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WHITE BOOK

WHITE BOOK

3rd Annual Forum

Better Foods for Better Health

CHALLENGES & SOLUTIONS

SEPTEMBER 12th to 14th 2012

Fondation Mérieux Conference Centre 'Les Pensières'
Veyrier-du-Lac - France

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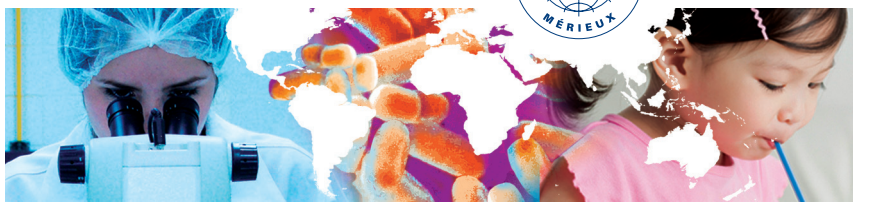
des racines pour la vie roots for life



WHITEBOOK

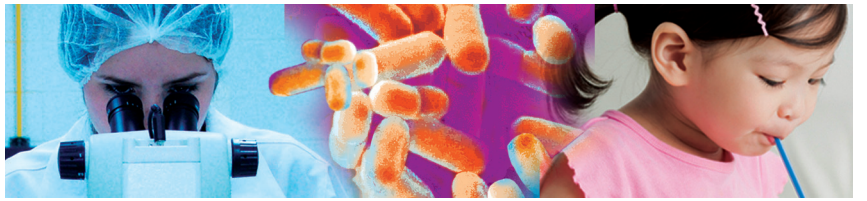
PREFACE

The international 'Better Foods for Better Health' Symposium is a unique platform attended by leading scientists, NGOs, policy stakeholders and key opinion leaders in the nutrition industry to broaden the scope and drive progress in nutrition - one of the major public health challenges today.

Initiated by Fondation Mérieux with the support of Mérieux NutriSciences, this Symposium stimulated new views to fertilise thinking on the intrinsic link between health and nutrition from scientific, business and regulatory perspectives.

Given that health matters occupy a pressing dimension in a global agenda, the Symposium fosters discussion on the latest scientific developments in nutrition in both developed and developing countries. Valuable insight from industry is provided by industry moderators, placing the consumer at the centre of the dialogue between scientific evidence and public policy makers.

'Personalised and Adaptative Nutrition', the theme of this year's symposium, illustrated the role personalised and adaptive nutrition holds for conditions such as cachexia, protecting the health of mother and child; reducing the risk of chronic disorders, obesity, diabetes, cardiovascular disease and cancer and for enhancing the quality of life from infancy to old age.



There is an urgent need for the development of validated methods to assess the nutritional value and impact of specific products, foods and food products, and for the harmonization of regional and global policies.

This White Paper provides a summary and recommendations of the stellar cast of participants who took part in the Symposium. It confirms the commitment of Scientists, leaders and stakeholders in the field of nutrition to promote 'Better Foods for Better Health'. Increasing dialogue between the scientific community, regulatory, nutrition and industry stakeholders is a top priority. The Foundation Mérieux and Mérieux NutriSciences are proud to contribute to this dialogue.

Alexandre Mérieux
Vice Président
Fondation Mérieux

Philippe Sans
President and CEO,
Mérieux NutriSciences

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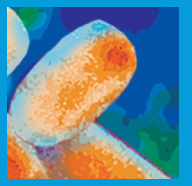


Better Foods for Better Health

CHALLENGES & SOLUTIONS

SEPTEMBER 12th to 14th 2012

On September 12-14th, 2012, experts from academia, international organizations, NGOs, regulatory authorities and industry met at Les Pensières, the Fondation Mérieux Conference Centre, for the third annual 'Better Foods for Better Health' forum organized by the Fondation with the support of Mérieux NutriSciences.

The objective of the meeting **'Personalized & Adapted Nutrition'** was to discuss how the latest developments in nutrition science could be translated into recommendations and products to reduce and eliminate undernutrition and malnutrition.

Personalized nutrition involves two trends:

An individual approach, based on high technologies involving super-gene science, trillions of data and multiplexing fast evolving methods. In this approach the classic research model, the Randomized Clinical Trial (RCT), does not apply. Other methodologies need to be found in order to validate the benefits of personalized nutrition.

'A group population trend', driven by emerging geographies, millions of undernourished people, and the current 'epidemic' of non-communicable diseases. In this approach, health economics is all-important and NGOs need to play a key role in preventing diseases for which existing prevention programs and drug treatment have had a disappointing impact.

While epidemiological studies show the relationship between diet and health conditions in large population groups, the new '-omics' tools are giving insight into the complex relationship between individual genetic background and nutrition.

This leads to the design of dietary advice and food products adapted to population groups, while, in parallel, the concept of personalized nutrition, adapted to the individual is emerging.

An important issue is the evaluation of such dietary recommendations and innovative food products. New models are to be developed because the classical models based on randomized clinical trials developed for the evaluation of drugs to treat disease do not apply to food products that aim at enhancing health and take into account individual specificities.

EXECUTIVESUMMARY

Considering the long term perspective of applied benefits for consumers via personalized nutrition, participants in the forum stressed the need to:

- foster research and stimulate innovation;
- better define groups of population (according to age, genetic background, metabolic profile, physical activity and lifestyle) in order to study and evaluate innovative approaches and products;
- establish nutritional profiles and measure 'healty status';
- define criteria for health that can be used to evaluate food products and to assess the benefits of personalized nutrition;
- integrate an open world for innovation in which new social media help to connect consumers directly to researchers. Social behavior and consumer acceptance will be key factors for regulators in balancing nutrition safety against personal freedom.

To this end, participants suggested:

- establishing a European consortium, 'Innovative Food–Nutrition Initiative', based on public-private partnerships, bringing together stakeholders from academia and industry, to define a common scientific approach and develop a 'pre-competitive nutrition research' program at European level.
- integrating additional non-medical criterias in order to assess the benefits of personalized nutrition, e.g. accessibility, affordability, freedom of the individual, value for the community, new psycho-socio behavioral models, and of course health economics.
- developing more science and harmonizing tools based on models that are specific to personalized nutrition: metabolic groups, sportsmen clusters, caloric restriction models, microbiome transplantation, etc.
- making dietary recommendations at lower levels of certainty than those required for drug authorization. The important point here is to assess the balance between the potential harm of making or not making a recommendation.

Participants suggested identifying a country or region which would most benefit from the implementation of such personalized dietary recommendations, according to their monitored impact, and according to new scientific discoveries and/or modifications in the environment. Annual meetings on Better Foods for Better Health could play a significant role in this monitoring process.

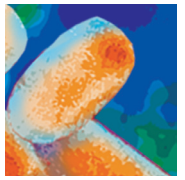
The next such meeting will take place at the Fondation Merieux, Les Pensières, Annecy, France, 18-20 September 2013.

'LET YOUR FOOD BE MEDICINE AND YOUR MEDICINE BE FOOD.'

..... Hippocrate

WHITEBOOK

3rd Annual Forum



Better Foods for Better Health

CHALLENGES & SOLUTIONS

SEPTEMBER 12th to 14th 2012

From basic research to personalized nutrition

Experts from academia, international organizations, NGOs, regulatory authorities and industry met for the third time at the Fondation Mérieux Conference Center for their annual brainstorming session on *Better Foods for Better Health*, to discuss the issues of malnutrition (including under- and over-nutrition) and approaches to secure food for a growing global population, as well as to translate basic research into food products that help prevent disease and promote health.

In a rapidly growing human population, elimination of nutriment deficiencies and undernutrition, as well as prevention of diseases linked to unbalanced nutrition are public health priorities worldwide. These priorities can only be addressed through the collaboration of all stakeholders: academia/scientists, governments, international organizations, policy makers and regulatory agencies, industry, communities and consumers.

Progress in research has shown the crucial role of nutrition in health and disease, especially at critical stages of life. Maternal and child nutrition during the first 1,000 days – from conception through age two – shapes a child's future. Nutrition also plays a crucial role in the elderly when nutrient deficiencies are frequent. An adapted alimentation may prevent or delay chronic diseases and some of the age-associated physiological impairments and enhance health and well-being.

The sequencing of the human genome associated with the development of novel tools such as the '-omics' and computing techniques opened the way to the study of gene-nutrient interactions, and the individual's response and susceptibility to particular diets. Therefore, the concept of personalized nutrition has emerged, aiming at adapting alimentation to the specificities of the individual.

Personalized or 'adaptive' dietary recommendations have been developed for different groups of the human population. However, there are still many scientific, regulatory, ethical and societal issues that have to be resolved before individual personalized nutrition becomes a reality. There is a need to define new systems to evaluate novel food products so as to regulate them without hindering innovation. The food industry, in partnership with stakeholders of the public sector, has an important role to play in the development of foods for health.

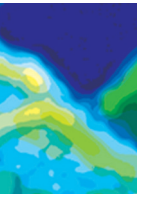
This report summarizes the presentations and discussions of the Third Forum on 'Better Foods for Better Health'. The names of speakers and discussants are listed at the end of the report.

Challenges in food security in a changing world

Progress in applied research and effective interventions have contributed to reducing hunger in the developing world. The First Millenium Development Goal (MDG) defined in 2000 - halving the prevalence of undernourishment in the developing world by 2015 - is within reach, but adequate and appropriate actions have to reverse the slowdown observed after 2006. Almost 870 million people are still chronically undernourished, which represents 12.5 percent of the global population, or one in eight people.

On the other hand, most of the world's 7 billion people have been experiencing structural alterations in their diets and eating patterns due to population growth, economic development, rapid urbanization, and fluctuation in food prices. During the past 30-plus years, the relative contributions of different foods to total energy intake have changed dramatically, with an increased intake in energy-dense foods that are rich in fat, salt and sugars but low in vitamins, minerals and other micronutrients and a decreased intake in starches, while fruit and vegetable consumption has not been growing sufficiently. This has resulted in the growing epidemic of chronic diseases such as cardiovascular diseases, diabetes, musculoskeletal disorders and cancers that afflicts both developed and developing countries.

The challenge is not only to reduce or eliminate undernutrition but also to reduce over- /mal-nutrition to ensure a long and healthy life. Solutions to problems of undernutrition and malnutrition clearly require efforts by a wide range of stakeholders, governments, regulators and policy makers, consumers, farmers and the food industry.



Global initiatives to reduce undernourishment

As highlighted by the Copenhagen Consensus - a think-tank that publicizes the best ways for governments and philanthropists to spend aid and development money - fighting malnourishment should be the top priority for policy-makers and philanthropists, and micronutrient interventions to fight hunger together with education would be the most worthy investment into human development. If universally applied current, low-cost interventions, antenatal supplements, complementary foods/feeding practices, and treatment of wasting, could avert 40% of the burden of undernutrition.

Until recently, the recommendation was to refer undernourished children to hospital to receive therapeutic diets along with medical care. The situation changed with the advent of ready-to-use therapeutic foods which allows for the management of large numbers of severely malnourished children over 6 months of age through outpatient setting.

Several initiatives have been established during the last 10 years. Created in 2002 at a Special Session of the UN General Assembly on Children, the Global Alliance for Improved Nutrition (GAIN) supports public-private partnerships to increase access to the missing nutrients in diets necessary for people's health. Population-based programs deliver staple foods and condiments fortified with vitamins and minerals to large populations through market-based approaches, while targeted programs deliver fortified food products including complementary foods and supplements to specific population groups including infants and young children, pregnant women and nursing mothers, school children, and undernourished people. These programs are supported by the GAIN premix facility (GPF) that provides services related to the certification and procurement of premix, a commercially prepared blend of vitamins and minerals used to fortify staple foods to food fortification projects around the world.

The Scaling-Up Nutrition (SUN) Movement, a country-led, global initiative to advance health and development through improved nutrition established in 2009, has brought together specialists from governments, academia, research institutions, civil society, private companies, development agencies, UN organizations and the World Bank to develop a 'Scale Up Nutrition Framework' of key considerations, principles and 'for action' priorities to address undernutrition.

The Bill & Melinda Gates Foundation supports a number of efforts including the Scale Up Nutrition (SUN). It has adopted a nutrition strategy based on research and implementation of effective evidence-based nutritional interventions and focuses on pregnant women and children up to 2 years of age.

Examples of initiatives and public-private partnerships had been presented in former 'Better Foods for Better Health' symposiums, with the description of 'Plumpy' Nut', a ready-to-use therapeutic food developed by Nutriset (BFBH, 2011), and the Grameen Danone Foods initiative to produce locally in Bangladesh a special yogurt, called Shakti Doi, that fulfills the nutritional requirements of children (BFBH 2010). Other examples were presented at the third edition of 'Better Foods for Better Health'; among these are the 'Food Chain Partnerships' between Bayer and several countries for implementing sustainable crop solutions from planting to harvesting, and the partnerships between BASF and producers of cooking oil or other local staples (flour, milk) from developing countries to fortify basic products with vitamin A.

Promising approaches to prevent and treat malnutrition are tested in research trials, in order to define those to be prioritized for implementation in low-resource settings. But it is also crucial to identify the underlying causes of undernutrition and to define how best nutritional advice or nutriments can be distributed and utilized. Such an approach was adopted by the '*Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes*' (GHESKIO) in Port-au-Prince for an intervention aimed at improving growth of uninfected children of HIV-infected mothers attending the GHESKIO pediatric clinic. With the help of nutritional experts in human ecology and clinical physicians at Weill Cornell Medical College (WCMC), they adopted a multi-faceted strategy that includes distribution of the nutritional supplements, charting the children's growth, individual nutritional counseling for the caregivers, and preventive health education and social support through 'mothers'clubs'. This promising intervention model can be adapted to other health contexts.

A critical windows of opportunity for prevention

Most interventions focus on pregnant women and young children, since the impact of malnutrition during this critical window is largely irreversible. Indeed maternal and child nutrition during the first 1,000 days – from conception through the age of two – shapes a child's future. This period can also be considered as a 'window of opportunity' to prevent early childhood undernutrition and irreversible damage: with adequate nourishment in the earliest years of life, children have an opportunity to grow, learn, become productive adults and break the cycle of poverty. In order to develop more effective interventions that promote healthy pregnancies and early childhood growth, it is necessary to foster a better understanding of the causes, potentiating risk factors, mechanistic pathways that result in impaired health of newborns.

The developmental origin of health and disease

The vast majority of non-communicable diseases, including cardiovascular diseases, metabolic syndrome and obesity, may have their origin during fetal life or even as early as the pre- or periconceptional periods. Environmental conditions during pregnancy can have irreversible effects on cell fate, organogenesis, metabolic pathways and physiology of the offspring, thereby influencing life-long physical and mental health. An adverse environment during specific windows of developmental programming may affect the long-term health and susceptibility to non-communicable diseases of the offspring in a sex-specific manner. The developing organism senses these maternally transmitted environmental cues during prenatal and early postnatal life, and modifies its metabolism and growth trajectory accordingly. Rapid changes in nutrition, with transition toward energy-dense diets observed in most countries may be at the origin of a mismatch between the fetal nutritional environment and the mature obesogenic environment, and explain the epidemic of metabolic diseases. Such predisposition can be transmitted to subsequent generation(s) with differences in response and susceptibility according to the sex of the individual.

The molecular mechanisms underlying this process involves epigenetic mechanisms that affect gene regulation through DNA methylation, covalent modifications of histones and non-coding RNAs. These epigenetic modifications are gene and cell-type specific. They affect gene expression without altering the genes themselves, and are generally stable during the mitotic cell divisions that continue throughout the life course, creating variation in the expression of the transcriptome without changes in the genome, and acting as a memory of the event long after exposure has ceased.

For example, methylation of specific CpG loci that can be detected in fetal tissues as well as in adult cells is a marker of differential risk of type 2 diabetes mellitus.

The impact of environmental factors on programming through epigenetic mechanisms varies, however, between individuals, which can explain the large inter-individual and across-generations variations in the proneness or resistance to develop chronic disease. Sexual dimorphism, i.e. the phenotypic differences between males and females, is largely due to epigenetic mechanisms, which explains that the same environmental insult may have a different effect according to the sex of the embryo.

However, in contrast to gene mutations, epigenetic events may be reversible, to a certain extent, in response to endogenous and exogenous signals. For example, exercise can induce acute changes in the methylation of genes in muscle, and nutritional interventions can improve health outcomes through epigenetic changes.

Epigenetic marks can persist over several successive generations, although inter-generational influences can amplify or attenuate phenotypic changes in the course of a few generations. This has been clearly demonstrated in experimental studies, where strains of obese diabetic mice gave birth to lean offspring with normal insulin sensitivity and glycemia even under high-fat diet when fed an appropriate diet during the periconceptual /gestation/ lactation period. Specific profiles of CpG

methylation and histone acetylation were associated with the obesity prone phenotype, while resistant mice had a different epigenetic landscape close to 'normality'. This effect, however, was observed only in female offspring, which illustrates the sexual dimorphism.

These results offer opportunities for novel epigenetic biomarkers of risk and for interventions targeting epigenetic pathways in early life. But many questions remain. If epigenetic changes are, in theory, flexible, can interventions really modify them without side effects?

Nutrition and aging

An adapted nutrition can also have an important impact in the elderly, the fastest-growing segment of the population. In 2005, it was estimated that almost 500 million people, or 8% of the worldwide population, were over 65 years of age. By 2030, the number of elderly people is expected to exceed one billion or 13% of the total population. As discussed during the symposium, the incidence and impact of malnutrition in elderly people is probably underestimated. Poor nutrition and malnutrition is estimated to occur in 15 to 50 percent of the elderly population, but the symptoms of malnutrition can easily be overlooked or attributed to a coexisting illness or disease.

Expanding knowledge on nutrition and on the physiological changes associated with aging can lead to an age-adapted approach to nutrition and life-style so as to prevent disease and improve the well-being and quality of life of the elderly. Indeed, aging is associated with a decrease in physiological performances that can be alleviated by specific nutriments. The progressive loss of muscle mass and muscle strength associated with normal aging requires a higher protein intake; the declining efficiency of UV-induced skin synthesis requires higher Vitamin D intake; impaired gastric acid-dependent absorption of food/protein bound Vitamin B12 requires a higher intake of crystalline Vitamin B12. In the elderly, tolerance to Vitamin A changes with alteration in hepatic lipid metabolism, processing, and release into the circulation. Iron requirements are lower with lower loss and utilization. All of these age-related changes occur as the physical activity-driven energy consumption and appetite decline.

Can an adapted nutrition also prevent aging itself, i.e. the deterioration of cells and tissues structure and function that occur independently of disease?

Caloric restriction to decrease the risk of age-associated morbidities and/or to increase lifespan

Prolonged calorie restriction (CR) has been shown to extend median and maximal lifespan in a variety of lower species (yeast, worms, fish, rats, and mice), and there are indications that caloric restriction could also be beneficial for humans. Okinawa island (Japan), where the energy intake per habitant is estimated to be ~85% of their daily energy balance requirement (i.e., a 15% CR), has the highest number of living centenarians in the world and the life expectancy at birth is higher in Okinawa than in the neighboring islands or in western countries.

A decreased risk of atherosclerosis and other age-related morbidities has been observed in individuals of the 'Calorie Restriction Society' who self-impose CR, compared to controls matched for age and body-mass index (BMI): serum cholesterol, LDL-cholesterol and serum thyroglobulin (TG) concentrations of the CR group were in the lowest 10% for people of their age. Blood pressure was remarkably low, with values in the range found for 10-year olds. In the same line, the weight loss observed in the participants of Biosphere 2 experiment [1] submitted to CR was associated with many favorable physiological, hematological, biochemical and metabolic modifications.

One long-term controlled trial in humans is currently conducted in the USA to study the effect of two years of caloric restriction (25%) in non obese humans (CALERIE, for Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy). The study, sponsored by the National Institute of Aging, is still ongoing but preliminary results of a pilot study showed that six months of CR produced favorable modifications in physiological outcomes such as improvement of biomarkers of cardiovascular and diabetes risk factors that are also considered as biomarkers of longevity.

It remains to be seen, however, whether subjects submitted to life-long CR live longer than their age- and sex-matched counterparts. A first indication could come from studies carried out in non-human primates. A preliminary report of a study conducted at the University of Baltimore showed that monkeys fed *ad libitum* over a period of 25 years had a 2.6-fold increased risk of death compared to those under caloric restriction. The results of a 20-year study conducted at the Wisconsin

1) In the late 1990's, an experiment of life in a closed artificial biosphere (Biosphere 2) was conducted in the USA to study global ecology and long-term closed ecological system dynamics. Eight individuals were isolated within this mini-world for 2 years. 100% of the air and water was recycled and all food grown inside. Food supply became quickly insufficient, and the participants experienced an approximate 750 calorie per day deficit resulting in an average of weight loss of 15%

National Primate Research Center (WNPRC) and published in 2009 indicate that initiating caloric restriction in adult rhesus monkeys (7–14 years) did, in fact, extend lifespan. At this time point, 50% of control-fed animals survived compared with 80% survival of CR animals. Further, CR delayed the onset of age-associated pathologies and reduced the incidence of diabetes, cancer, cardiovascular disease, and brain atrophy. Body weight-adjusted skeletal muscle mass declined somewhat in both groups but was far more rapid in the control group.

However, in contrast with the WNPRC study, the CR regimen implemented in young and older age rhesus monkeys at the National Institute on Aging (NIA) did not improve survival outcomes, although certain age-related diseases including diabetes, arthritis, diverticulosis and cardiovascular problems, occurred at an earlier age in monkeys on the standard diet compared to those on calorie restriction. These discrepancies could be explained by differences in genetics and dietary composition, which would matter more for longevity than a simple calorie count.

Should the most positive effects of CR observed in animals be confirmed in humans, the practicability and feasibility of caloric restriction in humans remain, nevertheless, questionable. According to extrapolations from animal experiments presented at the symposium, a 5-year life extension could be obtained by a 20% CR starting at age 25 and sustained for 52 years. If a 30% CR was initiated at age 55 for the next 22 years, the gain would only be 2 months. In these conditions, it is more appealing to search for organic or inorganic compounds that would mimic the biological effects of CR. If such compounds, often called 'CR mimetics' (such as resveratrol, a natural phenol found in grapes and other fruits, and in small quantities in red wine) prove truely effective in humans, then most individuals will no doubt opt to enjoy the effects of an anti-aging pill or drink rather than CR.

Antioxidants, Nutrition and Ageing – Miracles, Myths and Misunderstandings

CR decreases the levels of many growth factors, anabolic hormones, inflammatory cytokines, and oxidative markers that are deregulated in certain types of cancer. One hypothesis for the beneficial impact of CR is that the metabolic rate is reduced, which leads to reduced oxidative damage.

According to the Mitochondrial Free Radical Theory of Aging (MFRTA), aging is a consequence of the accumulation of cellular damage by free radicals produced during aerobic respiration. This theory has been supported by initial observations that longevity among species inversely correlates with generation of O^{2-} and H_2O_2, and that people with high blood levels of 'antioxidant vitamins' such as vitamin C, vitamin E or β-carotene were at lower risk of developing a variety of diseases, including cancer and type 2 diabetes. Biomarkers of oxidative damage are elevated in mild cognitive impairment, and all types of biomolecules in the brain of Alzheimer's disease (AD) patients present signs of elevated oxidative damage.

At this stage, the free radical-antioxidant theory was simple: since free radicals are bad, antioxidants are good, and taking antioxidants would prevent disease and make you live longer. Actually, it is not all that simple. High blood levels of antioxidant vitamins are markers of a diet rich in fruits and vegetables, which is itself protective against disease. It could thus be any component or a mixture of components in that diet that is protective. In addition, a few animal species such as naked mole rats combine high oxidative damage with a longer lifespan: they typically live 10 to 30 years, while common rats live about three years on average.

The results of studies on the effects of antioxidants on human disease development have been contradictory and confusing. Response to vitamin E in humans is heterogeneous. Not all of the elderly who receive supplemental vitamin E experience an improvement in immune response, and this variability in response cannot be fully explained by vitamin E status.

In the Heart Protection Study, the combination of synthetic vitamin E, vitamin C, and β-carotene administered daily had no effect on the incidence of cardiovascular events, while the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) trial showed that a combination of vitamin E and vitamin C taken for a period of 6 years significantly reduced carotid atherosclerosis progression, but the effect was seen only in hypercholesterolemic men (33% reduction). The double-blind, placebo-controlled, randomized trial on Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) demonstrated that daily administration of a combination of ascorbic acid, vitamin E, β-carotene, selenium and zinc decreased total cancer incidence and total mortality in men, but these beneficial effects of antioxidant supplementation disappeared during post-intervention follow-up. Another study did not support the routine use of dietary supplements containing B vitamins or omega 3 fatty acids for prevention of cardiovascular disease in people with a history of ischemic heart disease or ischemic stroke, at least when supplementation was introduced after the acute phase of the initial event.

Intervention trials with high-dose vitamin E had limited efficacy in Alzheimer disease; no improvement was observed in mild cognitive impairment; no beneficial effect on cardiovascular disease or cancer was detected. Some studies even suggested deleterious effects. A meta-analysis published in 2010 showed that vitamin E increased the risk for hemorrhagic stroke by 22%, although it reduced the risk of

ischemic stroke by 10%. Given the relatively small risk reduction of ischemic stroke and the generally more severe outcome of hemorrhagic stroke, it was concluded that indiscriminate widespread use of vitamin E should be cautioned against.

There are multiple explanations for this 'failure' of antioxidants, often referred to as the 'antioxidant paradox', in spite of the observation that oxygen radicals and other reactive oxygen species (ROS) are involved in several age-related diseases, including sarcopenia, cancer and neurodegenerative diseases.

One explanation could be the heterogeneity of the individual genetic background of participants in the various trials. Studies presented at the symposium showed that vitamin E supplementation specifically reduced cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and a specific haptoglobin 2-2 genotype that is linked with a reduced capacity to cope with hemoglobin-induced oxidative damage. Other studies showed that vitamin E had a specific anti-inflammatory effect in people genetically predisposed to higher inflammation because of higher TNF-α levels associated with the presence of the A allele of the TNF-α gene.

Another explanation, not exclusive of the preceding one, is that the human body has an endogenous antioxidant system that is carefully regulated by endogenous enzymes, and the contribution of the diet-derived antioxidants such as vitamins C and E in this highly regulated antioxidant system is not known. Indeed, this system seems to be capped at physiological levels, which could explain that well-nourished humans are unresponsive to high doses of dietary antioxidants. In addition, it may not be beneficial that the 'antioxidant defense network' removes all ROS, as some of the oxygen radicals and other reactive oxygen species made in the organism play essential roles in signaling and immune response. The endogenous antioxidant system must be adjusted to carefully control ROS levels so as to allow useful functions whilst minimizing oxidative damage.

On the other hand, weak 'pro-oxidants' that stimulate the endogenous antioxidant system and increase endogenous antioxidant levels could be a more useful approach to treatment and prevention of diseases than consuming large doses of dietary antioxidants. Several of the beverages commonly consumed by humans, such as green tea, black tea and red wine, that are supposed to have a beneficial antioxidant effect, are actually complex mixtures of anti- and pro-oxidants. This is also the case for flavonoids and other polyphenols, which have been shown to be associated with lower risk of developing some age-related diseases in humans in most, but not all, epidemiological studies. This disease-protective effect is often attributed to antioxidant activities. However, polyphenols can also exert pro-oxidant activities under certain experimental conditions. It has also been argued that polyphenols may exert antioxidant and other cytoprotective effects only locally in the gastrointestinal tract, where they are present at higher levels. They could have an impact by affecting both composition and metabolism of the intestinal microbiota.

The search for antioxidant compounds

Antioxidants are nevertheless still being investigated as a promising strategy for extending lifespan. Several compounds have been identified for their antioxidant activity, such as dark soy sauce, a traditional fermented seasoning in Asian countries, or mate tea, the roasted product derived from yerba mate (*Ilex paraguarienis*). The antioxidant activity of mate tea was observed both *in vitro* and in animal models. Its prolonged administration in humans resulted in decreased lipid peroxidation and increased levels of antioxidant enzymes in plasma, suggesting that regular consumption of mate tea may increase antioxidant defense of the body.

Most screening for antioxidant activities has been performed on cultured cells, with the implicit assumption that in vitro antioxidants will also be able to decrease oxidative damage in vivo and thereby extend lifespan. However, the capacity of cultured cells to identify antioxidants has been questioned. Compounds such as vitamin C can interact with some cell culture media to produce H_2O_2 at different rates, which could account for many or all of the conflicting results obtained using ascorbate in cultured cell assays: some authors showed inhibition of cell death by ascorbate, whereas others demonstrated that ascorbate was cytotoxic. The same applies for a variety of products, including flavonoids and other polyphenols that are instable in commonly-used culture media which they oxidize, rapidly generating cytotoxic levels of H_2O_2. Such effect may have led to artefacts in interpretations of the cellular effects of high concentrations of added polyphenols. Cell culture is certainly not a good model, and other models such as *Caenorhabditis elegans* may be more relevant to screen plant extracts for their effects on oxidative damage, ROS production and mitochondrial function.

In brief, there are still major challenges to be won in the ROS field: establishing the true role of ROS in aging; doing something about it; understanding redox signaling at the cellular and whole organism level, and developing antioxidants that work, especially in the brain to slow neurodegeneration.

The genetic basis of chronic diseases

A significant number of presentations and discussions were devoted to the interaction between nutrition and the genetic background. It has been known for decades that some genetic disorders, such as phenylketonuria (PKU), galactosemia or maple sugar urine disease (MSUD), can be controlled by special diets. These diseases are due to mutations in genes coding for enzymes involved in food metabolism. For example, individuals with phenylketonuria (PKU) cannot process part of a protein called phenylalanine (Phe) that is present in most foods. Accumulation of Phe in the organism can damage the brain and lead to mental retardation and seizures. If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but a special diet low in Phe must be followed throughout the individual's entire life. Galactosemia and lactose intolerances require elimination of galactose and lactose from the diet. Patients with MSUD cannot break down the amino acids leucine, isoleucine, and valine; accumulation of these chemicals in the blood can damage the brain during times of physical stress such as infection, fever, etc.. The disease can be controlled by a diet containing minimal levels of the amino acids.

With the development of large-scale genome-wide association studies (GWAS), in which large numbers of genetic variations occurring at a single nucleotide level (single-nucleotide polymorphism - SNP) are tested for association with the trait of interest, the field has taken huge steps toward understanding the genetic underpinnings of complex, multifactorial diseases and their relation with nutrition.

Searching for obesity genes

Candidate-gene and genome-wide association studies have identified numerous SNPs influencing the risk of obesity, but many of these potential associations have not been confirmed by further studies, partly due to potential interactions between multiple genetic and environmental factors, each variant contributing with small effects.

The first single nucleotide polymorphism robustly associated with increased body mass index (BMI) mapped to a gene now known as 'fat mass and obesity-associated' (*FTO*), which is affecting obesity by regulating appetite, and which effects can be reduced in adults by physical activity. Several studies have shown an association between –265T>C promoter polymorphism (rs5082) in the *APOA2* locus, energy intake and obesity. In populations with high saturated fat intake, homozygous carriers of minor allele (CC) had significantly higher energy and macronutrient intake and increased body weight compared to T-allele carriers, even after adjustment for other macronutrients. If saturated fat intake is low, this polymorphism does not seem to have an effect on BMI or obesity.

Actually, many of these SNPs are found in genes that are expressed or known to act in the central nervous system, and particularly in the hypothalamus like *FTO*, highlighting a likely neuronal component to the predisposition to obesity. Other SNPs related to obesity have been found in genes expressed in adipose tissue known to play a critical role in the complex equilibrium between energy uptake, storage and expenditure. For instance, a relationship has been found between obesity and polymorphisms in the *PLIN4* gene that is expressed mainly in adipose tissue and codes for a protein that facilitates uptake of free fatty acids from the blood in response to the nutritional state of the cell; or *CLOCK* genes that regulate the rhythmic expression of secreted bioactive substances such as adipokines (adoponectin, leptin, among others) which affect systemic metabolism.

Searching for diabetes genes

Type 2 diabetes (T2D) also results from the complex interplay between genetic variants and environmental factors, with obesity established as a primary risk factor. Excessive caloric intake and poor diet quality are also major independent factors underlying the T2D epidemic.

It has been estimated that 30% to 70% of T2D risk can be attributed to genetics. The role of genetics in T2D is strongly indicated by the higher concordance rate in monozygotic than in dizygotic twins. Family clustering and ethnic disparities of T2D incidence, hyperinsulinemia, and hyperglycemia provide further evidence but also warrant careful interpretation as families and ethnic groups share behaviors as well as genes.

Recent GWA studies have unveiled over 50 novel loci associated with T2D and more than 40 associated with T2D-related traits including fasting insulin, glucose, and proinsulin. With the exception of transcription factor-7-like 2 (TCF7L2) that is associated with a 40% increased risk, most variants contribute modestly to T2D risk and together explain only a small proportion of the family clustering of T2D, suggesting that many more loci await discovery.

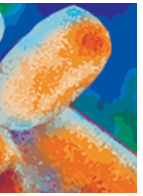
According to the function of the genes affected, these genetic variants associated with an increased risk of diabetes can be classified in two groups. The first group includes risk alleles that act through β-cell dysfunction, and are associated with impaired insulin secretion, such as the TCF7L2 variant rs7903146 allele mentioned

above, or the rs11558471 variant allele of the *SLC30A8* gene. *SLC30A8* encodes a zinc transporter that facilities zinc accumulation in intracellular vesicles and co-localizes with insulin in insulin-secreting-β cells. These genetic variants appear to be associated with T2D in non-obese individuals only.

The second group includes genetic variants that are associated to insulin resistance. This is the case of the peroxisome proliferator-activated receptor-c gene (*PPARG*) that is involved in the regulation of lipid and glucose metabolism. A proline to alanine substitution (Pro12Ala, rs1801282) in this gene has been implicated in the etiology of type 2 diabetes. These genes seem to be associated to diabetes in obese subjects only.

Indeed, these GWAS have also shown a link between specific alleles and the impact of nutritional interventions. For instance, individuals with the risk allele of the *FTO* variant rs1558902 will lose weight and have their body composition improved with a diet rich in proteins while carriers of the G allele at the *CLOCK* rs1801260 display greater difficulty in losing weight with low-energy diets than non-carriers.

Altogether, these studies give insight into the relationship between individuals and their nourishment. They also show the unique specificity of each individual and the complexity of interactions. Gene expression is highly regulated, by other genes, by epigenetic mechanisms and by the environment, which makes it difficult, at this stage, to integrate all data for personal individualized nutrition advice.



Impact of the microbiome on nutrition and health

An additional level of complexity comes from the interaction of the gut microbiota, now considered as a key 'endogenous' organ that participates in energy harvest from the diet and energy storage in the host, and modulates the host physiology. In fact, humans are meta-organisms, integrating functions of human and microbial genes, the latter representing ≈ 100 times the human genome. Huge research efforts, ssupported by the Human Microbiome and the MetaHit projects, as well as other major actors including the food industry, are unravelling the role that microbiota play in nutrition, key metabolic pathways and immunity.

The human microbiota, a dynamic ecosystem dominated by *bifidobacteria*, is established after birth and stabilizes during the first 2–3 years. The establishment of the bacterial ecosystem in early life is suggested to play a major role in the microbial composition and disease susceptibility throughout life.

Each human individual has a unique microbiome composition that remains relatively stable during most of a healthy adult's life, with several hundred species-level phylotypes dominated by the phyla *Bacteroidetes* and *Firmicutes*. This composition may vary at the bacterial level, but the overall phylogenetic profile can be categorized into 3 specific clusters of microbial groups that form stable networks, termed enterotypes. At the late stages of life, the microbiota composition becomes again less diverse, with a reduction in numbers of 'beneficial' bacteria.

Diet is an important factor in microbiota composition development. Breast-fed babies have a microbiota that is more heterogeneous than that of formula-fed babies and contain a higher taxonomic diversity. In addition, food habits can influence microbiota composition. Long-term diets rich in protein and animal fat correlate with the enterotype characterized by high levels of *Bacteroidetes*, while the *Prevotella* enterotype is associated with diets rich in carbohydrates. Malnutrition results in lower abundance of *Bacteroidetes*. Short-term dietary interventions have been shown to induce rapid changes in the microbiome, but without changing the overall enterotype.

Composition of intestinal microbiota is also determined by the host genotype. Studies have shown a higher similarity in the microbiota composition between monozygotic twins than between dizygotic twins, unrelated persons, marital couples and family members, thus clearly pointing to a strong effect of host genetics. It has been shown in a recent study, that the human *FUT2* gene, which determines the presence of ABH histo-blood group glycans in mucus lining the intestine, significantly affects the bacterial composition, particularly the bifidobacterial composition, in the intestine. The ABH secretor status determining the expression of the ABH and Lewis b glycan epitopes in the human intestine is linked with abundance of bifidobacteria in the intestine.

Some studies have shown an increase in the relative abundance of *Firmicutes* and decrease in *Bacteroidetes* in both obese mice and humans. In addition, transplantation of gut microbiota from obese mice to nonobese, germ-free mice resulted in transfer of metabolic syndrome-associated features from the donor to the recipient.

Alterations of the colonic microbiome composition induced by daily alcohol consumption could be responsible for the inflammatory state and endotoxemia observed in some alcoholics. Modulation of the intestinal microbiota through multiple inflammasome components has also been shown to be a critical determinant of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) that are associated with cirrhosis, portal hypertension and hepatocellular carcinoma.

Indeed, the combination of gut dysbiosis and genetic inflammasome deficiency can result in abnormal accumulation of bacterial products in the portal blood that passes through the liver which is especially vulnerable to their effects when hepatocytes have accumulated lipids.

New treatment strategies

Insight into the role of the gut metabolome in health and metabolic diseases thus opens the way to novel therapeutic interventions for acute or chronic diseases through correction of dysbiosis. These approaches include fecal microbiota transplants and administration of adapted diets, probiotics and/or prebiotics to enrich the gut with 'beneficial' species or to compensate for missing symbionts.

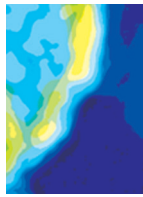
Fecal microbiota transplantation has been used by individual clinicians as an answer to severe disruption of the gut bacterial community. It is safe and inexpensive, and the most efficient therapy in recurrent or severe *Clostridium difficile* colitis: a prolonged response is obtained in 80-100% of patients.

Fecal transplantation could also be used for more common conditions, such as obesity and metabolic syndrome. A recent clinical trial showed that infusion of intestinal microbiota from lean volunteer donors to male recipients with metabolic syndrome led to increased levels of butyrate-producing intestinal microbiota associated with increased insulin sensitivity.

Studies are currently being conducted to verify whether comparable effects can be obtained by oral administration of probiotics, mainly lactic acid bacteria and *bifidobacteria*. If confirmed, this could offer a rationale for novel therapeutic interventions aimed at improving insulin sensitivity in humans.

Probiotics and/or prebiotics (nondigestible food ingredients that selectively stimulate the growth of beneficial microorganisms in the gastrointestinal tract) could also be used as alternative supplements to exert health benefits, including cholesterol-lowering effects on humans to control and/or prevent hypercholesterolemia. However, more clinical evidence is needed for a broader use of pro- and pre-biotics.

A growing number of researches indicate that some probiotic strains may be advantageous for the elderly, suggesting both health and cost-saving benefits in offering fermented dairy products. These benefits include: establishment of balanced intestinal microflora; improving colonization resistance; reduction of fecal enzymes; reduction of serum cholesterol; reduction of potential mutagens; reduction of lactose intolerance; synthesis of vitamins; predigestion of proteins; prevention of diarrhea.



Towards adapted and personalized nutrition

There is now an unprecedented potential for the rational design, production and testing of precise nutritional products, based on science, and targeted to particular populations. This could have a considerable impact on public health.

So far, dietary recommendations have been developed for different age groups: infants, children, adolescents, adults, athletes and seniors, and for specific conditions such as pregnancy, diabetes, hypercholesterolemia, hypertension, and many others. These dietary guidelines are based on broad definitions of nutrient and energy needs of individuals belonging to defined segments of the population.

National strategies have been developed for the reduction of chronic diseases and risk factors, with special emphasis on obesity. For example, in 2006 Brazil – one of the fastest ageing populations in the world that is facing a rise in the prevalence of overweight, diabetes and hypertension - adopted a broad health promotion policy that includes a series of actions in health education and disease and risk factor monitoring. Health care provision has been centered on healthy diets, physical activity, and reduction of smoking and alcohol consumption.

In Europe, the concern for overweight and obesity over the last decades led the European Commission to establish, in 2007, a 6-year Strategy for Europe on Nutrition, Overweight and Obesity-related Health. This strategy was put in place through two organizations: the EU Platform for Action on Diet, Physical Activity and Health, a forum for discussion among all stakeholders, including industry; and the High Level Group for Nutrition and Physical Activity, for exchange of policy ideas and best practises between Member States.

The European Commission has worked together with the High Level Group and the EU Platform on voluntary reformulation of foods to improve their nutritional value. Successful innovative foods lower in fat, salt and sugar content are already widely available and in some cases have led to new niches in the market place. However, food composition in Europe is still regulated at the national level, which is going to be a hindrance as long as there are national differences within Europe

Regulation to promote innovation

Japan was the first country to establish a regulation (FOSHU) to encourage the development of functional foods that could benefit public health and respond to the concerns of consumer groups and leading food companies about misleading health claims.

In Europe, regulation on nutrition and health claims made on foods was established 'to protect consumers, improve the free movement of goods, increase legal security for economic operators, ensure fair competition, and promote and protect innovation' [Regulation EC N° 1924/2006].

However, the process for health claim approval by European Food and Safety Authority (EFSA) has been considered as discouraging for industry. A large number of claims concerning certain categories of substances of particular interest for consumers, food business operators and academia have been rejected. In the area of probiotics, for example, no claim has been approved by September 2012. In the area of anti-oxidants, apart from vitamins and minerals, only olive polyphenols obtained a positive assessment and a consequent authorisation.

This was due, at least partly, to the fact that requirements for approval were not clearly defined when the first files were submitted to EFSA. And yet, two European concerted actions, Functional Food Science in Europe (FUFOSE) and Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM) had been carried out both to define the science-based evidence needed to support the development of food products that can have a beneficial effect on an identified physiological function in the body, and to establish criteria to assess the scientific substantiation of health claims (on enhanced function, or reduced risk of disease). Nevertheless, when the first files were submitted to EFSA, requirements for acceptation were not clearly defined. In the area of probiotics, EFSA has been since providing specific guidance on how it carries out its assessment, on the beneficial effects it accepts, and what are the endpoints to be considered in scientific studies.

There is, however, still a need to better define the type of evidence necessary for developing nutrition and health claims as well as dietary guidelines. Randomized clinical trials (RCTs) are the gold standard in evidence-based medicine; they have also been wholly adopted as the basis of nutrition and science policy and regulation. But as nutriments are different from drugs, they cannot be tested according the same rules. Since they are often under homeostatic control, there is a threshold above which increasing the dose does not translate into a biological effect. In addition, nutrients have multiple sites of action so it is possible to have abnormal function in one parameter, while other parameters requiring the same nutrient appear within normal ranges. Advancing evidence-based nutrition from its current version to one based upon more relevant and realistic criteria will depend upon research approaches that include RCTs but go beyond them. One has to find how the sometimes subtle effects of diet and nutrition can be delineated in human studies, and also to what proportion inter individual variations are important.

In addition, the definition of health status needs specification. If food products are to promote health, how does one define 'health'? If there are multiple markers of unhealthy states, the markers of a healthy state have to be identified. This constitutes a major challenge in nutrition research.

Another issue is defining the level of certainty necessary for recommendation and authorization of nutrients aimed at preventing disease and/or promoting health. Decisions concerning nutrient requirements or dietary recommendations to promote health could surely be made at a level of certainty somewhat less than required for drugs. The risk of harm is much lower with nutriments, while failing to act due to absence of conclusive randomized clinical trials may jeopardize the potential for achieving benefits with little risk and low cost. Indeed, making decisions in the absence of ultimate certainty requires a broad consideration of all research approaches along with revised estimates of the necessary certainty level and confidence needed to act in support of public health. The important point here is to assess the balance between the potential harm of making or not making a recommendation, which requires appropriate education and a new mind-set with regard to functional foods.

The challenges of individual personalized nutrition

When it comes to personalized nutrition at the individual level, it is necessary to integrate multiple research strategies and revise the current concept and definitions of evidence-based nutrition. Research studies are based on randomization to compare outcomes or responses between large groups in order to reduce the impact of individual variations. New concepts in the design of experiments have thus to be established.

A pilot experiment has been specifically designed to begin development of novel experimental designs and research strategies to analyze individual responses to interventions. This study, the Delta Vitamin Obesity study, a joint effort between the US Department of Agriculture, the US Food and Drug Administration (FDA), several American institutions and the Microsoft Research - University of Trento (Italy) Centre for Computational and Systems Biology (COSBI) is among the first of its kind, since it combines community-based participatory research with translational biomedical strategies that include molecular genetic nutrition research, looking for links between obesity and diet, physical activity, genetics, and body chemistry. Comparisons will be made from year to year, within age groups, between individual food intakes, physical activity measures, and individual genetic backgrounds. Data is analyzed both at the population and the individual level,

focusing on weighed food records, 11 metabolites, 1M genotyping arrays, 39 nutrients identified by 24 hour dietary intake recalls, accelerometer measures, and skin tone.

Additional challenges have to be met before individual personalized nutrition can be implemented. Personalized dietary advice will be based on personal information on food habits and lifestyle and on genotypic and phenotypic analysis of sample, blood, urine. New technologies and new measurement tools, biosensors and portable devices are to be developed that are non-invasive, highly accurate and robust, allow for real time monitoring and multiple readouts and be affordable while new biomarkers (host genome and gut microbiome) have to be identified and validated. A specific regulation will have to be established to guarantee the safety and performance of the tests. Solutions will have to be found that integrate nutrition and diagnostics into new prevention strategies and medical treatment.

Genetic information is complex, intimate and sensitive. It is often difficult to interpret and to understand. Still much is to be learned on gene regulation, and on interactions between the genome, the microbiome and the environment. The gut microbiome is associated with disease states, but it is difficult to sample directly; samples may not reflect the luminal content in other segments and mucosa-associated microbiota, and it is difficult to determine interactions and symbiosis. New tools to characterize changes in bacterial community functions and clear outcomes are still needed.

When a genetic predisposition to a disease is discovered in an individual, ideally all the family should be tested and benefit from preventive actions. The confidentiality limits in communication with family and with health insurance agencies must be clear and transparent.

Nutrition in children is another issue needing ethical consideration. In early life, nutrition has a major and lasting impact on growth, brain development, and health. The question, though, boils down to the education of parents.

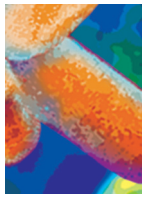
In order analyze the opportunities and challenges in a comprehensive manner in the field of personalized nutrition, the European project Food4Me has gathered an international group of experts to survey the current knowledge of personalized nutrition, to explore the application of individualized nutrition advice, to investigate consumer attitudes and to produce new scientific tools for implementation.

Introduction of personalized nutrition will require targeted and evidence-based information and education of consumers. Too much confidence in the effects of nutriments could lead consumers to forget about other equally important factors such as physical activity.

Who will be in charge of communicating on personalized nutrition? It was agreed that, while it is commonly expected that industry should fulfill a role in the education concerning healthy nutrition, its primary mission is, in fact, to provide full and detailed product information whereas the education remains mainly the role of health professionals. Nevertheless, the food industry may have to learn how to communicate better with the scientific community and with health care workers, as well as with consumers, and to be ready to reply to questions raised by regulators, politicians and consumers about such a complex concept.

The food industry has an important role to play to solve the growing problem of obesity, by producing and promoting healthy diets. Concrete actions taken by the food companies include global public commitment to address food reformulation, consumer information, responsible marketing, and promotion of healthy lifestyles. Further disease prevention depends on innovation, i.e., translating science into products that have added value, are palatable and affordable for the consumer and respond to their demand but that are also commercially viable.

However, bringing to market new, healthier products requires an increased investment in research, close interaction with those working on agricultural commodities, and deeper insights into how future consumers will respond to these products. Some consumers are concerned about having to compromise taste for better health, to pay more, or to give up something to which they are accustomed.



A paradigm shift

It has been known for centuries that food plays an important role in human health, and can contribute to its deterioration or to its improvement. Hippocrates, the father of medicine, already said: *'Let your food be medicine and your medicine be food.'* Personalized nutrition has been used for decades to palliate the effects of rare inborn metabolic errors. Most current nutrigenomic and nutrigenetics efforts aim to bring similar approaches to deal with common chronic diseases that have a polygenic and plurifactoral origin.

The initial findings in this area borne out by the data presented during the Forum show that the area of personalized nutrition is a promising one. Even if it is considered by some only to be achievable in the long term, it has nevertheless become a reality for specific groups or cohorts.

Further research using the cutting-edge tools of the '-omics' will open the way for a better understanding of the interactions between the human genes and their expression, the microbial genome, nutrition and lifestyle. These tools will also help to better define nutritional profiles, as well as groups of population according to metabolic biomarkers, physical activity and lifestyle. To this end, it was suggested during the Forum that a European consortium 'Innovative Food–Nutrition Initiative' be set up based on public-private partnerships. This consortium would bring together stakeholders from academia and industry in order to define a common scientific approach and develop a precompetitive pan-European nutrition research program.

New systems to evaluate both nutritional advice and products need to be defined, in order to regulate without hindering innovation. This could be done progressively, with the implementation and constant monitoring of pilot initiatives at regional levels. Annual meetings on 'Better Foods for Better Health' could play a significant role in this monitoring process. The results of these initiatives, new scientific discoveries and an ever changing environment may well call for regular updates of dietary guidelines and products.

The society will be impacted and those involved in social sciences will also be called upon to address the ethical issues associated with this new field of science. Communication will be important in this new area of personalized nutrition which will require a common effort from all stakeholders.

Interest in preventing diseases with functional foods and healthy lifestyle is growing. Individuals will increasingly be asked to know more about their background and family history in order to manage their own health. We are at the dawn of a new age.

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