Can we design biomarkers of health that are applicable in Nutrition research?

Ben van Ommen
How do we react to external changes and challenges?

Is our physiology capable of properly maintaining homeostasis?
Physiology is a shock absorber
# Biomarkers of bone health

## Table 1A. Bone Formation Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tissue</th>
<th>Analytical Method</th>
<th>Special Considerations</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone specific alkaline phosphatase (BAP)</td>
<td>Bone</td>
<td>Eletrophoresis, Lectin precipitation, IRMA, EIA</td>
<td>Osteoblast product. Some immunoassays show 20% cross-reactivity with the liver isoenzyme. Does not show circadian rhythm (Yang &amp; Grey, 2006). Half-life of 1-2 days, stable in serum.</td>
<td>Age, pubertal stage and gender in Thai population. (Chaihrkit $et al.$, 2005), Age, pubertal stage and gender in Caucasian population (Ruechenger $et al.$, 2007) Age, pubertal stage and gender in Caucasian population (Vander Sluis $et al.$, 2002) Other information from review (Yang &amp; Grey, 2006)</td>
</tr>
<tr>
<td>Osteocalcin (OC)</td>
<td>Bone, platelets</td>
<td>RIA, IRMA, ELISA</td>
<td>Osteoblast product. Blood has several immunoreactive forms; Highest concentration found in morning samples. Some obtained from bone resorption. Lipemia, hemolysis falsely decreases result. Collect on ice and separate from cells within 1h to minimise degradation. Short half-life and is degraded into fragments that may be more stable in serum sample.</td>
<td>Age, pubertal stage and gender in Thai population. (Chaihrkit $et al.$, 2005), Age, pubertal stage and gender in Caucasian population (Ruechenger $et al.$, 2007) Age, pubertal stage and gender in Caucasian population (Vander Sluis $et al.$, 2002) Other information from review (Yang &amp; Grey, 2006)</td>
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</table>
Many (essential) nutrients primarily serve to optimize the performance and resilience of overarching processes.
Nutrition and maintaining robustness?

The energy pulse and the control mechanisms

- Decreased flexibility
  - linked to ‘metabolic syndrome’
  - may result in damage

Oxidative stress
Inflammatory stress
Metabolic stress

energy

time
Nutrition and maintaining robustness?
The energy pulse and the control mechanisms

Optimal flexibility depends on:
- optimal damage control phenotype
- micronutrient levels
- antioxidant status
- anti-inflammatory elasticity
Same with studies in metabolic health:
Almost always in overweight or obese subject
What is health? The ability to adapt


[... a French physician, Georges Canguilhem, in his 1943 book, The Normal and the Pathological,] rejected the idea that there were normal or abnormal states of health. He saw health not as something defined statistically or mechanistically. Rather, he saw health as the ability to adapt to one’s environment.

Health is not a fixed entity. It varies for every individual, depending on their circumstances.
If health is about maintaining flexibility ...

... should we quantify flexibility to quantify health?

And if yes, HOW???
Challenge tests to measure diet related health:

- Lipid load
- Resistance (vaccination)
- Exercise
- Recovery heart rate → physical fitness
- OGTT → diabetes
The challenge concept:
Study and quantify the stress response curve
Health is maintained by a complex interaction of processes, each maintaining “homeostasis”, elasticity and robustness.
The challenge concept:
Stress response curve of glucose
Overall scheme of metabolic health & disease related processes

Caloric excess

- Metabolically healthy
- Metabolic syndrome
- Reversible process
- Irreversible process

Pathologies resulting from the ‘metabolic syndrome’

- Myocardial infarctions
- Heart failure
- Cardiac dysfunction
- Stroke
- Nephropathy
- Atherosclerosis
- β-cell failure

Risk factors of the ‘metabolic syndrome’

- High cholesterol
- High glucose
- Hypertension
- Dyslipidemia
- Glucose toxicity
- Endothelial inflammation
- Microvascular damage

Nakatsuji, Metabolism 2009
Many drugs interfere with these processes in “health care”

Caloric excess → Physical inactivity

- Visceral adiposity
- dyslipidemia
- Fatty liver
- Adipose IR
- Hepatic IR
- Metabolic inflammation

- Insulin resistance
- Systemic inflammation
- Glucose toxicity
- Fatty liver
- Lipid overload
- Adipose inflammation
- Vioxx
- Salicylate
- IBD
- Gut inflammation

- Hepatic inflammation
- Fibrosis
- Endothelial inflammation

- LXR agonist
- Atorvastatin
- Rosiglitazone
- Pioglitazone
- Metformin
- Glibenclamide

- Muscle metabolic inflexibility

- Microvascular damage
- Atherosclerosis
- Retinopathy
- Nephropathy
- Brain disorders
- Cardiac dysfunction
- Heart failure
- Myocardial infections

- Stroke
- Hypertension

- High cholesterol
- High glucose
- LDL elevated

- β-cell failure
- β-cell pathology
- Pathology

- Risk factor
- Gluc
- Irreversible process
- Reversible process

Metabolically healthy

- Many drugs interfere with these processes in “health care”
0 wk:

- BW 26.9
- GLUC 11.2
- INS
- TG 1.22
- CHOL 5.2

9 wk:

- 9 wk High Fat
- BW 35.9
- GLUC 12.5
- INS 2.21
- TG 2.58
- CHOL 13.6

16 wk HF:

- BW 42.7
- GLUC 15.0
- INS 4.32
- TG 3.07
- CHOL 20.3

16 wk LF:

- BW 29.3
- GLUC 11.1
- INS 0.65
- TG 1.13
- CHOL 5.8

16 wk Low Fat diet:

- Back to Low Fat

Continued High Fat + medication ???

‘lifestyle’

- BW 30.0
- GLUC 11.8
- INS 0.65
- TG 1.15
- CHOL 6.37
triglycerides

Hf 9 weeks  Hf 16 weeks  Chow  Life style

cholesterol

Hf 9 weeks  Hf 16 weeks  Chow  Life style

Fenofibrate

total adipose weight

Hf 9 weeks  Hf 16 weeks  Chow  Life style

liver weight

Hf 9 weeks  Hf 16 weeks  Chow  Life style

leevr weight

Hf 9 weeks  Hf 16 weeks  Chow  Life style

metformin  fenofibrate  atorvastatin  T0901317  Glibenclamide  Sitagliptin  Rosiglitazon  Pioglitazon  Vioxx  Salicylate
Fenofibrate reduces the amount of (visceral) adipose tissue, but...
The 5-year efficacy of diabetes type 2 treatment

Kahn, NEJM 2006
Visceral adiposity → LDL elevated → Glucose toxicity → Fatty liver → Gut inflammation → Systemic inflammation → Adipose inflammation → Adipose inflammation → Hepatic inflammation → High cholesterol → LDL elevated → Muscle metabolic inflexibility → Adipose IR → Hepatic IR → High glucose → Systemic insulin resistance → β-cell pathology → High cholesterol → High glucose → Dyslipidemia → Metabolically healthy → Caloric excess → Visceral adiposity → Ectopic lipid overload → Fatty liver → Hepatic inflammation → Fibrosis → Myocardial infarctions → Heart failure → Cardiac dysfunction → Brain disorders → Nephropathy → Retinopathy → Metabolically healthy → Systems flexibility is the key! For optimal “phenotypic flexibility”, each process needs to function optimally.
Many dietary ingredients optimize these processes
NUTRITION FOR DIABETICS

TNO is initiating a field lab for improvement of diabetes type 2 (T2D) healthcare by developing personalized treatments. Biomarkers and socio-psychological information will be used to offer tailored nutritional and lifestyle interventions to people with or at risk for T2D. Companies marketing and/or developing food products relevant for (pre-)diabetics may partner with us in this unique initiative to fight diabetes.

T2D is characterized by (multi-)organ insulin resistance, accompanied by pancreatic failure to produce insulin. Currently, diabetics receive similar treatments, consisting of general lifestyle advice (“eat less and exercise more”) and use of plasma glucose reducing agents. For prediabetics interventions are not common practice yet, despite clear evidence for the beneficial outcome. However, generic treatment strategies hardly address the problem of specific organ dysfunction. Furthermore, distinct T2D population subgroups have been reported, which require tailored approaches instead of a “one size fits all” treatment. Such tailored approaches should be evaluated in a “real world” setting in which social and psychological factors are also considered as these greatly determine the efficacy of dietary interventions. To reverse the trend of increasing incidence of T2D an integrated and personalized approach is needed, tackling biological, psychological and social factors at the same time.
Each organ has its specific processes related to metabolic health, and analytical methods to study/diagnose these.

**Relevant processes**

- Enterotypin, host-microbe interaction – "metabolic destiny"
- Gut-brain axis, energy expenditure regulation, Absorption, intestinal integrity, barrier
- Gut-mediated inflammation control
- Chylomicron production

**Relevant analysis**

- Bile acids in plasma & faeces
- Barrier function / (lactulose, mannitol, campesterol, sitosterol)
- Gut microbiota products in plasma (acetate, propionate, butyrate, IPA)
- 'Incretin' plasma proteins (GLP-1, PYY, Ghrelin, CCK-1)
- Lipoproteins in plasma (chylomicrons)
- LPS in plasma
- Metagenomics in faeces

**GUT**

- Reversible steatosis (lipoprotein, FA-oxidation)
- Insulin sensitivity (glucose homeostasis & control mechanisms)
- Energy metabolism (e.g. by FGF21)
- Inflammation / fibrosis
- Adipocyte production
- Toxicity, liver functioning, liver injury

**LIVER**

- Reversibility (localization, "jo-jo")
- Expandability (hyperplasia vs. hypertrophy, ECM modifications)
- Inflammation (macrophage infiltration)
- Insulin sensitivity (glucose homeostasis, lipolysis)
- Lipokine production
- Pediatric (non-invasive)

**ADIPOSE**

- Lipotoxicity (cellular accumulation of ceramides & diglycerides → altered insulin)
- Protein metabolism
- Metabolic flexibility – capacity to adapt muscle metabolism to carb / lipid switch, oxidative stress
- Heart muscle (Diabetes)

**MUSCLE**

- Reversibility and elasticity (BP regulation)
- Oxidative stress and microvascular damage
- Cholesterol, inflammatory stress and atherosclerosis
- Lipoprotein metabolism
- Endothelial flexibility and integrity

**VASCULAR SYSTEM**

- Lipotoxicity
- Macrophage infiltration
- Inflammatory stress response
- Resilience of inflammatory homeostasis
- Chronic low-grade inflammation
- Resolution of inflammation
- Nutrient sensing – inflammation control

**SYSTEMIC INFLAMMATION**

- Signalling in metabolic adaptive control
- Gut-Brain axis
- HPA axis
- Endocrine & pancreas response
- Lipid metabolism
- Inflammation in acute & chronic phase
- Metabolic flexibility

**SYSTEMIC PROCESSES**

- Lipid enzyme activities in plasma
- Oxylipids, cytokines and chemokines in plasma challenge test response
- Endocannabinoid, lipokines & 'incretins'
- Cytokines & Chemokines
- Carb vs fat oxidation switch
- Activity hypothalamus (scan)
- Parasympathetic activity (HRV)
- OGGT with metabolic profiling
Diagnosis assay: organ flexibility

**Gut**
- Host-microbe interaction
- Absorption, intestinal integrity, barrier function
- Gut-mediated inflammation control
- Chylomicron production

**Brain**
- Gut-Brain axis
- Endocrine responses
- HPA axis

**Adipose tissue**
- Lipoprotein metabolism
- Lipid metabolism
- Energy metabolism
- Macrophage infiltration
- NEFA
- Expandibility
- Lipokine/Adipokine production
- Insulin sensitivity

**Pancreas**
- Systemic insulin sensitivity
- b-cell failure

**Vasculature**
- NO metabolism
- Chronic low-grade inflammation
- Endothelial flexibility/integrity
- Reversibility of inflammation
- Microvascular damage
- Lipid droplet formation
- Arterial stiffness

**Liver**
- Adaptation carb/lipid switch
- Oxidative stress
- ER stress
- Tissue injury
- Fibrosis
- Toxicity
- Insulin sensitivity

**Muscle**
- Protein metabolism
- Oxidative stress
- ER stress
- Tissue injury
- Energy metabolism
- Insulin sensitivity

**Kidney**
- (re)absorption
- Urea cycle
- Tissue injury

**Vasculature**
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Gut
- Host-microbe interaction
- Absorption, intestinal integrity, barrier function
- Gut-mediated inflammation control
- Chylomicron production
- Gut hormones (Ghrelin, GIP, etc)

Brain
- Gut-Brain axis
- Endocrine responses
- HPA axis

Adipose tissue
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Liver
- Adaptation carb/lipid switch
- Oxidative stress
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- Fibrosis
- Toxicity
- Insulin sensitivity
- Lipoprotein metabolism
- Lipid metabolism (MG, TG)
- Bile production

Kidney
- (re)absorption
- Urea cycle
- Tissue injury

Muscle
- Protein metabolism
- Oxidative stress
- ER stress
- Tissue injury
- Energy metabolism
- Insulin sensitivity

Pancreas
- Systemic insulin sensitivity
- b-cell integrety

Vasculature
- NO metabolism
- Chronic low-grade inflammation
- Endothelial flexibility/integrity
- Resolving of inflammation
- Microvascular damage
- Lipid droplet formation
- Arterial stiffness
- Systolic/Diastolic BP
- Heart rate (BPM)
- Lipotoxicity

OGTT (plasma)
Gut
- Host-microbe interaction
- Absorption, intestinal integrity, barrier function
- Gut-mediated inflammation control
- Chylomicron production
- Gut hormones (Ghrelin, GIP, etc)

Brain
- Gut-Brain axis
- Endocrine responses
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Adipose tissue
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Liver
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- Lipid metabolism (MG, TG)
- Bile production

Muscle
- Protein metabolism
- Oxidative stress
- ER stress
- Tissue injury
- Energy metabolism
- Insulin sensitivity

Kidney
- (re)absorption
- urea cycle
- Tissue injury

OLTT (plasma): dairy, incl. carbs and proteins

Gut

Muscle

Liver

Kidney

Brain

Adipose tissue

Pancreas

Vasculature

Brain

Adipose tissue
Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status

Linette Pellis · Marjan J. van Erk · Ben van Ommen · Gertrud C. M. Bakker · Henk F. J. Hendriks · Nicole H. P. Cnubben · Robert Kleemann · Eugene P. van Someren · Ivana Bobeldijk · Carina M. Rubingh · Suzan Wopereis

Metabolomics  Received: 31 March 2011 / Accepted: 12 May 2011
Hepatic insulin sensitivity and peripheral insulin sensitivity

\[ Y = 0.971 + 1.055 \times X; \quad R^2 = 0.342 \]
effect of healthy diet components

- Supplement mix: based on mediterranean diet, contains resveratrol, vitamin E, vitamin C, tomato extract, green tea extract, fish oil

- Designed to exert effect on different **metabolism, oxidation** and **inflammation** pathways (based on literature)

- Test in homogeneous group of 35 men at the level of metabolite, protein and transcripts

_Bakker G, Pellis L, van Erk et al. AJCN 2010_
Eicosanoid related inflammation (but no effect PGE2)

- Increased expression of prostaglandin metabolism genes in adipose tissue
- Anti-inflammatory effects in adipose tissue: adiponectin, IL10RA, SOCS3

Bakker, AJCN 2010
Omics-driven oral LIPID tolerance test to perturb metabolic homeostasis, in order to reveal relationship between inflammation and metabolic state

500ml high fat dairy shake (706kcal)
- 21g protein (12en%),
- 46g fat (59en%) (27g saturated fat)
- 42g carbohydrates (30en%)
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

VCAM-1

Pellis, Metabolomics 2011
Fibrinogen in the human study after a standardized postprandial challenge

Pellis, Metabolomics, 2011
Effect of anti-inflammatory diet on inflammation in mice

Verschuren, J Nutr 2011
Verschuren, J Nutr 2011
Effect of anti-inflammatory diet on inflammation in mice

- ApoE3L mice on high cholesterol diet develop atherosclerosis
- Supplementation with food mix inhibits atherosclerosis development

HC: plaque in aorta
HC + food mix: no plaque in aorta

Verschuren, J Nutr 2011
Brain
Higher body fat percentage is associated with increased cortisol reactivity and impaired cognitive resilience in response to acute emotional stress

LR Mujica-Parodi\textsuperscript{1,2}, R Renelique\textsuperscript{1,2} and MK Taylor\textsuperscript{3}

Phenotypic Flexibility
Adaptation

The Best - Dressed Astronaut
Adipose tissue in healthy and unhealthy obesity

Gene

Environment

Behaviour

Excess energy intake, physical inactivity

Fat accumulation

Expandability of SC fat depots

Intact

Impaired

Ectopic fat deposition, visceral depots, liver fat

Healthy obesity

(10-25% of obese)

Unhealthy obesity

Blüher
Cur Op Lipidol 2010
Adipose expandability and membrane lipid composition

Adiponeogenesis
Tetrahydroxylated bile acid

(combined transcriptome, lipidome & in silico membrane simulation approach)
Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

1) **Metabolic flexibility** (Appropriate response to temporary macronutrient overload)

<table>
<thead>
<tr>
<th>Adaptation process</th>
<th>Dietary ingredients affect this process</th>
<th>Consequences of mal-functioning</th>
<th>Challenge test</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver metabolic flexibility</td>
<td>lipids, glucose, carnitine, choline, fructose, …</td>
<td>fatty liver, high cholesterol, high glucose, high triglycerides</td>
<td>OGTT, OLTT, OPTT</td>
<td>lipoprotein profile, plasma metabolome, turn-over of liver specific metabolites</td>
</tr>
<tr>
<td>adipose lipogenesis, lipolysis switch</td>
<td>availability of energy</td>
<td>improper function of adipose tissue, ectopic storage of lipids</td>
<td>OLTT</td>
<td>adipose tissue transcriptome, FFA availability, impaired switching from oxidation of fat to glucose by RQ</td>
</tr>
<tr>
<td>muscle carbohydrate / lipid switch mitochondrial efficiency</td>
<td>availability of energy</td>
<td>muscle insulin resistance</td>
<td>OLTT, OGTT</td>
<td>CK, respiratory quotient MRI fat distribution</td>
</tr>
</tbody>
</table>
**Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods**

2) Appropriate storage of excess energy in adipose tissue

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Adipose tissue flexibility in storing and releasing lipids as required for whole body energy metabolism</td>
<td>(saturated) fatty acids, excess dietary energy, resveratrol, etc.</td>
<td>Lipid accumulation in muscle tissues, low grade inflammation, insulin resistance</td>
<td>OGTT, OLTT, delta respiratory exchange ratio</td>
<td>MRI fat distribution, palmitoylate (16:1,n-7)</td>
</tr>
</tbody>
</table>
### Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

#### 3) Immune response - Optimal inflammatory tone

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</tr>
</thead>
<tbody>
<tr>
<td>inflammatory dynamics, appropriate hepatic acute phase response</td>
<td>excess dietary energy surplus of saturated fatty acids deficiencies for retinol, vitamin C, essential nutrients like fatty acids &amp; minerals (Se)</td>
<td>chronic (low-grade) inflammation, that has a potential role in cancer, CVD, diabetes, arthritis, ...</td>
<td>inflammation challenge test, OLTT ETEC ET infusion</td>
<td>Muscle &amp; adipose tissue expression of inflammatory mRNAs, plasma / tissue conc. of essential nutrients PBMC transcriptome Plasma and tissue concentrations of cytokines and other inflammatory markers</td>
</tr>
</tbody>
</table>
**Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods**

4) **Anti-oxidant defense capacity**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>oxidative stress adaptation</td>
<td>Plant polyphenols</td>
<td>Chronic increased oxidative stress, lack of oxidative stress response when needed</td>
<td>OGGT, OLT</td>
<td>uric acid, PBMC gene expression, lipid hydroperoxides, 8-iso-PgF2, MDA, 8-OHdG, total thiols, glutathione</td>
</tr>
</tbody>
</table>
Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

5) Vascular flexibility, blood pressure regulation, blood coagulation

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>blood pressure adaptation, flexible microvasculature</td>
<td>Salt, omega-3 fatty acids,</td>
<td>Arterial stiffness, hypertension, vascular insulin sensitivity</td>
<td>Exercise challenge test OGGT</td>
<td>Blood pressure, imaging, plasma metabolomics</td>
</tr>
</tbody>
</table>
# Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

## 6) Optimal DNA maintenance

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>DNA damage response to maintain genome integrity and DNA methylation patterns</td>
<td>Calorie restriction improves genome stability. B-vitamins (e.g. folic acid, vitamin B12, choline, betaine) are important for DNA damage repair and methylation pattern</td>
<td>Accumulation of gene and chromosomal mutations, Shortening and dysfunction of telomeres, increased risk for senescence and cancer</td>
<td>In vitro caloric restriction / excess and essential micronutrient deficiency / excess</td>
<td>Chromatin plasticity, DNA methylation, telomere length, gamma-H2AX phosphorylation, micronuclei, promoter DNA hypomethylation; gene expression, Folic acid, B12, methyl malonic acid</td>
</tr>
</tbody>
</table>
### 7) Maintenance of intestinal function

<table>
<thead>
<tr>
<th>Adaptation process</th>
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<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptation of intestinal microbiota, intestinal integrity &amp; permeability</td>
<td>Probiotics, fibres</td>
<td>Leakage from gut, suboptimal digestion with diarrhea or constipation, inflammation</td>
<td>OLTT, challenge with ETEC (enterotoxigenic Escherichia coli)</td>
<td>CRP, LPS</td>
</tr>
</tbody>
</table>
Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

8) Optimal concentration and mental performance

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>training</td>
<td>n-3 PUFAs, B-vitamins</td>
<td>Alzheimer’s disease, reduced cognitive function</td>
<td>Examination</td>
<td>MRI of the brain, ERP (evoked response potential)</td>
</tr>
</tbody>
</table>
So …

1. Can we stop treating nutrients as drugs please?

2. Diet is NOT about therapy or prevention, but about MAINTAINING OPTIMAL HEALTH

3. We need biomarkers that quantify health, not the onset of disease.

4. Health is the ability to maintain homeostasis in constantly changing environments

5. Design biomarkers that quantify stress responses

6. Many nutritional components “oil the flexibility machine” – focus “healthy diet development” on phenotypic flexibility.

7. Individual aspects may be important here
Phenotypic Flexibility Symposium

Jointly organized by
- NutriTech
- Bioclaims
- PhenFlex
- NuGO

El Escorial (Madrid)
4-6 February, 2013

www.nugo.org/phenflex