Supplementary Material

Omics biomarkers and an approach for their practical implementation to delineate health status for personalized nutrition strategies.

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Supplementary Table 1: Some of biomarkers of health included in the PREVENTOMICS platform

Biomarker	Scientific substantiation	References
IL6 CRP TNFA CCL2 (MCP1)	The adipose tissues of obese individuals contain an increased number of classically activated macrophages (in a pro-inflammatory state). Once activated, these macrophages secrete cytokines such as TNFA and IL6. IL-6 strongly stimulates hepatocytes to produce and release CRP. MCP1 is a potent chemoattractant playing a role in the recruitment of monocytes/macrophages from the blood stream into the adipose tissue. The chronic, low-grade inflammatory state associated with visceral obesity induces insulin resistance in the liver. Uncontrolled inflammation generates high levels of free radical production by the immune cells as part of the immune response.	(Choe et al. 2016; Liu et al. 2016; Skrypnik et al. 2017; Vykoukal and Davies 2011)
soluble ICAM1	Intercellular Adhesion Molecule 1 (ICAM1) is an intercellular adhesion molecule continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Upon cytokine stimulation, the concentrations greatly increase. ICAM1 can be induced by IL1 and TNFA and is expressed by the vascular endothelium, macrophages, and lymphocytes, thereby promoting the vascular adhesion and activation of inflammatory cells. ICAM1 can be cleaved from activated cells and circulates in the bloodstream.	(Sprague and Khalil 2009)
soluble CD14	Soluble Cluster of Differentiation 14 (sCD14) is expressed as an acute phase protein in response to LPS in other tissues and cells, including liver and adipocytes. It has been shown that non-obese participants have lower circulating sCD14 concentrations compared to obese. Circulating sCD14 concentrations have been positively associated with percent body fat, waist circumference and white blood cell count and negatively associated with insulin sensitivity. In contrast, circulating sCD14 has been positively associated with insulin sensitivity in morbidly obese participants.	(de Courten et al. 2016)
N-acetyl-glycoproteins	Glycosylation is one of the most common posttranslational modifications of secreted proteins. Glycoproteins are generally modified by the attachment and processing of a diversity of glycans at each glycosylation site. Several glycosylated markers have been linked to chronic inflammatory diseases, promoting questions about the links between inflammation and cancer.	(Arnold et al. 2008; Harpole, Davis, and Espina 2016)

Acetate	Acetate is an end-product of bacterial fermentation. Its levels can be increased in obesity and in type 2 diabetes (T2D). In morbidly obese subjects, the reletave abundance of *Firmicutes* was negatively correlated with HbA1c and positively associated with plasma acetate levels, indicating that gut microbiota composition is linked to insulin action in morbidly obese subjects, possibly through circulating acetate.	(Gonzalez-Franquesa et al. 2016; Moreno-Navarrete et al. 2017)
Lactate	Lactic acid plays a role in several biochemical processes and is produced in the muscles during intense activity. It is also an end-product of bacterial fermentation and is increased by dysfunction of metabolic tissues. Elevations in lactate have been consistently associated with T2D and obesity. Changes in plasma lactate during an oral glucose tolerance test (OGTT) are inversely correlated with fasting insulin.	(Gonzalez-Franquesa et al. 2016)
TMAO	L-Carnitine and choline, compounds that are found in red meat, are metabolized into TMAs that are oxidized further into trimethylamine N-oxide (TMAO) by the enzyme flavin-containing monooxygenase 3 (FMO3) in the liver. Plasma levels of TMAO are strongly correlated with cardiovascular disease (CVD). Chronic consumption of some foods, such as pistachios, are also able to modulate the urinary levels of TMAO in prediabetic subjects. TMAO is also associated with microbial dysbiosis.	(Chhibber-Goel et al. 2017; Gonzalez-Franquesa et al. 2016; Hernández-Alonso et al. 2017; Sonnenburg and Bäckhed 2016)
TMA	The microbial metabolism of phosphatidylcholine and of L-carnitine produces high levels of trimethylamine (TMA). Once it has been absorbed from the gut into the bloodstream, TMA circulates to the liver and is enzymatically oxidized to TMAO. A number of other diseases are associated with abnormal levels of TMA, including renal disorders, cancer, obesity, diabetes, cardiovascular diseases and neuropsychiatric disorders.	(Chhibber-Goel et al. 2016; Sonnenburg and Bäckhed 2016)
DMA	The urinary levels of the gut microbial metabolite dimethylamine (DMA) changed in subjects with cardiometabolic risk factors in response to the	(Hernández-Alonso et al.

	consumption of soy isoflavones consumption and in pre-diabetic individuals after the intake of pistachios.	2017; Reverri et al. 2017)
Glucose	Fasting plasma glucose level is a traditional biomarker used to assess alterations in carbohydrate metabolism and high levels are associated with risk of diabetes and insulin resistance.	(Aleksandrova, Mozaffarian, and Pischon 2018)
Insulin	High fasting and postprandial plasma insulin levels are considered as an indirect clinical feature of insulin resistance. Hyperinsulinemia is a key element of the metabolic syndrome and is suggested to mediate the association between visceral obesity and dyslipidemia, hypertension, type 2 diabetes, atherosclerosis, and cancer.	(Aleksandrova, Mozaffarian, and Pischon 2018)
HOMA-IR	The most frequently used index to determine insulin resistance based on fasting blood levels of glucose and insulin.	(van der Aa et al. 2017)
Leptin	Leptin and adiponectin are produced by adipose tissue and have opposing effects on insulin sensitivity, subclinical inflammation, endothelial function and atherosclerosis. Elevated levels of leptin contribute to the development of insulin resistance and chronic inflammation whereas adiponectin exerts anti-inflammatory and cardioprotective effects.	(Finucane et al. 2009; López-Jaramillo et al. 2014)
Adiponectin		
α-hydroxybutyrate	α-hydroxybutyrate (α-HB) is an organic acid by-product produced during the synthesis of α-ketobutyrate (α-KB), a product of amino acid metabolism (threonine and methionine) and glutathione anabolism in hepatic tissue. In insulin resistance, increased oxidative stress and lipid oxidation may cause chronic shifts in glutathione synthesis leading to elevated α-HB levels. This is demonstrated by increased urinary α-HB excretion in IR.	(Dorcely et al. 2017)
Succinate	Succinate is a citric acid cycle intermediate. Decreases in urinary fumarate and succinate contribute to the differentiation of patients with T2D from healthy individuals in a principal component analysis.	(Gonzalez-Franquesa et al. 2016)
Total cholesterol	These metabolites are altered in typical dyslipidaemia. Elevated fasting plasma triglycerides, high LDL-cholesterol and low HDL-cholesterol are risk factors for CDV. In obesity, enhanced lipolysis in adipose tissue, elevated plasma free fatty acid (FFA) levels and high levels of lipid metabolites in non-adipose tissues act as metabolic mediators of insulin resistance and inflammation, which, in turn, induce altered lipoprotein metabolism in the liver. The	(Klop, Elte, and Cabezas 2013; Perla et al. 2017; Suárez et al. 2017)
LDL-cholesterol		
HDL-cholesterol		
Triglycerides		

	catabolism of very low-density lipoproteins (VLDLs) is diminished, while the catabolism HDL is increased. Increased accumulation of fat (TC, TG, and other lipid metabolites) in the liver is associated with increased lipotoxicity and represents the primary insult in the pathogenesis of hepatic steatosis.	
PUFAs	PUFAs are fatty acids that contain more than one double bond in their backbone, and they include some subgroups identified by the position of the last double bond in their structure. PUFA n-3 include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), decosahexanoic acid (DHA) and derivatives, while PUFA n-6 linoleic acid (LA), arachidonic acid (AA) and derivatives. PUFA consumption has shown beneficial effects for human health. For example, PUFA n-3 consumption has been shown to be inversely correlated with coronary heart diseases (CHD) incidence.	(Calder 2017; Hammad, Pu, and Jones 2016; Zock et al. 2016)
DHA	DHA is a n-3 fatty acid found in oily fish and fish oil supplements. It is capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte–endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid AA and production of pro-inflammatory cytokines.	(Calder 2017)
LA	LA the predominant n-6 fatty acid. A systematic review and meta-analysis of prospective studies demonstrates that higher intake of LA is associated with a lower CHD risk as compared with saturated fatty acids but also independent of what other nutrients it replaces in the diet. ALA is also the precursor of AA and recent publications have questioned the evidence and rationale for dietary recommendations of this n-6 fatty acid.	(Farvid et al. 2014; Zock et al. 2016)
MUFAs	MUFAs are used as substrates for the synthesis of triglycerides, cholesteryl esters and membrane phospholipids. The saturated to monounsaturated fatty acid ratio affects membrane phospholipid composition and alteration in this ratio has been implicated in a variety of disease states including cardiovascular disease, obesity, and diabetes. Numerous beneficial physiologic effects have been attributed to unsaturated fatty acids, including protection from obesity, diabetes, cancer, and atherosclerosis.	(Hammad, Pu, and Jones 2016; Zock et al. 2016)
Oleic acid	Oleic acid (OA, C18:1n-9) is the predominant dietary MUFA, accounting for up to 92 % of dietary MUFA. Dietary MUFA consumption has been suggested	(Hammad, Pu, and Jones 2016)

	as inducing a 20 % reduction in the risk of CVD events, as evidenced by a large body of prospective cohort studies.	
Acylcarnitine profile	Acylcarnitines are fatty acid and carnitine esters formed in the cytosol to transport fatty acids into the mitochondrial matrix for β-oxidation. Acetylcarnitine is needed for the carnitine-dependent production of energy from different fatty acids and cell membrane structure maintenance. C3 and C5 acylcarnitines have been positive significantly associated with diabetes risk and insulin resistance. The combination of C3 and C5 acylcarnitines, together with branched chain amino acids (BCAAs), methionine, and glutamate/glutamine, was most robust for differentiating lean from obese patients.	(Dorcely et al. 2017; Gonzalez-Franquesa et al. 2016)
Glutamine	Glutamine has been significantly associated with diabetes risk. Glutamine levels are also reduced in insulin resistance. Glycine and glutamine were inversely associated with type 2 diabetes risk.	(Gonzalez-Franquesa et al. 2016; Guasch-Ferré et al. 2016)
Glycine	Glycine and glutamine were inversely associated with T2DM risk. Low glycine is associated with insulin resistance. Glycine levels are decreased in individuals with prediabetes.	(Dorcely et al. 2017; Gonzalez-Franquesa et al. 2016; Guasch-Ferré et al. 2016; Newgard 2017)
Tryptophan	In a Japanese population, alanine, glutamate, tryptophan, tyrosine, and BCAAs were positively correlated with visceral adiposity, while glycine was inversely correlated.	(Gonzalez-Franquesa et al. 2016)
Leucine	Leucine, isoleucine, and valine are BCAAs. High levels of BCAAs have been associated with increased diabetes risk and insulin resistance. Plasma levels of BCAAs also predict risk for developing T2DM in healthy individuals.	(Dorcely et al. 2017; Gannon, Schnuck, and Vaughan 2018; Guasch-Ferré
Isoleucine		
Valine		

		et al. 2016; Newgard 2017)
Phenylalanine	Phenylalanine and tyrosine are aromatic amino acids. High levels of these amino acids have been significantly associated with increased diabetes risk and insulin resistance. Fasting concentrations of these amino acids were already elevated as early as 12 years before the onset of T2DM.	(Dorcely et al. 2017; Gonzalez-Franquesa et al. 2016; Guasch-Ferré et al. 2016; Newgard 2017)
Tyrosine		
Glutamate	The clustering of glutamate/glutamine, C3 and C5 acylcarnitines with BCAAs defined a signature comprising metabolites generated during BCAA catabolism, suggesting fundamental alteration of BCAA metabolism in insulin resistant states. The glutamine-to-glutamate ratio are associated with lower risk of incident diabetes, even after adjustment for body mass index (BMI) and BCAAs. In a Japanese population, glutamate was positively correlated with visceral adiposity.	(Gonzalez-Franquesa et al. 2016; Newgard 2017)
Methionine	Methionine is increased in insulin-resistant states. The combination of C3 and C5 acylcarnitines, together with BCAAs and aromatic amino acids (AAA), methionine, and glutamate/glutamine, was particularly most robust for differentiating lean from obese patients.	(Dorcely et al. 2017; Gonzalez-Franquesa et al. 2016)
Alanine	Blood levels of alanine are elevated in obesity and alanine has also been associated with hyperglycaemia and T2D risk.	(Gonzalez-Franquesa et al. 2016)
Betaine	Plasma levels of the methyl donor betaine are reduced in individuals with insulin resistance. Plasma levels of choline, betaine and TMAO are strongly correlated with CVD.	(Gonzalez-Franquesa et al. 2016)
DMG	Higher baseline levels of urinary alanine, betaine, N,N-dimethylglycine (DMG), creatinine, and trimethylamine were associated with an increase in HbA1c from baseline to follow-up.	(Friedrich et al. 2017)

Choline	Plasma levels of choline, betaine and TMAO are strongly correlated with CVD.	(Gonzalez-Franquesa et al. 2016)
8-OHdG	8-hydroxy-2′-deoxyguanosine (8-OHdG) is a widely-used biomarker of oxidative DNA damages. It is altered in diabetes, hypertension and in patients with CVD.	(Di Minno et al. 2016)
8-iso-PGF2α	F2-isoprostane (8-iso-prostaglandin F2α) is a product of free radical-mediated oxidation of arachidonic acid, mostly in phospholipids. Altered in diabetes, hypercholesterolemia, hypertension and metabolic syndrome.	(Milne, Musiek, and Morrow 2005)
Pseudouridine	It is an isomer of the nucleoside uridine in which the uracil is attached via a carbon-carbon instead of a nitrogen-carbon glycosidic bond. It is the most prevalent of the over one hundred different modified nucleosides found in RNA. It is a marker of RNA damage.	(Zhang and Zhang 2015)

IL6: interleukin6; CRP: C-reactive protein; TNFA: tumor necrosis factor alpha; CCL2/MCP1: monocyte chemoattractant protein 1; LDL: low density lipoproteins; HDL: High density lipoproteins. The other abbreviations used are defined the first time that are mentioned in the table, section "Scientific substantiation".

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Supplementary table 2

References in alphabetical order

1-(Aulchenko et al. 2009); 2-(Comuzzie et al. 2012); 3-(Dastani et al. 2012); 4-(Dorajoo et al. 2015); 5-(Draisma et al. 2015); 6-(Hartiala et al. 2016); 7-(Hoffmann et al. 2018); 8-(Illig et al. 2010); 9-(Imaizumi et al. 2019); 10-(J. H. Y. Wu et al. 2013); 11-(Jerotic et al. 2019); 12-(Kathiresan et al. 2009); 13-(Kettunen et al. 2016); 14-(Kilpeläinen et al. 2016); 15-(Klarin et al. 2018); 16-(Kulminski et al. 2018); 17-(Ligthart et al. 2018); 18-(Ljungman et al. 2009); 19-(Lotta et al. 2016); 20-(Mahajan et al. 2015); 21-(Manning et al. 2012); 22-(Nagy et al. 2017); 23-(Peloso et al. 2014); 24-(Shin et al. 2014); 25-(Spracklen et al. 2017); 26-(Sun et al. 2018); 27-(Tin et al. 2016); 28-(Tintle et al. 2015); 29-(van Meurs et al. 2013); 30-(Wessel et al. 2015)

LIPID

	HDL	SFA	TG	TC	LDL	PUFA	LPCs	LA	OA	Leptin	Adipoq	MUFA	Acylcarnitine	DHA
ADIPOQ (rs182052)											3			
APOA5 (rs12272004)			1	1	1									
APOA5 (rs662799)	25		25											
APOE (rs429358)	15													
APOE (rs7412)	7			7	7									
ASCL1 (rs17450122)														
CADM3 (rs12075)														
COMT (rs4680)														
CPS1 (rs715)														
CUX1 (rs409224)						4								4
FADS1 (rs174547)			12	16		13	5	4						
FADS12 (rs174550)														
FGF21 (rs838133)														
GCKR (rs1260326)			7											
GCKR (rs780093)		10								14				
GLS2 (rs2657879)														
GSTP1 (rs1695)														
HFE (rs1800562)				7	7									
ICAM1 (rs5498)														
IL-6 (rs1800795)														
LEP (rs10487505)										14				
LPL (rs268)	23													
LPL (rs326)	7		7											
MTHFR (rs1801133)														
PNPLA3 (rs738409)				15										
PPARG (rs1801282)														
PPID (rs8396)												8		
SLC16A10 (rs14399)														
SLC16A9 (rs1171614)													5	
SLC2A2 (rs8192675)														
SOD2 (rs4880)														
TCF7L2 (rs7903146)														
TIMP3 (rs12678919)	7		7											
TRIM58 (rs3811444)									28					

CARBOHYDRATES

	Glucose	Val, Leu, Ile	Gln	Phe	Insulin	Tyr	Leptin	Adipoq	Acylcarnitine	Lactate
ADIPOQ (rs182052)								3		
APOA5 (rs12272004)										
APOA5 (rs662799)										
APOE (rs429358)										
APOE (rs7412)										
ASCL1 (rs17450122)				9						
CADM3 (rs12075)										
COMT (rs4680)										
CPS1 (rs715)										
CUX1 (rs409224)										
FADS1 (rs174547)										
FADS12 (rs174550)	30									
FGF21 (rs838133)										
GCKR (rs1260326)	24	19								27
GCKR (rs780093)							14			
GLS2 (rs2657879)			24							
GSTP1 (rs1695)										
HFE (rs1800562)										
ICAM1 (rs5498)										
IL-6 (rs1800795)										
LEP (rs10487505)							14			
LPL (rs268)										
LPL (rs326)										
MTHFR (rs1801133)										
PNPLA3 (rs738409)										
PPARG (rs1801282)					20					
PPID (rs8396)										
SLC16A10 (rs14399)						13				
SLC16A9 (rs1171614)									5	
SLC2A2 (rs8192675)	22									
SOD2 (rs4880)										
TCF7L2 (rs7903146)	21				21					
TIMP3 (rs12678919)										
TRIM58 (rs3811444)										

	OXIDATIVE STRESS		INFLAMMATION								
	Ox. Fragility	Betaine	CRP	IL6	SFA	CCL2	ICAM1	PUFA	LPCs	LA	DHA
ADIPOQ (rs182052)											
APOA5 (rs12272004)											
APOA5 (rs662799)											
APOE (rs429358)			17								
APOE (rs7412)											
ASCL1 (rs17450122)											
CADM3 (rs12075)						2					
COMT (rs4680)	24										
CPS1 (rs715)		6									
CUX1 (rs409224)								4			4
FADS1 (rs174547)								13	5	4	
FADS12 (rs174550)											
FGF21 (rs838133)	29										
GCKR (rs1260326)			17								
GCKR (rs780093)					10						
GLS2 (rs2657879)											
GSTP1 (rs1695)	26										
HFE (rs1800562)											
ICAM1 (rs5498)							26				
IL-6 (rs1800795)				18							
LEP (rs10487505)											
LPL (rs268)											
LPL (rs326)											
MTHFR (rs1801133)	29										
PNPLA3 (rs738409)											
PPARG (rs1801282)											
PPID (rs8396)											
SLC16A10 (rs14399)											
SLC16A9 (rs1171614)											
SLC2A2 (rs8192675)											
SOD2 (rs4880)	11										
TCF7L2 (rs7903146)											
TIMP3 (rs12678919)											
TRIM58 (rs3811444)											