Approches systémiques en Nutrition

Symposium JFN-CRNH : Spécificités méthodologiques de la recherche clinique en nutrition

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eisbm

CHU Grenoble
Université Grenoble Alpes

JFN 2013, Bordeaux

Déclaration d'intérêts en rapport avec la présentation, 5 dernières années

➢ **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

Oui *Société : Nutricia*

➢ **Essais cliniques, autres travaux, communications de promotion**

Non *Société: Nutricia*

➢ **Intérêts financiers (actions, obligations)**

Non

➢ **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

Non

➢ **Réception de dons sur une association dont je suis responsable**

Oui *Sociétés : Nutricia, Astra Zeneca*

➢ **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

Non

Sommaire

- **Pourquoi changer ?**
- **Qu'est-ce que l'approche systémique ?**
- **Médecine systémique, méthodes**
- **Mise en œuvre en Nutrition**

Biotechnology Journal 2012; 7 special issue on Systems biology and personalized medicine

Pourquoi changer ?

- **Augmentation non contrôlée des couts de Santé**
- **Efficience et justice en déclin**
- **Augmentation de l'incidence des maladies chroniques et cancers**
- **Limites des traitements actuels et difficultés majeures de l'innovation pharmaceutique**

Irruption de nouveaux paradigmes

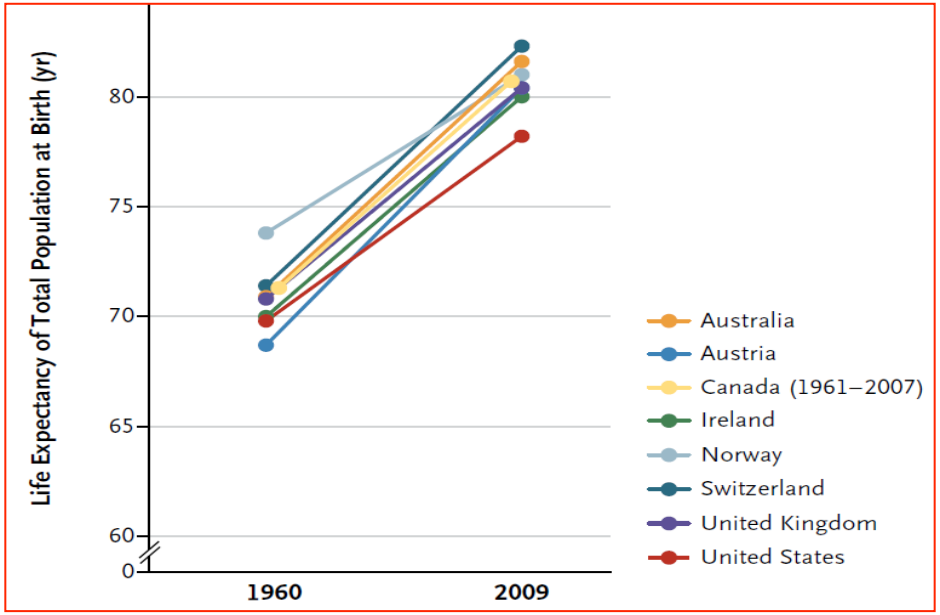
- **Explosion des données via « Exposome » & « Omics »**
  ***ou* comment utiliser ces informations au service des patients ?**

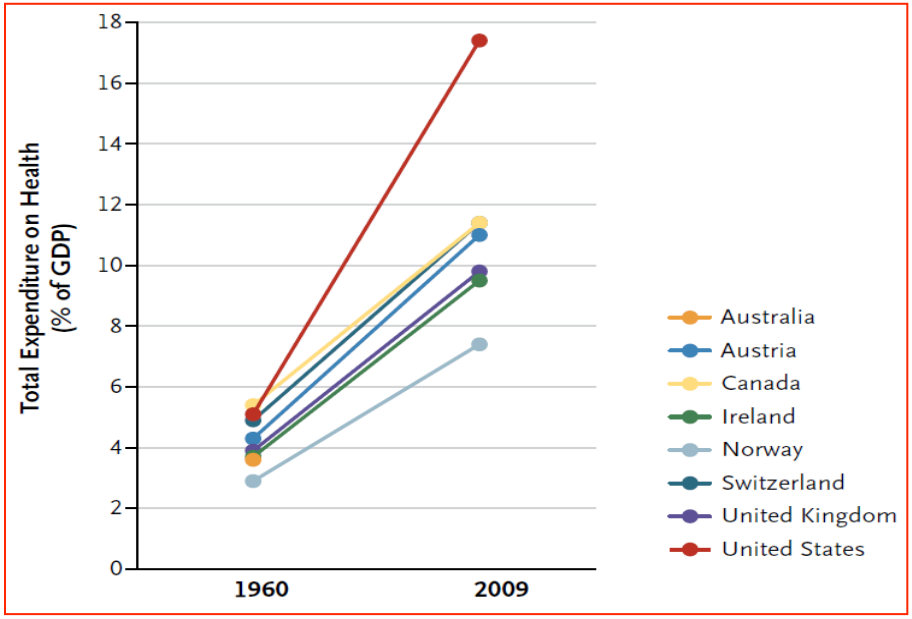
- **Médecine spécialisée *versus* systémique ?**

- **Médecine réactive *versus* proactive ?**

Augmentation non contrôlée des coûts de Santé

- **USA, 18% PIB 2009 à 30% en 2030; performance : dernier OCDE**
- **France, 12% PIB 2009, espérance vie 81 ans en 2009**





Efficience & Justice en déclin

Table 1. Cost per Quality-Adjusted Life-Year (QALY) Gained from Selected Clinical Strategies.*

Switch to an aromatase inhibitor for early-stage breast cancer vs. continued tamoxifen[8]	$22,900
Implant a cardioverter–defibrillator (primary prevention) vs. continued medical management[9]	$37,400 to $77,200
Perform fusion surgery for degenerative spondylolisthesis with spinal stenosis vs. conservative management[10]	$120,000
Prescribe trastuzumab for metastatic breast cancer vs. standard chemotherapy[11]	$150,000
Prescribe erlotinib for advanced pancreatic cancer vs. gemcitabine alone[12]	$370,000 to $500,000
Perform helical computed tomographic screening for lung cancer in 60-year-old former heavy smokers vs. no screening[13]	$2,300,000

* Values are given in 2008 U.S. dollars, with adjustment for inflation according to the Consumer Price Index. Numbers are the ratios of the added cost per person to the gain in QALYs per person.

NEJM 2010;362:460-5

Causes décès Monde 2008

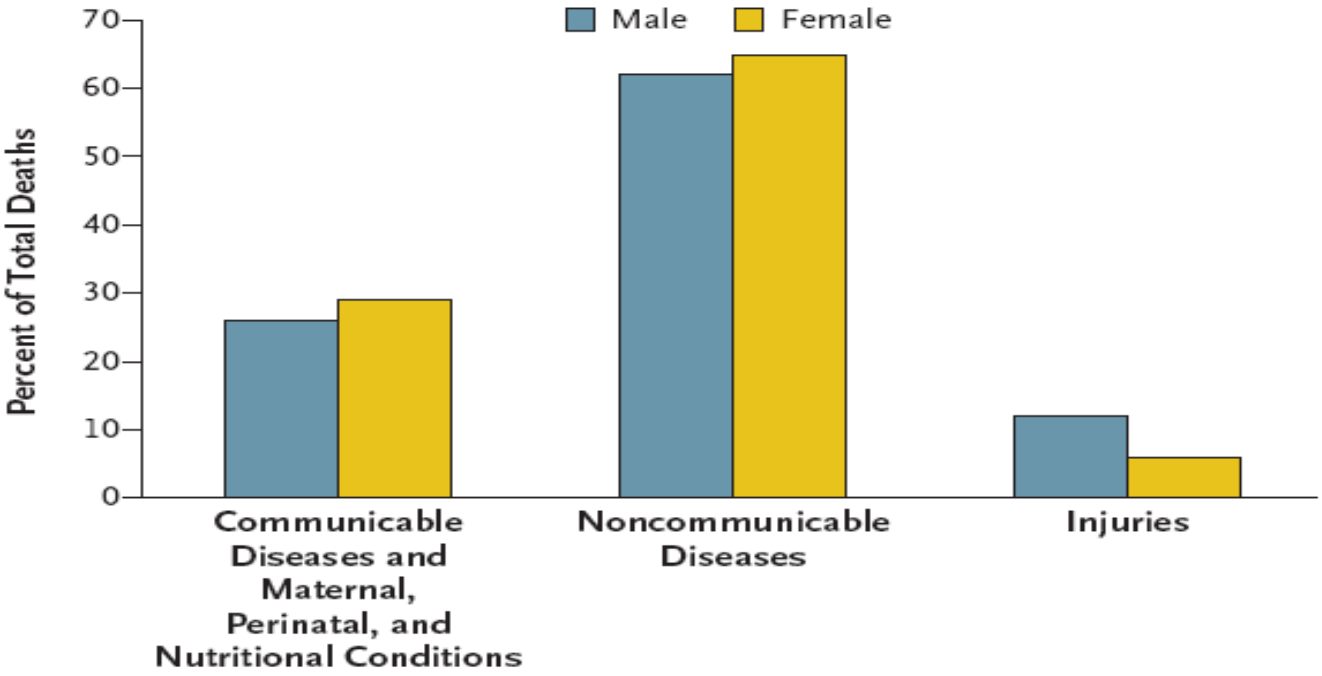
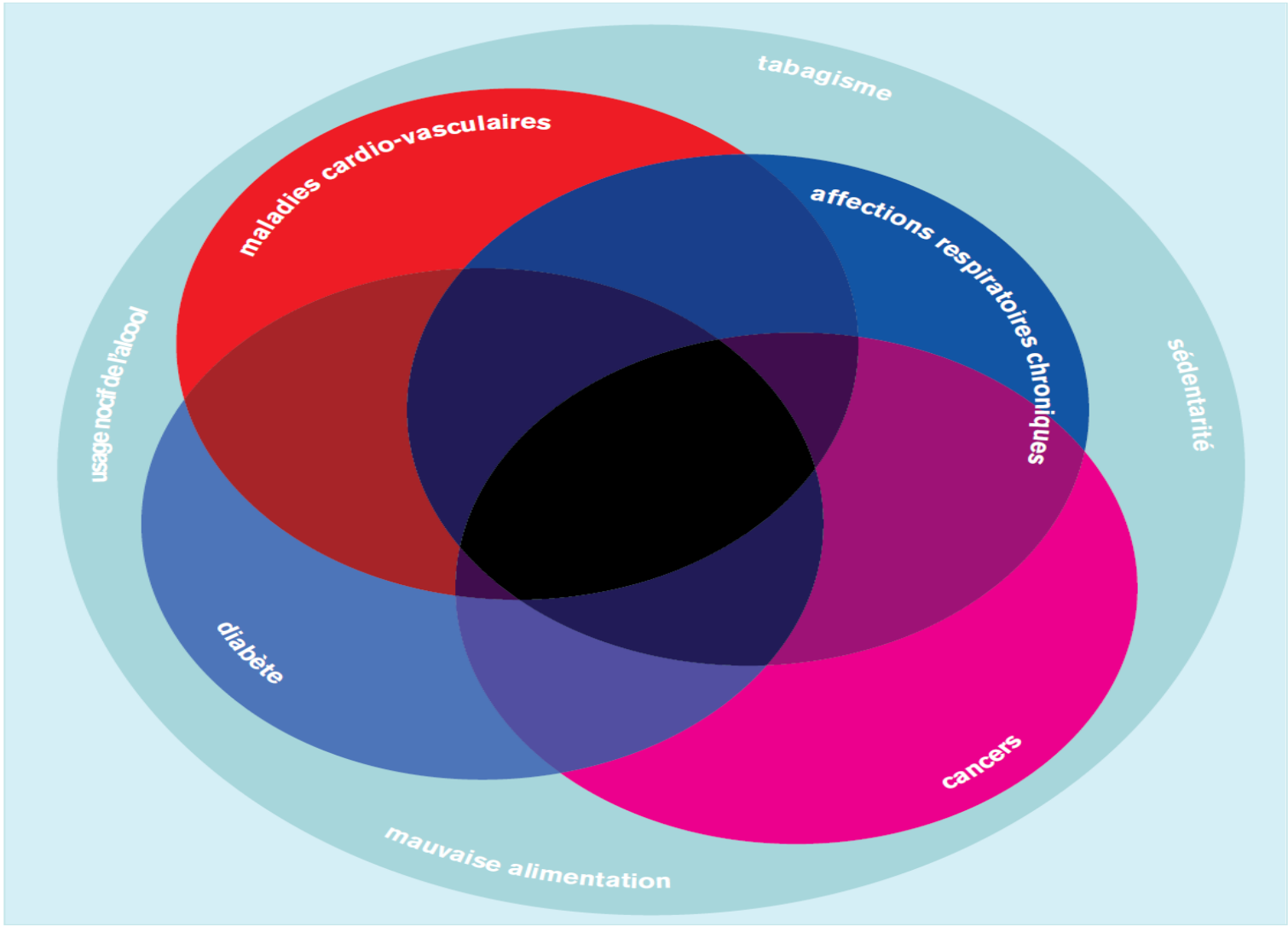
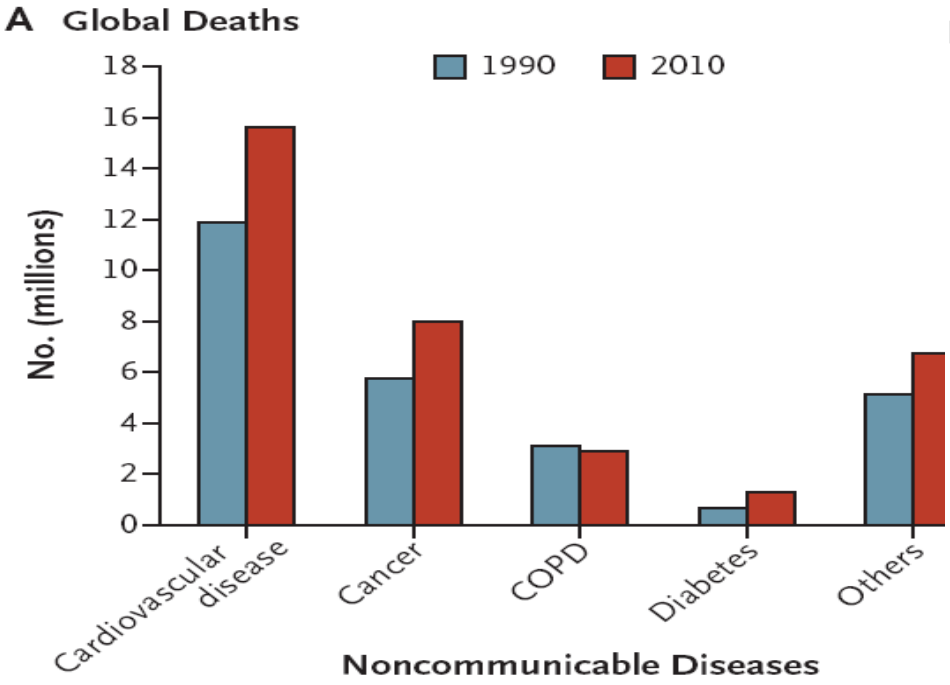


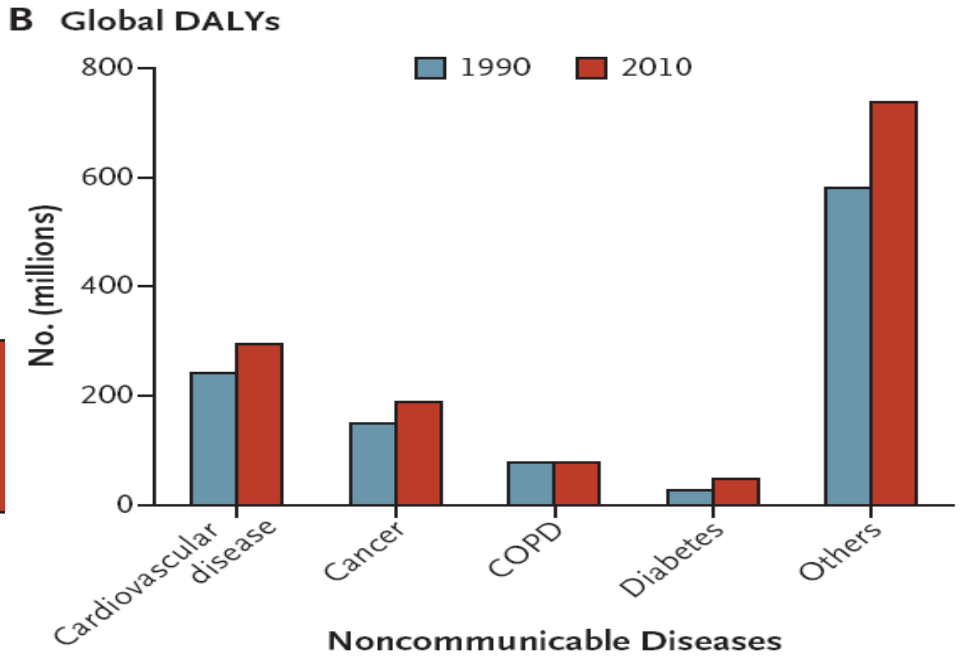
Figure 1. Global Deaths According to Cause and Sex, 2008.
Adapted from the World Health Organization (WHO).[4]

NEJM 2013;369:1336-43


tabagisme
maladies cardio-vasculaires
affections respiratoires chroniques
usage nocif de l'alcool
sédentarité
diabète
cancers
mauvaise alimentation

Causes décès et handicaps Monde 2008





NEJM 2013;369:1336-43

Décès aux USA 1950-2010 / 100 000 h / an

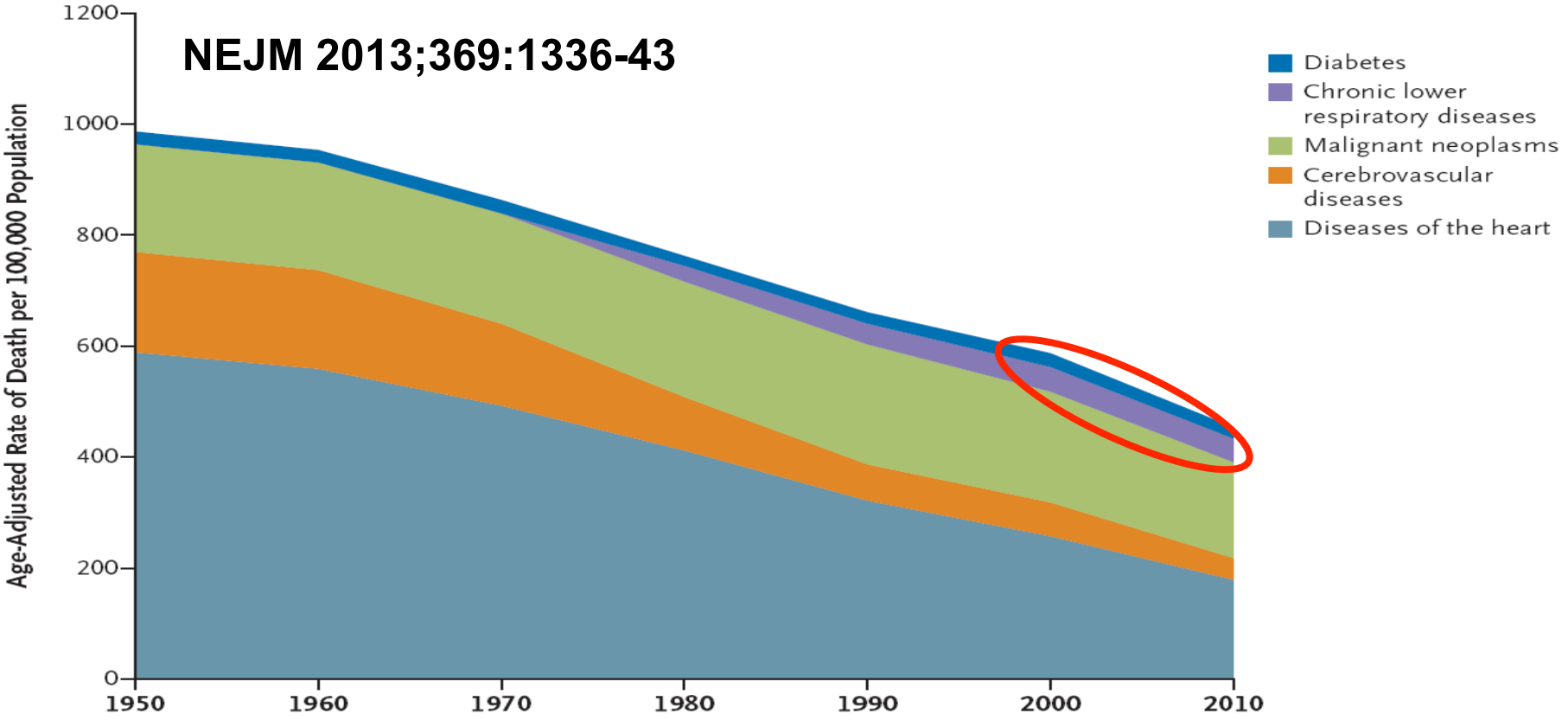
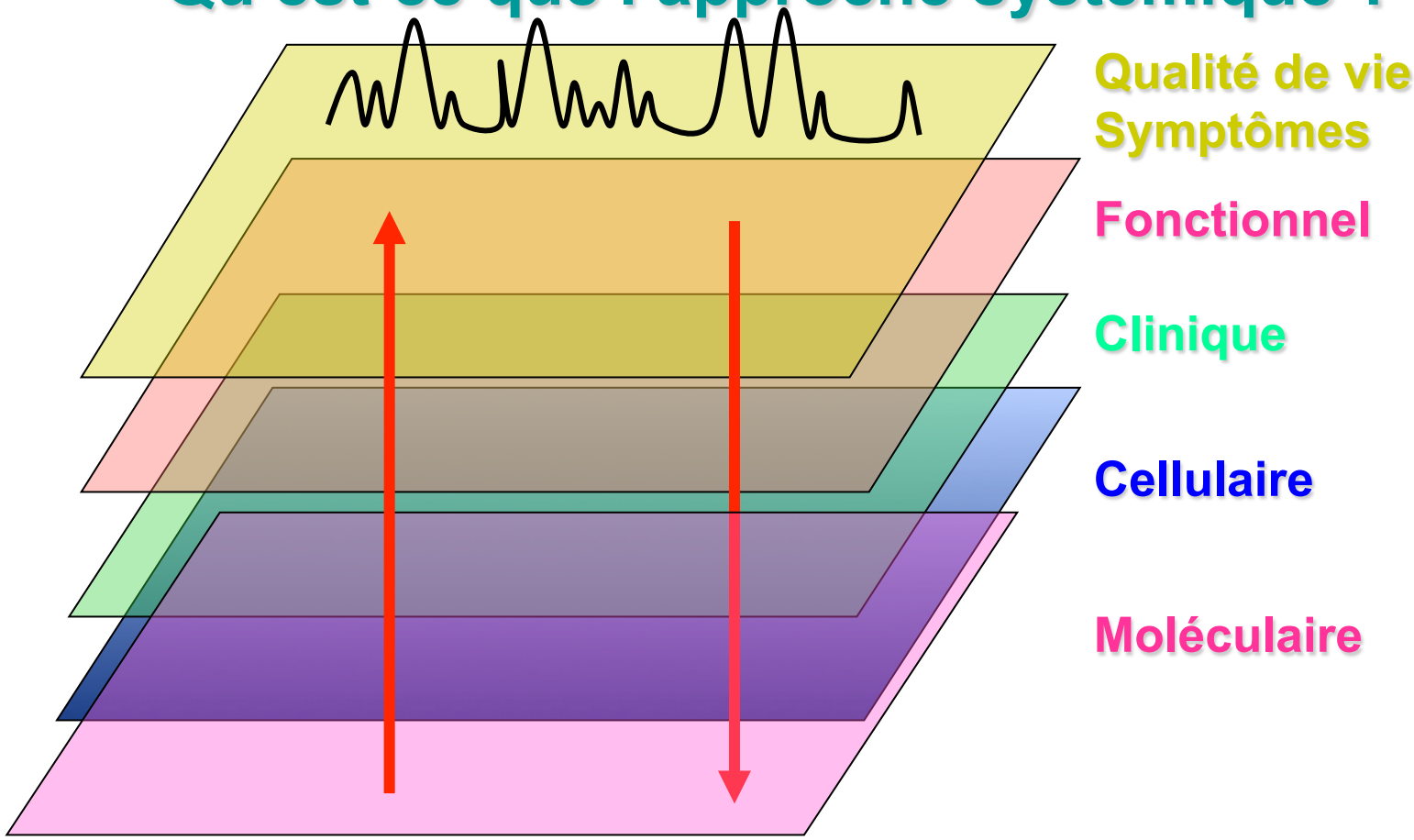


Figure 4. Declines in Rates of Death from Major Noncommunicable Diseases in the United States, 1950 to 2010.
Adapted from the National Center for Health Statistics, Centers for Disease Control and Prevention.[18]

Qu'est-ce que l'approche systémique ?



Auffray *et al*. (2009) Genome Med 2009;1:2 & Chest 2010; 137:1410-6

Qu'est-ce que l'approche systémique ?

- **Complexité de la biologie et des maladies**

- **3 niveaux de compréhension**
  - **briques ou modules**
  - **interconnexions**
  - **dynamique du système**

  } **Fonction *versus* Dysfonction**

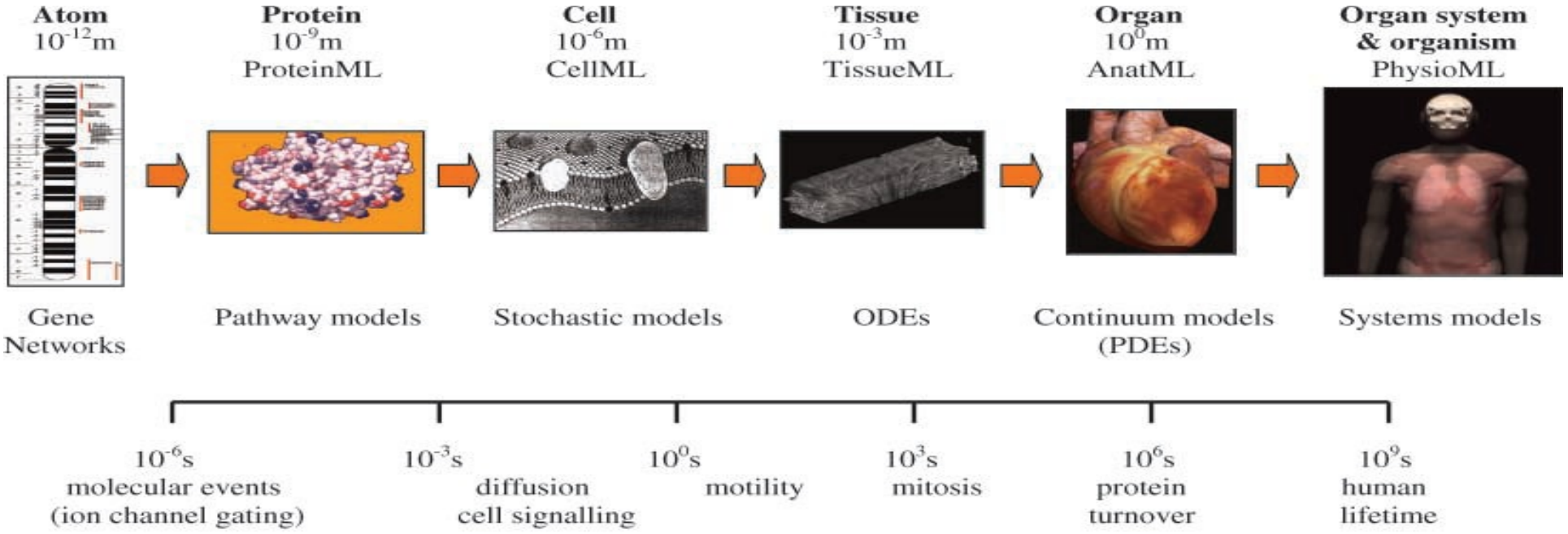
- **2 types d'informations**
  - **signaux environnementaux : air, exercice, nutrition, sommeil, stress, « exposome »**
  - **informations digitales génomiques**

- **Des informations aux phénotypes: réseaux et machines moléculaires**

Hood *et al.* Biotechnol. J. 2012;7:992-1001

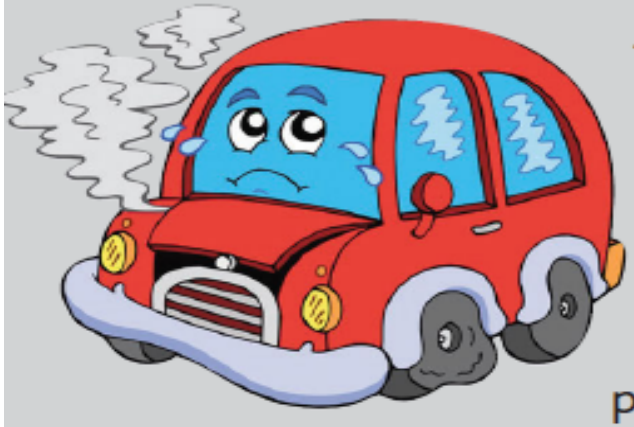
Qu'est-ce que l'approche systémique ?

Un grand défi de la biologie systémique intégrative:
l'intégration multi-échelle spatio-temporelle



Peter Hunter, University of Auckland – Denis Noble, Oxford University

Box 1: The car analogy to personalized medicine.



The paradigm shift required to make the change from today's medical practices to the predictive personalized medical care is revolutionary, but by no means unprecedented. A metaphor for this is how radically automobile "healthcare" has been digitally transformed over the past five decades by Moore's Law. In the late 1950s and 1960s, you took your car to the mechanic when you heard loud thumps or saw smoke come out of the engine. When you went in with such a "symptom," you invariably were told: "This is going to cost you," since you had burned up some key part of the mechanical or electrical systems. Cars in those days had limited lifetimes and typically "died of a chronic failure" before you reached 100 000 miles.

Médecine systémique : méthodes

Smarr L. Biotechnol. J. 2012;7:980-91

Médecine systémique : méthodes

As microprocessors, flash memory, and sensors exponentially decreased in cost, car manufacturers could afford to put more electronic devices into cars to measure moment-by-moment functioning of every key subsystem. Rather than wait until you have a costly "symptom," you now take your car into a service facility every 10 000 miles for "preventive maintenance," during which the car's measurements are digitally read out and compared with a database of all other cars of the same model. Should the data be out of range of the "norm", then you get "personalized car service," which involves a repair on a specific set of items determined by the sensor readings. The end result is that your car at 200 000 miles runs just as well as the day you bought it.

Smarr L. Biotechnol. J. 2012;7:980-91

Médecine systémique : méthodes

- **« Tracking » externe, les 5 piliers**
  Air, Nutrition, Exercice, Sommeil, Stress (cf. Table)

- **« Tracking » interne, sang**
  supplements, sys.t hemato., glucose, homones, foie/reins, CV, Inflammation

- **Genomics**
  - Humain, séquence complète 1000 $
  - Meta génome intestin
  - Meta génome arbre bronchique

- **Omics personnel**

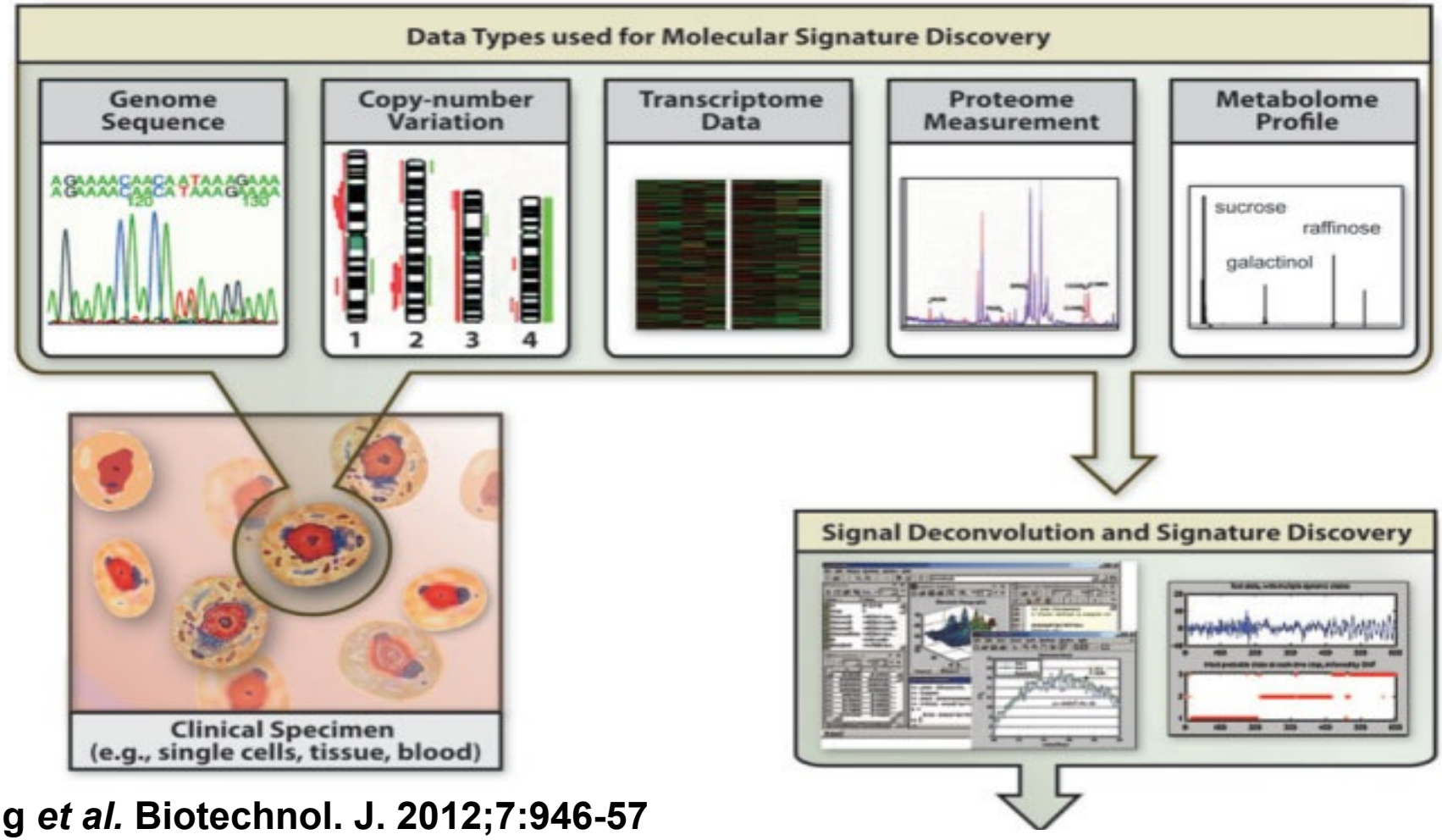
Smarr L. Biotechnol. J. 2012;7:980-91

Table 1. A list of consumer products of various degrees of intensity, for self-monitoring of the four pillars of health: nutrition, exercise, sleep and stress management

	Nutrition	Exercise	Sleep	Stress management
Entry Level	**Fitbit** (www.fitbit.com) **Calorie Counter** (www.myfitnesspal.com) Both use database look-up to log food and analyze caloric intake	**Omron** (www.omron.com) Pedometer to measure steps	**Fitbit, BodyMedia** Both measure the time in wake vs. sleep state and the caloric burn per minute during sleep	**Meditation Oasis Apps** (Simply Being, Rest & Relax) (www.meditationoasis.com) Smartphone apps to help novices to mediate
Intermediate Level	**USDA Nutrition database** (http://ndb.nal.usda.gov/) **Humanafit.com** (iPhone and Android apps) Good food database lookup, with fat, carbohydrates, protein. Also measures workouts	**Fitbit** 3D accelerometer measures daily steps and caloric burn **Polar WearLink** (www.polarusa.com) measures heart rate and links to exercise equip-ment	**Lark** (www.lark.com) Only works with Apple devices. Doesn't measure REM amounts. Has push notifications for behavior modification.	**StressEraser** (www.stresseraser.com) Portable biofeedback device for breathing and HRV[a)]
Advanced Level	**Self Nutrition Data** (http://nutritiondata.self.com/) **CRON-O-METER** (http://cronometer.com/) In addition to calories, fat, carbohydrates, protein both have detailed analysis of vitamins, nutrients, amino acids, minerals	**BodyMedia** (www.bodymedia.com) Able to sense skin temperature, galvanic skin response, and heat flux – also able to detect exercises such as yoga or free weights that do not involve stepping	**Zeo** (www.myzeo.com) Headband sensor records sleep state every 30 sec.Displays on bedside device and uploads to the cloud	**Heartmath's EM Wave Desktop PC** (www.heartmathstore.com) Wide range of biofeedback modes for PC driven by HRV pulse monitor

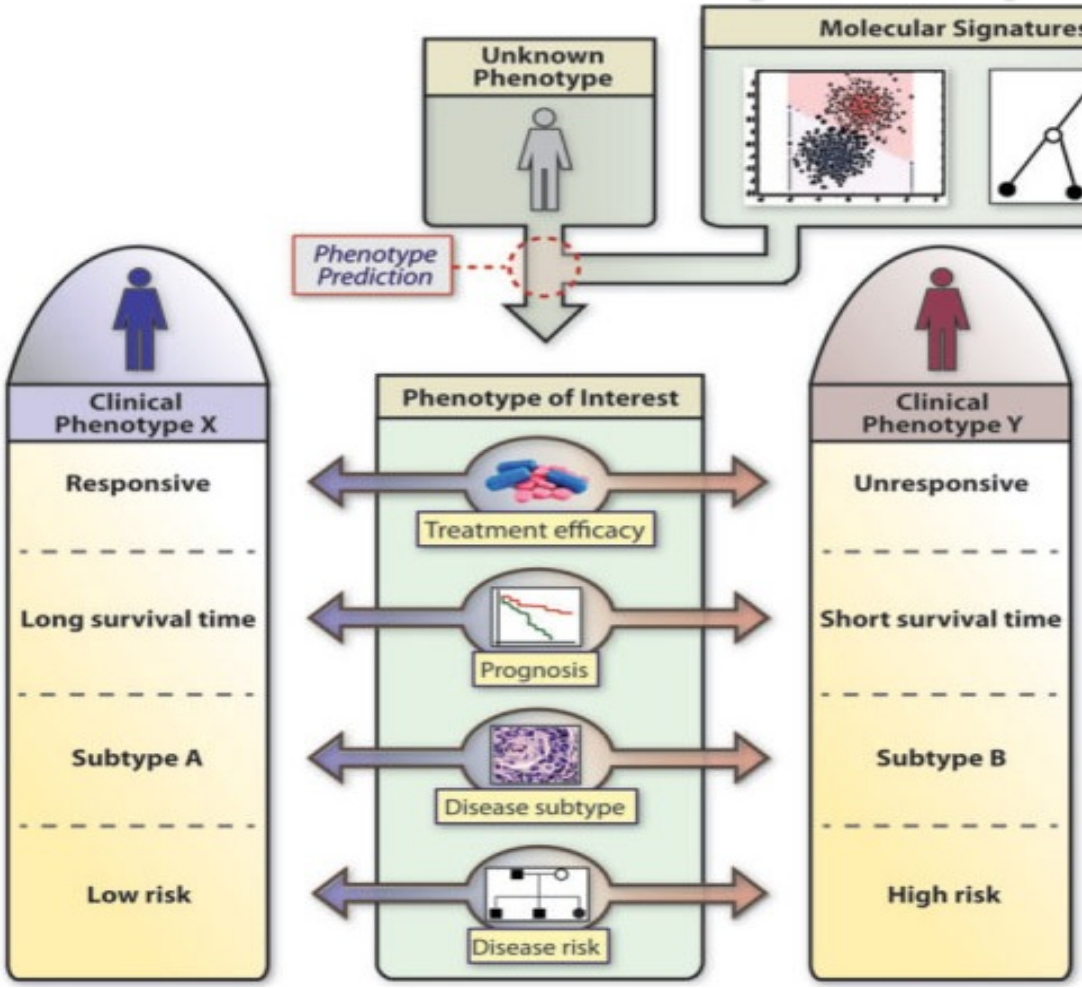
Smarr L. Biotechnol. J. 2012;7:980-91

Médecine systémique, méthodes



Sung *et al.* Biotechnol. J. 2012;7:946-57

Médecine systémique, méthodes

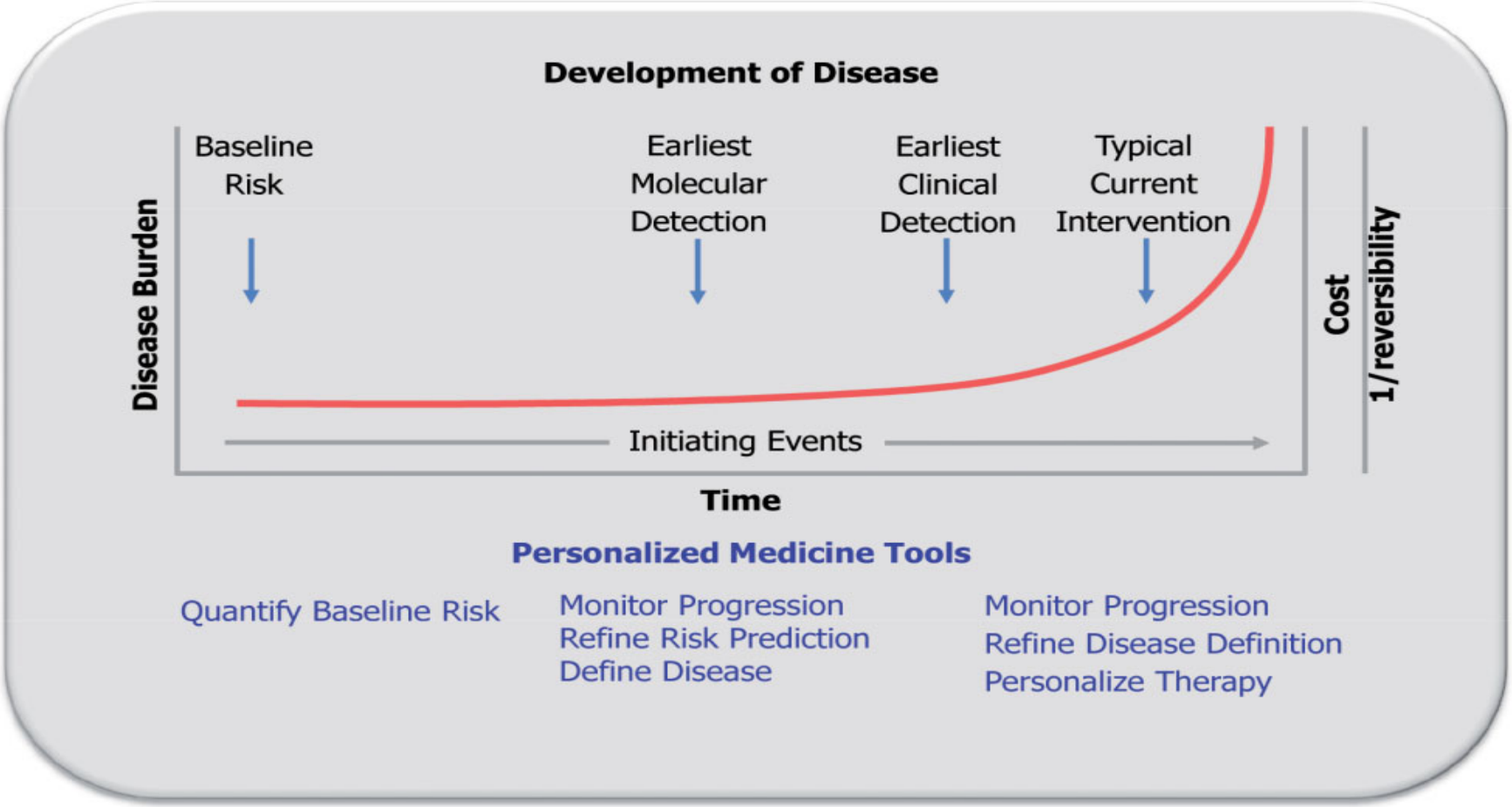


Sung *et al.* Biotechnol. J. 2012 ;7:946-57

Médecine systémique, mise en œuvre

- **Répondre à un besoin clinique clair**
- **Organisation Ville-Hôpital avec Associations de patients**
  Systèmes d'Information commun
- **Données prédéfinies, collectées de façon répétées pour certaines**
  - **exposomes**
  - **proteomic sang, 50 organes x 2 / an**
  - **variants génétiques « actionnables », 250 à ce jour**
  - **E-nose, SM**
  - **imagerie**
- **Réseau personnel des réseaux**
- **Intervention multimodale avant détérioration clinique**

Médecine systémique : mise en œuvre



Snyderman *et al.* Biotechnol. J. 2012;7:973-9

EISBM
European Institute of Systems Biology and Medicine

Une équipe fondatrice

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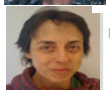

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Rhône Alpes un point d'ancrage européen d'une initiative internationale

Leroy HOOD
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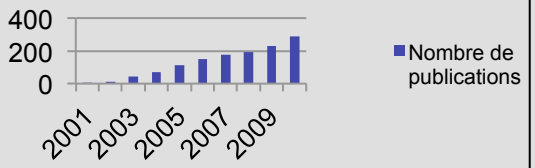
Avenir

Evolution du nombre de publications comprenant le terme "systems biology" dans le titre



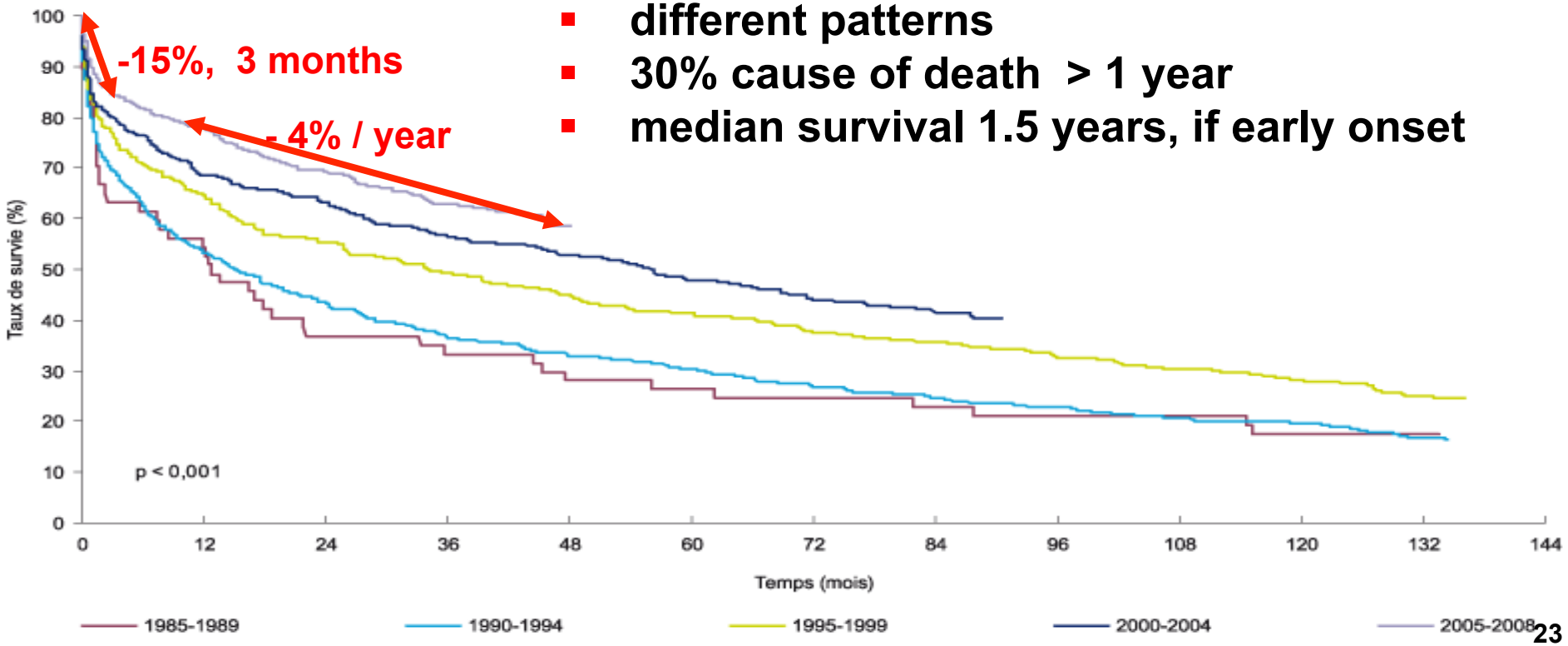
European projects involving the EISBM founding team

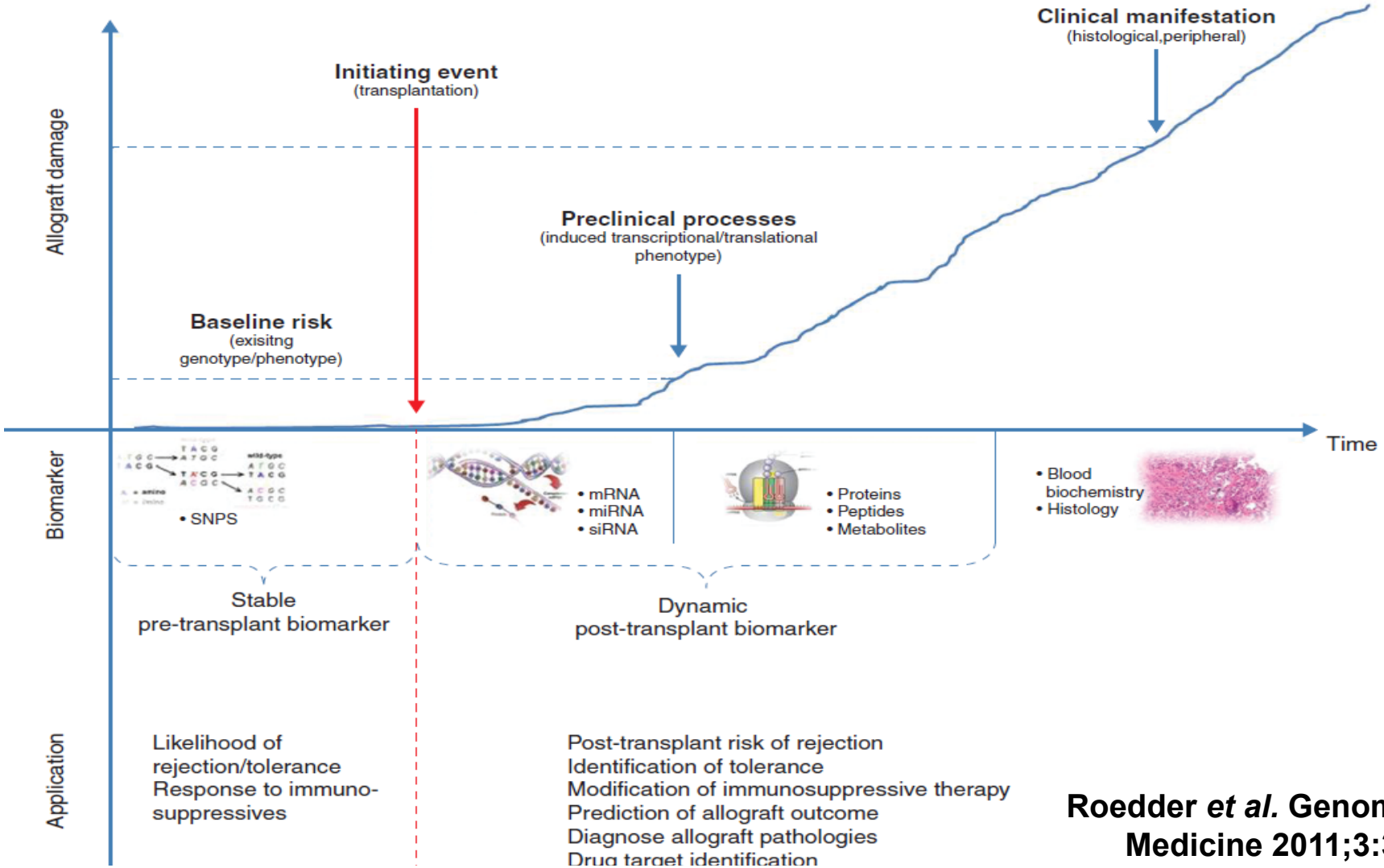
10 selected and financed projects

- U-BIOPRED
- MeDALL
- AirPROm
- Synergy-COPD
- SysPatho
- Screentox
- eTRIKS
- SysCLAD
- CASyM
- HIGHLIGHT

Médecine systémique, mise en œuvre

- Chronic Lung Allograft Dysfunction
  - BOS in 50% at 5 years
  - different patterns
  - 30% cause of death > 1 year
  - median survival 1.5 years, if early onset





Roedder *et al.* Genome Medicine 2011;3:37

SysCLAD Consortium

Cohort Of Lung Transplantation-COLT ***Bordeaux*****:** J. Jougon JF Velly; H. Rozé; E. Blanchard, C. Dromer; ***Bruxelles:*** M. Antoine, A. Belhaj, M. Cappello, B. Rondelet, M. Ruiz, Y. Sokolow, F. Vanden Eynden**,** G. Van Nooten**;** L. Barvais, J. Berré, S. Brimioulle, D. De Backer, J. Créteur, E. Engelman, I. Huybrechts, B. Ickx, T. J.C. Preiser, T. Tuna, L. Van Obberghe, N. Vancutsem, J.-L. Vincent; D. Abramowicz, P. De Vuyst, I. Etienne, F. Féry, F. Jacobs, C. Knoop, J.L. Vachiéry, P. Van den Borne, I. Wellemans **;** G. Amand, L. Collignon, M. Giroux ; ***Grenoble*****:** V. Bach, P.-Y. Brichon, P. Chaffanjon, O. Chavanon, A. de Lambert, S. Guigard, A. Pirvu, P. Porcu, R. Hacini ; P. Albaladejo, C. Allègre, D. Anglade, D. Bedague, P. Bouzat, E. Briot, O. Carle, M. Casez-Brasseur, D. Colas, G. Dessertaine, M. Durand, J. Duret, M.C. Fèvre, G. Francony, S. Gay, M.R Marino, D. Protar, D. Rehm, S. Robin, M. Rossi-Blancher, L. Saunier; P. Bédouch, A. Boignard, H. Bouvaist, A. Briault, B. Camara, M. Dubuc, S. Quêtant, J Maurizi, P. Pavèse, C. Pison, C. Saint-Raymond, N. Wion; C. Chérion; ***Lyon:*** O. Jegaden, J.-M. Maury, F. Tronc; O. Bastien, C. Flamens; J.-F. Mornex, F. Philit, A. Senechal, A. Tiberghien; A. Mezergues, C. Dubois; ***Paris, Hôpital Européen Georges Pompidou*****:** F. Le Pimpec Barthes, A. Bel, P. Mordant, P. Achouh; V. Boussaud; R Guillemain, D Méléard, MO Bricourt, B Cholley ; V Pezella; ***Marseille:*** M. Adda, M. Badier, B. Coltey B, X.B. D'journo, S. Dizier, C. Doddoli, N. Dufeu, H. Dutau, JM. Forel, JY. Gaubert, C. Gomez, M. Leone, A. Nieves, B. Orsini, L. Papazian L, M. Reynaud-Gaubert, A. Roch, JM. Rolain, V. Secq, P. Thomas, D. Trousse*;* ***Nantes*****:** O. Baron, P. Lacoste, C. Perigaud, J.C. Roussel; I. Danner, A Haloun A. Magnan, A Tissot; T. Lepoivre, M. Treilhaud; K Botturi-Cavaillès, Sophie Brouard, Richard Danger, Mallory Pain, Pierre-Joseph Royer; ***Hôpital Marie Lanelongue*****:** P. Dartevelle, E. Fadel, S. Mussot, D. Fabre, O. Mercier ; P. Viard, S. François ; J. Cerrina, P. Hervé, J. Le Pavec, F. Le Roy Ladurie ; ***Paris Hôpital Bichat:*** Y. Castier, P. Cerceau, F. Francis, G. Lesèche ; Nicolas Allou, Pascal Augustin, Sandrine Boudinet, Mathieu Desmard, Guillaume Dufour, Philippe Montravers ; Olivier Brugière, Gaëlle Dauriat, Gilles Jébrak, Hervé Mal, Armelle Marceau, Anne-Cécile Métivier, Gabriel Thabut ; B. Ait Ilalne ; ***Strasbourg:*** P. Falcoz, G. Massard, N. Santelmo; G. Ajob, O. Collange O. Helms, J. Hentz, A. Roche; B. Bakouboula, T. Degot, A. Dory, S. Hirschi, S. Ohlmann-Caillard, L. Kessler , R. Kessler, A. Schuller; K. Bennedif, S. Vargas; ***Suresnes:*** P. Bonnette, A. Chapelier, P. Puyo, E. Sage; J. Bresson, V. Caille, C. Cerf, J. Devaquet, V. Dumans-Nizard, ML. Felten, M. Fischler, AG. Si Larbi, M. Leguen, L. Ley, N. Liu, G. Trebbia; S. De Miranda, B. Douvry, F. Gonin, D. Grenet, A.M. Hamid, H. Neveu, F. Parquin, C. Picard, A. Roux, M. Stern; F. Bouillioud, P. Cahen, M. Colombat, C. Dautricourt, M. Delahousse, B. D'Urso, J. Gravisse, A. Guth, S. Hillaire, P. Honderlick, M. Lequintrec, E. Longchampt, F. Mellot, A. Scherrer, L. Temagoult, L. Tricot; M. Vasse, C. Veyrie, L. Zemoura; ***Toulouse*****:** J. Berjaud, L. Brouchet, M. Dahan ; F. Le Balle, O. Mathe ; H. Benahoua, A. Didier, A.L. Goin, M. Murris; L. Crognier, O. Fourcade;

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Editorial

Prediction of chronic lung allograft dysfunction: a systems medicine challenge

Christophe Pison, Antoine Magnan, Karine Botturi, Michel Sève, Sophie Brouard, Benjamin J. Marsland, Florian Ernst, Tobias Paprotka, Kevin Deplanche, Andreas Fritz, Valérie Siroux, Jean-Pierre Boissel, Paul A. Corris, Charles Auffray, Laurent P. Nicod and the SysCLAD consortium

Eur Respir J 2013, in press

Médecine systémique, mise en œuvre

- **COLT French prospective cohort since 09-2009 11 centres + Bruxelles**
  Swiss Transplant Cohort Study, STCS since 2008 in Lausanne- Genève, Zurich

- **VIII-2013, 827 + 223: 1050 transplanted, 512 reached year 2, 215 year 3**

- ***Donors: day 0***
  - **clinics**
  - **HLA**
  - **lung tissue**

- ***Recipients: before Tx, day-0 Tx, M6-M12 post LTx***
  - **clinics, e.CRF**
  - **Blood: HLA, transcriptomics x 2, proteomics x 2, miRNA x 1, lymphocytes subpopulations, exome sequencing**
  - **BAL: microbiote & macrophages polarization if available, , proteomics x 2**

- **Outcomes: to predict CLAD @ year-3 as soon as year-1**

Médecine systémique, mise en œuvre

OPEN ACCESS Freely available online PLoS COMPUTATIONAL BIOLOGY

A Systems Biology Approach Identifies Molecular Networks Defining Skeletal Muscle Abnormalities in Chronic Obstructive Pulmonary Disease

Nil Turan[1], Susana Kalko[2], Anna Stincone[1], Kim Clarke[1], Ayesha Sabah[1], Katherine Howlett[3], S. John Curnow[3], Diego A. Rodriguez[2], Marta Cascante[4], Laura O'Neill[3], Stuart Egginton[3], Josep Roca[2], Francesco Falciani[1]*

18 COPD patients vs 12 age-matched sedentary controls

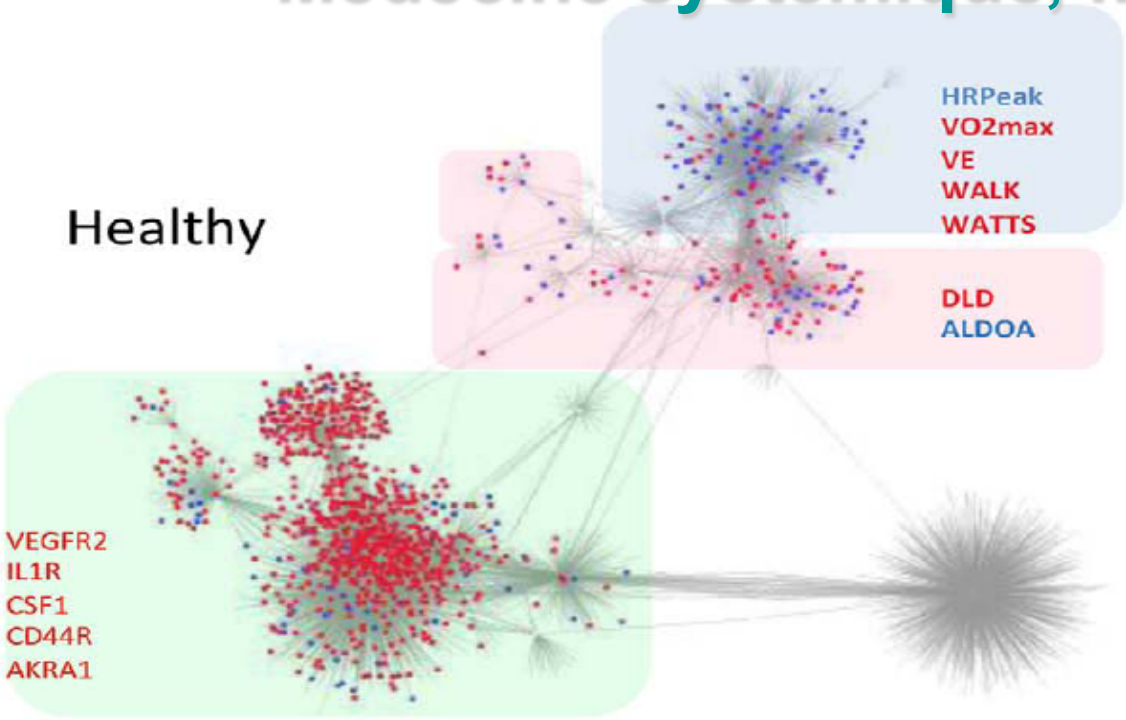
Effect of a 8-week rehabilitation program on muscle gene expression

-> altered responses in COPD patients mediated by :

- inflammation
- hypoxia
- nutritional status

Epigenetic control ?

Médecine systémique, mise en œuvre

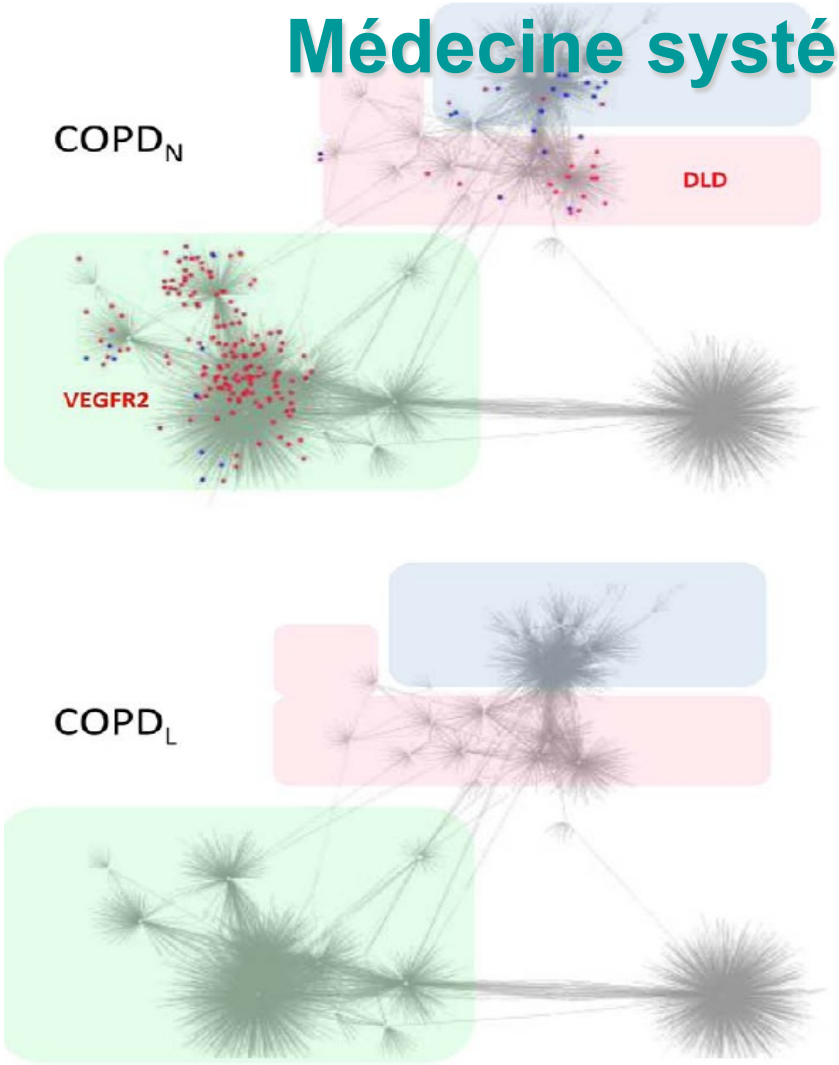


GOBP generation of precursor metabolites and energy (8)
GOCC mitochondrial inner membrane (6)
GOCC respiratory chain complex I (3)
GOCC ribonucleoprotein complex (9)
GOMF Cadmium ion binding (4)

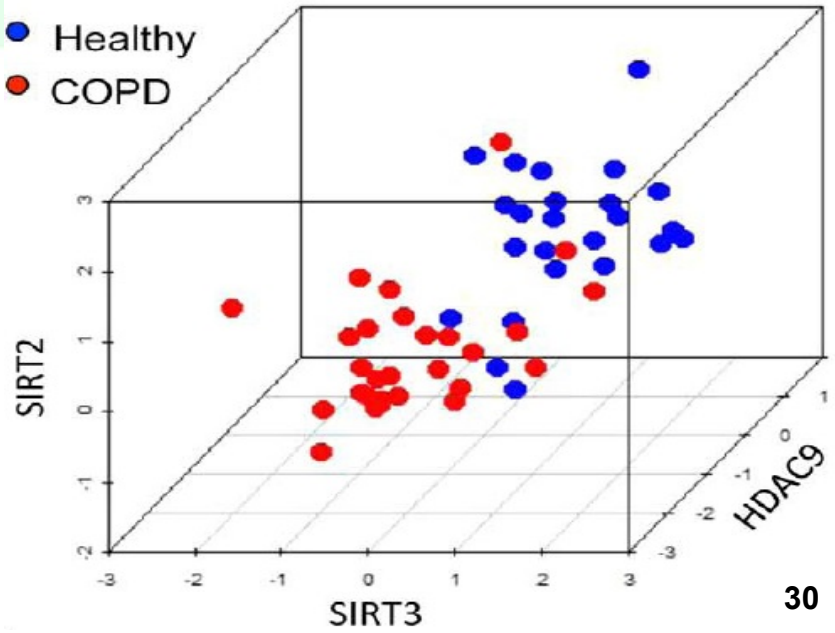
KEGG oxidative phosphorylation (10)
GOCC Mitochondrion (29)

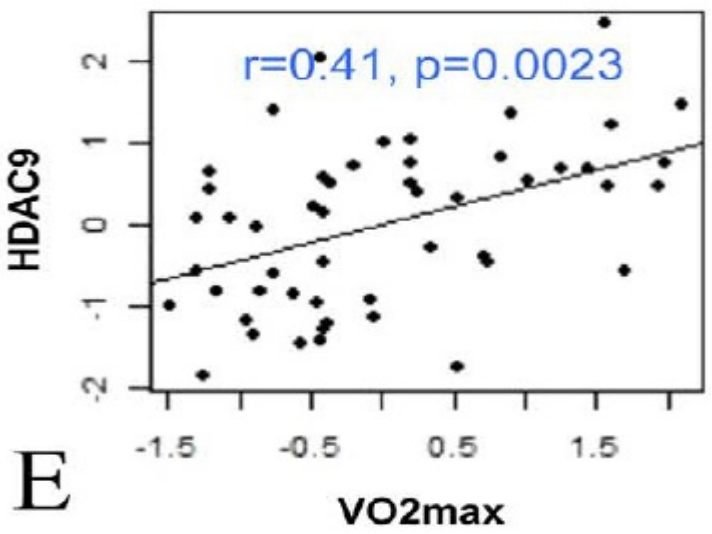
GOBP cell adhesion (85).
GOCC ECM (47).
KEGG Focal adhesion (28).
GOBP cell motility (41).
GOBP development process (173).
GOBP intracellular signalling cascade (86).
GOBP Cell proliferation (53).
GOBP inflammatory response (25)
GOBP blood vessel development (21)

Médecine systémique, mise en œuvre



GOCC ECM (15)
GOCC collagen (9)
KEGG Focal adhesion (15)
GOBP organ development (32)
GOBP localization of cell (13)
GOBP Regulation of cell proliferation (16)

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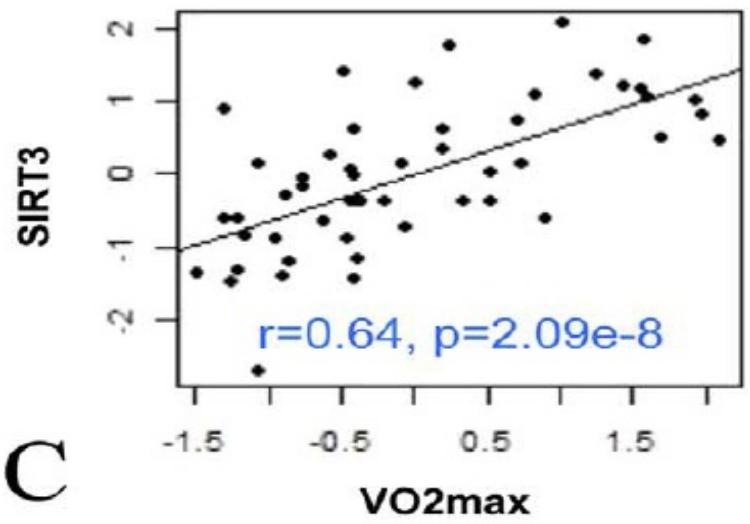
HDAC9
VO2max
E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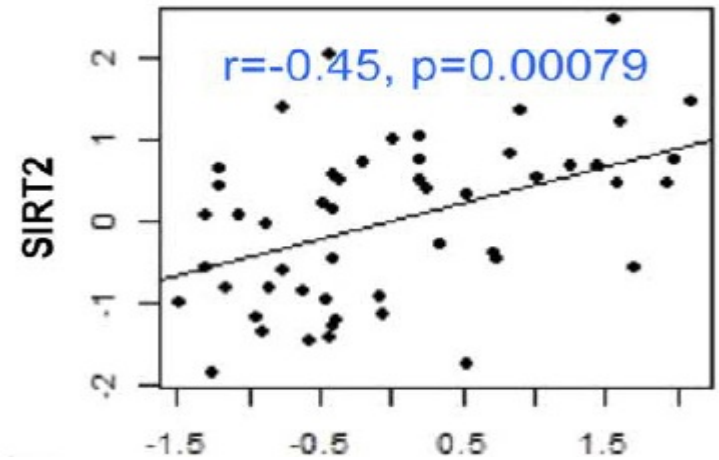
SIRT3
VO2max
C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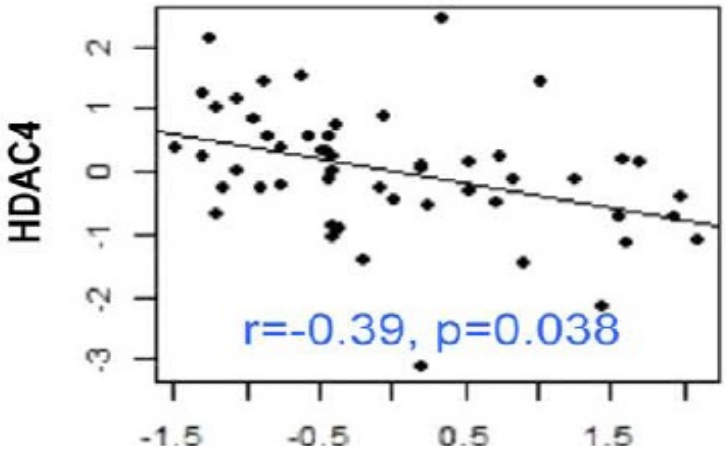
SIRT2


r=-0.39, p=0.038
HDAC4

31

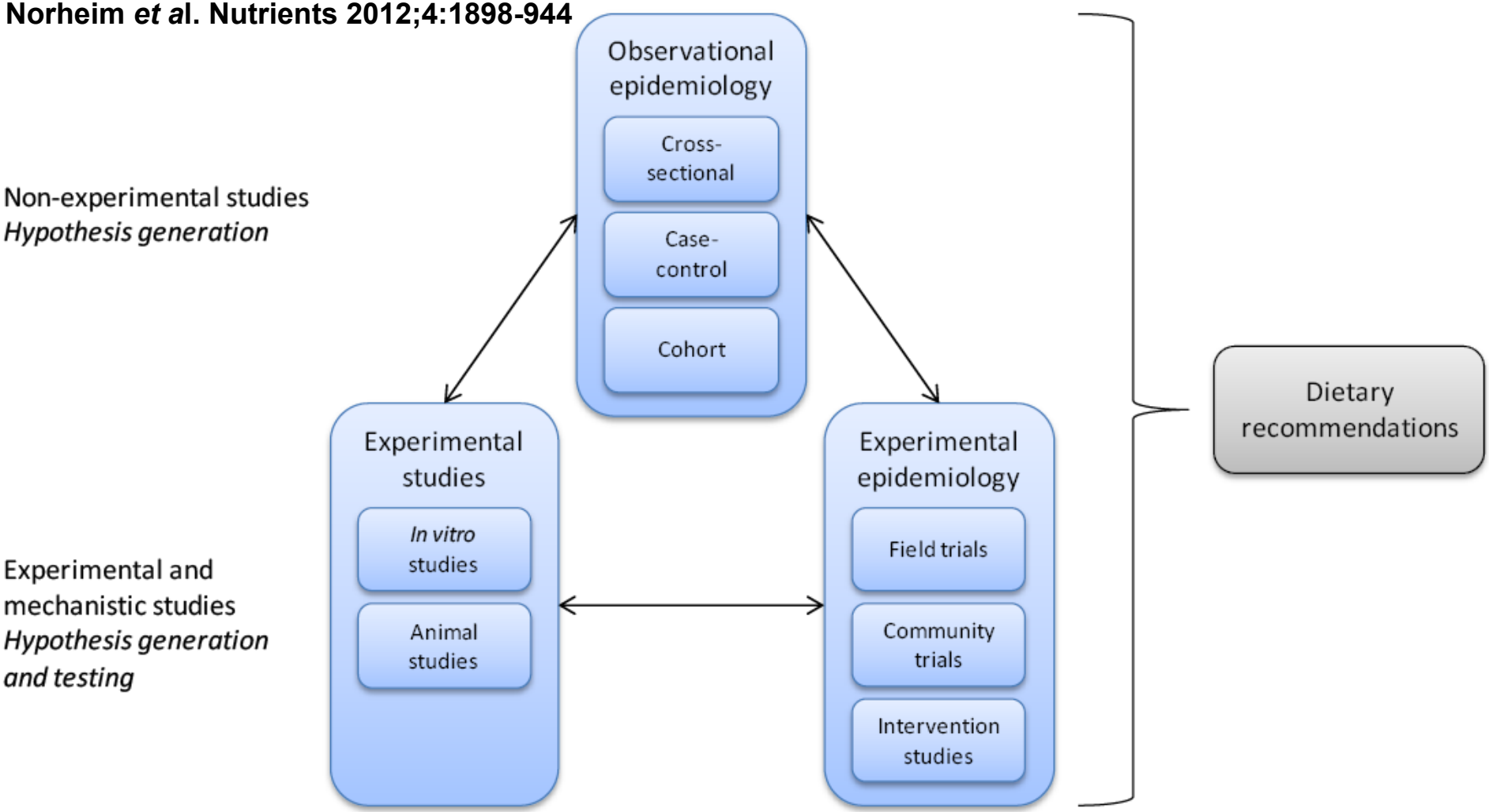
Médecine systémique, mise en œuvre en Nutrition

Table 1. Nutrition is complicated due to many variables.

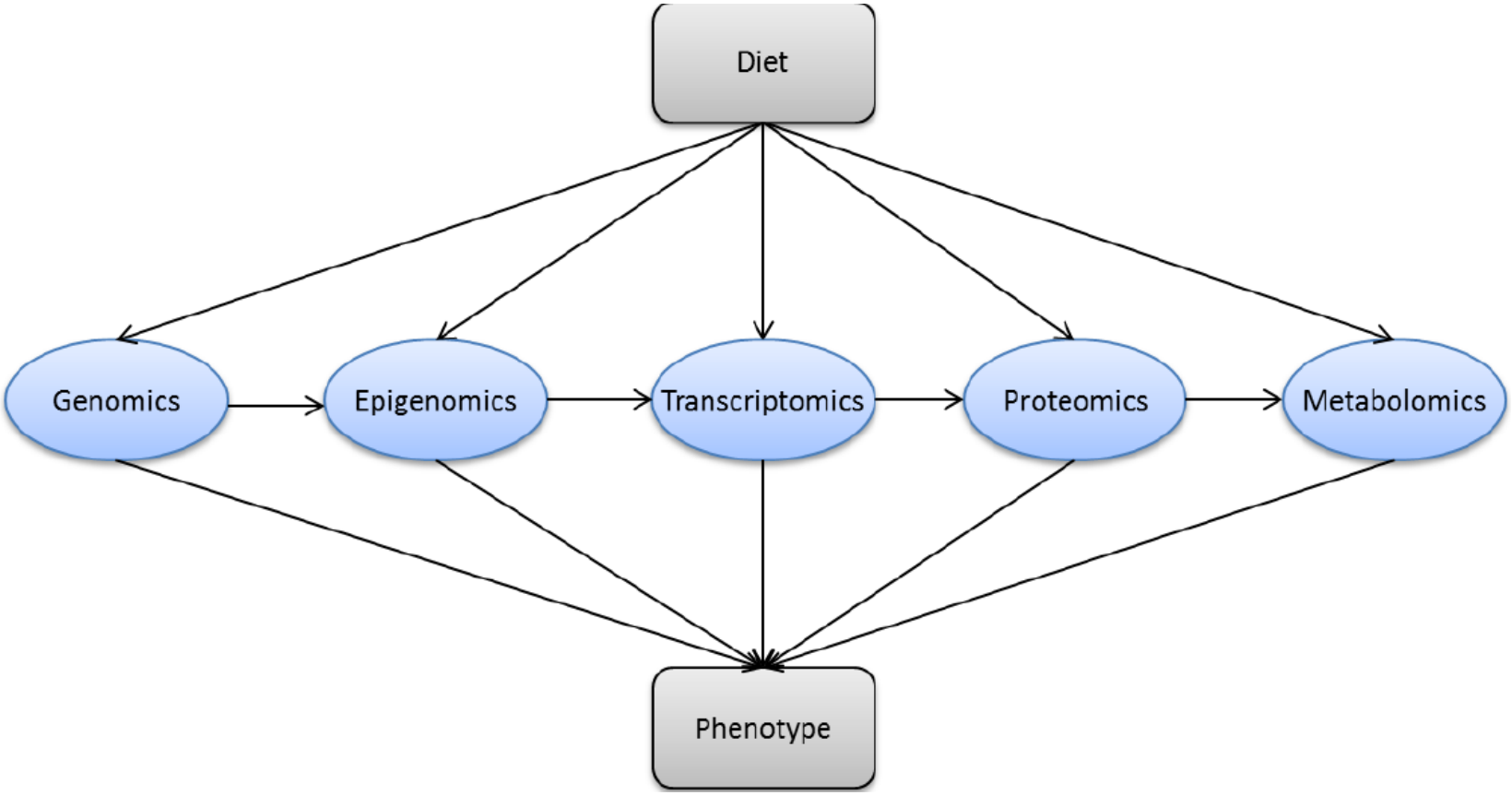
- We eat ~1.5 kg food & drink ~2 L liquid/day;
- About 40 essential nutrients are known;
- Thousands of known compounds in foods without known biological functions;
- Thousands of unknown compounds in foods without known biological functions;
- About 10^{13} cells in the body & about 10^{14} bacteria in the GI tractus;
- Mostly unknown and complicated interplay between diet and the microbiome;
- Many organs & some hundreds of cell types are found in the body;
- About 25,000 genes in human cells;
- Human genome includes 3 billion base pairs;
- Some millions single nucleotide polymorphisms (SNPs);
- A large epigenetic variation between individuals due to environmental factors;
- About 100,000 transcripts (mRNA);
- About 100,000 proteins;
- About 1000 lipids & thousands of water-soluble metabolites.

Norheim *et al*. Nutrients 2012;4:1898-944

Norheim *et al*. Nutrients 2012;4:1898-944



Médecine systémique, mise en œuvre en Nutrition



Norheim *et al*. Nutrients 2012;4:1898-944

Table 2. Methods in nutritional research.

Research Area	Technologies	Assessed Parameters
Epidemiology	Observational	Association between diet and health outcomes
	Experimental	and effects of controlled dietary changes
Genomics	Microarray	Association between genetic variation
	Next generation sequencing	(e.g., SNPs, alleles) and phenotypic traits
Epigenomics	Bisulfite sequencing	DNA methylation and histone modification
	ChiP-sequencing	
Transcriptomics	Microarray	mRNA levels and splice variants
	RNA sequencing	
Proteomics	Chromatography	Protein composition and
	Electrophoresis	posttranslational modifications
	Mass spectrometry	
	Protein microarrays	
Metabolomics	Gas liquid chromatography	Metabolites
	Liquid chromatography	
	Mass spectrometry	
	Nuclear magnetic resonance	

Norheim *et al*. Nutrients 2012;4:1898-944

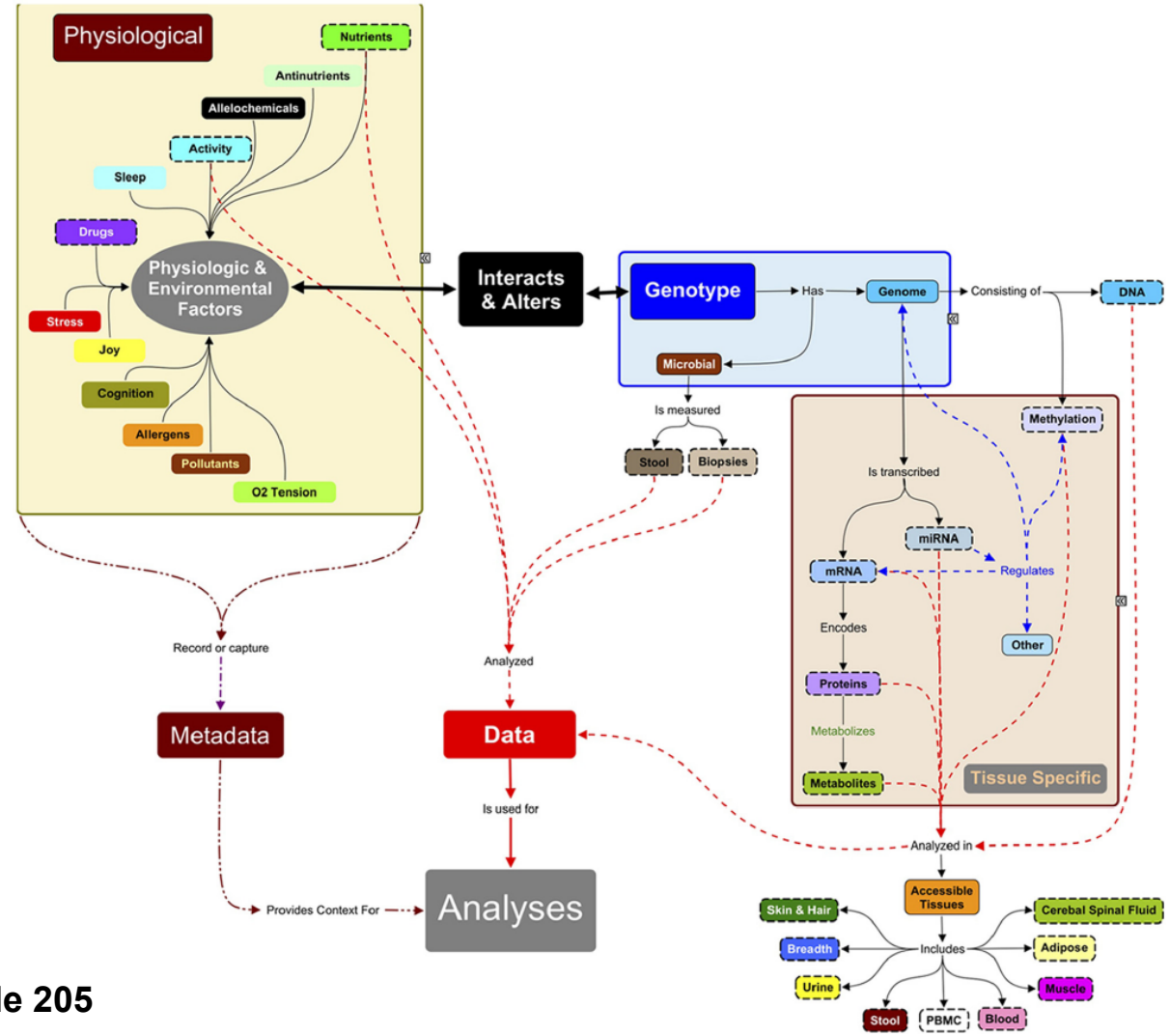
Microbiota	Sequencing the 16S rRNA gene Metaomics (includes all omics described above)	Microbe species composition; genome, transcriptome, proteome and metabolome of the microbiotic community
Imaging	CT MRI PET SPECT Optical imaging	Whole body dynamic non-invasive detection of body composition (fat and lean mass), gene regulation and molecular tracers and probes
Calorimetry	Indirect calorimetry Direct calorimetry	Energy intake and expenditure
Cognition	Cognitive tests (K-ABC, Fagan, ERP, Kendrick object learning, Trail making, Digit symbol, Block design, Mini-mental state examination, Oral word association), EEG	IQ (sequential & simultaneous processing, nonverbal abilities, recognition memory)
Systems biology	Mathematical modeling Statistical methods	Integrate large data sets to understand complex physiological systems

Applications

- **Approche holistique d'un tissu, muscle squelettique, graisse, foie..**
- **Effets des régimes alimentaires**
- **Challenges, test tolérance glucose, exercice, repas, jeune..**
- **Analyse longitudinales**

Norheim *et al*. Nutrients 2012;4:1898-944

Diabète type II



Kussmann *et al*.
Frontiers in Genetics 2013;4: Article 205

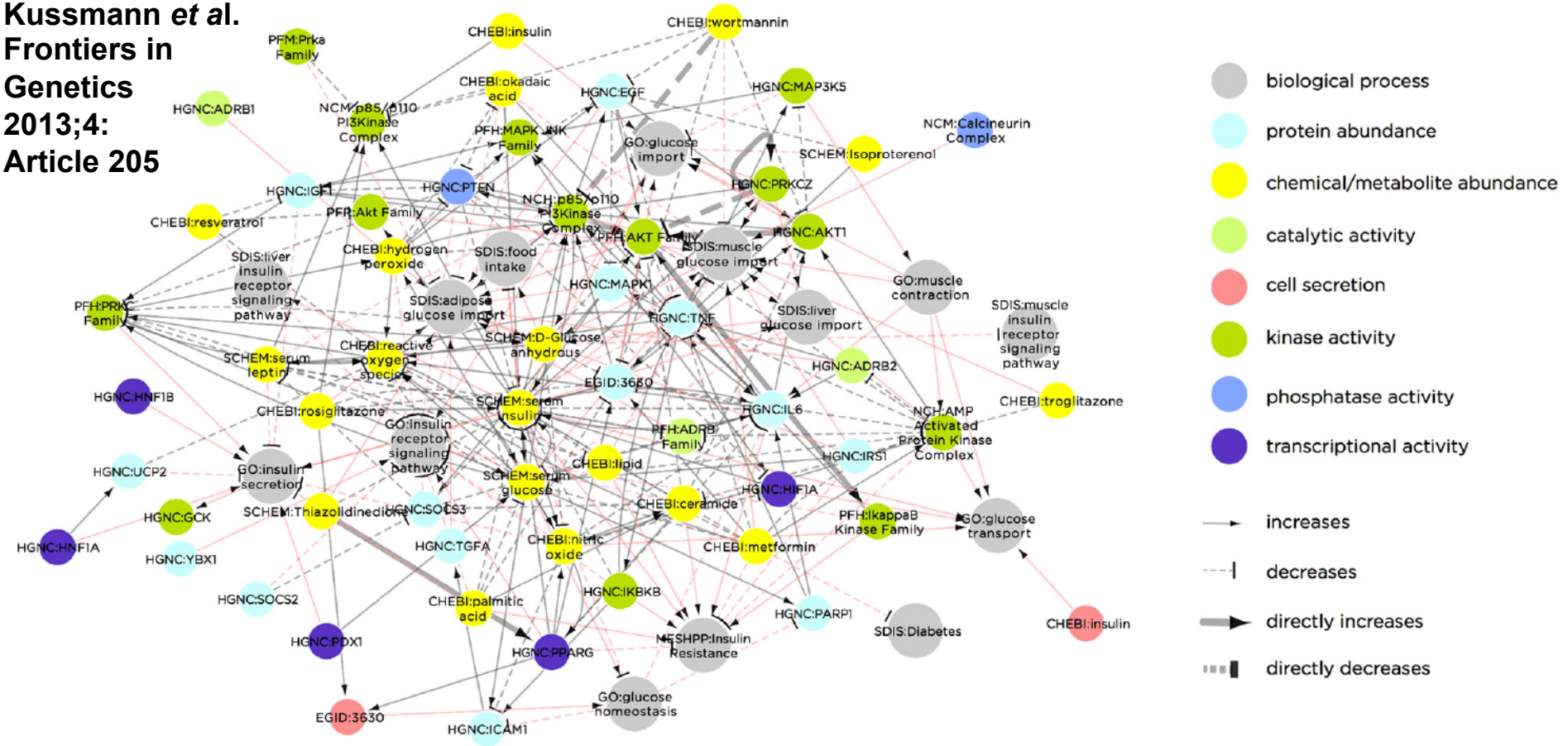
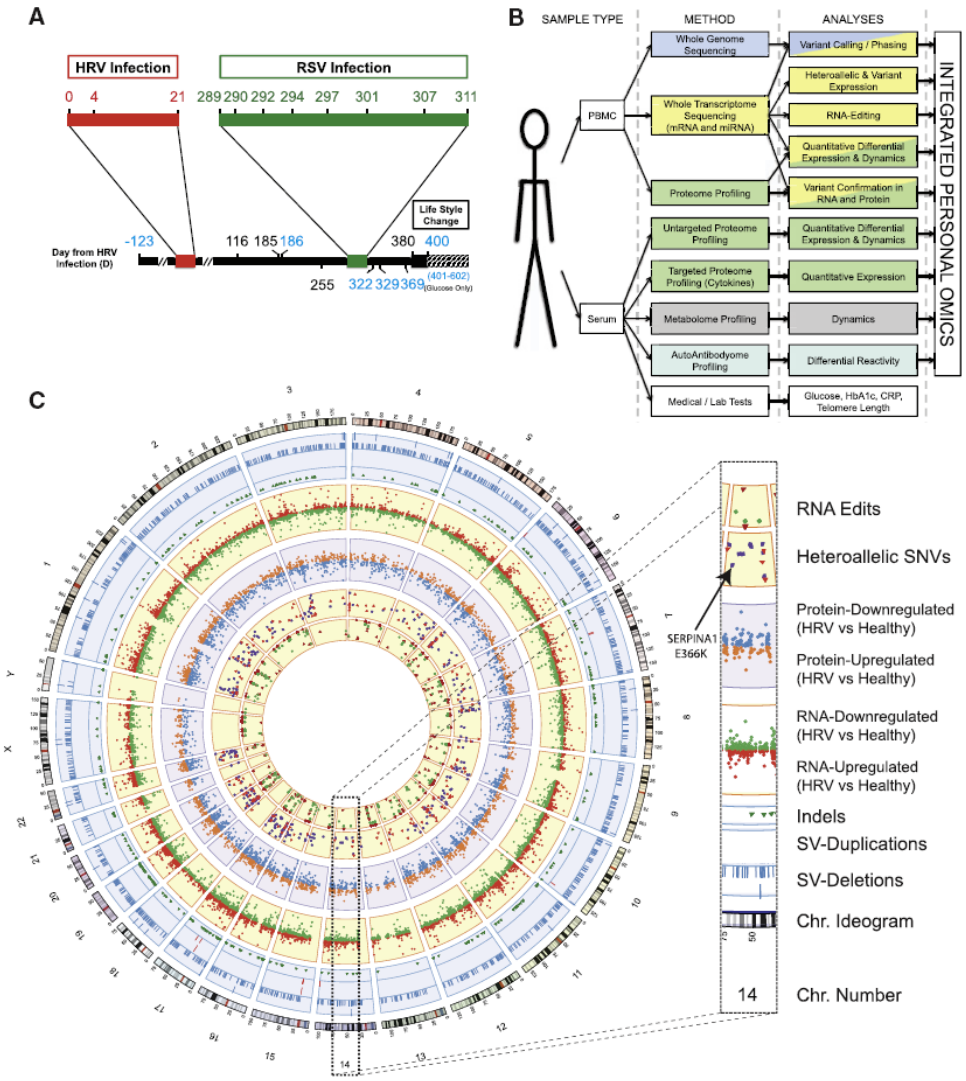


FIGURE 2 | Biological Expression Language framework network of biological molecules that are causally linked to the T2DM molecular phenotype. Node color indicates molecule type and/or molecular

Abbreviations in the network nodes are as follows: CHEBI, Chemicals of Biological Interest names (http://www.ebi.ac.uk/chebi/); EGID, Entrez Gene IDs (http://www.ncbi.nlm.nih.gov/gene); GO, Gene Ontology names

Personal omics profiling reveals dynamic molecular and medical phenotypes.

Chen et al. Cell 2012;148:1293-307



A

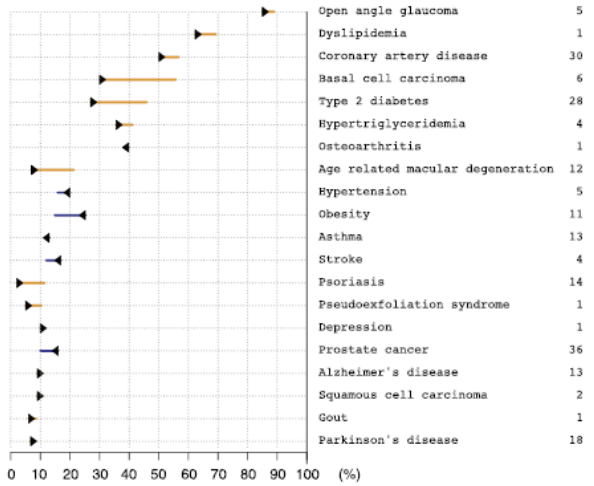
High Interest Disease-Associated Rare Variants.

Gene	Position	Genotype	OMIM
SERPINA1	14:94844947	C/T	Emphysema due to AAT deficiency
TERT	5:1294397	C/T	Aplastic anemia
KCNJ11	11:17409571	T/T	Type 2 diabetes
GCKR	2:27730939	T/T	Hypertriglyceridemia
NUP54	4:77055431	G/A	Nuclear Pore Complex Protein

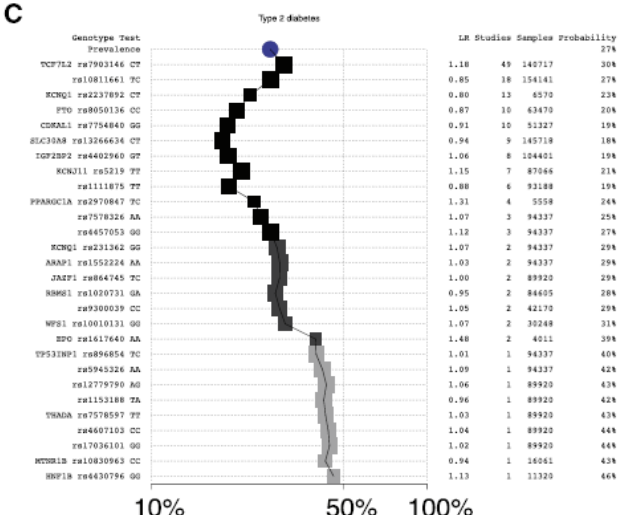
High Interest Drug-Related Variants.

Gene	rsID	Genotype	Drug Response Affected
	rs10811661	C/T	Troglitazone (Increased Beta-Cell Function)
CYP2C19	rs12248560	C/T	Clopidogrel (Increased Activation)
LPIN1	rs10192566	G/G	Rosiglitazone (Increased Effect)
SLC22A1	rs622342	A/A	Metformin (Increased Effect)
VKORC1	rs9923231	C/T	Warfarin (Lower Dose Required)

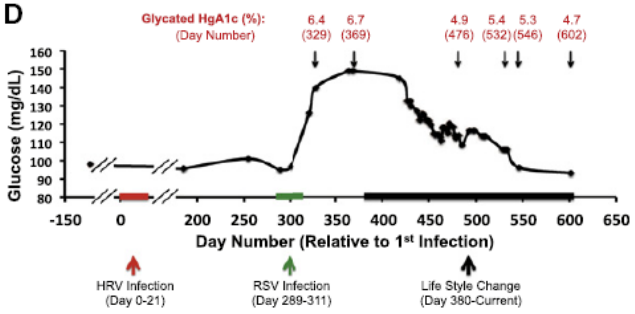
B



C



D



Coordinating CASyMedicine Systems across EUROPE

European Commission

Coordinating Systems Medicine across Europe
European Systems Medicine road-map discussions

From Systems Biology to Systems Medicine Workshops June 2010 – December 2013 – Horizon 2020

Predictive, Preventive, Personalized, Participatory Medicine

Systems biology and personalized medicine - the future is now. Auffray C, Hood L (2012) J Biotech 7:938-939

Revolutionizing medicine in the 21st century through systems approaches. Hood L, Balling R, Auffray C. (2012) Biotechnol J 7:992-1001

Messages importants

- **Cliniciens à impliquer le plus tôt possible**
- **Changements globaux : organisation recherche, soins et formations**
- **Basculer d'un système centré sur les structures à un système qui préserve la Santé dans la Communauté**
- **Passer d'une médecine « réactive » à une médecine « proactive »**
- **10% de la Santé est liée à des facteurs biologiques intrinsèques**
- **Faire mieux avec les mêmes budgets**
- **Démonstrateurs indispensables**