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*Molecular Nutrition Unit*

*Prof. Dr. Hannelore Daniel*

**Center Institute of Nutrition and Food Sciences**

# Research perspectives on Food and Health

***„innovation starts with science and science starts with courage and creativity“***

**Meeting of the Øresund FOOD Network, August 2008**

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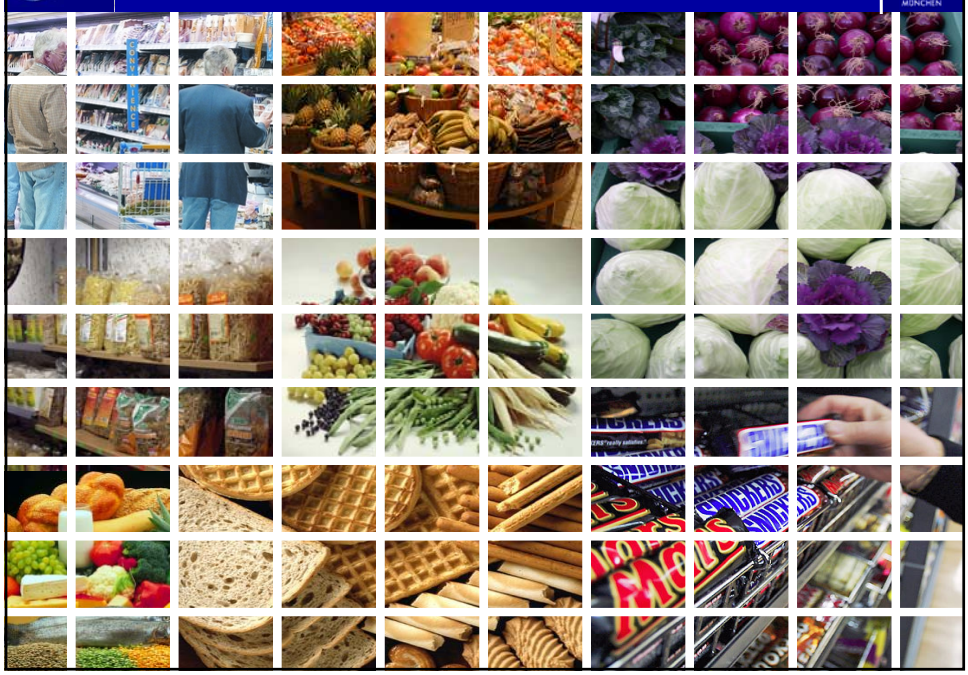

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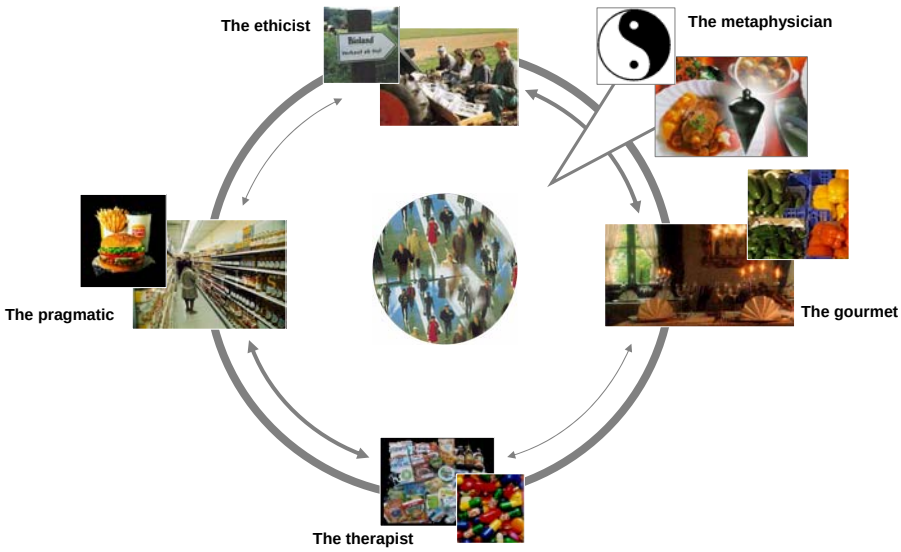
Where do we stand ?

In a highly diversified *„nutrition world“* !

Where do we go ?

**Pluralism PURE !**

## *Pluralism with diffusion: consumers are different !*

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## The food sector mirrors all societal developments

### *globalisation, new ecology, individualisation*

**Globalisation and regionalisation (direct marketing)**

**Convenience II - chilled, ready to eat**

**Fusion kitchen, asian systems gastronomy, *Cuisine de Monde***

**Not satiety but distinction and socialising**

**Trusted food**

**Food and eating as expression of art and culture**

**Health food and personalisation**

## The ground is set for a new dimension of nutrition and food research


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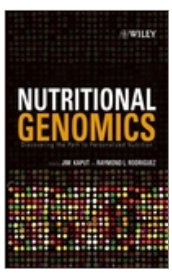
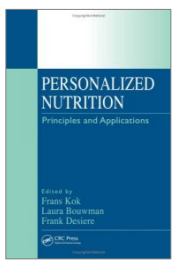
## The ground is set for a new dimension of nutrition and food research



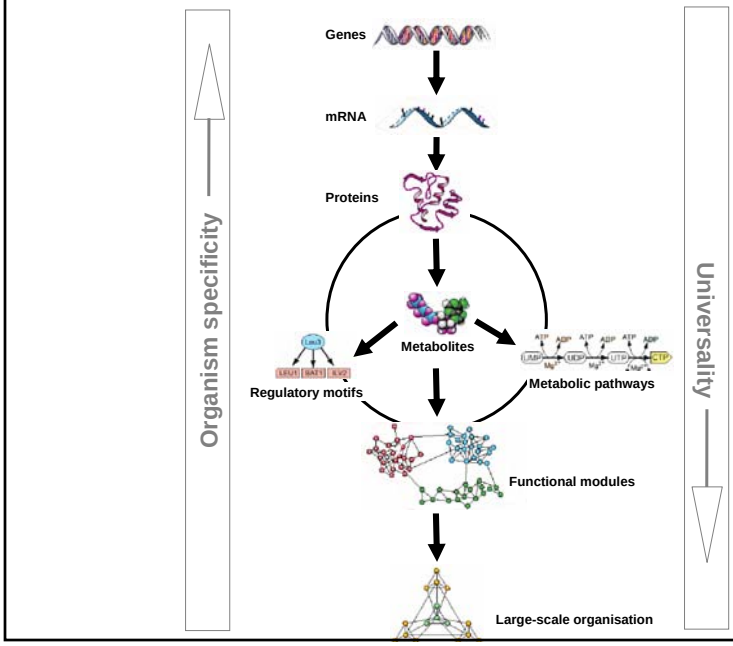

**Nutritional Genomics: Discovering the Path to Personalized Nutrition**

Publisher: WILEY | ISBN: 978-0-471-68319-3 | Hardcover | 496 pages




**Personalized Nutrition: Principles and Applications**

Publisher: CRC | 2007-08-24 | ISBN 0849392810 | Pages: 304

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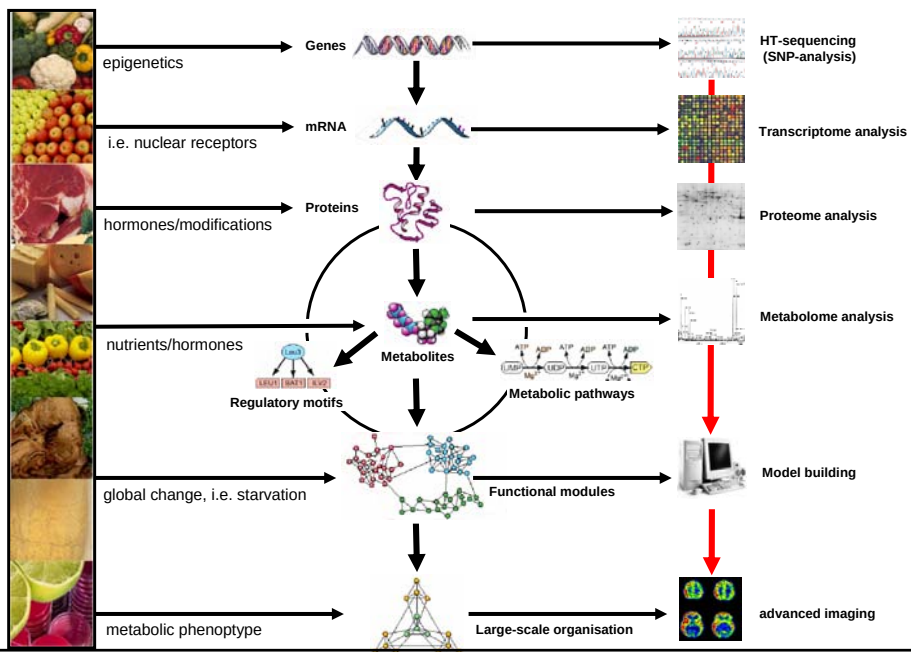
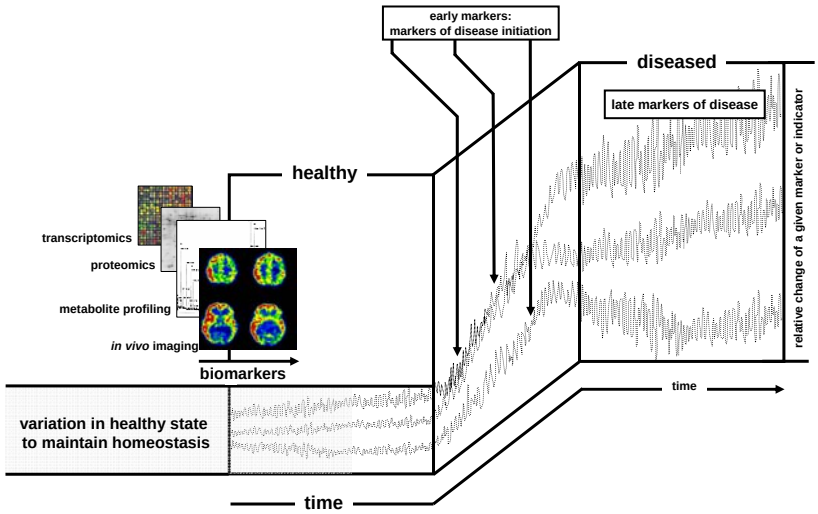
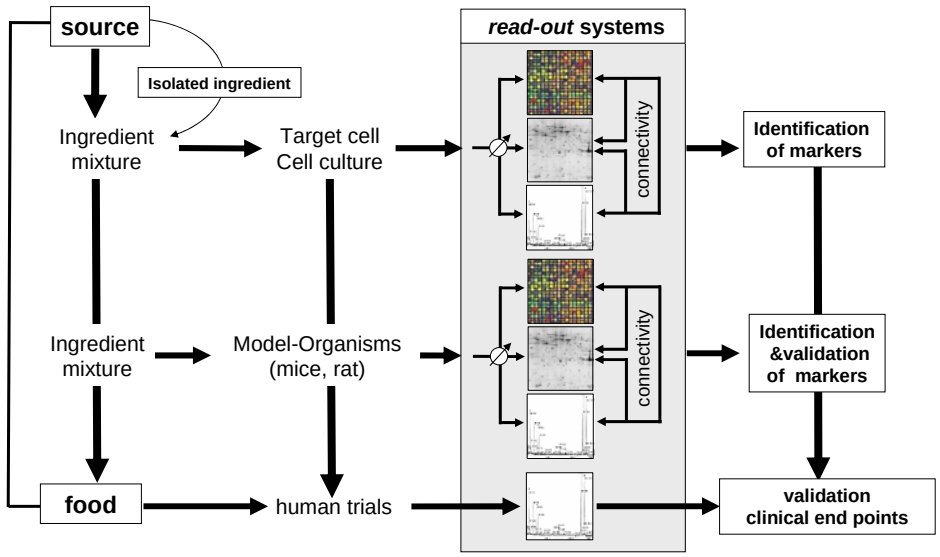


## … taken into metabolic biomarker discovery

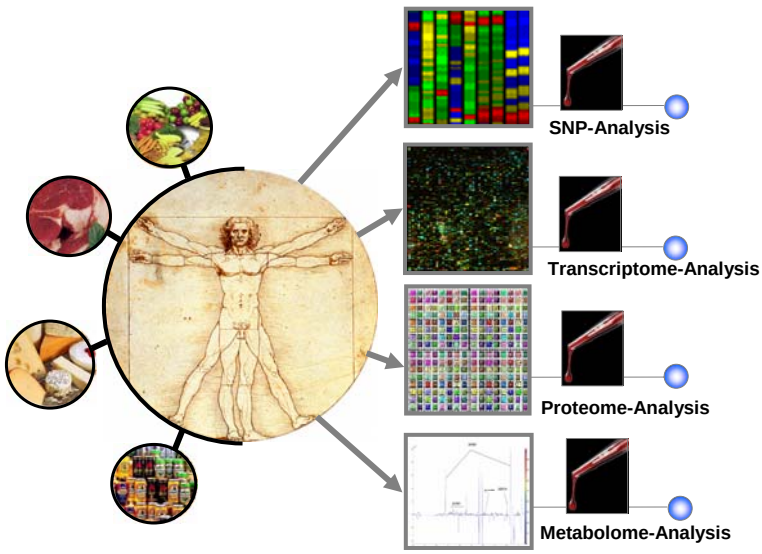





## Omics-applications in food product development



## Profiling-techniques for comprehensive genotyping/phenotyping

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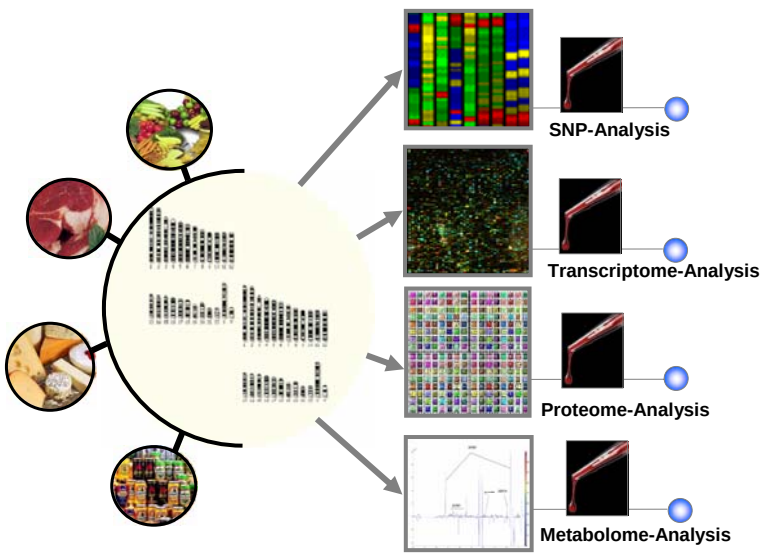
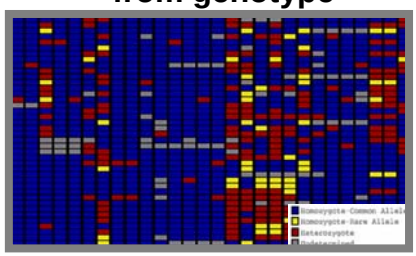
## Profiling-techniques for comprehensive genotyping/phenotyping



## from genotype



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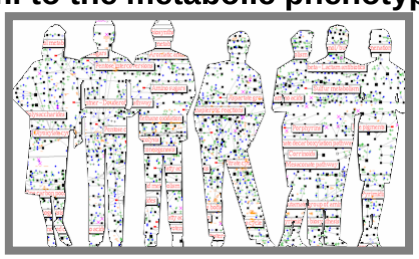
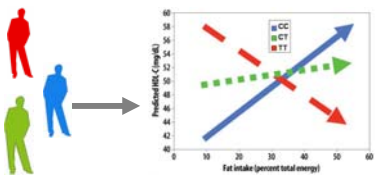
## ….. to the metabolic phenotype



## ……to individual susceptibilities

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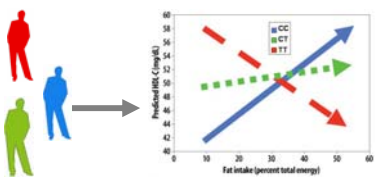
## ……to individual susceptibilities



## Genotyping approaches for identifying susceptibility genes

***What is the „state of the art“ ?***

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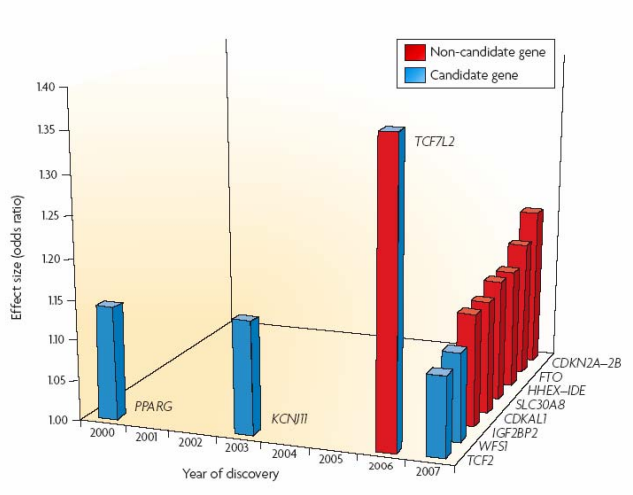
## susceptibility genes for non-insulin dependent diabetes

***EXT2*** **(Exostosin 2)**
**pancreas development**
***WFS1*** **(Wolfram syndrome 1/wolframin)**
**survival signal beta cells**
***CDKN2A/2B*** **(Cyclin-dependent kinase inhibitor 2A/2B)**
**Tumorsuppressorgene**
***SCL30A8*** **(solute carrier family 30 [zinc transporter], member 30)**
**insulin secretion**
***TCF2/HNF1B*** **(HNF1 homoeobox B)**
**associated with T2D and (invers) prostata cancer**
**CDKAL1: Cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1: OR 1.39 per allele (p = 0.0004)**
**Mechanism: Reduced insulin incretion**
***HHEX*****: Homoeobox, haematopoietically expressed:**
**OR 0.81 per allele (p = 0.009)**
**Mechanism: Reduced insulin incretion**
***IGF2BP2*****: Insulin-like growth factor 2 binding protein 2**
**OR 1.15 per allele (p = 0.049)**
**Mechanism: pancreas development?, reduced insulin secretion**
***PPARG*** ***(peroxisome proliferator-activated receptor)***
**OR 0.76 per Allel (p = 0.010)**
**Mechanism: fat regulation**
***FTO*** **(Fat mass and obesity associated)**
**OR 1.15 per allele (p = 0.047)**
**Mechanism: Appetite regulation?**

## susceptibility genes for non-insulin dependent diabetes

T2D-Risk-SNPs in 11 genes




Nat Rev Genet 2007;8:657

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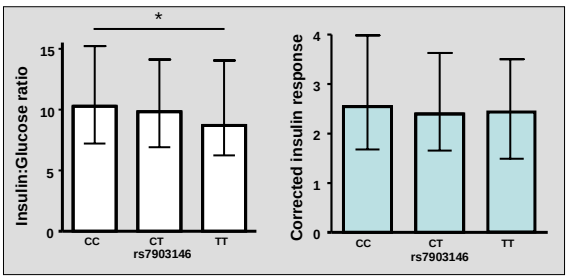
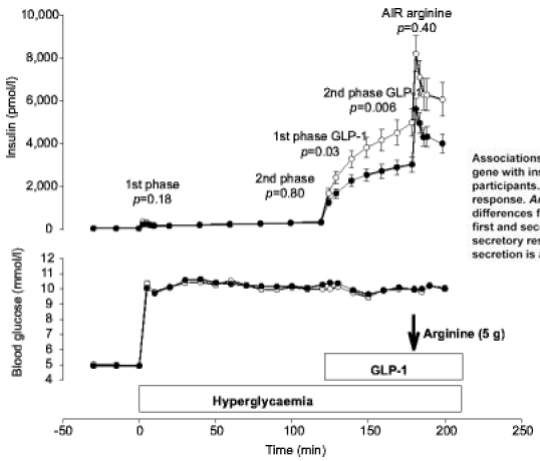
## *TCF7L2:* a single polymorphism




Effects of Genotype at rs7903146 on Insulin Secretion at Baseline as Measured by the Mean (±SE) Insulin:Glucose Ratio (Panel A) and the Corrected Insulin Response (Panel B)

**What does TCF7L2 do ?**

## *TCF7L2*: what is the basis of its function?




Associations between the genotypes of rs7903146 polymorphism in the *TCF7L2* gene with insulin secretion during a hyperglycaemic clamp in 73 German participants. *Open circles* CC; *closed circles* CT and TT. *AIR* Acute insulin response. *Arrow* Administration of 5 g arginine. The *p* values show the differences for first and second phases of glucose-induced insulin secretion, first and second phases of GLP-1-induced insulin secretion and acute insulin secretory response to arginine (AIR) (for calculation see 'Methods'; insulin secretion is adjusted for insulin sensitivity)

**Diabetologia. 2007 December; 50(12): 2443–2450.**

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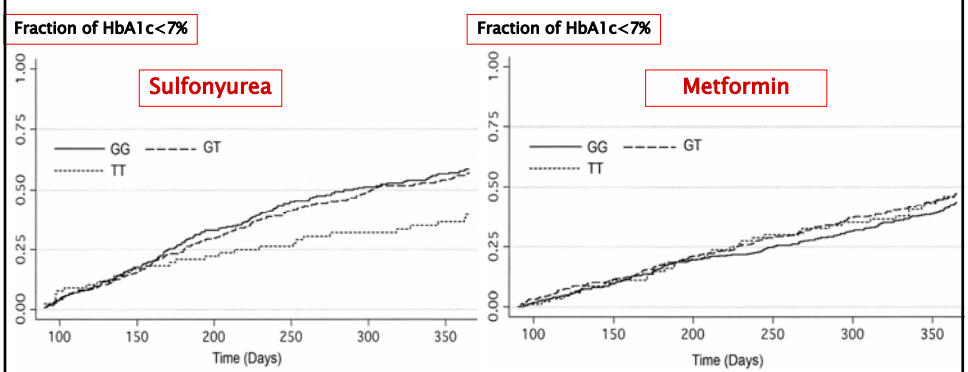
## *TCF7L2* and pharmacotherapy

**GoDARTS** (Scotland): *TCF7L2*-risk variant associated with therapy failure with sulfonyl area and no association with metformin

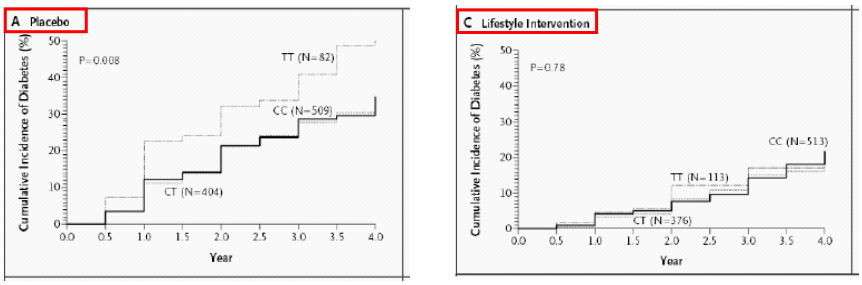



**Kaplan-Meier plots showing the proportion of patients, by genotype at rs1225372, who achieve a target HbA1C <7% after being initiated on treatment with a sulfonylurea or metformin.**

**Diabetes 56:2178-2182, 2007**

# *TCF7L2* and Lifestyle-Intervention

**DPP (Diabetes Prevention Program)**




**Incidence of Diabetes According to Treatment Group and Genotype at Variant rs7903146**

JC Florez: NEJM 2006;355:241

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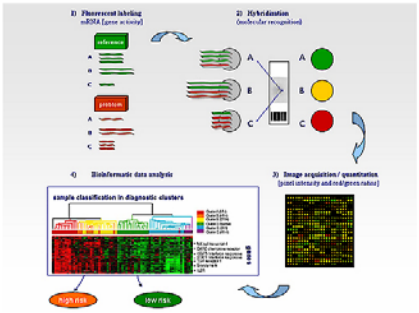
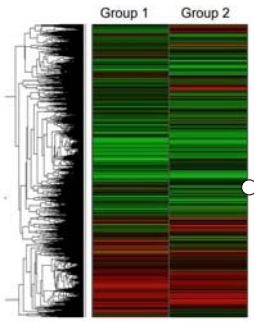
# Profiling techniques in basic science applications

## TRANSCRIPTOMICS

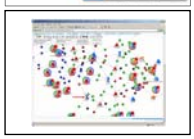
## Principles of transcript profiling






Promotor analysis and prediction

Pathway analysis tools





## Micro-Array-Analysís for the identification of „caloric restriction mimetics“

Old mice (20 months)

8 weeks

Caloric restriction (CR8)
or
Metformin (50 mg/g)
Glipizide (25 mg/g)

4x CR8
4x Metformin (MET)
4x Glipizide (GLIP)

Whole genome mouse arrays

| Group | Sig. regulated genes |
|---|---|
| CR8 | 218 |
| MET | 349 |
| GLIP | 79 |

**Metformin**

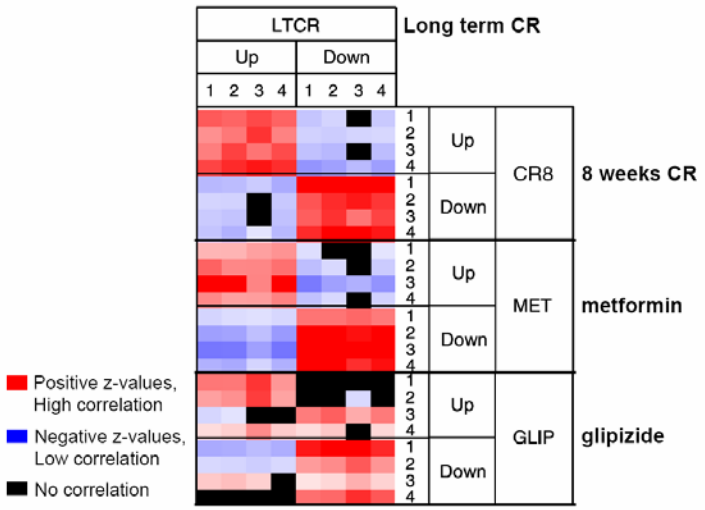
**Glipizide (Sulfonylurea-derivate)**

**Resveratrol**

**2-deoxy-D-Glucose**

Methods Mol Biol. 2007;371:143-9.

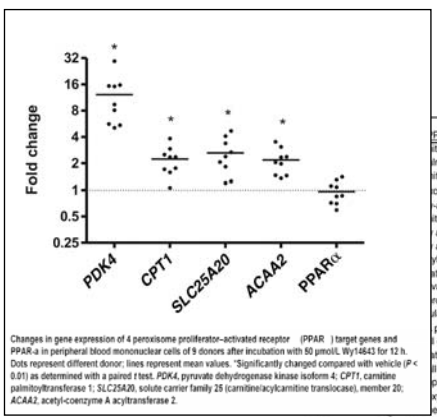
## Micro-Array-Analysís for the identification of „caloric restriction mimetics“



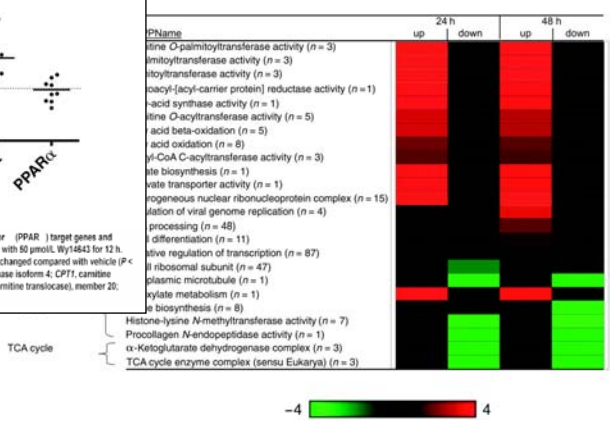

Physiol Genomics. 2005 Nov 17;23(3):343-50.



## Micro-Array-Analysís for the identification of gene targets of FASTING in humans

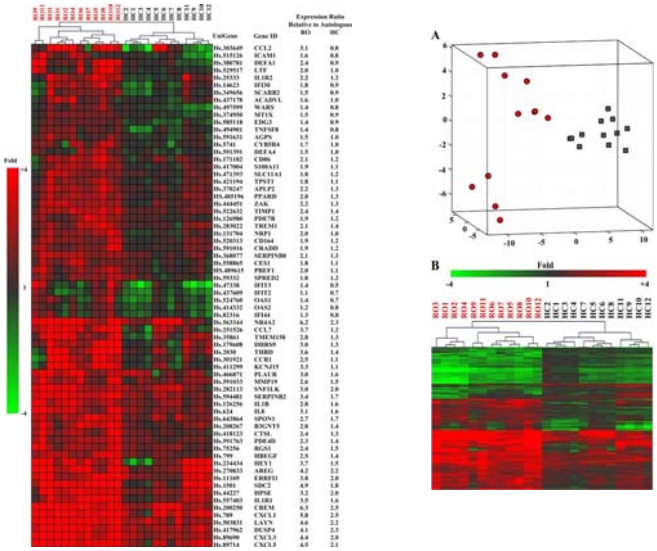



Changes in gene expression of 4 peroxisome proliferator–activated receptor (PPAR ) target genes and PPAR-a in peripheral blood mononuclear cells of 9 donors after incubation with 50 μmol/L Wy14643 for 12 h. Dots represent different donor; lines represent mean values. *Significantly changed compared with vehicle ($P < 0.01$) as determined with a paired $t$ test. *PDK4*, pyruvate dehydrogenase kinase isoform 4; *CPT1*, carnitine palmitoyltransferase 1; *SLC25A20*, solute carrier family 25 (carnitine/acylcarnitine translocase), member 20; *ACAA2*, acetyl-coenzyme A acyltransferase 2.




Am J Clin Nutr. 2007 Nov;86(5):1515-23.

**Identification of a molecular signature in human type 1 diabetes mellitus using serum and functional genomics.**




Hierarchical clustering using 68 well-annotated genes up-regulated by RO sera.
Expression profiles induced by PBMCs cultured with RO (*n* = 12) and HC (*n* = 12) sera distinctly cluster

J Immunol. 2008 Feb 1;180(3):1929-37

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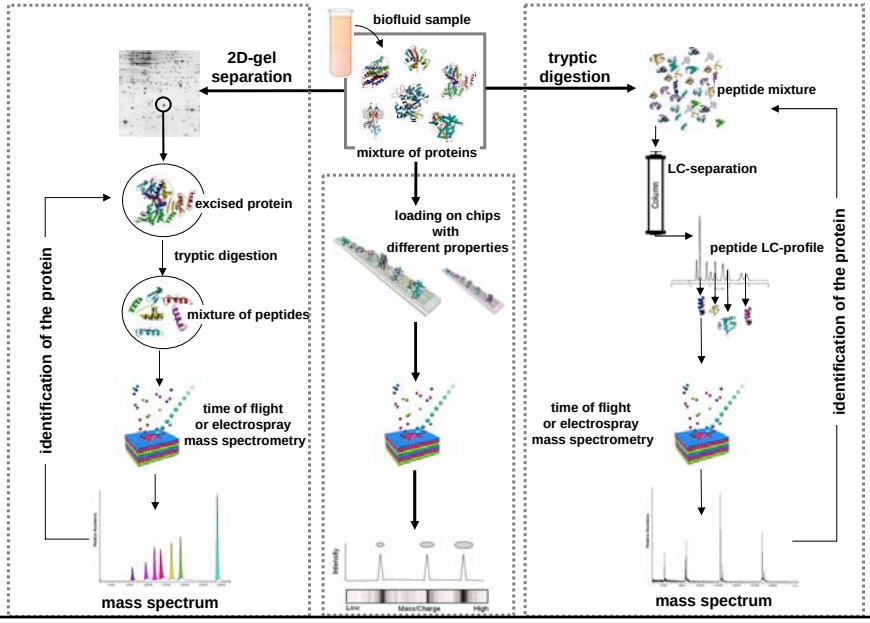
# Profiling techniques in basic science applications

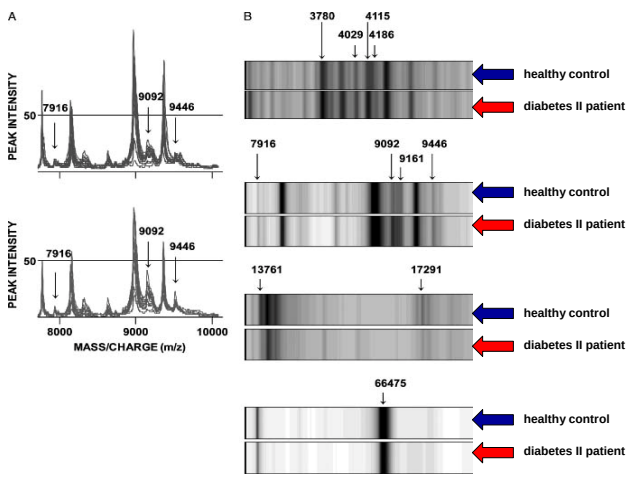
## PROTEOMICS

## principles in proteome analysis





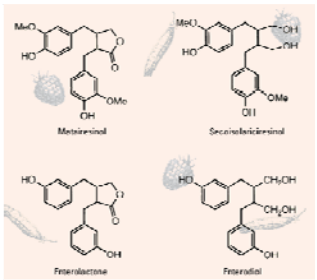

## Serum protein patterns in newly diagnosed type 2 diabetes mellitus: influence of diabetic environment and family history of diabetes

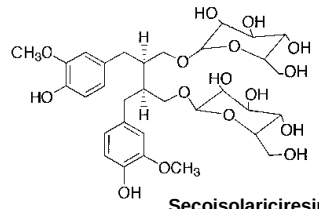



Panel A shows serum SELDI-TOF mass spectra in the mass range 7.5-10 kDa. The top spectra are from individuals with normal glucose tolerance ($n$ = 20) and the bottom spectra are from individuals with type 2 diabetes ($n$ = 20). Arrows indicate three of the differentially displayed proteins ($p$ < 0.05). Panel B displays all the proteins, which were found to have different serum levels, when comparing serum samples from normal glucose tolerant individuals with individuals with type 2 diabetes, using SELDI-TOF MS. The representative gel views of a normal glucose tolerant person (top) and a type 2 diabetes person (bottom) are shown

**Diabetes Metab Res Rev. 2008 Feb;24(2):148-54**

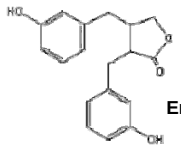
**The human peripheral blood mononuclear cell proteome responds to a dietary flaxseed-intervention and proteins identified suggest a protective effect in atherosclerosis**





**Secoisolariciresinol-diglycoside**

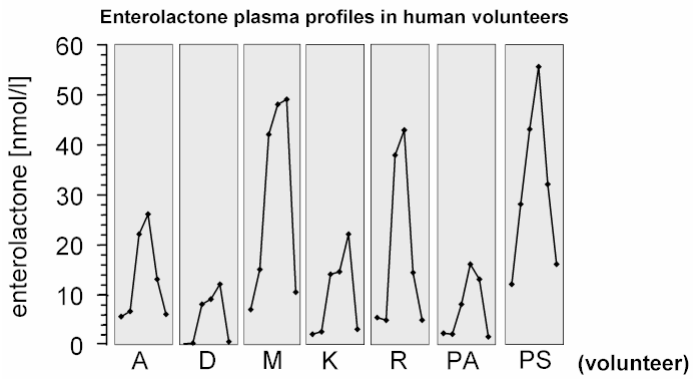
intestinal microflora



**Enterolactone**

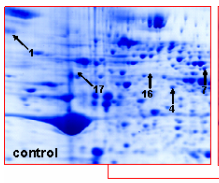


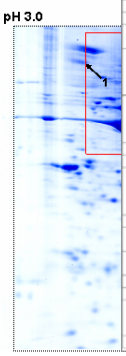
**Healthy volunteers received for seven-days of the dietary intervention every morning 0.4 g per kg body weight of a commercially available shooted linseed.**




| Phase | Day | Mean (nmol/L) | SEM | Median (nmol/L) | 25. Percentile | 75. Percentile |
|---|---|---|---|---|---|---|
| Pre-phase | -7 | 4.8 | 1.5 | 5.5 | 1.4 | 7.2 |
| | 0 | 8.4 | 3.9 | 5.4 | 1.4 | 14.2 |
| Intervention-phase | 2 | 24.9 | 5.9 | 21.8 | 8.1 | 42.4 |
| | 3 | 30.4 | 7.0 | 25.7 | 14.7 | 48.5 |
| | 7 | 22.0 | 5.2 | 14.8 | 12.1 | 32.0 |
| Washout-phase | 21 | 6.2 | 2.0 | 5.3 | 1.5 | 10.6 |

## Proteome changes in PBMC upon a flaxeed intervention in human vollunteers




| Spot No | Protein description | Theoretical M./pI | Measured M./pI | Protein amount | | % Sequence-coverage | Accession No |
|---|---|---|---|---|---|---|---|
| | | | | Intervention phase/pre-phase | Washout-phase/pre-phase | | |
| | **Chaperons** | | | | | | |
| 1 | Chaperonin-containing TCP-1 beta subunit homolog | 96/6.4 | 58/6.0 | 2.05 | 0.86 | 36 | AAC98906 |
| 2 | Peroxiredoxin 4 | 38/5.3 | 31/5.9 | 3.70 | 1.05 | 64 | Q13162 |
| 3 | T-complex protein 1 subunit alpha (TCP-1-alpha) | 121/5.8 | 61/5.8 | 2.01 | 0.95 | 30 | P17987 |
| 4 | 60 kDa heat shock protein, mitochondrial precursor (hsp60) | 210/4.6 | 61/5.7 | only in intervention | n.d. | 41 | P10809 |
| | **Cytoskeletal proteins** | | | | | | |
| 5 | LIM protein | 48/7.7 | 38/7.6 | 2.88 | 1.55 | 37 | JC2324 |
| 6 | Beta 5-tubulin | 51/5.4 | 51/5.4 | 0.50 | 0.77 | 49 | AAH20946 |
| | **Metabolism** | | | | | | |
| 7 | Pyruvate kinase isozymes M1/M2 | 134/8.7 | 58/8.0 | 2.04 | 1.84 | 51 | P14618 |
| 8 | Protein-L-isoaspartate (D-aspartate) O-methyltransferase(EC 2.1.1.77) splice form I | 38/6.6 | 25/6.8 | 0.24 | 0.60 | 49 | P22061 |
| 9 | Long-chain-fatty-acid beta-oxidation multienzyme complex alpha chain precursor, mitochondrial | 160/10.4 | 160/10.4 | only in pre-phase | 0.99 | 35 | P40939 |
| 10 | Cyclophilin A | 21/8.7 | 18/7.7 | only in pre-phase | 0.76 | 50 | P62937 |
| 11 | TALDO 1 protein | 54/5.4 | 37/5.8 | only in intervention | only in intervention | 26 | AAH18847 |
| 12 | Phosphoglycerate mutase 1 (Phosphoglycerate mutase isozyme B) (PGAM-B) (BPG-dependent PGAM 1) | 39/6.9 | 29/6.8 | 2.86 | 1.65 | 56 | P36871 |
| | **Gene regulation** | | | | | | |
| 13 | Purine-nucleoside phosphorylase (EC 2.4.2.1) | 47/6.9 | 32/6.5 | 2.06 | 1.89 | 62 | P00491 |
| 14 | Stress-induced-phosphoprotein 1 | 154/6.8 | 63/6.4 | 2.01 | only in pre-phase | 44 | P31948 |
| | **Other proteins** | | | | | | |
| 15 | Platelet glycoprotein IIIa/II | 220/4.5 | 86/5.0 | 0.45 | 0.52 | 23 | B36268 |
| 16 | Chain B, Crystal Structure Of Desoxy-Human Hemoglobin Beta6 Glu->trp | 13/6.5 | 16/7.3 | 0.30 | 0.54 | 67 | 6HBWB |
| 17 | Gelsolin precursor | 103/9.6 | 86/5.9 | only in pre-phase | 1.42 | 23 | P06396 |

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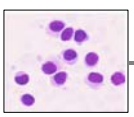
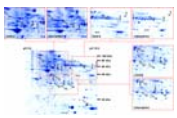
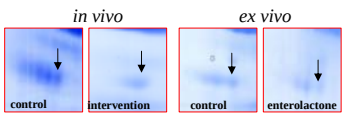


24h

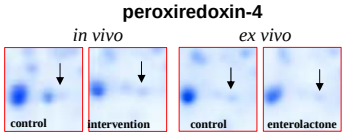
**50 nM enterolactone**



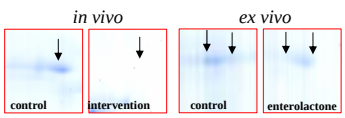
**platelet glycoprotein**

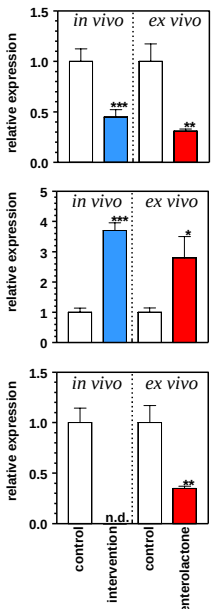



**peroxiredoxin-4**




**LCFABOMC**



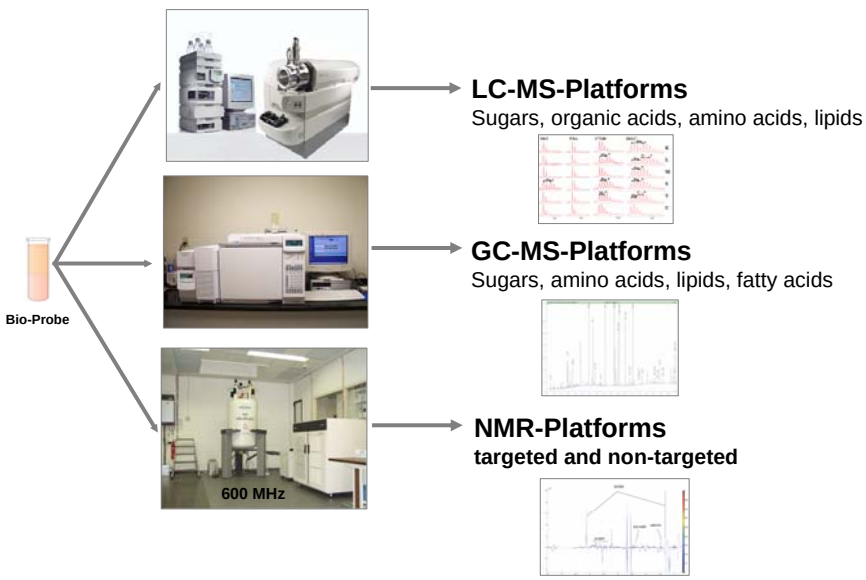

**Proteomics. 2007 Sep;7(18):3278-88.**

# Profiling techniques in basic science applications

## METABOLOMICS



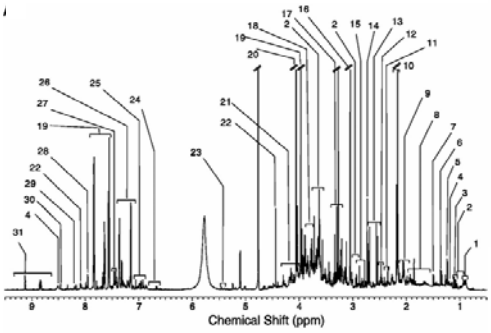
**principles in metabolome analysis**



# NMR based non-targeted metabolite-profiling

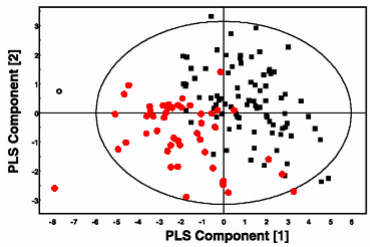
## A metabolomic comparison of urinary changes in type 2 diabetes

**Metabolomic analysis of human urine**




*A*: high-resolution 700-MHz $^1$H-NMR spectrum of an aqueous urine sample from a healthy control volunteer with the relevant resonance assignments shown. Each resonance corresponds to a chemical moiety within a particular metabolite with the intensity proportional to the concentration of that metabolite. *1*, -hydroxybutyrate/valerate; *2*, amino acids; *3*, valerate; *4*, unassigned; *5*, ß-hydroxybutyrate; *6*, lactate; *7*, alanine; *8*, amino acids/ornithine; *9*, *N*-acetyl groups/aspartate/glutamate; *10*, methionine; *11*, oxalacetate/pyruvate; *12*, ß-hydroxybutyrate/glutamine/glutamate; *13*, citrate; *14*, DMA; *15*, TMA/DMO; *16*, creatine/creatinine; *17*, taurine; *18*, PAG; *19*, hippurate; *20*, creatine/creatinine; *22*, uridine bases; *22*, NMN acid; *23*, allantoin; *24*, unassigned pyrimidine; *25*, 3-hydroxypropionic acid/tyrosine; *26*, meta-hydroxyphenyl-propionic acid (mHPPA)-sulfate/indoxyl sulfate; *27*, PAG; *28*, *N*-methyl-2-pyridone-5-carboxamide (2PY); *29*, NMN amide; *30*, formate; *31*, NMN amide/NMN acid.

**PLS-DA score plot of the healthy subjects compared with the type 2 diabetes mellitus (T2DM) patients.**





Physiol. Genomics 29: 99-108, 2007

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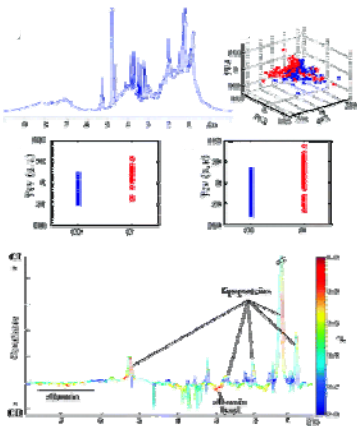
# NMR based non-targeted metabolite-profiling

**Metabolomics of plasma and urine identifies food preferences**



Multivariate data analysis of 1H NMR plasma metabolic profiles. (a) A 600 MHz 1H NMR spectrum of human plasma. (b) 3D PCA scores plot for data from standard 1H NMR spectra from all plasma samples collected while under dietary control; blue square, "chocolate desiring"; red circle, "chocolate indifferent"; PC1, PC2, and PC4, 55%, 12%, and 6% of the total variance, respectively. (c) O-PLS-DA cross-validated scores (Tcv) plot (Q2 = 0.15 (7-fold cross-validation) of samples before chocolate/placebo intake (P2-1 and P4-1). CD and CI indicate "chocolate desiring" and "chocolate indifferent" subjects, respectively. (d) O-PLS-DA cross-validated scores plot (Q2 = 0.36 (7-fold cross-validation) of all samples showing that chocolate consumption has little effect on the model. (e) Coefficients plot derived from all the plasma samples. The O-PLS-DA coefficients plots are presented using a back-scaling transformation, as described previously,19 which allows each variable to be plotted with a color code which relates to the significance of class discrimination as calculated from the correlation matrix. Positive peaks are from metabolites that are higher in the "chocolate indifferent" class.

J Proteome Res. 2007 Nov;6(11):4469-77. Epub 2007 Oct 12.

# From the research lab into the commercial environment

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Sciona – Optimal health through genetics

**Heart Health**
Analyzes twelve of your genes that may play an important role in determining how your body manages overall heart health; and, in relation to your genes, assesses nine key diet and lifestyle action areas. Heart health depends on a complex balance of environmental, dietary, and genetic factors. We have analyzed your DNA for a collection of genes that, according to the latest research, are believed to play an important part in heart health. These genes have a variety of functions, including: antioxidant activity; homocysteine levels; cholesterol; blood flow; and inflammation.

**Bone Health**
Analyzes four of your genes that may play an important role in determining how your body manages overall bone health; and, in relation to your genes, assesses seven key diet and lifestyle action areas. This analysis can identify certain variations in one or more of your bone health genes which may lead to the formation of altered proteins that may have an affect on your bone structure. These altered□□roteins may lead to bone loss, particularly if your diet lacks certain nutrients vital for bone health or if you are not physically active enough. But, this loss of bone may be slowed with proper attention to nutrition and lifestyle.

**Insulin Resistance**
Analyzes five of your genes that may play an important role in d
overall insulin resistance; and, in relation to your genes, assess
Insulin resistance refers to the diminished ability of the body's
insulin hormone. To compensate, the pancreas secretes more in
the bloodstream. Physicians suspect that insulin resistance ma
most common health disorders including type 2 diabetes, high
disrupted fat metabolism.

**Genetic Assessment for Antioxidant and Detoxification**
Analyzes five of your genes that may play an important role in de
overall antioxidant/detoxification health; and, in relation to your
lifestyle action areas. Antioxidant activity is an important compo
against common health disorders, including heart disease, chron
accelerated aging. Detoxification genes are a very important part
protect you from harmful substances, which can be found in the
Medical research has shown that toxin build-up may be associat
cardiovascular disease and some types of cancer.

**Inflammation Health**
Analyzes six of your genes that may play an important role in de
inflammation; and, in relation to your genes, assesses four key
Inflammation is an essential, protective response of your body's
the presence of a protein to which you have an allergic reaction.
completed, these genes "turn off" until they are needed again ar
sometimes these genes remain "on" longer than they should, ar
are too strong
or unnecessary.

Jennie Ahlgren, Ethics, Lund University

## *The strive for health*

### Genetic tests and personalised nutritional advice

**70 % were willing to have a genetic test done in order to get personalised nutritional advice**

**67 % were willing to have a genetic test done for some other health purpose (e.g. to know how much they would be able to smoke without risking their health)**

**43 % said they would have a genetic test done even though they were likely to suffer psychologically from it**

**70 % believes that their quality of life would benefit from following a personalized diet**

**More than 70 % would choose a longer life with poorer quality of life over a shorter life with maintained quality of life**

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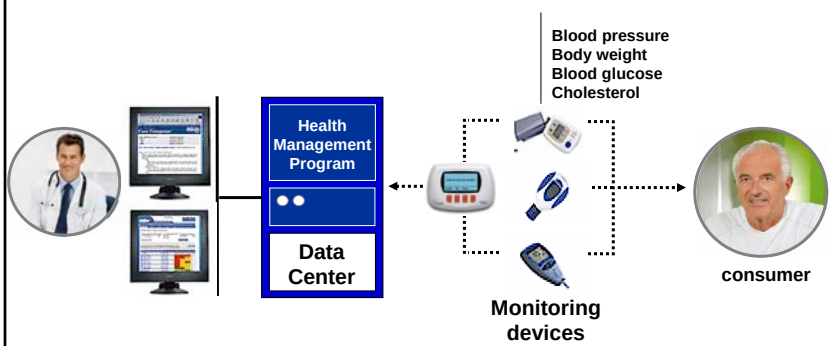
# Future perspectives

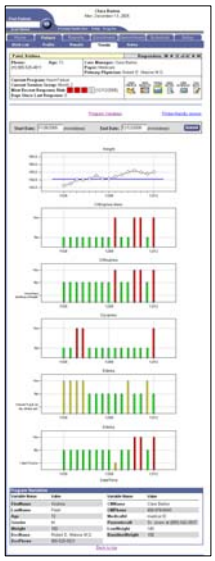
## The personal nutrition advisor





## The HEALTH-service package

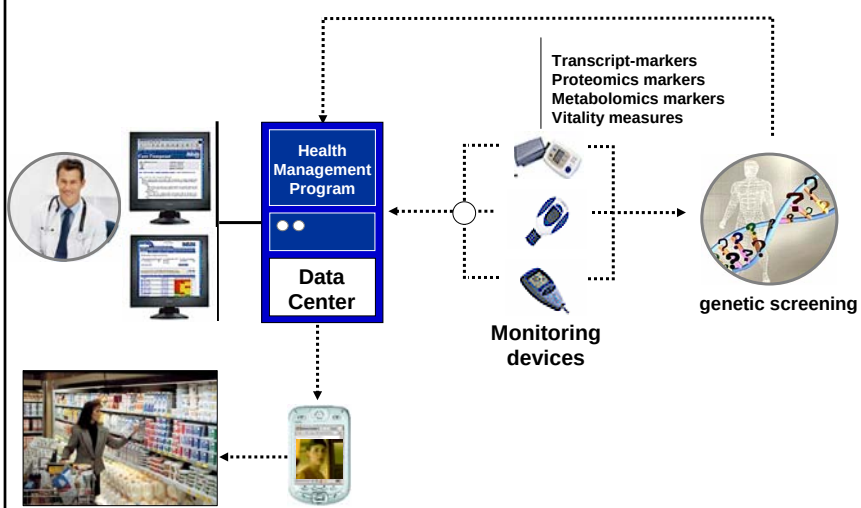


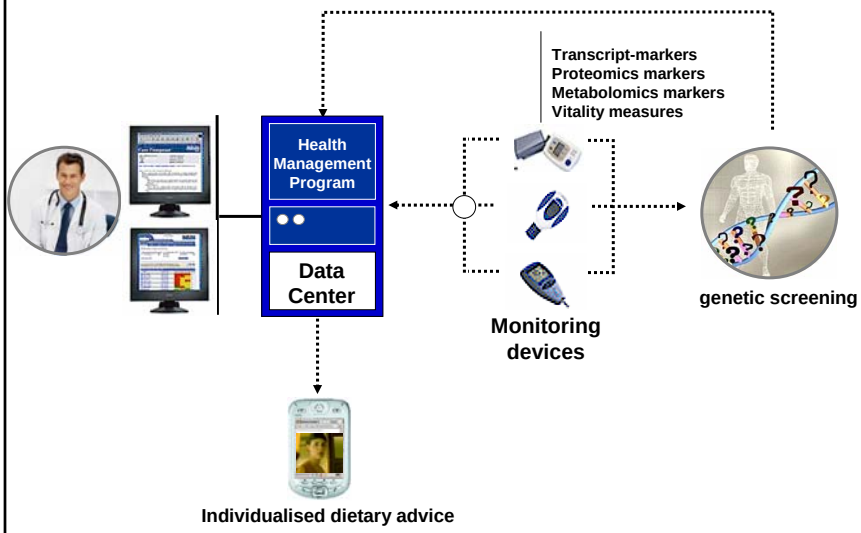




## The HEALTH-service package



# The HEALTH-service package

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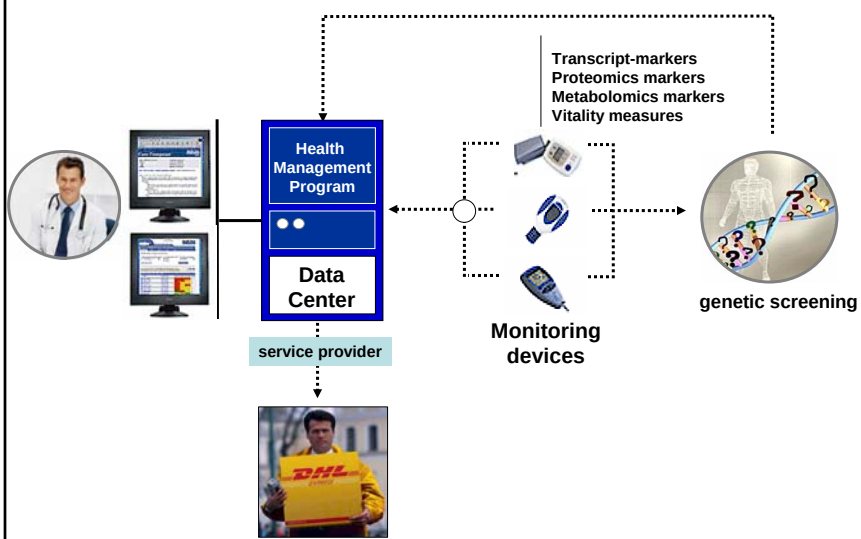
# The HEALTH-service package



# Summary

- Die breathtaking progress in biosciences and the worldwide efforts for comprehensive genotyping and disease risk-assessment set the basis for individualised nutrition concepts
- The personalisation creates new markets with a fast spectrum of services and products and combinations thereof
- Commercially offered genotyping in combination with dietary advice currently lacks a sufficient scientific basis and advice is therefore mostly generic
- Comprehensive geno- and phenotyping in the end only communicates STATISTICAL RISKS and therefore COMPLIANCE becomes the central element.