Public health genomics, nutrition and well-being: ...............the future

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THE NUTRIGENOMICS & DNA DAMAGE DIAGNOSTICS TEAM

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• EU Cancer Risk Bio-markers Program
• DPI-Victoria

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HUMAN
International Collaborative Project on Micronucleus frequency in human populations

Coordinating Group
Michael Fenech (Australia) Chairman
Stefano Bonassi (Italy)
Wushou Chang (Taiwan)
Nina Holland (USA)
Errol Zeiger (USA)
Micheline Kirsch-Volders (Belgium)

Founded Toulouse 1997

• 40 labs
• 16 countries
• >12,000 subjects
• >70,000 person years
“It is always advisable to perceive clearly our ignorance”. -Charles Darwin

“For a scientist, it is a unique experience to live through a period in which his/her field of endeavour comes to bloom — to be witness to those rare moments when the dawn of understanding finally descends upon what appeared to be confusion only a while ago — to listen to the sound of darkness crumbling.” - George E. Palade
GREAT DIVERSITY IN EXPOSOMES, NUTRIOMES GENOMES & EPIGENOMES

Italy                                       Germany                                     USA
Poland                                       Mexico                                   Ecuador
Bhutan                                       Chad                                   Egypt
Dietary patterns & 1 week’s food
FEEDING MORE & BETTER WITH LESS

• WHICH FOODS ARE THE MOST NUTRIENT DENSE?
• WHICH OF THESE ARE EASIEST TO GROW SUSTAINABLY?
• WHICH OF THESE HAVE THE LEAST IMPACT ON THE PLANET?
• WHICH OF THESE CAN BE EFFICIENTLY STORED?
• WHICH IS THE MINIMUM SET OF THESE FOODS TO MEET NUTRITIONAL REQUIREMENTS?
# NUTRIENT DENSITY VS CLIMATE IMPACT OF BEVERAGES

Smedman A et al. 2010 Food & Nutrition Research 54: 5170

## NDCI of Common Beverages

<table>
<thead>
<tr>
<th>Food item</th>
<th>Percentage of NNR in 100 g product</th>
<th>Number of nutrients ≥5% of NNR</th>
<th>Nutrient density</th>
<th>GHG emission</th>
<th>NDCI index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>126</td>
<td>9</td>
<td>53.8</td>
<td>99</td>
<td>0.54</td>
</tr>
<tr>
<td>Soft drink</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>109</td>
<td>0</td>
</tr>
<tr>
<td>Orange juice</td>
<td>90</td>
<td>4</td>
<td>17.2</td>
<td>61</td>
<td>0.28</td>
</tr>
<tr>
<td>Beer</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>101</td>
<td>0</td>
</tr>
<tr>
<td>Red wine</td>
<td>24</td>
<td>1</td>
<td>1.2</td>
<td>204</td>
<td>0.01</td>
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<tr>
<td>Mineral water</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Soy drink</td>
<td>53</td>
<td>3</td>
<td>7.6</td>
<td>30</td>
<td>0.25</td>
</tr>
<tr>
<td>Oat drink</td>
<td>32</td>
<td>1</td>
<td>1.5</td>
<td>21</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*NNR = Nordic Nutrition Recommendations; Nutrient density = Percentage of NNR in 100 g of product Number of nutrients ≥5% of NNR; GHG = Greenhouse gas emissions*
Folic acid content of vegetables (DFE µg per 100g)*

*Data from USDA National Nutrient database. DFE = dietary folate equivalent. DFE values are shown in brackets.

<table>
<thead>
<tr>
<th>High Folate (HF) Vegetables</th>
<th>Low Folate (LF) Vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulses</td>
<td>Leafy or cruciferous vegetables</td>
</tr>
<tr>
<td>Red Kidney beans (130)</td>
<td>Broccoli (93)</td>
</tr>
<tr>
<td>Mung beans (60)</td>
<td>Brussel sprouts (60)</td>
</tr>
<tr>
<td>Chickpeas (171)</td>
<td>Cabbage (43)</td>
</tr>
<tr>
<td>Lentils (180)</td>
<td>Endive (142)</td>
</tr>
<tr>
<td>Peas (59)</td>
<td>Spinach (146)</td>
</tr>
<tr>
<td>Lima beans (50)</td>
<td>Lettuce (73)</td>
</tr>
<tr>
<td><strong>Mean (108)</strong></td>
<td><strong>Mean (93)</strong></td>
</tr>
<tr>
<td><strong>Mean (100)</strong></td>
<td><strong>Mean (16)</strong></td>
</tr>
</tbody>
</table>

Eating the “wrong” vegetables could lead to folate deficiency.

Folate RDA 400µg requires eating:

2.5Kg LF veg/d or
0.4Kg HF veg/d
The responsible and effective translation of genome-based knowledge for the benefit of population health. (Bellagio workshop, April 2005)
A strong consensus had emerged around certain principles which have grown out of the practice of public health genomics:

- The explicit rejection of genetic exceptionalism
- An emphasis upon the importance of translation supported by a strong evidence base
- Understanding the limits of personalised medicine

http://www.phgfoundation.org/
“NUTRIGENOMICS”

DIET ENVIRONMENT LIFE-STYLE

GENETICS
DNA
THE BLUEPRINT

EPIGENETICS
METHYLATED DNA HISTONES, miRNA
WHAT HAS BEEN PROGRAMMED

TRANSCRIPTOMICS & PROTEOMICS
RNA, PROTEINS
WHAT APPEARS TO HAPPEN

METABOLOMICS & GENOMICS
METABOLITES & GENOME STABILITY

WHAT HAS HAPPENED

Kussmann et al Nature Outlook 2010
TO UNDERSTAND PREDISPOSITION

TO UNDERSTAND PROGRAMMING

PERSONALISED NUTRITIONAL INTERVENTION

TO MEASURE MOLECULAR RESPONSE

TO SHOW EFFICACY & SAFETY

GENETICS

EPIGENETICS

TRANSCRIPTOMICS & PROTEOMICS

METABOLOMICS & GENOMICS

―ETICS‖ & ―OMICS‖ FOR PERSONALISED NUTRITION

Kussmann et al Nature Outlook 2010

NUTRIGENETICS

NUTRIGENETICS
The Micronutrient Genomics Project Operational Pipeline

**Infrastructure component**

- **Micronutrient Expert Groups**
  - Identify functional genetic variations
  - Identify pathways & interactions

- **Bioinformatics Team**
  - Link to databases
  - Create biological networks

**Research component**

- **Research Collaborations**
  - Perform in vitro & mechanistic studies
  - Selection of relevant genetic variations
  - Link to omics data & results
  - Perform human intervention studies
  - Link to nutritional phenotype database

Establish relationships between genetic variations, micronutrients and optimal health

---

http://www.nugo.org/micronutrients
DRAFT MGP ROADMAP 2011 & BEYOND

STAGE 1
- COMPLETE GENE LISTS FOR KEY VITAMINS, MINERALS, PHYTONUTRIENTS
  - IDENTIFY COMMON SNPs FOR EACH GENE (>=10% ALLEL FREQUENCY) WITH STRONG FUNCTIONAL EFFECTS ON...

STAGE 2
- STAGE 1
- EURRECA

STAGE 3
- BUILD METABOLIC PATHWAYS & MATHEMATICAL MODELS TO PREDICT DIETARY REQUIREMENTS FOR DIFFERENT GENOTYPES

STAGE 4
- EFFECTS OF COMMON SNPs & MICRONUTRIENT CONCENTRATION ON...
  - ENZYME ACTIVITY BOUNDING AFFINITY
  - TISSUE NUTRIENT & METABOLITE CONCENTRATION
  - GENOME STABILITY & EPIGENOME GENE EXPRESSION
  - HEALTH & DISEASE OUTCOMES

STAGE 5
- IMPROVE KNOWLEDGE ON APPROPRIATE BIOMARKERS OF ADEQUACY AND OPTIMAL HEALTH FOR EACH MICRONUTRIENT

STAGE 6
- DEFINE/DEVELOP APPROPRIATE IN VITRO/IN VIVO MODELS
  - TEST PREDICTIONS IN APPROPRIATE IN VITRO/IN VIVO MODELS

STAGE 7
- BIOMARKERS FOR VALIDATION OF PERSONALISED NUTRITION ADVICE
  - BOND
CROSS-SPECIES IN VIVO TRANSFER OF DNA & miRNA VIA FOODS ..........ARE WE INDEED BECOMING GENETICALLY WHAT WE EAT?

Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA

- Rice miRNA
- Ingestion
- Absorption
- Reduced Expression
- LDL receptor adapter protein 1
- Increased LDL in blood

Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota

- Marine bacteria Zobellia In Nori
- Ingestion absorption
- Genetic transfer of Zobellia CAZ genes to Bacteroides
- Improved algal carbohydrate digestion via acquired agarases & porphyranases
NUTRIENT ARRAYS – THE ROSETTA STONE FOR UNLOCKING PERSONALISED NUTRITION FOR GENOME MAINTENANCE

IDENTIFY COMBINATIONS THAT OPTIMISE GENOME STABILITY AND CELL GROWTH

Fenech M, Genome Integrity 20101: 11-15
A NUCLEOCENTRIC VIEW OF AGEING FROM WOMB TO TOMB

The ageing genome and epigenome: damaged beyond repair? Is genomic damage reversible?

DNA damage increases with age ....or.... poor choices of nutrition, life-style, physical and socio-psychological environments?

What is the threshold of DNA damage we should allow?

Can we design “exposomes” that enable us to stay below this threshold?

Fenech et al. 2000
% variation in genome damage with increased intake relative to lowest tertile of intake

** P < 0.006

-50 -40 -30 -20 -10 0 10 20 30 40 50 60 70

mid-tertile
highest tertile

Vitamin E Calcium Folate Retinol Nicotinic acid β-Carotene Riboflavin Pantothenic acid Biotin

PROPOSED ROAD-MAP TO DETERMINE DRVs FOR DNA DAMAGE PREVENTION

**NUTRITION VARIABLES**
- SINGLE MICRONUTRIENT
- MICRONUTRIENT COMBINATION
- FUNCTIONAL FOOD
- FOOD GROUP
- DIETARY PATTERN

**STUDY DESIGN**
- IN VITRO MODELS
- IN VIVO CROSS-SECTIONAL STUDIES
- PLACEDBO-CONTROLLED TRIALS

**OUTCOME MEASURES**
**PRIMARY**
- DNA DAMAGE BIOMARKERS:
  - MICRONUCLEUS
  - CYTOME ASSAYS
  - COMET ASSAY
  - DNA OXIDATION
  - DNA METHYLATION
  - TELOMERE LENGTH
  - mtDNA DELETION

**SECONDARY**
- TISSUE MICRONUTRIENT CONCENTRATION

**DRVs FOR GENOME STABILITY**
- DATABASES ON VITAMIN & MINERAL REQUIREMENTS FOR GENOME STABILITY IN DIVERSE GENETIC BACKGROUNDS AT THE VARIOUS LIFE-STAGES

LIFE-STYLE IS ALSO AN IMPORTANT DETERMINANT OF CHROMOSOMAL DNA DAMAGE

**LIFE-STYLE HPI INDEX**

<table>
<thead>
<tr>
<th>Factors</th>
<th>MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
<td>Std. error</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.698</td>
</tr>
<tr>
<td>Drinking</td>
<td>-0.174</td>
</tr>
<tr>
<td>Sleeping hours*</td>
<td>-1.288</td>
</tr>
<tr>
<td>Mental stress</td>
<td>0.724</td>
</tr>
<tr>
<td>Exercise**</td>
<td>-2.315</td>
</tr>
<tr>
<td>Breakfast</td>
<td>0.142</td>
</tr>
<tr>
<td>Working time**</td>
<td>-2.194</td>
</tr>
<tr>
<td>Nutrition Balance*</td>
<td>-2.304</td>
</tr>
</tbody>
</table>

Smokers
Non-smokers
Often
No or moderate
Poor
Good or moderate
No or seldom
≥2 times per week
< 7 h
≥7 h
< 9 h
Excessive
Slight or mild
No eating
Eating

<table>
<thead>
<tr>
<th>FOLATE</th>
<th>PUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAMIN E</td>
<td>OXIDATIVE STRESS</td>
</tr>
<tr>
<td>VITAMIN D</td>
<td>OBESITY</td>
</tr>
<tr>
<td>Ω3-FATTY ACIDS</td>
<td>PSYCHOLOGICAL STRESS</td>
</tr>
<tr>
<td>CEREAL FIBRE</td>
<td>PROCESSED MEAT</td>
</tr>
<tr>
<td>MULTIVITAMIN USE</td>
<td>HOMOCYSTEINE</td>
</tr>
</tbody>
</table>

LONGER

CURRENT “limited” KNOWLEDGE

SHORTER

TELOMERES

Accelerated telomere shortening in response to life stress

Elissa S. Epel, Elizabeth H. Blackburn, Sue Lin, Firdaus S. Dhabhar, Nancy E. Adler, Jason D. Morrow, and Richard M. Cawthon

Correlations

<table>
<thead>
<tr>
<th></th>
<th>Perceived stress, n</th>
<th>Years of caregiving, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telomere length</td>
<td>–0.31* (-0.27†), 54</td>
<td>–0.40* (-0.43*), 36</td>
</tr>
<tr>
<td>Telomerase activity</td>
<td>–0.24† (-0.24†), 59</td>
<td>–0.35† (-0.32†), 37</td>
</tr>
<tr>
<td>Oxidative stress index</td>
<td>0.27† (0.22), 44</td>
<td>0.33† (0.38†), 30</td>
</tr>
</tbody>
</table>

Childhood Adversities Are Associated with Shorter Telomere Length at Adult Age both in Individuals with an Anxiety Disorder and Controls

Laura Kananne1,2, Ida Surakka3,4, Sami Pirkola5,6, Jaana Suvisaari5, Jouko Lönnqvist5,6, Leena Peltonen2,3,4,7,8, Samuli Ripatti3,4, Iliris Hovatta1,2,5

Regression model

<table>
<thead>
<tr>
<th></th>
<th>β1</th>
<th>se²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder</td>
<td>–0.080</td>
<td>0.069</td>
<td>0.224</td>
</tr>
<tr>
<td>GHQ-12 score3</td>
<td>–0.002</td>
<td>0.009</td>
<td>0.838</td>
</tr>
<tr>
<td>Number of childhood adversities4</td>
<td>–0.090</td>
<td>0.032</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Which diets and life-styles re-activate telomerase?
High protein (TWD) or high carbohydrate (HC) weight-loss diets reverse telomere shortening in rectum in over-weight men.

O’Callaghan, Clifton, Noakes, Fenech. Rejuvenation Res. 2009

2 way ANOVA
P<0.0001
Lifestyle modifications included:
• Low fat (10% of calories from fat), whole foods, plant-based diet high in fruits, vegetables, unrefined grains, legumes, and low in refined carbohydrates;
• Moderate aerobic exercise (walking 30 min/day, 6 days/week);
• Stress management (gentle yoga-based stretching, breathing, meditation, imagery, and progressive relaxation techniques 60 min/day, 6 days/week), and a 1-h group support session once per week.
• Supplementation with soy (one daily serving of tofu plus 58 g of a fortified soy protein powdered beverage), fish oil (3 g daily), vitamin E (100 IU daily), selenium (200 µg daily), and vitamin C (2 g daily).
Can meditation slow rate of cellular aging? cognitive stress, mindfulness, and telomeres

INCREASING AWARENESS THAT WE ARE 3-D BEINGS

*lack of fear/neuroticism?
“We are at the threshold of a new era in which harm to the genome can be efficiently diagnosed and prevented.

A person’s DNA damage profile should become a routine biomarker of health status.

Prevention of DNA damage will soon achieve its rightful place as one of the most important objectives of global health strategies.”
Personalised diets and life-styles for morbidity compression or life extension? Which is the most cost-effective model?

- **Present life-span & morbidity**: $\$
- **Life extension with morbidity extension**: $\$
- **Morbidity compression but no life extension**: $
- **Life extension & morbidity compression**: $\$

COST

- **$\$**
- **$\$\$\$**
- **$\$**
- **$\$**
NUTRITION 2020 & BEYOND

PERSONALISED ADVICE BASED ON AN ALMOST COMPLETE UNDERSTANDING OF NUTRITIONAL & LIFE-STYLE REQUIREMENTS TAILED TO GENOTYPE, EPIGENOTYPE & LIFE-STAGE

IMPROVED:
- METABOLIC FLEXIBILITY,
- GENOME INTEGRITY,
- REGENERATIVE POTENTIAL
- MORBIDITY COMPRESSION

FUNCTIONAL FOOD OR DIET +/- LIFE-STYLE

BIOMARKERS SPECIFIC TO FUNCTIONALITY

INEXPENSIVE ROBUST BIOMARKERS TO VERIFY FUNCTIONALITY & SAFETY

GENOTYPE/ EPIGENOTYPE

INEXPENSIVE ROBUST GENOTYPE & EPIGENOTYPE DIAGNOSTICS
PERSONALISED NUTRITIONAL COUNTERMEASURES FOR MICROGRAVITY & COSMIC RADIATION-INDUCED DNA DAMAGE FOR SPACE TRAVELLERS AND EXTRA-TERRESTRIAL COLONIES
A NEW “HIPPOCRATIC” OATH FOR OUR PIONEER DOCTORS OF HEALTH?

I swear to fulfill, to the best of my ability and judgment, this covenant:

• I shall endeavour to use the knowledge given to me to help my fellow beings to stay as healthy as possible at the genome, cellular, organ, system and psychological level so that they will not require to be cured from a preventable disease.

• I shall appropriately use the best validated diagnostics available so I can determine with certainty the extent to which my fellow human has drifted from optimal health and the causes of such harm.

• I shall use holistic methods including nutrition, life-style, environmental and socio-psychological approaches that are best suited to return my fellow human to optimal well-being sustainably, within their means, so that they will not require my services to provide a cure for a preventable disease.

• At the community level, I shall contribute to create ecologically viable, enjoyable, stimulating environments and caring but challenging societies, allowing equal opportunity for realising one’s purpose and creative potential whilst securing optimal health to do so.
BETTER ENVIRONMENTS ........ BETTER WORK-LIFE BALANCE
MINDSCAPE

A CONVERGENT PERSPECTIVE, COMBINING EVOLUTIONARY BIOLOGY, GENOMICS, ENVIRONMENTAL NEUROBIOLOGY AND CLINICAL MEDICINE TO UNDERSTAND LIFE, MIND, CONSCIOUSNESS AND HAPPINESS

We now live in an era when stem cells are taken out of the body and expanded in vitro before being returned to the body.

Stem cell or iPS cell cytogenetic abnormalities constitute a roadblock to regenerative therapies because they increase the rate of senescence and the risk of oncogenic transformation.

Determining the optimal nutriome in culture medium that prevent chromosomal instability for each stem cell or iPS culture is therefore important not only to predict in vivo requirements but also in vitro nutrient requirements for DNA damage prevention.
PERSONALISED CANCER GROWTH CONTROL IN CANCER SURVIVORS BY DIETARY RESTRICTION?

1. DISCOVERY OF ACQUIRED GENETIC MUTATIONS THAT MAKE A CANCER DEPENDENT ON A SPECIFIC NUTRIENT

2. VERIFICATION OF CANCER GROWTH CONTROL BY IN VITRO RESTRICTION TESTS

3. DESIGN DIETARY PATTERNS TO RESTRICT NUTRIENT IN VIVO
IS IT POSSIBLE TO INCREASE THE HEALTHY LIFE-SPAN AND COMPRESS MORBIDITY?


- Which dietary and life-style factors compress morbidity?
- Which biomarkers predict morbidity compression?
- Can we design personalised functional foods for morbidity compression?

Progression of disability in Runner's Club and Community Control groups over 21 years from an average age of 58

Table 1: US life expectancy 1900–2007 from various ages. Average number of years of life remaining.

<table>
<thead>
<tr>
<th>From age</th>
<th>1900</th>
<th>1920</th>
<th>1940</th>
<th>1960</th>
<th>1980</th>
<th>2000</th>
<th>2007</th>
<th>Gain, Years 1900–2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>49.2</td>
<td>65.4</td>
<td>63.6</td>
<td>69.9</td>
<td>73.9</td>
<td>76.9</td>
<td>77.9</td>
<td>28.7</td>
</tr>
<tr>
<td>65</td>
<td>11.9</td>
<td>12.5</td>
<td>12.8</td>
<td>14.4</td>
<td>16.5</td>
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<tr>
<td>75</td>
<td>7.1</td>
<td>7.5</td>
<td>7.6</td>
<td>8.7</td>
<td>10.5</td>
<td>11.3</td>
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<td>85</td>
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<td>100</td>
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<td>1.5</td>
<td>2.1</td>
<td>1.9</td>
<td>2.7</td>
<td>2.6</td>
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<td>1.0</td>
</tr>
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</table>