125), one hundred and twenty-five to one hundred and fifty (125-150), one hundred and fifty to one hundred and seventy five (150-175), one
30 hundred and seventy-five to two hundred (175-200), two hundred to two hundred and ten (200-210), two hundred and ten to two hundred and twenty (210-220), two hundred and twenty to two hundred and thirty (220-230), two hundred and thirty to two hundred and forty

(230- 240), two hundred and forty to two hundred and fifty (240-250), and two hundred and fifty to more than two hundred and fifty (250+).

Diagnostic and Prognostic Methods

5 The risk of developing Diabetes or Pre-Diabetes can be detected with a “pre-determined level of predictability” by examining an “effective amount” of DBRISKMARKER proteins, nucleic acids, polymorphisms, metabolites, and other analytes in a test sample (e.g., a subject derived sample) and comparing the effective amounts to reference or index values, often utilizing mathematical algorithms in order to combine
10 information from results of multiple individual DBRISKMARKERS into a single measurement or index. Subjects identified as having an increased risk of Diabetes or a pre-diabetic condition can optionally be selected to receive treatment regimens, such as administration of prophylactic or therapeutic compounds such as “diabetes-modulating drugs” as defined herein, or implementation of exercise regimens or dietary supplements to
15 prevent or delay the onset of Diabetes or Pre-Diabetes. A sample isolated from the subject can comprise, for example, blood, plasma, blood cells, endothelial cells, tissue biopsies, lymphatic fluid, serum, bone marrow, ascites fluid, interstitial fluid (including, for example, gingival crevicular fluid), urine, sputum, or other bodily fluids.

 The amount of the DBRISKMARKER protein, nucleic acid, polymorphism,
20 metabolite, or other analyte can be measured in a test sample and compared to the normal control level. The term “normal control level”, means the level of a DBRISKMARKER protein, nucleic acid, polymorphism, metabolite, or other analyte, or DBRISKMARKER physiology or indices, typically found in a subject not suffering from Diabetes or a pre-diabetic condition and not likely to have Diabetes or a pre-diabetic condition, e.g., relative to
25 samples collected from young subjects who were monitored until advanced age and were found not to develop Diabetes or a pre-diabetic condition. Alternatively, the normal control level can mean the level of a DBRISKMARKER protein, nucleic acid, polymorphism, metabolite, or other analyte typically found in a subject suffering from Diabetes or a pre-diabetic condition. The normal control level can be a range or an index. Alternatively, the
30 normal control level can be a database of patterns from previously tested subjects. A change in the level in the subject-derived sample of a DBRISKMARKER protein, nucleic acid, polymorphism, metabolite, or other analyte compared to the normal control level can indicate that the subject is suffering from or is at risk of developing Diabetes or a pre-diabetic

condition. In contrast, when the methods are applied prophylactically, a similar level compared to the normal control level in the subject-derived sample of a DBRISKMARKER protein, nucleic acid, polymorphism, metabolite, or other analyte can indicate that the subject is not suffering from, is not at risk or is at low risk of developing Diabetes or a pre-diabetic condition.

The difference in the level of DBRISKMARKERS is preferably statistically significant. By “statistically significant”, it is meant that the alteration is greater than what might be expected to happen by chance alone. Statistical significance can be determined by any method known in the art. For example, statistical significance can be determined by p -value. The p -value is a measure of probability that a difference between groups during an experiment happened by chance. ($P(z > z_{\text{observed}})$). For example, a p -value of 0.01 means that there is a 1 in 100 chance the result occurred by chance. The lower the p -value, the more likely it is that the difference between groups was caused by treatment. An alteration is statistically significant if the p -value is at least 0.05. Preferably, the p -value is 0.04, 0.03, 0.02, 0.01, 0.005, 0.001 or less. As noted below, and without any limitation of the invention, achieving statistical significance generally but not always requires that combinations of several DBRISKMARKERS be used together in panels and combined with mathematical algorithms in order to achieve a statistically significant DBRISKMARKER index.

The “diagnostic accuracy” of a test, assay, or method concerns the ability of the test, assay, or method to distinguish between subjects having Diabetes or a pre-diabetic condition, or at risk for Diabetes or a pre-diabetic condition is based on whether the subjects have a “clinically significant presence” or a “clinically significant alteration” in the levels of a DBRISKMARKER. By “clinically significant presence” or “clinically significant alteration”, it is meant that the presence of the DBRISKMARKER (e.g., mass, such as milligrams, nanograms, or mass per volume, such as milligrams per deciliter or copy number of a transcript per unit volume) or an alteration in the presence of the DBRISKMARKER in the subject (typically in a sample from the subject) is higher than the predetermined cut-off point (or threshold value) for that DBRISKMARKER and therefore indicates that the subject has Diabetes or a pre-diabetic condition for which the sufficiently high presence of that protein, nucleic acid, polymorphism, metabolite or analyte is a marker.

The present invention may be used to make categorical or continuous measurements of the risk of conversion to Type 2 Diabetes, thus diagnosing a category of subjects defined as Pre-Diabetic.

In the categorical scenario, the methods of the present invention can be used to discriminate between Normal and Pre-Diabetes subject cohorts. In this categorical use of the invention, the terms “high degree of diagnostic accuracy” and “very high degree of diagnostic accuracy” refer to the test or assay for that DBRISKMARKER (or DBRISKMARKER index; wherein DBRISKMARKER value encompasses any individual measurement whether from a single DBRISKMARKER or derived from an index of DBRISKMARKERS) with the predetermined cut-off point correctly (accurately) indicating the presence or absence of Pre-Diabetes. A perfect test would have perfect accuracy. Thus, for subjects who have Pre-Diabetes, the test would indicate only positive test results and would not report any of those subjects as being “negative” (there would be no “false negatives”). In other words, the “sensitivity” of the test (the true positive rate) would be 100%. On the other hand, for subjects who did not have Pre-Diabetes, the test would indicate only negative test results and would not report any of those subjects as being “positive” (there would be no “false positives”). In other words, the “specificity” (the true negative rate) would be 100%. See, e.g., O’Marcaigh AS, Jacobson RM, “Estimating The Predictive Value Of A Diagnostic Test, How To Prevent Misleading Or Confusing Results,” Clin. Ped. 1993, 32(8): 485-491, which discusses specificity, sensitivity, and positive and negative predictive values of a test, e.g., a clinical diagnostic test. In other embodiments, the present invention may be used so as to discriminate Pre-Diabetes from Diabetes, or Diabetes from Normal. Such use may require a different DBRISKMARKER panel, mathematical algorithm, and/or cut-off point, but be subject to the same aforementioned measurements of diagnostic accuracy for the intended use.

In the categorical diagnosis of a disease, changing the cut point or threshold value of a test (or assay) usually changes the sensitivity and specificity, but in a qualitatively inverse relationship. For example, if the cut point is lowered, more subjects in the population tested will typically have test results over the cut point or threshold value. Because subjects who have test results above the cut point are reported as having the disease, condition, or syndrome for which the test is conducted, lowering the cut point will cause more subjects to be reported as having positive results (e.g., that they have Diabetes, Pre-Diabetes, or a pre-diabetic condition). Thus, a higher proportion of those who have Diabetes or Pre-Diabetes will be indicated by the test to have it. Accordingly, the sensitivity (true positive rate) of the test will be increased. However, at the same time, there will be more false positives because more people who do not have the disease, condition, or syndrome (e.g., people who are truly

“negative”) will be indicated by the test to have DBRISKMARKER values above the cut point and therefore to be reported as positive (e.g., to have the disease, condition, or syndrome) rather than being correctly indicated by the test to be negative. Accordingly, the specificity (true negative rate) of the test will be decreased. Similarly, raising the cut point will tend to decrease the sensitivity and increase the specificity. Therefore, in assessing the accuracy and usefulness of a proposed medical test, assay, or method for assessing a subject’s condition, one should always take both sensitivity and specificity into account and be mindful of what the cut point is at which the sensitivity and specificity are being reported because sensitivity and specificity may vary significantly over the range of cut points.

There is, however, an indicator that allows representation of the sensitivity and specificity of a test, assay, or method over the entire range of test (or assay) cut points with just a single value. That indicator is derived from a Receiver Operating Characteristics (“ROC”) curve for the test, assay, or method in question. See, e.g., Shultz, “Clinical Interpretation Of Laboratory Procedures,” chapter 14 in Teitz, *Fundamentals of Clinical Chemistry*, Burtis and Ashwood (eds.), 4th edition 1996, W.B. Saunders Company, pages 192-199; and Zweig et al., “ROC Curve Analysis: An Example Showing The Relationships Among Serum Lipid And Apolipoprotein Concentrations In Identifying Subjects With Coronary Artery Disease,” *Clin. Chem.*, 1992, 38(8): 1425-1428.

An ROC curve is an x-y plot of sensitivity on the y-axis, on a scale of zero to one (e.g., 100%), against a value equal to one minus specificity on the x-axis, on a scale of zero to one (e.g., 100%). In other words, it is a plot of the true positive rate against the false positive rate for that test, assay, or method. To construct the ROC curve for the test, assay, or method in question, subjects can be assessed using a perfectly accurate or “gold standard” method that is independent of the test, assay, or method in question to determine whether the subjects are truly positive or negative for the disease, condition, or syndrome (for example, coronary angiography is a gold standard test for the presence of coronary atherosclerosis). The subjects can also be tested using the test, assay, or method in question, and for varying cut points, the subjects are reported as being positive or negative according to the test, assay, or method. The sensitivity (true positive rate) and the value equal to one minus the specificity (which value equals the false positive rate) are determined for each cut point, and each pair of x-y values is plotted as a single point on the x-y diagram. The “curve” connecting those points is the ROC curve.

The ROC curve is often used in order to determine the optimal single clinical cut-off or treatment threshold value where sensitivity and specificity are maximized; such a situation represents the point on the ROC curve which describes the upper left corner of the single largest rectangle which can be drawn under the curve.

5 The total area under the curve (“AUC”) is the indicator that allows representation of the sensitivity and specificity of a test, assay, or method over the entire range of cut points with just a single value. The maximum AUC is one (a perfect test) and the minimum area is one half (e.g. the area where there is no discrimination of normal versus disease). The closer the AUC is to one, the better is the accuracy of the test. It should be noted that implicit in all
10 ROC and AUC is the definition of the disease and the post-test time horizon of interest.

By a “high degree of diagnostic accuracy”, it is meant a test or assay (such as the test of the invention for determining the clinically significant presence of DBRISKMARKERS, which thereby indicates the presence of Diabetes or a pre-diabetic condition) in which the AUC (area under the ROC curve for the test or assay) is at least 0.70, desirably at least 0.75,
15 more desirably at least 0.80, preferably at least 0.85, more preferably at least 0.90, and most preferably at least 0.95.

By a “very high degree of diagnostic accuracy”, it is meant a test or assay in which the AUC (area under the ROC curve for the test or assay) is at least 0.80, desirably at least 0.85, more desirably at least 0.875, preferably at least 0.90, more preferably at least 0.925,
20 and most preferably at least 0.95.

Alternatively, in low disease prevalence tested populations (defined as those with less than 1% rate of occurrences per annum), ROC and AUC can be misleading as to the clinical utility of a test, and absolute and relative risk ratios as defined elsewhere in this disclosure can be employed to determine the degree of diagnostic accuracy. Populations of subjects to
25 be tested can also be categorized into quartiles, where the top quartile (25% of the population) comprises the group of subjects with the highest relative risk for developing or suffering from Diabetes or a pre-diabetic condition and the bottom quartile comprising the group of subjects having the lowest relative risk for developing Diabetes or a pre-diabetic condition. Generally, values derived from tests or assays having over 2.5 times the relative
30 risk from top to bottom quartile in a low prevalence population are considered to have a “high degree of diagnostic accuracy,” and those with five to seven times the relative risk for each quartile are considered to have a very high degree of diagnostic accuracy. Nonetheless, values derived from tests or assays having only 1.2 to 2.5 times the relative risk for each

quartile remain clinically useful are widely used as risk factors for a disease; such is the case with total cholesterol and for many inflammatory markers with respect to their prediction of future cardiovascular events.

The predictive value of any test depends on the sensitivity and specificity of the test, and on the prevalence of the condition in the population being tested. This notion, based on Bayes' theorem, provides that the greater the likelihood that the condition being screened for is present in a subject or in the population (pre-test probability), the greater the validity of a positive test and the greater the likelihood that the result is a true positive. Thus, the problem with using a test in any population where there is a low likelihood of the condition being present is that a positive result has limited value (i.e., more likely to be a false positive). Similarly, in populations at very high risk, a negative test result is more likely to be a false negative. By defining the degree of diagnostic accuracy, i.e., cut points on a ROC curve, defining an acceptable AUC value, and determining the acceptable ranges in relative concentration of what constitutes an effective amount of the DBRISKMARKERS of the invention allows for one of skill in the art to use the DBRISKMARKERS to diagnose or identify subjects with a pre-determined level of predictability.

Alternative methods of determining diagnostic accuracy must be used with continuous measurements of risk, which are commonly used when a disease category or risk category (such as Pre-Diabetes) has not yet been clearly defined by the relevant medical societies and practice of medicine.

"Risk" in the context of the present invention can mean "absolute" risk, which refers to that percentage probability that an event will occur over a specific time period. Absolute risk can be measured with reference to either actual observation post-measurement for the relevant time cohort, or with reference to index values developed from statistically valid historical cohorts that have been followed for the relevant time period. "Relative" risk refers to the ratio of absolute risks of a subject's risk compared either to low risk cohorts or average population risk, which can vary by how clinical risk factors are assessed. Odds ratios, the proportion of positive events to negative events for a given test result, are also commonly used (odds are according to the formula $p/(1-p)$ where p is the probability of event and $(1-p)$ is the probability of no event) to no-conversion. Alternative continuous measures which may be assessed in the context of the present invention include time to Diabetes conversion and therapeutic Diabetes conversion risk reduction ratios.

For such continuous measures, measures of diagnostic accuracy for a calculated index are typically based on linear regression curve fits between the predicted continuous value and the actual observed values (or historical index calculated value) and utilize measures such as R squared, p values and confidence intervals. It is not unusual for predicted values using such algorithms to be reported including a confidence interval (usually 90% or 95% CI) based on a historical observed cohort's predictions, as in the test for risk of future breast cancer recurrence commercialized by Genomic Health (Redwood City, California).

The ultimate determinant and gold standard of true risk conversion to Diabetes is a actual conversions within a sufficiently large population and observed over the length of time claimed. However, this is problematic, as it is necessarily a retrospective point of view, coming after any opportunity for preventive interventions. As a result, subjects suffering from or at risk of developing Diabetes or a pre-diabetic condition are commonly diagnosed or identified by methods known in the art, and future risk is estimated based on historical experience and registry studies. Such methods include, but are not limited to, measurement of systolic and diastolic blood pressure, measurements of body mass index, *in vitro* determination of total cholesterol, LDL, HDL, insulin, and glucose levels from blood samples, oral glucose tolerance tests, stress tests, measurement of human serum C-reactive protein (hsCRP), electrocardiogram (ECG), c-peptide levels, anti-insulin antibodies, anti-beta cell-antibodies, and glycosylated hemoglobin (HbA_{1c}). Additionally, any of the aforementioned methods can be used separately or in combination to assess if a subject has shown an "improvement in Diabetes risk factors." Such improvements include, without limitation, a reduction in body mass index (BMI), a reduction in blood glucose levels, an increase in HDL levels, a reduction in systolic and/or diastolic blood pressure, an increase in insulin levels, or combinations thereof.

The oral glucose tolerance test (OGTT) is principally used for diagnosis of Diabetes Mellitus or pre-diabetic conditions when blood glucose levels are equivocal, during pregnancy, or in epidemiological studies (Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications, Part 1, World Health Organization, 1999). The OGTT should be administered in the morning after at least 3 days of unrestricted diet (greater than 150 g of carbohydrate daily) and usual physical activity. A reasonable (30-50 g) carbohydrate-containing meal should be consumed on the evening before the test. The test should be preceded by an overnight fast of 8-14 hours, during which water may be consumed. After collection of the fasting blood sample, the subject should drink 75 g of anhydrous

glucose or 82.5 g of glucose monohydrate in 250-300 ml of water over the course of 5 minutes. For children, the test load should be 1.75 g of glucose per kg body weight up to a total of 75 g of glucose. Timing of the test is from the beginning of the drink. Blood samples must be collected 2 hours after the test load. As previously noted, a diagnosis of impaired
5 glucose tolerance (IGT) has been noted as being only 50% sensitive, with a >10% false positive rate, for a 7.5 year conversion to diabetes when used at the WHO cut-off points. This is a significant problem for the clinical utility of the test, as even relatively high risk ethnic groups have only a 10% rate of conversion to Diabetes over such a period unless otherwise enriched by other risk factors; in an unselected general population, the rate of
10 conversion over such periods is typically estimated at 5-6%, or less than 1% per annum.

Other methods of measuring glucose in blood include reductionimetric methods known in the art such as, but not limited to, the Somogyi-Nelson method, methods using hexokinase and glucose dehydrogenase, immobilized glucose oxidase electrodes, the o-toluidine method, the ferricyanide method and the neocuprine autoanalyzer method. Whole blood glucose
15 values are usually about 15% lower than corresponding plasma values in patients with a normal hematocrit reading, and arterial values are generally about 7% higher than corresponding venous values. Subjects taking insulin are frequently requested to build up a "glycemic profile" by self-measurement of blood glucose at specific times of the day. A "7-point profile" is useful, with samples taken before and 90 minutes after each meal, and just
20 before going to bed.

A subject suffering from or at risk of developing Diabetes or a pre-diabetic condition may also be suffering from or at risk of developing arteriovascular disease, hypertension or obesity. Type 2 Diabetes in particular and arteriovascular disease have many risk factors in common, and many of these risk factors are highly correlated with one another. The
25 relationships among these risk factors may be attributable to a small number of physiological phenomena, perhaps even a single phenomenon. Subjects suffering from or at risk of developing Diabetes, arteriovascular disease, hypertension or obesity are identified by methods known in the art. For example, Diabetes is frequently diagnosed by measuring fasting blood glucose levels or insulin. Normal adult glucose levels are 60-126 mg/dl.
30 Normal insulin levels are $7 \text{ mU/mL} \pm 3 \text{ mU}$. Hypertension is diagnosed by a blood pressure consistently at or above 140/90. Risk of arteriovascular disease can also be diagnosed by measuring cholesterol levels. For example, LDL cholesterol above 137 or total cholesterol above 200 is indicative of a heightened risk of arteriovascular disease. Obesity is diagnosed

for example, by body mass index. Body mass index (BMI) is measured (kg/m^2 (or $\text{lb}/\text{in}^2 \times 704.5$)). Alternatively, waist circumference (estimates fat distribution), waist-to-hip ratio (estimates fat distribution), skinfold thickness (if measured at several sites, estimates fat distribution), or bioimpedance (based on principle that lean mass conducts current better than fat mass (i.e. fat mass impedes current), estimates % fat) is measured. The parameters for normal, overweight, or obese individuals is as follows: Underweight: BMI < 18.5 ; Normal: BMI 18.5 to 24.9; Overweight: BMI = 25 to 29.9. Overweight individuals are characterized as having a waist circumference of > 94 cm for men or > 80 cm for women and waist to hip ratios of ≥ 0.95 in men and ≥ 0.80 in women. Obese individuals are characterized as having a BMI of 30 to 34.9, being greater than 20% above "normal" weight for height, having a body fat percentage $> 30\%$ for women and 25% for men, and having a waist circumference > 102 cm (40 inches) for men or 88 cm (35 inches) for women. Individuals with severe or morbid obesity are characterized as having a BMI of ≥ 35 . Because of the interrelationship between Diabetes and arteriovascular disease, some or all of the individual DBRISKMARKERS and DBRISKMARKER panels of the present invention may overlap or be encompassed by biomarkers of arteriovascular disease, and indeed may be useful in the diagnosis of the risk of arteriovascular disease.

Risk prediction for Diabetes Mellitus or a pre-diabetic condition can also encompass risk prediction algorithms and computed indices that assess and estimate a subject's absolute risk for developing Diabetes or a pre-diabetic condition with reference to a historical cohort. Risk assessment using such predictive mathematical algorithms and computed indices has increasingly been incorporated into guidelines for diagnostic testing and treatment, and encompass indices obtained from and validated with, *inter alia*, multi-stage, stratified samples from a representative population. A plurality of conventional Diabetes risk factors are incorporated into predictive models. A notable example of such algorithms include the Framingham Heart Study (Kannel, W.B., et al, (1976) Am. J. Cardiol. 38: 46-51) and modifications of the Framingham Study, such as the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), also known as NCEP/ATP III, which incorporates a patient's age, total cholesterol concentration, HDL cholesterol concentration, smoking status, and systolic blood pressure to estimate a person's 10-year risk of developing arteriovascular disease, which is commonly found in subjects suffering from or at risk for developing Diabetes

Mellitus, or a pre-diabetic condition. The same Framingham algorithm has been found to be modestly predictive of the risk for developing Diabetes Mellitus, or a pre-diabetic condition.

Other Diabetes risk prediction algorithms include, without limitation, the San Antonio Heart Study (Stern, M.P. et al, (1984) *Am. J. Epidemiol.* 120: 834-851; Stern, M.P. et al, (1993) *Diabetes* 42: 706-714; Burke, J.P. et al, (1999) *Arch. Intern. Med.* 159: 1450-1456), Archimedes (Eddy, D.M. and Schlessinger, L. (2003) *Diabetes Care* 26(11): 3093-3101; Eddy, D.M. and Schlessinger, L. (2003) *Diabetes Care* 26(11): 3102-3110), the Finnish-based Diabetes Risk Score (Lindström, J. and Tuomilehto, J. (2003) *Diabetes Care* 26(3): 725-731), and the Ely Study (Griffin, S.J. et al, (2000) *Diabetes Metab. Res. Rev.* 16: 164-171), the contents of which are expressly incorporated herein by reference.

Archimedes is a mathematical model of Diabetes that simulates the disease state person-by-person, object-by-object and comprises biological details that are continuous in reality, such as the pertinent organ systems, more than 50 continuously interacting biological variables, and the major symptoms, tests, treatments, and outcomes commonly associated with Diabetes.

Archimedes includes many diseases simultaneously and interactively in a single integrated physiology, enabling it to address features such as co-morbidities, syndromes, treatments and other multiple effects. The Archimedes model includes Diabetes and its complications, such as coronary artery disease, congestive heart failure, and asthma. The model is written in differential equations, using object-oriented programming and a construct called "features". The model comprises the anatomy of a subject (all simulated subjects have organs, such as hearts, livers, pancreases, gastrointestinal tracts, fat, muscles, kidneys, eyes, limbs, circulatory systems, brains, skin, and peripheral nervous systems), the "features" that determine the course of the disease and representing real physical phenomena (e.g., the number of milligrams of glucose in a deciliter of plasma, behavioral phenomena, or conceptual phenomena (e.g., the "progression" of disease), risk factors, incidence, and progression of the disease, glucose metabolism, signs and tests, diagnosis, symptoms, health outcomes of glucose metabolism, treatments, complications, deaths from Diabetes and its complications, deaths from other causes, care processes, and medical system resources. For a typical application of the model, there are thousands of simulated subjects, each with a simulated anatomy and physiology, who will get simulated diseases, can seek care at simulated health care facilities, will be seen by simulated health care personnel in simulated facilities, will be given simulated tests and treatments, and will have simulated outcomes. As

in reality, each of the simulated patients is different, with different characteristics, physiologies, behaviors, and responses to treatments, all designed to match the individual variations seen in reality.

The model is built by development of a non-quantitative or conceptual description of the pertinent biology and pathology – the variables and relationships – as best they are understood with current information. Studies are then identified that pertain to the variables and relationships, and typically comprise basic research, epidemiological, and clinical studies that experts in the field identify as the foundations of their own understanding of the disease. That information is used to develop differential equations that relate the variables. The development of any particular equation in the Archimedes model involves finding the form and coefficients that best fit the available information about the variables, after which the equations are programmed into an object-oriented language. This is followed by a series of exercises in which the parts of the model are tested and debugged, first one at a time, and then in appropriate combinations, using inputs that have known outputs. The entire model can then be used to simulate a complex trial, which demonstrates not only the individual parts of the model, but also the connections between all the parts. The Archimedes calculations are performed using distributed computing techniques. Archimedes has been validated as a realistic representation of the anatomy, pathophysiology, treatments and outcomes pertinent to Diabetes and its complications (Eddy, D.M. and Schlessinger, L. (2003) *Diabetes Care* 26(11) 3102-3110).

The Finland-based Diabetes Risk Score is designed as a screening tool for identifying high-risk subjects in the population and for increasing awareness of the modifiable risk factors and healthy lifestyle. The Diabetes Risk Score was determined from a random population sample of 35- to 64-year old Finnish men and women with no anti-diabetic drug treatment at baseline, and followed for 10 years. Multivariate logistic regression model coefficients were used to assign each variable category a score. The Diabetes Risk Score comprises the sum of these individual scores and validated in an independent population survey performed in 1992 with a prospective follow-up for 5 years. Age, BMI, waist circumference, history of anti-hypertensive drug treatment and high blood glucose, physical activity, and daily consumption of fruits, berries, or vegetables were selected as categorical variables.

The Finland-based Diabetes Risk Score values are derived from the coefficients of the logistic model by classifying them into five categories. The estimated probability (p) of

drug-treated Diabetes over a 10-year span of time for any combination of risk factors can be calculated from the following coefficients:

$$p(Diabetes) = \frac{e^{(\beta_0 + \beta_{1x1} + \beta_{2x2} + \dots)}}{1 + e^{(\beta_0 + \beta_{1x1} + \beta_{2x2} + \dots)}}$$

where β_0 is the intercept and $\beta_1, \beta_2,$ and so on represent the regression coefficients of the various categories of the risk factors $x_1, x_2,$ and so on.

The sensitivity relates to the probability that the test is positive for subjects who will get drug-treated Diabetes in the future and the specificity reflects the probability that the test is negative for subjects without drug-treated Diabetes. The sensitivity and the specificity with 95% confidence interval (CI) were calculated for each Diabetes Risk Score level in differentiating the subjects who developed drug-treated Diabetes from those who did not. ROC curves were plotted for the Diabetes Risk score, the sensitivity was plotted on the y-axis and the false-positive rate (1-specificity) was plotted on the x-axis. The more accurately discriminatory the test, the steeper the upward portion of the ROC curve, and the higher the AUC, the optimal cut point being the peak of the curve.

Statistically significant independent predictors of future drug-treated Diabetes in the Diabetes Risk Score are age, BMI, waist circumference, antihypertensive drug therapy, and history of high blood glucose levels. The Diabetes Risk Score model comprises a concise model that includes only these statistically significant variables and a full model, which includes physical activity and fruit and vegetable consumption.

The San Antonio Heart Study is a long-term, community-based prospective observational study of Diabetes and arteriovascular disease in Mexican Americans and non-Hispanic Caucasians. The study initially enrolled 3,301 Mexican-American and 1,857 non-Hispanic Caucasian men and non-pregnant women in two phases between 1979 and 1988. Participants were 25-64 years of age at enrollment and were randomly selected from low, middle, and high-income neighborhoods in San Antonio, Texas. A 7-8 year follow-up exam followed approximately 73% of the surviving individuals initially enrolled in the study. Baseline characteristics such as medical history of Diabetes, age, sex, ethnicity, BMI, systolic and diastolic blood pressure, fasting and 2-hour plasma glucose levels, fasting serum total cholesterol, LDL, and HDL cholesterol levels, as well as triglyceride levels, were compiled and assessed. A multiple logistic regression model with incident Diabetes as the dependent variable and the aforementioned baseline characteristics were applied as independent

variables. Using this model, univariate odds ratios can be computed for each potential risk factor for men and women separately and for both sexes combined. For continuous risk factors, the odds ratios can be presented for a 1-SD increment. A multivariate predicting model with both sexes combined can be developed using a stepwise logistic regression procedure in which the variables that had shown statistically significant odds ratios when examined individually were allowed to enter the model. This multivariable model is then analyzed by ROC curves and 95% CIs of the areas under the ROC curves estimated by non-parametric algorithms such as those described by DeLong (DeLong E.R. et al, (1988) Biometrics 44: 837-45). The results of the San Antonio Heart Study indicate that pre-diabetic subjects have an atherogenic pattern of risk factors (possibly caused by obesity, hyperglycemia, and especially hyperinsulinemia), which may be present for many years and may contribute to the risk of macrovascular disease as much as the duration of clinical Diabetes itself.

Despite the numerous studies and algorithms that have been used to assess the risk of Diabetes or a pre-diabetic condition, the evidence-based, multiple risk factor assessment approach is only moderately accurate for the prediction of short- and long-term risk of manifesting Diabetes or a pre-diabetic condition in individual asymptomatic or otherwise healthy subjects. Such risk prediction algorithms can be advantageously used in combination with the DBRISKMARKERS of the present invention to distinguish between subjects in a population of interest to determine the risk stratification of developing Diabetes or a pre-diabetic condition. The DBRISKMARKERS and methods of use disclosed herein provide tools that can be used in combination with such risk prediction algorithms to assess, identify, or diagnose subjects who are asymptomatic and do not exhibit the conventional risk factors.

The data derived from risk prediction algorithms and from the methods of the present invention can be compared by linear regression. Linear regression analysis models the relationship between two variables by fitting a linear equation to observed data. One variable is considered to be an explanatory variable, and the other is considered to be a dependent variable. For example, values obtained from the Archimedes or San Antonio Heart analysis can be used as a dependent variable and analyzed against levels of one or more DBRISKMARKERS as the explanatory variables in an effort to more fully define the underlying biology implicit in the calculated algorithm score (see Examples). Alternatively, such risk prediction algorithms, or their individual inputs, which are generally DBRISKMARKERS themselves, can be directly incorporated into the practice of the present

invention, with the combined algorithm compared against actual observed results in a historical cohort.

A linear regression line has an equation of the form $Y = a + bX$, where X is the explanatory variable and Y is the dependent variable. The slope of the line is b , and a is the intercept (the value of y when $x = 0$). A numerical measure of association between two variables is the “correlation coefficient,” or R , which is a value between -1 and 1 indicating the strength of the association of the observed data for the two variables. This is also often reported as the square of the correlation coefficient, as the “coefficient of determination” or R^2 ; in this form it is the proportion of the total variation in Y explained by fitting the line.

10 The most common method for fitting a regression line is the method of least-squares. This method calculates the best-fitting line for the observed data by minimizing the sum of the squares of the vertical deviations from each data point to the line (if a point lies on the fitted line exactly, then its vertical deviation is 0). Because the deviations are first squared, then summed, there are no cancellations between positive and negative values.

15 After a regression line has been computed for a group of data, a point which lies far from the line (and thus has a large residual value) is known as an outlier. Such points may represent erroneous data, or may indicate a poorly fitting regression line. If a point lies far from the other data in the horizontal direction, it is known as an influential observation. The reason for this distinction is that these points have may have a significant impact on the slope

20 of the regression line. Once a regression model has been fit to a group of data, examination of the residuals (the deviations from the fitted line to the observed values) allows one of skill in the art to investigate the validity of the assumption that a linear relationship exists. Plotting the residuals on the y -axis against the explanatory variable on the x -axis reveals any possible non-linear relationship among the variables, or might alert the skilled artisan to investigate

25 “lurking variables.” A “lurking variable” exists when the relationship between two variables is significantly affected by the presence of a third variable which has not been included in the modeling effort.

Linear regression analyses can be used, *inter alia*, to predict the risk of developing Diabetes or a pre-diabetic condition based upon correlating the levels of DBRISKMARKERS

30 in a sample from a subject to that subjects’ actual observed clinical outcomes, or in combination with, for example, calculated Archimedes risk scores, San Antonio Heart risk scores, or other known methods of diagnosing or predicting the prevalence of Diabetes or a pre-diabetic condition. Of particular use, however, are non-linear equations and analyses to

determine the relationship between known predictive models of Diabetes and levels of DBRISKMARKERS detected in a subject sample. Of particular interest are structural and synactic classification algorithms, and methods of risk index construction, utilizing pattern recognition features, including established techniques such as the Kth-Nearest Neighbor, Boosting, Decision Trees, Neural Networks, Bayesian Networks, Support Vector Machines, and Hidden Markov Models. Most commonly used are classification algorithms using logistic regression, which are the basis for the Framingham, Finnish, and San Antonio Heart risk scores. Furthermore, the application of such techniques to panels of multiple DBRISKMARKERS is encompassed by or within the ambit of the present invention, as is the use of such combination to create single numerical “risk indices” or “risk scores” encompassing information from multiple DBRISKMARKER inputs. An example using logistic regression is described herein in the Examples.

Factor analysis is a mathematical technique by which a large number of correlated variables (such as Diabetes risk factors) can be reduced to fewer “factors” that represent distinct attributes that account for a large proportion of the variance in the original variables (Hanson, R.L. et al, (2002) Diabetes 51: 3120-3127). Thus, factor analysis is well suited for identifying components of Diabetes Mellitus and pre-diabetic conditions such as IGT, IFG, and Metabolic Syndrome. Epidemiological studies of factor “scores” from these analyses can further determine relations between components of the metabolic syndrome and incidence of Diabetes. The premise underlying factor analysis is that correlations observed among a set of variables can be explained by a small number of unique unmeasured variables, or “factors”. Factor analysis involves two procedures: 1) factor extraction to estimate the number of factors, and 2) factor rotation to determine constituents of each factor in terms of the original variables.

Factor extraction can be conducted by the method of principal components. These components are linear combinations of the original variables that are constructed so that each component has a correlation of zero with each of the other components. Each principal component is associated with an “eigen-value,” which represents the variance in the original variables explained by that component (with each original variable standardized to have a variance of 1). The number of principal components that can be constructed is equal to the number of original variables. In factor analysis, the number of factors is customarily determined by retention of only those components that account for more of the total variance than any single original variable (i.e., those components with eigen-values of >1).

Once the number of factors has been established, then factor rotation is conducted to determine the composition of factors that has the most parsimonious interpretation in terms of the original variables. In factor rotation, "factor loadings," which represent correlations of each factor with the original variables, are changed so that these factor loadings are made as close to 0 or 1 as possible (with the constraint that the total amount of variance explained by the factors remains unchanged). A number of methods for factor rotation have been developed and can be distinguished by whether they require the final set of factors to remain uncorrelated with one another (also known as "orthogonal methods") or by whether they allow factors to be correlated ("oblique methods"). In interpretation of factor analysis, the pattern of factor loadings is examined to determine which original variables represent primary constituents of each factor. Conventionally, variables that have a factor loading of >0.4 (or less than -0.4) with a particular factor are considered to be its major constituents. Factor analysis can be very useful in constructing DBRISKMARKER panels from their constituent components, and in grouping substitutable groups of markers.

Levels of an effective amount of DBRISKMARKER proteins, nucleic acids, polymorphisms, metabolites, or other analytes also allows for the course of treatment of Diabetes or a pre-diabetic condition to be monitored. In this method, a biological sample can be provided from a subject undergoing treatment regimens, e.g., drug treatments, for Diabetes. Such treatment regimens can include, but are not limited to, exercise regimens, dietary supplementation, surgical intervention, and treatment with therapeutics or prophylactics used in subjects diagnosed or identified with Diabetes or a pre-diabetic condition. If desired, biological samples are obtained from the subject at various time points before, during, or after treatment. Levels of an effective amount of DBRISKMARKER proteins, nucleic acids, polymorphisms, metabolites, or other analytes can then be determined and compared to a reference value, e.g. a control subject or population whose diabetic state is known or an index value or baseline value. The reference sample or index value or baseline value may be taken or derived from one or more subjects who have been exposed to the treatment, or may be taken or derived from one or more subjects who are at low risk of developing Diabetes or a pre-diabetic condition, or may be taken or derived from subjects who have shown improvements in Diabetes risk factors as a result of exposure to treatment. Alternatively, the reference sample or index value or baseline value may be taken or derived from one or more subjects who have not been exposed to the treatment. For example, samples may be collected from subjects who have received initial treatment for Diabetes or a

pre-diabetic condition and subsequent treatment for Diabetes or a pre-diabetic condition to monitor the progress of the treatment. A reference value can also comprise a value derived from risk prediction algorithms or computed indices from population studies such as those disclosed herein.

5 The DBRISKMARKERS of the present invention can thus be used to generate a “reference expression profile” of those subjects who do not have Diabetes or a pre-diabetic condition such as impaired glucose tolerance, and would not be expected to develop Diabetes or a pre-diabetic condition. The DBRISKMARKERS disclosed herein can also be used to generate a “subject expression profile” taken from subjects who have Diabetes or a pre-
10 diabetic condition like impaired glucose tolerance. The subject expression profiles can be compared to a reference expression profile to diagnose or identify subjects at risk for developing Diabetes or a pre-diabetic condition, to monitor the progression of disease, as well as the rate of progression of disease, and to monitor the effectiveness of Diabetes or pre-Diabetes treatment modalities. The reference and subject expression profiles of the present
15 invention can be contained in a machine-readable medium, such as but not limited to, analog tapes like those readable by a VCR, CD-ROM, DVD-ROM, USB flash media, among others. Such machine-readable media can also contain additional test results, such as, without limitation, measurements of conventional Diabetes risk factors like systolic and diastolic blood pressure, blood glucose levels, insulin levels, BMI indices, and cholesterol (LDL and
20 HDL) levels. Alternatively or additionally, the machine-readable media can also comprise subject information such as medical history and any relevant family history. The machine-readable media can also contain information relating to other Diabetes-risk algorithms and computed indices such as those described herein.

Differences in the genetic makeup of subjects can result in differences in their relative
25 abilities to metabolize various drugs, which may modulate the symptoms or risk factors of Diabetes or a pre-diabetic condition. Subjects that have Diabetes or a pre-diabetic condition, or at risk for developing Diabetes or a pre-diabetic condition can vary in age, ethnicity, body mass index (BMI), total cholesterol levels, blood glucose levels, blood pressure, LDL and HDL levels, and other parameters. Accordingly, use of the DBRISKMARKERS disclosed
30 herein allow for a pre-determined level of predictability that a putative therapeutic or prophylactic to be tested in a selected subject will be suitable for treating or preventing Diabetes or a pre-diabetic condition in the subject.

To identify therapeutics or drugs that are appropriate for a specific subject, a test sample from the subject can be exposed to a therapeutic agent or a drug, and the level of one or more of DBRISKMARKER proteins, nucleic acids, polymorphisms, metabolites or other analytes can be determined. The level of one or more DBRISKMARKERS can be compared to sample derived from the subject before and after treatment or exposure to a therapeutic agent or a drug, or can be compared to samples derived from one or more subjects who have shown improvements in Diabetes or pre-Diabetes risk factors as a result of such treatment or exposure. Examples of such therapeutics or drugs frequently used in Diabetes treatments, and may modulate the symptoms or risk factors of Diabetes include, but are not limited to, sulfonyleureas like glimepiride, glyburide (also known in the art as glibenclamide), glipizide, gliclazide; biguanides such as metformin; insulin (including inhaled formulations such as Exubera), and insulin analogs such as insulin lispro (Humalog), insulin glargine (Lantus), insulin detemir, and insulin glulisine; peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists such as the thiazolidinediones including troglitazone (Rezulin), pioglitazone (Actos), rosiglitazone (Avandia), and isaglitazone (also known as netoglitazone); dual-acting PPAR agonists such as BMS-298585 and tesaglitazar; insulin secretagogues including metglitinides such as repaglinide and nateglinide; analogs of glucagon-like peptide-1 (GLP-1) such as exenatide (AC-2993) and liraglutide (insulinotropin); inhibitors of dipeptidyl peptidase IV like LAF-237; pancreatic lipase inhibitors such as orlistat; α -glucosidase inhibitors such as acarbose, migitol, and voglibose; and combinations thereof, particularly metformin and glyburide (Glucoavance), metformin and rosiglitazone (Avandamet), and metformin and glipizide (Metaglip). Such therapeutics or drugs have been prescribed for subjects diagnosed with Diabetes or a pre-diabetic condition, and may modulate the symptoms or risk factors of Diabetes or a pre-diabetic condition.

A subject sample can be incubated in the presence of a candidate agent and the pattern of DBRISKMARKER expression in the test sample is measured and compared to a reference profile, e.g., a Diabetes reference expression profile or a non-Diabetes reference expression profile or an index value or baseline value. The test agent can be any compound or composition or combination thereof. For example, the test agents are agents frequently used in Diabetes treatment regimens and are described herein.

Table 1 comprises the two-hundred and sixty (260) DBRISKMARKERS of the present invention. One skilled in the art will recognize that the DBRISKMARKERS presented herein encompasses all forms and variants, including but not limited to,

polymorphisms, isoforms, mutants, derivatives, precursors including nucleic acids, receptors (including soluble and transmembrane receptors), ligands, and post-translationally modified variants, as well as any multi-unit nucleic acid, protein, and glycoprotein structures comprised of any of the DBRISKMARKERS as constituent subunits of the fully assembled structure.

5

Table 1: DBRISKMARKERS

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
1	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	sulfonylurea receptor (SUR1), HI; SUR; HHF1; MRP8; PHHI; SUR1; ABC36; HRINS	ABCC8
2	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	sulfonylurea receptor (SUR2a), SUR2; ABC37; CMD10; FLJ36852	ABCC9
3	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	angiotensin-converting enzyme (ACE) - ACE1, CD143, DCP, DCP1, CD143 antigen; angiotensin I converting enzyme; angiotensin converting enzyme, somatic isoform; carboxycathepsin; dipeptidyl carboxypeptidase 1; kininase II; peptidase P; peptidyl-dipeptidase A; testicular ECA	ACE
4	adenylate cyclase activating polypeptide 1 (pituitary)	adenylate cyclase activating polypeptide	ADCYAP1
5	adiponectin, C1Q and collagen domain containing	Adiponectin - ACDC, ACRP30, APM-1, APM1, GBP28, adiponectin, adipocyte, C1Q and collagen domain containing; adipocyte, C1Q and collagen domain-containing; adiponectin; adipose most abundant gene transcript 1; gelatin-binding protein 28	ADIPOQ
6	adiponectin receptor 1	G Protein Coupled Receptor AdipoR1 - ACDCR1, CGI-45, PAQR1, TESBP1A	ADIPOR1
7	adiponectin receptor 2	G Protein Coupled Receptor AdipoR2 - ACDCR2, PAQR2	ADIPOR2
8	adrenomedullin	adrenomedullin - AM, preproadrenomedullin	ADM
9	adrenergic, beta-2-, receptor, surface	G Protein- Coupled Beta-2 Adrenoceptor - ADRB2R, ADRBR, B2AR, BAR, BETA2AR, beta-2 adrenergic receptor; beta-2 adrenoceptor; catecholamine receptor	ADRB2
10	advanced glycosylation end product-specific receptor	RAGE - advanced glycosylation end product-specific receptor RAGE3;	AGER

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		advanced glycosylation end product-specific receptor variant sRAGE1; advanced glycosylation end product-specific receptor variant sRAGE2; receptor for advanced glycosylation end-products; soluble receptor	
11	agouti related protein homolog (mouse)	AGRT, ART, ASIP2, & Agouti-related transcript, mouse, homolog of; agouti (mouse) related protein; agouti related protein homolog	AGRP
12	angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	angiotensin I; pre-angiotensinogen; angiotensin II precursor; angiotensinogen (serine (or cysteine) peptidase inhibitor, clade A, member 8); angiotensinogen (serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 8)	AGT
13	angiotensin II receptor, type 1	G protein-Coupled Receptor AGTR1A - AG2S, AGTR1A, AGTR1B, AT1, AT1B, AT2R1, AT2R1A, AT2R1B, HAT1R, angiotensin receptor 1; angiotensin receptor 1B; type-1B angiotensin II receptor	AGTR1
14	angiotensin II receptor-associated protein	angiotensin II - ATRAP, ATI receptor-associated protein; angiotensin II, type I receptor-associated protein	AGTRAP
15	alpha-2-HS-glycoprotein	A2HS, AHS, FETUA, HSGA, Alpha-2HS-glycoprotein; fetuin-A	AHSG
16	v-akt murine thymoma viral oncogene homolog 1	Ser/Thr kinase Akt - PKB, PRKBA, RAC, RAC-ALPHA, RAC-alpha serine/threonine-protein kinase; murine thymoma viral (v-akt) oncogene homolog-1; protein kinase B; rac protein kinase alpha	AKT1
17	v-akt murine thymoma viral oncogene homolog 2	PKBBETA, PRKBB, RAC-BETA, Murine thymoma viral (v-akt) homolog-2; rac protein kinase beta	AKT2
18	albumin	Ischemia-modified albumin (IMA) - cell growth inhibiting protein 42; growth-inhibiting protein 20; serum albumin	ALB
19	Alstrom syndrome 1	ALSS	ALMS1
20	archidonate 12-lipoxygenase	LOG12, 12(S)-lipoxygenase; platelet-type 12-lipoxygenase/arachidonate 12-	ALOX12

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		lipoygenase	
21	ankyrin repeat domain 23	DARP, MARP3, Diabetes related ankyrin repeat protein; muscle ankyrin repeat protein 3	ANKRD23
22	apelin, AGTRL 1 Ligand	XNPEP2, apelin, peptide ligand for APJ receptor	APLN
23	apolipoprotein A-I	apolipoproteins A-1 and B, amyloidosis; apolipoprotein A-I, preproprotein; apolipoprotein A1; preproapolipoprotein	APOA1
24	apolipoprotein A-II	Apolipoprotein A-II	APOA2
25	apolipoprotein B (including Ag(x) antigen)	apolipoproteins A-1 and B - Apolipoprotein B, FLDB, apoB-100; apoB-48; apolipoprotein B; apolipoprotein B48	APOB
26	apolipoprotein E	APO E - AD2, apoprotein, Alzheimer disease 2 (APOE*E4-associated, late onset); apolipoprotein E precursor; apolipoprotein E3	APOE
27	aryl hydrocarbon receptor nuclear translocator	dioxin receptor, nuclear translocator; hypoxia-inducible factor 1, beta subunit	ARNT
28	Aryl hydrocarbon receptor nuclear translocator-like	Bmal1, TIC; JAP3; MOP3; BMAL1; PASD3; BMAL1c; bHLH-PAS protein JAP3; member of PAS superfamily 3; ARNT-like protein 1, brain and muscle; basic-helix-loop-helix-PAS orphan MOP3	ARNTL
29	arrestin, beta 1	beta arrestin - ARB1, ARR1, arrestin beta 1	ARRB1
30	arginine vasopressin (neurophysin II, antidiuretic hormone, Diabetes insipidus, neurohypophyseal)	copeptin - ADH, ARVP, AVP-NP11, AVRP, VP, arginine vasopressin-neurophysin II; vasopressin-neurophysin II-copeptin, vasopressin	AVP
31	bombesin receptor subtype 3	G-protein coupled receptor; bombesin receptor subtype 3	BRS3
32	betacellulin	betacellulin	BTC
33	benzodiazepine receptor (peripheral)	PBR - DBI, IBP, MBR, PBR, PKBS, PTBR, mDRC, pk18, benzodiazepine peripheral binding site; mitochondrial benzodiazepine receptor; peripheral benzodiazepine receptor; peripheral benzodiazepine receptor; peripheral-type benzodiazepine receptor	BZRP
34	complement component 3	complement C3 - acylation-stimulating protein cleavage product; complement component C3, ASP; CPAMD1	C3

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
35	complement component 4A (Rodgers blood group)	complement C4 - C4A anaphylatoxin; Rodgers form of C4; acidic C4; c4 propeptide; complement component 4A; complement component C4B	C4A
36	complement component 4B (Chido blood group)	C4A, C4A13, C4A91, C4B1, C4B12, C4B2, C4B3, C4B5, C4F, CH, CO4, CPAMD3, C4 complement C4d region; Chido form of C4; basic C4; complement C4B; complement component 4B; complement component 4B, centromeric; complement component 4B, telomeric; complement component C4B	C4B
37	complement component 5	anaphylatoxin C5a analog - CPAMD4	C5
38	Calpain-10	calcium-activated neutral protease	CAPN10
39	cholecystokinin	cholecystokinin	CCK
40	cholecystokinin (CCK)-A receptor	CCK-A; CCK-A; CCKRA; CCK1-R; cholecystokinin-1 receptor; cholecystokinin type-A receptor	CCKAR
41	chemokine (C-C motif) ligand 2	Monocyte chemoattractant protein-1 (MCP-1) - GDCF-2, GDCF-2 HC11, HC11, HSMCR30, MCAF, MCP-1, MCP1, SCYA2, SMC-CF, monocyte chemoattractant protein-1; monocyte chemotactic and activating factor; monocyte chemotactic protein 1, homologous to mouse Sig-je; monocyte secretory protein JE; small inducible cytokine A2; small inducible cytokine A2 (monocyte chemotactic protein 1, homologous to mouse Sig-je); small inducible cytokine subfamily A (Cys-Cys), member 2	CCL2
42	CD14 molecule	CD14 antigen - monocyte receptor	CD14
43	CD163 molecule	CD163 - M130, MM130 - CD163 antigen; macrophage-associated antigen, macrophage-specific antigen	CD163
44	CD36 molecule (thrombospondin receptor)	fatty acid translocase, FAT; GP4; GP3B; GPIV; PASIV; SCARB3, PAS-4 protein; collagen type I; glycoprotein IIIb; cluster determinant 36; fatty acid translocase;	CD36

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		thrombospondin receptor; collagen type I receptor; platelet glycoprotein IV; platelet collagen receptor; scavenger receptor class B, member 3; leukocyte differentiation antigen CD36; CD36 antigen (collagen type I receptor, thrombospondin receptor)	
45	CD38 molecule	T10; CD38 antigen (p45); cyclic ADP-ribose hydrolase; ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase	CD38
46	CD3d molecule, delta (CD3-TCR complex)	CD3-DELTA, T3D, CD3D antigen, delta polypeptide; CD3d antigen, delta polypeptide (TiT3 complex); T-cell receptor T3 delta chain	CD3D
47	CD3g molecule, gamma (CD3-TCR complex)	T3G; CD3-GAMMA, T3G, CD3G gamma; CD3g antigen, gamma polypeptide (TiT3 complex); T-cell antigen receptor complex, gamma subunit of T3; T-cell receptor T3 gamma chain; T-cell surface glycoprotein CD3 gamma chain precursor	CD3G
48	CD40 molecule, TNF receptor superfamily member 5	Bp50, CDW40, TNFRSF5, p50, B cell surface antigen CD40; B cell-associated molecule; CD40 antigen; CD40 antigen (TNF receptor superfamily member 5); CD40 type II isoform; CD40L receptor; nerve growth factor receptor-related B-lymphocyte activation molecule; tumor necrosis factor receptor superfamily, member 5	CD40
49	CD40 ligand (TNF superfamily, member 5, hyper-IgM syndrome)	CD40 Ligand (CD40L) (also called soluble CD40L vs. platelet-bound CD40L), CD154, CD40L, HIGM1, IGM, IMD3, T-BAM, TNFSF5, TRAP, gp39, hCD40L, CD40 antigen ligand; CD40 ligand; T-B cell-activating molecule; TNF-related activation protein; tumor necrosis factor (ligand) superfamily member 5; tumor necrosis factor (ligand) superfamily, member 5 (hyper-IgM syndrome); tumor necrosis factor ligand superfamily member 5	CD40LG
50	CD68 molecule	GP110; SCARD1; macrophage; CD68	CD68

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		CD68 antigen; macrophage antigen CD68; scavenger receptor class D, member 1	
51	cyclin-dependent kinase 5	PSSALRE; cyclin-dependent kinase 5	CDK5
52	complement factor D (adipsin)	ADN, DF, PFD, C3 convertase activator; D component of complement (adipsin); adipsin; complement factor D; properdin factor D	CFD
53	CASP8 and FADD-like apoptosis regulator	FLIP - caspase 8 inhibitor, CASH; FLIP; MRIT; CLARP; FLAME; Casper; c-FLIP; FLAME-1; I-FLICE; USURPIN; c-FLIPL; c-FLIPR; c-FLIPS; CASP8AP1, usurpin beta; FADD-like anti-apoptotic molecule; Inhibitor of FLICE; Caspase-related inducer of apoptosis; Caspase homolog; Caspase-like apoptosis regulatory protein	CFLAR
54	Clock homolog (mouse)	clock protein; clock (mouse) homolog; circadian locomoter output cycles kaput protein	CLOCK
55	chymase 1, mast cell	chymase 1 - CYH, MCT1, chymase 1 preproprotein transcript E; chymase 1 preproprotein transcript I; chymase, heart; chymase, mast cell; mast cell protease I	CMA1
56	cannabinoid receptor 1 (brain)	cannabinoid receptor 1 - CANN6, CB-R, CB1, CB1A, CB1K5, CNR, central cannabinoid receptor	CNR1
57	cannabinoid receptor 2 (macrophage)	cannabinoid receptor 2 (macrophage), CB2, CX5	CNR2
58	cortistatin	CST-14; CST-17; CST-29; cortistatin-14; cortistatin-17; cortistatin-29; precortistatin	CORT
59	carnitine palmitoyltransferase I	CPT1; CPT1-L; L-CPT1, carnitine palmitoyltransferase I; liver	CPT1A
60	carnitine palmitoyltransferase II	CPT1, CPTASE	CPT2
61	complement component (3b/4b) receptor 1	complement receptor CR1; KN; C3BR; CD35; CD35 antigen; C3b/C4b receptor; C3-binding protein; Knops blood group antigen; complement component receptor 1; complement component (3b/4b) receptor 1, including Knops blood group system	CR1
62	complement component (3d/Epstein Barr virus) receptor 2	complement receptor CR2; C3DR; CD21	CR2

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
63	CREB binding protein (Rubinstein-Taybi syndrome)	Cbp; CBP; RTS; RSTS, CREB-binding protein	CREBBP
64	C-reactive protein, pentraxin-related	C-Reactive Protein, CRP, PTX1	CRP
65	CREB regulated transcription coactivator 2	Torc2 (transcriptional coactivator); transducer of regulated cAMP response element-binding protein (CREB) 2	CRTC2
66	colony stimulating factor 1 (macrophage)	M-CSF - colony stimulating factor 1; macrophage colony stimulating factor	CSF1
67	cathepsin B	cathepsin B - procathepsin B, APPS; CPSB, APP secretase; amyloid precursor protein secretase; cathepsin B1; cysteine protease; preprocathepsin B	CTSB
68	cathepsin L	CATL, MEP, major excreted protein	CTSL
69	cytochrome P450, family 19, subfamily A, polypeptide 1	ARO, ARO1, CPV1, CYAR, CYP19, P-450AROM, aromatase; cytochrome P450, family 19; cytochrome P450, subfamily XIX (aromatization of androgens); estrogen synthetase; flavoprotein-linked monooxygenase; microsomal monooxygenase	CYP19A1
70	Dio-2, death inducer-obliterator 1	death associated transcription factor 1; BYE1; DIO1; DATF1; DIDO2; DIDO3; DIO-1	DIDO1
71	dipeptidyl-peptidase 4 (CD26, adenosine deaminase complexing protein 2)	dipeptidylpeptidase IV - ADABP, ADCP2, CD26, DPPIV, TP103, T-cell activation antigen CD26; adenosine deaminase complexing protein 2; dipeptidylpeptidase IV; dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2)	DPP4
72	epidermal growth factor (beta-urogastrone)	URG - urogastrone	EGF
73	early growth response 1	zinc finger protein 225; transcription factor ETR103; early growth response protein 1; nerve growth factor-induced protein A	EGR1
74	epididymal sperm binding protein 1	E12, HE12, epididymal secretory protein	ELSPBP1
75	ectonucleotide pyrophosphatase/phosphodiesterase 1	ENPP1 - M6S1, NPP1, NPPS, PC-1, PCA1, PDNP1, Ly-41 antigen; alkaline phosphodiesterase 1;	ENPP1

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		membrane component, chromosome 6, surface marker 1; phosphodiesterase I/nucleotide pyrophosphatase 1; plasma-cell membrane glycoprotein 1	
76	E1A binding protein p300	p300, E1A binding protein p300, E1A-binding protein, 300kD; E1A-associated protein p300	EP300
77	coagulation factor XIII, A1 polypeptide	Coagulation Factor XIII - Coagulation factor XIII A chain; Coagulation factor XIII, A polypeptide; TGase; (coagulation factor XIII, A1 polypeptide); coagulation factor XIII A1 subunit; factor XIIIa, coagulation factor XIII A1 subunit	F13A1
78	coagulation factor VIII, procoagulant component (hemophilia A)	Factor VIII, AHF, F8 protein, F8B, F8C, FVIII, HEMA, coagulation factor VIII; coagulation factor VIII, isoform b; coagulation factor VIIIc; factor VIII F8B; procoagulant component, isoform b	F8
79	fatty acid binding protein 4, adipocyte	fatty acid binding protein 4, adipocyte - A-FABP	FABP4
80	Fas (TNF receptor superfamily, member 6)	soluble Fas/APO-1 (sFas), ALPS1A, APO-1, APT1, Apo-1 Fas, CD95, FAS1, FASTM, TNFRSF6, APO-1 cell surface antigen; CD95 antigen; Fas antigen; apoptosis antigen 1; tumor necrosis factor receptor superfamily, member 6	FAS
81	Fas ligand (TNF superfamily, member 6)	Fas ligand (sFasL), APT1LG1, CD178, CD95L, FASL, TNFSF6, CD95 ligand; apoptosis (APO-1) antigen ligand 1; fas ligand; tumor necrosis factor (ligand) superfamily, member 6	FASLG
82	free fatty acid receptor 1	G protein-coupled receptor 40 - FFA1R, GPR40, G protein-coupled receptor 40	FFAR1
83	fibrinogen alpha chain	Fibrin, Fib2, fibrinogen, A alpha polypeptide; fibrinogen, alpha chain, isoform alpha preproprotein; fibrinogen, alpha polypeptide	FGA
84	forkhead box A2	(Foxa2); HNF3B; TCF3B; hepatic nuclear factor-3-beta; hepatocyte nuclear factor 3, beta	FOXA2

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
85	forkhead box O1A	FKH1; FKHR; FOXO1; forkhead (Drosophila) homolog 1 (rhabdomyosarcoma); forkhead, Drosophila, homolog of, in rhabdomyosarcoma	FOXO1A
86	ferritin	FTH; PLIF; FTHL6; PIG15; apoferritin; placenta immunoregulatory factor; proliferation-inducing protein 15	FTH1
87	glutamate decarboxylase 2	glutamic acid decarboxylase (GAD65) antibodies; Glutamate decarboxylase-2 (pancreas); glutamate decarboxylase 2 (pancreatic islets and brain, 65kD)	GAD2
88	galanin	GALN; GLNN; galanin-related peptide	GAL
89	gastrin	gastrin - GAS	GAST
90	glucagon	glucagon-like peptide-1, GLP-1, GLP2, GRPP, glicentin-related polypeptide; glucagon-like peptide 1; glucagon-like peptide 2	GCG
91	glucokinase	hexokinase 4, maturity to onset Diabetes of the young 2; GK; GLK; HK4; HHH3; HKIV; HXKP; MODY2	GCK
92	gamma-glutamyltransferase 1	GGT; GTG; CD224; glutamyl transpeptidase; gamma-glutamyl transpeptidase	GGT1
93	growth hormone 1	growth hormone - GH, GH-N, GHN, hGH-N, pituitary growth hormone	GH1
94	ghrelin/obestatin preprohormone	ghrelin - MTLRP, ghrelin, obestatin, ghrelin; ghrelin precursor; ghrelin, growth hormone secretagogue receptor ligand; motilin-related peptide	GHRL
95	gastric inhibitory polypeptide	glucose-dependent insulinotropic peptide	GIP
96	gastric inhibitory polypeptide receptor	GIP Receptor	GIPR
97	glucagon-like peptide 1 receptor	glucagon-like peptide 1 receptor	GLP1R
98	guanine nucleotide binding protein (G protein), beta polypeptide 3	G-protein beta-3 subunit - G protein, beta-3 subunit; GTP-binding regulatory protein beta-3 chain; guanine nucleotide-binding protein G(I)/G(S)/G(T) beta subunit 3; guanine nucleotide-binding protein, beta-3 subunit; hypertension associated protein; transducin beta chain 3	GNB3

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
99	glutamic-pyruvate transaminase (alanine aminotransferase)	glutamic-pyruvate transaminase (alanine aminotransferase), AAT1, ALT1, GPT1	GPT
100	gastrin releasing peptide (bombesin)	bombesin; BN; GRP-10; proGRP; preproGRP; neuromedin C; pre-progastrin releasing peptide	GRP
101	gelsolin (amyloidosis, Finnish type)	gelsolin	GSN
102	hemoglobin	CD31; alpha-1 globin; alpha-1-globin; alpha-2 globin; alpha-2-globin; alpha one globin; hemoglobin alpha 2; hemoglobin alpha-2; hemoglobin alpha-1 chain; hemoglobin alpha 1 globin chain, NCBI Reference Sequences (RefSeq)	HBA1
103	hemoglobin, beta	HBD, beta globin	HBB
104	hypocretin (orexin) neuropeptide precursor	orexin A; OX; PPOX	HCRT
105	hepatocyte growth factor (hepapoietin A; scatter factor)	Hepatocyte growth factor (HGF) - F-TCF, HGFB, HPTA, SF, fibroblast-derived tumor cytotoxic factor; hepatocyte growth factor; hepatopoietin A; lung fibroblast-derived mitogen; scatter factor	HGF
106	hepatocyte nuclear factor 4, alpha	hepatocyte nuclear factor 4 - HNF4, HNF4a7, HNF4a8, HNF4a9, MODY, MODY1, NR2A1, NR2A21, TCF, TCF14, HNF4-alpha; hepatic nuclear factor 4 alpha; hepatocyte nuclear factor 4 alpha; transcription factor-14	HNF4A
107	haptoglobin	haptoglobin - hp2-alpha	HP
108	hydroxysteroid (11-beta) dehydrogenase 1	Corticosteroid 11-beta-dehydrogenase, isozyme 1; HDL; 11-DH; HSD11; HSD11B; HSD11L; 11-beta-HSD1	HSD11B1
109	heat shock 70kDa protein 1B	HSP70-2, heat shock 70kD protein 1B	HSPA1B
110	islet amyloid polypeptide	Amylin - DAP, IAP, Islet amyloid polypeptide (Diabetes-associated peptide; amylin)	IAPP
111	intercellular adhesion molecule 1 (CD54), human rhinovirus receptor	soluble intercellular adhesion molecule-1, BB2, CD54, P3.58, 60 bp after segment 1; cell surface glycoprotein; cell surface glycoprotein P3.58; intercellular adhesion molecule 1	ICAM1
112	interferon, gamma	IFNG: IFG; IFI	IFNG

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
113	insulin-like growth factor 1 (somatomedin C)	IGF-1: somatomedin C. insulin-like growth factor-1	IGF1
114	insulin-like growth factor 2 (somatomedin A)	IGF-II polymorphisms (somatomedin A) - C11orf43, INSIGF, pp9974, insulin-like growth factor 2; insulin-like growth factor II; insulin-like growth factor type 2; putative insulin-like growth factor II associated protein	IGF2
115	insulin-like growth factor binding protein 1	insulin-like growth factor binding protein-1 (IGFBP-1) - AFBP, IBP1, IGF-BP25, PP12, hIGFBP-1, IGF-binding protein 1; alpha-pregnancy-associated endometrial globulin; amniotic fluid binding protein; binding protein-25; binding protein-26; binding protein-28; growth hormone independent-binding protein; placental protein 12	IGFBP1
116	insulin-like growth factor binding protein 3	insulin-like growth factor binding protein 3: IGF-binding protein 3 - BP-53, IBP3, IGF-binding protein 3; acid stable subunit of the 140 K IGF complex; binding protein 29; binding protein 53; growth hormone-dependent binding protein	IGFBP3
117	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	ikk-beta; IKK2; IKKB; NFKB1KB; IKK-beta; nuclear factor NF-kappa-B inhibitor kinase beta; inhibitor of nuclear factor kappa B kinase beta subunit	IKKB
118	interleukin 10	IL-10, CSIF, IL-10, IL10A, TGIF, cytokine synthesis inhibitory factor	IL10
119	interleukin 18 (interferon-gamma-inducing factor)	IL-18 - IGIF, IL-18, IL-1g, IL1F4, IL-1 gamma; interferon-gamma-inducing factor; interleukin 18; interleukin-1 gamma; interleukin-18	IL18
120	interleukin 1, alpha	IL 1 - IL-1A, IL1, IL1-ALPHA, IL1F1, IL1A (IL1F1); hematopoietin-1; preinterleukin 1 alpha; pro-interleukin-1-alpha	IL1A
121	interleukin 1, beta	interleukin-1 beta (IL-1 beta) - IL-1, IL1-BETA, IL1F2, catabolin; preinterleukin 1 beta; pro-interleukin-1-beta	IL1B
122	interleukin 1 receptor antagonist	interleukin-1 receptor antagonist (IL-1Ra) - ICIL-1RA, IL-1ra3, IL1F3, IL1RA, IRAP, IL1RN (IL1F3);	IL1RN

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		intracellular IL-1 receptor antagonist type II; intracellular interleukin-1 receptor antagonist (icIL-1ra); type II interleukin-1 receptor antagonist	
123	interleukin 2	interleukin-2 (IL-2) - IL-2, TCGF, lymphokine, T cell growth factor; aldesleukin; interleukin-2; involved in regulation of T-cell clonal expansion	IL2
124	interleukin 6 (interferon, beta 2)	Interleukin-6 (IL-6), BSF2, HGF, HSF, IFNB2, IL-6	IL6
125	interleukin 6 receptor	interleukin-6 receptor, soluble (sIL-6R) - CD126, IL-6R-1, IL-6R-alpha, IL6RA, CD126 antigen; interleukin 6 receptor alpha subunit	IL6R
126	interleukin 8	Interleukin-8 (IL-8), 3-10C, AMCF-I, CXCL8, GCP-1, GCP1, IL-8, K60, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1, SCYB8, TSG-1, b-ENAP, CXC chemokine ligand 8; LUCT/interleukin-8; T cell chemotactic factor; beta-thromboglobulin-like protein; chemokine (C-X-C motif) ligand 8; emoctakin; granulocyte chemotactic protein 1; lymphocyte-derived neutrophil-activating factor; monocyte derived neutrophil-activating protein; monocyte-derived neutrophil chemotactic factor; neutrophil-activating factor; neutrophil-activating peptide 1; neutrophil-activating protein 1; protein 3-10C; small inducible cytokine subfamily B, member 8	IL8
127	inhibin, beta A (activin A, activin AB alpha polypeptide)	activin A - EDF, FRP, Inhibin, beta-1; inhibin beta A	INHBA
128	insulin	insulin, proinsulin	INS
129	insulin receptor	CD220, HHF5	INSR
130	insulin promoter factor-1	IPF-1, PDX-1 (pancreatic and duodenal homeobox factor-1)	IPF1
131	insulin receptor substrate 1	HIRS-1	IRS1
132	insulin receptor substrate-2	IRS2	IRS2
133	potassium inwardly-rectifying channel, subfamily J, member 11	ATP gated K+ channels, Kir 6.2; BIR; HHF2; PHHI; IKATP; KIR6.2	KCNJ11
134	potassium inwardly-rectifying channel, subfamily J, member 8	ATP gated K+ channels, Kir 6.1	KCNJ8

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
135	klotho	klotho	KL
136	kallikrein B, plasma (Fletcher factor) 1	kallikrein 3 - KLK3 - Kallikrein, plasma; kallikrein 3, plasma; kallikrein B plasma; kininogenin; plasma kallikrein B1	KLKB1
137	leptin (obesity homolog, mouse)	leptin - OB, OBS, leptin; leptin (murine obesity homolog); obesity; obesity (murine homolog, leptin)	LEP
138	leptin receptor	leptin receptor, soluble - CD295, OBR, OB receptor	LEPR
139	legumain	putative cysteine protease 1 - AEP, LGMN1, PRSC1, asparaginyl endopeptidase; cysteine protease 1; protease, cysteine, 1 (legumain)	LGMN
140	lipoprotein, Lp(a)	lipoprotein (a) [Lp(a)], AK38, APOA, LP, Apolipoprotein Lp(a); antiangiogenic AK38 protein; apolipoprotein(a)	LPA
141	lipoprotein lipase	LPL - LIPD	LPL
142	v-maf musculoaponeurotic fibrosarcoma oncogene homolog A (avian)	MafA (transcription factor) - RIPE3b1, hMafA, v-maf musculoaponeurotic fibrosarcoma oncogene homolog A	MAFA
143	mitogen-activated protein kinase 8 interacting protein 1	IB1, JIP-1, JIP1, PRKM8IP, JNK-interacting protein 1; PRKM8 interacting protein; islet-brain 1	MAPK8IP1
144	mannose-binding lectin (protein C) 2, soluble (opsonic defect)	COLEC1, HSMBPC, MBL, MBP, MBP1, Mannose-binding lectin 2, soluble (opsonic defect); mannan-binding lectin; mannan-binding protein; mannose binding protein; mannose-binding protein C; soluble mannose-binding lectin	MBL2
145	melanocortin 4 receptor	G protein coupled receptor MC4	MC4R
146	melanin-concentrating hormone receptor 1	G Protein-Coupled Receptor 24 - GPR24, MCH1R, SLC1, G protein-coupled receptor 24; G-protein coupled receptor 24 isoform 1, GPCR24	MCHR1
147	matrix metalloproteinase 12 (macrophage elastase)	Matrix Metalloproteinases (MMP), HME, MME, macrophage elastase; macrophage metalloelastase; matrix metalloproteinase 12; matrix metalloproteinase 12 (macrophage elastase)	MMP12
148	matrix metalloproteinase 14 (membrane-inserted)	Matrix Metalloproteinases (MMP), MMP-X1, MT1-MMP, MTMMP1, matrix	MMP14

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		metalloproteinase 14; matrix metalloproteinase 14 (membrane-inserted); membrane type 1 metalloprotease; membrane-type matrix metalloproteinase 1; membrane-type-1 matrix metalloproteinase	
149	matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	Matrix Metalloproteinases (MMP), MMP-2, CLG4, CLG4A, MMP-II, MONA, TBE-1, 72kD type IV collagenase; collagenase type IV-A; matrix metalloproteinase 2; matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase); matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase); matrix metalloproteinase-II; neutrophil gelatinase	MMP2
150	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	Matrix Metalloproteinases (MMP), MMP-9, CLG4B, GELB, 92kD type IV collagenase; gelatinase B; macrophage gelatinase; matrix metalloproteinase 9; matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase); matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); type V collagenase	MMP9
151	nuclear receptor co-repressor 1	NCoR; thyroid hormone- and retinoic acid receptor-associated corepressor 1	NCOR1
152	neurogenic differentiation 1	neuroD (transcription factor) - BETA2, BHF-1, NEUROD	NEUROD1
153	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1(p105)	nuclear factor, kappa B (NFkB); DNA binding factor KBF1; nuclear factor NF-kappa-B p50 subunit; nuclear factor kappa-B DNA binding subunit	NFKB1
154	nerve growth factor, beta polypeptide	B-type neurotrophic growth factor (BNGF) - beta-nerve growth factor; nerve growth factor, beta subunit	NGFB
155	non-insulin-dependent Diabetes Mellitus (common, type 2) 1	NIDDM1	NIDDM1
156	non-insulin-dependent Diabetes Mellitus (common, type 2) 2	NIDDM2	NIDDM2
157	Noninsulin-dependent Diabetes	NIDDM3	NIDDM3

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
	Mellitus 3		
158	nischarin (imidazoline receptor)	imidazoline receptor; IRAS; I-1 receptor candidate protein; imidazoline receptor candidate; imidazoline receptor antisera selected	NISCH
159	NF-kappaB repressing factor	NRF; ITBA4 gene; transcription factor NRF; NF-kappa B repressing factor; NF-kappa B-repressing factor	NKRF
160	neuronatin	Peg5	NNAT
161	nitric oxide synthase 2A	NOS, type II; nitric oxide synthase, macrophage	NOS2A
162	Niemann-Pick disease, type C2	epididymal secreting protein 1 - HE1, NP-C2, epididymal secretory protein; epididymal secretory protein E1; tissue-specific secretory protein	NPC2
163	natriuretic peptide precursor B	B-type Natriuretic Peptide (BNP), BNP, brain type natriuretic peptide, pro-BNP?, NPPB	NPPB
164	nuclear receptor subfamily 1, group D, member 1	Human Nuclear Receptor NR1D1 - EAR1, THRA1, THRAL, ear-1, hRev, Rev-erb-alpha; thyroid hormone receptor, alpha-like	NR1D1
165	nuclear respiratory factor 1	NRF1; ALPHA-PAL; alpha palindromic-binding protein	NRF1
166	oxytocin, prepro- (neurophysin I)	oxytocin - OT, OT-NPI, oxytocin-neurophysin I; oxytocin-neurophysin I, preproprotein	OXT
167	purinergic receptor P2Y, G-protein coupled, 10	G Protein Coupled Receptor P2Y10 - P2Y10, G-protein coupled purinergic receptor P2Y10; P2Y purinoceptor 10; P2Y-like receptor	P2RY10
168	purinergic receptor P2Y, G-protein coupled, 12	G Protein- Coupled Receptor P2Y12 - ADPG-R, HORK3, P2T(AC), P2Y(AC), P2Y(ADP), P2Y(cyc), P2Y12, SP1999, ADP-glucose receptor; G-protein coupled receptor SP1999; Gi-coupled ADP receptor HORK3; P2Y purinoceptor 12; platelet ADP receptor; purinergic receptor P2RY12; purinergic receptor P2Y, G-protein coupled 12; purinergic receptor P2Y12; putative G-protein coupled receptor	P2RY12
169	purinergic receptor P2Y, G-protein coupled, 2	Purinoceptor 2 Type Y (P2Y2) - HP2U, P2RU1, P2U, P2U1,	P2RY2

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		P2UR, P2Y2, P2Y2R, ATP receptor; P2U nucleotide receptor; P2U purinoceptor 1; P2Y purinoceptor 2; purinergic receptor P2Y2; purinoceptor P2Y2	
170	progesterone-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine protein)	glycodelin-A; glycodelin-F; glycodelin-S; progesterone-associated endometrial protein	PAEP
171	paired box gene 4	Pax4 (transcription factor) - paired domain gene 4	PAX4
172	pre-B-cell colony enhancing factor 1	visfatin; nicotinamide phosphoribosyltransferase	PBEF1
173	phosphoenolpyruvate carboxykinase 1 (PEPCK1)	PEPCK1; PEP carboxykinase; phosphopyruvate carboxylase; phosphoenolpyruvate carboxylase	PCK1
174	proprotein convertase subtilisin/kexin type 1	proprotein convertase 1 (PC1, PC3, PCSK1, cleaves pro-insulin)	PCSK1
175	placental growth factor, vascular endothelial growth factor-related protein	placental growth factor - PLGF, PIGF-2	PGF
176	phosphoinositide-3-kinase, catalytic, alpha polypeptide	PI3K, p110-alpha, PI3-kinase p110 subunit alpha; PtdIns-3-kinase p110; phosphatidylinositol 3-kinase, catalytic, 110-KD, alpha; phosphatidylinositol 3-kinase, catalytic, alpha polypeptide; phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, alpha isoform	PIK3CA
177	phosphoinositide-3-kinase, regulatory subunit 1 (p85 alpha)	phosphatidylinositol 3-kinase; phosphatidylinositol 3-kinase, regulatory, 1; phosphatidylinositol 3-kinase-associated p-85 alpha; phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha); phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	PIK3R1
178	phospholipase A2, group XIA	PLA2G12, group XII secreted phospholipase A2; group XIA secreted phospholipase A2	PLA2G12A
179	phospholipase A2, group IID	phospholipase A2, secretory - SPLASH, sPLA2S, secretory phospholipase A2s	PLA2G2D
180	plasminogen activator, tissue	tissue Plasminogen Activator (tPA), T-PA, TPA, alteplase; plasminogen activator, tissue type; reteplase; t-plasminogen	PLAT

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		activator; tissue plasminogen activator (t-PA)	
181	patatin-like phospholipase domain containing 2	Adipose tissue lipase, ATGL - ATGL, TTS-2.2, adipose triglyceride lipase; desnutrin; transport-secretion protein 2.2; triglyceride hydrolase	PNPLA2
182	proopiomelanocortin (adrenocorticotropin/ beta-lipotropin/ alpha-melanocyte stimulating hormone/ beta-melanocyte stimulating hormone/ beta-endorphin)	proopiomelanocortin - beta-LPH; beta-MSH; alpha-MSH; gamma-LPH; gamma-MSH; corticotropin; beta-endorphin; met-enkephalin; lipotropin beta; lipotropin gamma; melanotropin beta; N-terminal peptide; melanotropin alpha; melanotropin gamma; pro-ACTH-endorphin; adrenocorticotropin; pro-opiomelanocortin; corticotropin-lipotrophin; adrenocorticotropic hormone; alpha-melanocyte-stimulating hormone; corticotropin-like intermediary peptide	POMC
183	paraoxonase 1 ESA, PON, Paraoxonase	paraoxonase - ESA, PON, Paraoxonase	PON1
184	peroxisome proliferative activated receptor, alpha	Peroxisome proliferator-activated receptor (PPAR), NR1C1, PPAR, hPPAR, PPAR alpha	PPARA
185	peroxisome proliferative activated receptor, delta	Peroxisome proliferator-activated receptor (PPAR), FAAR, NR1C2, NUC1, NUCI, NUCII, PPAR-beta, PPARB, nuclear hormone receptor 1, PPAR Delta	PPARD
186	peroxisome proliferative activated receptor, gamma	Peroxisome proliferator-activated receptor (PPAR), HUMPPARG, NR1C3, PPARG1, PPARG2, PPAR gamma; peroxisome proliferative activated receptor gamma; peroxisome proliferator activated-receptor gamma; peroxisome proliferator-activated receptor gamma 1; ppar gamma2	PPARG
187	peroxisome proliferative activated receptor, gamma, coactivator 1	Pgc1 alpha; PPAR gamma coactivator-1; ligand effect modulator-6; PPAR gamma coactivator variant form3	PPARGC1A
188	protein phosphatase 1, regulatory (inhibitor) subunit 3A (glycogen and sarcoplasmic reticulum binding subunit, skeletal muscle)	PP1G, PPP1R3, protein phosphatase 1 glycogen-associated regulatory subunit; protein phosphatase 1 glycogen-binding regulatory	PPP1R3A

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		subunit 3; protein phosphatase type-1 glycogen targeting subunit; serine /threonine specific protein phosphatase; type-1 protein phosphatase skeletal muscle glycogen targeting subunit	
189	protein phosphatase 2A, regulatory subunit B' (PR 53)	protein phosphatase 2A - PP2A, PR53, PTPA, PP2A, subunit B'; phosphotyrosyl phosphatase activator; protein phosphatase 2A, regulatory subunit B'	PPP2R4
190	protein kinase, AMP-activated, beta 1 non-catalytic subunit	on list as adenosine monophosphate kinase? - AMPK, HAMPKb, 5'-AMP-activated protein kinase beta-1 subunit; AMP-activated protein kinase beta 1 non-catalytic subunit; AMP-activated protein kinase beta subunit; AMPK beta -1 chain; AMPK beta 1; protein kinase, AMP-activated, noncatalytic, beta-1	PRKAB1
191	protein kinase, cAMP-dependent, catalytic, alpha	PKA (kinase) - PKACA, PKA C-alpha; cAMP-dependent protein kinase catalytic subunit alpha; cAMP-dependent protein kinase catalytic subunit alpha, isoform 1; protein kinase A catalytic subunit	PRKACA
192	protein kinase C, epsilon	PKC-epsilon - PKCE, nPKC-epsilon	PRKCE
193	proteasome (prosome, macropain) 26S subunit, non-ATPase, 9 (Bridge-1)	Bridge-1; homolog of rat Bridge 1; 26S proteasome regulatory subunit p27; proteasome 26S non-ATPase regulatory subunit 9	PSMD9
194	prostaglandin E synthase	mPGES - MGST-IV, MGST1-L1, MGST1L1, PGES, FIG12, PP102, PP1294, TP53I12 Other Designations: MGST1-like 1; glutathione S-transferase 1-like 1; microsomal glutathione S-transferase 1-like 1; p53-induced apoptosis protein 12; p53-induced gene 12; tumor protein p53 inducible protein 12	PTGES
195	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Cyclo-oxygenase-2 (COX-2) - COX-2, COX2, PGG/HS, PGHS-2, PHS-2, hCox-2, cyclooxygenase 2b; prostaglandin G/H synthase and cyclooxygenase; prostaglandin-endoperoxide	PTGS2

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		synthase 2	
196	protein tyrosine phosphatase, mitochondrial 1	PTPMT1 - PLIP, PNAS-129, NB4 apoptosis/differentiation related protein; PTEN-like phosphatase	PTPMT1
197	Peptide YY	PYY1	PYY
198	retinol binding protein 4, plasma (RBP4)	RBP4; retinol-binding protein 4, plasma; retinol-binding protein 4, interstitial	RBP4
199	regenerating islet-derived 1 alpha (pancreatic stone protein, pancreatic thread protein)	regenerating gene product (Reg); protein-X; lithostathine 1 alpha; pancreatic thread protein; regenerating protein I alpha; islet cells regeneration factor; pancreatic stone protein, secretory; islet of langerhans regenerating protein	REG1A
200	resistin	resistin - ADSF, FIZZ3, RETN1, RSTN, XCP1, C/EBP-epsilon regulated myeloid-specific secreted cysteine-rich protein precursor 1; found in inflammatory zone 3	RETN
201	ribosomal protein S6 kinase, 90kDa, polypeptide 1	S6-kinase 1 - HU-1, RSK, RSK1, S6K-alpha 1, (ribosomal protein S6 kinase, 90kD, polypeptide 1); p90-RSK 1; ribosomal protein S6 kinase alpha 1; ribosomal protein S6 kinase, 90kD, 1; ribosomal protein S6 kinase, 90kD, polypeptide 1	RPS6KA1
202	Ras-related associated with Diabetes	RAD, RAD1, REM3, RAS (RAD and GEM) like GTP binding 3	RRAD
203	serum amyloid A1	Serum Amyloid A (SAA), PIG4, SAA, TP53I4, tumor protein p53 inducible protein 4	SAA1
204	selectin E (endothelial adhesion molecule 1)	E-selectin, CD62E, ELAM, ELAM1, ESEL, LECAM2, leukocyte endothelial cell adhesion molecule 2; selectin E, endothelial adhesion molecule 1	SELE
205	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6	corticosteroid-binding globulin; transcortin; corticosteroid binding globulin; serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6	SERPINA6
206	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	plasminogen activator inhibitor-1 - PAI, PAI-1, PAI1, PLANH1, plasminogen activator inhibitor, type I; plasminogen activator	SERPINE1

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		inhibitor-1; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	
207	serum/glucocorticoid regulated kinase	Serum/Glucocorticoid Regulated Kinase 1 - SGK1, serine/threonine protein kinase SGK; serum and glucocorticoid regulated kinase	SGK
208	sex hormone-binding globulin	sex hormone-binding globulin (SHBG) - ABP, Sex hormone-binding globulin (androgen binding protein)	SHBG
209	thioredoxin interacting protein	Sirt1; SIR2alpha; sir2-like 1; sirtuin type 1; sirtuin (silent mating type information regulation 2, <i>S. cerevisiae</i> , homolog) 1	SIRT1
210	solute carrier family 2, member 10	glucose transporter 10 (GLUT10); ATS	SLC2A10
211	solute carrier family 2, member 2	glucose transporter 2 (GLUT2)	SLC2A2
212	solute carrier family 2, member 4	glucose transporter 4 (GLUT4)	SLC2A4
213	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1(ERR)	ERR - ATRC1, CAT-1, ERR, HCAT1, REC1L, amino acid transporter, cationic 1; ecotropic retroviral receptor	SLC7A1
214	SNF1-like kinase 2	Sik2; salt-inducible kinase 2; salt-inducible serine/threonine kinase 2	SNF1LK2
215	suppressor of cytokine signaling 3	CIS3, Cish3, SOCS-3, SSI-3, SSI3, STAT induced STAT inhibitor 3; cytokine-induced SH2 protein 3	SOCS3
216	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	ASV, SRC1, c-SRC, p60-Src, proto-oncogene tyrosine-protein kinase SRC; protooncogene SRC, Rous sarcoma; tyrosine kinase pp60c-src; tyrosine-protein kinase SRC-1	SRC
217	sterol regulatory element binding transcription factor 1	sterol regulatory element-binding protein 1c (SREBP-1c)	SREBF1
218	solute carrier family 2, member 4	SMST, somatostatin-14, somatostatin-28	SST
219	somatostatin receptor 2	somatostatin receptor subtype 2	SSTR2
220	somatostatin receptor 5	somatostatin receptor 5 - somatostatin receptor subtype 5	SSTR5
221	transcription factor 1, hepatic; LF-B1, hepatic nuclear factor (HNF1)	HNF1 α ; albumin proximal factor; hepatic nuclear factor 1; maturity onset Diabetes of the young 3; Interferon production regulator factor (HNF1)	TCF1
222	transcription factor 2, hepatic; LF-B3; variant hepatic nuclear factor	hepatocyte nuclear factor 2 - FJHN, HNF1B, HNF1beta, HNF2, LFB3, MODY5,	TCF2

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		VHNF1, transcription factor 2	
223	transcription factor 7-like 2 (T-cell specific, HMG-box)	TCF7L2 - TCF-4, TCF4	TCF7L2
224	transforming growth factor, beta 1 (Camurati-Engelmann disease)	TGF-beta: TGF-beta 1 protein; diaphyseal dysplasia 1, progressive; transforming growth factor beta 1; transforming growth factor, beta 1; transforming growth factor-beta 1, CED, DPD1, TGFB	TGFB1
225	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	TG2, TGC, C polypeptide; TGase C; TGase-H; protein-glutamine-gamma-glutamyltransferase; tissue transglutaminase; transglutaminase 2; transglutaminase C	TGM2
226	thrombospondin 1	thrombospondin - THBS, TSP, TSP1, thrombospondin-1p180	THBS1
227	thrombospondin, type I, domain containing 1	TMTSP, UNQ3010, thrombospondin type I domain-containing 1; thrombospondin, type I, domain 1; transmembrane molecule with thrombospondin module	THSD1
228	tumor necrosis factor (TNF superfamily, member 2)	TNF-alpha (tumour necrosis factor-alpha) - DIF, TNF-alpha, TNFA, TNFSF2, APC1 protein; TNF superfamily, member 2; TNF, macrophage-derived; TNF, monocyte-derived; cachectin; tumor necrosis factor alpha	TNF
229	tumor necrosis factor (TNF superfamily, member 2)	tumor necrosis factor receptor 2 - DIF, TNF-alpha, TNFA, TNFSF2, APC1 protein; TNF superfamily, member 2; TNF, macrophage-derived; TNF, monocyte-derived; cachectin; tumor necrosis factor alpha	TNF
230	tumor necrosis factor receptor superfamily, member 1A	tumor necrosis factor receptor 1 gene R92Q polymorphism - CD120a, FPF, TBPI, TNF-R, TNF-R-I, TNF-R55, TNFAR, TNFR1, TNFR55, TNFR60, p55, p55-R, p60, tumor necrosis factor binding protein 1; tumor necrosis factor receptor 1; tumor necrosis factor receptor type 1; tumor necrosis factor-alpha receptor	TNFRSF1A
231	tumor necrosis factor receptor superfamily, member 1B	soluble necrosis factor receptor - CD120b, TBPII, TNF-R-II, TNF-R75, TNFBR, TNFR2,	TNFRSF1B

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
		TNFR80, p75, p75TNFR, p75 TNF receptor; tumor necrosis factor beta receptor; tumor necrosis factor binding protein 2; tumor necrosis factor receptor 2	
232	tryptophan hydroxylase 2	enzyme synthesizing serotonin; neuronal tryptophan hydroxylase, NTPH	TPH2
233	thyrotropin-releasing hormone	thyrotropin-releasing hormone	TRH
234	transient receptor potential cation channel, subfamily V, member 1	vanilloid receptor 1 - VR1, capsaicin receptor; transient receptor potential vanilloid 1a; transient receptor potential vanilloid 1b; vanilloid receptor subtype 1, capsaicin receptor; transient receptor potential vanilloid subfamily 1 (TRPV1)	TRPV1
235	thioredoxin interacting protein	thioredoxin binding protein 2; upregulated by 1,25-dihydroxyvitamin D-3	TXNIP
236	thioredoxin reductase 2	TR; TR3; SELZ; TRXR2; TR-BETA; selenoprotein Z; thioredoxin reductase 3; thioredoxin reductase beta	TXNRD2
237	urocortin 3 (stresscopin)	archipelin, urocortin III, SCP, SPC, UCNIII, stresscopin; urocortin 3	UCN3
238	uncoupling protein 2 (mitochondrial, proton carrier)	UCPH, uncoupling protein 2; uncoupling protein-2	UCP2
239	upstream transcription factor 1	major late transcription factor 1	USF1
240	urotensin 2	PRO1068, U-II, UCN2, UII	UTS2
241	vascular cell adhesion molecule 1	(soluble) vascular cell adhesion molecule-1, CD106, INCAM-100, CD106 antigen, VCAM-1	VCAM1
242	vascular endothelial growth factor	VEGF - VEGFA, VPF, vascular endothelial growth factor A; vascular permeability factor	VEGF
243	vimentin	vimentin	VIM
244	vasoactive intestinal peptide	vasoactive intestinal peptide - PHM27	VIP
245	vasoactive intestinal peptide receptor 1	vasoactive intestinal peptide receptor 1 - HVR1, II, PACAP-R-2, RCD1, RDC1, VIPR, VIRG, VPAC1, PACAP type II receptor; VIP receptor, type I; pituitary adenylate cyclase activating polypeptide receptor, type II	VIPR1
246	vasoactive intestinal peptide receptor 2	Vasoactive Intestinal Peptide Receptor 2 - VPAC2	VIPR2
247	von Willebrand factor	von Willebrand factor, F8VWF, VWD, coagulation factor VIII VWF	VWF

DBRISKMARKER	Official Name	Common Name	Entrez Gene Link
248	Wolfram syndrome 1 (wolframin)	DFNA14, DFNA38, DFNA6, DIDMOAD, WFRS, WFS, WOLFRAMIN	WFS1
249	X-ray repair complementing defective repair in Chinese hamster cells 6	Ku autoantigen, 70kDa; Ku autoantigen p70 subunit; thyroid-lupus autoantigen p70; CTC box binding factor 75 kDa subunit; thyroid autoantigen 70kD (Ku antigen); thyroid autoantigen 70kDa (Ku antigen); ATP-dependent DNA helicase II, 70 kDa subunit	XRCC6
250	c-peptide	c-peptide	
251	cortisol	cortisol - hydrocortisone is the synthetic form	
252	vitamin D3	vitamin D3	
253	estrogen	estrogen	
254	estradiol	estradiol	
255	digitalis-like factor	digitalis-like factor	
256	oxytomodulin	oxytomodulin	
257	dehydroepiandrosterone sulfate (DHEAS)	dehydroepiandrosterone sulfate (DHEAS)	
258	serotonin (5-hydroxytryptamine)	serotonin (5-hydroxytryptamine)	
259	anti-CD38 autoantibodies	anti-CD38 autoantibodies	
260	gad65 autoantibody	gad65 autoantibody epitopes	

One skilled in the art will note that the above listed DBRISKMARKERS come from a diverse set of physiological and biological pathways, including many which are not commonly accepted to be related to diabetes. For convenience and ease of analysis, a representative subset of approximately fifty of the disclosed DBRISKMARKERS was studied in depth in order to elucidate the more important pathways. Figure 1 is a matrix depicting DBRISKMARKER physiological and biological pathways and categories, with reference to the Kyoto University Encyclopedia of Genes and Genomes (KEGG) pathway numbers and descriptions. These database inquiries to KEGG (and subsequent literature searches to update that database) were combined with experimental work interrogating actual human serum samples from relevant populations cohorts, as detailed below in the Examples section. This was done in order to ascertain the actual levels of expression, translation and blood serum precense of this representative group of DBRISKMARKERS, so as to calibrate the DBRISKMARKER results with respect to Normal, Pre-Diabetes, and Diabetes cohorts.

In Figure 1, the highlighted horizontal rows of the matrix indicate the most significant biomarker signals and algorithm contributors to the DBRISKMARKER panels that constitute

the invention. The highlighted vertical columns indicate the KEGG pathways numbers and their descriptions which have representation by the most statistically significant DBRISKMARKERS for the classification of individuals or cohorts with Pre-Diabetes, or prediabetic conditions, from those within Normal non-diabetic populations. The total counts in the bottom row of the figure indicate mentions only due to the highlighted DBRISKMARKERS. Although there was broad general representation across most of the listed pathways by one or another DBRISKMARKERS, a differing concentration of pathways appear evident in the more statistically significant DBRISKMARKERS versus less significant DBRISKMARKERS. As will be detailed below, these groupings of different DBRISKMARKERS even within those high significance segments may presage differing signals of the stage or rate of the progression of the disease.

The strongest signal comes from inflammatory markers concentrated on the cytokine-cytokine receptor and adipocytokine signaling pathways, and significantly the Jak-STAT signalling pathway, which is concentrated in a group of markers including LEP (Leptin) and HP (Haptoglobin). Another overlapping signal also covers the MAPK and insulin signaling pathways and, interestingly, the mTOR signaling pathway, coming from DBRISKMARKERS including ILGFBP3 (Insulin-like growth factor binding protein 3) and such DBRISKMARKERS as VEGF. This group also has the overlapping involvement of ECM-receptor interaction and cell adhesion molecule (CAMs) pathways, together with complement and coagulation cascades and hematopoietic cell lineages and toll-like receptor pathways, perhaps indicating endothelial and vascular changes, and is further represented by CD14 and CSF1 (M-CSF). A final signal, involving the DBRISKMARKERS such as VEGF and SELE (E-Selectin), is concentrated on focal adhesion, ECM and other pathways related to vascular and endothelial remodeling. The kinetics of these expression relative to status of pre-diabetic risk remains to be ascertained and validated, but it is believed that such distinct patterns may allow a more biologically detailed and clinically useful signal from the DBRISKMARKERS as well as opportunities for pattern recognition within the DBRISKMARKER panel algorithms combining the biomarker signals.

The above discussion for convenience focuses on a subset of the DBRISKMARKERS; other DBRISKMARKERS and even biomarkers which are not listed in the above table but related to these physiological and biological pathways may prove to be useful given the signal and information provided from these studies. To the extent that other participants within the total list of DBRISKMARKERS are also relevant pathway

participants in Pre-Diabetes they may be functional equivalents to the biomarkers thus far disclosed. DBRISKMARKERS provided they additionally share certain defined characteristics of a good biomarker, which would include both this biological process involvement and also analytically important characteristics such as the bioavailability of said markers at a useful signal to noise ration, and in a useful sample matrix such as blood serum. Such requirements typically limit the usefulness of many members of a biological KEGG pathway, as this is unlikely to be generally the case, and frequently occurs only in pathway members that constitute secretory substances, those accessible on the plasma membranes of cells, as well as those that are released into the serum upon cell death, due to apoptosis or for other reasons such as endothelial remodeling or other cell turnover or cell necrotic processes, whether or not said is related to the disease progression of Pre-Diabetes and Diabetes. However, the remaining and future biomarkers that meet this high standard for DBRISKMARKERS are likely to be quite valuable. Our invention encompasses such functional and statistical equivalents to the aforelisted DBRISKMARKERS. Furthermore, the statistical utility of such additional DBRISKMARKERS is substantially dependent on the cross-correlation between markers and new markers will often be required to operate within a panel in order to elaborate the meaning of the underlying biology.

As is shown in Figure 2, many DBRISKMARKERS within the aforementioned representative set of fifty (50) are closely correlated and clustered in groups that thus rise or fall in their concentration with each other (or in opposite directions to each other). While this may offer multiple opportunities for new and useful DBRISKMARKERS within known and previously disclosed biological pathways, our invention hereby anticipates and claims such useful biomarkers that are functional or statistical equivalents to those listed, and such correlations and DBRISKMARKER concentrations are disclosed hereby referenced and disclosed herein, as are the potential identities of other biological pathway members in .

Figure 2 also illustrates several differing patterns of markers that are useful in the diagnosis in subjects of Pre-Diabetes and Diabetes from Normal; several specific clusters of markers are clearly observable from the aforementioned human sample data and in the figure. As earlier mentioned, individual DBRISKMARKERS provide differing pathway and physiological information, and one aspect of the invention are methods of arriving at DBRISKMARKER panels which provide sufficient information for improvements in performance over traditional risk assessment techniques. Figure 3 and 4 encompasses the listing of the KEGG pathways with three or more (in the case of Figure 3), or only one or two

(in the case of Figure 4) of the DBRISKMARKERS listed above respectively highlighted within the relevant pathways as colored icons.

It was previously noted that many of the individual markers listed, when used alone and not as a member of a multi-marker panel of DBRISKMARKERS, have little or no statistically significant differences in their concentration levels between Normal, Pre-Diabetes, and Diabetes populations, and thus cannot reliably be used alone in classifying any patient between those three states (Normal, Pre-Diabetes, or Diabetes). As also previously mentioned, a common measure of statistical significance is the p value, which indicates the probability that an observation has arisen by chance rather than correlation or causation; preferably, such p values are 0.05 or less, representing a 95% chance that the observation of interest arose by other than chance. Figure 5 details such statistical analysis for our entire representative list of fifty DBRISKMARKERS, disclosing the DBRISKMARKER concentrations and studying the variances between and within patient samples across all three subject populations, based on established one -factor ANOVA (analysis of variance) statistical techniques. It is particularly noteworthy that only one (IL-18) of the fifty studied DBRISKMARKERS has a p value under 0.05 indicating reliable utility in disease classification; in many cases the p values indicate very significant odds of random chance having had the predominant role in describing the observed concentration variances between and within the subject populations. It can be concluded that when taken individually such DBRISKMARKERS are of limited use in the diagnosis of Diabetes or Pre-Diabetes.

Despite this individual marker performance, it is the subject matter of our invention that certain specific combinations of two or more DBRISKMARKERS of the present invention can also be used as multi-marker panels comprising combinations of DBRISKMARKERS that are known to be involved in one or more physiological or biological pathways, and that such information can be combined and made clinically useful through the use of various statistical classification algorithms, including those commonly used such as logistic regression. In fact, it is the further detailed subject matter of the invention, that such algorithms, when optimized for their best clinical classification performance (as measured by line fitting statistics such as R^2) across a reasonably large group of potentially contributing DBRISKMARKERS as continuous measurements of the risk of conversion to Type 2 Diabetes, will commonly share one of of a discrete number of multimarker components motifs and combinations. These include, solely within the representative group of DBRISKMARKERS previously assayed, strong significance around

groupings around the marker LEPTIN (LEP), and in particular the various permutations and component combinations of LEPTIN, HAPTOGLOBIN (HP), INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 3 (IGFBP3), and RESISTIN (RETN) including, without limitation, the various subsets of two or more of each of the foregoing markers, and the combination of those sets with additional markers. An alternative general strategy to that of using LEPTIN and its supporting cluster of partner markers involves the use of TNFR1 and CD26, typically together as a cluster, but either alone or with other markers (including with the use of LEPTIN and any of the other individually mentioned family of markers in panels of three or more DBRISKMARKERS). A third, generally lower performing strategy than that of LEP is to use more generalized markers of inflammation, such as C-REACTIVE PROTEIN (CRP), RECEPTOR FOR ADVANCED GLYCOSYLATION ENDPRODUCTS (RAGE, now AGER), and general cytokines, adipocytokines, and complement and coagulation cascade members such as IL-18, ADIPONECTIN (ADIPOQ), ADIPISIN (aka COMPLEMENT FACTOR D or CFD), and PAI-1 (SERPINE1), among the others disclosed, in larger numbers or in combination with more specific DBRISKMARKERS.

The general concept of how two less specific or lower performing biomarkers are combined into novel and more useful combinations for the purpose of diagnosing PRE-DIABETES, is a subject and key aspect of the invention. An illustrative example, Figure 6 presents individual marker performance for LEPTIN and HAPTOGLOBIN in the top two panels showing each marker alone. In the lower left panel, the two tests are shown used together combined in a simple clinical classification rule, where the tested subject is considered a positive panel test for disease if either marker is above its individual ROC defined clinical cut-off level (those used in the previous panels). This type of “either A or B” rule is very commonplace in medicine; for example, a patient is considered dylipidemic if any one of the three total cholesterol, HDL or triglycerides measurements are above certain individual cut-offs for each test.

As the lower left panel indicates, while the test has maintained its sensitivity (a larger patient cohort might show an improvement, but LEPTIN had excellent starting performance, and only one false negative remains). However, specificity has declined dramatically, to a level worse than either marker alone, due to the higher number of false positives called (58 together versus 29 for LEPTIN alone or 45 for HAPTOGLOBIN alone). More typically, an improvement in sensitivity at the cost of a drop in specificity is expected when two markers are used in this way together.

In contrast, in the lower right panel, the same two markers are tested together when combined using a standard logistic regression algorithm. In this scenario, sensitivity remains maintained, but specificity has increased to a higher level than either marker is capable of alone. The logistic algorithm scenario is shown across all cut-offs in the following ROC curve, and has the a higher AUC than either marker alone (unfortunately, again due to the small sample size of the disease cohort, this AUC difference does not quite make statistical significance; however, it is clear from the preceding categorical analysis that the combination is a superior test, with a lower false positive rate and false negative rate)).

This example illustrated several concepts. The first is that multiple markers can often yield better performance than the individual components when proper mathematical and clinical algorithms are used; this is often evident in both sensitivity and specificity, and results in a greater AUC. The second key concept is that there is often novel unperceived information in existing markers, as was necessary in order to achieve the new algorithm combined level of specificity. The final concept is that this hidden information may hold true even for markers which are generally regarded to have suboptimal clinical performance on their own, as did the HAPTOGLOBIN in the example, at only 62.5% sensitivity and 41.5% specificity, a conclusion which would not be obvious prior to testing the two markers together with an algorithm. In fact, the suboptimal performance in terms of high false positive rates on the individual test in may very well be the indicator that some important additional information is contained within the tests results – information which would not be elucidated absent the combination with a second marker and a mathematical algorithm. The example in Figure 6 was shown using actual patient marker data and calculated diabetes risk outcomes.

Figure 7 is a further demonstration of the synergy and often unforeseeable benefits and impacts of multi-marker approach. It demonstrates that a marker which is perceived as a valuable and heavily weighted determinant when used alone, or even with one or several other markers, may significantly change in its contribution with the addition of new information in the form of additional biomarkers. The graph depicts the change in the logistic regression coefficient (or marker loading) for the first marker as a second through fourty-eighth marker is added. It indicates that the weighing of the marker has changed with the provision of more markers and more information to the re-optimized algorithm. This is again using an actual example of how the inventors developed several of the multimarker approaches disclosed here by using a search algorithm which seeks the best additional marker

from the group of fifty to add to the algorithm at each step, improving the algorithm output or clinical index measurement with each additional marker. Figure 8 presents that same improved performance at each DBRISKMARKER addition, as measured by R^2 versus the calculated reference Diabetes expected conversion rate curve, through the addition of multiple DBRISKMARKERS step by step utilizing a “forward selection” algorithm comparing all possible remaining additions to the panel at each given panel size, and then choosing the one with the highest improvement in performance.

The disadvantages of such forward selection techniques is the possibility of non-step wise solutions, where synergistic information can be gained by also testing a “step backwards” in order to reassess each existing markers remaining contribution (as noted, the beta coefficients do change) and to test for such synergies that might be cloaked by the legacy steps taken to get to the current panel size. This forward and backwards technique can be combined with a balancing factor providing input as to when the additional complexity of more markers outweighs the incremental gain to further marker additions, a searching technique commonly called a “stepwise.” searching algorithm. It is clear from the R^2 graph in Figure 8 that the return to additional markers decreases over time if each step is taken in an optimal manner – eventually, there just is no more relevant clinical information to be fed to the algorithm, and additional markers largely bring complexity and redundant information, decreasing algorithm usability and reliability.

Several techniques can be used to generate such best marker addition algorithms, building the optimal DBRISKMARKER additions at each step. Figure 9 is a depiction of a non-stepwise technique – total enumeration of ALL of the possibilities, which is increasingly possible given advances in computer power – but not typically employed for problems over a certain size and complexity. The graph depicts a three dimensional cube with a list of all the markers on each of the x, y, and axes. Marker combinations are depicted by interior cubes within the interior of the base cube; an interactive user interface allows the viewer to highlight algorithms with specific members or levels of performance. The cube pictured represented a total of over two hundred thousand individual logistic regression calculations covering all possible combinations of approximately sixty DBRISKMARKERS, each with intercept, coefficients and R^2 calculated. The “rods” suspended within the cube represent high contribution markers, such as LEPTIN, TNFR1, and CD26, which for one or more second marker partners, have a much higher than average algorithm performance, irrespective of their third partners, thus describing a straight line through the cube. Such a

technique, which is an inherent part of the invention, comprising a mechanism for selecting the best DBRISKMARKER combination, has the added benefit of allowing complete trends to be seen across the entire space of probabilities – trends which may be continued in larger panels and enable deeper insight into marker interrelationships and biology, ultimately and
5 allowing higher effectiveness in DBRISKMARKER panel construction.

Figure 10 is a histogram depicting the distribution of the R^2 performance measure across the entire set of possible three marker combinations shown previously in Figure 9. Clearly there is a division of a relatively small minority of high performance algorithms, regardless of the technique used in panel construction.

10 Other statistical tools such as factor and cross-marker correlation/covariance analysis allow more rationale approaches to panel construction. Figure 11 is a mathematical clustering and classification tree showing the Euclidean standardized distance between the DBRISKMARKERS as shown in Figure 1 and 2. While such grouping may or may not give direct insight into the biology and desired informational content targets for ideal Pre-
15 Diabetes algorithms, it is the result of a method of factor analysis intended to group collections of markers with similar information content (see Examples below for more statistical techniques commonly employed).

Figure 12 presents tables of selected DBRISKMARKERS dividing them into two key classes of Key Individual Markers and Key Combination Markers, useful in constructing
20 various categories of DBRISKMARKER Panels. As previously noted, the position of the individual DBRISKMARKER on the panel is closely related to its provision of incremental information content for the algorithm, so the order of contribution is highly dependent on the other constituent DBRISKMARKERS in the panel.

A DBRISKMARKER panel is comprised of a series of individual DBRISKMARKER
25 components. Within our study using 50 representative DBRISKMARKERS, there are three core marker approaches which can be used independently or, when larger panels are desired, in combination in order to achieve high performance in a DBRISKMARKER panel: the first, which we term the Key Individual Marker approach in Figure 11, centers first on LEPTIN as the core marker with the highest individual contribution to R^2 and continues through a rank
30 ordering of other Key Individual Marker positions such as HAPTOGLOBIN, ILGF1BP, RESISTIN, MMP2, ACE, COMPC4, and CD14. While substitution is possible with this approach, several forward search algorithms have demonstrated and confirmed the order of the core markers shown below as a high relative contribution to R^2 in representative

populations for the diagnoses of Pre-Diabetes from Normal. In general, for smaller panels, the higher performing panels are generally chosen first from the core marker listed under Key Individual Markers, with highest levels of performance when each of the eight marker positions is occupied. The earlier positions such as Marker Position 1 (LEPTIN) have the
5 typically have the potential for the highest contributions.

An second alternative approach is to begin building a DBRISKMARKER panel using what we have defined in Figure 11 as Key Combination Markers, which achieve high performance primarily through their close interaction in sets, most particularly the TNFR1 – CD26 pairing, but also pairing and supporting various members of the Key Individual
10 Markers, where they are identified as common substitution strategies that still arrive at high overall DBRISKMARKER panel performance, In fact, as a group, some substitutions of Key Individual Markers for Key Combination Markers is beneficial for panels over a certain size, particularly when Key Marker substitution has already occurred, or when panel size is beyond the core eight Key Marker positions.

Key Combination Markers do not have a set order of hierarchy or order beyond the
15 common upfront pairing of TNFR1 and CD26, and of several of the other members with Key Individual Markers, notably E-Selctin, MCSF, and VEGF. Often the Key Combination Markers are added late in a DBRISKMARKER panel construction approach, of when factor and information redundancy makes multiple statistically similar high performance solutions
20 to the optimal DBRISKMARKER panel possible.

A final, third approach is to work within the group of more generalized inflammation cytokine, adipokine and coagulation markers, including CRP, RAGE, IL-18, ADIPONECTIN, ACTIVIN_A, and ADIPISIN, This is a common fill-in strategy for
25 approaches begun with Key Individual or Key Combination Markers, as the more generalized and broad information content of some of these multi-potent markers (such as CRP and RAGE in particular) makes them amenable to being added to many different panel combinations without creating information redundancy.

Examples of specific DBRISKMARKER panel construction using the above general techniques are also disclosed herein, without limitation of the foregoing, our techniques of
30 marker panel construction, or the applicability of alternative DBRISKMARKERS or biomarkers from functionally equivalent classes which are also involved in the same constituent physiological and biological pathways.

KEY INDIVIDUAL MARKERS								
Marker Position	1	2	3	4	5	6	7	8
Core Marker	LEPTIN	HAPTOGLOBIN	ILGF3	RESISTIN	MMP2	ACE	COMPC4	CD14
Frequently Combined With	HAPTOGLOBIN ILGF3 CD26 RAGE ADIPONECTIN	LEP ILGF3 TNFR1 ADIPONECTIN CRP ADIPSIN	LEP HAPTOGLOBIN RESISTIN TNFR1 CRP	LEP HAPTOGLOBIN TNFR1 - CD26 CRP RAGE	LEP HAPTOGLOBIN RESISTIN TNFR1 - CD26 IL18 ADIPSIN PAL1 CRP	LEP HAPTOGLOBIN RESISTIN TNFR1 - CD26 PAL1 IL18 ADIPSIN CRP	LEP HAPTOGLOBIN TNFR1 - CD26 RAGE IL18 ADIPONECTIN CRP	LEP HAPTOGLOBIN TNFR1 - CD26 CRP RAGE IL18 ADIPONECTIN
Key Marker Substitution Strategies	TNFR1 - CD26 CRP ILSSOLR ADIPSIN CD40_LIGAND	TNFR1 - CD26 IL18 RAGE FETUIN_A ADIPONECTIN HGF	TNFR1 - CD26 E_SELECTIN VEGF ADIPSIN ICAM CD40_LIGAND RAGE C_PEPTIDE ADIPONECTIN	MCSF TNFR1 - CD26 ADIPSIN ACTIVIN_A INFAMMA	E_SELECTIN MCSF FIBRINOGEN	CD26 E_SELECTIN FIBRINOGEN	E_SELECTIN VEGF MCSF ACTIVIN_A C_PEPTIDE ICAM	E_SELECTIN MCSF CD26 ICAM FAS CD40_SOLUBLE

KEY COMBINATION MARKERS								
Marker Position	9	10	11	12	13	14	15	16
Substitution Marker	E_SELECTIN	MCSF	VEGF	TNFR1	CD_26	FIBRINOGEN	AGRP	TNFA
Alternative Substitution Strategies	ADIPSIN ILSSOLR MMP2	ICAM ADIPSIN ACTIVIN_A	CD40_LIGAND ADIPSIN INFAMMA	ICAM ACTIVIN_A HGF	HGF ACTIVIN_A ICAM	ACTIVIN_A CD40_LIGAND ICAM	MMP2 INFAMMA ACTIVIN_A	CD40_LIGAND ADIPSIN IL18

Marker Position	17	18	19	20
Substitution Marker	MCP_1	TGFB1	COMP_C3	AKT1
Alternative Substitution Strategies	ACTIVIN_A MMP2 IL_6	ICAM C_PEPTIDE ACTIVIN_A	ICAM ADIPSIN MMP2	ACTIVIN_A ADIPSIN ICAM

Figure 12 is a listing of 25 high performing DBRISKMARKER panels using three DBRISKMARKERS selected from Position Categories according to the method disclosed herein. Logistic regression algorithms using said panels had calculated R² values ranging from 0.300 to 0.329 when employed on samples in the described example and non-diabetic patient cohort.

Figure 13 is a listing of 25 high performing DBRISKMAKER panels using eight DBRISKMARKERS selected from Position Categories according to the method disclosed herein, using single marker substitution from a base set of markers assembled using a backwards seeking algorithm with an AIC feedback loop (see methods below). Logistic regression algorithms using said panels had calculated R² values ranging from 0.310 to 0.475 when employed on samples in the described example and non-diabetic patient cohort.

Figure 14 is a listing of 55 high performing DBRISKMAKER panels using eighteen DBRISKMARKERS selected from Position Categories according to the method disclosed herein, using single marker substitution with three options from a starting set of markers previously assembled using a backwards seeking algorithm with an AIC feedback loop (see methods below). Logistic regression algorithms using said panels had calculated R² values ranging from 0.523 to 0.6105 when employed on samples in the described example and non-diabetic patient cohort.

Levels of the DBRISKMARKERS can be determined at the protein or nucleic acid level using any method known in the art. For example, at the nucleic acid level, Northern and

Southern hybridization analysis, as well as ribonuclease protection assays using probes which specifically recognize one or more of these sequences can be used to determine gene expression. Alternatively, expression can be measured using reverse-transcription-based PCR assays (RT-PCR), e.g., using primers specific for the differentially expressed sequence of genes. Expression can also be determined at the protein level, e.g., by measuring the levels of peptides encoded by the gene products described herein, or activities thereof. Such methods are well known in the art and include, e.g., immunoassays based on antibodies to proteins encoded by the genes, aptamers or molecular imprints.. Any biological material can be used for the detection/quantification of the protein or its activity. Alternatively, a suitable method can be selected to determine the activity of proteins encoded by the marker genes according to the activity of each protein analyzed.

The DBRISKMARKER proteins, polypeptides, mutations, and polymorphisms thereof can be detected in any suitable manner, but is typically detected by contacting a sample from the subject with an antibody which binds the DBRISKMARKER protein, polypeptide, mutation, or polymorphism and then detecting the presence or absence of a reaction product. The antibody may be monoclonal, polyclonal, chimeric, or a fragment of the foregoing, as discussed in detail above, and the step of detecting the reaction product may be carried out with any suitable immunoassay. The sample from the subject is typically a biological fluid as described above, and may be the same sample of biological fluid used to conduct the method described above.

Immunoassays carried out in accordance with the present invention may be homogeneous assays or heterogeneous assays. In a homogeneous assay the immunological reaction usually involves the specific antibody (e.g., anti- DBRISKMARKER protein antibody), a labeled analyte, and the sample of interest. The signal arising from the label is modified, directly or indirectly, upon the binding of the antibody to the labeled analyte. Both the immunological reaction and detection of the extent thereof can be carried out in a homogeneous solution. Immunochemical labels which may be employed include free radicals, radioisotopes, fluorescent dyes, enzymes, bacteriophages, or coenzymes.

In a heterogeneous assay approach, the reagents are usually the sample, the antibody, and means for producing a detectable signal. Samples as described above may be used. The antibody can be immobilized on a support, such as a bead (such as protein A and protein G agarose beads), plate or slide, and contacted with the specimen suspected of containing the antigen in a liquid phase. The support is then separated from the liquid phase and either the

support phase or the liquid phase is examined for a detectable signal employing means for producing such signal. The signal is related to the presence of the analyte in the sample. Means for producing a detectable signal include the use of radioactive labels, fluorescent labels, or enzyme labels. For example, if the antigen to be detected contains a second binding site, an antibody which binds to that site can be conjugated to a detectable group and added to the liquid phase reaction solution before the separation step. The presence of the detectable group on the solid support indicates the presence of the antigen in the test sample. Examples of suitable immunoassays are oligonucleotides, immunoblotting, immunofluorescence methods, chemiluminescence methods, electrochemiluminescence or enzyme-linked immunoassays.

Those skilled in the art will be familiar with numerous specific immunoassay formats and variations thereof which may be useful for carrying out the method disclosed herein. See generally E. Maggio, *Enzyme-Immunoassay*, (1980) (CRC Press, Inc., Boca Raton, Fla.); see also U.S. Pat. No. 4,727,022 to Skold et al. titled "Methods for Modulating Ligand-Receptor Interactions and their Application," U.S. Pat. No. 4,659,678 to Forrest et al. titled "Immunoassay of Antigens," U.S. Pat. No. 4,376,110 to David et al., titled "Immunometric Assays Using Monoclonal Antibodies," U.S. Pat. No. 4,275,149 to Litman et al., titled "Macromolecular Environment Control in Specific Receptor Assays," U.S. Pat. No. 4,233,402 to Maggio et al., titled "Reagents and Method Employing Channeling," and U.S. Pat. No. 4,230,767 to Boguslaski et al., titled "Heterogenous Specific Binding Assay Employing a Coenzyme as Label."

Antibodies can be conjugated to a solid support suitable for a diagnostic assay (e.g., beads such as protein A or protein G agarose, microspheres, plates, slides or wells formed from materials such as latex or polystyrene) in accordance with known techniques, such as passive binding. Antibodies as described herein may likewise be conjugated to detectable labels or groups such as radiolabels (e.g., ^{35}S , ^{125}I , ^{131}I), enzyme labels (e.g., horseradish peroxidase, alkaline phosphatase), and fluorescent labels (e.g., fluorescein, Alexa, green fluorescent protein) in accordance with known techniques.

Antibodies can also be useful for detecting post-translational modifications of DBRISKMARKER proteins, polypeptides, mutations, and polymorphisms, such as tyrosine phosphorylation, threonine phosphorylation, serine phosphorylation, glycosylation (e.g., O-GlcNAc). Such antibodies specifically detect the phosphorylated amino acids in a protein or proteins of interest, and can be used in immunoblotting, immunofluorescence, and ELISA

assays described herein. These antibodies are well-known to those skilled in the art, and commercially available. Post-translational modifications can also be determined using metastable ions in reflector matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) (Wirth, U. et al. (2002) *Proteomics* 2(10): 1445-51).

5 For DBRISKMARKER proteins, polypeptides, mutations, and polymorphisms known to have enzymatic activity, the activities can be determined *in vitro* using enzyme assays known in the art. Such assays include, without limitation, kinase assays, phosphatase assays, reductase assays, among many others. Modulation of the kinetics of enzyme activities can be determined by measuring the rate constant K_M using known algorithms, such as the Hill plot,
10 Michaelis-Menten equation, linear regression plots such as Lineweaver-Burk analysis, and Scatchard plot.

Using sequence information provided by the database entries for the DBRISKMARKER sequences, expression of the DBRISKMARKER sequences can be detected (if present) and measured using techniques well known to one of ordinary skill in the
15 art. For example, sequences within the sequence database entries corresponding to DBRISKMARKER sequences, or within the sequences disclosed herein, can be used to construct probes for detecting DBRISKMARKER RNA sequences in, e.g., Northern blot hybridization analyses or methods which specifically, and, preferably, quantitatively amplify specific nucleic acid sequences. As another example, the sequences can be used to construct
20 primers for specifically amplifying the DBRISKMARKER sequences in, e.g., amplification-based detection methods such as reverse-transcription based polymerase chain reaction (RT-PCR). When alterations in gene expression are associated with gene amplification, deletion, polymorphisms, and mutations, sequence comparisons in test and reference populations can be made by comparing relative amounts of the examined DNA sequences in the test and
25 reference cell populations.

Expression of the genes disclosed herein can be measured at the RNA level using any method known in the art. For example, Northern hybridization analysis using probes which specifically recognize one or more of these sequences can be used to determine gene expression. Alternatively, expression can be measured using reverse-transcription-based
30 PCR assays (RT-PCR), e.g., using primers specific for the differentially expressed sequences.

Alternatively, DBRISKMARKER protein and nucleic acid metabolites can be measured. The term "metabolite" includes any chemical or biochemical product of a metabolic process, such as any compound produced by the processing, cleavage or

consumption of a biological molecule (e.g., a protein, nucleic acid, carbohydrate, or lipid). Metabolites can be detected in a variety of ways known to one of skill in the art, including the refractive index spectroscopy (RI), ultra-violet spectroscopy (UV), fluorescence analysis, radiochemical analysis, near-infrared spectroscopy (near-IR), nuclear magnetic resonance spectroscopy (NMR), light scattering analysis (LS), mass spectrometry, pyrolysis mass spectrometry, nephelometry, dispersive Raman spectroscopy, gas chromatography combined with mass spectrometry, liquid chromatography combined with mass spectrometry, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) combined with mass spectrometry, ion spray spectroscopy combined with mass spectrometry, capillary electrophoresis, NMR and IR detection. (See, WO 04/056456 and WO 04/088309, each of which are hereby incorporated by reference in their entireties) In this regard, other DBRISKMARKER analytes can be measured using the above-mentioned detection methods, or other methods known to the skilled artisan.

Kits

The invention also includes a DBRISKMARKER-detection reagent, e.g., nucleic acids that specifically identify one or more DBRISKMARKER nucleic acids by having homologous nucleic acid sequences, such as oligonucleotide sequences, complementary to a portion of the DBRISKMARKER nucleic acids or antibodies to proteins encoded by the DBRISKMARKER nucleic acids packaged together in the form of a kit. The oligonucleotides can be fragments of the DBRISKMARKER genes. For example the oligonucleotides can be 200, 150, 100, 50, 25, 10 or less nucleotides in length. The kit may contain in separate containers a nucleic acid or antibody (either already bound to a solid matrix or packaged separately with reagents for binding them to the matrix), control formulations (positive and/or negative), and/or a detectable label. Instructions (e.g., written, tape, VCR, CD-ROM, etc.) for carrying out the assay may be included in the kit. The assay may for example be in the form of a Northern hybridization or a sandwich ELISA as known in the art.

For example, DBRISKMARKER detection reagents can be immobilized on a solid matrix such as a porous strip to form at least one DBRISKMARKER detection site. The measurement or detection region of the porous strip may include a plurality of sites containing a nucleic acid. A test strip may also contain sites for negative and/or positive controls. Alternatively, control sites can be located on a separate strip from the test strip. Optionally, the different detection sites may contain different amounts of immobilized

nucleic acids, e.g., a higher amount in the first detection site and lesser amounts in subsequent sites. Upon the addition of test sample, the number of sites displaying a detectable signal provides a quantitative indication of the amount of DBRISKMARKERS present in the sample. The detection sites may be configured in any suitably detectable shape and are typically in the shape of a bar or dot spanning the width of a test strip.

Alternatively, the kit contains a nucleic acid substrate array comprising one or more nucleic acid sequences. The nucleic acids on the array specifically identify one or more nucleic acid sequences represented by DBRISKMARKERS 1-260. In various embodiments, the expression of 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 40, 50, 100, 125, 150, 175, 200, 210, 220, 230, 240 or more of the sequences represented by DBRISKMARKERS 1-260 can be identified by virtue of binding to the array. The substrate array can be on, e.g., a solid substrate, e.g., a "chip" as described in U.S. Patent No. 5,744,305. Alternatively, the substrate array can be a solution array, e.g., xMAP (Luminex, Austin, TX), Cyvera (Illumina, San Diego, CA), CellCard (Vitra Bioscience, Mountain View, CA) and Quantum Dots' Mosaic (Invitrogen, Carlsbad, CA).

The skilled artisan can routinely make antibodies, nucleic acid probes, e.g., oligonucleotides, aptamers, siRNAs, antisense oligonucleotides, against any of the DBRISKMARKERS in Table 1.

20

EXAMPLES

Example 1

The protein biomarker panels were determined by analyzing 64 proteins in human serum samples derived from a group of 96 normal, pre-diabetic, and diabetic persons.

Source Reagents: A large and diverse array of vendors that were used to source immunoreagents as a starting point for assay development, such as, but not limited to, Abazyme, Abnova, Affinity Biologicals, AntibodyShop, Biogenesis, Biosense Laboratories, Calbiochem, Cell Sciences, Chemicon International, Chemokine, Clontech, Cytolab, DAKO, Diagnostic BioSystems, eBioscience, Endocrine Technologies, Enzo Biochem, Eurogentec, Fusion Antibodies, Genesis Biotech, GloboZymes, Haematologic Technologies, Immunodetect, Immunodiagnostik, Immunometrics, Immunostar, Immunovision, Biogenex, Invitrogen, Jackson ImmunoResearch Laboratory, KMI Diagnostics, Koma Biotech, LabFrontier Life Science Institute, Lee Laboratories, Lifescreen, Maine Biotechnology Services, Mediclone, MicroPharm Ltd., ModiQuest, Molecular Innovations, Molecular

Probes, Neoclone, Neuromics, New England Biolabs, Novocastra, Novus Biologicals, Oncogene Research Products, Orbigen, Oxford Biotechnology, Panvera, PerkinElmer Life Sciences, Pharmingen, Phoenix Pharmaceuticals, Pierce Chemical Company, Polymun Scientific, Polysciences, Inc., Promega Corporation, Proteogenix, Protos Immunoresearch, 5 QED Biosciences, Inc., R&D Systems, Repligen, Research Diagnostics, Roboscreen, Santa Cruz Biotechnology, Seikagaku America, Serological Corporation, Serotec, SigmaAldrich, StemCell Technologies, Synaptic Systems GmbH, Technopharm, Terra Nova Biotechnology, TiterMax, Trillium Diagnostics, Upstate Biotechnology, US Biological, Vector Laboratories, Wako Pure Chemical Industries, and Zeptomatrix. A search for capture antibodies, detection 10 antibodies, and analytes was performed to configure a working sandwich immunoassay. The reagents were ordered and received into inventory.

Immunoassays were developed in three steps: Prototyping, Validation, and Kit Release. Prototyping was conducted using standard ELISA formats when the two antibodies used in the assay were from different host species. Using standard conditions, anti-host 15 secondary antibodies conjugated with horse radish peroxidase were evaluated in a standard curve. If a good standard curve was detected, the assay proceeded to the next step. Assays that had the same host antibodies went directly to the next step (e.g., mouse monoclonal sandwich assays).

Validation of a working assay was performed using the Zeptosense detection platform 20 from Singulex, Inc. (St. Louis, MO). The detection antibody was first conjugated to the fluorescent dye Alexa 647. The conjugations used standard NHS ester chemistry, for example, according to the manufacturer. Once the antibody was labeled, the assay was tested in a sandwich assay format using standard conditions. Each assay well was solubilized in a denaturing buffer, and the material was read on the Zeptosense platform.

25 FIG. 1 shows a typical result for a working standard curve. Once a working standard curve was demonstrated, the assay was typically applied to 24 serum samples to determine the normal distribution of the target analyte across clinical samples. The amount of serum required to measure the biomarker within the linear dynamic range of the assay was determined, and the assay proceeded to kit release. For the initial 39 validated assays, 0.004 30 microliters were used per well on average.

Each component of the kit including manufacturer, catalog numbers, lot numbers, stock and working concentrations, standard curve, and serum requirements were compiled

into a standard operating procedures for each biomarker assay. This kit was then released for use to test clinical samples.

Samples were collected from several sources. In all cases, sufficient clinical annotations were available to calculate risk factors using the model developed by Stern et al. (2002). Typically, a minimum of the following clinical annotations were available from each study: Date of collection, age, sex, height, weight, waist, BMI, ethnicity, family history, diastolic and systolic blood pressure, fasting glucose levels, cholesterol. The samples were collected using standard protocols, and were stored at -80C from the time of collection.

Clinical samples arrived frozen on dry ice, and each sample was stored at -80C. Each sample typically had many clinical annotations associated with it. The clinical annotations associated with each sample set were brought into a standardized nomenclature prior to import. All of the clinical annotations associated with each sample were then imported into a relational database.

The frozen aliquots of clinical samples were thawed and aliquotted for use in the laboratory. Each clinical sample was thawed on ice, and aliquots were dispensed into barcoded tubes (daughter tubes). Each daughter tube was stored at -80C until it was needed for the immunoassays. The daughter tubes were then arrayed into sample plates. Each barcoded daughter tube to be assayed was arrayed into barcoded 96 or 384 well plates (sample plates). The daughter tube to sample plate well mapping was tracked by the relational database.

Each sample plate was prepared for immunoassay analysis. The 384 well barcoded assay plates were dedicated to one biomarker per plate. Typically, 4-12 assay plates were derived from each sample plate depending upon the amount of serum required for each assay. The sample plate went through a series of dilutions to ensure that the clinical samples were at an appropriate dilution for each immunoassay. The clinical samples were then deposited into the assay plate wells in triplicate for each marker. Again, tracking of each sample plate well to assay plate well was tracked in the relational database. The assays were then be processed using standard immunoassay procedures, and the assay plate was read on the Zeptosense instrument. Each run contained data for a single biomarker across about 384 clinical samples. The resulting data files were then imported back into the relational database, where standard curves were calculated and the concentration values for each biomarker for each sample were calculated. FIG. 2 shows an example of single molecule detection data across 92 samples for 25 biomarkers.

The biomarker values assigned to each clinical sample were reassociated with the original clinical annotations. The quantitative biomarker data were correlated to the clinical annotations associated with each sample. Diabetes risk over 7.5 years was calculated using the model developed by Stern et al. (2002). The clinical model is of the form of a logistic equation

$$p = 1/(1 + e^{-x}),$$

where

$$x = -13.415 + 0.028(\text{age}) + 0.661(\text{sex}) + 0.412(\text{MA}) + 0.079(\text{FG}) + 0.018(\text{SBP}) - 0.039(\text{HDL}) + 0.070(\text{BMI}) + 0.481(\text{family history}).$$

In this equation, p = the probability of developing diabetes over the 7.5 year follow-up period; age is in years; sex = 1 if female, 0 if male; MA = 1 if Mexican American, 0 if non-Hispanic white; FG = fasting glucose in mg/dL; SBP = systolic blood pressure in mm Hg; HDL = high-density lipoprotein cholesterol level in mg/dL; BMI = body mass index in kg/m²; and family history = 1 if at least one parent or sibling has diabetes or 0 if not (Stern et al. 2002).

In order to estimate risk for the cohort patient samples, the following modifications were made to these parameters. First, African Americans and Hispanics were included in the high risk group with Mexican Americans and patients with a diagnosis of hypertension were assumed to have a $SBP=150$ and patients without an $SBP=125$. The rest of the data were available in the clinical record. Raw concentration data for each marker were \log_{10} transformed and used as the inputs for several linear regression models on the logit transform of risk (x in the above equation).

Linear regression of x on the \log_{10} biomarker concentration on each univariate, bivariate, and tri-variate basis by marker sets was performed via a complete search of all combinations. The quality of models was judged on the basis of the coefficient of determination, R^2 .

Models larger than three markers were developed using forward, backward, and stepwise selection based on Akaike Information Criterion (AIC). Alternatives to these marker sets were identified by eliminating each marker and searching the remaining set for the best replacement, where 'best' is the marker with the highest R^2 value.

A full model was also created by adding a single variable to the null model one by one until all markers were used. Each marker was selected based on the coefficient of determination of the complete marker set being used up to that point. Selected fits of these models were used to calculate sensitivity and specificity of any individual model.

5 The uniqueness/similarity of biomarker concentrations was investigated using principle components analysis (PCA), Hierarchical clustering, and simple correlation. The results of the PCA were evaluated graphically using scree plots, bi-plots, and sample projections to quantify how much independent variation existed among these markers. Hierarchical clustering, using the standardized (mean=0, sd=1) concentrations, was based on
 10 euclidian distance as a distance metric and Ward’s method as the means of agglomeration. Clusters were used to identify markers behaving similarly.

The following is an illustrative example of a method that was used in developing protein biomarker tests in accordance with the invention.

Assay Analyte: C-Reactive Protein

15 Table 2: Components

Component	Vendor	Catalog Number	Lot Number
C-Reactive Protein	US Biologicals	C7907-26A	L5042910
Capture Antibody	US Biologicals	C7907-09	L4030562
Detection Antibody	US Biologicals	C7907-10	L2121306M

Each individual well on a NUNC Maxisorp 384-well plate was coated with 20 µl of capture antibody diluted in coating buffer (0.05 M carbonate, pH 9.6; diluted to 1 µg/mL and prepared immediately before use) and incubated overnight at room temperature. The plate
 20 was then washed three times in 100 µl of Wash buffer A (PBS with 0.1% Tween 20), and blocked in 30 µl PBS buffer containing 1% BSA, 5% sucrose, 0.05% NaN₃ for analyte capture for at least two hours at room temperature. After incubation, blocking buffer was removed and the blocked plates air-dried for at least 5 hours at room temperature and prepared for storage at 4°C or for Zeptosense assay.

25 Samples were diluted 1:400 in Assay Buffer (BS buffer containing 1% BSA, 0.1% Triton X-100. To the blocked and dried plate, 20 µl/well of standards and diluted unknown samples were added and allowed to incubate overnight at room temperature. After incubation, the plate was washed five times in wash buffer B (BS buffer with 0.02% Triton X-100 and 0.0001% BSA), detection antibody A647 was diluted to 50 ng/ml in assay buffer

and was added to the wells in an amount of 20 µl/well. The detection antibody was allowed to bind for 2 hours at room temperature, after which the plate was washed five times in 100 µl of wash buffer B. A standard curve was generated using a control diluted to 100 ng/ml in a calibrator. Serial dilutions from 100 ng/ml to 0.01 pg/ml in calibrator diluent (assay buffer + additional 5% BSA) were prepared. FIG 1 is a representative standard curve using IL-1 receptor antagonist. Elution buffer (4 M urea, 1X BS with 0.02% Triton X-100, and 0.001% BSA) was added in an amount of 20 µl/well and incubated for half an hour at room temperature, after which the samples were analyzed on a Zeptosense instrument.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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CLAIMS

What is claimed is:

1. A method with a predetermined level of predictability for assessing a risk of development of Diabetes Mellitus or a pre-diabetic condition in a subject comprising:
 - a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and
 - b. measuring a clinically significant alteration in the level of the two or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.
2. The method of claim 1, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
3. The method of claim 1, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
4. The method of claim 1, wherein the level of DBRISKMARKERS is measured electrophoretically or immunochemically.
5. The method of claim 4, wherein the immunochemical detection is by radioimmunoassay, immunofluorescence assay or by an enzyme-linked immunosorbent assay.
6. The method of claim 1, wherein the subject has not been previously diagnosed or identified as having the Diabetes Mellitus or the pre-diabetic condition.
7. The method of claim 1, wherein the subject is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.
8. The method of claim 1, wherein the sample is serum, blood plasma, blood cells, endothelial cells, tissue biopsies, ascites fluid, bone marrow, interstitial fluid, sputum, or urine.
9. The method of claim 1, wherein the level of expression of five or more DBRISKMARKERS is measured.
10. The method of claim 1, wherein the level of expression of ten or more DBRISKMARKERS is measured.

11. The method of claim 1, wherein the level of expression of twenty-five or more DBRISKMARKERS is measured.
12. The method of claim 1, wherein the level of expression of fifty or more DBRISKMARKERS is measured.
13. A method with a predetermined level of predictability for diagnosing or identifying a subject having Diabetes Mellitus or a pre-diabetic condition comprising:
 - a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and
 - b. comparing the level of the effective amount of the two or more DBRISKMARKERS to a reference value.
14. The method of claim 13, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
15. The method of claim 13, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
16. The method of claim 13, wherein the reference value is an index value.
17. The method of claim 13, wherein the reference value is derived from one or more risk prediction algorithms or computed indices for the Diabetes or pre-diabetic condition.
18. The method of claim 13, wherein the sample is serum, blood plasma, blood cells, endothelial cells, tissue biopsies, ascites fluid, bone marrow, interstitial fluid, sputum, or urine.
19. A method with a predetermined level of predictability for assessing a risk of impaired glucose tolerance in a subject comprising:
 - a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and
 - b. measuring a clinically significant alteration in the level of the two or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of impaired glucose tolerance in the subject.
20. The method of claim 19, wherein the level of DBRISKMARKERS is measured electrophoretically or immunochemically.

21. The method of claim 19, wherein the level of DBRISKMARKERS is measured by specific oligonucleotide hybridization.
22. The method of claim 20, wherein the immunochemical detection is by radio-immunoassay, immunofluorescence assay or by an enzyme-linked immunosorbent assay.
23. The method of claim 19, wherein the subject has not been previously diagnosed as having impaired glucose tolerance.
24. The method of claim 19, wherein the subject is asymptomatic for the impaired glucose tolerance.
25. The method of claim 19, wherein the sample is serum, blood plasma, blood cells, endothelial cells, tissue biopsies, ascites fluid, bone marrow, interstitial fluid, sputum, or urine.
26. The method of claim 19, wherein the level of expression of five or more DBRISKMARKERS is measured.
27. The method of claim 19, wherein the level of expression of ten or more DBRISKMARKERS is measured.
28. The method of claim 19, wherein the level of expression of twenty-five or more DBRISKMARKERS is measured.
29. The method of claim 19, wherein the level of expression of fifty or more DBRISKMARKERS is measured.
30. A method with a predetermined level of predictability for diagnosing or identifying a subject having impaired glucose tolerance comprising:
 - a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and
 - b. comparing the level of the effective amount of the two or more DBRISKMARKERS to a reference value.
31. The method of claim 30, wherein the sample is serum, blood plasma, blood cells, endothelial cells, tissue biopsies, ascites fluid, bone marrow, interstitial fluid, sputum, or urine.
32. The method of claim 30, wherein the reference value is an index value.
33. The method of claim 30, wherein the reference value is derived from one or more risk prediction algorithms or computed indices for impaired glucose tolerance.

34. A method with a predetermined level of predictability for assessing the progression of Diabetes Mellitus or a pre-diabetic condition in a subject, comprising:
 - a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time;
 - b. detecting the level of an effective amount of two or more DBRISKMARKERS in a second sample from the subject at a second period of time;
 - c. comparing the level of the effective amount of the two or more DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value.
35. The method of claim 34, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
36. The method of claim 34, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
37. The method of claim 34, wherein the subject has previously been diagnosed or identified as suffering from the Diabetes Mellitus or the pre-diabetic condition.
38. The method of claim 34, wherein the subject has previously been treated for the Diabetes Mellitus or the pre-diabetic condition.
39. The method of claim 34, wherein the subject has not been previously diagnosed or identified as suffering from the Diabetes Mellitus or the pre-diabetic condition.
40. The method of claim 34, wherein the subject is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.
41. The method of claim 34, wherein the first sample is taken from the subject prior to being treated for the Diabetes Mellitus or the pre-diabetic condition.
42. The method of claim 34, wherein the second sample is taken from the subject after being treated for the Diabetes Mellitus or the pre-diabetic condition.
43. The method of claim 34, wherein the reference value is derived from one or more subjects who have suffered from Diabetes Mellitus or a pre-diabetic condition.
44. A method with a predetermined level of predictability for assessing the progression of impaired glucose tolerance associated with Diabetes Mellitus or a pre-diabetic condition in a subject comprising:

- a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time;
 - b. detecting the level of an effective amount of two or more DBRISKMARKERS in a second sample from the subject at a second period of time;
 - c. comparing the level of the effective amount of the two or more DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value.
45. The method of claim 44, wherein the subject is suffering from the Diabetes Mellitus or the pre-diabetic condition.
 46. The method of claim 44, wherein the subject has previously been treated for the Diabetes Mellitus or the pre-diabetic condition.
 47. The method of claim 44, wherein the subject has not been previously diagnosed or identified as having impaired glucose tolerance or suffering from the Diabetes Mellitus or the pre-diabetic condition.
 48. The method of claim 44, wherein the subject is asymptomatic for the impaired glucose tolerance, or is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.
 49. The method of claim 44, wherein the first sample is taken from the subject prior to being treated for the impaired glucose tolerance, Diabetes Mellitus, or the pre-diabetic condition.
 50. The method of claim 44, wherein the second sample is taken from the subject after being treated for the impaired glucose tolerance, Diabetes Mellitus, or the pre-diabetic condition.
 51. The method of claim 44, wherein the reference value is derived from one or more subjects who have suffered from impaired glucose tolerance, Diabetes Mellitus, or a pre-diabetic condition.
 52. A method with a predetermined level of predictability for monitoring the effectiveness of treatment for Diabetes Mellitus or a pre-diabetic condition comprising:
 - a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time;

- b. detecting the level of an effective amount of two or more DBRISKMARKERS in a second sample from the subject at a second period of time;
 - c. comparing the level of the effective amount of the two or more DBRISKMARKERS detected in step (a) to the amount detected in step (b), or to a reference value, wherein the effectiveness of treatment is monitored by a change in the level of the effective amount of two or more DBRISKMARKERS from the subject.
53. The method of claim 52, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
54. The method of claim 52, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
55. The method of claim 52, wherein the subject is suffering from the Diabetes Mellitus or the pre-diabetic condition.
56. The method of claim 52, wherein the subject has previously been treated for the Diabetes Mellitus or the pre-diabetic condition.
57. The method of claim 52, wherein the first sample is taken from the subject prior to being treated for the Diabetes Mellitus or the pre-diabetic condition.
58. The method of claim 52, wherein the second sample is taken from the subject after being treated for the Diabetes Mellitus or the pre-diabetic condition.
59. The method of claim 52, wherein the treatment for the Diabetes Mellitus or the pre-diabetic condition comprises exercise regimens, dietary supplements, therapeutic agents, surgical intervention, and prophylactic agents.
60. The method of claim 52, wherein the reference value is derived from one or more subjects who show an improvement in Diabetes risk factors as a result of one or more treatments for the Diabetes Mellitus or the pre-diabetic condition.
61. The method of claim 52, wherein the effectiveness of treatment is additionally monitored by detecting changes in body mass index (BMI), insulin levels, blood glucose levels, HDL levels, systolic and/or diastolic blood pressure, or combinations thereof.
62. The method of claim 61, wherein changes in blood glucose levels are detected by an oral glucose tolerance test.

63. A method with a predetermined level of predictability for selecting a treatment regimen for a subject diagnosed with or at risk for Diabetes Mellitus or a pre-diabetic condition comprising:
 - a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time;
 - b. optionally detecting the level of an effective amount of two or more DBRISKMARKERS in a second sample from the subject at a second period of time;
 - c. comparing the level of the effective amount of the two or more DBRISKMARKERS detected in step (a) to a reference value, or optionally, to the amount detected in step (b).
64. The method of claim 63, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
65. The method of claim 63, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
66. The method of claim 63, wherein the subject is suffering from the Diabetes Mellitus or the pre-diabetic condition.
67. The method of claim 63, wherein the subject has previously been treated for the Diabetes Mellitus or the pre-diabetic condition.
68. The method of claim 63, wherein the subject has not been previously diagnosed or identified as suffering from Diabetes Mellitus or the pre-diabetic condition.
69. The method of claim 63, wherein the first sample is taken from the subject prior to being treated for the Diabetes Mellitus or the pre-diabetic condition.
70. The method of claim 63, wherein the second sample is taken from the subject after being treated for the Diabetes Mellitus or the pre-diabetic condition.
71. The method of claim 63, wherein the treatment for the Diabetes Mellitus or the pre-diabetic condition comprises exercise regimens, dietary supplements, therapeutic agents, surgical intervention, and prophylactic agents.
72. The method of claim 63, wherein the reference value is derived from one or more subjects who show an improvement in Diabetes risk factors as a result of one or more treatments for the Diabetes Mellitus or the pre-diabetic condition.

73. The method of claim 72, wherein the improvement is monitored by detecting a reduction in body mass index (BMI), a reduction in blood glucose levels, an increase in insulin levels, an increase in HDL levels, a reduction in systolic and/or diastolic blood pressure, or combinations thereof.
74. The method of claim 73, wherein the reduction in blood glucose levels is measured by oral glucose tolerance test.
75. A Diabetes Mellitus reference expression profile, comprising a pattern of marker levels of an effective amount of two or more markers selected from the group consisting of DBRISKMARKERS 1-260, taken from one or more subjects who do not have the Diabetes Mellitus.
76. The profile of claim 75, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
77. An impaired glucose tolerance reference expression profile, comprising a pattern of marker levels of an effective amount of two or more markers selected from the group consisting of DBRISKMARKERS 1-260, taken from one or more subjects who do not have impaired glucose tolerance.
78. A Diabetes Mellitus subject expression profile, comprising a pattern of marker levels of an effective amount of two or more markers selected from the group consisting of DBRISKMARKERS 1-260 taken from one or more subjects who have the Diabetes Mellitus, are at risk for developing the Diabetes Mellitus, or are being treated for the Diabetes Mellitus.
79. The profile of claim 78, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
80. An impaired glucose tolerance subject expression profile, comprising a pattern of marker levels of an effective amount of two or more markers selected from the group consisting of DBRISKMARKERS 1-260 taken from one or more subjects who have impaired glucose tolerance, are at risk for developing impaired glucose tolerance, or are being treated for impaired glucose tolerance.
81. A kit comprising a plurality of DBRISKMARKER detection reagents that detect the corresponding DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260, sufficient to generate the profiles of claims 75, 77, 78, or 80.

82. The kit of claim 81, wherein the detection reagent comprises one or more antibodies or fragments thereof.
83. The kit of claim 81, wherein the detection reagent comprises one or more oligonucleotides.
84. The kit of claim 81, wherein the detection reagent comprises one or more aptamers.
85. A machine readable media containing one or more Diabetes Mellitus reference expression profiles according to claim 75, or one or more Diabetes Mellitus subject expression profiles according to claim 78, and optionally, additional test results and subject information.
86. A machine readable media containing one or more impaired glucose tolerance reference expression profiles according to claim 77, or one or more impaired glucose tolerance subject expression profiles according to claim 80, and optionally, additional test results and subject information.
87. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of a physiological or biochemical pathway associated with Diabetes Mellitus or a pre-diabetic condition.
88. The panel of claim 87, wherein the physiological or biochemical pathway comprises autoimmune regulation, inflammation and endothelial function, focal adhesions, leukocyte transendothelial migration, natural killer cell mediated cytotoxicity, regulation of the actin cytoskeleton, adherens/tight/gap junctions, and extracellular matrix-receptor interaction, adipocyte development and maintenance, hematopoietic cell lineage, complement and coagulation cascades, intra- and extracellular cell signaling pathways.
89. The panel of claim 87, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
90. The panel of claim 87, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
91. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of a site associated with Diabetes Mellitus or a pre-diabetic condition.
92. The panel of claim 90, wherein the site comprises beta cells, endothelial cells, skeletal and smooth muscle, or peripheral, cardiovascular, or cerebrovascular arteries.

93. The panel of claim 90, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
94. The panel of claim 90, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
95. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of the progression of Diabetes Mellitus or a pre-diabetic condition.
96. The panel of claim 95, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
97. The panel of claim 95, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
98. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are indicative of the speed of progression of Diabetes Mellitus or a pre-diabetic condition.
99. The panel of claim 98, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
100. The panel of claim 98, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
101. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are specific to one or more types of Diabetes Mellitus.
102. The panel of claim 101, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
103. A DBRISKMARKER panel comprising one or more DBRISKMARKERS that are specific to a pre-diabetic condition.
104. The panel of claim 103, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
105. A DBRISKMARKER panel comprising two or more DBRISKMARKERS selected from the group consisting of: Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (ILGF3), Resistin (RETN), Matrix Metalloproteinase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (C4A), CD14 molecule (CD14), selectin E (SELE), colony stimulating factor 1 (macrophage; CSF1), and vascular endothelial growth factor (VEGF), c-reactive protein (pentraxin-related;CRP), Tumor Necrosis Factor

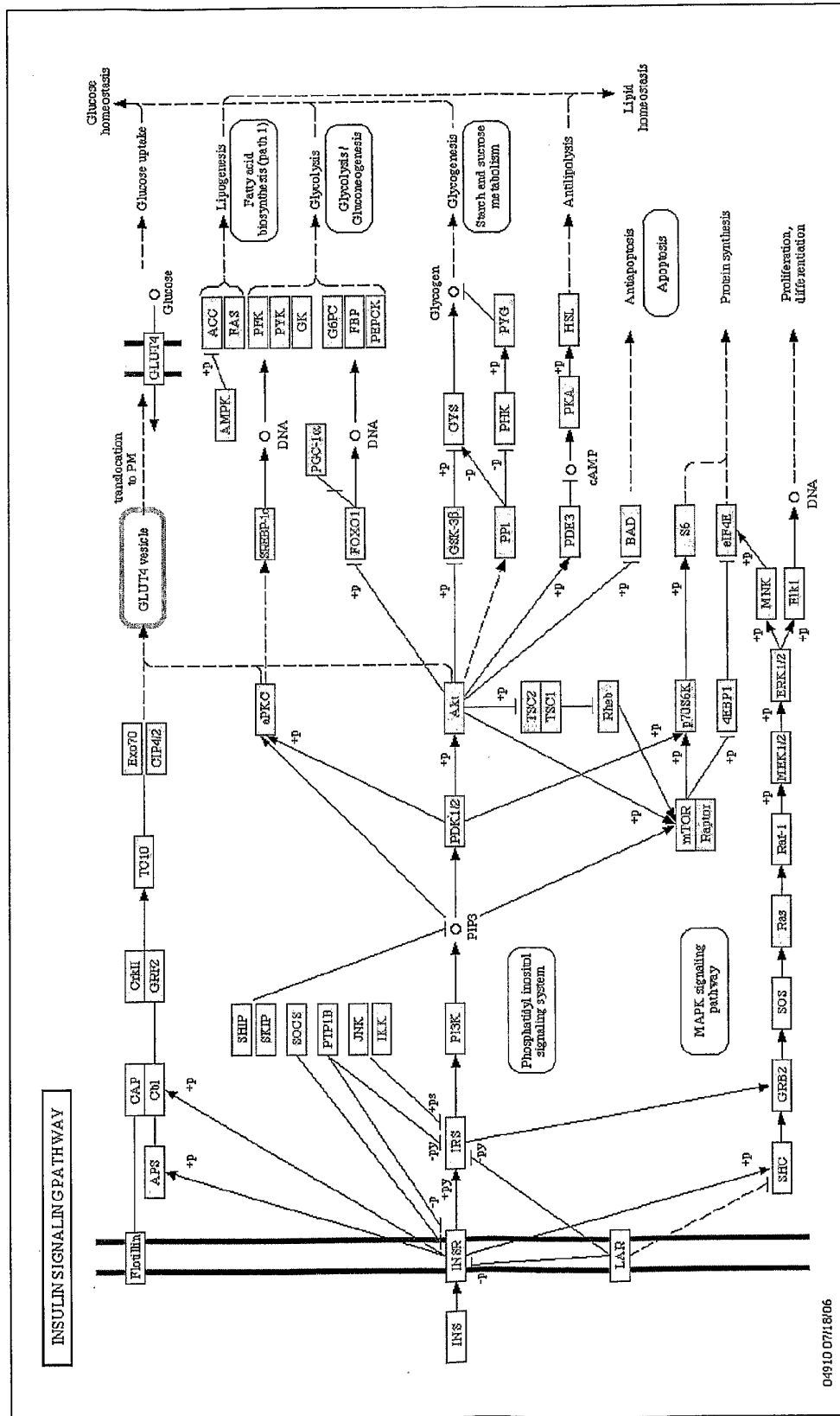
- Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), and CD26 (dipeptidyl peptidase 4; DPP4).
106. A method for treating one or more subjects at risk for developing Diabetes Mellitus or a pre-diabetic condition, comprising:
 - a. detecting the presence of increased levels of at least two different DBRISKMARKERS present in a sample from the one or more subjects; and
 - b. treating the one or more subjects with one or more Diabetes-modulating drugs until altered levels of the at least two different DBRISKMARKERS return to a baseline value measured in one or more subjects at low risk for developing the Diabetes Mellitus or the pre-diabetic condition, or a baseline value measured in one or more subjects who show improvements in Diabetes risk markers as a result of treatment with one or more Diabetes-modulating drugs.
 107. The method of claim 105, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
 108. The method of claim 105, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
 109. The method of claim 105, wherein the Diabetes-modulating drugs comprise sulfonylureas; biguanides; insulin, insulin analogs; peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists; dual-acting PPAR agonists; insulin secretagogues; analogs of glucagon-like peptide-1 (GLP-1); inhibitors of dipeptidyl peptidase IV; pancreatic lipase inhibitors; α -glucosidase inhibitors; and combinations thereof.
 110. The method of claim 105, wherein the improvements in Diabetes risk markers as a result of treatment with one or more Diabetes-modulating drugs comprise a reduction in body mass index (BMI), a reduction in blood glucose levels, an increase in insulin levels, an increase in HDL levels, a reduction in systolic and/or diastolic blood pressure, or combinations thereof.
 111. A method of evaluating changes in the risk of impaired glucose tolerance in a subject diagnosed with or at risk for developing a pre-diabetic condition, comprising:
 - a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a first sample from the subject at a first period of time;

- b. optionally detecting the level of an effective amount of two or more DBRISKMARKERS in a second sample from the subject at a second period of time;
 - c. comparing the level of the effective amount of the two or more DBRISKMARKERS detected in step (a) to a reference value, or optionally, the amount in step (b).
112. The method of claim 110, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
113. The method of claim 110, wherein the subject is suffering from the pre-diabetic condition.
114. The method of claim 110, wherein the subject has previously been treated for the pre-diabetic condition.
115. The method of claim 110, wherein the subject has not been previously diagnosed or identified as suffering from the pre-diabetic condition.
116. The method of claim 110, wherein the subject is asymptomatic for the pre-diabetic condition.
117. The method of claim 110, wherein the first sample is taken from the subject prior to being treated for the pre-diabetic condition.
118. The method of claim 110, wherein the second sample is taken from the subject after being treated for the pre-diabetic condition.
119. The method of claim 110, wherein the treatment for the pre-diabetic condition comprises exercise regimens, dietary supplements, therapeutic agents, surgical intervention, and prophylactic agents.
120. The method of claim 110, wherein the reference value is derived from one or more subjects who have suffered from impaired glucose tolerance.
121. A method of differentially diagnosing disease states associated with Diabetes Mellitus or a pre-diabetic condition in a subject comprising:
- a. detecting the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject; and
 - b. comparing the level of the effective amount of the two or more DBORISKMARKERS detected in step (a) to the Diabetes Mellitus disease

- subject expression profile of claim 78, to the impaired glucose tolerance subject expression profile of claim 80, or to a reference value.
122. The method of claim 120, wherein the Diabetes Mellitus comprises Type 1 Diabetes, Type 2 Diabetes, or gestational Diabetes.
 123. The method of claim 120, wherein the pre-diabetic condition comprises IFG, IGT, Metabolic Syndrome, or Syndrome X.
 124. The method of claim 120, wherein the subject has not previously been diagnosed or identified as suffering from the Diabetes Mellitus or the pre-diabetic condition.
 125. The method of claim 120, wherein the subject has not been previously treated for the Diabetes Mellitus or the pre-diabetic condition.
 126. The method of claim 120, wherein the subject has been previously treated for the Diabetes Mellitus or the pre-diabetic condition.
 127. The method of claim 120, wherein the subject is asymptomatic for the Diabetes Mellitus or the pre-diabetic condition.
 128. In a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the improvement comprising:
 - a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of DBRISKMARKERS 1-260 in a sample from the subject, and
 - b. measuring a clinically significant alteration in the level of the two or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.
 129. In a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the improvement comprising:
 - a. measuring the level of an effective amount of one or more DBRISKMARKERS selected from the group consisting of: Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (IGFBP3), Resistin (RETN), Matrix Metalloproteinase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (C4A), CD14 molecule (CD14), selectin E (SELE), colony stimulating

- factor 1 (macrophage; CSF1), and vascular endothelial growth factor (VEGF), c-reactive protein (pentraxin-related; CRP), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), and CD26 (dipeptidyl peptidase 4; DPP4), and
- b. measuring a clinically significant alteration in the level of the one or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.
130. In a method of diagnosing or identifying a subject at risk for developing Diabetes or a pre-diabetic condition by analyzing Diabetes risk factors, the improvement comprising:
- a. measuring the level of an effective amount of two or more DBRISKMARKERS selected from the group consisting of: Leptin (LEP), Haptoglobin (HP), Insulin-like growth factor binding protein 3 (IGFBP3), Resistin (RETN), Matrix Metallopeptidase 2 (MMP-2), Angiotensin I converting enzyme (peptidyl dipeptidase A)-1 (ACE), complement component 4A (C4A), CD14 molecule (CD14), selectin E (SELE), colony stimulating factor 1 (macrophage; CSF1), and vascular endothelial growth factor (VEGF), c-reactive protein (pentraxin-related; CRP), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), RAGE (Advanced Glycosylation End Product-specific Receptor [AGER]), and CD26 (dipeptidyl peptidase 4; DPP4), and
- b. measuring a clinically significant alteration in the level of the two or more DBRISKMARKERS in the sample, wherein the alteration indicates an increased risk of developing Diabetes Mellitus or a pre-diabetic condition in the subject.

FIG. 3E



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FIG. 3F

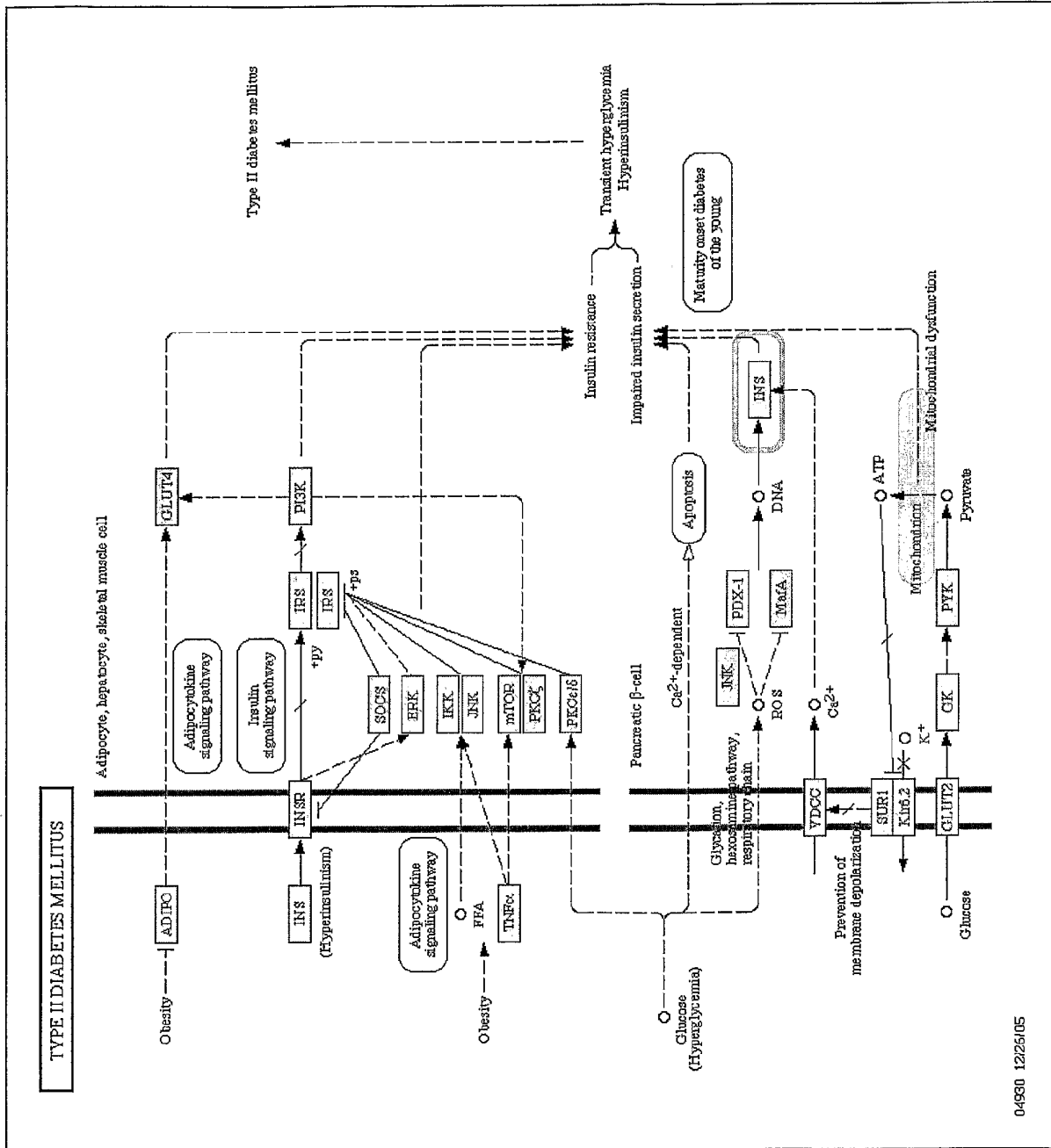


FIG. 3G

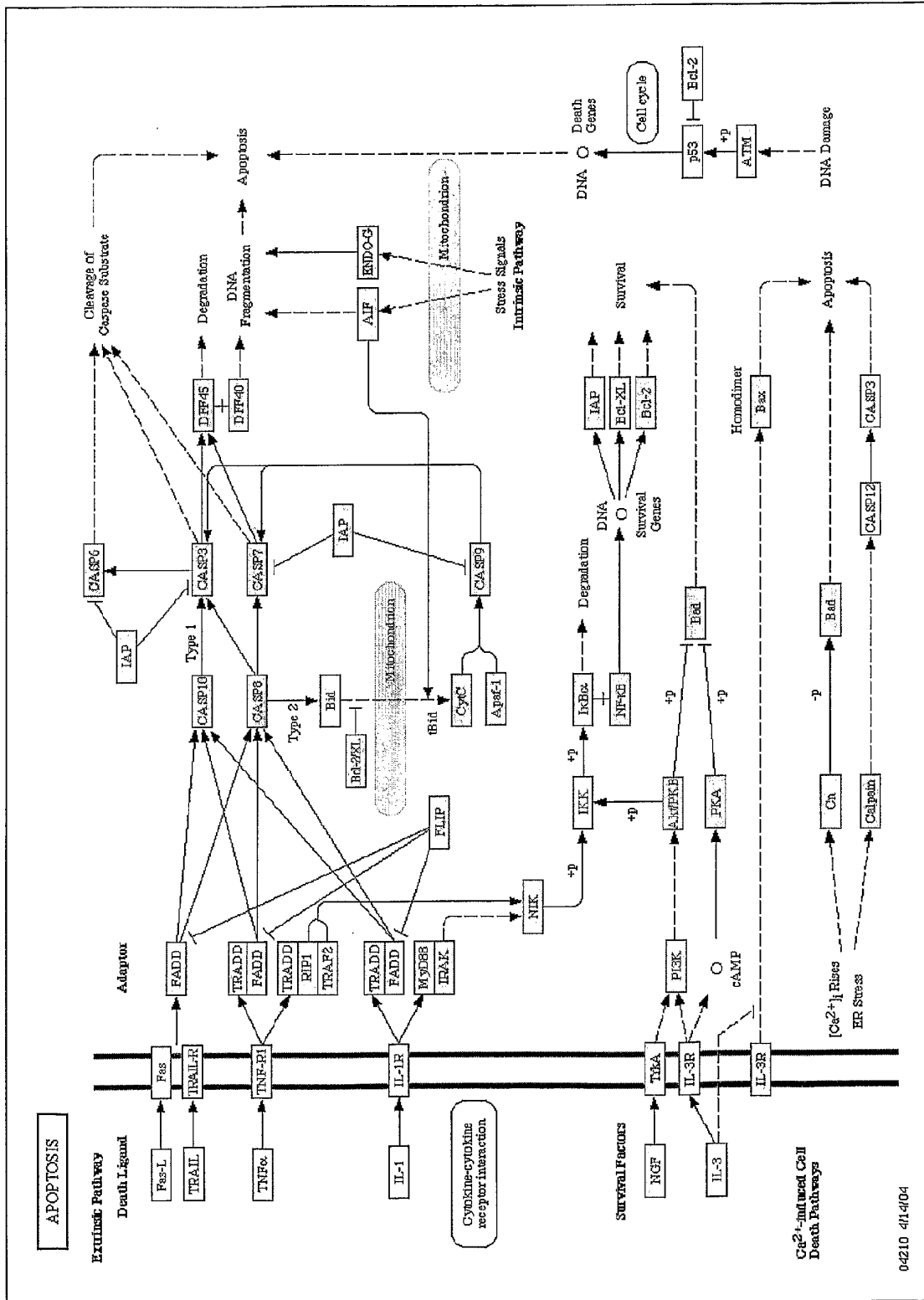


FIG. 3I

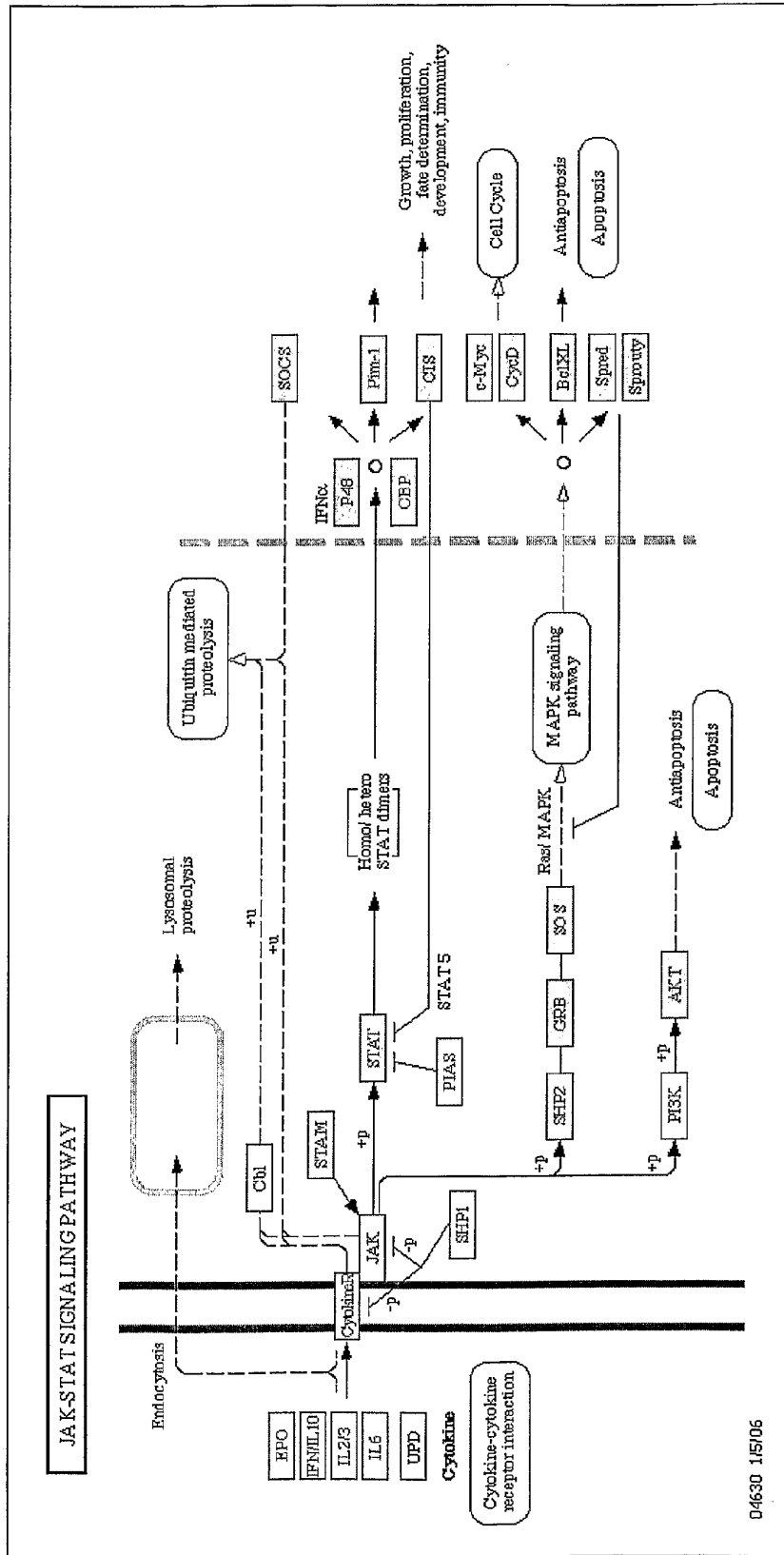


FIG. 3M

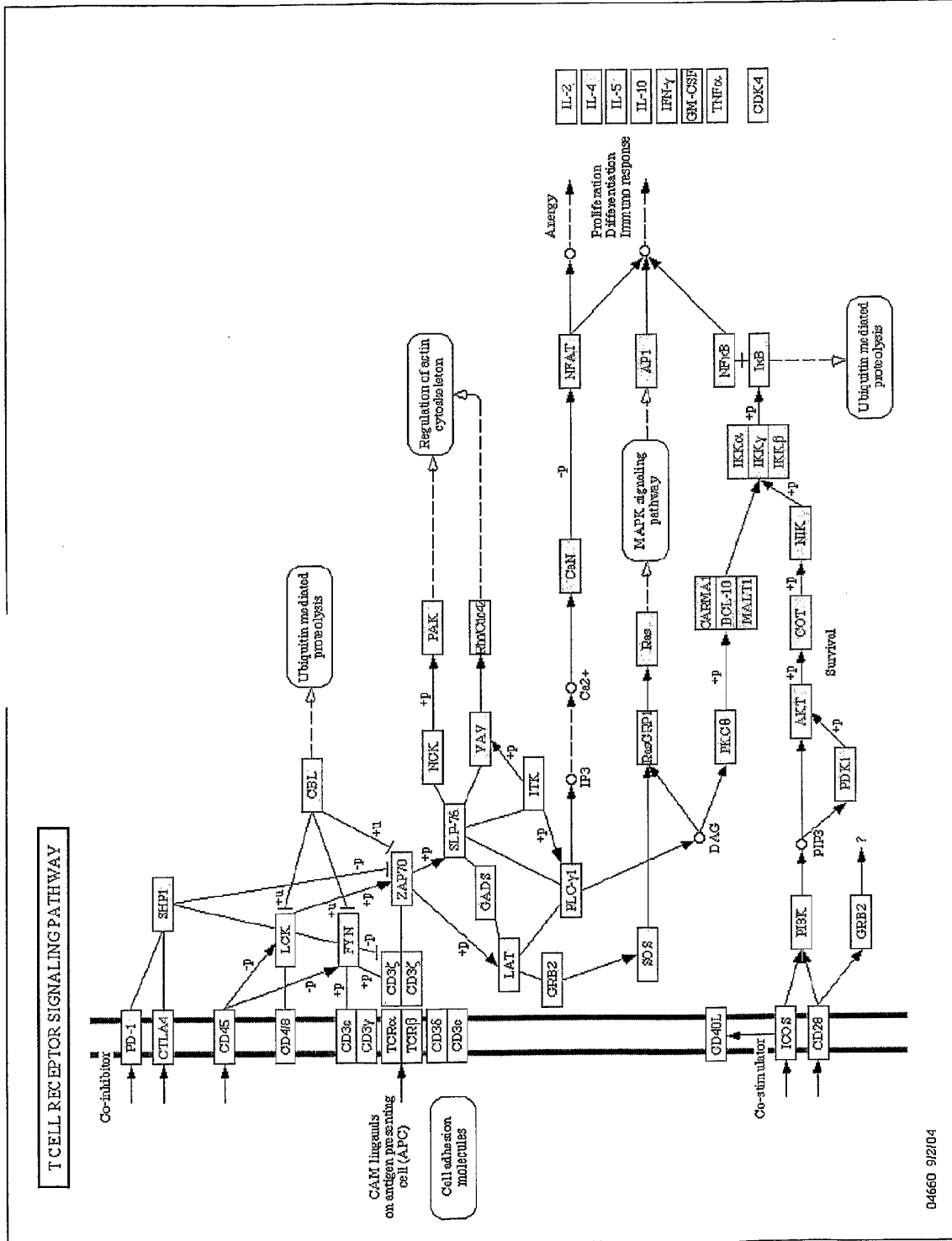
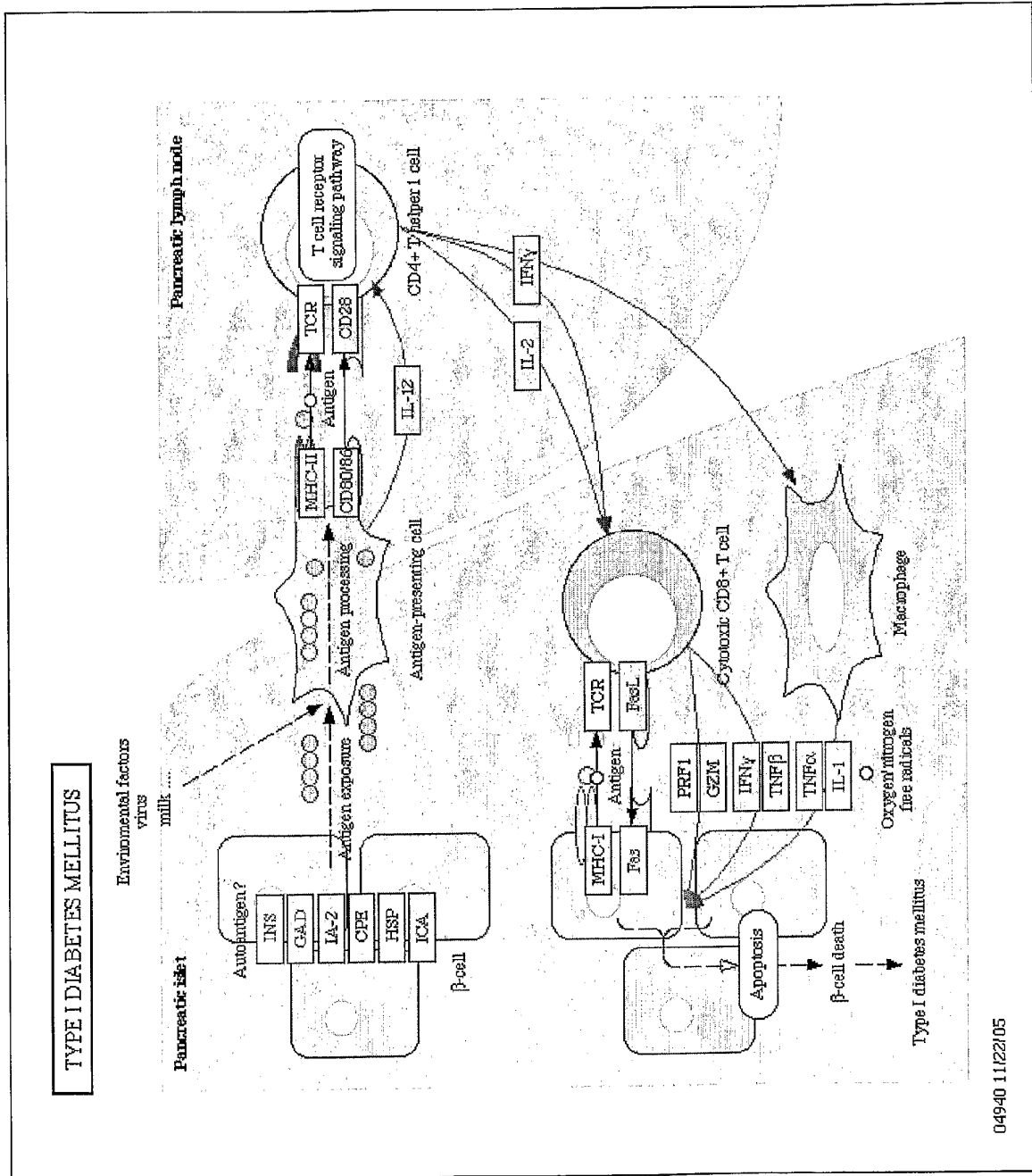
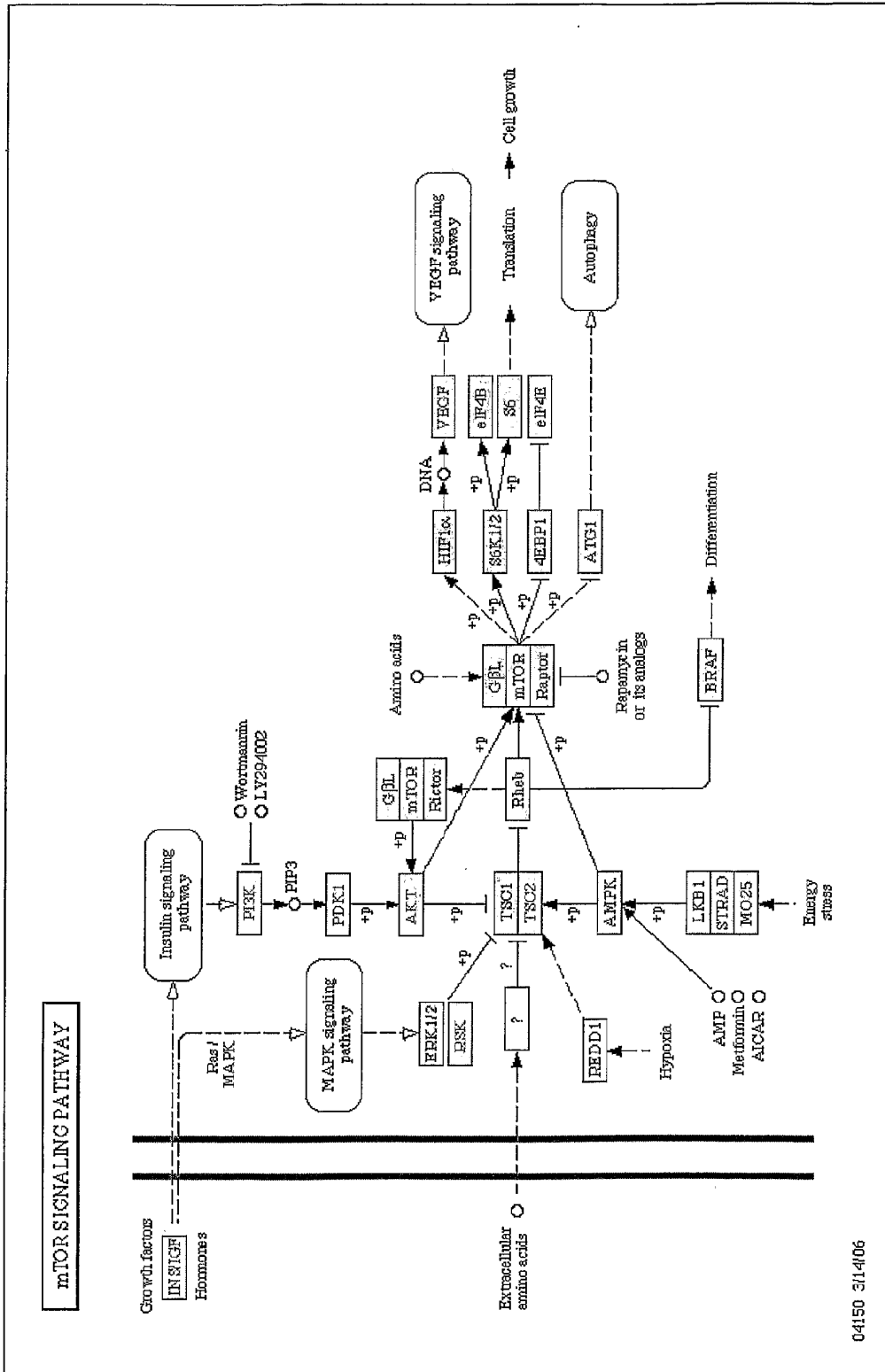


FIG. 30



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FIG. 3Q



04150 3/14/06

FIG. 3R

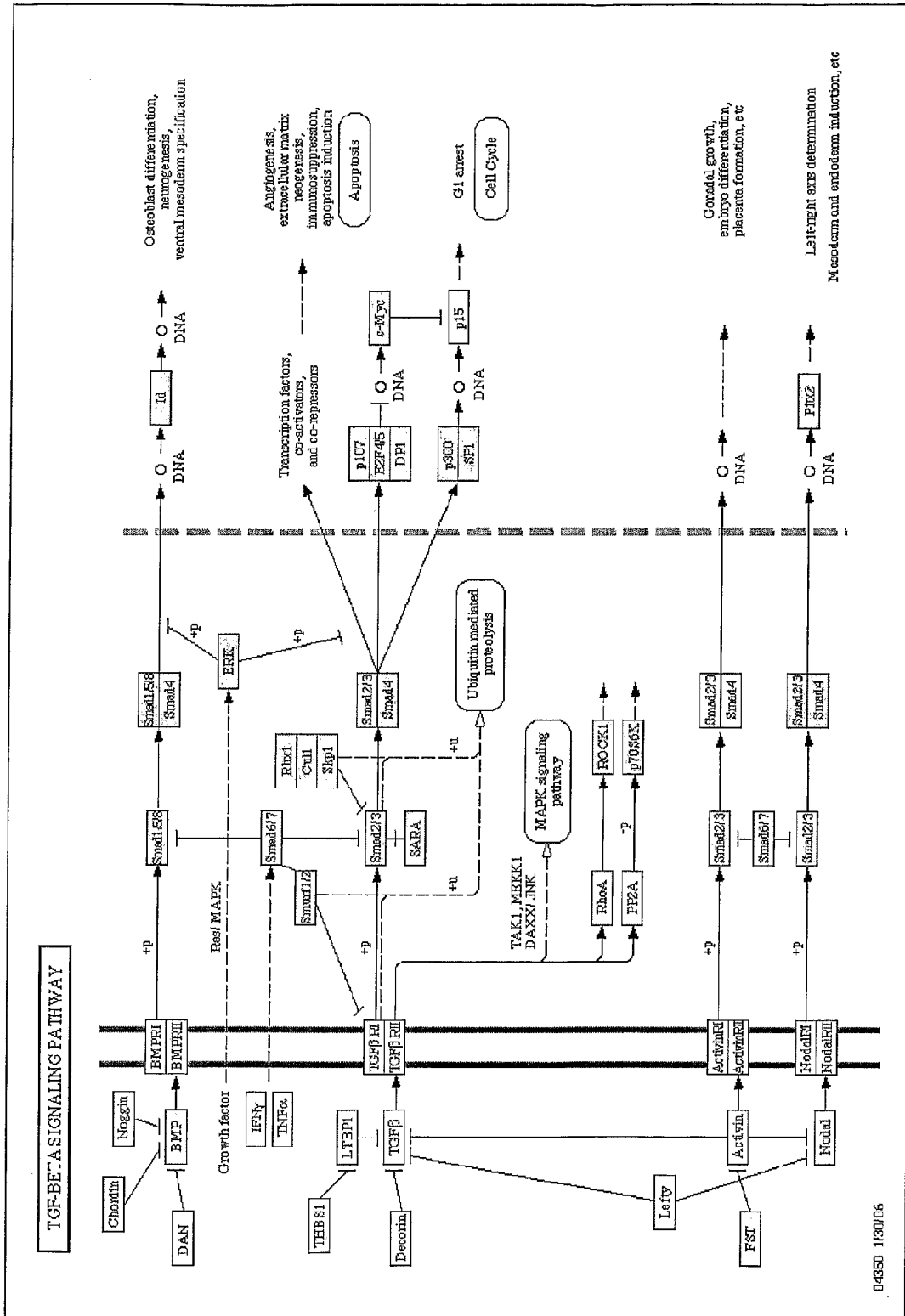
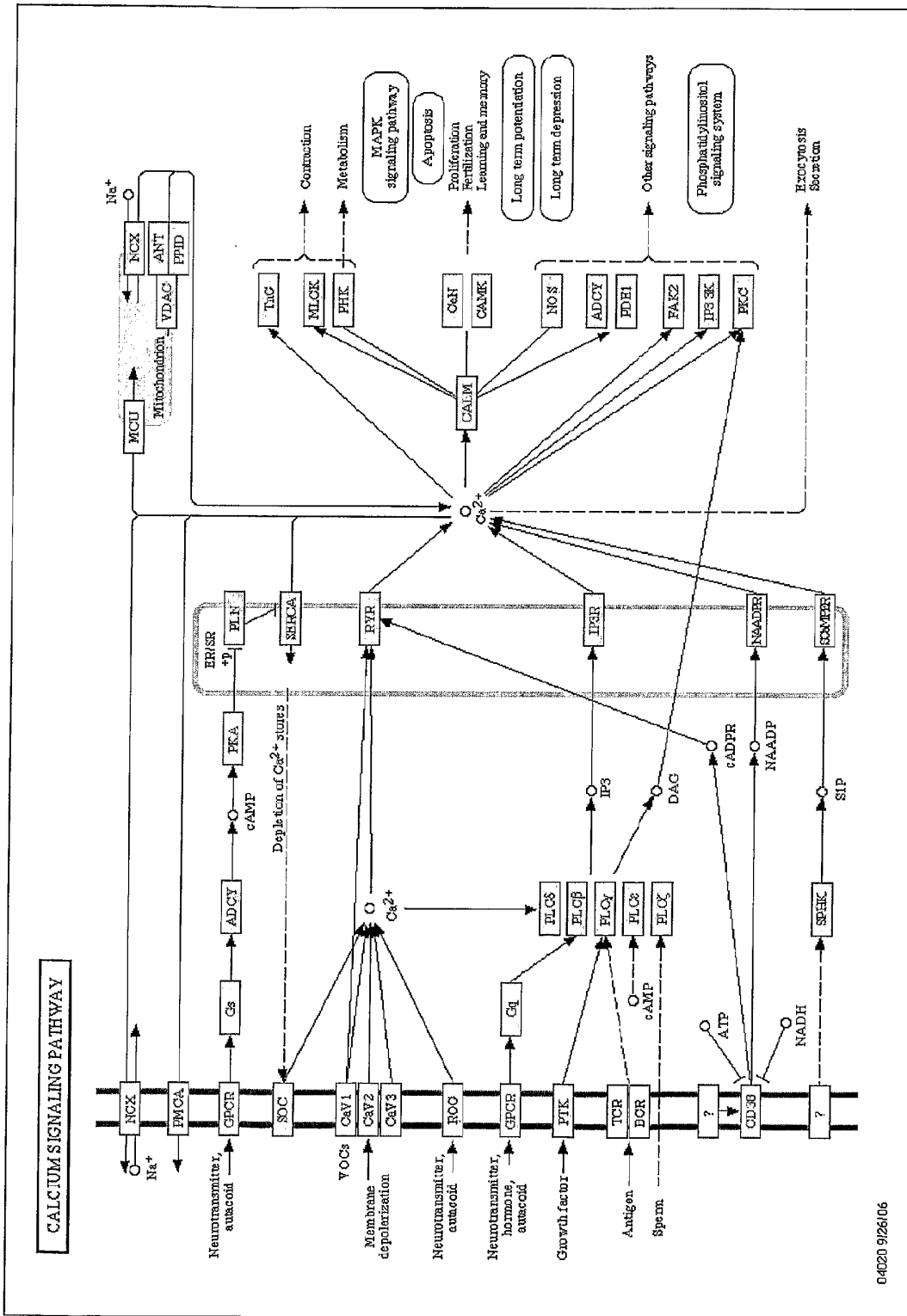
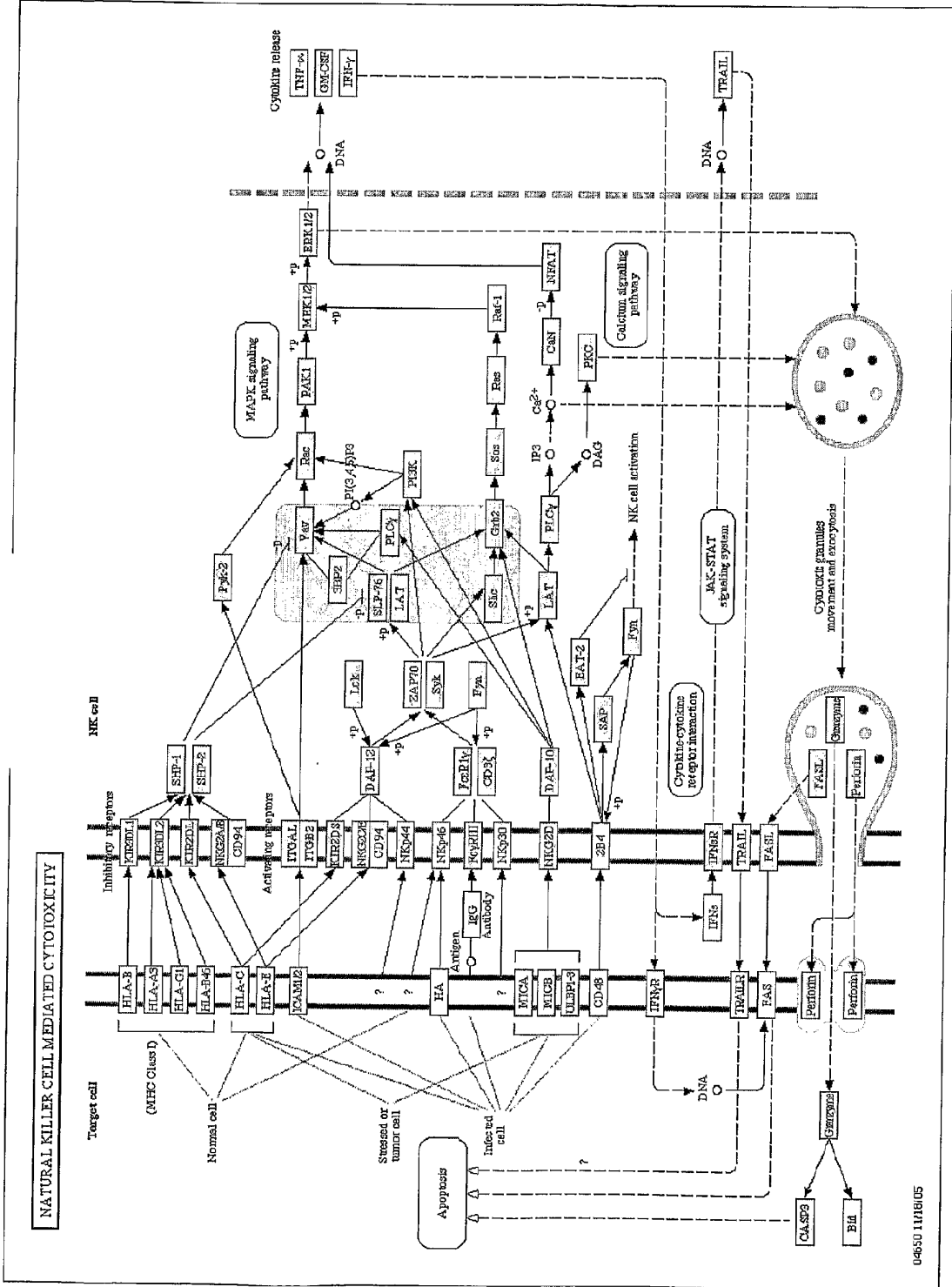


FIG. 3S



04020 9/26/06

FIG. 3T



04650 11/16/05

FIG. 3U

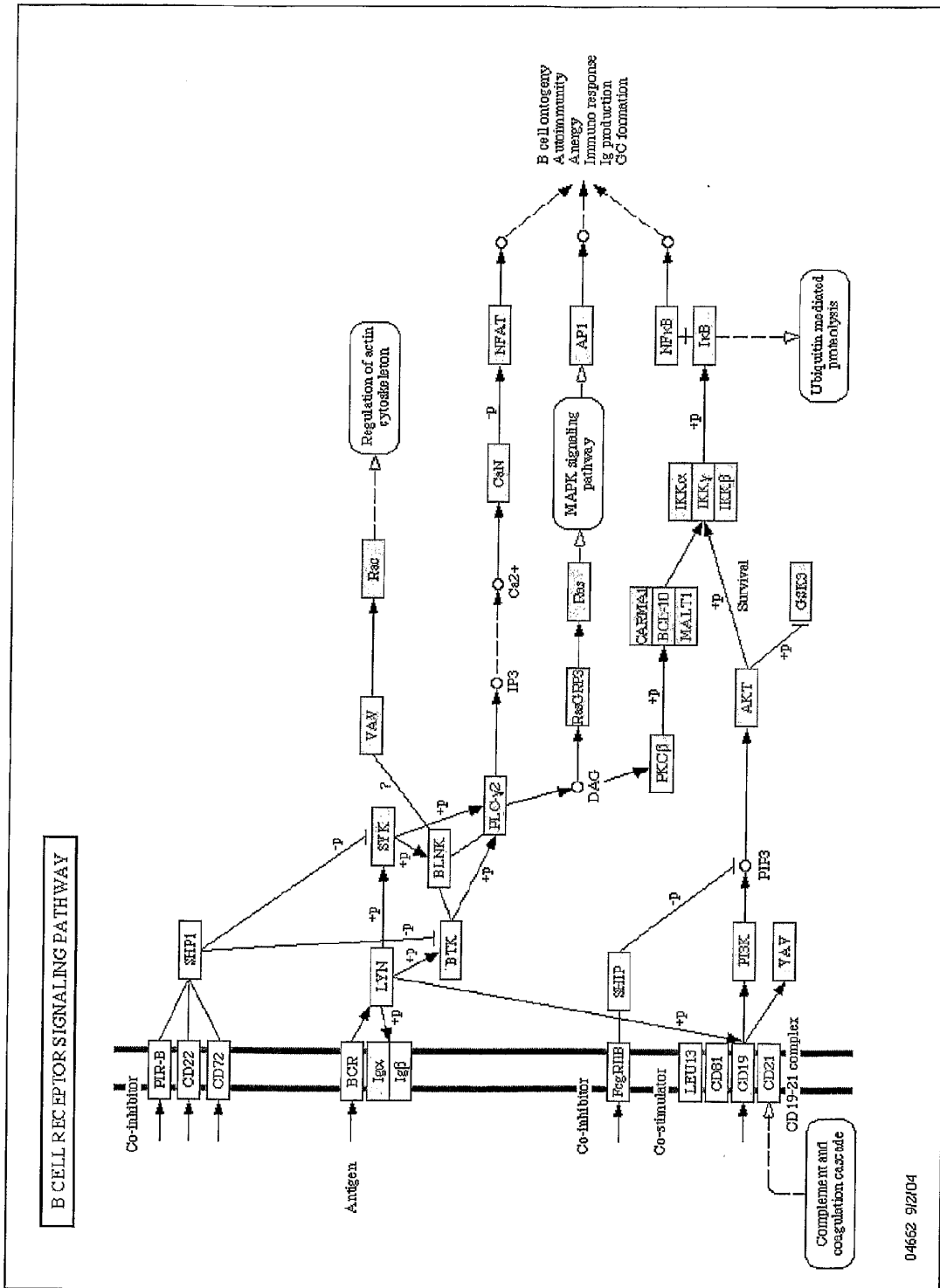
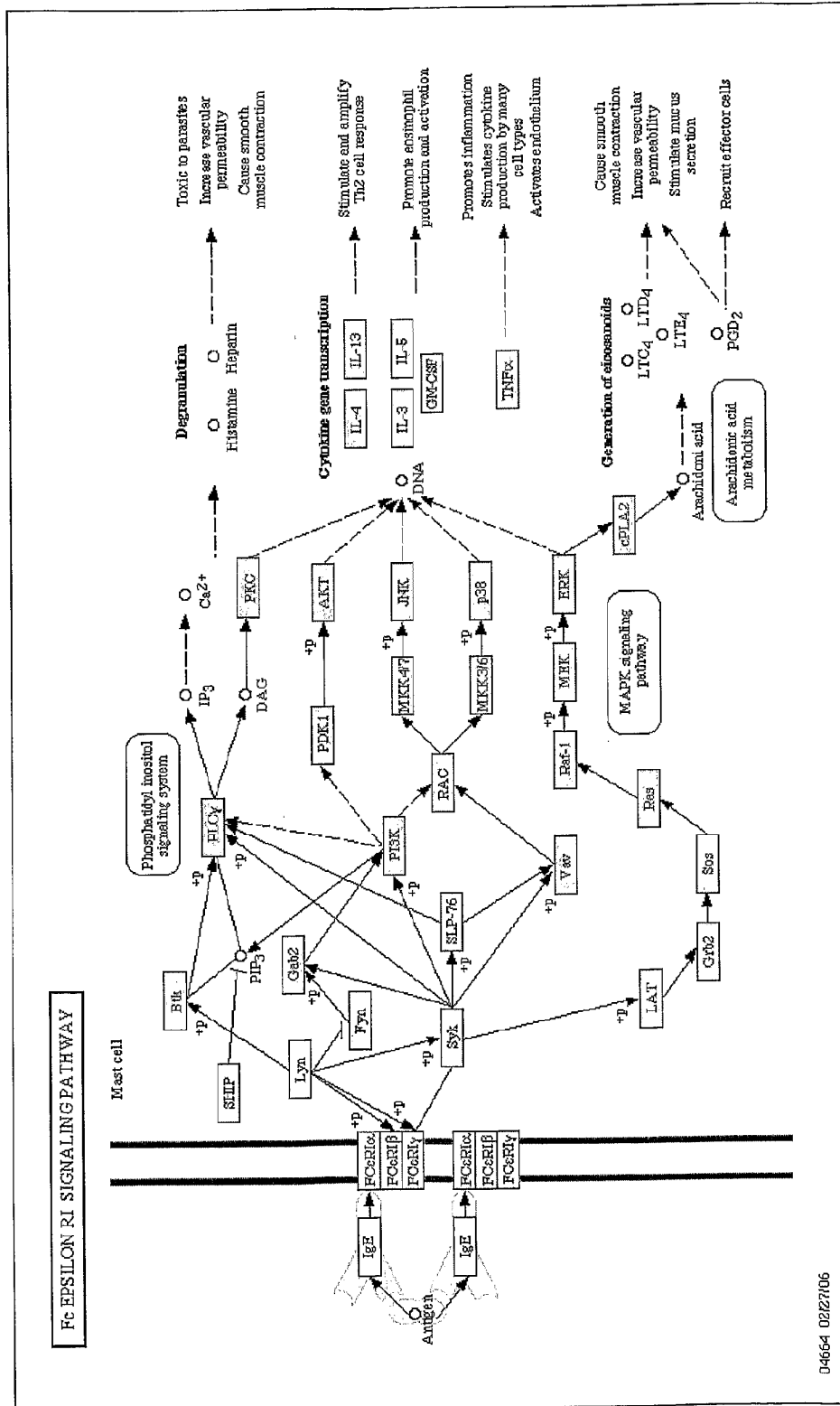


FIG. 3V



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FIG. 3W

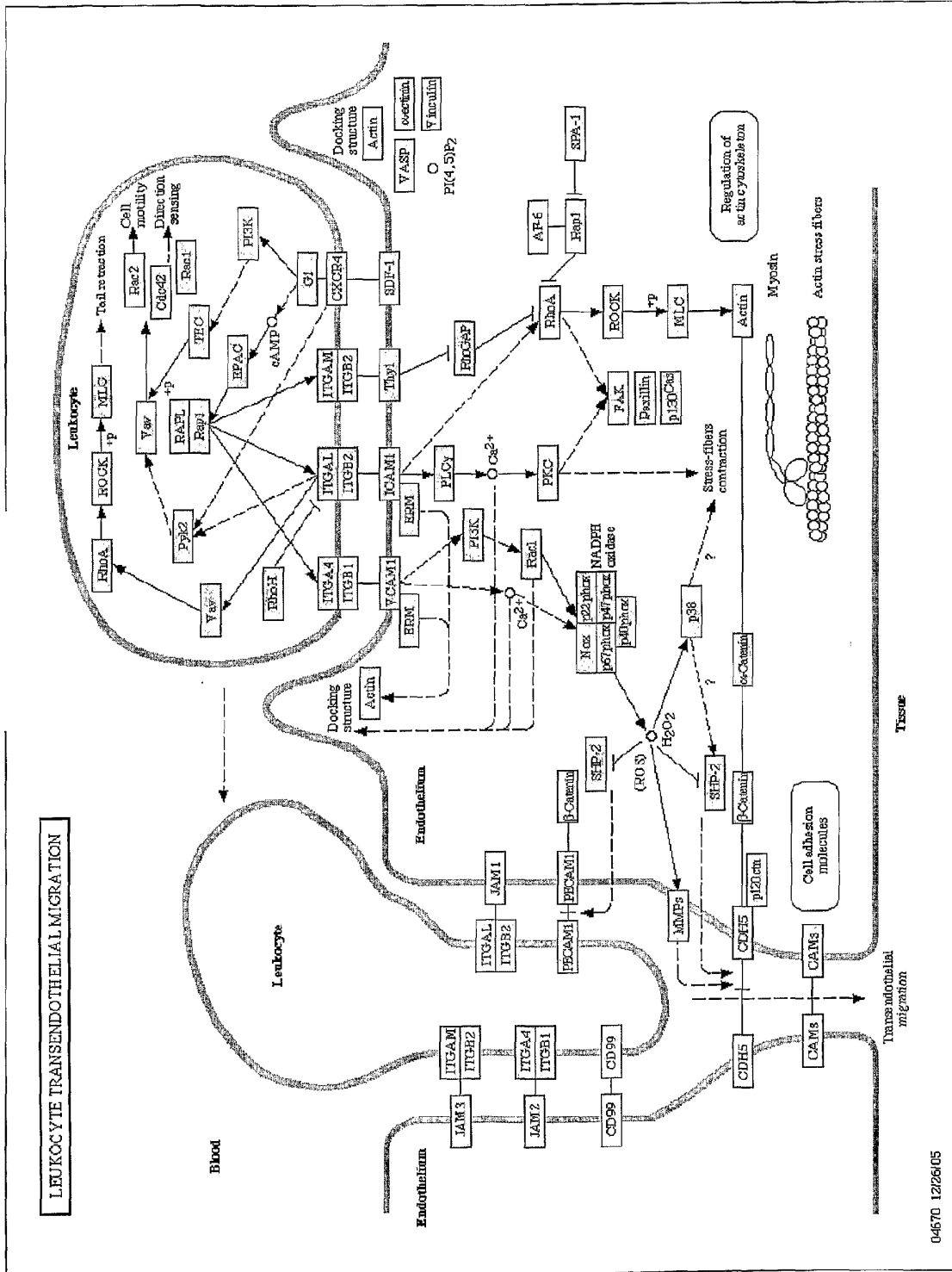
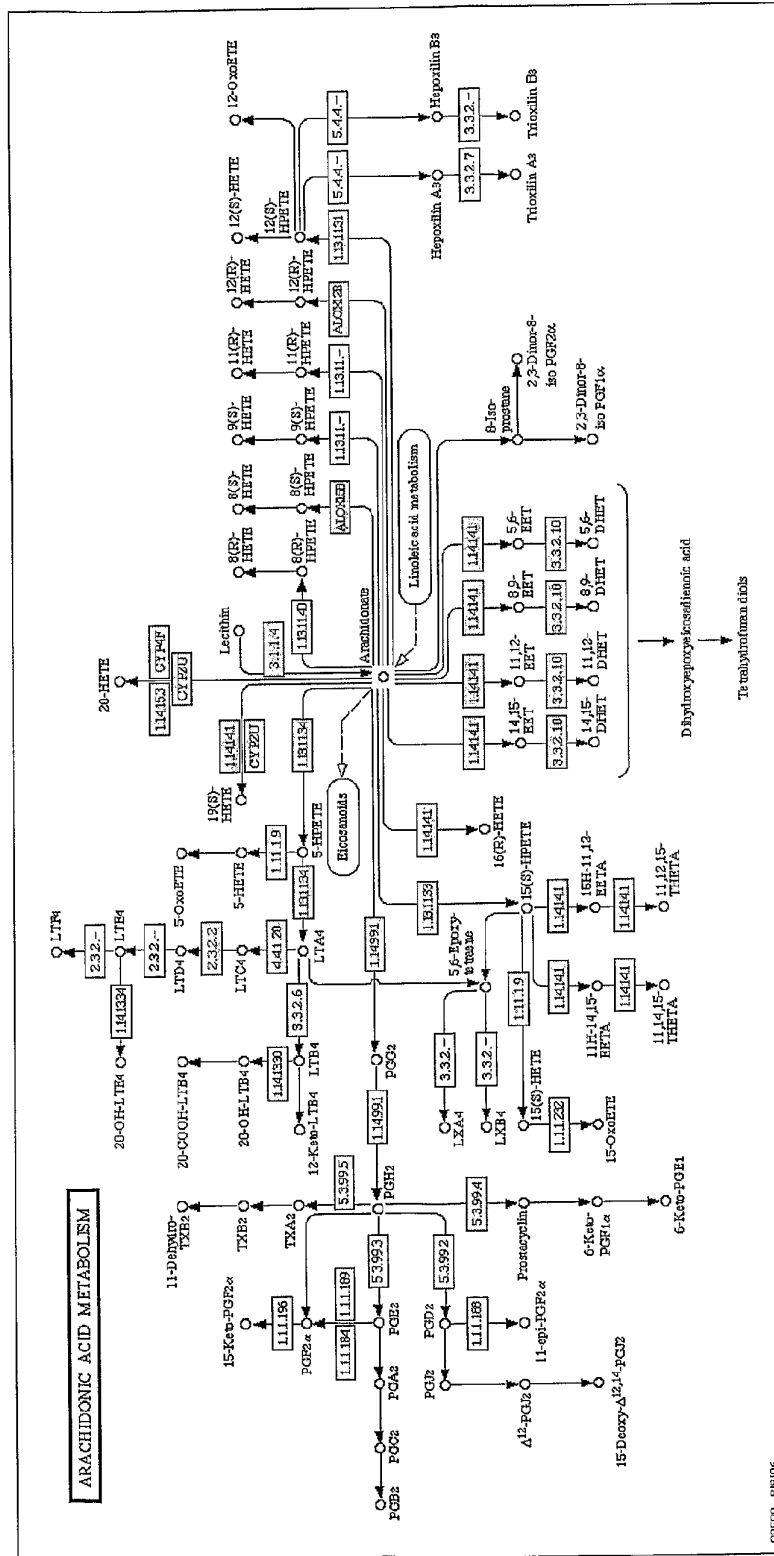
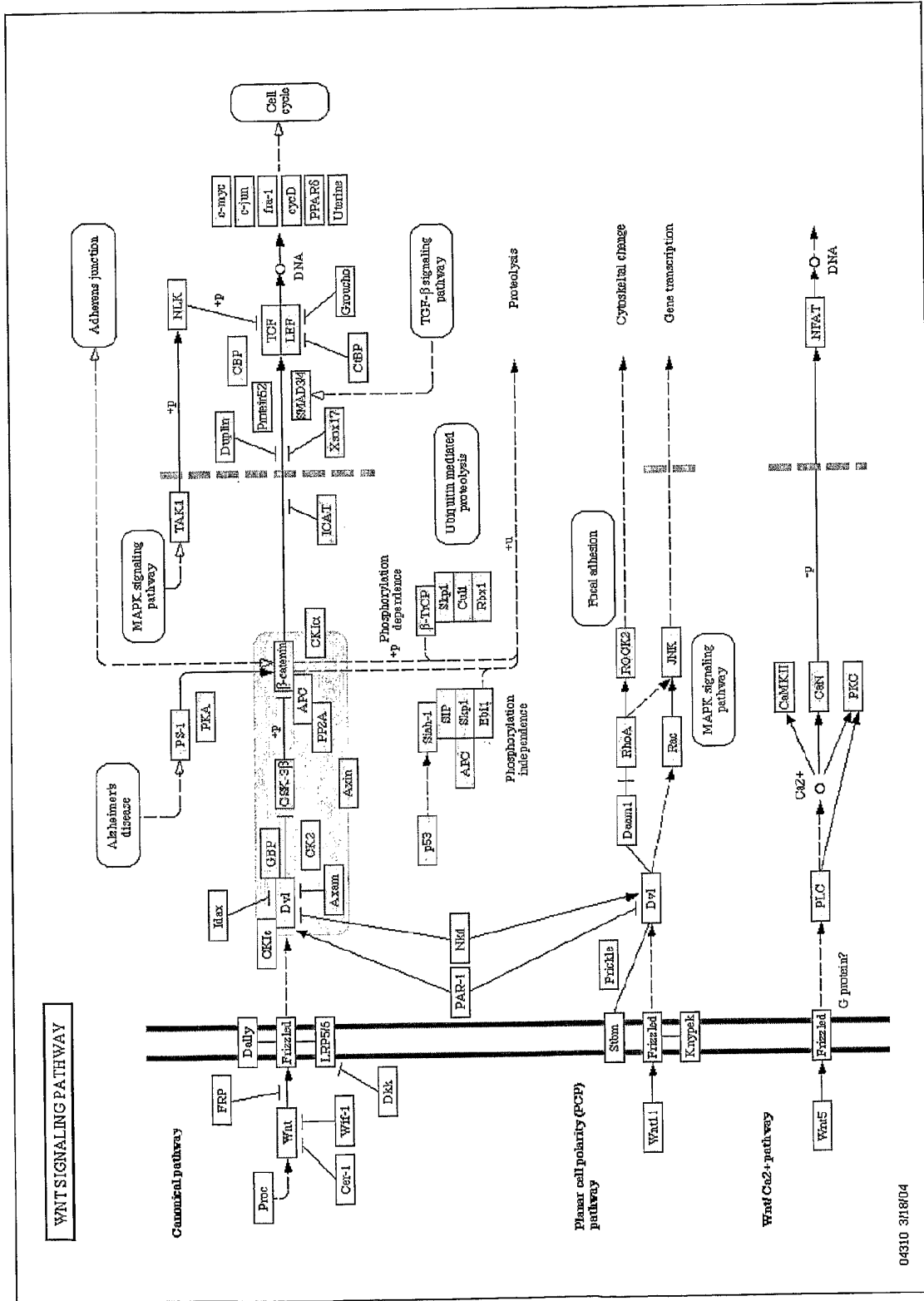


FIG. 3X



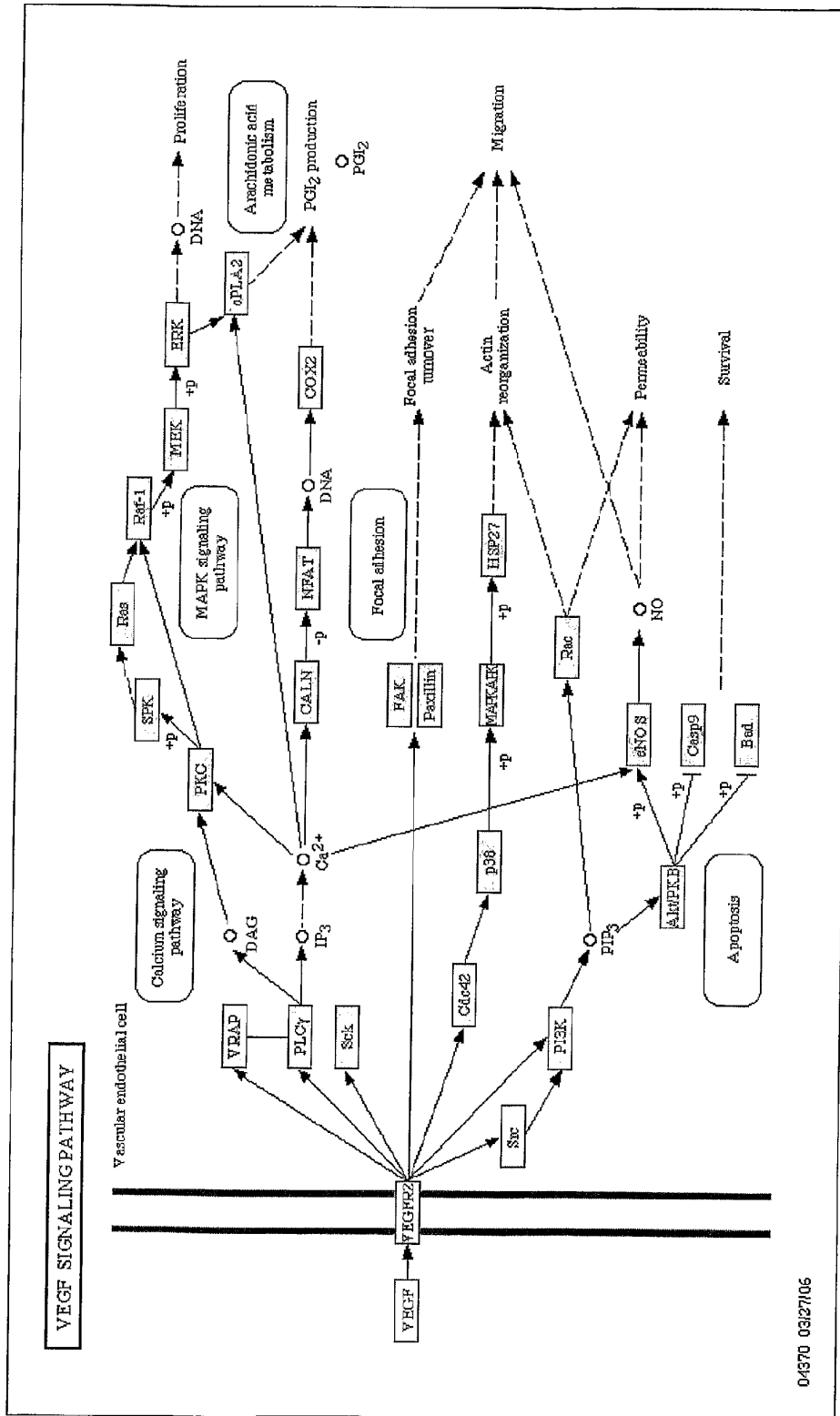
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FIG. 3Y



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FIG. 3Z



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FIG. 3CC

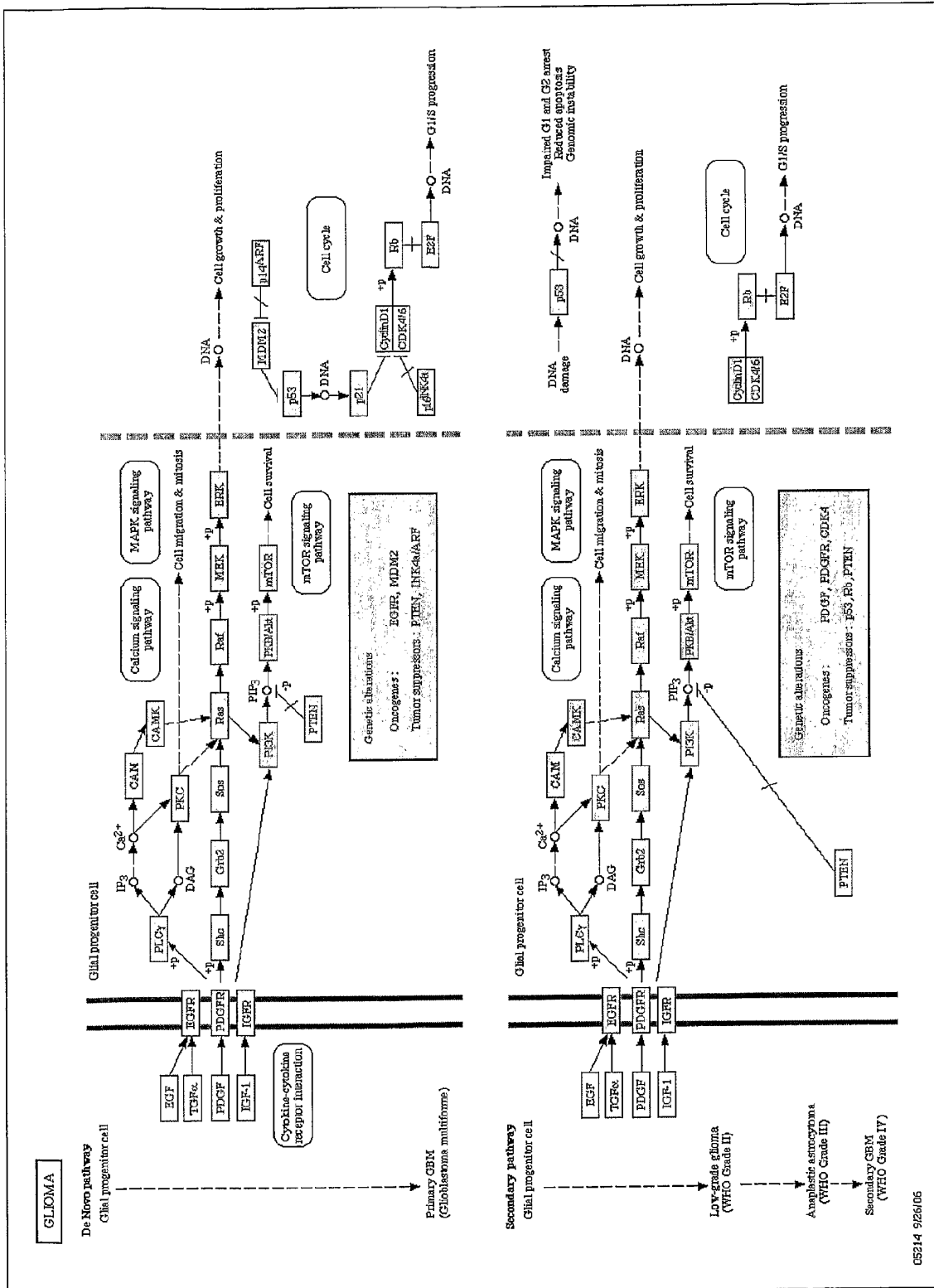


FIG. 3EE

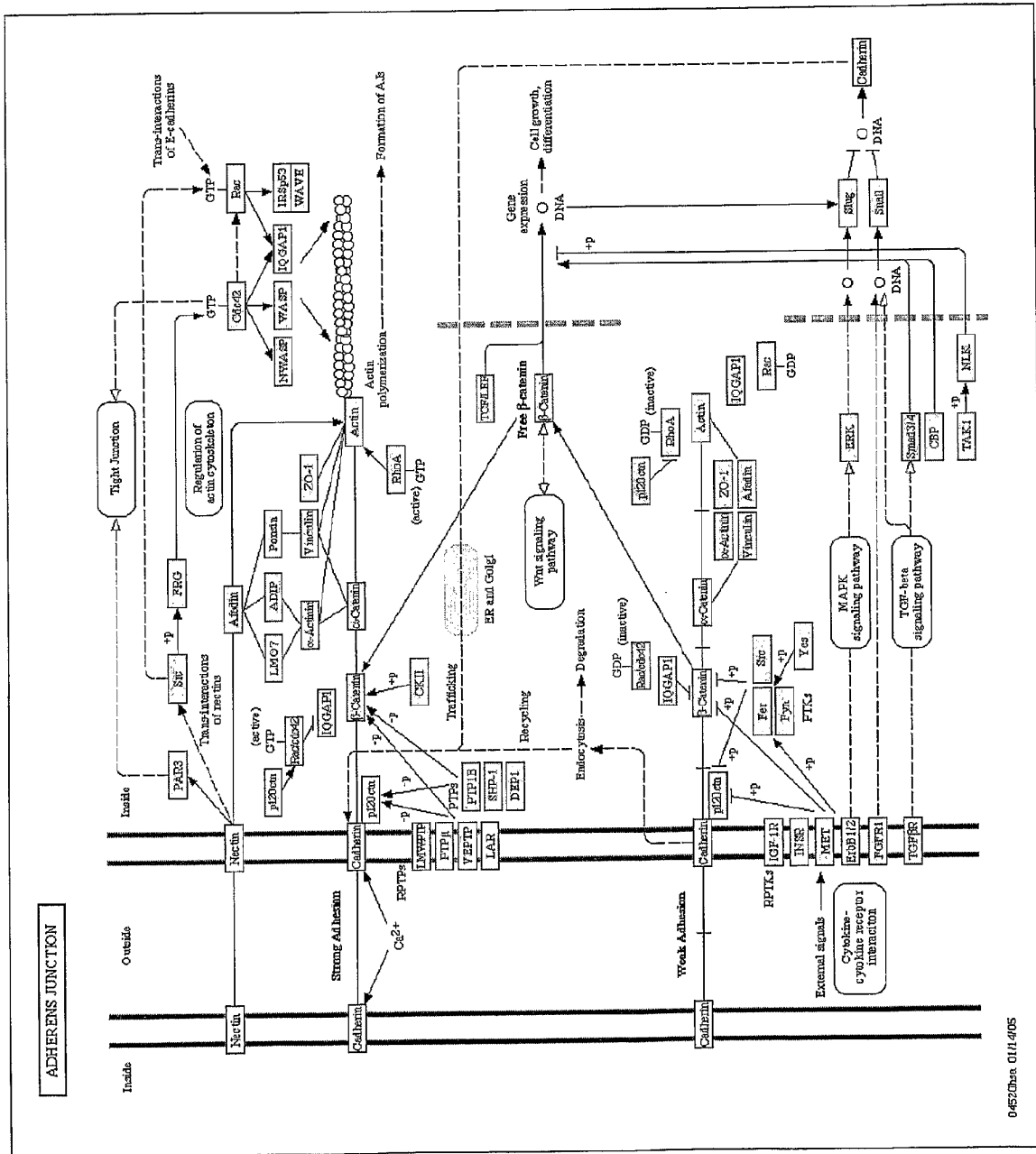


FIG. 3GG

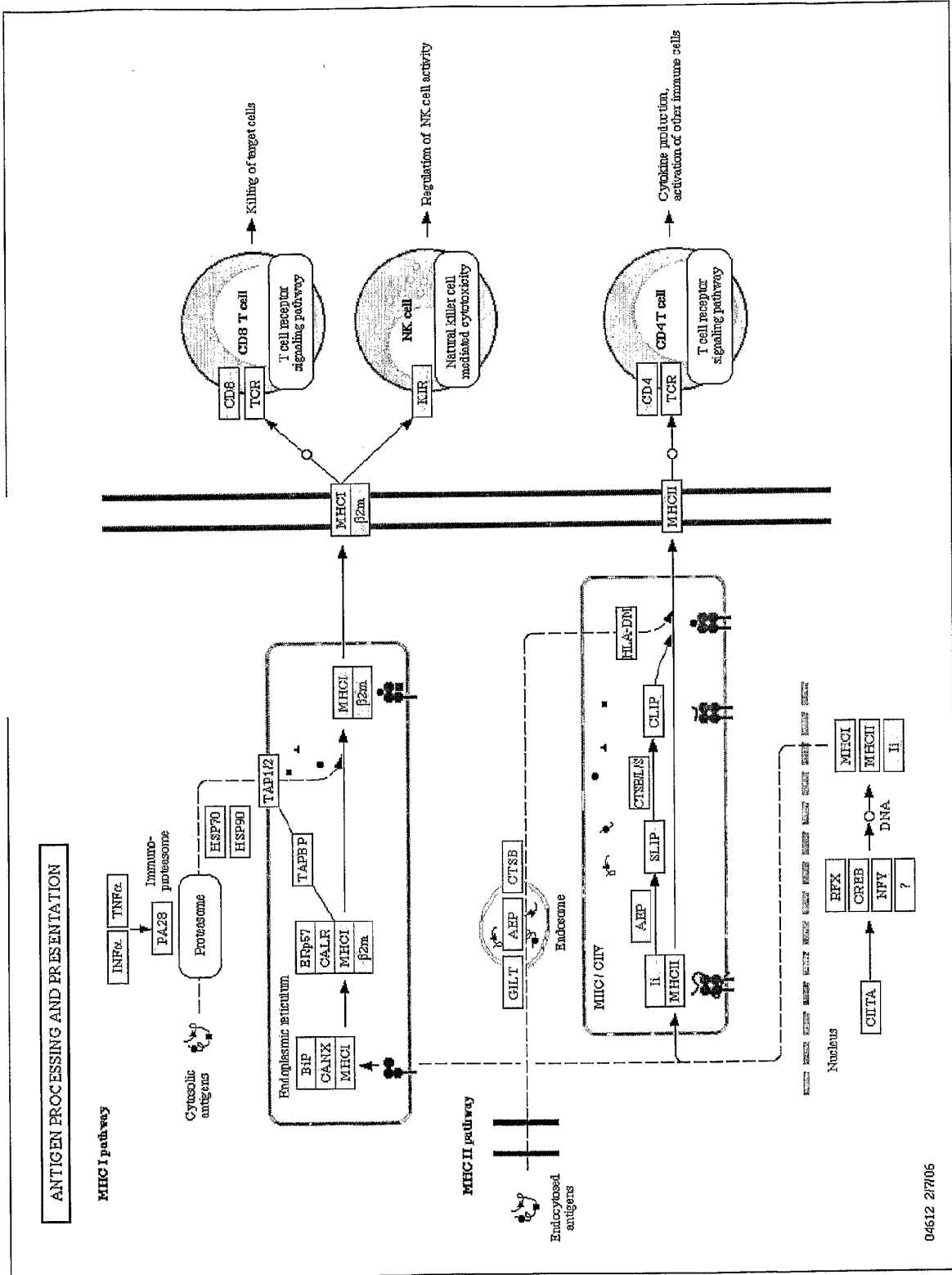
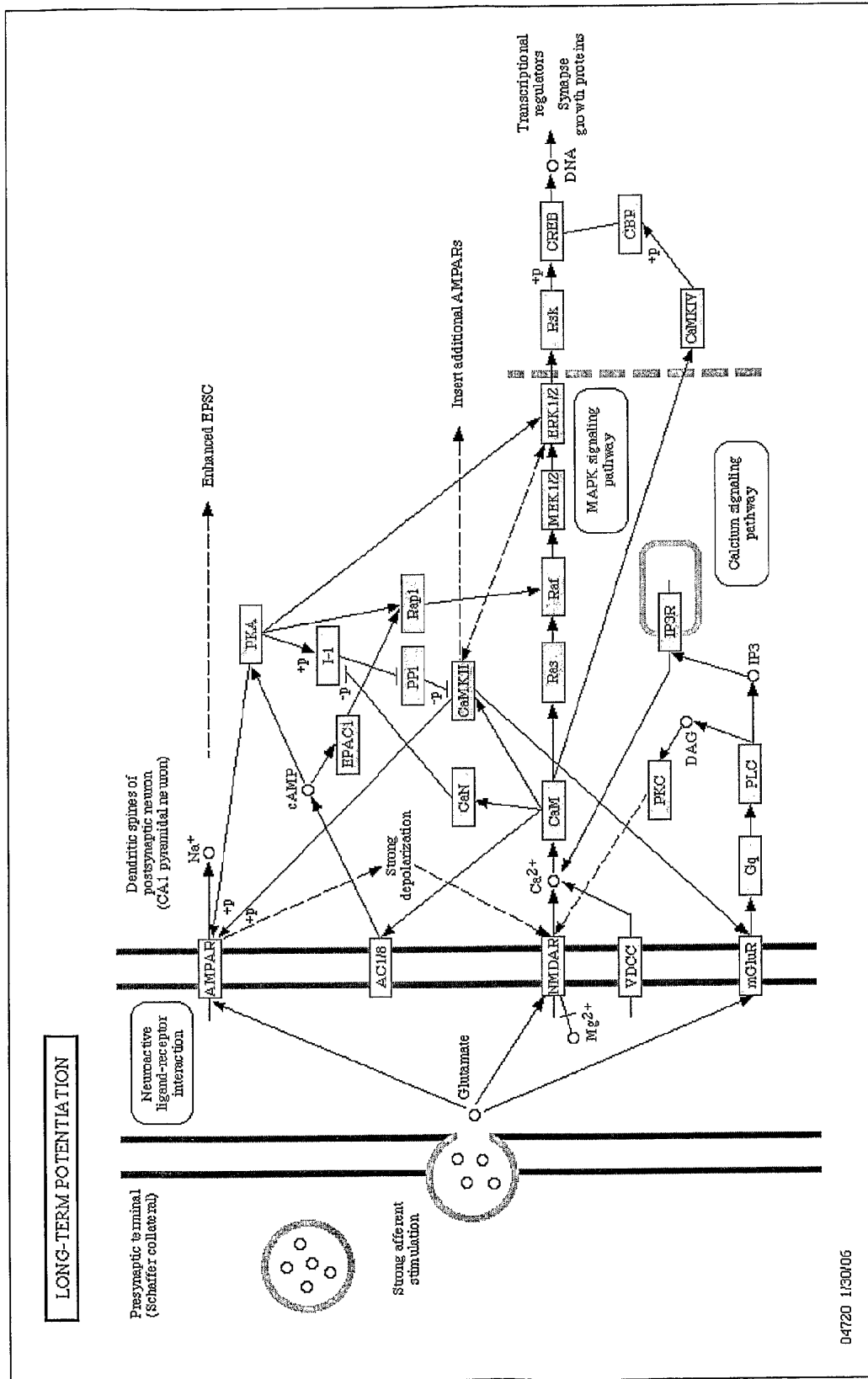


FIG. 3HH



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FIG. 3II

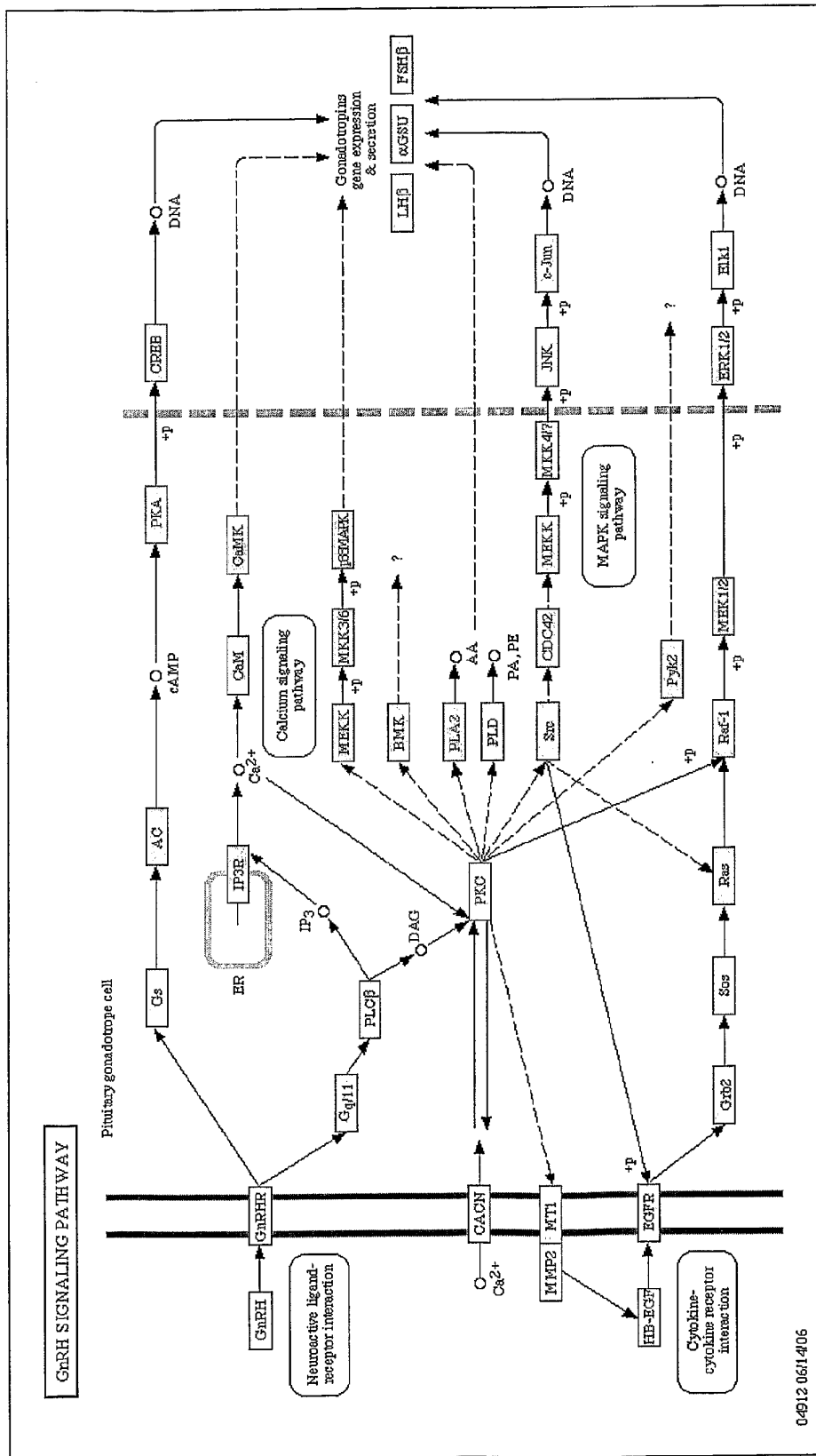


FIG. 3KK

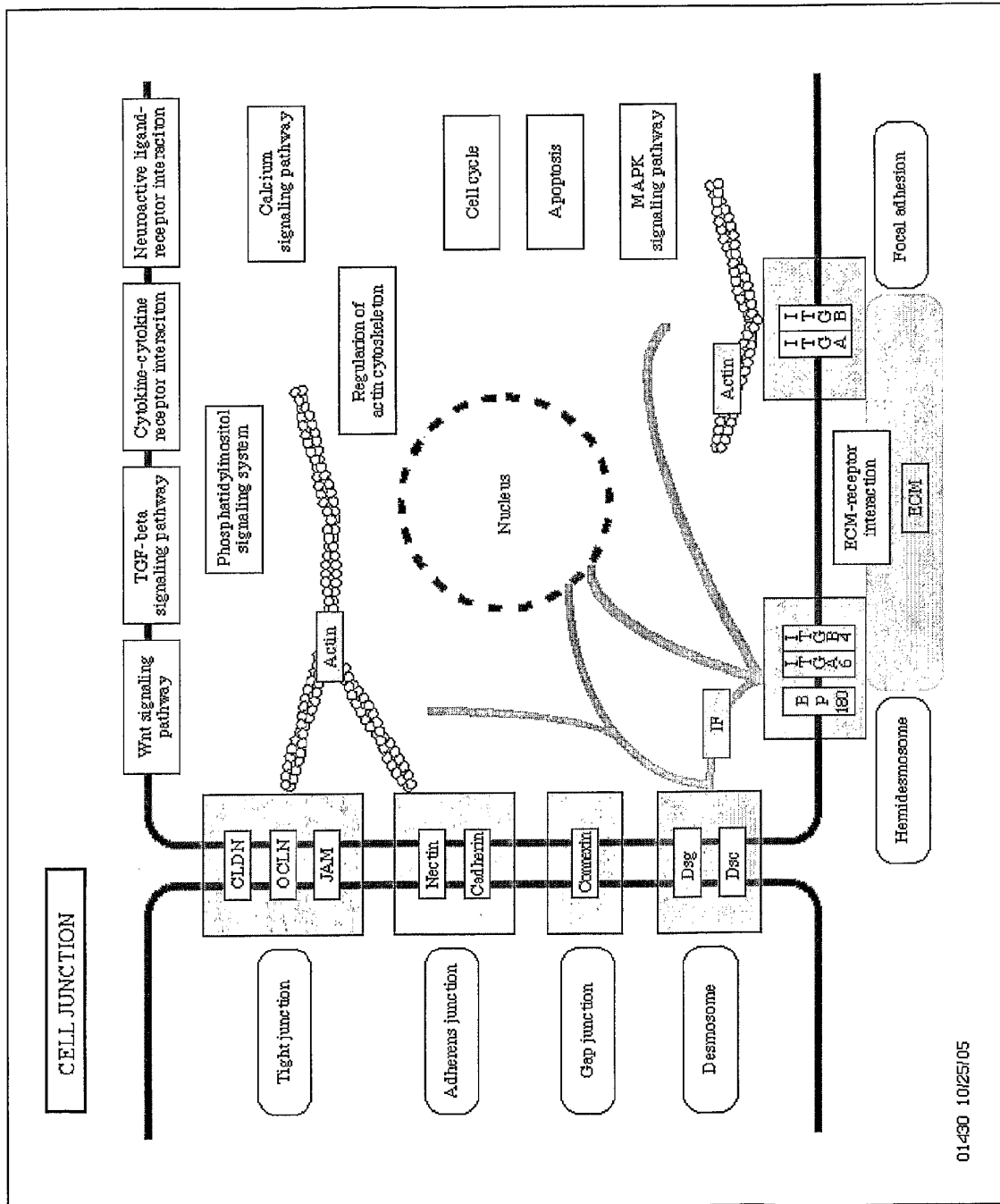
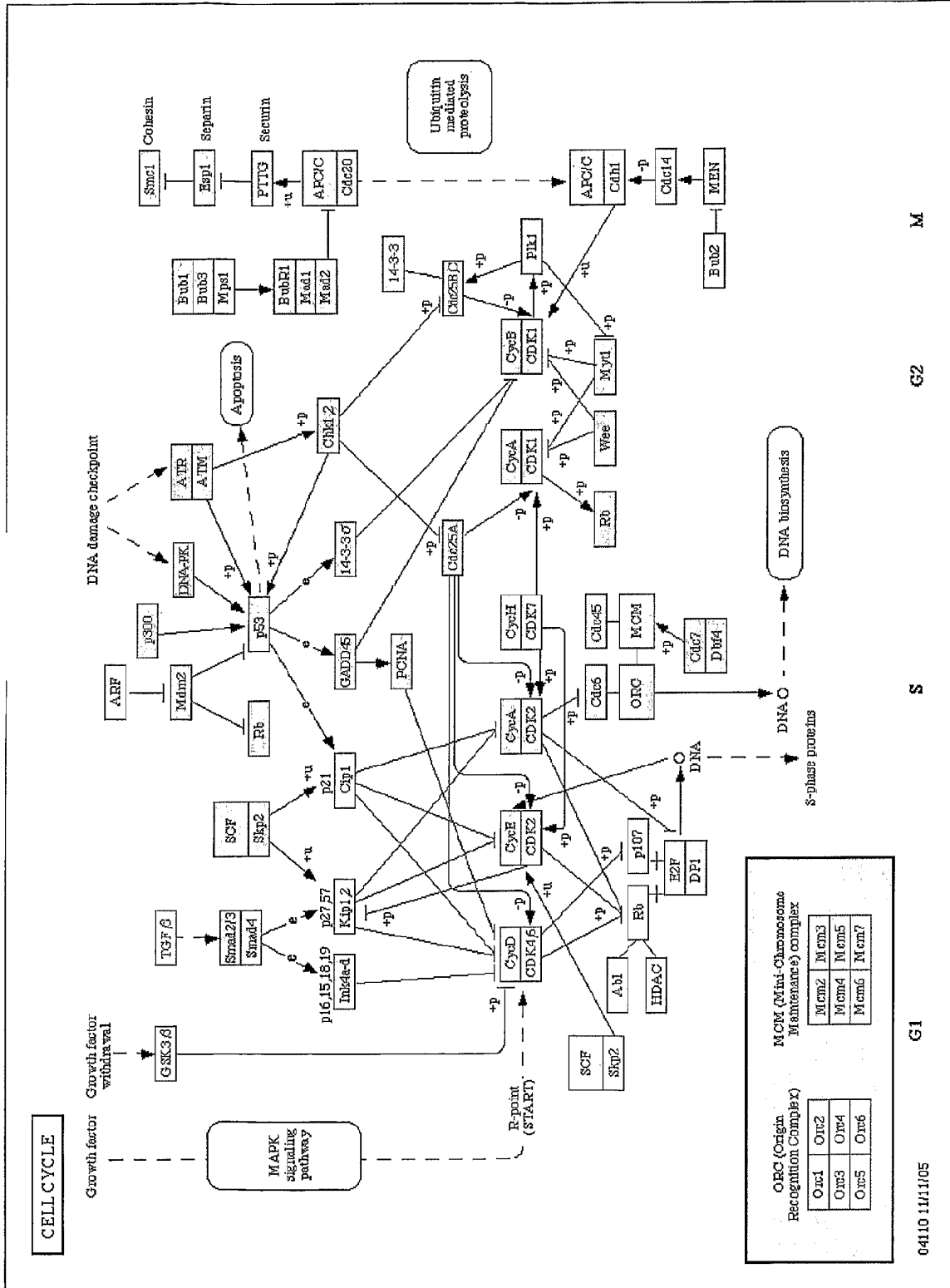
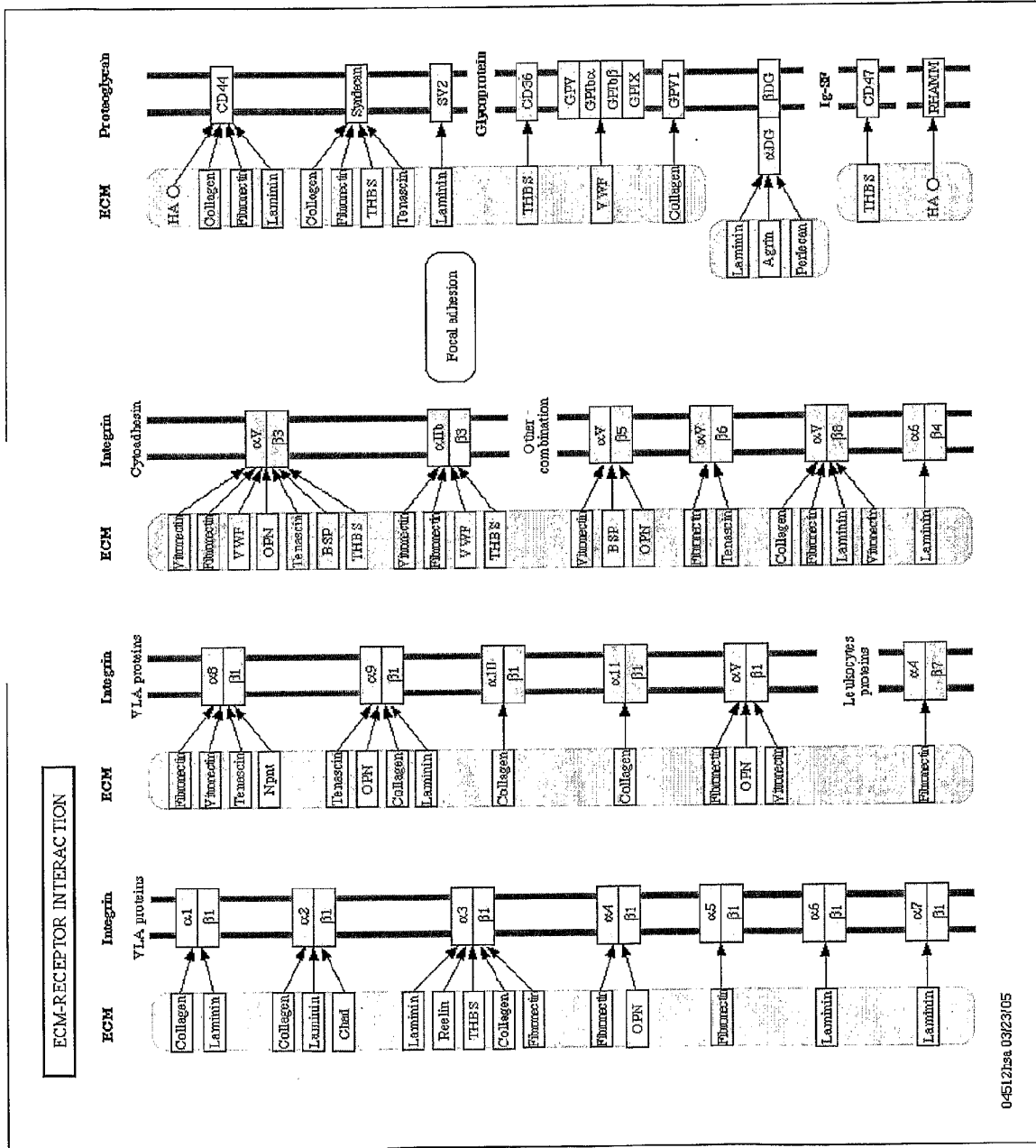


FIG. 3MM



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FIG. 3NN



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FIG. 300

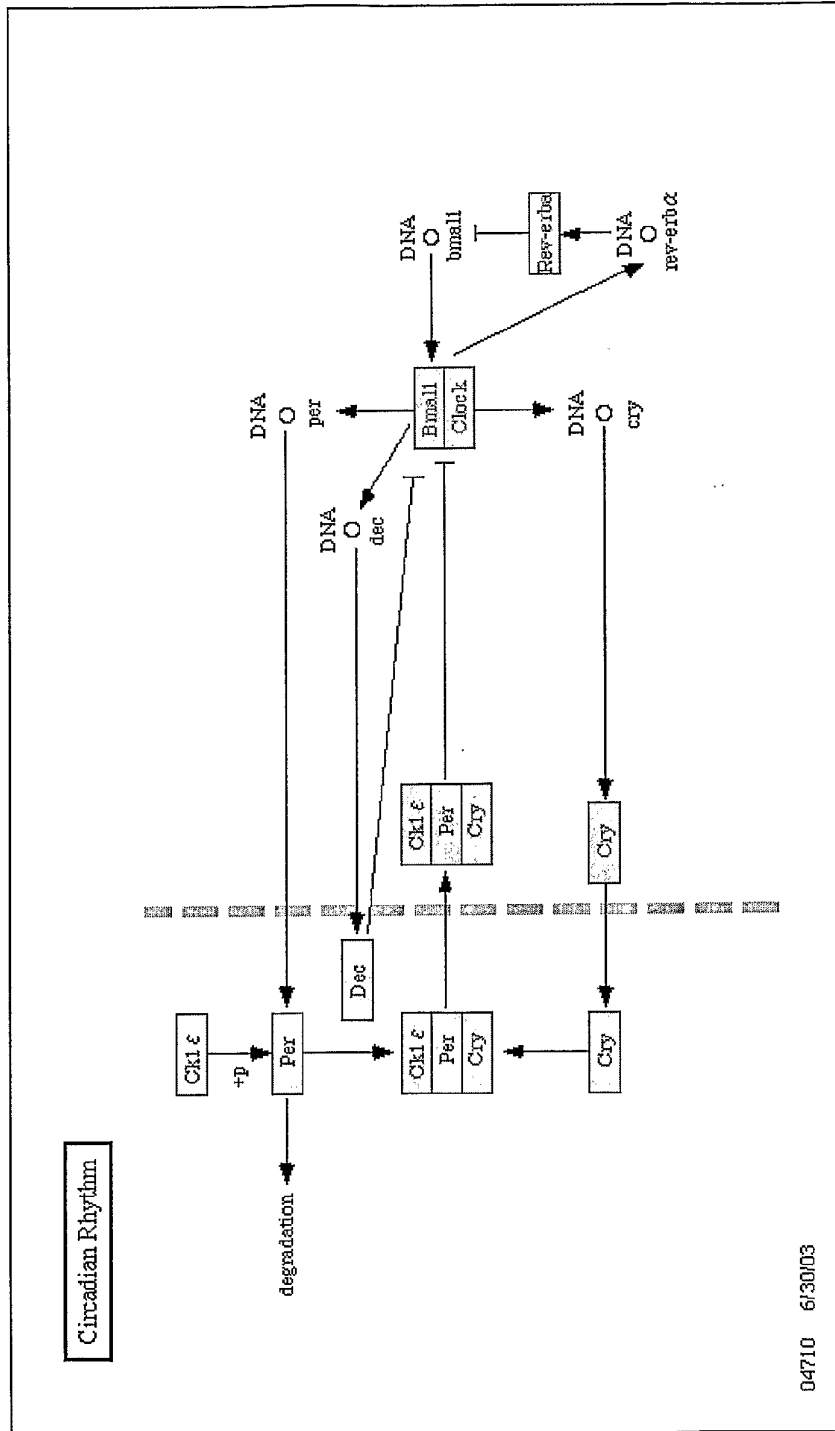


FIG. 3PP

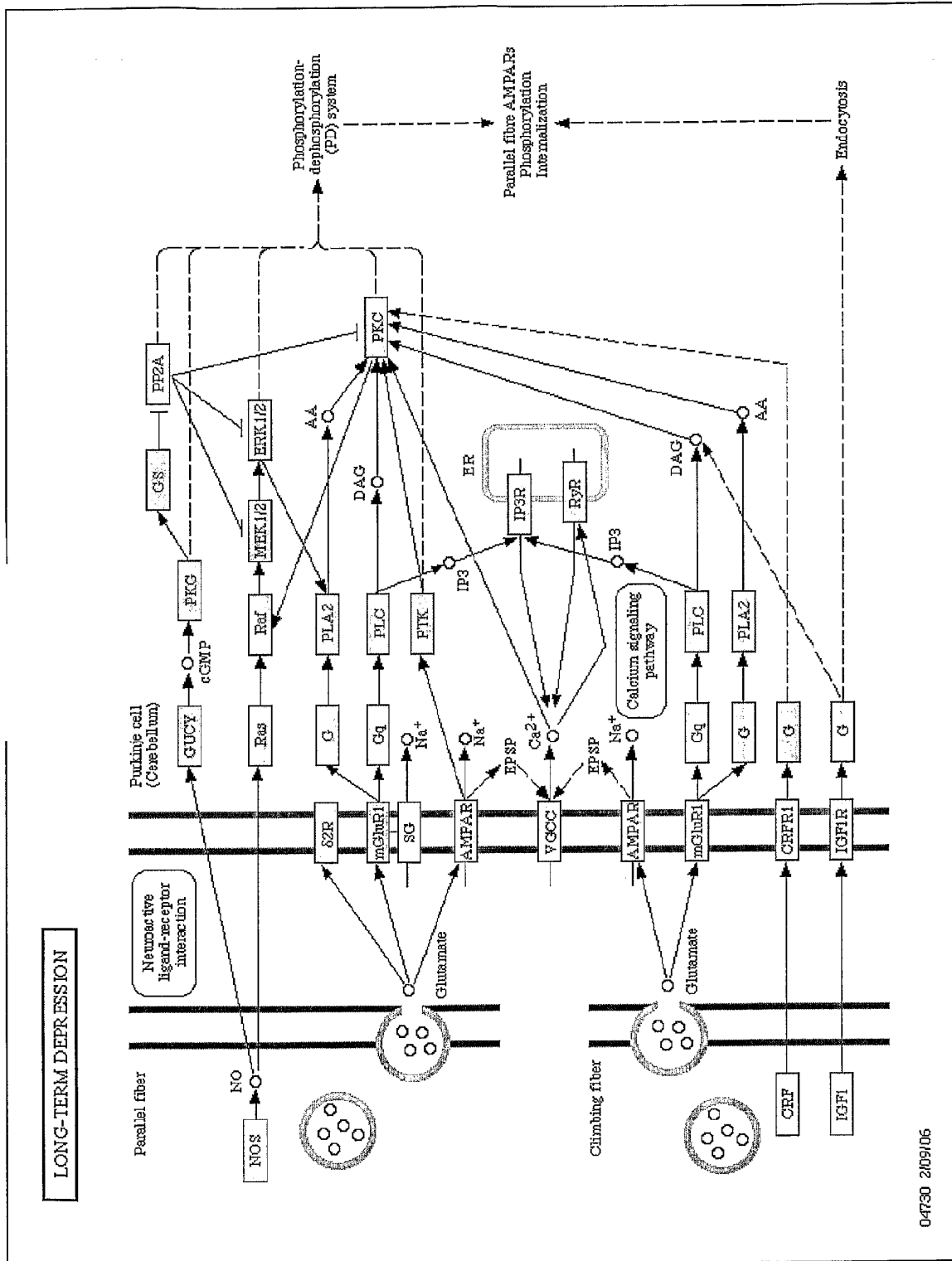


FIG. 3QQ

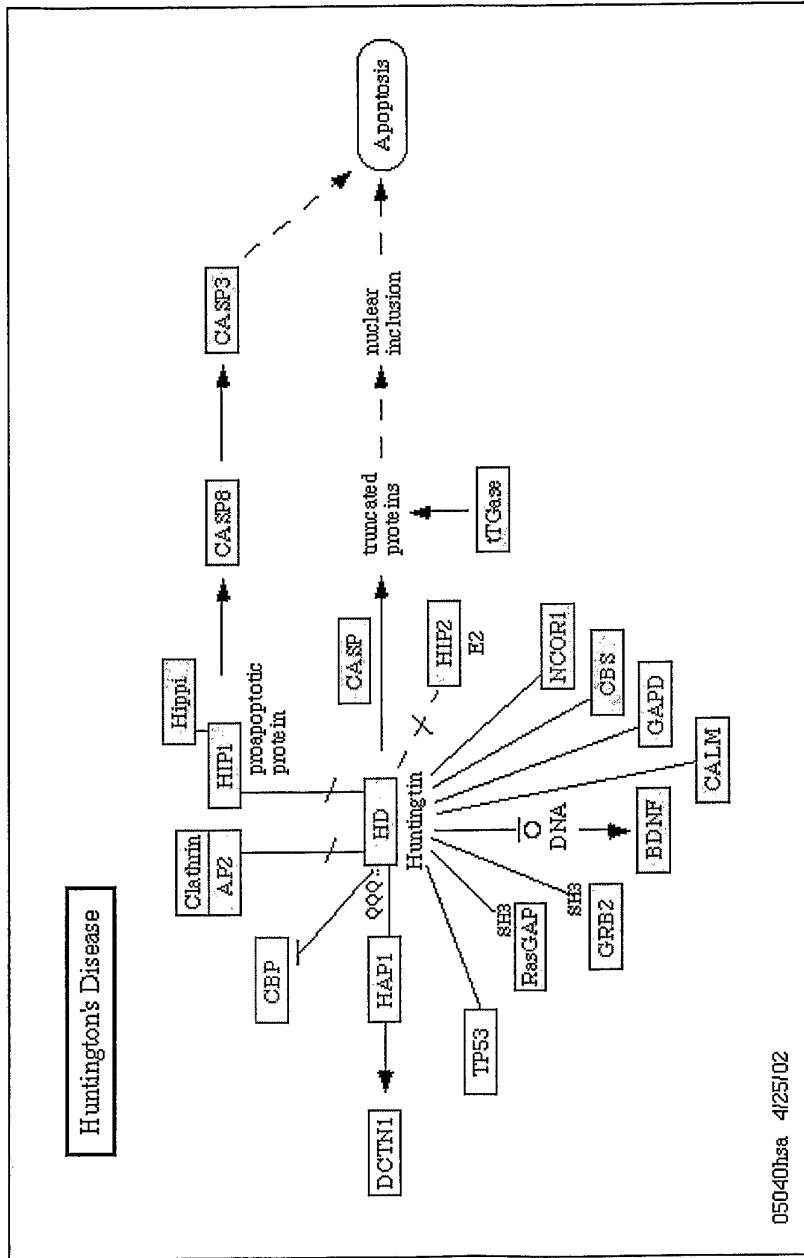


FIG. 4A

hsa00251 Glutamate metabolism 2572 GAD2; glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa) [EC:4.1.1.15] [SP:DCE2_HUMAN] 2875 GPT; glutamic-pyruvate transaminase (alanine aminotransferase) [EC:2.6.1.2] [SP:ALAT1_HUMAN]

hsa00252 Alanine and aspartate metabolism 2572 GAD2; glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa) [EC:4.1.1.15] [SP:DCE2_HUMAN] 2875 GPT; glutamic-pyruvate transaminase (alanine aminotransferase) [EC:2.6.1.2] [SP:ALAT1_HUMAN]

hsa00430 Taurine and hypotaurine metabolism 2572 GAD2; glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa) [EC:4.1.1.15] [SP:DCE2_HUMAN] 2678 GGT1; gamma-glutamyltransferase 1 [EC:2.3.2.2]

hsa00500 Starch and sucrose metabolism 2645 GCK; glucokinase (hexokinase 4, maturity onset diabetes of the young 2) [EC:2.7.1.2] [SP:H XK4_HUMAN] 5167 ENPP1; ectonucleotide pyrophosphatase/phosphodiesterase 1 [EC:3.1.4.1 3.6.1.9] [SP:ENPP1_HUMAN]

hsa00770 Pantothenate and CoA biosynthesis 23411 SIRT1; sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae) [EC:3.5.1.-] 5167 ENPP1; ectonucleotide pyrophosphatase/phosphodiesterase 1 [EC:3.1.4.1 3.6.1.9] [SP:ENPP1_HUMAN]

FIG. 4B

hsa02010 ABC transporters - General 10060 ABCC9; ATP-binding cassette, sub-family C (CFTR/MRP), member 9 6833 ABCC8; ATP-binding cassette, sub-family C (CFTR/MRP), member 8 [SP:ABCC8_HUMAN]

hsa04140 Regulation of autophagy 3458 IFNG; interferon, gamma [SP:IFNG_HUMAN] 3630 INS; insulin [SP:INS_HUMAN]

hsa04330 Notch signaling pathway 1387 CREBBP, RST5; CREB binding protein (Rubinstein-Taybi syndrome) [EC:2.3.1.48] [SP:CBP_HUMAN] 2033 EP300; E1A binding protein p300 [EC:2.3.1.48] [SP:EP300_HUMAN]

hsa04540 Gap junction 1950 EGF; epidermal growth factor (beta-urogastrone) [SP:EGF_HUMAN] 5566 PRKACA; protein kinase, cAMP-dependent, catalytic, alpha [EC:2.7.11.11] [SP:KAPCA_HUMAN]

hsa04742 Taste transduction 2784 GNB3; guanine nucleotide binding protein (G protein), beta polypeptide 3 [SP:GGB3_HUMAN] 5566 PRKACA; protein kinase, cAMP-dependent, catalytic, alpha [EC:2.7.11.11] [SP:KAPCA_HUMAN]

hsa05010 Alzheimer's disease 348 APOE; apolipoprotein E [SP:APOE_HUMAN] 4023 LPL; lipoprotein lipase [EC:3.1.1.34] [SP:LPL_HUMAN]

hsa05050 Dentatorubro pallidoluysian atrophy (DRPLA) 3630 INS; insulin [SP:INS_HUMAN] 3643 INSR; insulin receptor [EC:2.7.10.1] [SP:INSR_HUMAN]

FIG. 4C

hsa00010 Glycolysis / Gluconeogenesis 2645 GCK; glucokinase (hexokinase 4, maturity onset diabetes of the young 2) [EC:2.7.1.2] [SP:H XK4_HUMAN]

hsa00020 Citrate cycle (TCA cycle) 5105 PCK1; phosphoenolpyruvate carboxykinase 1 (soluble) [EC:4.1.1.32] [SP:PPCKC_HUMAN]

hsa00052 Galactose metabolism 2645 GCK; glucokinase (hexokinase 4, maturity onset diabetes of the young 2) [EC:2.7.1.2] [SP:H XK4_HUMAN]

hsa00071 Fatty acid metabolism 1374 CPT1A; carnitine palmitoyltransferase 1A (liver) [EC:2.3.1.21] [SP:CPT1A_HUMAN]

hsa00140 C21-Steroid hormone metabolism 3290 HSD11B1, HSD11B, HSD11; hydroxysteroid (11-beta) dehydrogenase 1 [EC:1.1.1.146] [SP:DHI1_HUMAN]

hsa00150 Androgen and estrogen metabolism 3290 HSD11B1, HSD11B, HSD11; hydroxysteroid (11-beta) dehydrogenase 1 [EC:1.1.1.146] [SP:DHI1_HUMAN]

hsa00230 Purine metabolism 5167 ENPP1; ectonucleotide pyrophosphatase/phosphodiesterase 1 [EC:3.1.4.1 3.6.1.9] [SP:ENPP1_HUMAN]

hsa00240 Pyrimidine metabolism 10587 TXNRD2; thioredoxin reductase 2 [EC:1.8.1.9]

hsa00330 Arginine and proline metabolism 4843 NOS2A, NOS2; nitric oxide synthase 2A (inducible, hepatocytes) [EC:1.14.13.39] [SP:NOS2A_HUMAN]

FIG. 4D

hsa00361 gamma-Hexachlorocyclohexane degradation 5444 PON1, PON;
 paraoxonase 1 [EC:3.1.1.2 3.1.8.1] [SP:PON1_HUMAN]
hsa00363 Bisphenol A degradation 5444 PON1, PON; paraoxonase 1 [EC:3.1.1.2
 3.1.8.1] [SP:PON1_HUMAN]
hsa00380 Tryptophan metabolism 121278 TPH2; tryptophan hydroxylase 2
 [EC:1.14.16.4]
hsa00410 beta-Alanine metabolism 2572 GAD2; glutamate decarboxylase 2
 (pancreatic islets and brain, 65kDa) [EC:4.1.1.15] [SP:DCE2_HUMAN]
hsa00450 Selenoamino acid metabolism 2678 GGT1; gamma-glutamyltransferase 1
 [EC:2.3.2.2]
hsa00460 Cyanoamino acid metabolism 2678 GGT1; gamma-glutamyltransferase 1
 [EC:2.3.2.2]
hsa00480 Glutathione metabolism 2678 GGT1; gamma-glutamyltransferase 1
 [EC:2.3.2.2]
hsa00521 Streptomycin biosynthesis 2645 GCK; glucokinase (hexokinase 4, maturity
 onset diabetes of the young 2) [EC:2.7.1.2] [SP:HKK4_HUMAN]
hsa00561 Glycerolipid metabolism 4023 LPL; lipoprotein lipase [EC:3.1.1.34]
 [SP:LIPL_HUMAN]

FIG. 4E

hsa00564 Glycerophospholipid metabolism 26279 PLA2G2D; phospholipase A2, group IID [EC:3.1.1.4] [SP:PA2GD_HUMAN]
hsa00565 Ether lipid metabolism 26279 PLA2G2D; phospholipase A2, group IID [EC:3.1.1.4] [SP:PA2GD_HUMAN]
hsa00591 Linoleic acid metabolism 26279 PLA2G2D; phospholipase A2, group IID [EC:3.1.1.4] [SP:PA2GD_HUMAN]
hsa00620 Pyruvate metabolism 5105 PCK1; phosphoenolpyruvate carboxykinase 1 (soluble) [EC:4.1.1.32] [SP:PPCKC_HUMAN]
hsa00650 Butanoate metabolism 2572 GAD2; glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa) [EC:4.1.1.15] [SP:DCE2_HUMAN]
hsa00710 Carbon fixation 2875 GPT; glutamic-pyruvate transaminase (alanine aminotransferase) [EC:2.6.1.2] [SP:ALAT1_HUMAN]
hsa00740 Riboflavin metabolism 5167 ENPP1; ectonucleotide pyrophosphatase/phosphodiesterase 1 [EC:3.1.4.1 3.6.1.9] [SP:ENPP1_HUMAN]
hsa00860 Porphyrin and chlorophyll metabolism 2495 FTH1; ferritin, heavy polypeptide 1 [EC:1.16.3.1]
hsa00930 Caprolactam degradation 23411 SIRT1; sirtuin (silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) [EC:3.5.1.-]

FIG. 4F

hsa04070 Phosphatidylinositol signaling system 5295 PIK3R1;
phosphoinositide-3-kinase, regulatory subunit 1 (p85 alpha)

hsa04340 Hedgehog signaling pathway 5566 PRKACA; protein kinase, cAMP-dependent, catalytic, alpha [EC:2.7.11.11] [SP:KAPCA_HUMAN]

hsa04360 Axon guidance 1020 CDK5; cyclin-dependent kinase 5
[EC:2.7.11.22] [SP:CDK5_HUMAN]

hsa04740 Olfactory transduction 5566 PRKACA; protein kinase, cAMP-dependent, catalytic, alpha [EC:2.7.11.11] [SP:KAPCA_HUMAN]

hsa05130 Pathogenic Escherichia coli infection - EHEC 929 CD14; CD14 molecule [SP:CD14_HUMAN]

hsa05131 Pathogenic Escherichia coli infection - EPEC 929 CD14; CD14 molecule [SP:CD14_HUMAN]

FIG. 5A

Adiponectin
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	6542665.54	96325.559	6521761235
High Risk	10	808925.86	90892.586	10528669658
T2DM	12	528480.614	44040.051	513491655.7

MMP 2
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	28598.4005	391.75091	1059604.025
High Risk	10	930.098315	93.009832	6643.293837
T2DM	12	894.908141	82.075678	6861.502424

AdipIn
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	35624.8138	508.67197	9377956.613
High Risk	10	2468.33812	246.83381	99229.04139
T2DM	9	1232.27003	136.91689	45182.55514

CD 14
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	71	32496.6878	457.69883	9473555.525
High Risk	10	1205.19913	120.51991	11567.35238
T2DM	12	1027.7561	85.646342	966.8056249

C Peptide
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	58	6306528.2	1087343.5	4.64372E+11
High Risk	8	6201364.14	775170.52	1.90543E+11
T2DM	7	5587223.32	798174.75	1.78902E+11

E-Selectin
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	55.8685624	0.7704322	3.182492264
High Risk	10	5.7862001	0.57862	0.084659411
T2DM	12	6.76816557	0.5655139	0.05894195

Thrombospondin
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	9881.11926	132.61807	5319.722029
High Risk	10	1205.24015	120.52401	1413.926895
T2DM	12	1647.15071	137.25899	4124.898979

CDK5
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	42411.5377	580.97597	248286.9324
High Risk	10	6208.08126	620.80813	422404.8224
T2DM	12	4783.62908	398.63576	30991.42176

TGF beta
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	64	31.240078	0.5785366	0.281546000
High Risk	5	5.84154426	1.1683089	2.115745108
T2DM	7	6.21317849	0.8875969	1.36596359

VEG-F
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	70	6.15025145	0.0877607	0.051856478
High Risk	9	0.52214059	0.0591267	0.004815677
T2DM	12	0.52242148	0.0435351	0.004924717

CD 28
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	443.676898	6.0777657	35.32751052
High Risk	10	51.8528675	5.1852867	11.77991101
T2DM	12	48.7664733	4.0639728	8.067917962

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	21463253871	2	10731626935	1.732198	0.182614	3.095433
Within Groups	5.66976E+11	92	6195380649			
Total	5.91438E+11	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1570312.26	2	785156.13	0.946131	0.391985	3.095433
Within Groups	76347075.99	92	829859.5216			
Total	77917398.25	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1536559.720	2	769279.8632	0.066363	0.608239	3.100059
Within Groups	702590151.7	88	7983978.995			
Total	704126711.4	90				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2137668.004	2	1068834.002	0.145033	0.865196	3.097898
Within Groups	663263627.8	90	7369595.865			
Total	665401295.8	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.0449E+12	2	5.42442E+11	1.314947	0.276039	3.127676
Within Groups	2.88764E+13	70	4.1252E+11			
Total	2.99613E+13	72				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.738194311	2	0.369097155	0.147402	0.863315	3.095433
Within Groups	230.3697365	92	2.504016896			
Total	231.1079328	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1677.186905	2	838.5934525	0.166734	0.646669	3.095433
Within Groups	462716.9359	92	5029.531912			
Total	464394.1228	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	380889.7678	2	190444.8839	0.785732	0.454332	3.095433
Within Groups	22019208.08	92	239339.2291			
Total	22400108.84	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.011792731	2	1.005896365	2.006363	0.142935	3.142809
Within Groups	31.58020607	63	0.501273112			
Total	33.5919988	65				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.021343265	2	0.010671633	0.265931	0.774847	3.100059
Within Groups	3.67079425	88	0.041713571			
Total	3.692137515	90				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	45.32878467	2	22.66439234	0.741944	0.479016	3.095433
Within Groups	2910.353354	92	30.547131905			
Total	2955.682138	94				

FIG. 5B

CD40 Ligand
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	68	60.6622740	0.7434153	2.353579305
High Risk	9	8.58173461	0.9446372	1.499309324
T2DM	12	3.13483416	0.2512362	0.014717775

ICAM
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	557951.274	7643.1581	139217124.2
High Risk	10	52895.3846	5289.5385	6271426.29
T2DM	12	150355.923	12529.66	122402684.8

MCP-1
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	12.7041862	0.17403	0.088662761
High Risk	10	1.92994663	0.1929947	0.023107361
T2DM	12	1.50720988	0.1256008	0.005167069

TNFR1
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	90.7521704	0.4212826	0.030240623
High Risk	10	4.69888064	0.4698881	0.05832765
T2DM	12	5.6748668	0.4729056	0.032639912

TNF-alpha
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	54	10.6547721	0.1973106	0.31546984
High Risk	8	0.2739026	0.0342378	0.004745034
T2DM	9	0.03629266	0.0040326	9.35754E-05

CRP
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	4618.08479	63.231435	69392.64377
High Risk	10	212.833463	21.283346	885.1046514
T2DM	12	188.815571	15.734631	656.4205998

WAF
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	169146.408	2317.0741	796967.658
High Risk	10	23139.915	2313.9915	1352809.317
T2DM	12	27707.8274	2308.9856	655249.1815

Fcγh1 A
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	7593722.5	120297.6	9.41046E+11
High Risk	10	6690876.12	669087.61	7.06018E+11
T2DM	12	12709657.4	1059153.9	7.41438E+11

IL6sol R
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	68.3474016	0.9362658	0.782554963
High Risk	10	7.56039142	0.7560391	0.440052771
T2DM	12	5.14767605	0.428973	0.091608452

Comp C3
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	73	712273662	9757173.3	2.89352E+14
High Risk	10	67046057.2	6704605.7	6.71795E+13
T2DM	12	64653460.3	5412788.4	4.23251E+13

MCSF
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	70	4.63562262	0.0663232	0.000943854
High Risk	9	0.57422266	0.0638026	0.000221964
T2DM	11	0.65819923	0.0598272	0.000142492

EGF
SUMMARY

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.088581949	2	1.534290975	0.776874	0.463041	3.102552
Within Groups	160.8461851	86	1.874655641			
Total	172.9147671	88				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	330052496.2	2	165026248.1	1.329749	0.26958	3.095433
Within Groups	11417505309	92	124103318.6			
Total	11747557805	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.030123163	2	0.015061584	0.207798	0.812751	3.065433
Within Groups	6.868322797	92	0.07248177			
Total	6.898445965	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.0427172821	2	0.02135861	0.6426	0.528267	3.095433
Within Groups	3.091857743	92	0.033281082			
Total	3.104630563	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.416436171	2	0.208218085	0.849202	0.432242	3.131672
Within Groups	16.75316062	69	0.2416370308			
Total	17.17161659	70				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	34409.18655	2	17204.09327	0.315819	0.729979	3.095433
Within Groups	5011658.62	92	54474.54913			
Total	5046066.706	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	708.2906181	2	354.145309	0.00043	0.99957	3.095433
Within Groups	75836699.03	92	824007.4895			
Total	75809997.32	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.19249E+12	2	5.96247E+11	0.666803	0.51581	3.095433
Within Groups	8.22652E+13	92	8.94187E+11			
Total	8.34577E+13	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.75771922	2	1.37885961	2.069043	0.132144	3.095433
Within Groups	61.3110054	92	0.656423972			
Total	64.06872462	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.47746E+14	2	1.23873E+14	0.519782	0.656356	3.065433
Within Groups	2.19252E+16	92	2.38317E+14			
Total	2.21729E+16	94				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.000396676	2	0.000198337	0.25264	0.777393	3.101296
Within Groups	0.068327226	87	0.00078537			
Total	0.0687239	89				

ANOVA

FIG. 5C

Groups	Count	Sum	Average	Variance
Low Risk	72	12.6940361	0.1763061	0.023769094
High Risk	10	1.67682459	0.1676825	0.020557532
T2DM	11	1.98168695	0.1801534	0.033131163

Betacellulin

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	10	0.50122079	0.0501221	0.014374195
High Risk	3	0.09379773	0.0312659	0.002264183
T2DM	3	0.02187234	0.0072903	1.0489E-05

FAS

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	99.8700145	1.3870835	0.08979971
High Risk	10	14.8815121	1.4881512	0.275535159
T2DM	11	17.2362316	1.5669301	0.076675824

RAGE

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	0.89968022	0.0124956	5.72843E-05
High Risk	10	0.14755707	0.0147557	6.68198E-05
T2DM	11	0.13777404	0.0125249	0.000105594

LEPTIN

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	331.357709	4.6021904	66.32520979
High Risk	10	86.9143631	8.6914363	102.0044553
T2DM	11	73.5949725	6.690452	44.13606452

AgRP

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	62	1.21625255	0.0196008	0.000705036
High Risk	8	0.07956911	0.0099461	2.86373E-05
T2DM	10	0.1045932	0.0104599	8.98104E-05

ILGFBP3

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	1359.60915	18.699571	22.88739922
High Risk	10	182.890594	18.289059	29.12214859
T2DM	11	172.725089	15.702281	6.585759577

Resistin

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	1431.43619	19.881056	91.34763269
High Risk	10	194.100243	19.410024	102.8132046
T2DM	11	232.583922	21.143593	99.42608118

IL1RA

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	63	33.843918	0.537205	3.715229918
High Risk	10	2.01804762	0.2018048	0.010442467
T2DM	11	2.22948169	0.2026783	0.01217806

IL6

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	0.1085509	0.0015077	6.87579E-06
High Risk	10	0.02705513	0.0027056	8.4704E-06
T2DM	11	0.02321809	0.0021107	3.22869E-06

IL1b

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	68	728.586007	10.7145	70.82159067
High Risk	10	129.897417	12.989742	95.87878545
T2DM	10	106.389466	10.638949	15.47093721

CD40 Soluble

SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	57	0.55702437	0.0097724	0.000721440

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.003885746	2	0.001942873	0.016085	0.982081	3.097698
Within Groups	2.20393512	90	0.024488168			
Total	2.204820866	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.00442972	2	0.00221486	0.215008	0.809347	3.805555
Within Groups	0.133917095	13	0.010301315			
Total	0.138346815	15				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.35915304	2	0.17957652	1.679619	0.192236	3.097698
Within Groups	9.622354059	90	0.106915045			
Total	9.981507109	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	4.54414E-05	2	2.27207E-05	0.357212	0.700611	3.097698
Within Groups	0.005724501	90	6.36056E-05			
Total	0.005769942	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	171.3334076	2	85.6667038	1.241448	0.293866	3.097698
Within Groups	6210.490636	90	69.00545153			
Total	6381.824046	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.001225764	2	0.000612882	1.072104	0.347341	3.115366
Within Groups	0.044018039	77	0.000571663			
Total	0.045243803	79				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	95.95606023	2	47.97754012	2.210979	0.115512	3.097698
Within Groups	1952.971568	90	21.69968408			
Total	2048.926548	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	18.85723729	2	9.428618644	0.100957	0.904074	3.097698
Within Groups	8405.281574	90	93.38201749			
Total	8424.138812	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.786943134	2	0.883471567	0.31038	0.734036	3.109311
Within Groups	230.55996977	81	2.846419725			
Total	232.32691318	83				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.46265E-05	2	7.31326E-06	1.103052	0.336301	3.097698
Within Groups	0.000596702	90	6.63002E-05			
Total	0.000911328	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	46.33892341	2	23.16946171	0.342672	0.710847	3.103839
Within Groups	5747.194079	85	67.61404793			
Total	5793.533007	87				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.000756818	2	0.000378409	0.671542	0.514091	3.123807

FIG. 5D

High Risk	9	0.02809166	0.0031213	1.6634E-05
T2DM	9	0.01481475	0.0016461	3.36272E-06

AKT1
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	33	18.3035467	0.5546529	4.385196821
High Risk	5	0.96889016	0.193378	0.120485378
T2DM	3	0.05190269	0.0173009	7.1763E-05

IL-8
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	53	25.1476338	0.4744837	0.850037547
High Risk	9	7.20869006	0.8006956	5.197743533
T2DM	10	1.10225678	0.1102257	0.045288416

activin A
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	59	32.8673262	0.5566781	1.442015651
High Risk	7	0.85091747	0.1215596	0.004849452
T2DM	9	1.8729777	0.2192197	0.098988285

ACE
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	17876.866	248.28896	30281.09223
High Risk	10	2393.00582	239.30058	21884.08962
T2DM	11	3793.60834	344.87349	40837.5526

MMF-9
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	24407821.8	338997.53	47692562804
High Risk	10	2957417.87	295741.79	48693007870
T2DM	11	4237594.34	385235.85	29134980725

IL-10
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	60	1.1944029	0.0199087	0.007257846
High Risk	9	0.04930808	0.0054789	2.4724E-05
T2DM	11	0.03950812	0.0035807	3.69062E-06

VCAM
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	67304.4481	934.78387	195153.4261
High Risk	10	7139.86228	713.98623	148428.2392
T2DM	11	9329.29215	848.11745	209209.0399

INF-gamma
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	1.98999756	0.0276384	5.13101E-05
High Risk	10	0.26601604	0.0266016	4.882E-06
T2DM	11	0.29716724	0.0270152	3.31148E-06

HGF
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	21.4838351	0.298388	0.397671716
High Risk	10	2.72221033	0.272221	0.020928655
T2DM	11	2.67441317	0.2431295	0.01191666

FAS-Lg
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	12.7821734	0.1775302	0.003134941
High Risk	10	1.98251004	0.198251	0.001692512
T2DM	11	2.05900538	0.1869999	0.005045394

NGF
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	259.590874	3.6054288	405.1253301
High Risk	10	43.9273288	4.3927329	58.03994386
T2DM	11	8.20710167	0.7461002	1.490273146

Within Groups	0.040560788	72	0.000563344
Total	0.041317406	74	

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.233823097	2	0.616911548	0.165486	0.847249	3.244815
Within Groups	140.8084233	38	3.705484824			
Total	142.042233	40				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2.279264359	2	1.13963218	0.912324	0.408379	3.129644
Within Groups	86.19158645	69	1.249153427			
Total	88.47085081	71				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.946776456	2	0.973388228	0.832506	0.439159	3.125764
Within Groups	93.01509521	71	1.169226693			
Total	94.96187166	73				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	93250.46471	2	46625.23236	1.522937	0.223636	3.097698
Within Groups	2755379.971	90	30615.33301			
Total	2848630.435	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	73795084391	2	36897532195	0.807021	0.449987	3.097698
Within Groups	4.11486E+12	90	45720662478			
Total	4.18865E+12	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.003732071	2	0.001866036	0.335371	0.716112	3.115366
Within Groups	0.428435706	77	0.0055641			
Total	0.432167776	79				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	98320.53327	2	49160.26564	0.251185	0.778421	3.097698
Within Groups	17255638.33	90	191731.537			
Total	17352158.87	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.36459E-05	2	6.82295E-06	0.14793	0.862701	3.097698
Within Groups	0.004151013	90	4.61224E-05			
Total	0.004164659	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.03193246	2	0.01596623	0.051629	0.949709	3.097698
Within Groups	27.83221625	90	0.309246847			
Total	27.8641487	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.004193302	2	0.002096651	0.654597	0.522108	3.097698
Within Groups	0.286266725	90	0.003202964			
Total	0.290460027	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	90.1633857	2	45.07669285	0.138079	0.871214	3.097698
Within Groups	29381.10666	90	326.4567407			

FIG. 5E

IL18
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	18.6022506	0.2583646	0.018316361
High Risk	10	4.02510087	0.4025101	0.018740797
T2DM	11	3.86927781	0.3516616	0.026416589

Fibrinogen
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	1433743293	19913101	2.66421E+15
High Risk	9	139702020	15522447	1.57528E+14
T2DM	11	164372209	14942928	6.16979E+13

Comp C4
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	60315521.1	837715.57	1.03588E+12
High Risk	10	10257949.7	1025795	7.4479E+11
T2DM	11	16149482	1468134.7	9.81511E+11

PAI-1
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	10710.4567	148.75634	9838.151053
High Risk	10	1995.50152	199.55015	11810.75339
T2DM	11	2039.16962	185.37906	6962.53664

Haptoglobin
SUMMARY

Groups	Count	Sum	Average	Variance
Low Risk	72	381781883	5024748.4	3.4984E+13
High Risk	10	70463933.5	7046393.4	3.86077E+13
T2DM	11	48270115.5	4388192.3	1.10864E+13

Total	29471.26005	92
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ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	0.239046784	2	0.119023392	6.180198	0.003055	3.097698
Within Groups	1.733294714	90	0.01925883			
Total	1.971341499	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.48902E+14	2	1.74401E+14	0.08126	0.922031	3.097698
Within Groups	1.91036E+17	89	2.14647E+15			
Total	1.91385E+17	91				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.88984E+12	2	1.94492E+12	1.943507	0.149164	3.097698
Within Groups	9.00655E+13	90	1.00073E+12			
Total	9.39554E+13	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	31633.83714	2	15916.91857	1.627942	0.202061	3.097698
Within Groups	874430.8717	90	9715.698574			
Total	906064.7088	92				

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	4.34501E+13	2	2.17251E+13	0.664555	0.517008	3.097698
Within Groups	2.9422E+15	90	3.26911E+13			
Total	2.98565E+15	92				

FIG. 6

INDIVIDUAL MARKER PERFORMANCE AT CLINICAL CUTOFFS

LEPTIN Diagnosis	Pre-Diabetes		Total
	Pre-Diabetes	Normal	
Pre-Diabetes	7	29	36
Normal	1	48	49
Total	8	77	85

Prevalence	
Population	-
Sample	0.094117647

	95% CI	
	Sensitivity	87.5%
Specificity	62.3%	50.6% to 73.1%

Positive predictive value	19.4%
Negative predictive value	98.0%
Efficiency	94.7%

HAPTOGLOBIN Diagnosis	Pre-Diabetes		Total
	Pre-Diabetes	Normal	
Pre-Diabetes	5	45	50
Normal	3	32	35
Total	8	77	85

Prevalence	
Population	-
Sample	0.094117647

	95% CI	
	Sensitivity	62.5%
Specificity	41.6%	30.4% to 53.4%

Positive predictive value	10.0%
Negative predictive value	91.4%
Efficiency	43.5%

COMBINED MARKER PERFORMANCE USING EITHER MARKER CUTOFF AS A POSITIVE DIAGNOSIS

Either Marker Above Cutoff	Pre-Diabetes		Total
	Pre-Diabetes	Normal	
Pre-Diabetes	7	58	65
Normal	1	19	20
Total	8	77	85

Prevalence	
Population	-
Sample	0.094117647

	95% CI	
	Sensitivity	87.5%
Specificity	24.7%	15.6% to 35.8%

Positive predictive value	10.8%
Negative predictive value	95.0%
Efficiency	30.6%

COMBINED MARKER PERFORMANCE USING MATHEMATICAL ALGORITHM (LOGISTIC REGRESSION)

Logistic Regression Model	Pre-Diabetes		Total
	Pre-Diabetes	Normal	
Pre-Diabetes	7	25	32
Normal	1	52	53
Total	8	77	85

Prevalence	
Population	-
Sample	0.094117647

	95% CI	
	Sensitivity	87.5%
Specificity	67.9%	55.9% to 77.8%

Positive predictive value	21.9%
Negative predictive value	98.1%
Efficiency	69.4%

COMBINED MARKER PERFORMANCE VERSUS INDIVIDUAL MARKERS - ROC CURVE ANALYSIS USING MATHEMATICAL ALGORITHM (LOGISTIC REGRESSION)

Curve	Area	SE	p	95% CI of Area	Pre-Diabetes = Pre-Diabetes
HAPTOGLOBIN	0.613	0.1173	0.1666	0.384 to 0.843	have higher values
LEP	0.736	0.0685	<0.0001	0.952 to 0.921	have higher values
ZMod_1	0.794	0.0790	<0.0001	0.940 to 0.949	have higher values

Contrast	Difference	p
HAPTOGLOBIN v LEP	-0.173	-
HAPTOGLOBIN v ZMod_1	-0.181	0.1093
LEP v ZMod_1	-0.008	-

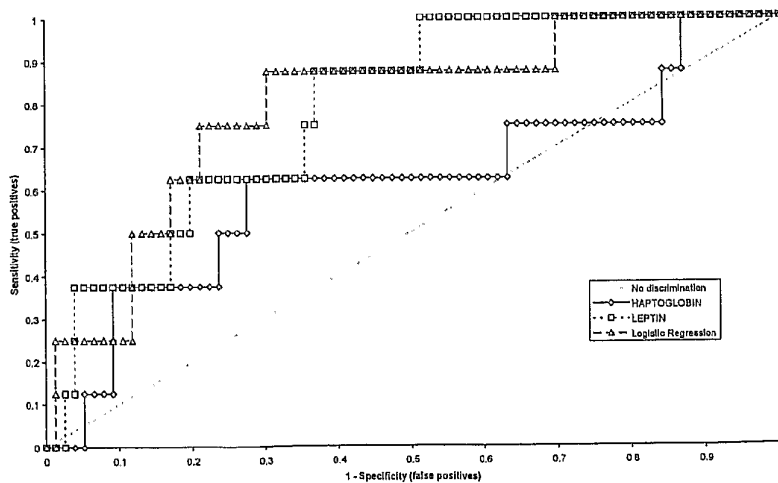


FIG. 7

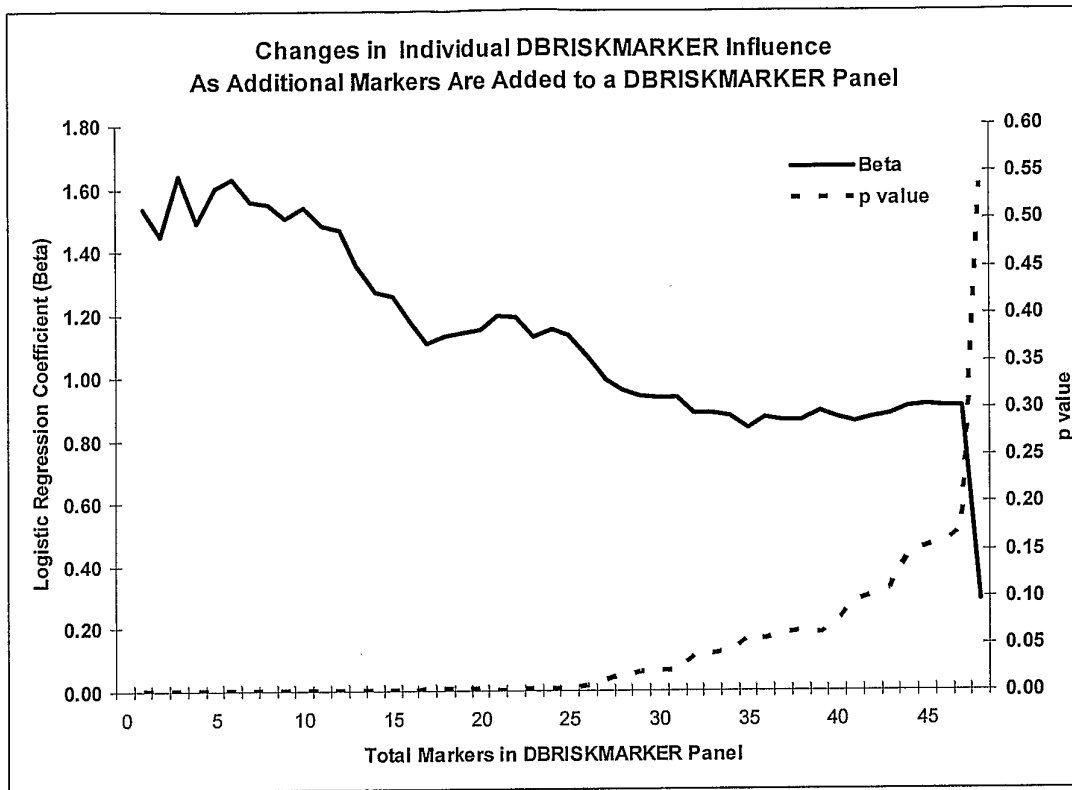


FIG. 8

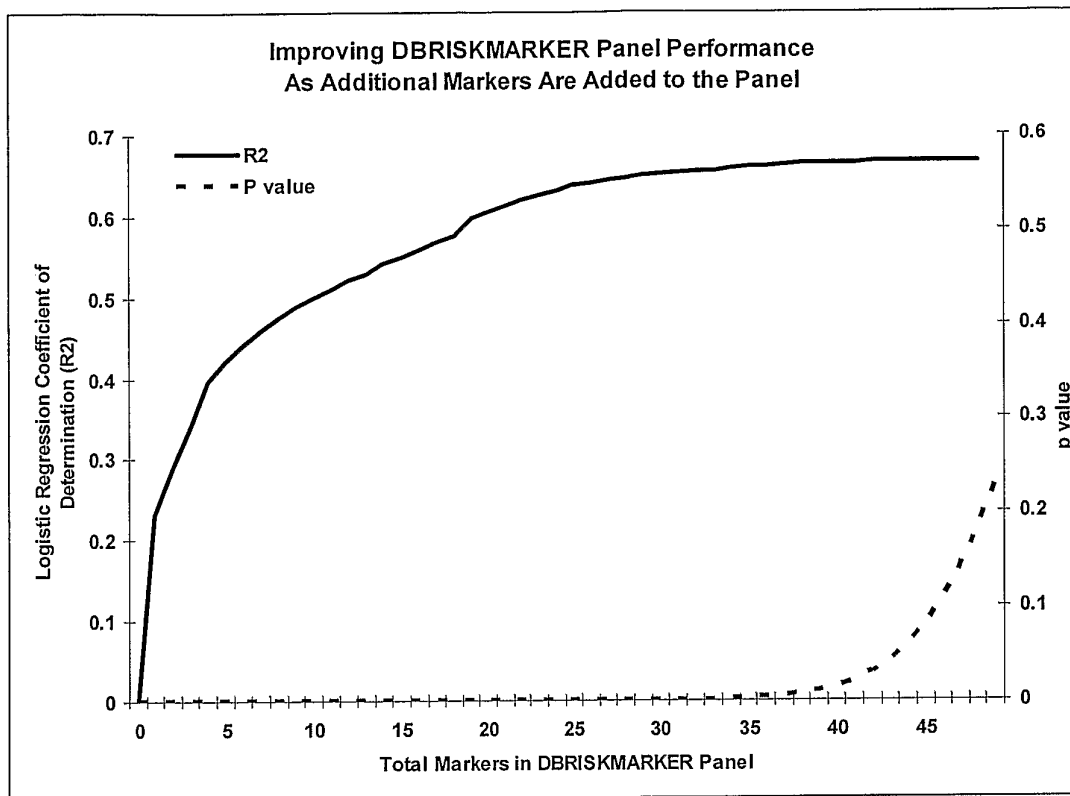


FIG. 9

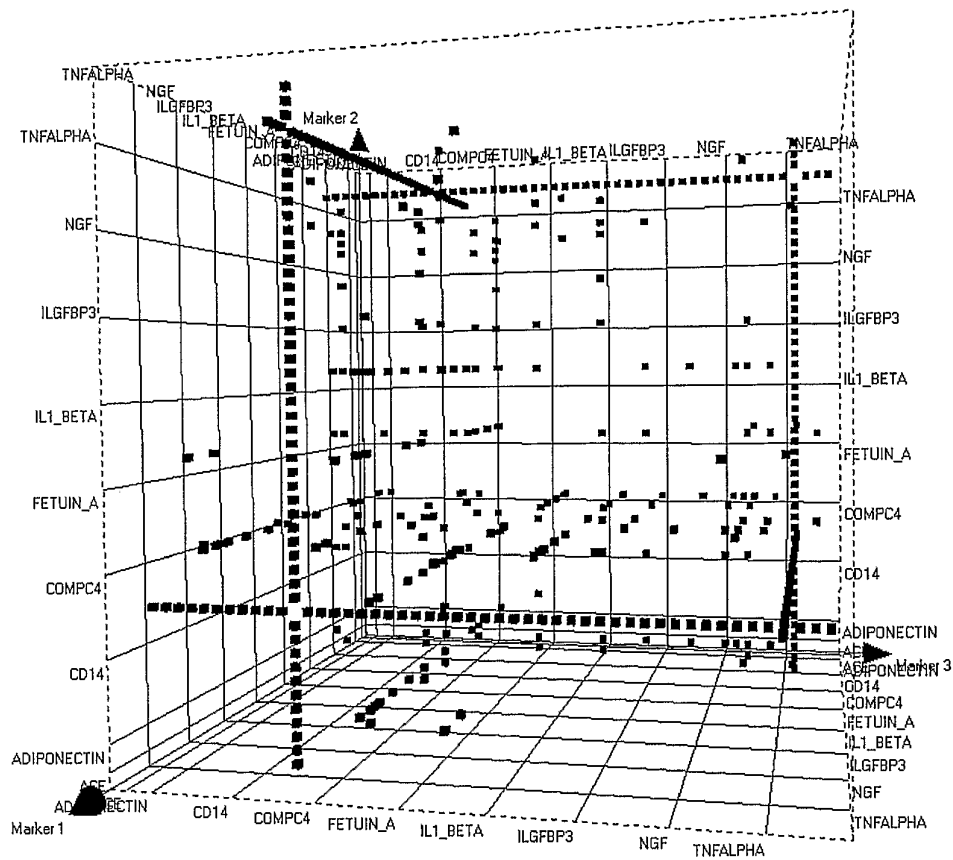


FIG. 10

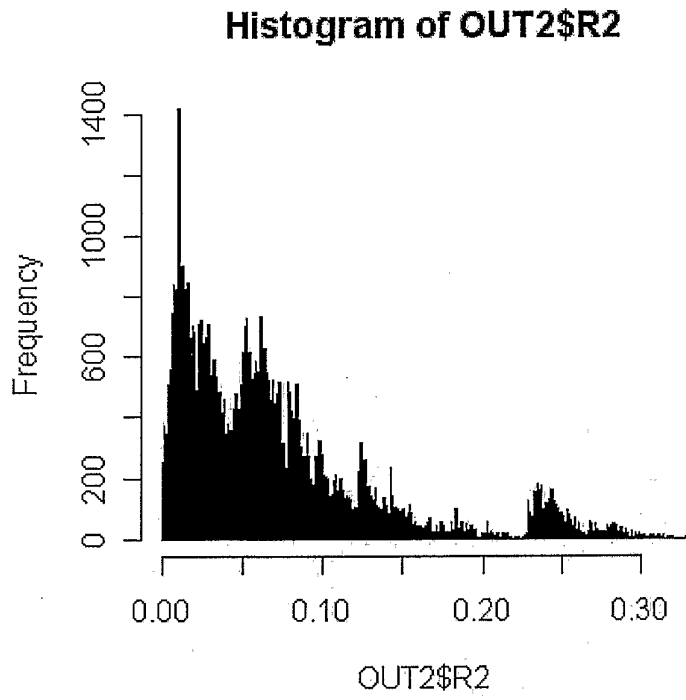


FIG. 11

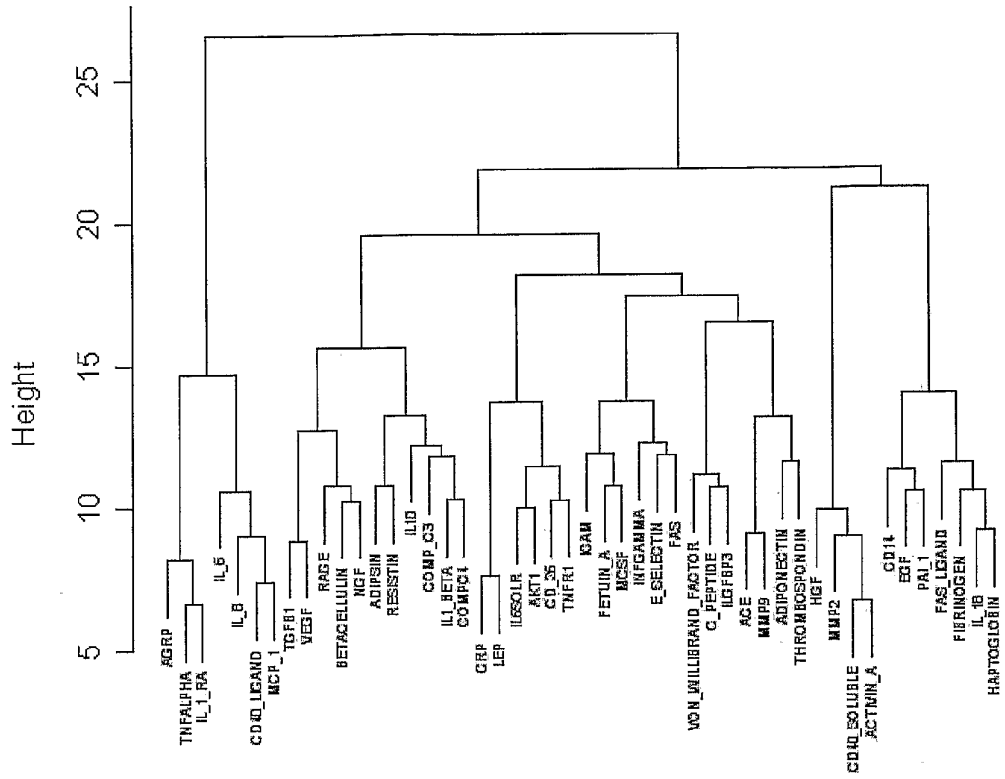


FIG. 12

KEY INDIVIDUAL MARKERS

Marker Position	1	2	3	4	5	6	7	8
Core Marker	LEPTIN	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
Frequently Combined With	HAPTOGLOBIN ILGFBP3 CD26 RAGE ADIPONECTIN	LEP ILGFBP3 TNFR1 ADIPONECTIN CRP ADIPSIN	LEP HAPTOGLOBIN RESISTIN TNFR1 CRP	LEP HAPTOGLOBIN TNFR1 CD26 CRP RAGE	LEP HAPTOGLOBIN RESISTIN TNFR1 CD26 IL18 ADIPSIN PAL1 CRP	LEP HAPTOGLOBIN RESISTIN TNFR1 CD26 PAL1 IL18 ADIPSIN CRP	LEP HAPTOGLOBIN TNFR1 CD26 RAGE IL18 ADIPONECTIN CRP	LEP CRP HAPTOGLOBIN TNFR1 CD26 RAGE IL18 ADIPONECTIN
Key Marker Substitution Strategies	CRP TNFR1 CD26 ILSSOLR ADIPSIN CD40_LIGAND	IL18 TNFR1 CD26 RAGE FETUIN_A ADIPONECTIN HGF	ADIPSIN TNFR1 CD26 E_SELECTIN ICAM CD40_LIGAND RAGE C_PEPTIDE ADIPONECTIN VEGF	MCSF TNFR1 CD26 ADIPSIN ACTIVIN_A INFGAMMA	E_SELECTIN MCSF FIBRINOGEN	CD26 E_SELECTIN FIBRINOGEN	E_SELECTIN VEGF MCSF ACTIVIN_A C_PEPTIDE ICAM	E_SELECTIN MCSF CD26 ICAM FAS CD40_SOLUBLE

KEY COMBINATION MARKERS

Marker Position	9	10	11	12	13	14	15	16
Substitution Marker	E_SELECTIN	MCSF	VEGF	TNFR1	CD_26	FIBRINOGEN	AGRP	TNFALPHA
Alternative Substitution Strategies	ADIPSIN ILSSOLR MMP2	ICAM ADIPSIN ACTIVIN_A	CD40_LIGAND ADIPSIN INFGAMMA	ICAM ACTIVIN_A HGF	HGF ACTIVIN_A ICAM	ACTIVIN_A CD40_LIGAND ICAM	MMP2 INFGAMMA ACTIVIN_A	CD40_LIGAND ADIPSIN IL_8

Marker Position	17	18	19	20
Substitution Marker	MCP_1	TGFB1	COMP_C3	AKT1
Alternative Substitution Strategies	ACTIVIN_A MMP2 IL_6	ICAM C_PEPTIDE ACTIVIN_A	ICAM ADIPSIN MMP2	ACTIVIN_A ADIPSIN ICAM

FIG. 13

	DBRISKMARKER1	DBRISKMARKER2	DBRISKMARKER3
3-Panel 1	LEP	HAPTOGLOBIN	ILGFBP3
3-Panel 2	LEP	TNFR1	CD 26
3-Panel 3	LEP	CD 26	ILGFBP3
3-Panel 4	LEP	HAPTOGLOBIN	C PEPTIDE
3-Panel 5	LEP	HAPTOGLOBIN	ADIPONECTIN
3-Panel 6	LEP	HAPTOGLOBIN	MCSF
3-Panel 7	LEP	RAGE	ILGFBP3
3-Panel 8	LEP	HAPTOGLOBIN	ADIPSIN
3-Panel 9	LEP	RESISTIN	ILGFBP3
3-Panel 10	LEP	HAPTOGLOBIN	RESISTIN
3-Panel 11	LEP	HAPTOGLOBIN	CD 26
3-Panel 12	LEP	HAPTOGLOBIN	COMPC4
3-Panel 13	LEP	HAPTOGLOBIN	MMP2
3-Panel 14	LEP	RAGE	CD 26
3-Panel 15	LEP	HAPTOGLOBIN	ACE
3-Panel 16	LEP	HAPTOGLOBIN	RAGE
3-Panel 17	LEP	ADIPONECTIN	ILGFBP3
3-Panel 18	LEP	HGF	ILGFBP3
3-Panel 19	LEP	HAPTOGLOBIN	ICAM
3-Panel 20	LEP	HAPTOGLOBIN	E SELECTIN
3-Panel 21	LEP	MMP2	ILGFBP3
3-Panel 22	LEP	CD 26	ADIPONECTIN
3-Panel 23	LEP	RAGE	RESISTIN
3-Panel 24	LEP	HAPTOGLOBIN	VEGF
3-Panel 25	LEP	TNFR1	ILGFBP3

FIG. 14

	DBRISKMARKER1	DBRISKMARKER2	DBRISKMARKER3	DBRISKMARKER4	DBRISKMARKER5	DBRISKMARKER6	DBRISKMARKER7	DBRISKMARKER8
8-Panel 1	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 2	CRP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 3	TNFR1	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 4	IL6SOLR	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 5	LEP	IL 18	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 6	LEP	CD 26	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 7	LEP	RAGE	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 8	LEP	HAPTOGLOBIN	ADIPSIN	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 9	LEP	HAPTOGLOBIN	CD 26	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 10	LEP	HAPTOGLOBIN	E SELECTIN	RESISTIN	MMP2	ACE	COMP4	CD14
8-Panel 11	LEP	HAPTOGLOBIN	ILGFBP3	MCSF	MMP2	ACE	COMP4	CD14
8-Panel 12	LEP	HAPTOGLOBIN	ILGFBP3	CD 26	MMP2	ACE	COMP4	CD14
8-Panel 13	LEP	HAPTOGLOBIN	ILGFBP3	ADIPSIN	MMP2	ACE	COMP4	CD14
8-Panel 14	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	E SELECTIN	ACE	COMP4	CD14
8-Panel 15	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MCSF	ACE	COMP4	CD14
8-Panel 16	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	FIBRINOGEN	ACE	COMP4	CD14
8-Panel 17	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	CD 26	COMP4	CD14
8-Panel 18	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	E SELECTIN	COMP4	CD14
8-Panel 19	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	FIBRINOGEN	COMP4	CD14
8-Panel 20	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	E SELECTIN	CD14
8-Panel 21	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	VEGF	CD14
8-Panel 22	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	MCSF	CD14
8-Panel 23	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	E SELECTIN
8-Panel 24	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	MCSF
8-Panel 25	LEP	HAPTOGLOBIN	ILGFBP3	RESISTIN	MMP2	ACE	COMP4	CD 26

FIG. 15

n	80				
<hr/>					
Pre-Diabetes	n				
Normal	61				
Pre-Diabetes	19				
<hr/>					
Curve	Area	SE	p	95% CI of Area	CATEGORY = Pre-Diabetes
3 DBRISKMARKER Panel	0.704	0.0753	0.0033	0.557 to 0.852	have higher values
8 DBRISKMARKER Panel	0.800	0.0535	<0.0001	0.695 to 0.905	have higher values
18 DBRISKMARKER Panel	0.841	0.0554	<0.0001	0.733 to 0.950	have higher values
<hr/>					
Contrast	Difference	p			
3 Panel v 8 Panel	-0.096	0.1151			
3 Panel v 18 Panel	-0.137	0.0461			
8 Panel v 18 Panel	-0.041	0.3098			

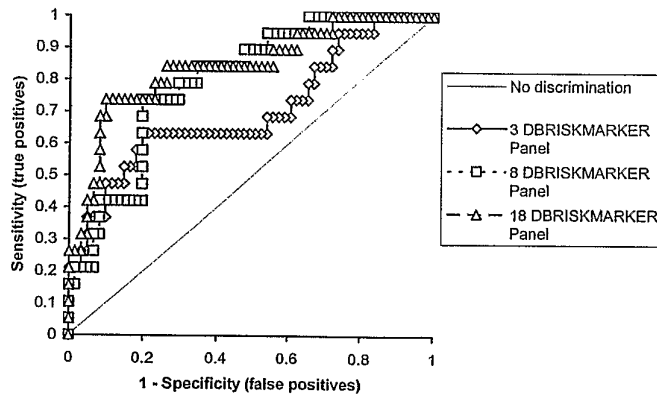


FIG. 16

n | 84 (cases excluded: 1 due to missing values)

CATEGORY	n
Normal	64
Pre-Diabetes	20

Curve	Area	SE	p	95% CI of Area	CATEGORY = Pre-Diabetes
HAPTOGLOBIN	0.612	0.0748	0.0675	0.465 to 0.758	have higher values
ILGFBP3	0.566	0.0795	0.2017	0.411 to 0.722	have higher values
LEP	0.730	0.0671	0.0003	0.599 to 0.862	have higher values

Contrast	Difference	p
HAPTOGLOBIN v ILGFBP3	0.045	-
HAPTOGLOBIN v LEP	-0.119	-
ILGFBP3 v LEP	-0.164	-

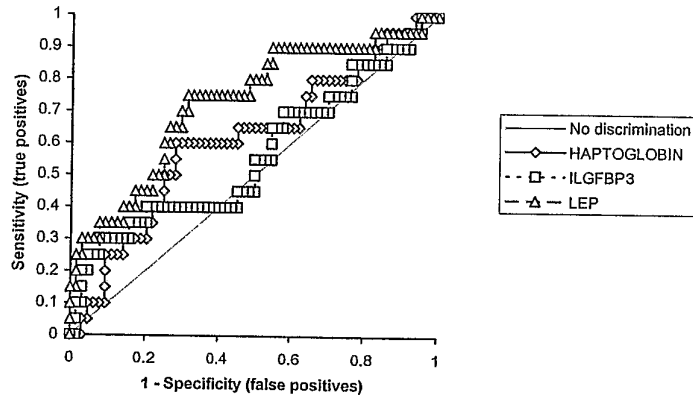


FIG. 17

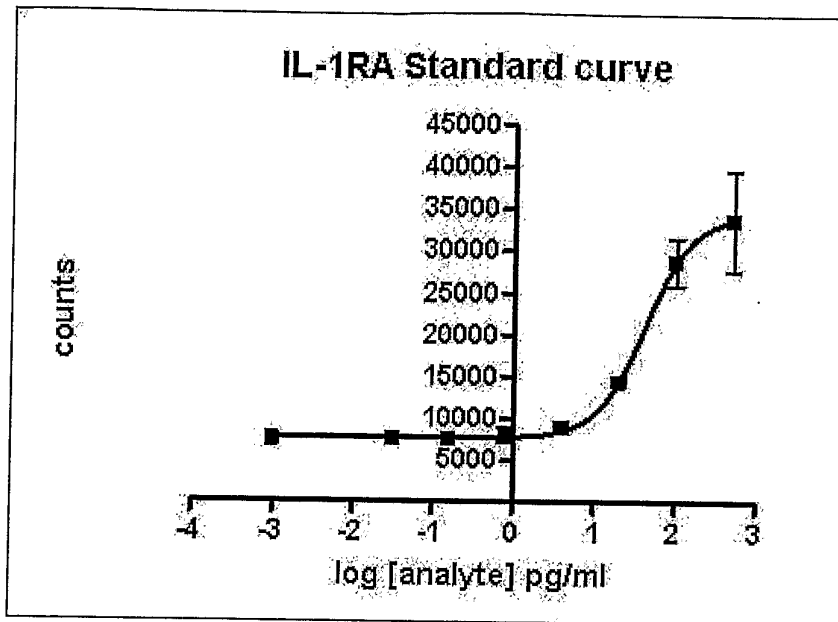


FIG. 1: Standard curve for IL-1 Receptor Agonist

FIG. 18

