WHITE BOOK

6 th Annual Forum

Better Foods for Better Health

CHILDHOOD NUTRITION: BUILDING A HEALTHY LIFE

MARCH 20th to 22nd 2018

Les Pensières, Center for Global Health
Veyrier-du-Lac - France

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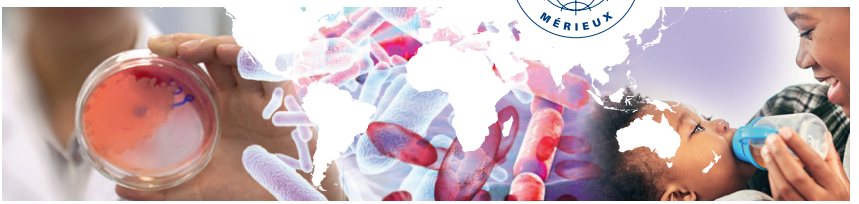

WHITE BOOK

PREFACE

Improving nutrition for the burgeoning global population is one of today's major public challenges. Over the past eight years, "Better Foods for Better Health", our international symposium dedicated to pursuing advances in nutrition, has brought together leading scientists, NGOs, policy stakeholders and key opinion leaders to exchange ideas and drive progress for this global cause.

Fondation Mérieux, the inaugurator of the Symposium, with the support of Mérieux NutriSciences, has sought new views on the fundamental link between health and nutrition from scientific, business and regulatory perspectives.

With health matters occupying a pressing dimension, the Symposium is dedicated to sharing the latest scientific developments in nutrition in both developed and developing countries. Valuable insight from industry is provided by esteemed moderators, placing the consumer at the centre of the dialogue between scientific evidence and public policy makers.

This year's symposium, **"Childhood nutrition: building a healthy life"**, addressed the role of good nutrition for survival, physical growth, mental development, performance, productivity, health and well-being across the entire life-span: from the earliest stages of fetal development, at birth, and through infancy, childhood, adolescence and on into adulthood.

Increasing dialogue between the scientific community, regulatory, nutrition and industry stakeholders is a top priority. This White Book provides a summary and recommendations of the stellar cast of participants who took part in the Symposium, confirming their commitment to promoting "Better Foods for Better Health".

Alexandre Mérieux
Vice President
Fondation Mérieux

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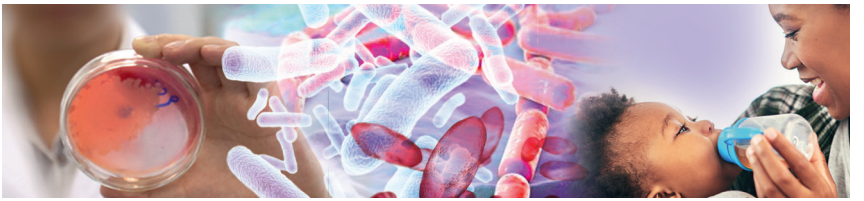

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6th Annual Forum

Better Foods for Better Health

CHILDHOOD NUTRITION: BUILDING A HEALTHY LIFE

MARCH 20th to 22nd 2018

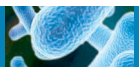
The sixth Better Foods for Better Health symposium, organized by the Fondation Mérieux with the support of Mérieux NutriSciences, was held from March 20 to 22, 2018, at Les Pensières Center for Global Health in Veyrier-du-Lac, France. Part of a series of symposia held once every two years, Better Foods for Better Health is dedicated to sharing the latest scientific developments in nutrition in both developed and developing countries by bringing together scientists, industry stakeholders and public policymakers.

With the theme **'Childhood nutrition: building a healthy life'**, this year's meeting sought to present the context of infant and childhood nutrition, as well as the challenges and unmet needs in low and middle-income countries and industrialized nations, with a particular focus on obesity and malnutrition, infections, allergy, and the emerging field linking nutrition and behavior.

EXECUTIVE SUMMARY

The symposium produced a number of messages:

- Diet during the first years of life has long-term effects on growth and metabolism, the immune system and the susceptibility to developing infections and allergies, as well as on behavior and cognitive development.
- A recurrent theme of the symposium was the need for more, and more accurate data on nutrition to support effective interventions.
- The microbiota appears key in linking diet, immunity, metabolism, cognition and behavior. A better understanding of these connections will be required to design microbiota-derived diagnostics and interventions.
- The impact of many nutritional interventions has been disappointing probably because they were employed too late. Interventional studies would likely be most impactful during the prenatal or early postnatal period.
- More generally, it is important to have a narrative about nutrition that inspires policymakers to dedicate more resources and establish more interventions in this area. Nutrition plays a large role in people's health, a fact that is not always reflected in the resources dedicated to it, compared to infectious disease.



Symposium participants brought up several issues for the future:

- New tools to assess nutrition efficiency and safety in children must be developed. Specifically, there is a need, for example, to define robust biomarkers associated with micronutrient status and to follow these over time.
- Dietary reference intakes and reference values must be defined in various contexts — in developing vs. industrialized countries, and in healthy vs. diseased individuals.
- More clarity is needed with regulatory agencies to establish protocols on designing trials to demonstrate a benefit of a product.
- To optimize the efficacy of nutritional interventions, a worldwide, coordinated research agenda, involving a large number of international stakeholders, might go a long way toward addressing nutritional deficiencies and other food-related issues.

Protecting health and combating disease can be achieved through improved nutrition, innovation and increased dialogue among all stakeholders. In this respect, the Fondation Mérieux hopes that participants profited from the sixth "Better Foods for Better Health" symposium. By fostering exchanges between global experts from the public and private sectors, the symposium sought to provide a platform to discuss and improve childhood nutrition worldwide.

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KEYNOTE LECTURE:

Assessment and control of nutritional deficiency diseases: generating better data for more coherent programs

Kenneth Brown, University of California, Davis (USA)

Seven million children died before age 5 in 2011, 45 percent from undernutrition, mostly in lower-income settings in sub-Saharan Africa, and South and Southeast Asia. Despite the fact that nutrition is responsible for such a high percentage of child mortality, the global programs and resources devoted to it remain inadequate, and compare unfavorably with resources devoted to childhood infection-related deaths. One reason for this is that there is a lack of reliable data to establish more coherent public-health nutrition programs.

Though it is often thought of as a single condition, "undernutrition" encompasses many types of nutritional disorders — fetal growth restriction; stunting, underweight and wasting; micronutrient deficiencies; and sub-optimal infant feeding procedures — each of which must be addressed differently. A Lancet series on nutrition estimated the prevalence and deaths from different nutritional deficiencies. For example, two-thirds of neural tube defect-related deaths could be avoided with maternal folic acid supplementation: 80,000 to 100,000 preventable deaths.

However, data on nutritional deficiencies is often hard to come by and of questionable quality when it is available. There is a particular dearth of information on vitamin and mineral (micronutrient) status. More data would identify at-risk populations, suggest courses of action and allow the assessment of deployed programs. The ultimate goal would be to have more and better-targeted nutrition programs.

To improve the quantity and quality of data on population nutritional status, novel methods are being developed for anthropometry, dietary analysis and biochemical

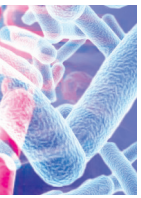
assessment. Of these, Brown feels that biochemical assessment, using biomarkers of micronutrient status, though potentially challenging and costly, as the best option for obtaining quality data on nutritional deficiencies. Though a number of innovative new approaches to perform biochemical assessment in the field have been introduced, there is a need for more regional labs, standardized methods and reference materials, more training, and quality control of personnel and systems.

Reliable nutritional data could be used to help make decisions on:

- agricultural policy
- food importation
- large-scale food fortification

A lack of data may have consequences for a population's nutritional status, including:

- failure to recognize existing problems
- missing those at risk or providing insufficient nutrients
- unnecessary/redundant coverage, resulting in:
  - unnecessary costs
  - risk of excessive intake of nutrients



Brown offered the example of a program in Cameroon to fortify food with micronutrients. As an advisor to Helen Keller International in 2007, Brown helped carry out a baseline assessment for a vitamin A fortification program to determine the best ingredients to fortify and the estimated impact of the program. After collecting information on dietary intake in different regions of the country, his team discovered that the government's proposed program of fortified, industrially produced edible oil did not reach the highest-risk population in the north, which consumed locally produced (unfortified) peanut oil. With this data, an optimized model was designed using multiple fortified foodstuffs. In a 10-year simulation created by Brown's team, their new proposal covered the same number of children as the original, but with a cost savings of $16 million. "Rather than firing off blind, as seems to happen with many public-health nutrition programs, what we need is better data," Brown said.

SESSION 1 • GROWTH AND METABOLISM

The early impact of food on children's growth and metabolism and how to prevent malnutrition and metabolic diseases

Dietary reference intakes around distinct nutritional needs

Patrick J. Stover, Texas A&M University (USA)

A variety of tools have been created to engineer the food supply for the growing world population. These include diet diversification, fortification and supplementation. What we must decide as a society is, are the dietary and nutrient recommendations that guide these tools adequate for nutritional status and the prevention of deficiency? For metabolic or other function? For chronic disease prevention? For general disease management? In other words, what should we expect from the food supply?

The prevalence of chronic disease is growing in all populations globally and across all subgroups, particularly in the United States, where diet-related chronic disease represents 1 trillion US dollars in healthcare costs. As such, the National Academies of Science and Medicine addressed this issue with a consensus report outlining a number of challenges and guiding principles for using food and nutrients to prevent chronic disease.

Chronic diseases are complex traits influenced not only by diet but also by age, genetics, epigenetics and environment, with risk determined by interactions between them. As the majority of chronic diseases are not affected by single nutrients or single nutrient pathways, research, recommendations and ultimately interventions should rather address the interaction of nutrients affecting different biological systems in a network of nutrient pathways.

Furthermore, it is known that susceptibility for chronic diseases can begin during the earliest stages of human development as demonstrated by Jiang, *et al*. in which maternal choline intake was demonstrated to alter the epigenetic state of fetal cortisol-regulating genes. In response to in utero exposures through stem-cell programming, with maternal nutrition being among the best-studied *in utero*

exposures that prevent or accelerate the onset of chronic disease. Once established, disease states and/or disease treatment can cause whole-body or tissue-specific nutrient depletion, excess or impaired utilization resulting in the need for altered nutrient intakes.

But what we also know is that as you age these epigenetic landscapes that are set very early in embryonic development decay with age. And so one of the questions that arise is, if you are going to use nutrition to prevent chronic disease that is associated with decay of these networks, can nutrition reverse if not at lease delay the decay of the epigenetic landscapes? And although it has been demonstrated that older people who remain "healthy" tend to retain these epigenetic landscapes (Nature reviews), the question of whether diet plays a role in their decay still remains an open question.

Not only do we want to set recommendations to prevent chronic disease, we also want to manage chronic disease once it is established. Although there are no consensus guidelines for estimating the nutritional needs of individuals or subgroups with a diagnosed chronic disease, it has been recognized that once established, disease states and/or disease treatment can cause whole-body or tissue-specific nutrient depletion, excess or impaired utilization resulting in the need for altered nutrient intakes. But current status and functional biomarkers for assessing nutrient needs in healthy populations may not apply in diseases states, and can be poor predictive indicators of chronic disease risk. Several examples of factors that affect nutrient status and/or biomarkers of status are presented here (increased rates of catabolism, tissue redistribution and/or excretion, decreased rates of gut and blood-brain barrier transport, decreased rates of synthesis).

In an upcoming workshop at the National Academies of Science, Engineering and Medicine, consideration for proposed standards of special nutritional needs will be discussed to:

■ Establish a robust biological premise explaining differences in nutrients, relevant biomarkers and nutrient intervention mechanism:

- How and why are nutrient needs different?
- What are the relevant biomarkers of nutritional deficiency?
- Is the nutrient intervention having a physiological or "drug' (off-target) effect?

■ Evaluate efficacy of interventions:

- Does increased intake address the nutritional deficiency?
- Does increased intake improve clinical outcome(s)?
- Classify clinical subgroups with distinctive nutrient needs:
- Can you identify responders *versus* non-responders?

What do consumers need to know in the midst of these partially answered questions? As disease data and nutrient status data is becoming more accessible in real time, how can technology such as cell phones be used to help process this information and provide proper guidance? Stover and colleagues at Microsoft are integrating such data into biosynthesis network models, investigating how computer informatics can play a role in better understanding systems biology.

Dietary Interventions for Infants and Children in Low and Middle Income Countries

Robert E. Black, Johns Hopkins University (USA)

Childhood undernutrition, including stunting of linear growth and wasting (i.e., low weight for height), is highly prevalent in low and middle-income countries (LMICs). According to the latest UN estimates, there are currently about 155 million stunted children under five in the world, 52 million wasted children in the world and 17 million (or 2.5 percent) severely wasted children in the world.

In addition to other causes of childhood undernutrition such as zinc deficiency, infectious disease, diets insufficient in caloric adequacy and quality play a key role in growth faltering in the first two years of life. Dr. Black presented the experience to date with dietary interventions that addressed the problem of undernutrition, stunting and wasting, particularly in LMICs, with a focus on the importance of intervention during this early part of childhood.

Victoria CG *et al*. demonstrated a pattern of change in z-scores compared to the WHO standard for growth using cross-sectional survey data. In the LMICs presented, there is not much difference in stunting and wasting in LMICs compared to the WHO standard overall for children at birth. However, we see a very rapid decline in z-score with age in the first two years of life. Leroy *et al*. show consistent patterns of this decline in their research and go on to demonstrate that it is also relevant to consider what happens after this early period of childhood, as well as the size of the gap between stunting and wasting levels in LMICs compared to WHO standards — both are important indicators for the effectiveness of dietary interventions to reduce stunting and to prevent wasting.

Global patterns of stunting and wasting differ by region, with the highest rates of stunting and wasting in South Asia and sub-Saharan Africa, but overall support the need for concern about this early period of childhood and the conclusion that the first two years of life are critical for nutrition. Thus, to enable healthier growth and prevent nutritional deficiencies, interventions have focused on infant and young child feeding.

Guigliani, *et al*. show that, although breastfeeding promotion affects practice (it doubles the rate of exclusive breastfeeding for the first six months and increases the duration), breastfeeding alone does not have substantial effects on growth and thus is not the entire solution. Complementary feeding interventions must thus be considered. These include 1) nutrition education: breastfeeding, timely introduction of complementary foods, diverse diets, responsive feeding and hygienic preparation and feeding behaviors as well as 2) food supplementation: introduction of macronutrient-dense supplements (either from outside support programs or local resources) and specifically lipid-based nutrient supplements (LNS), a family of products designed to deliver nutrients to vulnerable people. They are nutrient dense, require no cooking and can be stored for months. They are resistant to bacterial contamination and available in different levels of energy density. Both LNS and other food supplements include additional micronutrients such as omega-3 and some fatty acids.

Through a systematic review of studies, Dr. Black and his colleagues concluded that nutrition education is currently the most effective intervention in food-secure populations and food supplementation is the most effective intervention in food-insecure populations to reduce stunting and have some small effects on wasting. Nevertheless, the current magnitude of the effect compared to the total deficits of these populations is not adequate. LNS have been demonstrated to have effects similar to food supplements in food-insecure populations but studies remain limited.

Evidence, limited for the moment to observational studies, suggest that in some populations some catch-up in stature can occur when introducing LNS during adolescence. The correlation however is not entirely understood. For example, introduction of nutritional support during puberty can delay menstruation and therefore affect growth negatively. More evidence is required here.

As for the risk of obesity due to food supplementation, it is known that during the first two years of life, there is little risk, though at later ages some risk has been demonstrated and such interventions should be introduced with care.

Dairy intake and bone growth during childhood

Joseph M. Kindler, Purdue University (USA)

In the US, the recommended serving of dairy per day is two cups for children 2 to 3 years of age, and up to three cups per day for adolescents 14 to 18 years of age. These recommendations focus on low-fat dairy products and differ from recommendations around the globe. For example, in South Africa the recommendation is 1 to 3 cups per day and in the UK, it is recommended to consume "some" dairy daily. Currently, we know that in the US, children from ages 1 to 2 years old are meeting these recommendations, but data from the US National Health and Nutrition Examination Survey suggest that the average dairy consumption in children greater than 2 years is only about 1.9 servings per day.

Why is dairy to important? It provides a variety of essential nutrients including calcium, magnesium, vitamin D and potassium among others, and consuming these nutrients has been demonstrated to have consequences on bone health as well as obesity.

Adolescence is a critical moment of bone growth, measured often by peak bone mass, which ultimately prevents fracture. Between 10 to 20 years of life there is a large amount of adult bone mass accrual (90 percent). Many factors influence bone mass, including race, age, sex, body composition, physical activity and diet. When dairy recommendations are not met, low nutrient levels result in low bone mass and ultimately in increased skeletal fracture (Weaver *et al*.). Sioen *et al*. further demonstrate that physical activity may even have an additive affect with dairy consumption in improving bone health. The National Osteoporosis Foundation recently published a consensus paper on the determinants of peak bone mass and graded each with a letter grade from A to D, with dairy graded as B, a moderate grade compared to other determinants, with room for improvement particularly when it comes to the need for more evidence from intervention trials.

If the evidence of the influence of dairy on bone health is relatively adequate, what do we know about how it influences obesity? Although a recent meta-analysis of observational studies investigated the association of dairy consumption with the risk of obesity and found that overall, there is a lower risk of obesity with increased dairy consumption, randomized controlled trials (RCTs) are lacking to further support this correlation. Similarly, RCTs are lacking to support the suggestion that dairy consumption may also mitigate the risk of obesity-related diseases such as type-2 diabetes, cardiovascular disease and hypertension, especially in children.

How to assess nutrition and provide practical recommendations to the family

Maria Hassapidou, Alexander Technological Educational Institute of Thessaloniki (Greece)

Healthy nutrition prevents the risks of malnutrition, obesity and related metabolic diseases in childhood and adulthood, improves the quality of life in childhood and is necessary for optimal growth — that is, physical, mental and emotional growth — and is essential to the development of healthy eating habits that will last for a lifetime.

The World Health Organization's European Food and Nutrition Action Plan from 2015 to 2020 clearly states that of the six WHO regions, Europe is most affected by obesity as a leading cause of disability and death, with a high prevalence of overweight and obesity among children and adolescents, particularly in southern Europe. This prevalence is higher in the children of less educated families, and Europe's most deprived groups continue to bear the greatest impact of overweight and obesity.

In 2015, the Childhood Obesity Task Force of the European Association for the Study of Obesity (EASO) published a position paper on childhood obesity as a chronic disease demanding specific healthcare. This paper not only aims to draws attention to one of the one of the greatest health challenges of our society but also proposed a unique window of opportunity for lifetime impact on health to the scientific community, policymakers and society at large.

The WHO Regional Office for Europe established a European childhood obesity surveillance system (COSI) in most European countries, routinely measuring trends in overweight and obesity in primary-school children (6-9 years). Data collected from 2007 to 2010 showed a north-south gradient of overweight. More recent data (2016) showed a plateau of prevalence of overweight and obesity with an actual decrease in southern countries. Under this system, dietary data is assessed using a number of tools (each with varying cost and accuracy), including dietary recall, questionnaires, dietary history and food diary. The energy content and specific nutrients in each food documented in such dietary data can then be calculated using food composition tables, and the daily intakes can be compared with the recommended daily intake. More data is certainly required here, both in terms of surveillance and the energy content of a number of foods.

Overall, the greatest gap in dietary data is for children under the age of 5. Baker and his colleagues provide practical tips for health providers in assessing

overweight and obesity in their patients. Rodrigo *et al*. demonstrate the difficulty in assessment, also providing recommendations.

The High Level Group on Nutrition and Physical Activity and the EU Platform for Action on Diet, Physical Activity and Healthcare are responsible for supporting the implementation of these strategies and via an EU Action Plan on Childhood Obesity to contribute to halting the rise in overweight and obesity in children and young people (0-18 years) by 2020. One of the key areas of action in the plan includes informing and empowering families and promoting and encouraging family-based programs. Another European-level project, the Joint Action on Nutritional and Physical Activity, also addressed halting the rise of overweight and obesity. The final results of this project have just been published; one major conclusion is that a multi-sector approach — in which the child is considered part of the home, family, school community, environment, country, etc. — is crucial. Based on the project's surveys, it was agreed that the best environments for intervention are the school and the home, the major barrier to success is marketing and the greatest facilitator of success is family support.

A systematic review (Kothandan) concluded that family and school-based interventions have a considerable effect, depending on age. Family-based interventions were shown to be more affective before the age of 12, whereas after 12 years of age, school interventions were more effective. One observed limitation in such interventions is their short-term nature. A number of studies have demonstrated the importance of beginning interventions as early as possible, such as during pre-school (Stark *et al*.). Literature also suggests that parent-only intervention is better than nothing, but interventions including parents and children are most successful (Loveman *et al*.).

ROUNDTABLE 1

Socio-economical and regulatory issues in relation to children nutrition

Moderator: Patrick J. Stover

Panelists: Robert E. Black; Joseph M. Kindler; Maria Hassapidou; DeAnn Liska, Biofortis (USA); José Saavedra, Nestlé Nutrition (Switzerland); Seppo Salminen, University of Turku (Finland)

Dr. Stover started off the panel with a very general question.

How are we going to move forward in terms of developing the required evidence base in a context of high standards for outcomes-driven research? How do we do this given the complexity of the connections between nutrition, health and chronic disease modified by many factors including environment and social behavioral factors and complexity of evaluating the efficacy of nutrition interventions?

As a gastrointestinal microbiologist, Seppo Salminen, suggested that more comprehensive meta-analysis will allow for more convincing conclusions. The role of microbes in non-communicable disease is still emerging and there maybe new non-communicable factors that further complicate this context.

José Saavedra proposed the need for prioritization. We can best decide what outcomes to study, how to best gather data on those outcomes, interpret them and ultimately come up with recommendations, by considering these decisions in terms of return on investment.

While supporting the two previous panelists, Robert Black provided details as to what these priorities might look like. Recognizing the importance of nutrition and environment during the fetal period into the first two years of life, he suggests more data needs to be gathered in low and middle-income countries around the maternal influences on the growth of the fetus and ultimately the infant. And although infectious diseases that contributed to undernutrition (e.g. diarrhea) still contribute, Dr. Black felt we need to further investigate intestinal exposure to microorganisms, many of which do not cause disease overtly, but result in changes in the functioning of the gut and the microbiome and contribute to impaired growth and development.

DeAnn Liska focused on the need to improve the quality of data in nutrition research through randomized controlled trials (RCTs). She underscored the importance of setting recommendations in nutrition and child development on RCT data as opposed to observational trials as they have often been done in the past. Recognizing that funding can be a barrier, she proposed the need to increase the number and improve the quality of RCTs. Dr. Liska suggested that specific standards for how RCTs should be conducted in the field of nutrition are imperative and will support reproducibility and reliability of data. In her view "the majority of past RCTs don't have baseline data, they don't have a lot of dietary background data and they don't meet a lot of higher quality standards. So these are the areas we can focus on".

Maria Hassapidou emphasized the importance of investing in cost-effective research, recommending that to attract funding for RCTs in nutrition research, whether from public or private sectors, researchers must have some foresight on the way results will be used. A major part of the work accomplished by the Joint Action on Nutrition and Physical Activity (JANPA) included providing EU MS Ministers of Health with an evidence base and economic rationale for action to fight the childhood obesity epidemic.

Joseph Kindler echoed previous points about the need for improved RCTs, emphasizing the challenge of funding by using the example of bone mass research, which requires a significant investment of time and resources. More affordable and alternative solutions for generating a sound evidence base could include investigating biomarkers of bone. But according to Dr. Kindler, variability in children makes these measurements less indicative. Increasingly sensitive data on phenotyping could also be promising, but "doesn't couple well with the history of data that's already been accrued, so comparing across studies also becomes difficult." In the end, investments are needed to conduct well-controlled well-conducted randomized studies with good rigor and control.

The panel was further prompted to consider the following question:

Chronic disease prevalence is highest in low-income communities. Given the expectation to set guidelines based on efficacious interventions, efforts to lower chronic disease should clearly be focused with this subgroup. However, people in low-income communities also have the least access to the type of foods and related science and technologies that have been presented during this meeting offering potential solutions to chronic disease. So how do we make sure that, if the focus is to use nutrition to lower chronic disease, low-income communities not only benefit from such solutions, but actually drive their success as a community?

Dr. Kindler emphasized the importance of developing educational strategies to translate research findings into consumable, digestible solutions. As one barrier in access to adequate dairy and fiber consumption may include lack of skills and knowledge for preparing food in a way that maintains nutrient integrity while being palatable for children, education programs in meal preparation can be very important.

For lower-income areas of Europe, Dr. Hassapidou shared that reformulation is frequently discussed as a possibility for improving nutrition. In her opinion, food labeling and educational campaigns must also be improved so that all families, regardless of income or education, can understand what they are eating. As schools have become major food procurers, and are responsible for feeding the child community regardless of socioeconomic status, we must also set guidelines in Europe to make sure they are providing the best possible nutrients to all children, from low income families or not.

Dr. Liska reminded the group that we have to consider the consumers and their values when designing interventions and recommendations. The aim should not be to change consumer values, but to work within these values when proposing solutions.

Joseph Black remarked that chronic disease prevention recommendations were initially based on observational studies of dose response, often lacking the population heterogeneity required to make more nuanced recommendations for subsets of the population. Unfortunately, RCTs also often lack heterogeneity, even more so in low-income countries. Within the framework of the developmental origins of chronic disease hypothesis, those who are disadvantaged and undernourished early in life are at greater risk for chronic disease and may experience differential benefits or effects of micronutrients in their life course. As such, we must consider long-term studies and evaluations. One solution to making this possible in all countries, including LMICs with far less resources to support such research, is to pursue a more collaborative, unified or harmonized process, which may provide more efficient data collection and subsequent setting of recommendations.

Jose Saavedra reminded the audience that we must distinguish between low socio-economic status in "food secure" countries and low socio-economic status in "food insecure" countries and recognize that recommendations will not be the same in each. Within these subgroups he suggested the need for harmonized regulations, which do not currently exist. For this and adequate education to reach consumers, a certain dialogue is needed between policymakers, regulators and healthcare professionals and researchers.

Dr. Salminen suggested that locally integrated government-sponsored interventions, such as a probiotic intervention in a small province of Argentina where the government supported the creation of companies to produce a probiotic product for school meals, can not only stimulate local activity but also provide children with nutritional supplements and ultimately prevent disease. He also echoed the need for dialogue between policymakers and warned that if in Europe we have such difficulty to come to consensus on nutrient profiles, closing the gap between higher and lower-income countries will only be more difficult.

Dr. Stover asked the final question: Between people and the food supply and product design is industry. So when you talk about the role of industry in assisting the public-health community in preventing chronic disease through food, what are the major regulatory barriers both within and across countries?

The two industry experts on the panel noted the following barriers.

■ 1. Lack of common regulatory language

A food company that seeks to make food to prevent disease becomes more like a drug company, and the language used to regulate these activities must be agreed upon within regulatory agencies and between regulatory agencies, policymakers and the food industry.

■ 2. Need for increased education

Adequate dietary intake guidelines are not enough. Only when the offer that industry can provide meets the demand that education can we find ourselves in a healthier place.

■ 3. Limitations on food claims

Compared to drug regulation which is centralized on the national level with the Food and Drug Administration food producers must consider regulations on the national level from the Federal Trade Commission, from the attorney generals at the state level and individual lawsuits.

Marc Bonneville, Scientific and Medical Affairs Director at Institut Mérieux, commented on inter-individual variability in populations that makes drawing conclusions from cross-sectional studies difficult. Dr. Bonneville suggested rather that focus should be on longitudinal studies in which the trend and evolution can be studied on the individual level for a particular marker. Dr. Bonneville followed up with a question to the group on how to best use well-designed, small-scale clinical studies to validate interventions. Dr. Stover added one such innovative example in recommendations for the fortification of foods with folic acid to prevent neural tube effects in which big data on folate blood levels and neural tube defects was used to computer-generate a dose-response relationship which was validated by smaller, more affordable and well-controlled clinical studies.

SESSION 2 • IMMUNITY, ALLERGY AND INFECTIONS

Immune status and susceptibility to allergy and infections; the role of diet and specific ingredient strategies

Determinants of allergenicity and modulation of allergies. Rationale for perinatal intervention. Prebiotics example

Marie Bodinier, French National Institute for Agricultural Research (INRA), Nantes-Angers Center (France)

Today, 30 to 40 percent of the world population is affected by allergies, for which there is currently neither a cure nor any effective preventive strategy. Allergies — which can be classified as atopic dermatitis, respiratory allergies or food allergies — are linked to microbial, mucosal and immune disorders. Allergies are the most common and earliest signs of the immune system's vulnerability to the modern environment.

The microbiota is a complex system, unique to each individual, and plays a major role in immune response modulation. The microbiota is implanted at birth and can be modified by the environment, including by diet, antibiotics and infection. A balanced microbiota will have a positive effect on health, while a dysfunctional microbiota will have a negative one. Therefore an examination of how nutrition might affect the microbiota and therefore allergies is of particular interest.

The perinatal period is a critical time of risk and opportunity. During gestation, delivery and lactation there are transfers of bacteria and immune factors from the mother to the fetus or child. In addition, the environment in pregnancy and early childhood can have an effect on future disease susceptibility.

There are a variety of nutritional strategies that are aimed at allergy prevention. Bodinier's research focuses on the effects of prebiotics, nondigestible food ingredients that can modulate the microbiota, immune system and gut. She cited a number of postnatal and perinatal human and animal studies (10 postnatal animal, two human studies and one meta-analysis, as well as four perinatal animal studies) that are very encouraging in that they indicate that prebiotic

supplementation can assist in allergy prevention. She is involved with two ongoing human studies, SYMBA and PREGALL, which recruited 652 and 376 pregnant women, respectively.

These two studies hope to:

- demonstrate the interest of prebiotics in preventing allergies;
- define the most effective timing and duration of maternal prebiotics supplementation;
- demonstrate the importance of microbiota and immune system balance early in life related to the emergence of allergies.

Links between malnutrition and intestinal "infections" in children from lower middle income countries: the MAL-ED longitudinal birth cohort study

Mark Miller, University of California, Berkeley (USA)

Stunting is the most prevalent condition of child malnutrition worldwide, associated with negative health and economic outcomes later in life. The Malnutrition and Enteric Disease study (MAL-ED) is a longitudinal study of the role of enteric infections in health outcomes in children living in resource-poor settings across diverse geographical areas. This study began in November 2009, at eight sites on three continents: southern Asia (Mirpur, Bangladesh; Vellore, India; Bhaktapur, Nepal; Naushero Feroz, Pakistan), Latin America (Fortaleza, Brazil; Iquitos, Peru) and sub-Saharan Africa (Limpopo, South Africa; Haydom, Tanzania). The cohort is still being followed. With 16 million data points, Miller characterized it as the "Framingham Study of the gut."

The study's goal is to better understand the complicated interrelationships among enteric infections, nutrition and other environmental exposures and child growth. The overarching hypothesis of the MAL-ED study was that repeated enteropathogen infections in infants and young children affect physical growth. About 2,000 children were followed from birth with collections of blood, urine and stool made over a period of 60 months, in addition to the recording of many other factors (height, weight, head circumference, diet, cognitive tests).

Some of the major findings of MAL-ED thus far include:

- Neonatal and maternal factors were found to play a more influential role than postnatal factors during early childhood.
- Less than 5 percent of the children at six of eight sites are fed according to the WHO recommendation for exclusive breastfeeding for six months (at several of the sites, it was common to give neonates solid food).
- Despite close follow-up during the study, 23 to 70 percent of the children were stunted.
- There was a high incidence of pathogen carriage without diarrhea (with some children having more than 25 pathogens).
- Diarrhea does not appear to be associated with linear growth in children, but pathogen load does.

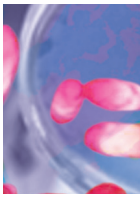
The research therefore suggests:

- Maternal interventions, especially during pregnancy, are likely to have intergenerational effects and a lasting impact on birth weight and child growth outcomes.
- Initiatives to address childhood stunting should also consider improvements to the composition of complementary foods (i.e., higher protein) and strategies to reduce gut pathogen exposure.

The gut microbiome: an emerging modifiable risk factor for improving immune function and child health

Saurabh Mehta, Cornell University (USA)

Studies increasingly show that the gut microbiome plays a central role in multiple metabolic and immune system pathways that have multiple effects, including risk of infection, cognitive function and overall health. The gut is the largest immune organ in the body and recent research highlights the additional role of the microbiome in the early development of the immune system, vaccine responses and autoimmunity.



There is limited information on how the composition and diversity of the gut microbiome varies by nutritional status and geographical settings. Furthermore, diet is one of the few nonpharmacological means of modifying the gut microbiome and there are few studies evaluating the impact of dietary interventions. Mehta reported that his team is working with a cohort of 250 12-to-18-month-old children based in the urban slums of Mumbai. These children are participating in a nine-month dietary intervention, set to end July 31, 2018, that will examine differences by nutritional status, long-term changes in this status and the impact of the intervention. Specifically, his team's research is examining the effect of iron and zinc-fortified pearl millet on growth and immune competence. In addition, the team is working with a New York City cohort that includes children with chronic kidney disease, which is a major driver of malnutrition and altered immune function, and a trial near Bangalore, examining the effect of four different bio-fortified crops on 400 six-month-olds and their mothers.

Mehta emphasized that:

- Research in this area is still in its infancy and many studies are underway.
- Though he is awaiting longitudinal data, preliminary data suggests that the gut microbiome is linked to various child health outcomes and may be modifiable.

His preliminary data indicates that children in high-burden settings may have slower microbiome development or a more immature microbiome.

ROUNDTABLE 2

Immune fortification and allergy control strategies, regulatory issues (new ingredients and medical food) and interventional approaches using connecting devices

Moderator: Mark Miller

Participants: Marie Bodinier; Saurabh Mehta; Sandra Einerhand, Science & Innovation (The Netherlands); Patrice Malard, H&H Group (China)

Mark Miller moderated a roundtable that looked further at some of the issues raised by Session 2, on immunity, allergy and infections. The first question raised the issue of how to translate studies of the type discussed during the session into public interventions. Saurabh Mehta noted that he would only consider his studies using biofortified foods successful if they found effective treatments that could be offered to the general public. However, he considered it a "big challenge" to determine what would be considered an efficacious treatment, as "effective" would have to be clearly defined. Sandra Einerhand said that we must understand the needs of the mother and the infant, and that benefits must be clearly clinically proven. Furthermore, she stated that we must "start from the end: what is the need? And then we must go back to design the clinical program." Marie Bodinier remarked that though it was easy to test strategies on mice in the lab, alternative animal models should also be used. Ultimately, though, her focus is to go to clinical trial to demonstrate the efficacy of a therapy. Patrice Malard noted the many uncertainties in the field, such as the origin of the bacteria in an infant's microbiota (breast milk, the umbilical cord, the placenta?), and in the case of allergies, how allergies develop: from food or cutaneous contact?

A follow-up question looked at the best animal models, how they can be utilized and how they compare to human clinical studies. Panelists discussed the convenience of mouse models, but agreed that piglets are more adequate models

for human pathologies, though more expensive to use. It may also be important to develop *in vitro* models to demonstrate immune effects in early stages. Einerhand commented that it is "important to do preclinical studies if we want to understand the mechanism of action and compare different ingredients or products, but ultimately we must do clinical studies to show the benefit in pregnant or lactating women. In animals, the microbiota is different, the immune system is also different." Mehta noted that in his microbiome work, his team has found it helpful to establish partnerships with people who do basic science to facilitate the "back and forth" needed to test hypotheses.

Miller wondered about humans' coevolution with allergens, if it might be compared with our coevolution with microbes — is it better to be exposed to allergens at an early age? Are we in a too-clean environment or not clean enough? Bodinier remarked that the timing of sensitization by an allergen is not well understood — whether during pregnancy, through breastfeeding, through cutaneous food contact when at the table — but in the beginning, it might be through skin sensitization. Children often first develop atopic dermatitis, then food allergies are seen in older children, then asthma is seen in adolescents and adults.

There was some disagreement among panelists about the impact of breastfeeding and C-sections on future allergy status. Mehta remarked that a number of studies have indicated that increased hygiene decreases microbiota diversity and increases allergies and autoimmune diseases.

The discussion turned to regulatory agencies and what they consider appropriate models for safety and efficacy. With products categorized as food and not a drug, it is often not possible to make a health claim. Regulations differ according to country, with some countries having a category midway between food and drugs (in the EU it is "food for special medical purposes"), for which health claims are possible. There was a general consensus that standards are lacking, with regulatory agencies offering some guidance but no established protocols of how to design a trial to demonstrate a benefit. Malard felt that for probiotics, the US has clear guidelines but EMEA is lagging behind. When asked what they would say to regulators of funders, Einerhand again evoked the lack of guidance from regulatory agencies, suggesting that, for example, that the European Food Safety Authority (EFSA) might form a pre-assessment panel to offer upfront advice. "That could be a way to promote innovation and to help academia and companies do clinical trials that in the end would lead to a benefit accepted by regulators." Malard emphasized that it was necessary to insist to health authorities on the importance of food, not just drugs, in addressing health problems.

Nutritional challenges for children in China

Wei Cai, Shanghai Jiao Tong University (China)

As a transitional society, China has witnessed many changes in the last 40 years. We know globalization and urbanization have played a major role in changes in dietary patterns and lifestyle. And as in many transitional societies, China is faced with challenges in addressing premature birth and malnutrition, childhood obesity, growth faltering and increased food allergies.

Global epidemiological data on premature infants shows that China has the second-highest premature infant rate in the world. According to the 2005 national survey, this represented 7.8 percent of the population (1 to 1.2 million people). Recently, this yearly rate increased from 1.2 million to 1.4 million premature births, mostly due to increased multiple births resulting from a relaxation in China's One-Child Policy, in which some couples are permitted to have two children.

Growth faltering continues to be most problematic in low and middle-income countries in Southeast Asia and Africa. In China, the 2009 UNICEF report on Nutritional Status in Children and Mothers reported that although China has made great progress, 12.7 million children still suffer from growth faltering. Great differences exist between urban and rural areas, with rural areas having a much higher prevalence, particularly in the mountain areas. When comparing regions, one study in Dr. Cai's group assessed malnutrition, underweight and anemia, finding a much higher prevalence in China's southwest region, particularly among children below 2 years of age.

Despite continued undernutrition reported in rural areas, the traditional low-fat, high-carbohydrate diet has been replaced by a westernized fat-rich diet in cities. As a result, obesity and other chronic diseases are increasing in China, as it is across the world. For example, in Beijing and Shanghai in 2004 12.5 percent of 6-to-8-year-olds were reported as overweight and 15 percent as obese. Over the past 30 years, prevalence of obesity increased from 2 to 11 percent since the 80s.

To address this double burden of malnutrition, the Chinese government has implemented several programs, which provide nutritional supplements for school children in rural areas, and nutritional lunches and one-hour outside exercise programs for school children in the cities. Dr. Cai and his research team have also been investigating nutritional education intervention programs that have demonstrated success.

Food allergies in China are more common in infants than in adults, affecting 6 to 8 percent of children. The most common food allergies include cow's milk, egg

white and peanuts, among others. Lactose intolerance has been reported to be higher in the eastern provinces of China compared to the rest of the country's population.

Dr. Cai concludes that more high-quality research is required to support policies, regulations and interventions. In his view, China needs to join the international academic activity in nutrition, which for the moment remains limited.

SESSION 3 • DIET AND BEHAVIOR

Links between diet, microbiota and behavioral changes: preclinical, clinical and epidemiological studies

Links between nutrition and cognition in children

Maureen Black, University of Maryland School of Medicine (USA)

Brain development and early cognitive development occurs through a series of epigenetic changes that are influenced by the genetic blueprint and surrounding environment. As neuroscientific research now suggests that this process starts prenatally, it is becoming clear that the timing of environmental influences, including adequate nutrients, during the first 1,000 days of life are essential for the rest of development, ultimately influencing adult health and growth, learning and academics, and behavior and emotions.

Micronutrients, vitamins and minerals not made in the body play a fundamental role in brain and cognitive development. Sufficient iodine intake has been identified as a key to preventing intellectual disability and is even associated with attention deficit hyperactivity disorder (Velasco). As a transporter of oxygen to the brain, iron is also essential to healthy cognitive development and represents the

most common micronutrient deficiency in the world. Current intervention trials introduce multiple micronutrients together either through supplements or fortification, as these and additional deficiencies often occur together.

Macronutrients — also fundamentally necessary for growth — including carbohydrates, protein, fats and cholesterol, are often responsible for stunting in children when inadequate. A meta-analysis of related studies reports that there is a strong association with lower cognitive performance and being stunted prior to age two.

Additional studies have concluded that environmental influences the first 1,000 days of life have an impact on academic performance, reduced economic capacity, and even negative consequences for the growth and development of the next generation (Walker).

It is estimated that 43 percent of the world's children under five, or 249 million children, are at risk of not reaching developmental potential, with the highest rates in sub-Saharan Africa and some parts of Asia. Although more data is needed to more accurately determine prevalence, it is clear even with these estimates that both the problem and the opportunity for intervention are significant.

The relationship between nutrition and cognitive development is also influenced by feeding behavior. This was demonstrated by the BLISS study, suggesting that allowing children older than 6 months to self-feed can predispose them to adequate nutrition and thus better growth. It has also been concluded that feeding behavior is bi-directional. By responding to infants' cues, caregivers can best influence their infants' feeding behavior.

Dr. Black and her colleagues offer a number of recommendations based on these findings, incorporating health, nutrition, security and safety, responsive care giving and early learning. From a life-course perspective — what happens early in life helps establish a strong trajectory into adolescence and adulthood, and then into the next generation — Dr. Black underscored the importance of early childhood policies and programs for children to develop the intellectual skills, creativity and well-being required to become healthy and productive adults and in turn raise healthy and productive children.

Gut-brain axis (microbiota, epithelial barrier, probiotics intervention…)

Michel Neunlist, INSERM (France)

Preclinical data shows how nutrition in a large sense and more specifically how microbiota is able to regulate brain devolvement and brain behavior. This is a very recent and innovative field, one that has spanned just the last 10 years.

Evolutionarily speaking, the brain and the gut have evolved in parallel. They are the two organs that have allowed humans to evolve from bacteria — allowing survival (and subsequently reproduction) and the ability to adapt to environmental challenges.

In this context, the gut, which represents one of the largest surfaces open to the environment (and also contains the second largest number of neurons after the brain), plays an increasingly recognized role in the development and maturation of the brain. In particular, gut microbiota has been shown to be a central regulator of both gut and brain maturation during both early (Collins *et al*.) and later periods (Caputi *et al*.) of life.

A number of animal studies have recently demonstrated the potential impact of microbiota on health. Braniste *et al*. demonstrated that maternal microbiota enhances closure of the blood-brain barrier in rats, suggesting that gut microbiota/blood-brain barrier communication is initiated during gestation and propagated throughout life.

A growing body of work implicates microbially produced metabolites as crucial executors of diet-based microbial influence on the host. Neunlist and his team have demonstrated that butyrate or histone deacetylase inhibitors might be used, along with nutritional approaches, to treat various gastrointestinal motility disorders associated with the inhibition of colonic transit. It is thus becoming increasingly accepted that butyrate-producing bacteria and butyrate per se may be beneficial for human health.

Other studies have demonstrated how microbiota may influence behavior. Through their research, Diaz Heijtz and his colleagues suggest that the microbiota may modulate exploratory and anxiety behavior. Reyes *et al*. have shown that a maternal low-protein diet impairs spatial acquisition and memory retention in male offspring, suggesting that microbiota may influence memory and learning later in life.

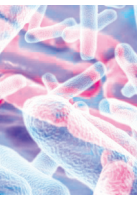
Yet other studies suggest that autism spectrum disorder (ASD) may be a pathology of the microbiota-gut-brain axis (Coretti *et al*.) and more specifically that maternal immune activation induces microbiota-gut-brain-axis dysfunctions with ASD-like symptoms (Hsia *et al*.). If indeed the gut microbiome plays a causative role in autism spectrum disorder and other chronic diseases, then the manipulation of the microbiome could potentially be leveraged as a therapeutic approach to improve symptoms.

ROUNDTABLE 3

The nutritional impact on cognitive and behavioral performance

Moderator: Louise Dye, University of Leeds (UK)

Participants: Michele Neunlist; Angèle Gibot, PiLeJe (France)



Louise Dye moderated a roundtable on diet and behavior, emphasizing in opening remarks her concern for the loss of human capital that a poor diet in early childhood can instigate. Her first question raised the issue of translating animal experiments to humans. Michel Neunlist conceded that there are many differences between human and mice brains, and suggested pigs as being closer to humans for the brain and perhaps for the gut. Even in mice, he noted, there is a large diversity of response because of the genetic diversity of mice; in humans the diversity is even larger. "A major goal is to perform clinical studies but in very stratified populations," he said.

Dye remarked that she saw a parallel between Maureen Black's presentation on the reduction of proteins, fruits and vegetables in food-insecure families and maternal protein restriction on learning and development in mice. She also noted that fruits and vegetables contain nutrients that have an impact on the gut microbiota as well as on cognitive function. In the absence of these, she asked Angèle Gibot if supplements could be used. Gibot said that her company had

shown that polyphenols extracted from plants had an effect on diabetes through the interaction with the microbiota, therefore she agreed that in the absence of a diversified, well-balanced diet, supplements could be an important strategy.

An audience member asked Neunlist how sure he was that behavioral changes in germfree rodents he used as models were microbiota-related, as germfree rodents were effectively "sick animals." He also asked about the possibility of moving away from animal models altogether. Neunlist disagreed that germfree mice were diseased, but said that all models are imperfect. Neunlist said different methods were used to get a picture of the microbiota as a whole. He said he sees animals as an integrated system, which are needed, but agreed that alternatives were necessary. He suggested that human organs grown in sheep might be a possible alternative.

Dye commented that food insecurity is a chronic stressor, and that Maureen Black had suggested that maternal stress has an impact on childhood development. Dye asked about possible interventions to address stress. Gibot answered that her team had performed preclinical studies to modulate the microbiota to reduce stress symptoms and to compensate for early-life stress — which could have relevance for children with attention deficit, hyperactivity or autistic disorders. She said it was too early to recommend a specific intervention but that she hoped to perform clinical trials.

Dye wondered if the explosion of autism diagnoses was simply due to improved diagnosis, and asked if there was a clear causal link between the microbiota and autistic disorders. Neunlist said that the same diagnostic tools were available years ago, so this would not account for the number of autism cases diagnosed, however, he agreed that people are more aware of the disorder. Nevertheless, he felt this was not the only explanation for the increase, but that environmental factors are strongly linked. Causation, however, is difficult to establish.

CLOSING LECTURE:

Nutrition of the future

Ben van Ommen, The Netherlands Organization for Applied Scientific Research (The Netherlands)

Our health is based on a complex network of interactions between pathways, mechanisms, processes and organs. Many of these processes function in a continuously changing environment (e.g., diet, infections, stress, temperature, exercise) while striving to maintain internal homeostasis by adapting to these changes ("systems flexibility"). Disease onset occurs when and where these adaptive processes fail. Diet plays both a positive and negative role. Many nutrients serve specifically to optimize these "flexibility processes." Prolonged caloric excess and an unbalanced diet cause a loss of flexibility in long-term adaptation processes with negative health consequences. As unhealthy eating has become commonplace, more than half of healthcare costs are related to our lifestyle.

New methodologies and concepts of health quantification and optimization may help to change this. Studies show that the effect of nutrition and bioactive compounds on individuals is highly dependent on genetics. Van Ommen stressed the need to establish molecular phenotypes and for biomarkers to quantify the stress response to external changes (not during homeostasis). With such data on individual processes, it is already possible to optimize personalized diets. In one study (Blanco-Rojo *et al*., 2015), diabetic subjects were given a glucose-tolerance test to establish four insulin-resistance phenotypes and then were randomly assigned to either a Mediterranean diet or a low-fat diet. Depending on the phenotype, it was found that certain subjects benefited more from the Mediterranean diet while others achieved more benefit from the low-fat diet. "Patients are entitled to this type of treatment," Van Ommen commented of the inexpensive procedure.

Turning to his vision of the future of nutrition, Van Ommen remarked that regulatory agencies such as EFSA and the FDA are set up to protect consumers, but if consumers had their personalized health data, he wondered, "What if consumers could make their own choices?" He imagined a smartphone application that could scan a food product to inform consumers if it was beneficial for their phenotype. He also recommended a Child Health Passport that contained not only (mostly nonactionable) growth data but also cognitive tests, parental observations, medications, genetics and more that could act as a "bio-passport," potentially leading to concrete actions (such as nutritional supplementation).

Broaching the topic of big data, Van Ommen noted that it is already being used to power healthcare algorithms. He therefore advocated for health data to be accessible to individuals and for individuals to own their own health data. He cited the example of the Holland Health Data Cooperative, which compiles health data for the benefit of the members of the cooperative. Rather than allowing a third-party technology giant to amass health data for profit, Van Ommen stated it was his "passion" to see health data used ethically. He foresaw a future health economy based on services rather than products that would provide personalized nutrition and precision medicine.

WHITEBOOK

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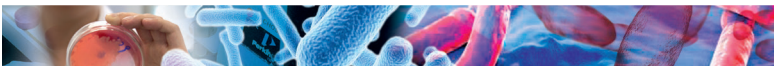

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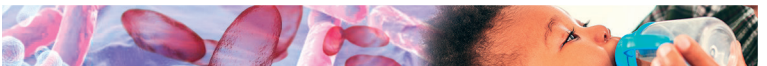

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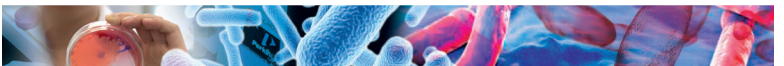

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