Nutrigenomics and Nutrigenetics
The Scientific Context

Christian Bréchot
Vice-President Institut Merieux
Scientific and Medical Affairs

christian.brechot@institut-merieux.com

Biomarkers

Nutrigenomics

Effect of food and nutrients on the genome expression
Risk: Obesity, Diabetes type 2 etc..

Personalised Health Care

Personalised Nutrition? (Personalised Dietary and Phenotype analysis)

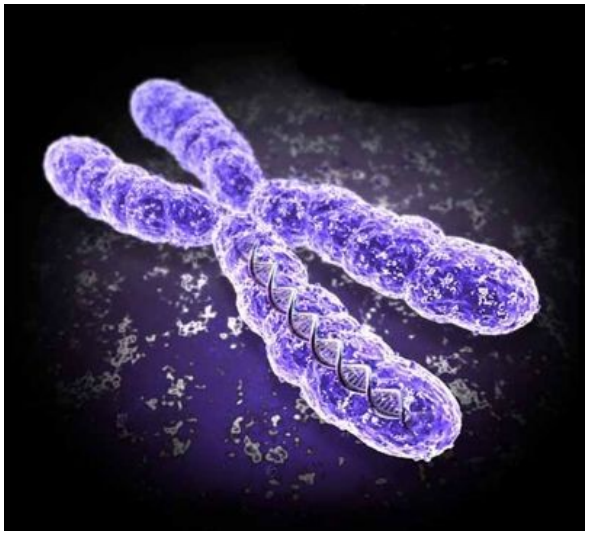
DNA-based tests and counselling

Nutrigenetics

Impact of genetics on the food and nutrients effects

Nutrigenomics

Specific groups
or
Individual, Personal,
Patterns of Response?



Nutrigenetics

Modified from S Massart

Scientific Background

- **Nutritional environment modifies the expression of genes: Which biomarkers?**

- **Nutrients metabolism is dependent on genetics and this may impact health**

- **Single gene-related diseases are rare but have a clear impact**

- **Multiple gene-related diseases are the most frequent and much more complex to analyze: Wich impact?**

A representative example of modern Nutrigenomics

- **Diet-driven changes:**

Anti-inflammatory diet mix in healthy but overweight men:

The effects are personal and can be revealed by a visualisation method (« health Space »)

Three patterns of changes, in three different group of individuals:

Metabolic and oxydative response

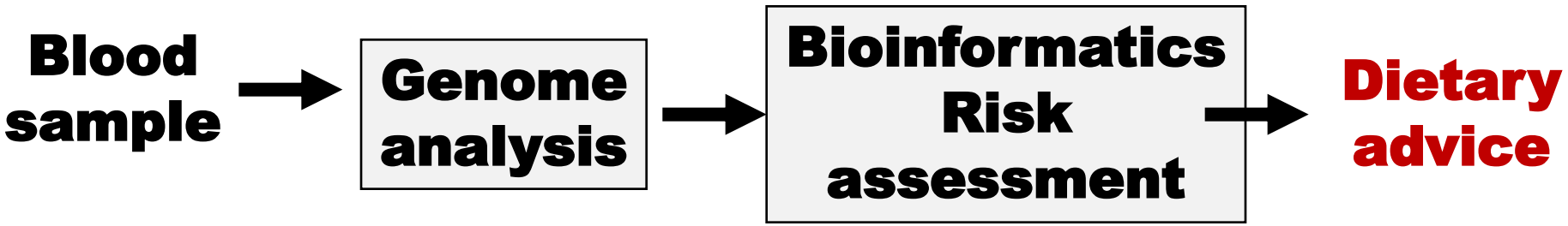
Metabolic and oxydative with low inflammatory response

Inflammation markers

Bakker et al Am J Clin Nutr 2010; 91 (4) 1044-1059

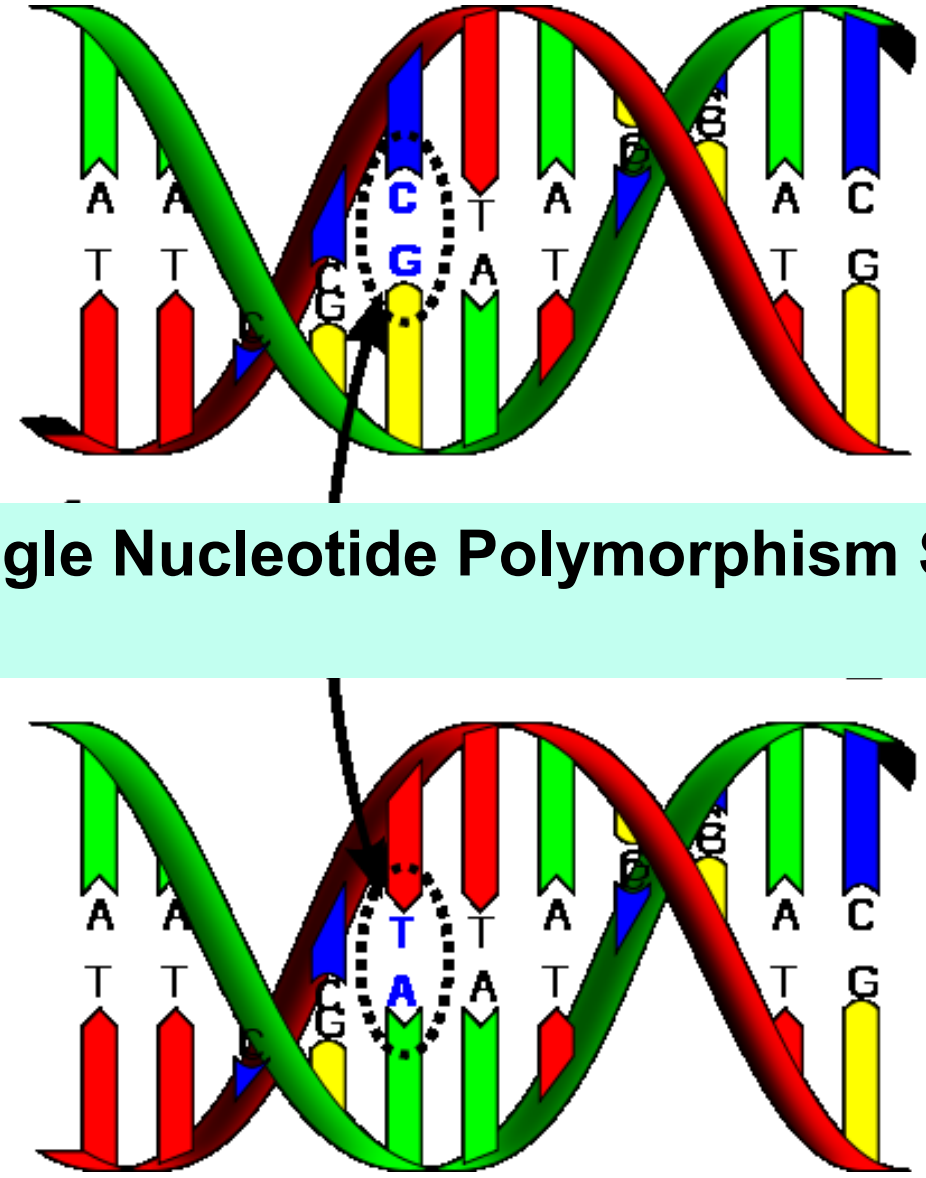
Dietary advice based on genetics

The "vision"



Only 24.000 genes…However, 9.000.000 variants

- ❑ Single Nucleotide Polymorphisms (SNP)
- ❑ Sequencing



Single Nucleotide Polymorphism SNP

Nutrigenetics today

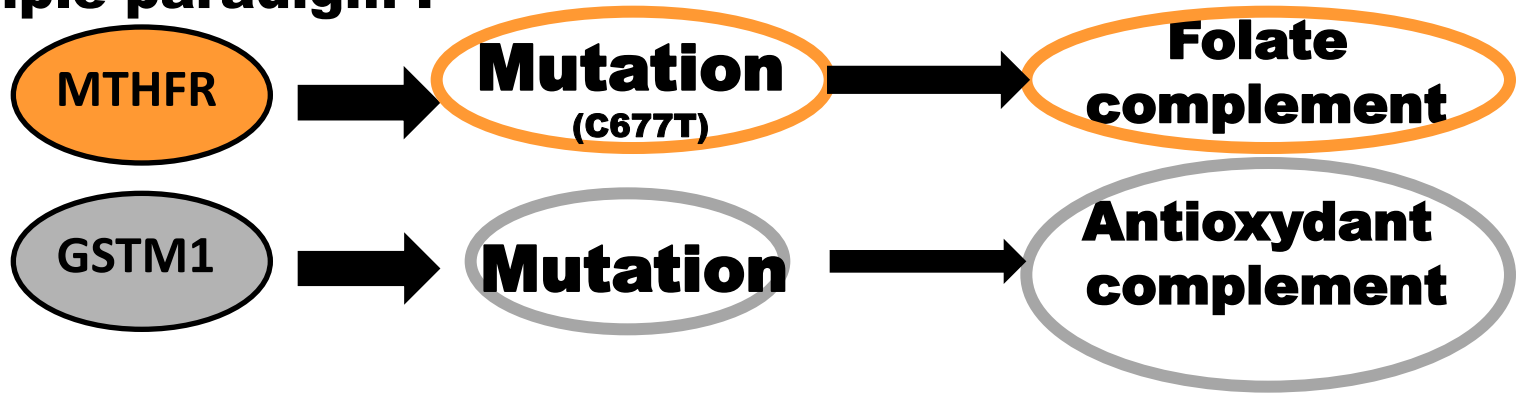
Genome sequencing, SNPs analyses

- **Only coding regions (sequencing)**

- **20-50 genes: NAT2, MTHFR, T2R, AMY1, G Proteins**

  - **Weight Management,**
  - **Heart health,**
  - **Nutritional needs,**
  - **Bone health**

- **Simple paradigm :**



S Massart

Personalised Nutrition Testing now offered by companies

Examples:

-Sciona
-Genelex
-Market Amerika
-SuraCell

Test pricing: 100 to 1000 US$

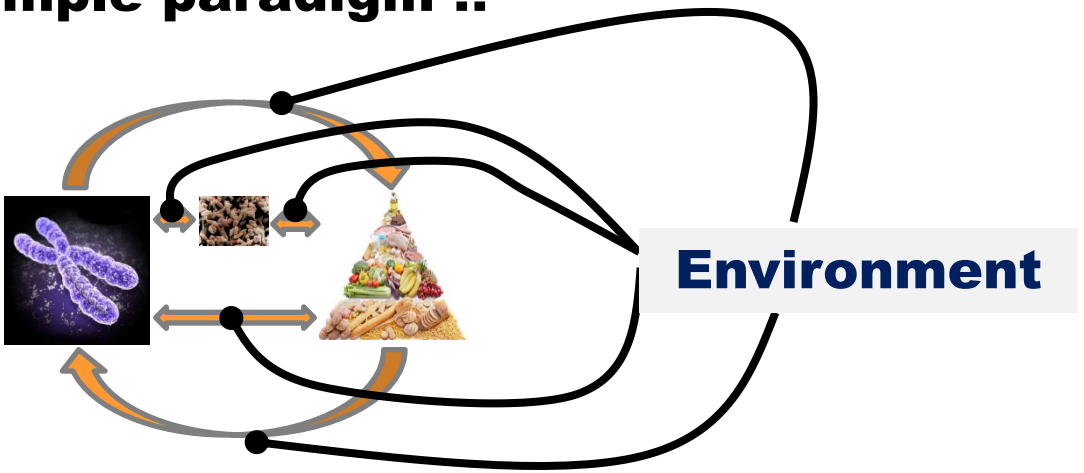
Insulin Resistance

- **"Analyzes five of your genes that may play an important role in determining how your body manages overall insulin resistance"**
- **"..assesses five key diet and lifestyle action areas"**

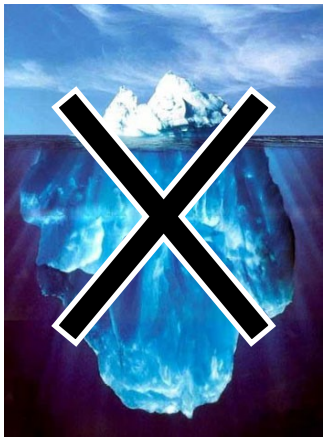
Gene Analyzed	Role of the Gene in Insulin Resistance	Genetic Variation Screened For Variations Found in Your Gene	Percentage of Population with this Gene Variation*
VDR	Mechanism of Insulin Secretion	CTaqIT	70.6
VDR		TBsmIC	69.6
IL-6	Inflammatory Response; Response of Cells to Insulin	G(-174)C	36.3
TNF-α		G(-308)A	16.5
PPARγ	Glucose and Lipid Metabolism	Pro12A	61.0
ACE	Blood Pressure Regulation	II/DD	10.3

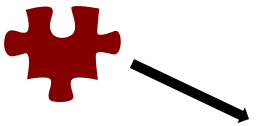
*The population frequencies given are normalized for the U.S. population data from the U.S. 2002 Census Report. Population frequencies can vary for different ethnic groups, so for more detailed information, please turn to the Population Frequency Data Table in the Reference Section of your report.

- **Not a simple paradigm !!**

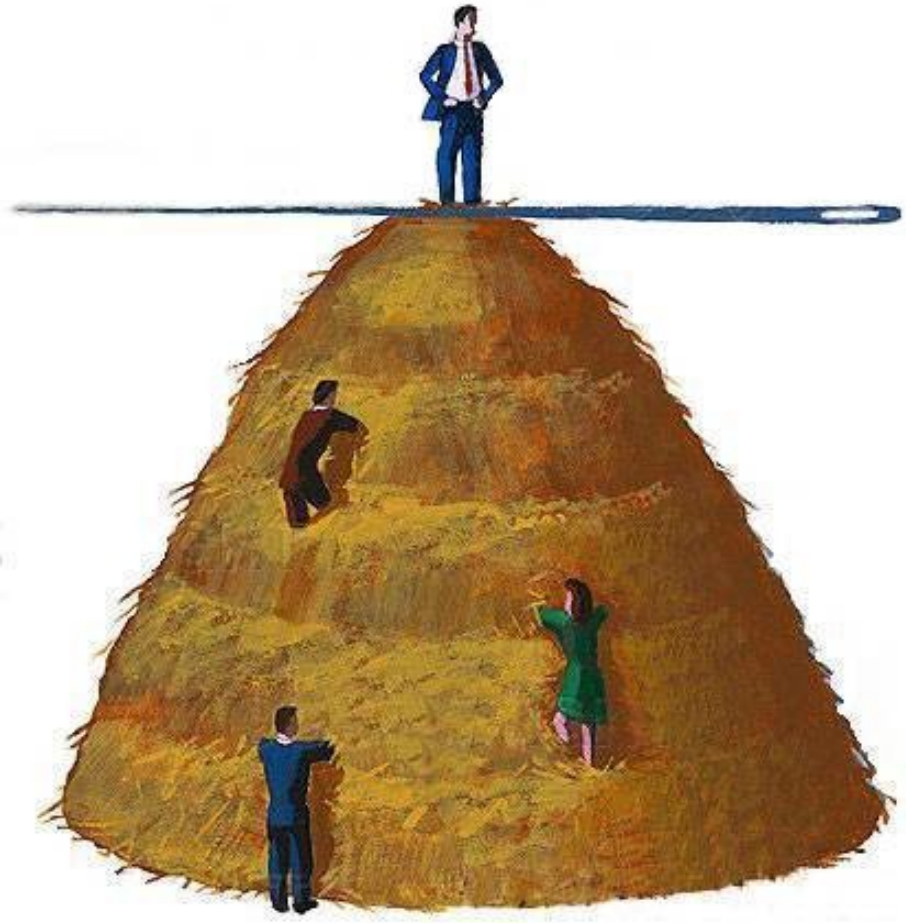


- **Technology:**
  - **Studying 20 genes = <0.003 % of the genome**
  - **Studying 1M mutations (Microarray) = 0.03 % of the genome**





S Massart



10-30 million SNPs believed to exist (4 million known)

How useful is data on 1 SNP?

The future relies on Genome Wide Association Studies (GWAS) (+100,000 SNPs)

The number of copies of the 16p11.2 region predicts BMI

Mirror extreme BMI phenotypes associated with gene dosage (Genome Wide Association Study (GWAS))

Deletion
Hemizygosity
(600 Kb region)

Normal Dosage

Duplication

Relative risk: 43 fold

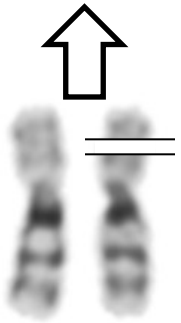
8.3 (23.2 Males)
(4.7 Females)

Number of patients: 95 000

S Jacquemont et al Nature 2011

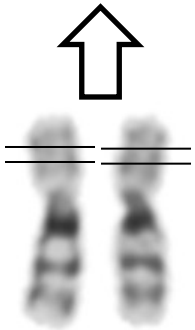
Contrasting phenotypes

autism



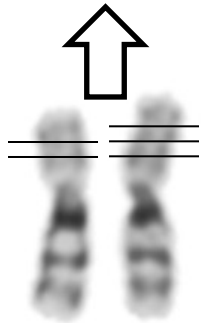
deletion

sociability



normal dosage

schizophrenia

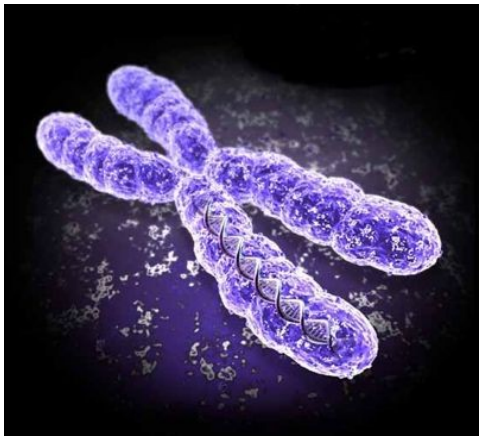


duplication

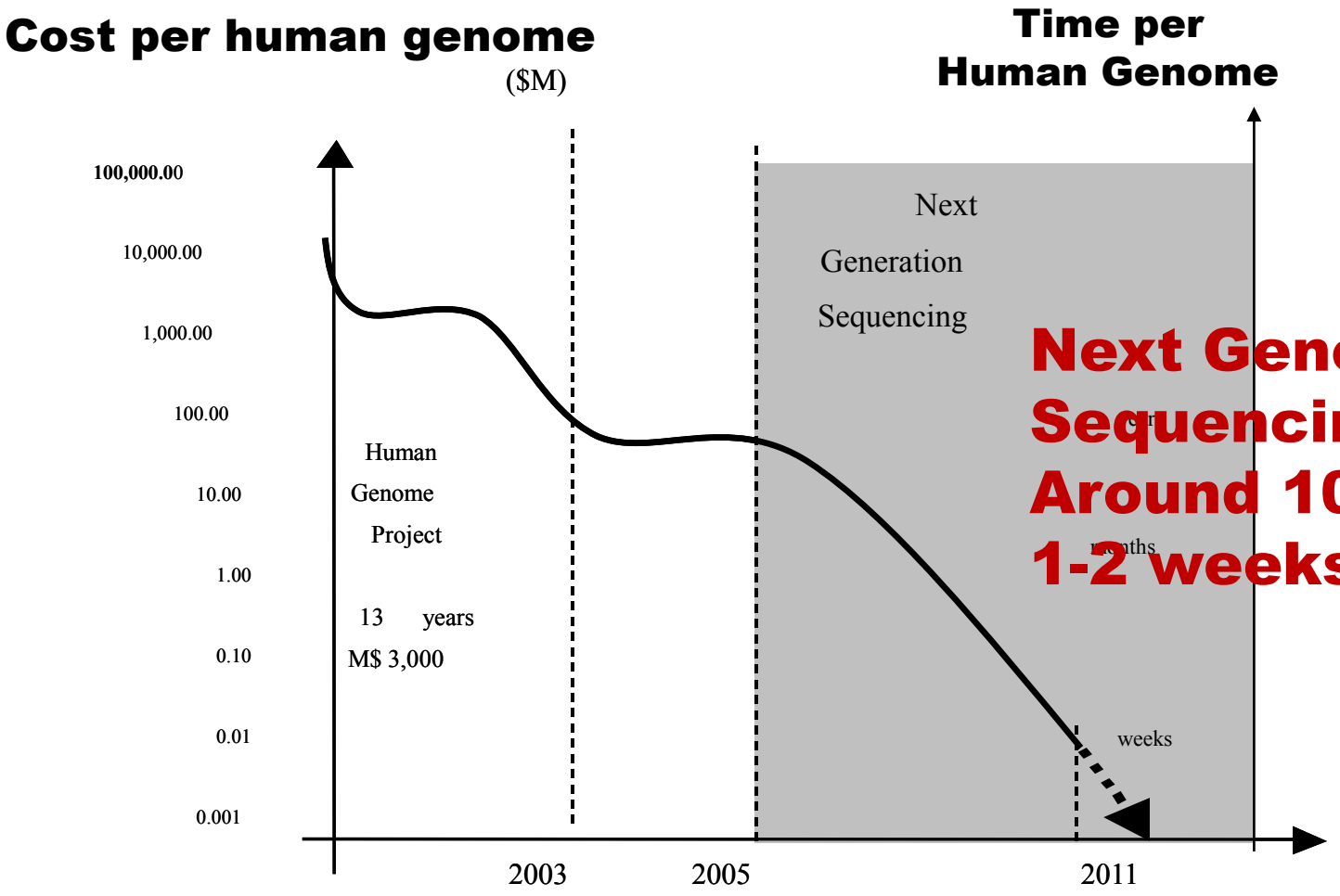
➢ **Understanding also relies on plenty of genomic variations, including :**

- **Non coding DNA**
- **Epigenome**
- **Metagenome**

➢ **Genome Sequencing will be a key technology to reveal those variants :**



DNA sequencing is now amenable to a diagnostic test context



Next Generation Sequencing
Around 1000 US$
1-2 weeks

Key issue: Integration of data, bioinformatics

The real impact of genetic testing ?

❑ The Case against:

- What does it mean to test for one gene polymorphism?
- Even in studies based on GWAS or deep sequencing the relative risk which is evidenced is very low: around 2-3 fold

❑ The Case for:

- Well targeted single genetic trait may have a profound impact: ex: cholesterol levels

- With the advent of whole genome sequencing and progress in bioinformatics, combination of several polymorphism may lead to significant risk factors identification

Potential Benefits

- **At the population level**

Identify subgroups who might be particularly responsive or resistant to dietary intervention

Provide a better understanding of the mechanisms involved in disease susceptibility

- **At the individual level**

Increase awareness of risk

Motivate behavior changes (diet, life style)

Enhance prevention

Limitations (1)

- **Technological**:

Bioinformatics

Interpretation of data: Misleading claims

- **Psychological impact** (individual and family)

- **Medical**: Attention drawn away from other modifiable risk factors, decreased use of other services, false sense of security

Limitations (2)

- **Public Health**:

Increased costs associated with personalized diets and designer foods

Targeting vulnerable populations

Concerns surrounding confidentiality, insurance

Dilute or contradict public health messages

"Buyer Beware"

A recent report by the Government Accountability Office highlighted a few of the concerns with four examples of DTC nutrigenomic tests.

- **The GAO report raised concerns that the tests may mislead consumers by making unsound and ambiguous predictions about health risks.**

- **In addition, the test results frequently include recommendations for the consumer to purchase dietary supplements that may be significantly overpriced compared with similar products available through a supermarket or pharmacy and that may, in fact, be harmful for some individuals.**

USA: FDA implication

- **Direct to consumer (DTC) genetic testing remains as a business model**
  - **Some bodies have issued statements against DTC genetic model**
    - **Failure of interpretation, incorrect decision-making**
  - **Others have championed DTC genetic testing model**
    - **Personal empowerment, proactive health strategies**
  - **Others request appropriate oversight for DTC genetic testing**
    - **Protect individuals from incorrect information, protect privacy**
- **FDA working with companies to come into compliance with FDA regulations for medical devices**
- **Panel intended to gain broad-based information on important issues in DTC genetic testing**

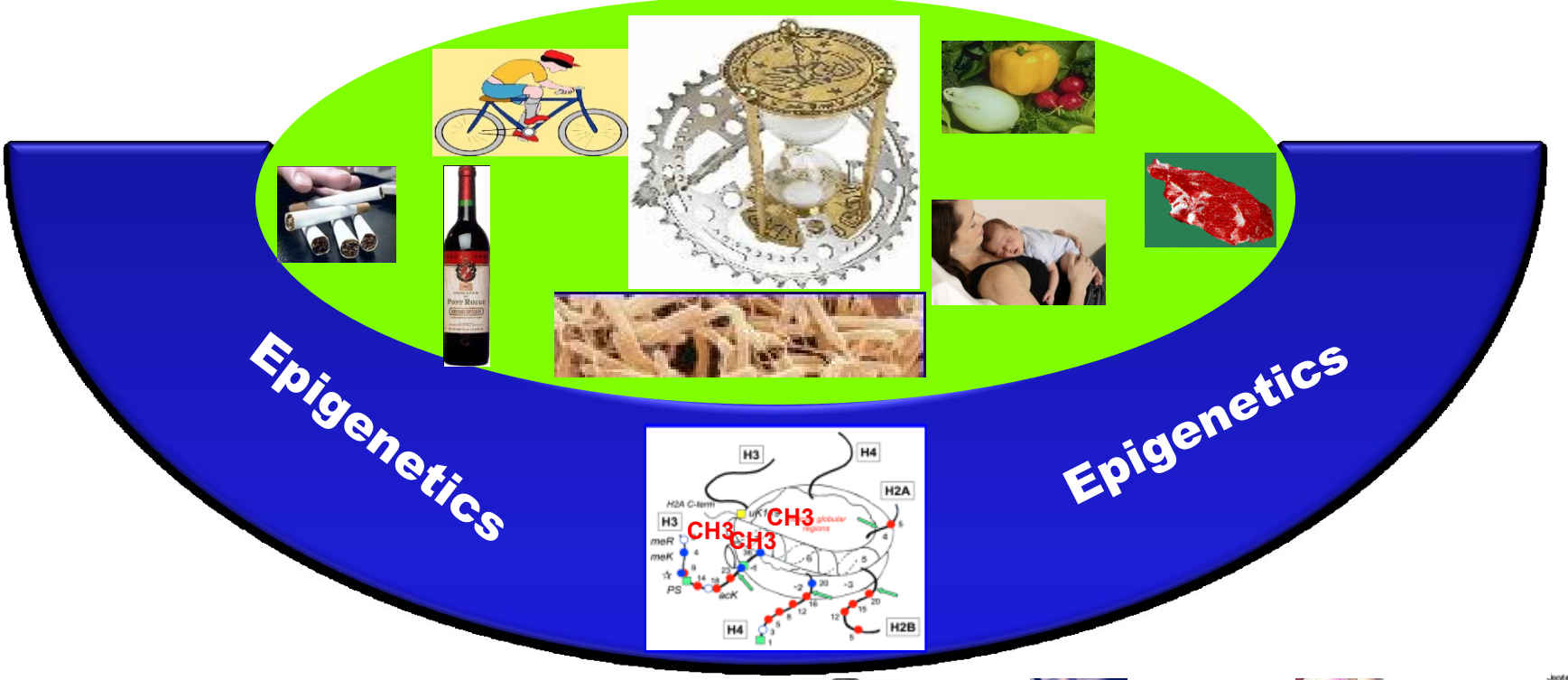
Nutrigenomics

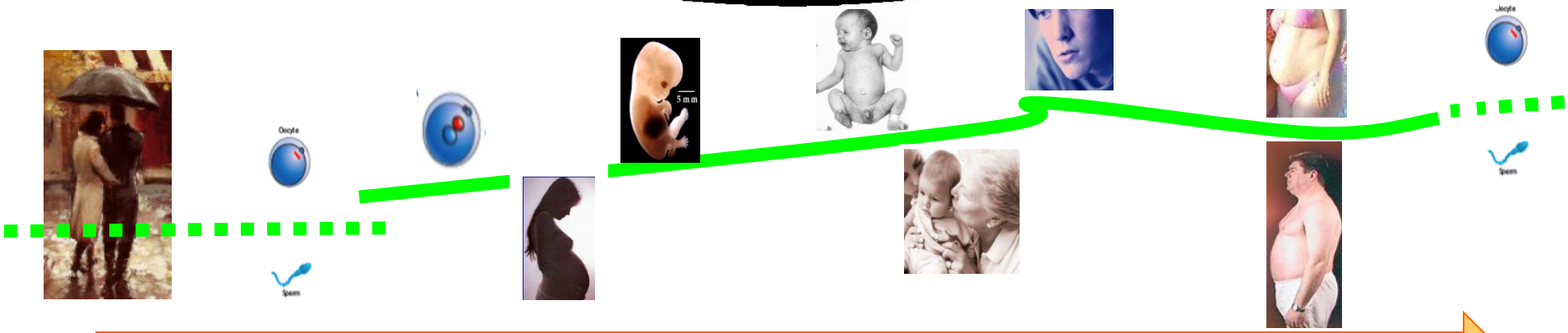
Specific groups
or
Individual, Personal,
patterns of response?

Epigenetics

Nutrigenetics

Modified from S Massart





Long term effects

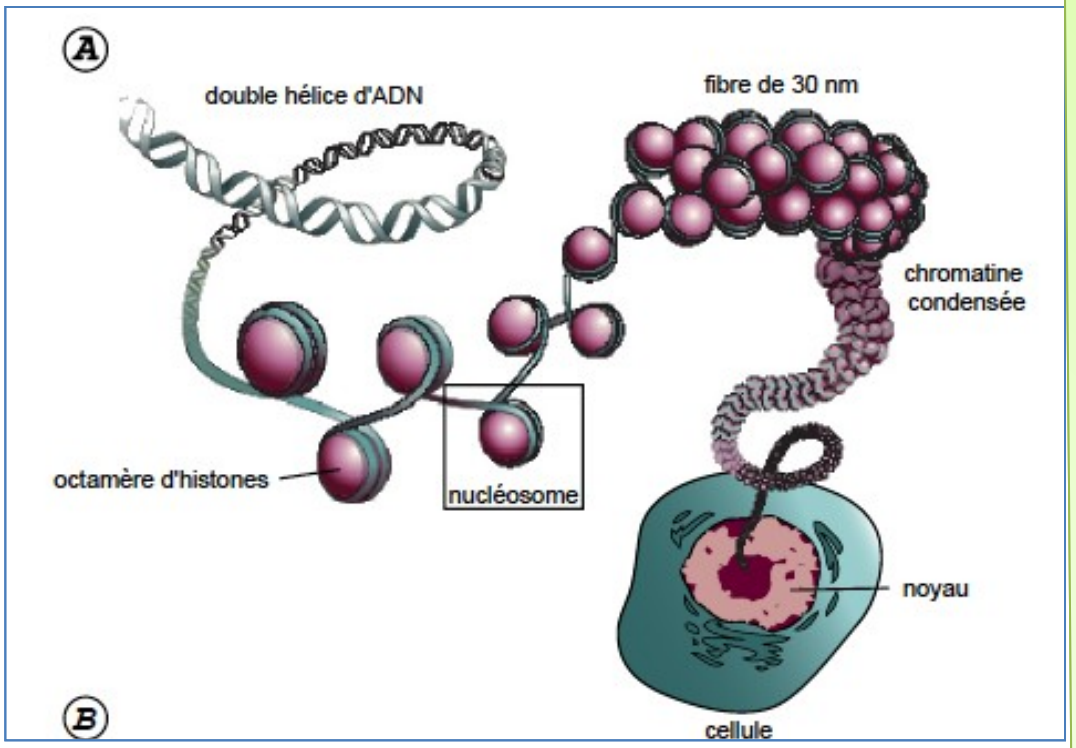
Ageing

Sexual dimorphism

If DNA is the hardware, epigenetics is the software that tells genes what to do

Genetics
DNA sequence variations
irreversible

Epigenetics
post translational modifications
reversible



Transcription (expression)

Repair
Replication,
Condensation,
X Inactivation,
Genomic imprinting
Ageing
etc...

Archives

C Junien

The reversibility of altered states of chromatin is essential for interactions with the environment

INRA

An on-going construction

The actors : codes, marks and transcription factors accessibility

Caloric restriction,

Stress

Resveratrol

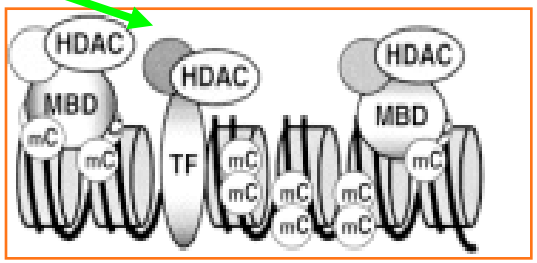
5 AzaC

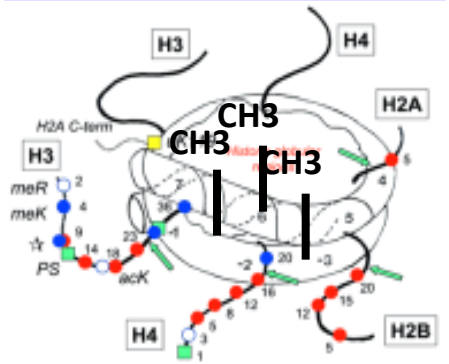
Folates

CpG, non-CpG, OHmC

Code DNA Methylation (CH3)

Silencing of gene expression





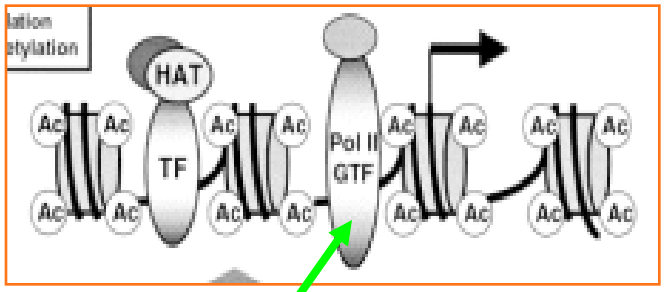
Code Corepressors/ Coactivators

Chromatin Remodeling

Flexible!

But heritable

Thru cell division



Code Histones Variants + modifications

9 ≠ classes of marks

≥ 50 activating/repressive marks (sites)

Tissue- stage-specific expression of genes

+

NcRNA

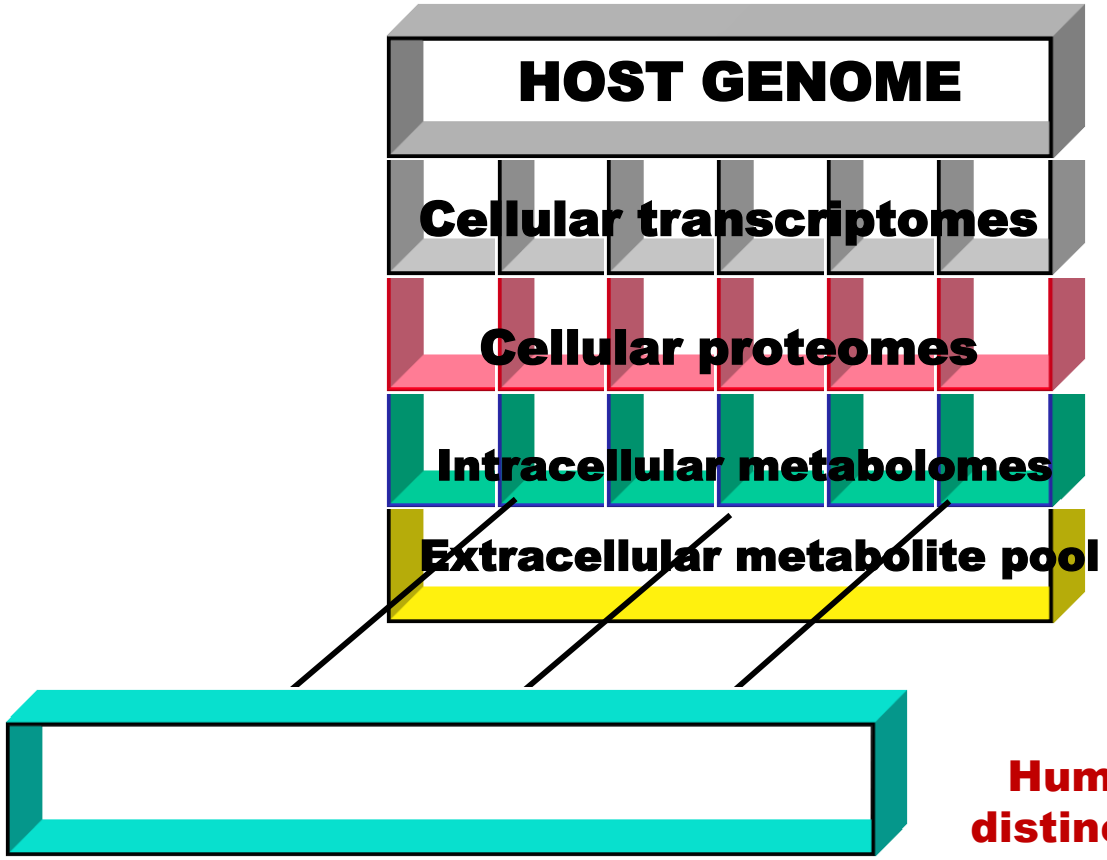
Folates *Fibers/SCFA, butyrate/ sulphoraphane*

Valproate, Trichostatine A (TSA)

C Junien

The Metabolome interactions

(Nicholson, J. et al Nature, Rev. Microbiology, 2005, 3, 2-8)



Humans: > 500 functionally distinct NORMAL cell types/ca. 10 trillion parenchymal cells

nature

Vol 453|15 May 2008|doi:10.1038/nature06882

LETTERS

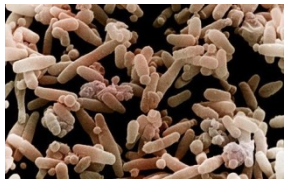
Human metabolic phenotype diversity and its association with diet and blood pressure

Holmes, E. et al (2008) ***453*** *396-400.*

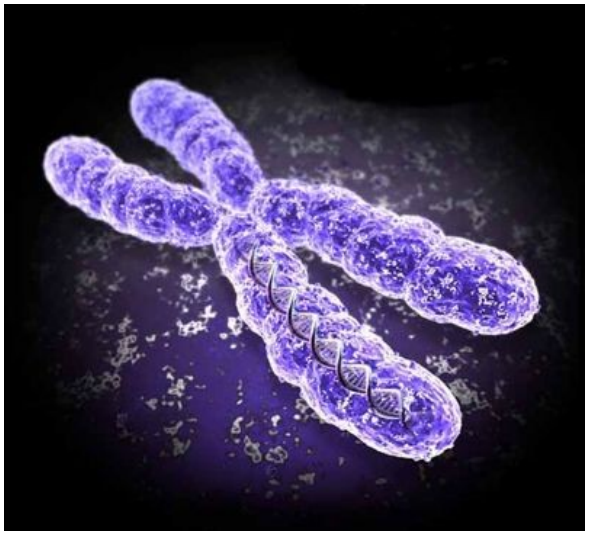
THE "METABOLOME-WIDE ASSOCIATION STUDY" (MWAS) CONCEPT

"The broad non-selective analysis and statistical interrogation of metabolic phenotypes in relation to epidemiologic end-points and risk factors to generate testable physiological or pathway hypotheses".

Nutrigenomics



Intestinal
Metagenomics

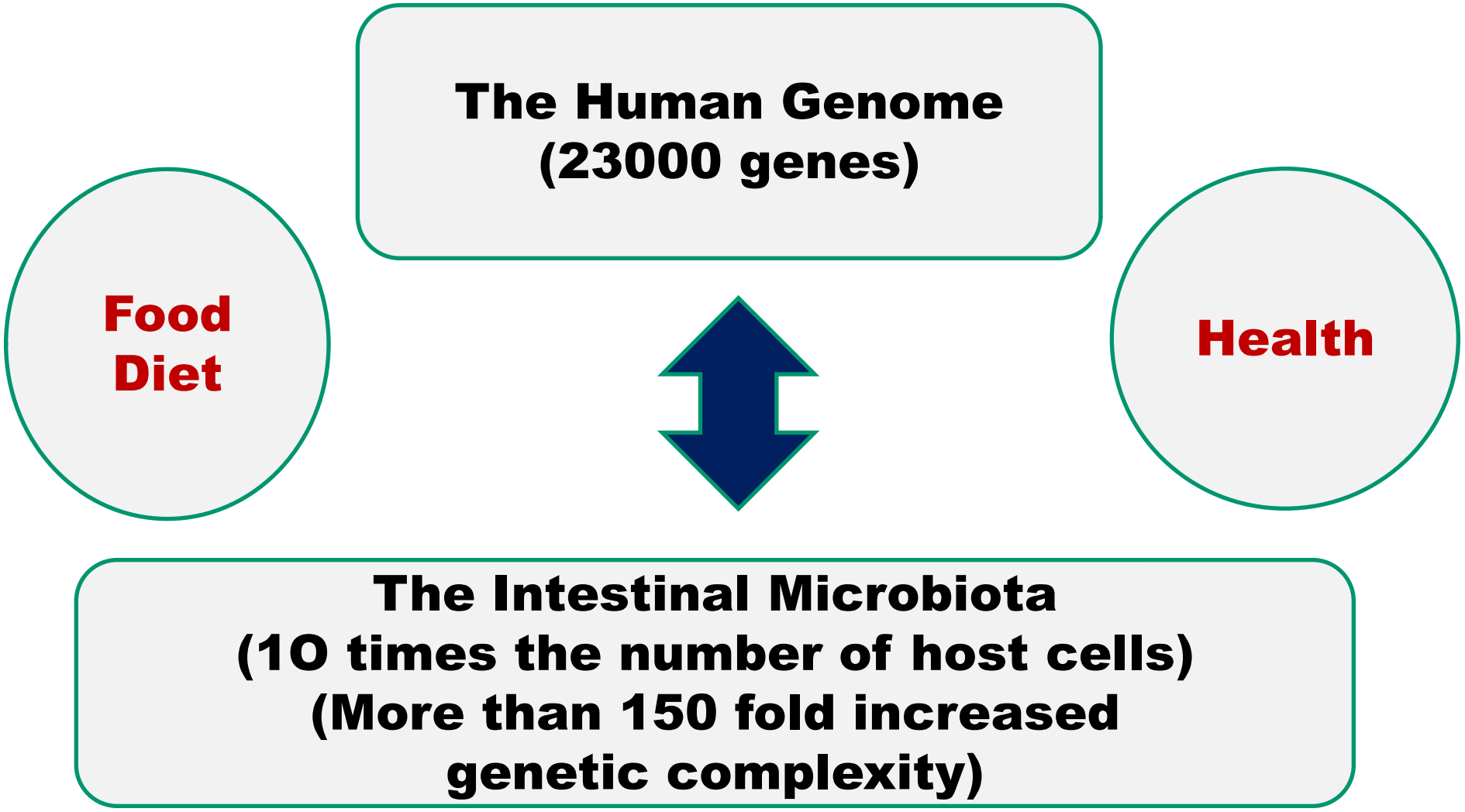


Genomics
Epigenetics

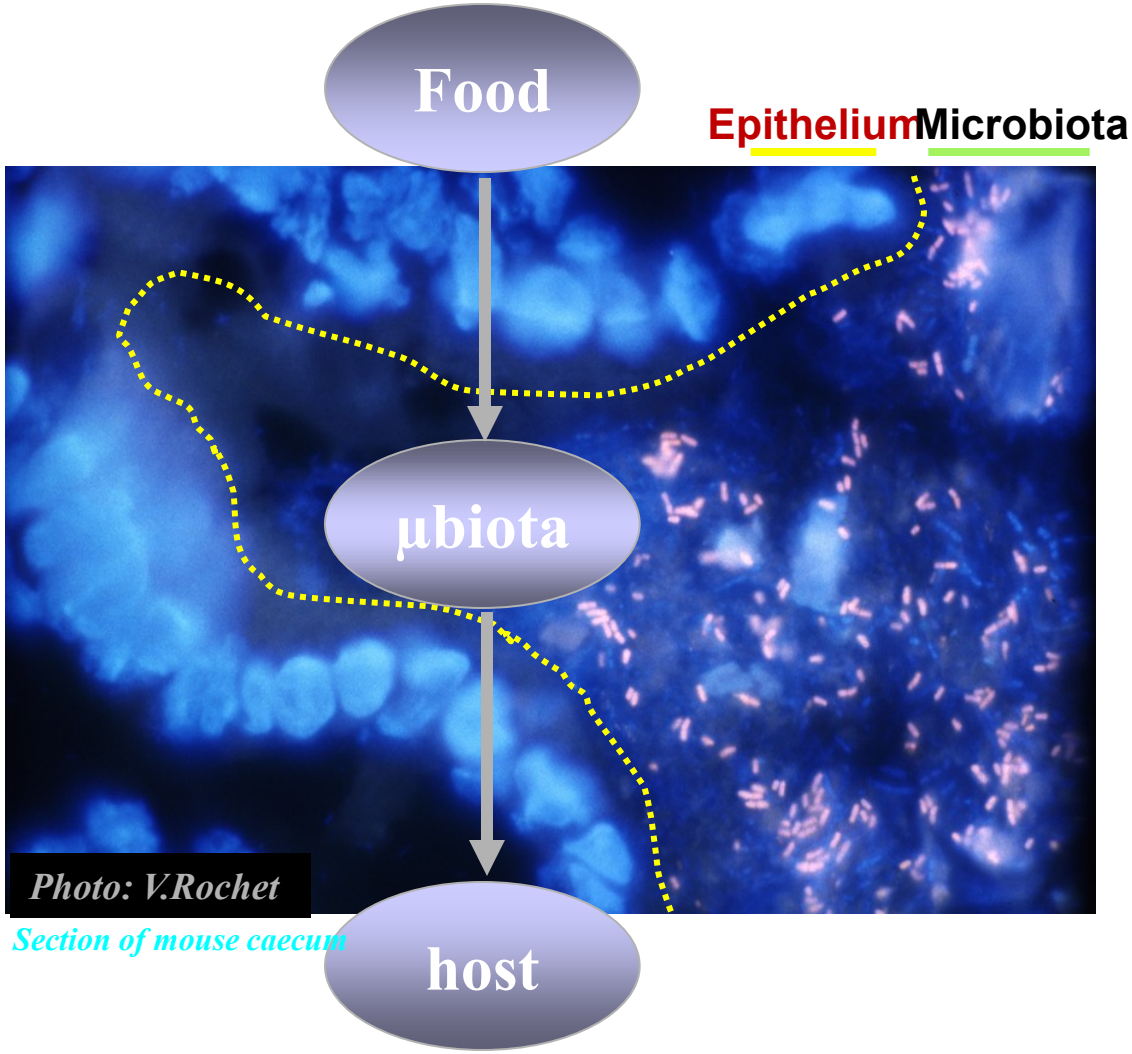
Nutrigenetics

Modified from S Massart

The Interface between our two genomes: A novel paradigm for nutrition



The human intestinal microbiota : dense, structurally and functionally diverse

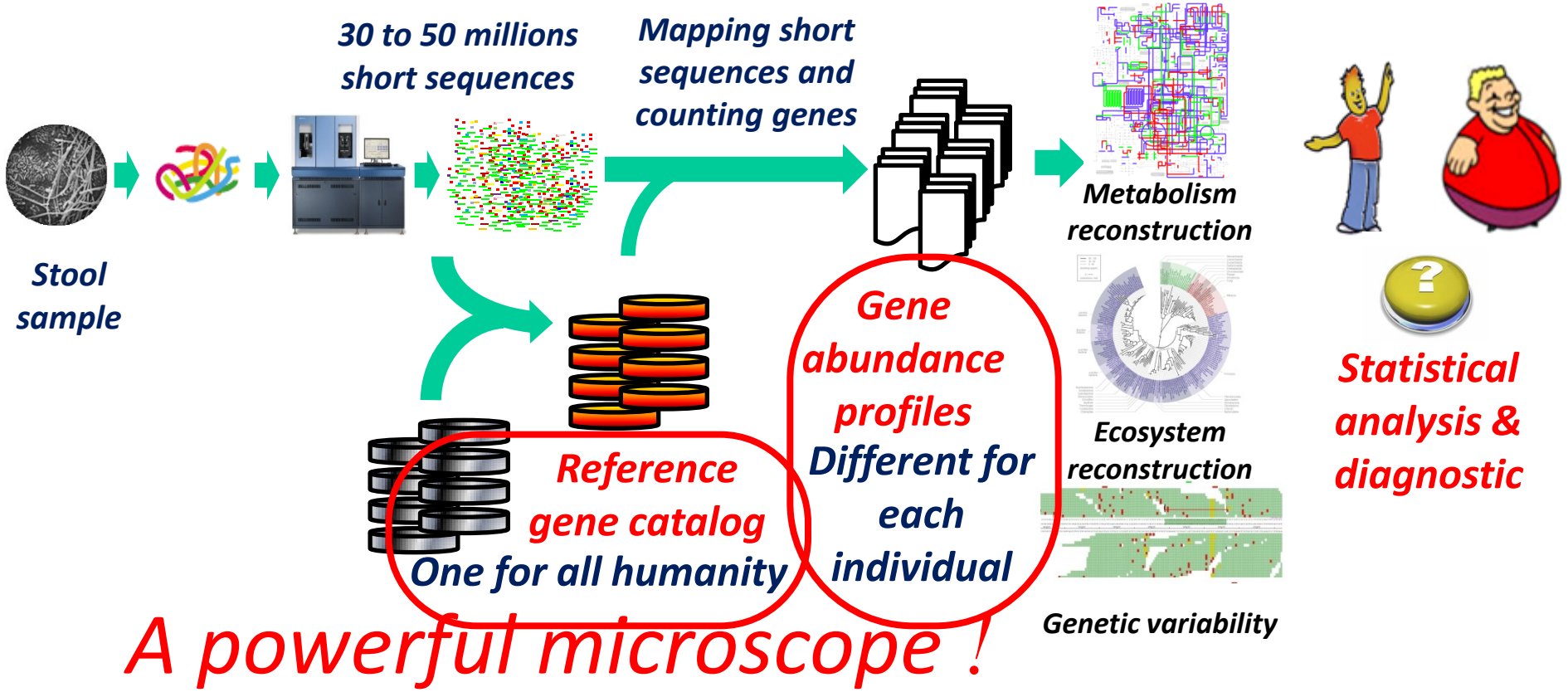


Health <-> Disease

- faecal microbiota : 100 trillions microorganisms
- hundreds of species ...
- normal consortium adapted and functionally stable

- nutrition, physiology, immunity & protection

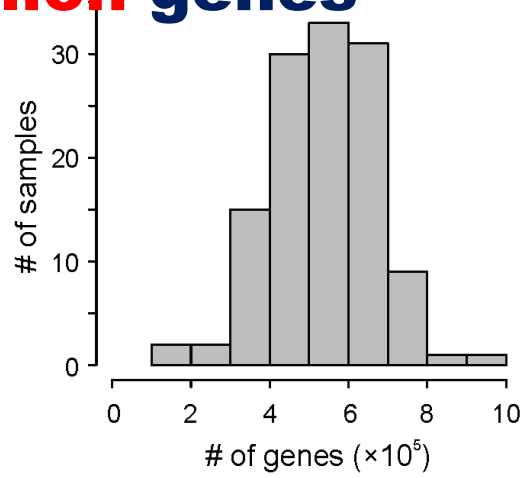
Quantitative metagenomics



H Blottière

Human intestinal microbial genes are largely shared in the cohort

Each individual has ~540 000 of the 3.3 million genes



40 % of an individual's genes are shared with at least 50 % of individuals of the cohort

Rare genes = genes shared by less than 20 % of individuals = 2.4 million genes

We are all rather similar!

But not identical!!

MetaHIT

ARTICLE

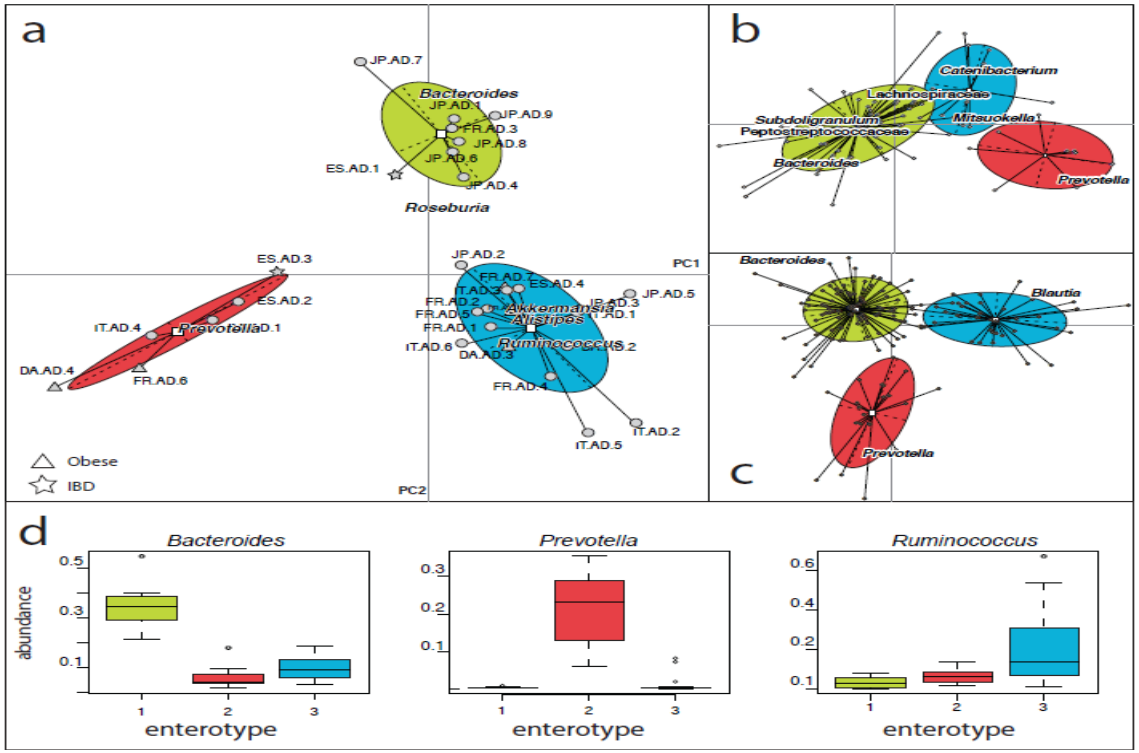
doi:10.1038/nature09944

Enterotypes of the human gut microbiome

Manimozhiyan Arumugam[1]*, Jeroen Raes[1,2]*, Eric Pelletier[3,4,5], Denis Le Paslier[3,4,5], Takuji Yamada[1], Daniel R. Mende[1], Gabriel R. Fernandes[1,6], Julien Tap[1,7], Thomas Bruls[3,4,5], Jean-Michel Batto[7], Marcelo Bertalan[8], Natalia Borruel[9], Francesc Casellas[9], Leyden Fernandez[10], Laurent Gautier[8], Torben Hansen[11,12], Masahira Hattori[13], Tetsuya Hayashi[14], Michiel Kleerebezem[15], Ken Kurokawa[16], Marion Leclerc[7], Florence Levenez[7], Chaysavanh Manichanh[9], H. Bjørn Nielsen[8], Trine Nielsen[11], Nicolas Pons[7], Julie Poulain[3], Junjie Qin[17], Thomas Sicheritz-Ponten[8,18], Sebastian Tims[15], David Torrents[10,19], Edgardo Ugarte[3], Erwin G. Zoetendal[15], Jun Wang[17,20], Francisco Guarner[9], Oluf Pedersen[11,21,22,23], Willem M. de Vos[15,24], Søren Brunak[8], Joel Doré[7], MetaHIT Consortium†, Jean Weissenbach[3,4,5], S. Dusko Ehrlich[7] & Peer Bork[1,25]

May 2011

Europeans, Americans, Asians.
n=33;
Sanger



Danes
n=85;
Illumina

US
n=154;
454

MetaHIT

Enterotypes can be viewed as "blood groups" but the reasons for their existence remains to be elucidated

Recent publication: online September 1st (Wu et al, Science)

"Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes"

Bacteroides **enterotype → protein and animal fat ?**

Prevotella **enterotype → carbohydrate ?**

Not modified by short term (10 days) diet intervention

(2 enterotypes found, based on 16S rDNA only – inadequate resolution ?)

They should allow patient stratification & aid to develop personalized medicine and nutrition

H Blottiere

Vol 444|21/28 December 2006|doi:10.1038/nature05414 nature

ARTICLES

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

BRIEF COMMUNICATIONS

NATURE|Vol 444|21 December2006

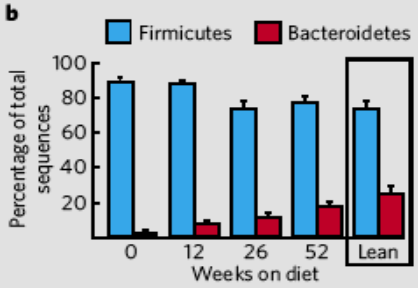
MICROBIAL ECOLOGY

Human gut microbes associated with obesity

Ruth E. Ley, Peter J. Turnbaugh, Samuel Klein, Jeffrey I. Gordon

Washington University School of Medicine, St Louis, Missouri 63108, USA

Suggested that Obese Individuals may have a lower Bacteroidetes: Firmicutes ratio than Lean Individuals – and this can be modulated by diet.



Modern 'non-infectious' human diseases with associated gut microbiotal disorders.

Gastric ulcers (***Helicobacter pylori***)
Colon and other cancers.....
Autoimmune (AI) diseases
Inflammatory bowel diseases- Ulcerative Colitis & Crohn's (type IV)
Type 1 diabetes (type IV)- may be prevented by gut bugs and parasites
Primary biliary cirrhosis
Celiac disease (type IV hypersensitivity)
others too?

Insulin resistance related conditions
Type 2 diabetes and obesity...
Allergies & related immune disorders
Asthma, Eczema, Psoriasis.....(others?)
Neuropsychiatric disorders?
Autism (?), Schizophrenia?.....(others?)
Hypertension....

From: J Nicholson

Inter- and Multidisciplinarity

Handling of data: knowledge management
Bioinformatics, Systems Biology
« Big Science » and « curiosity-driven » science

Information Technology For Health « services » Business model

Nutrigenomics nutrigenetics

Public health Ethics

Cohorts Clinical studies (Interventional) Evidence based

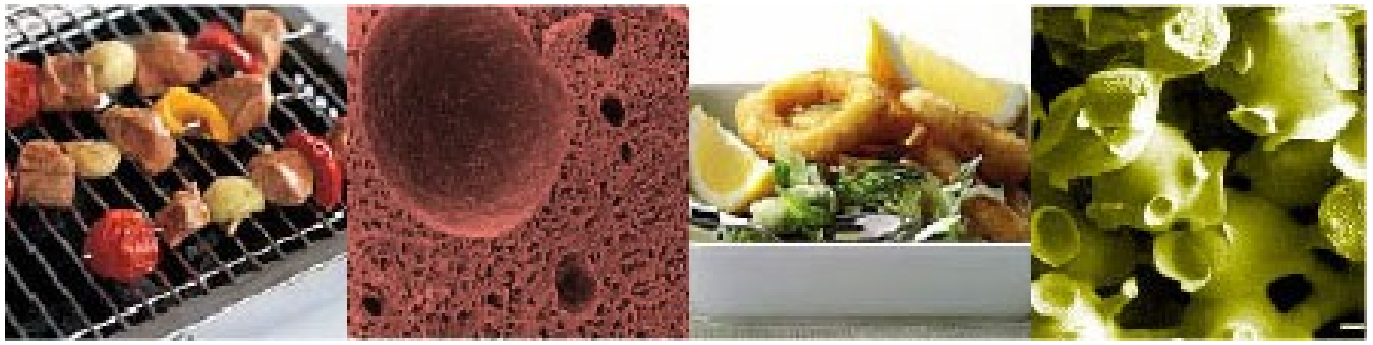
Technologies: « omics »
-Sequencing
- Epigenetic analysis
- Proteomics
-Metabonomics

Research Consortia And Networks

NuGO is a world-leading network integrating nutritional genomics in Europe.

NuGO is funded by the European Commission

2004-506360



The European Nutrigenomics Organisation:
linking genomics, nutrition and health research (NuGO)

NuGO activities
Representative examples

Challenges of molecular nutrition research :
the nutritional phenotype database to store, share and evaluate nutritional systems biology studies
Ben Omnen et al.

Time-Resolved and Tissue-Specific Systems Analysis of the pathogenesis of Insulin Resistance
Robert Kleemann et al

Nutritigenomics and Nutrigenetics

A real and most important case for the future of Personalised Health Care

Questions and Challenges

- Evidence based ? To be substantiated
- Mechanisms ?
- Which impact?:
  - group of individuals?
  - individuals ?
  - novel biomarkers ?
  - novel sciencific model:
    integration of data
    multidisciplinarity