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TOWARDS A SCIENCE AND INNOVATION AGENDA

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FOREWORD

The OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT), in line with its current Mandate and under the Programmes of Work and Budget (PWB) for 2015-16, pursued analytical work on the assessment of policies to support healthy ageing and to bring together scientists from academia and industry with regulators and policy makers to address gaps and barriers to innovation within the microbiome, food, nutrition and new therapeutic approaches.

The report builds on an OECD workshop organised in May 2016 entitled, "The Microbiome, Diet and Health: Assessing the Gaps in Science and Innovation." Hosted in Brussels by the Belgian Delegation to the BNCT, this workshop (hereinafter, "The Brussels Workshop").

A special note of appreciation is extended to Dr. Kathleen D'Hondt, policy analyst at the department of Economy, Science and Innovation of the Flemish Government, who was the primary author of this report, with important input from the OECD Secretariat; Dr. Alexandre Bartsev, scientific advisor for microbiota research at St. Antoine Hospital, Paris; Dr. Peter Raeymaekers, science journalist; and members of the Secretariat of the BNCT. This work received support from the Department for Economy, Science and Innovation of the Flemish Government in Belgium, BIAC, and Nestlé Health Science. Mr. Randy Holden edited the report.

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THE MICROBIOME, DIET AND HEALTH: TOWARDS A SCIENCE AND INNOVATION AGENDA

EXECUTIVE SUMMARY

After the first projects undertaken to study and map the human genome were completed and the results published, an entirely new chapter opened in the field of genomics as attention turned to characterising diverse microbial ecosystems. It has become clear that these systems perform all kinds of important work – within soils and aquatic environments as well as in and on all living organisms. Efforts to advance the science have been global, with the involvement of international collaborations proving key.

There is now strong evidence that microbiomes – the ecosystems of micro-organisms interacting in and with particular environments in the human body – play an important role in human health, as there are clear linkages to many of the major non-communicable diseases (NCDs), which account for nearly 50% of healthy life years lost and are central to the United Nations health strategy. Evidence is accumulating that through diet, the gut microbiome can be altered to generate greater wellbeing, offer better protection against non-communicable diseases, and perhaps even to cure such conditions.

The food and pharmaceutical industries recognise the potential for new understanding of the microbiome to translate into products. Interested parties range from food ingredient producers, consumer goods companies and medical device companies to biotech firms and technology service providers. The food industry is preparing to develop personalised diets and specific food for particular target groups to prevent or treat certain chronic conditions. Meanwhile, industry – as well as academic partners – is calling for public-private partnerships to stimulate this translation of scientific knowledge into new products and treatments.

Although the relevant actors are gaining scientific insights ever more rapidly, challenges remain in terms of developing an evidential base, standardisation of terms and protocols, and a credible and well-tailored regulatory framework. While the field genuinely holds promise, it is also subject to hype. Many health claims ascribed to food products targeting the microbiome lack sufficient scientific substantiation and are merely associative, with no established causal pathway. If such a promising scientific field is to lead to innovative applications, policies on science and innovation could be improved in five areas: *1)* science policy; *2)* enabling translational science; *3)* public-private collaboration; *4)* regulatory frameworks; and *5)* skills, communication and the public.

Science policy

International networking of research, together with structural funding for transcontinental microbiome research programmes, will be important for advancing this field. Several large data infrastructure projects currently make information accessible, but there is a need to further connect databases and information sources. Further, new international consortia should move beyond microorganisms found in humans and link the different microbiome research communities, i.e., plant, environmental, animal and marine research. Large consortia should not be funded to the exclusion of smaller, well-targeted research projects that address well-formulated research questions and encourage hypothesis-driven science, and move beyond mere tool development and cataloguing. As a general matter, developing applications that build on microbiome science will require deeper understanding: of the host-microbiome nexus; of what constitutes a healthy microbiome; and of causal relations between microbiomes and health throughout the life span.

Enabling translational science

There is a need for guidance and improvement in regulatory-targeted clinical programming and research. Standard protocols are required for clinical design, marker validation and statistical interpretation. Existing standardisation activities could be deepened and made more international, but should remain flexible enough to encourage innovative approaches. Better characterisation of a healthy gut will be important for establishing disease biomarkers.

Public-private collaboration

Partnerships between public and private partners (food and pharmaceutical) could lead to more rapid advances. There are known challenges for data sharing in such partnerships, where negotiations can founder on issues of data ownership. Industrial actors, much more than academia, can be hesitant to deposit large data sets in public repositories out of concerns about competition. There is more leeway for precompetitive activities among industrial partners and academia than is currently recognised. Policy should encourage pre-competitive arrangements featuring broad access. At a minimum, public or private research funds should be spent in such a way that complementary information is generated rather than duplicative data, but this requires of course good conditions for accessing data.

Regulatory frameworks

The current frameworks for evaluating the health claims of new food products and new dietary approaches in certain countries could be improved and made more transparent. Terminology and categories could must be clarified both within and across regulatory systems, especially for terms such as nutraceuticals, pharma biotics, functional foods and probiotics. International harmonisation of regulatory terminology may be desirable, given the flow of products across borders and the mandate for regulatory clarity across systems. Within certain national regulatory systems, the food and drug regulatory frameworks could be better matched to handle foods making health claims, by: 1) harmonising the terminology used in the various regulations; 2) agreeing on how health claims should be analysed; and 3) designing regulatory frameworks that respond properly to new products on the food-drug continuum. Post-marketing surveillance – common practice in the pharmaceutical industry – would be useful to increase the evidence base of certain products. According to some actors, the focus should be on quality and safety, not on categorisation of the health claim.

Skills, communication and the public

Moving from mere cataloguing to insights into physical processes and novel applications will require new technology development, engineering, computer modelling and bioinformatics. The future workforce and scientists should be trained to combine these skills so that the field can grow and mature. As validated insights open new approaches to addressing many chronic conditions, healthcare professionals should be able to apply new and validated insights. Information needs to be provided to consumers and citizens in a clear and understandable way. This requires concerted action from all responsible actors – the research community, food and healthcare professionals, industry, regulatory opinion leaders, the media and policy makers. Ongoing citizen science initiatives for characterisation and data sharing have generated broad enthusiasm for the field, and should help enable societal dialogue and communication. The information and understanding stemming from citizens are an important resource, but the quality of data must be scrutinised carefully. Bringing in regulators, scientists, citizens and industry into dialogue will continue to be helpful in highlighting the key challenges in this area, and in identifying the steps necessary to enable innovation and advance public health.

INTRODUCTION

"Micro-organisms may be small, but their impacts are mighty."

Dr Jo Handelsman, Associate Director for Science at the White House Office of Science and Technology Policy (OSTP) in the United States, 2016 Brussels Workshop

The human microbiome can be defined as the combination of all microbial genomes that live in and on the human body. The communities of such microbial organisms are jointly called microbiota and consist of bacteria, archaebacteria, fungi, viruses and unicellular organisms. Different symbiotic or commensal microbial populations are found in the mouth, on the skin, in the vagina or in the gastrointestinal tract; this last population is the densest one and contains the highest biodiversity. The gut microbial population consists of over 1 000 species, representing about 1.5 kg of weight. Recent calculations estimate that the bacterial cells hosted by our bodies are in the same order as the number of body cells in a human (Sender, Fuchs and Milo, 2016).

Microbiome science carries great potential for human health; that is one of the reasons it is a field garnering so much public research investment. Public health is facing major challenges caused by the increasing incidence of complex and common diseases, especially the so-called non-communicable diseases (NCDs). The underlying causes of diseases such as obesity, metabolic syndrome, type 2 diabetes, allergies, food intolerances, Alzheimer's and other neuro-psychiatric disorders are still not well understood at the molecular level, and effective treatments are still largely lacking. According to a study of the World Economic Forum in 2011, NCDs are expected to cost USD 47 trillion by 2030 or 75% of the annual global GDP in 2010 (Bloom *et al.*, 2011). Increasing scientific evidence has identified the human gut microbiome as a key biological factor conditioned by nutrition and interfacing the genome and the environment.

New technologies have enabled the microbiomes to be characterised without any need for isolating and purifying single species organisms and growing them in pure cultures. It is only since "omics" technologies became available that organisms could be characterised as part of the community. Moreover, a combination of omics technologies now not only allows microbiomes to be characterised in a descriptive way, based on identification of their genomes, but also generates insight on the functioning of the microbial ecosystems. The microbial ecosystems hosted by our bodies provide us with genetic variation and gene functions that human cells did not furnish on their own (Grice and Segre, 2012). The gut microbiome is estimated to add to our body 150 times the number of genes in the human body (Qin et al., 2010).[1]

While nutrition plays a well-known role in health, recent scientific studies are linking food to an array of health conditions in new ways. Food may even have a determining influence prior to birth and influence the development of complex pathologies (Gluckman et al., 2008).[2] Imbalance of the gut microbiome has been associated with an increasing risk of a number of diseases and has even been suggested to be a determining factor in neuropsychological pathologies, although in neither case is a causal role firmly established. (Hanage, 2014; Mayer et al., 2014; Sun and Chang, 2014).

Better understanding of the complex interplay of diet, nutrition and the microbiome is expected to contribute positively to health and the economy, by enabling development of innovative and cost-efficient diagnostics, preventive measures, and treatments for complex diseases linked to nutrition and health status. Indeed, as the microbial ecosystems in the human gut become better understood, greater efforts are being made to understand the impact of the different food products on the composition and functioning of microbial communities.

New insights into the functioning of the microbiome could inform the consumption of healthier food as well as the development of food products offering health benefits. There is a steady trend towards the production of food products claiming to have positive and unique effects on human health. The food industry is increasingly focused on developing personalised diets and specific food for specific target groups, to prevent or treat certain chronic conditions. These products may operate through influencing the gut microbiome.

The pharmaceutical industry and several innovative biotechnology companies have also targeted the human microbiome in addressing chronic diseases and as a source of novel bioactive compounds. Although the relevant actors are gaining scientific insights ever more rapidly, challenges remain in terms of developing an evidential base, standardisation, and acceptance of a globally unified regulatory framework, the proliferation of exaggerated health claims, and the difficulties involved in developing rigorous testing protocols within existing regulatory frameworks (Ash and Mueller, 2016).

Given the promise of this new scientific field, its potential utility for human health and within the food industry, and the problem of hype and exaggerated claims, this report analyses the key barriers to innovation around the microbiome. For one thing, before therapies and nutritional approaches are adopted, there is a need to demonstrate the causal role of microbiome in diseases and methods need to be developed for diagnoses and treatment. The existing scientific, institutional, and industrial landscape presents important challenges and opportunities that should be tackled by scientists, policymakers, regulators, and citizens alike. These stretch across science policy, international scientific collaboration, regulatory policy, innovation policy, and stakeholder communication.

The main findings of the report include:

Science Policy

International collaboration and funding should be enhanced. The microbiome is a field in which international collaborations have proved important and will likely remain so. International networking of research, together with structural funding for transcontinental microbiome research programmes, will be important for advancing this field. These programmes should stimulate mutual data generation and data exchange among research groups across the globe.

Multilateral funding collaborations on big data should be fostered. Several large data infrastructure projects currently make information accessible, but there is a need to further connect databases and information sources. Databases should be accessible across different microbiomes and across different countries and continents. Productive use of data requires standardisation of generating, storing and analysing the data.

Smaller, well-targeted research projects remain greatly important. Apart from large consortia for big data generation, there should also be room for smaller, well-targeted research projects. New research projects should address well-formulated research questions and encourage hypothesis-driven science, rather than merely engage in tool development and cataloguing.

Multidisciplinary collaboration in many microbiome fields should be encouraged. New international consortia should move beyond human biota, and link the different microbiome research communities: understanding the functioning of microbiomes in plant, environmental, animal and marine research may be translated to human microbiomes. The human gut microbiome research community should be linked with other – including non-human microbiome – communities, to share common themes and to learn from each other's experiences.

Funding should seek to address key unanswered questions:

1. Science must define a healthy microbiome. Expanding the study of the normal gut microbiome composition and the factors influencing normal variation is an essential step on the path towards robust microbiome-based diagnostics, preventive care, and new microbiome-based health products and foods.

2. Research on the host-microbiome nexus is key to unlocking the microbiome's potential, and should therefore be intensified. This includes work on mutual microbial interactions and on host-microbiota signalling and physiological alterations.

3. Causal relationships and interactions between microbiota and human biologic systems (including metabolic and immune systems) should be characterised over the course of the human life span, from infancy to old age. The knowledge on the interactions between the microbiome and the very young and the very old host needs to be expanded, deepened and consolidated.

Enabling translational science

Building a clinical research base and causal inferences – The field as a whole must focus on moving from description to causal inference for human disease. There is a need for guidance and improvement in regulatory-targeted clinical programming and research, particularly as pertains to clinical design, marker validation, statistical interpretation, and dossier strategy and elaboration.

Translating new scientific insights into applications poses significant challenges. First there is an urgent need for validated biomarkers and intermediate endpoints to develop applications for diagnosis and follow up of interventions targeting the gut microbiome for better health. This will open the way towards personalised dietary strategies and the development of novel food products for therapeutic and preventative applications.

Furthermore standardisation of protocols and technologies, as well as validated model systems need to be agreed before large-scale applications in hospitals and health centres can be started.

Validating biomarkers for healthy and dysbiotic microbiomes. Although a healthy gut microbiota is usually linked to biodiversity and diverse functionality, more in-depth research is needed to identify a "healthy" vs. a "dysbiotic" gut and understand and characterise the normal variation of the healthy microbiome.

Standardising – Methodologies for studying the microbiome are still not fully standardised. Standardised technologies, practices and models are beneficial since they make results comparable and to allow unbiased analysis by independent researchers and before large-scale applications in hospitals and health centres can be introduced. International efforts to develop standard operating procedures (SOPs) are under way in, for example, the International Human Microbiome Standards (IHMS) project funded by the Seventh Framework Programme of the European Commission (EC FP7).[3] However, the 2 projects with perhaps the most potential to influence the field, the Human Microbiome Project and the EC IHMS appear to have developed protocols independently. Harmonising these protocols should be considered. Finally, although the use of standard procedure is recognised by all stakeholders active in this field, some flexibility is necessary to encourage innovative approaches.

Innovation policies

Recognising the potential for industry. The food and pharmaceutical industries are recognising the potential for fresh understanding of the microbiome to translate into products. Interested parties range from food ingredient producers, consumer goods companies, the pharmaceutical industry and medical device

companies to biotech firms and technology service providers. A new spectrum of health-enhancing foods and transformative treatments are on the horizon.

Forming public-private partnerships. Industry as well as academic partners is calling for public-private partnerships to stimulate the translation of scientific knowledge into new products and treatments. Public and private partners, e.g., in food and pharmaceuticals, could lead to more rapid advances. Several such partnerships in the field have already been set up.[4] More funding than currently allocated is required to support the high costs of metagenomics and other omics technologies. Often, those costs are too high to build larger cohorts. Use of smaller cohorts limits validity of the results and eventually leads to a larger loss of budget, as analyses need to be reproduced according to statistically relevant orders of magnitude.

Balancing innovation incentives, open access, and intellectual property ownership rights. There is general agreement that access to databases and data deposition in public databases should be promoted. Often, discussions on data sharing in public-private partnerships quickly focus on ownership of the data. Industrial actors, much more than academia, can be hesitant to deposit large data sets in public repositories out of concerns about competition. Policy should find a balance between the mandate for open access and the realities of preserving rights that help bring in investment. At a minimum, public or private research funds should be spent in such a way that complementary information is generated across the public and private sector rather than duplicative data. But there is actually more leeway for precompetitive activities among industrial partners and academia than is currently recognised. Opportunities for combining open access science and protected industrial development are present in precompetitive research spaces.

Regulatory frameworks

Clarifying evaluation procedures for health claims regarding food. As a whole, regulations and regulatory processes should be science based, predictable, clear and efficient; to the extent possible, they should include reasonably detailed timelines, be enforceable, and facilitate innovation and the free movement of goods. In certain jurisdictions, the current frameworks for evaluating health claims for new food products and new dietary approaches may benefit from more workable and transparent procedures. According to some actors, the focus should be on quality and safety, and not on categorisation of the health claim. Regulations should be simplified where possible.

Clarifying terminology and categories within and among regulatory systems. Terms like nutraceuticals, pharma biotics, functional foods and probiotics have formal definitions in some systems but not others, even as they are being used to make claims about the health effects of foods on the microbiome. For example, quasi-scientific claims like “probiotic” are not currently regulated in the United States but qualify as a health claim under the EFSA regulation in the European Union.

Reaching international agreement on terminology. Given the flow of products across borders, harmonisation of terminology should be considered.

Establishing post-marketing surveillance. Post-marketing surveillance, common practice in the pharmaceutical industry, could be used to increase the evidence base of certain products.

Improving the match between food and drug regulatory regimes. Certain food and drug regulatory frameworks could be better matched to handle foods making health claims, by considering: *1)* the harmonising of terminology used in the various regulations; *2)* agreement on how health claims should be analysed; and *3)* the design of regulatory frameworks that are more responsive to new products on the food-drug continuum.

Skills, communication and the public

Building an interdisciplinary workforce. There seems to be broad agreement that moving from mere cataloguing to insights into physical processes and novel applications will require work across a range of disciplines. Microbiologists will have to work with engineers, those in bio-informatics, physicians, as well as experts in all types of "omics" technologies. There is a need for new technology development, engineering, and computer modelling and bioinformatics. The future workforce and scientists should be trained to combine these skills so that the field can grow and mature.

Training of healthcare professionals. As validated insights permit new approaches to addressing many chronic conditions, healthcare professionals should be trained to take on board these approaches, even if they lie outside the typical medical paradigm. Information and training campaigns should build awareness and trust in the novel dietary approaches targeting the gut microbiome.

Providing good information clearly. As stated above, hype and misleading claims are endemic in this field, and can entirely" undermine the innovation process if the field loses credibility. Beyond basic safety, consumers and patients are entitled to the assurance that claims are accurate so that they can make informed decisions and choices. Therefore, information needs to be provided in a clear and understandable way. This requires a concerted action by all responsible actors from the research community, food and healthcare professionals, industry, regulatory opinion leaders, the media, and policy makers.

Harnessing citizen science, cautiously. There seems to be strong public interest in the microbiome, as evidenced by large-scale citizen science projects to characterise microbiomes and track diet. These projects generate broad enthusiasm for the field and should help enable societal dialogue and communication. The information and understanding they produce are an important resource, but the quality of the data must be scrutinised carefully.

Facilitating multi-stakeholder deliberation. Bringing in regulators, scientists and industry will continue to be helpful in highlighting key challenges and identifying the steps necessary to enable innovation and advance public health. These stakeholders should also seek out forums to engage the broader public such as science fairs, information websites and educational activities.

First, this report reviews the state of microbiome knowledge in the arena of the human gut, pointing out areas of key knowledge and topics seen to require more work. Second, the report examines and evaluates of the current modes and mechanisms of international cooperation in the microbiome area. Third, the study assesses activities and the commercial potential of industries arrayed around microbiome science, e.g., food ingredient producers, pharmaceutical industry and medical device companies, and biotech and technology service providers. Finally, important hurdles to innovation in this area are identified and these are addressed in a set of policy implications.

GUT MICROBIOME: STATE OF KNOWLEDGE

OECD countries are investing significant time, funding and energy in microbiome research in recent years, and are likely to continue to do so. This commitment has paid off in terms of improving characterisation, deepening functional understanding, and building human and physical capital. Much of this funding is under the rubric of improving food, health and nutrition, i.e. a mission-driven agenda. The strong linkages among diet, microbiome and health validate this approach, but key questions remain. The notion that gut microbial composition is determined in part by diet is becoming accepted, but a holistic understanding is far from complete (David et al., 2014). Long-term and wide-reaching studies are needed to understand the mechanism through which food components are active and which microbial species have an active role in metabolising or producing such active compounds. It remains unclear, for instance, what determines permanent changes in the gut microbiota, and how certain nutritional interventions can improve health.

Thorough metabolomics studies are needed to understand the role of microbial enzymes and signalling through microbial metabolites. These metabolites influence the host metabolism and host immune system. On top of that, these interactions evolve over the course of the human life span. Understanding of physiological alterations that impact the gut microbiome and initiate susceptibility to disease is needed to deliver on the promise of a positive impact on human health, through development of new therapeutic applications – including personalised diets – targeting the gut microbiome.

The health benefits are thus tantalising, but remain difficult to substantiate. Indeed, despite the hype, more research is needed before one is able to systematically use current microbiome science to produce better health and wellbeing. Drawing on presentations at the Brussels Workshop, the next section outlines some recently developed insights about the gut microbiome and its potential role in aiding human health and nutrition and. Key knowledge gaps are also discussed.

The functional interface between human genetics and diet

Accumulating scientific evidence indicates that human gut microbiota is a key biological interface between human genetics and environmental conditions such as diet. It can be considered an essential organ in the human body, although its composition and therefore functioning can vary depending on external factors (Evans, Morris and Marchesi, 2013). On the other hand, the gut microbiome is not a homogeneous or stand-alone community: the whole digestive tract should be considered. Characterisation of the microbial ecosystems in the different parts of the digestive tract and the communication and interaction among those ecosystems is needed.

Recent advances: Different enterotypes linked to diet and disease

Some scientists hold that human gut microbiomes can be classified into what are called enterotypes; these have been compared to blood types (Arumugam et al., 2011).

Three distinct enterotypes have been identified despite the diversity of the microbial population that inhabits the gut. Each of the three is characterised by an increased presence of a certain microbial genus, although a broader study indicated that the boundaries between enterotypes are less clear-cut than first described (Yong, 2012; Knights et al., 2014). These enterotypes are not linked to ethnic background, age, weight or gender, although that the composition of the gut microbiome is influenced by these factors. More strikingly, some enterotypes have been linked to obesity, diabetes, cancer and other diseases – even neurological – although the causal relationship still needs to be proved (Shreiner, Kao and Young, 2015).

In addition, it was shown that short-term dietary changes alter the microbial composition, although not the enterotype; the latter is influenced by long-term dietary pattern (Wu et al., 2011; David et al., 2014).

It has long been known that gut bacterial ecosystems are essential for food digestion; these provide enzymes for the production of vitamins and essential amino acids that are not produced by normal human cells. Now it has been learned that, for example, enterotype 1 favours the production of vitamin B7, while enterotype 2 favours the production of vitamin B1.

These findings lead to the hypothesis that diets may be tailored on an individual basis to meet personal requirements;[5] for specified target groups, tailored diets may work as preventive medicine. In addition, there are ongoing studies to define diets for treating certain diseases (Bushman, Lewis and Wu, 2013). However, it is still unclear what a healthy microbiome is; how it is kept in balance; what determines changes; and how the interaction and signalling with the host functions. Such primary knowledge is required before therapies targeting the microbiome can be developed. This was a key message in the workshop.

A healthy gut microbiome

Characterising a healthy intestinal microbiome is one of the goals of Jeroen Raes, Professor at the VIB Centre for the Biology of Disease at the University of Leuven, Belgium. Based on two independent, extensively phenotyped cohorts, the Flemish Gut Flora Project and the Dutch LifeLines-DEEP study – involving a total of nearly 4 000 participants, the VIB Centre identified a total of 664 different microbial genera across the different samples. A subset of 14 bacterial genera was found to be a universal core microbiota found in 95% of all tested individuals.

Based on the clinical data, documented with health and lifestyle information from questionnaires, Raes identified 69 factors – from stool consistency to consumption of dark chocolate or beer – associated with variation of the microbiota from over 1 000 samples from the Flemish Gut Flora Project (Falony et al., 2016). Direct associations found with antibiotics or laxatives were not entirely unexpected; more surprisingly, associations were found with immunosuppressants and hormones.

The fact that factors like dark chocolate and beer can be associated with different compositions of the gut microbiomes indicate that diet should be taken into account when planning clinical trials to test the safety and efficacy of new drugs. Very often such trials are run in Asian countries, where the diet is very different from the western diet where the drugs will also be marketed. The effect of a drug can be different in a different microbial ecosystem. There are examples of drugs that are inactivated by gut microbes, while others need the action of gut microbes to become activated (Nayak and Turnbaugh, 2016; Spanogiannopoulos et al., 2016). Other examples exist of drugs and their gut metabolite having different mechanisms of action and different targets. The microbiome may thus directly impact drug-drug or drug-host interactions. In other cases gut microbial enzymes are shown to influence the clearance of drugs.

Dr. Jo Handelsman pointed out that understanding how drugs influence and impact the microbiome, and how the microbiome produces varying effects on drugs opens the door to a whole new realm of research. Among other things, understanding these interactions will help predict which patients will or will not respond to certain drugs.

Infant microbiome

Diet is not the only influence on the composition of the gut microbiota, which also changes on its own during the lifespan. In the Brussels Workshop, Douwe van Sinderen, Lead Principal Investigator at APC Microbiome Institute, reported on results from the INFANTMET study. The goals of this study are to define the composition and functional performance of the baseline microbiota in developing infants. It was

shown that at one week following birth, the composition of the infant's gut microbiome is significantly influenced by the mode and time of delivery. Strikingly, the guts of new-borns, if born on term, are not very different whether they are delivered by vaginal birth or caesarean section. This seemingly contrasts with the long held notion that infants are born sterile: their intestine is instead already colonised by microbes in utero. On the other hand, the microbiome of infants born preterm through vaginal delivery is very different from infants born on term through vaginal delivery. When compared to preterm vaginal birth, major differences in the composition of the gut flora are also seen when birth is by emergency caesarean, which very often relates to premature birth.

Another factor influencing the composition of the gut microbiome is the way the infant is fed (breast vs. formula feeding); equally important prenatal factors centre on the health and behaviour of the mother during pregnancy – diet, metabolic health, lifestyle, stress, medication use, mother's genotype, etc. Surprisingly, even the fact of whether the mother had been breast fed as an infant was seen to influence the infant's intestinal microbiome.

Outcomes from this research are important for developing better guidelines, health recommendations, weaning programmes and educational programmes for an optimal pregnancy and delivery. These in turn can improve health outcomes for the infant, supporting early life development and healthy ageing. It is expected that this type of work will also lead to the development of nutrition that supports a healthy infant gut microbiome. Not only evidence-based infant nutrition, but also innovative food products targeting expectant mothers are being developed. Again, the need to characterise and understand what a healthy microbiome is, in this case that of infants, was reported to be fundamental. The mechanisms of gut colonisation after birth also need to be better understood. Still unclear is how the transfer from mother to infant occurs, and which factors influence such colonisation.

Ageing and microbiome

The gut ecosystem changes significantly during the life span due to several factors, such as changing diets, inflammation, and age-related reduction of gut motility and permeability. Patrizia Brigidi, Professor in Fermentation Biotechnology at the University of Bologna in Italy, reported during the workshop on a comparative study on healthy gut microbiomes between young, elderly and centenarian persons. Strikingly, little difference is seen in gut microbiome composition between the young and healthy elderly; they also have similar biodiversity. Centenarians on the other hand show a gut microbiome that is lower in diversity and that has a higher number of microbes with a higher inflammatory potential. Metabolic characteristics of centenarian gut microbiota correspond to a reduced tryptophan bioavailability, which may be correlated to cognitive impairment and increased immune activation. Also observed is an increased tyrosine metabolism that leads to increased levels of metabolites that may be correlated to cancer, depression and diabetes. In an elderly population, a reduction of butyrate producers and the increase of pro-inflammatory micro-organisms are observed in the gut of frail, pre-frail and hospitalised elderly. This can severely compromise health through supporting and consolidating chronic inflammation and metabolic deregulation.

The differences observed in gut microbiota in different age groups suggest that modulating the microbiota could keep older people healthier longer. Characterisation of the gut microbiome may help to stratify this heterogeneous population, and is likely to be highly relevant in developing dietary guidelines to increase the number of healthy life years. It is striking that although the population is ageing, the number of healthy life years is not following at the same rate. Moreover, dietary guidelines for the elderly are largely lacking even though this population is increasingly aware of their health and interested in healthy diets. This is an important aspect for market development, and was the subject of the NU-AGE project that ran for five years until April 2016 during the Seventh Framework programme of the EC.[6] Dietary

strategies targeting the gut microbiome could inhibit the so-called "inflamm-ageing" process, the chronic inflammation condition in elderly.

Multi-centred longitudinal studies will be needed to validate the future outcomes of dietary interventions and to characterise how diet, ageing and the gut microbiome are linked to increasing the number of healthy life years.

Dysbiosis

The importance of a healthy microbiome was demonstrated in experiments with germ-free-bred mice as early as 1981 (Wostmann, 1981). These mice have severe growth, developmental, and immunological problems in addition to behavioural impacts (Desbonnet et al., 2015). Imbalances in the normal structure and function of the microbiota, or dysbiosis, have been shown to be linked to many different non-communicable diseases, although the causality is more difficult to demonstrate. Dysbiosis of the gut microbiota is characterised by species that induce a reduction of short chain fatty acid production, increased mucus degradation, reduced hydrogen and methane production, in combination with an increased hydrogen sulphide potential, and higher abundance of bacteria containing lipopolysaccharide endotoxins. These characteristics are associated with an increased potential for inflammation (Le Chatelier et al., 2013).

Effect of diet on the gut flora

Francisco Guarner, Consultant of Gastroenterology at the Digestive System Research Unit of the University Hospital Vall d'Hebron in Barcelona (Spain), in his presentation at the workshop, linked dysbiosis of the gut microbiota resolutely to inappropriate food habits. After the Second World War, dietary guidelines were developed to combat malnutrition and emphasised mainly food that is easily digested and absorbed in the upper gastrointestinal tract (small intestine). However, requirements to build a healthy colon microbial ecosystem were largely neglected. A long-term prospective study demonstrated that increasing vegetables, nuts, grains, fruits and yoghurt in the diet favour a healthy gut microbiota and leads to weight loss (Mozaffarian et al., 2011).

These findings are in agreement with the idea that dysbiosis of the gut microbiome can be prevented and treated by providing appropriate prebiotics, and that a healthy diet will increase microbial biodiversity in the gut. Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving the host health (Gibson and Roberfroid, 1995). A model has been described to illustrate how complex carbohydrates from prebiotics are degraded by so-called primary degraders that provide substrates for the secondary degraders to produce such end-products as short chain fatty acids that are used by the host metabolism (Wong et al., 2006).

Moreover, prebiotics are likely to form the matrix needed for the micro-organisms to colonise the intestine. One of the main challenges in the field today is to determine the requirements of this matrix for maintaining an optimal colonisation that ensures better health according to specific individual needs. Those needs must be met by metabolites and essential amino acids produced by gut micro-organisms that cannot be produced by the host itself. Several of such metabolites have linked to risks of certain diseases.

So far in most cases, and although diet clearly determines metabolite patterns, the individual factor seems to be more important (Heinzmann et al., 2012). The same conclusion was drawn from results during the FP7 Satin project. Douwina Bosscher, Global Leader Nutrition Science at Cargill, illustrated this during the workshop when she reported on the effect of resistant starch on glycaemia. It was found that diet could be accounted for only about 3% of the interpersonal variation in gut composition, while 61 % depends on other factors.

A recent study clearly demonstrated that response to nutrition is personal and that identical foods can produce healthy and unhealthy responses in different individuals. An algorithm was developed that predicted the individualised post-meal blood sugar response (Zeevi et al., 2015). Based on this algorithm, diets could be adapted to trigger a good or a bad sugar response. Strikingly, the good diet favoured growth of beneficial microbiome bacteria, whereas the unhealthy diet led to decreasing numbers of these bacteria. This is the first major study indicating that personalised diet is possible and that it can alter the microbiome.

Although the response to diet is largely individual, recent studies demonstrated that large differences are seen in the functioning of the gut microbiota of undernourished, obese or lean individuals.

Effect of under-nutrition on microbiome functioning

Although more research is needed to understand the mechanism, it has been shown that gut microbiota from undernourished and over-nourished individuals functions very differently. Recently, it was shown that the gut flora of undernourished children is immature and, when transplanted in germ-free mice, transmits the phenotypes associated with undernourishment, such as growth impairment (Blanton et al., 2016). Moreover, the growth defects in mice were prevented when healthy microbiota could colonise the mice with the immature microbiota. Work from Charbonneau et al. (2016) then showed that when sialated oligosaccharides – present at 20 times higher levels in human breast than in bovine milk – are added to the diet of model organisms colonised with gut flora from undernourished children, the combination induces a beneficial effect on growth and metabolism, through acting on the microbiota. These findings may lead to the development of relatively easy and inexpensive treatments of undernourished children, and may therefore be highly significant in the poorest areas of the world.

Effect of over-nutrition on microbiome functioning

Other studies demonstrated that the gut microbiota of obese humans or mice also are different from those of lean individuals. Moreover, when transplanted in the gut of germ-free mice, the gut flora from obese mice induced a greater increase of body fat than when the transplant was of lean counterparts. In comparing human twins, it was shown that the gut flora of obese individuals had a lower bacterial diversity than the lean counterpart of twin pairs. Differences in metabolic pathways and microbial genes were also observed (Turnbaugh et al., 2009).

The need for hypothesis-driven research

While the major international collaborative projects have proved valuable, there is also a need for smaller, creative hypothesis-driven research. According to Dr. Raes, “Generalisation and validation of research findings in multinational collaborations is essential, but sufficient structural, long-term funding of national and international microbiome initiatives is as crucial. New research projects should address well-formulated research questions and encourage hypothesis driven science, rather than mere tool development and cataloguing. Apart from large consortia for big data generation, there should also be room for smaller, well-targeted research projects.” Another gap identified is that it is almost impossible to get funding for

collaborative projects in which US and European scientists team up. Many more international mechanisms for funding, especially for smaller and medium-sized collaborative projects, are needed.

THE INSTITUTIONAL LANDSCAPE OF PUBLIC MICROBIOME SCIENCE

International consortia

From an international science policy perspective, an obvious first question is whether there are adequate modes and mechanisms of international scientific co-operation in the arena of microbiome research. Microbiomes are a field in which international collaborations have been of great importance, and likely will remain so. For one thing, more data can power up studies of all kinds. For instance, given the expectations stemming from new insights on the human microbiota and the complexity of the system, there is a strong argument for major population studies. To reach a level of statistical relevance that will allow understanding of normal variation, the gut flora of at least 40 000 individuals need to be characterised (Raes, 2016).

There has just been a renewed call for a large global microbiome consortium by scientists from Germany, the People's Republic of China (hereafter "China") and the United States. The scientists emphasised the need for an International Microbiome Initiative (IMI), rather than national efforts, to ensure standardised approaches and to achieve coherence among the many different microbiome projects (Dubilier, McFall-Ngai and Zhao, 2015). The European Commission has also recently developed an international policy initiative on the microbiome in October 2016, as part of a larger "International Bioeconomy Platform".

These efforts follow on the heels of two prior international efforts. In 2008 the "Human Microbiome Project" was launched by US National Institutes of Health (NIH) to characterise the human microbiome and analyse its role in health by using omics technologies.[7] The project focused not only on cataloguing bacterial genes, but also on developing new tools for computational analysis and ethical issues. In its second phase from 2013 to 2015, with a budget of USD 22.1 million, the programme focused on improved understanding of the human microbiome's role in health and disease.[8] NIH earmarked another USD 1.5 million for a small set of new research projects between 2016 and 2017 in this field. Deeper insights are expected on how host-microbiota interactions can modulate specific host phenotypes related to obesity, digestive and liver diseases, as well as the role of the microbiome in nutrition.[9] An assessment of US microbiome research published in January 2016 estimated national spending on research efforts at USD 922 million between 2012 and 2014 (Stulberg et al., 2016). Over 59% of the budget was covered by the NIH.

Again in 2008, the International Human Microbiome Consortium was launched with the support of the Seventh Framework Programme of the European Commission (EC FP7).[10] The purpose was to share related data and make those data freely available to the global scientific community. The database also includes information from other major initiatives, such as the NIH Human Microbiome Project and MetaHIT (Metagenomics of the Human Intestinal Tract), another EC-funded initiative under the Seventh Framework Programme. Other contributors to the consortium included the Commonwealth Scientific and Industrial Research Organization (Australia), the Canadian Institute of Health Research and Genome Canada, and the Ministry of Science and Technology (China). The consortium is open to other partners willing and able to participate in accordance with its policies of the consortium. Members now also include France, Japan, Gambia, Korea and Ireland. The consortium aims to harmonise work focused on the human microbiome and co-ordinates the activities and policies of international groups.

MetaHIT, active between 2008 and 2012, had similar goals and a budget of more than EUR 21 million, of which over half was supplied by EC FP7. That consortium involved over 50 researchers from 8 countries – including the People's Republic of China (hereafter " China") – and

14 research and industrial institutions. The project generated a catalogue of 3.3 million bacterial genes (Qin et al., 2010), and began to describe three basic microbiomic "enterotypes" that a human might have (Wu *et al.*, 2011), although the enterotype theory is not universally accepted. Insights from this project opened perspectives for early detection of chronic diseases, personalised or stratified medicine, and development of nutrition that will help cure certain diseases.

European initiatives

Several EU funding programmes in the past have supported a large portfolio of projects on microbiome-related research. Already in the Fifth Framework Programme of the European Commission (EC FP5), the Commission funded a good number of projects on food and so-called functional food products. The fundaments for today's research related to gut microbiomes were laid in projects such as Infabio,[11] ProEUHealth (Mattila-Sandholm et al., 2002) and Crownalife (Silvi et al., 2003). These endeavours continue today, with many more projects funded under Horizon 2020. Total investment so far has reached EUR 600 million. The idea is to continue investing at least at the same pace, or even accelerating. Already within the first two years of Horizon 2020, around EUR 400 million was spent on microbiome related research.

One of the current major European projects dedicated to the human gut microbiome was launched in 2013:[12] MyNewGut is a five-year project with an estimated total cost of over EUR 13 million, towards which it received EC funding of almost EUR 9 million.[13] The goals of this project are to generate a better understanding of how the gut microbiome influences our health; to identify how the microbiome is functioning; and to ascertain how it is influenced by diet.

Some of these projects focus directly on the link between the gut microbiome and host health. An ambitious endeavour in this respect is MetaCardis, which aims to identify the effects of gut microbiota on cardio metabolic diseases; systems biology is employed to understand such multifactorial human diseases and their co-morbidities.[14] MetaCardis began in 2012 and runs to 2017. It brings 14 project partners from 6 EU countries together, and has received EUR 12 million in EC support.

In spring 2016, the Joint Programming Initiative on A Healthy Diet for a Healthy Life (JPI HDHL) began supporting work on the microbiome.[15] JPIs bundle national R&D programmes to address global societal challenges that single states cannot address individually; a Strategic Research Agenda is developed to achieve the stated goals. In JPI HDHL, 25 countries joined forces to address, as one of their goals, chronic diseases that are linked to poor diet. In 2015, the JPI launched a call for proposals for research projects addressing intestinal microbiomics, to gain more knowledge on how diet affects the gut microbiota and how this in turn affects human health and development of non-communicable diseases. A budget of over EUR 7 million was awarded to six projects, encompassing 20 research groups worldwide, that began in March 2016.[16]

A strong take-home message from the Brussels Workshop was the desirability of deeper cross-Atlantic (and indeed multi-continental) collaboration on microbiomes. Science policy makers agreed that such international consortia should move beyond human biota, and link the different microbiome research communities. Understanding the functioning of microbiomes in the context of plant, environmental, animal and marine research may be translated to the human microbiomes. As whole, international networking around microbiome research, together with structurally funded research programmes is believed to be the key to moving forward in this field.

National initiatives

In addition to projects that explicitly took an explicitly international approach, there are many national microbiome projects at the national level. These represent a critical component of the multi-level landscape of microbiome work.

Belgium

In 2013, the Flemish Government in Belgium allocated a budget of EUR 700 000 to support an ambitious Flemish Gut Flora project in the VIB (Vlaams Instituut voor Biotechnologie) Centre for the Biology of Disease at the University of Leuven**.** The aim of this project is to carry out population-wide longitudinal studies. A logistic system was set up to collect stool samples from volunteers after a public call to contribute. The project created a great deal of interest and sympathy from the public. By April 2016 over 5 000 people had participated, and close to 4 000 samples have already been characterised. In addition to stool samples, the project collects general information on lifestyle, health, quality of life, general wellbeing and dietary habits as well as genetic background, including family comparisons; it then links this information to the stool samples characterised.

Although the importance of this project is acknowledged, it has proved a challenge to raise funding sufficient to match the project's ambitions. The total running cost is estimated at between EUR 1.5 million and EUR 2 million, and the funding must continue over the long term. In addition, international collaboration is needed to improve the statistical relevance of the studies' results. In time it was recognised that access to and collaboration with multinational cohorts is not easy, very often for reasons of privacy.

Canada

Canada has major programmes that were developed by the government.[17] In 2008, the Canadian Institutes of Health Research (CIHR) provided CAD 500 000 to award projects with a single grant of up to CAD 100 000 for one year. The CIHR Institute of Nutrition, Metabolism and Diabetes committed to funding two additional projects. The total budget was increased in partnership with the CIHR Institute of Circulatory and Respiratory Health (ICRH), the CIHR Institute of Gender and Health (IGH), the Institute of Nutrition, Metabolism and Diabetes (INMD), and the CIHR Ethics Office. In total, twelve projects were awarded. This allowed individual researchers working in the area of the human microbiome to begin forming teams as an initial step towards finding additional national and international research financing to create better understanding of the human microbiome and its translation.

Furthermore, in July 2009 the CIHR Institute of Infection and Immunity launched the Canadian Microbiome Initiative (CMI). A budget of CAD 13.3 million was provided for the funding of projects covering 2010 to 2012.

France

MetaGenoPolis (MGP) is a public-private demonstration project funded by INRA – the country's National Institute for Agricultural Research – and the French Initiative for Future Investments. Due to run from 2013 to 2017, it has received a budget of EUR 19 million to develop microbiome-based therapeutic products.[18] This recognised centre of excellence housed at the University of Lyon focuses on translational research within the human intestinal metagenomics research and development space, bringing together medical, academic and industrial communities. Their know-how and expertise is gathered into four scientific platforms (bio banking, high-throughput sequencing, functional metagenomics and big data storage and analysis), and is complemented by an ethical centre. The aim of MGP is to ascertain impacts on health and disease through focusing on the human gut microbiota, using quantitative and

functional metagenomics technologies. With a team of 80 people, the centre is running 75 projects and has 30 contracts with industry.

Ireland

The APC (Alimentary Pharmacobiotic Centre) Microbiome Institute is the Irish research institute for diet, medicine and the microbiome.[19] The APC Microbiome Institute was established in 2003 as a partnership between University College Cork and Teagasc, which is the country's Agriculture and Food Development Authority, and is hosted by the University of Cork. It is set up as a public-private partnership among industry, academia and other public partners. The institute is governing a EUR 70 million budget for 2013-19 from the Science Foundation Ireland and industry funding.[20] The work of the institute is focusing on microbiome research and development for new therapies for chronic debilitating gastrointestinal disorders. The country turned its attention to the gut microbiome early on. In 2008-13 the Irish Government supported ELDERMET, a Metagenomics of the Elderly programme. ELDERMET is a unique metagenomics project aiming to understand the relationship between diet, gut flora and health in those over 65 years old. The thinking is that through controlling the gut flora by diet, health and wellbeing may improve.

United Kingdom

Due to open in 2018, the Quadram Institute (QI) will integrate research teams from Institute of Food Research (IFR); the University of East Anglia (UEA)'s Faculty of Science; Norwich Medical School; and the Norfolk and Norwich University Hospitals (NNUH) National Health Service (NHS) Foundation Trust gastrointestinal endoscopy facility. There is a strong microbiome focus in the institute's science vision going forward. The initial multimillion-pound investment for the Quadram Institute is being provided by the Biotechnology and Biological Sciences Research Council (BBSRC) together with IFR, NNUH and UEA.

United States

US scientists recently called for a harmonised effort to address microbiomes or microbial ecosystems in general and, more particularly, to push the transition from description to causality and engineering (Alivisatos et al., 2015). Such a Unified Microbial Initiative would be an interdisciplinary effort to develop and advance tools that will lead to better understanding of how the microbial organisms interact with each other and with their hosts. In response to this call, the US Government announced on 13 May 2016 the National Microbiome Initiative (NMI).

The first phase of the initiative involved consultation with different federal agencies, scientists, technology creators, engineers and the public. The participants concluded that there are crosscutting themes and common questions to be answered in relation to all microbiomes. Better understanding in one type of microbiome can help predict how others are working.

The NMI has three goals. The first is to support interdisciplinary research that will enable collaboration across different microbiomes, to answer fundamental questions about microbiomes in diverse ecosystems. This is important, as some systems are easier to manipulate and study for genetic analysis than human microbiomes. Insight establishing the main principles according to which microbial ecosystems interact and function can then be tested in other microbiomes, including the human microbiome.

The second goal of NMI is to develop technology platforms that enable manipulation and analysis at the physical and (bio) chemical levels, and that will involve nanotechnology and microchemistry. These technologies would help to build an understanding of the spatial distribution of the microorganisms, which in turn will reveal their architecture and how chemical communication is achieved. Computational tools

will benefit modelling and mathematical testing, and platform technologies aid the development of applications to manipulate microbiomes in a controlled and predictable way, so as to produce reliable changes.

The third major goal is to train a new workforce that has the requisite cross-disciplinary skills – biological, technological and computational. Indeed, further development in this field will require the combined expertise of microbiologists, bioinformatics specialists, engineers, health professionals, molecular biologists and those in the different omics technologies. Citizen science and dedicated educational programmes will contribute to achieving these goals.

The relevant Federal agencies are estimated to together invest about USD 120 million in this initiative. In addition, stakeholders and institutions in all sectors – including private foundations, companies and academic institutions – have announced new commitments for microbiome R&D of over USD 400 million, in cash and in-kind contributions. This includes a contribution of USD 100 million from the Bill & Melinda Gates Foundation, over four years, to study the effect of the microbiome on malnutrition and ways to manipulate soil microbiomes for crop protection to improve agricultural yields in sub-Saharan Africa. The NMI is envisioned to run over the next five years.

INDUSTRY AND THE MICROBIOME

A wide range of products

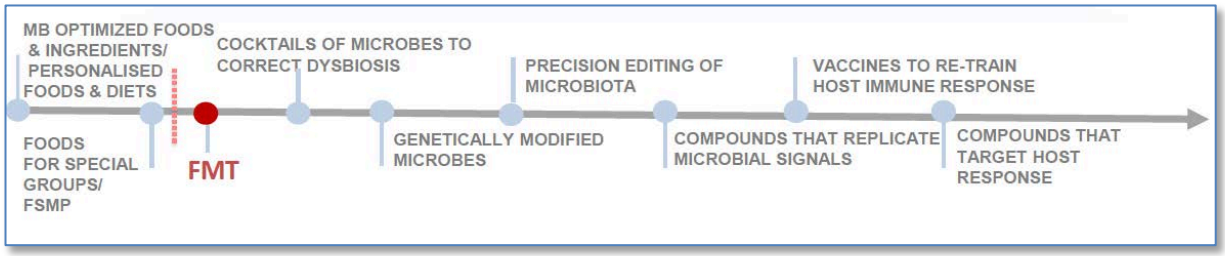
Given the wide range of conditions and diseases affected by the functioning of the gut microbiome, the industry is cognisant of the huge potential to be unleashed with fresh understanding of microbiomes and how they function. Interest ranges from food ingredient producers, consumer goods companies, pharmaceutical industry and medical device companies to biotech and technology service providers.

Consumer healthcare offers promising growth opportunities for which pharmaceutical companies are starting to compete with consumer good companies for market share. The importance of food for health was already underlined in ancient Greece, Hippocrates: "Let food be thy medicine and medicine be thy food." And in many other traditional cultures, the food is seen as a key to better health and a trusted approach against certain conditions.

Since the microbiome can play a critical role determining health, disease and wellness, a whole new spectrum of health-enhancing foods and transformative treatments are on the horizon.

At the Brussels Workshop, Dr. Colette Shortt described how new knowledge of the microbiome promised to help optimise novel foods and ingredients, including cocktails of microbes, fibres and prebiotics; food and food supplements with authorised health claims, medical foods, personalised food and diet solutions, medicines targeting the microbiome directly, vaccines to re-establish the host-immune response, and replacement of the microbiome by faecal transplantation (Figure 1).

Figure 1 A spectrum of new health-enhancing foods and transformative treatments



Notes: FSMP = Food for special medical purposes; FMT = Faecal microbiota transplantation.

Source: Shortt (Johnson & Johnson), 2016.

Industry sectors involved in developing applications based on new insights from microbiome research range from agro-food sector, biotechnology companies and diagnostics companies to pharmaceuticals, cosmetics and animal nutrition and health. Technology developers are also involved, and interest may extend even to app developers for personal health monitoring to keep track of personal diet for a better gut microbiome.

In the field of microbiome therapeutics, companies are developing an entire range of products – from undefined consortia for faecal microbiota transplantation to better characterised consortia. Some approaches try to identify minimal functional mixtures of bacteria cultures to be used for faecal transfer. Gut bacteria are also a source of new enzymes and chemical compounds, or they can be used as a vehicle

to produce compounds or drugs in the gut by synthetic biology. Companies have been focusing on each of these developments.

Although care must be taken not to enter into unrealistic hype, the potential of microbiome-based applications for the industry is estimated to be very high. Investors valuated the first microbiome company that went public in June 2015 to be worth USD 1.9 billion, even before it had a real product on the market. Venture funds provided over USD 130 million, half of which came from Nestlé.[21] The company works on the development of a pill containing a mixture of identified bacterial strains to treat *Clostridium difficile* infections, to replace FMT.[22] Two of its drugs are currently being tested in clinical trials in the United States.[23]

Market estimations and prognoses for microbiome-based applications are in general very positive, although the numbers show significant variation. This variation may be explained by the fact that it is not always very clear what is included in the analysis, as different terms are used for which there is no general global agreement of definitions. According to the World Health Organization (WHO), probiotics are defined as "live organisms which, when administered in adequate amounts, confer a health benefit on the host" (Schlundt, 2001). However, no legal definition of probiotics exists in the United States or in other countries, which allows the marketing of products labelled as "probiotics" that do not meet the fundamental criteria stipulated in the scientific definition (Sanders, 2008). According to the European Union (EU) regulations, following advice of the European Food Safety Authority (EFSA), health benefits need to be specific, measurable and beneficial. Most health claims attributed to probiotics are not approved, as scientific evidence fails on one of these criteria.

Terms like nutraceuticals, pharma biotics and functional foods are not taken up in the EU regulation, while in some other regulatory bodies they are. In addition, different organisations that represent the industry are using those terms. A more detailed discussion is found below.

Market size

A market analysis published in January 2016 projected that the global human microbiome market would be worth USD 294 million by 2019, and reach USD 658 million by 2023, corresponding to a compound annual growth rate (CAGR) of 22.3%.[24] In this analysis the human microbiome market is segmented on the basis of applications, which include therapeutics and diagnostics, diseases, products – including probiotics, prebiotics, foods, medical foods, supplements, devices and drugs – and geography.

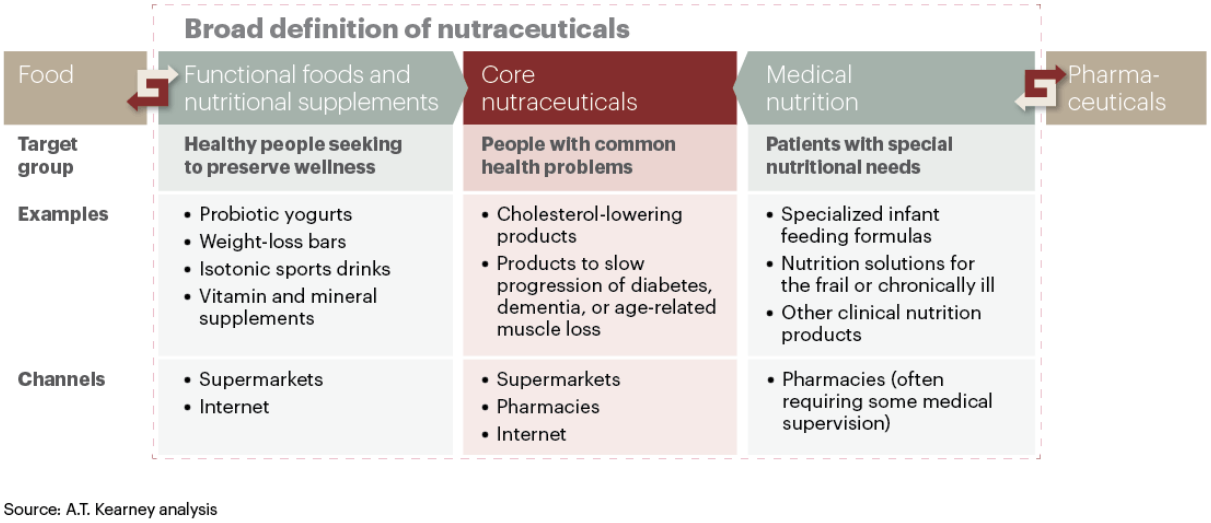
There is also a segmentation of the market on the basis of research spending, including products -- such as instruments and consumables – and technology. Technologies include cell culturing, high-throughput screening, omics and computational tools. The estimates are based on analysis of the current key players in the human microbiome markets, which are Enterome Bioscience (France), Yakult Honsha Co., Ltd (Japan), and in the United States, E.I. Du Pont de Nemours and Company, Metabiomics Corporation, ViThera Pharmaceuticals, Second Genome, Inc. Vedanta BioSciences, Inc., Osel, Inc. and Merck & Co., Inc. It is expected that therapeutics will account for the largest market share in the human microbiome market by 2019. This market is driven by factors such as increasing incidence of lifestyle diseases, ageing of the population, and technological developments. The probiotics market is expected to account for the largest market share among the products.

Market share on the basis of diseases is expected to be most significant from addressing acute diarrhoea and obesity.

According to an analysis of AT Kearney, the so-called nutraceuticals market is increasing in size and importance (Figure 2).[25] Nutraceuticals occupy a position between food and medical nutrition. In this

analysis, annual sales were approximately USD 150 billion, corresponding to about one-fifth the size of global pharmaceutical industry turnover, when narrowly defining nutraceuticals – i.e. not including infant nutrition, food intolerance products, diabetes control, medical nutrition or weight management solutions. When including the latter, the market size was estimated to rise to USD 420 billion with a projected growth rate of 7% over the next couple of years (Figure 3).

Figure 2 Nutraceuticals play in the continuum between food and pharmaceuticals

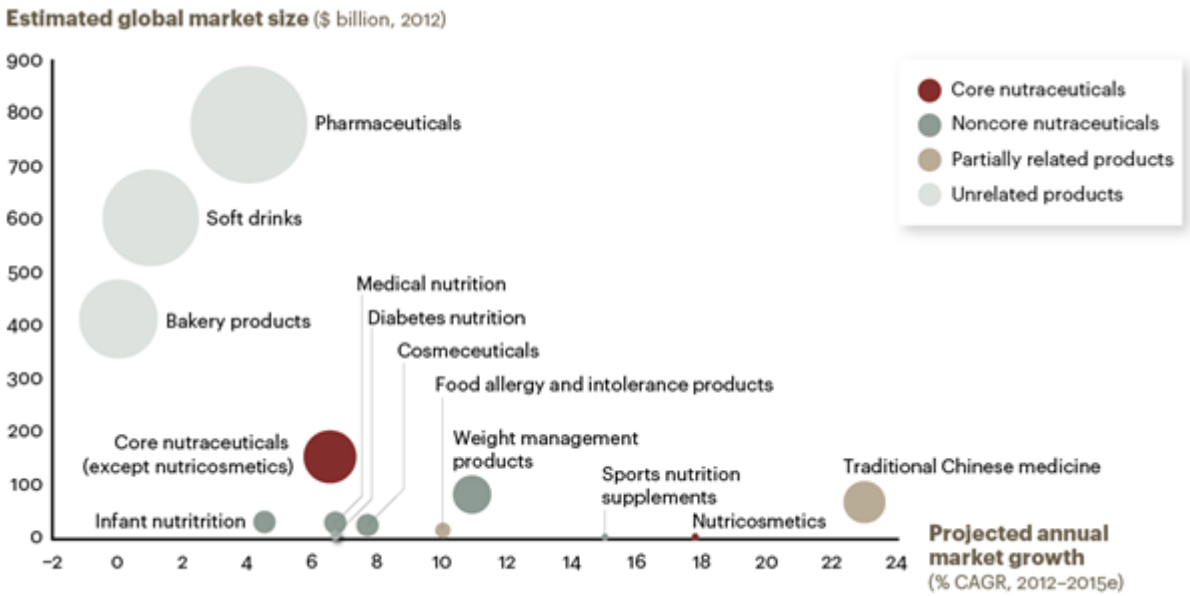


Source: A.T. Kearney, 2014.

It was reasoned that the growth rate could even be much stronger if a solid regulatory framework is in place so as to guarantee medical credibility. Medical credibility is the crucial factor to increase acceptance by consumers and health professionals.

It is likely that food and pharmaceutical companies will start collaborating more closely in the future.

Figure 3 Nutraceutical market size and projected growth



Note: Data are from Frost & Sullivan, World Health Organization, Kalorama Information, Infiniti Research, Transparency Market Research, Bourne Partners, Global Industry Analysts, Government of Canada, MarketsandMarkets, BCC Research, GBI Research.

Source: A.T. Kearney, 2014.

The food industry

An important segment of the food industry focuses on development and production of healthy nutrition. Large budgets are invested in the research departments of these companies, and they become key players in international research consortia that target the gut microbiome for innovative health solutions.

Some of the food companies concentrate on niche markets for the development of food products with specific health claims, some targeting the gut microbiome in particular. Food companies will logically be most interested in developing markets for pre- and probiotics.

One of the pioneers was Nestlé, which in 2011 set up the Nestlé Institute of Health Sciences on the campus of the Swiss Federal Institute for Technology in Lausanne. The institute carries out fundamental research for the understanding of health and disease and for developing science-based nutritional solutions for the maintenance of health. The Nestlé Institute of Health Sciences hosts 160 scientists and collaborators from around the world. One of the research lines focuses on better understanding of the human gut microbiome.

Danone also is investing significantly in research to develop specialised food products for special target groups, such as babies and the elderly. In 2013, Nutricia Research Utrecht (Netherlands) in the Utrecht Science Park was inaugurated, and is meant to be the main development hub of the group in this field; it currently employs 400 people.[26]

At the Brussels Workshop, Dr. Douwina Bosscher presented Cargill's interest in the development of innovative healthy food products for a healthy microbiome. Given that it figures among the top three consumer concerns, the company seeks new opportunities to develop innovative products contributing to digestive health from its existing portfolio on the use of grain products and derivatives. Cargill's fibre roadmap covers whole grains to bran, milled to different sizes that bring different properties, and further to enzymatic-treated fractions for improved accessibility of oligosaccharides for better digestion. While different fractions have different effects on the relative abundance of certain gut bacteria, such changes are mostly not permanent and disappear after a certain period. Research is ongoing to determine how a healthy microbiome can be maintained.

Knowledge is required about the food fibre structure, the polymers and monomers, including structural and physicochemical aspects and ingredient properties that promote gut health and nutrient availability. This would help develop computer simulation models to understand the mechanistic interactions of these structures with the microbiota and host; which can then be tested in vitro prior to testing the effect of nutritional interventions tested in animals and human.

Something companies need to consider when developing new products is consumer acceptance and willingness to pay for the additional benefits of the new products, as the costs of the requisite research will be reflected in the products. Indeed, the different fibre fractions are a source for different components with different properties, but every extra step in production brings an extra cost and thus creates an increased risk for the company.

Moreover, scientific evidence of health benefits is essential to build consumer trust, but this further contributes to product development costs. Computer simulations may help control high resource needs of clinical trials. Computer simulation models should not, however, supplant rigorous randomised controlled trials that are the basis of approved health claims. The research to support health claims may be funded in part by industry as they reap the benefits of marketing advantages resulting from using health claims. However, the role of the funder and scientists in these relations must be fully transparent.

Also to consider in terms of wellbeing, factors such food texture and flavour are important to consumers for pleasure and appetite satisfaction.

Cargill is building its portfolio on corporate-funded, (mainly) applied research and on partnering into multidisciplinary research consortia focused on both applied and basic research, such as participation into FP7 projects MetaCardis and MyNewGut. Given that the scientific challenges are enormous, collaborations are also of vital importance for industry, although mainly in precompetitive projects or in complementary fields.

Technology providers

A number of validated testing systems are in fact already being used. A dynamic simulation model of the gastrointestinal tract, called the Simulator of the Human Intestinal Microbial Ecosystem – SHIME® – was developed at Ghent University (Belgium), and was the basis of PRODIGEST, a spinoff company launched in 2008.[27] SHIME provides a unique, scientifically validated and internationally accepted dynamic model of the complete gastrointestinal tract to study physicochemical, enzymatic and microbial parameters in a controlled in vitro setting. The model can be used to study the metabolic fate of food and microbial and pharmaceuticals compounds over a period of several weeks.

Easy sampling allows generation of detailed mechanistic information on the intestinal fate of compounds, such as factors affecting the bioavailability of active compounds (e.g. formulation or matrix

effects), metabolic/fermentative processes that affect the structure or nature of active compounds, and local activity profiles in the gastrointestinal tract.

The specific setup of the SHIME allows long-term experiments to be performed (up to several months) with a stable, in vitro-adapted microbial community and using physiologically relevant product doses.

The possibility of sampling large volumes from each colon area allows parallel analyses to be performed without impacting the resident microbial community.

Intestinal bacteria are largely present in the intestinal lumen, yet only a fraction of the micro-organisms in the gastrointestinal tract selectively adhere to the mucus layer that covers the gut wall. To evaluate this fraction of bacteria, which are supposed to play a key role in human health as they live in very close contact with the host, ProDigest developed M-SHIME® (Mucus-SHIME) a model in which a mucosal compartment is integrated into the colonic regions of the SHIME®, allowing the microbiota to adhere to the gut mucus layer under representative conditions.

These adhering bacteria play an important role as a "barrier" against pathogens, by instructing mucosal immune responses and occupying a niche at the expense of potentially harmful colonizers. The evaluation of changes in bacterial adhesion due to, for instance, a prebiotic treatment or the specific adhesion capacity of probiotic strains is therefore a crucial step in studying host-microbiota interactions and resulting health effects.

These models allow the testing of new cocktails of microbiota mixed with prebiotics. These cocktails are often referred to as next generation probiotics. Such cocktails are being designed to increase healthy ageing in general. Cocktails of micro-organisms, mostly bacteria, are also being tested for health benefits in combinations with conditions that mimic various chronic conditions such as metabolic syndrome (Cani and Van Hul, 2015).

The pharmaceutical industry

The fact that the human microbiome strongly influences our health is paving the way to a new type of medicine. Indeed, addressing a disease through interfering with the microbiome is a previously unexpected approach, one that goes beyond the idea of healthy food as a preventive measure ensuring for healthy life. The impact of the human microbiome and the gut microbiome in particular on human health is so unexpected, large and complex that a new approach of diagnoses and treatments needs to be envisioned. These new developments have not been ignored by pharmaceutical companies.

Janssen Research and Development, LCC – one of the Janssen Pharmaceutical Companies of Johnson and Johnson – launched the Janssen Human Microbiome Institute (JHMI) at the beginning of 2015.[28] Janssen Pharmaceutical Companies have been experimenting with open innovation for several years, and now the JHMI will operate by fostering external collaborations through anchor research centres in the United States (Cambridge, MA) and Europe (Beerse, Belgium). Key to the new institute's strategy is to create an international network involving people at the Johnson & Johnson Innovation centres and at the different Janssen R&D sites both in Europe and throughout the United States, and to engage the external community from both academic centres and biotechnology companies.[29]

Illustrative of the interest of Johnson & Johnson in the human microbiome as a potential area for transformative innovation is its vehicle JLINX that was designed to support start-up companies focused on this area. Launched in March 2016 by Johnson & Johnson Innovation, JLINX will provide access to infrastructure, venture capital and investment, and expertise to accelerate innovation and build businesses.

Similar open innovation platforms and research partnerships are being set up by other pharmaceutical companies, such as GlaxoSmithKline PLC,[30] Pfizer Inc.[31] and Dupont.[32] In addition to the large players in the market, several start-up companies are trying to bring innovative applications (therapeutics and diagnostics) to the market. Insight Pharma Reports wrote about a market survey in July and August 2014;[33] twenty-three microbiome companies were identified along with twelve microbiome-related deals, five of which involve the participation of big pharma. The Janssen Biotech unit reported to be active in three of these deals. The report acknowledged that it is still early days for commercial activities, but two-thirds of the 63 respondents agreed that this field will become more important in the future, and that investments in translational efforts are justified. The expectation was reported that the microbiome work would provide major contributions to healthcare. Two-thirds of the respondents believe that big pharma will be very actively involved in further developments the field over the next decade.

The follow-up of the report, published in January 2016, identified 28 microbiome companies, mostly active in developing therapeutics. The number of microbiome-related deals increased to 15, and include 4 partnerships between small companies and big pharma The online survey was expanded to 119 individuals, less than half of whom worked in industry and more than half in academia. Nearly half of the respondents expect that new personalised bio therapeutics will become very important in the future. Two-thirds expect that in the next two years industry efforts in the field will increase.

HURDLES TO INNOVATION

Although achieving better food and health motivates large national investments in microbiome science, innovation linked to microbiome potential faces hurdles. These challenges are at the level of basic understanding, translational insight and computational analysis and interpretation, but also concern product characterisation and manufacturing. So far, this report has indicated where science and science policy might best be directed if translation and innovation is a central goal. In light of the previous discussion of industrial applications and needs, a set of other challenges must be met should the microbiome have a major positive impact on the food and health system as a whole.

Improving translational science

From description to prediction

The science of gut microbiota must move from description and association to causality in health outcomes. At the Brussels meeting, Dr. Colette Shortt, Director of Global Regulatory Affairs at the Consumer Global Franchise Organisation at Johnson & Johnson stressed the need to develop better understanding of the functioning of microbial ecosystems and how these determine health or disease. This will lead to the understanding of how the gut microbiome functions as a virtual organ that has an essential role in general health to open the way to the development of novel therapeutics.

Research should focus on achieving an understanding of the interactions within the microbial ecosystem and with the host; how these ecosystems reach an equilibrium; what determines resilience and robustness; and how response occurs after the ecosystem was disturbed: what determines whether the ecosystem returns to its original state or to another equilibrium? How microbiomal ecosystems reach equilibrium after being disturbed, whether as a return to the original composition or transformation to a new stable composition, is not understood (Box 1).

Box 1. One equilibrium is not the other

Known examples of disturbances of microbiomes indicate that the return to equilibrium poses very difficult questions. One example is the effect of the oil spill of the Deepwater Horizon disaster, after which the ocean microbiome was very severely disturbed (Hazen et al., 2010; Redmond and Valentine, 2012; Yang et al., 2016). The ocean microbiome has been restored in the meantime, but it is different from before. It is difficult to know which of the microbial ecosystems is or was the better one, now or before the oil spill; first it must be determined what a “healthy” microbiome is. In contrast to that example, some microbial ecosystems are resilient to major disturbances and simply return to the original state. A well-described example comes from the Wisconsin lakes that are regularly mixed by pumping water from one basin to the other, thereby extensively mixing the microbial population in the different water layers. After about ten days the microbial ecosystems go back to the original composition (Shade et al., 2012). The factors that determine resilience or reaching a new equilibrium require further research to become understood.

Source: Handelsman, 2016.

Moving towards these goals, an important challenge is to characterise the gut metabolome, i.e. the collection of metabolites generated by the gut microbial flora that interact within the gut microbiome and with the host. Understanding the role of the gut metabolome will generate understanding of how it functions. So far however, only 2% of the metabolites produced by a typical microbial community corresponds to known structures – and of these, only a small fraction is on known biochemical pathways.

Markers and models

Dr. Shortt emphasised the need for validated predictive biomarkers and preclinical models to successfully translate new insights into applications targeting the microbiome. This field will only develop with:

- standardised methodologies for sample collection and processing techniques
- improvement of shotgun metagenomics sequencing to enhance characterisation of samples with low abundance of microbial DNA/RNA
- the development of models for analysis of large, complex data sets.

Microbiome markers will allow the identification of intermediate endpoints, a major step towards the development of personalised dietary patterns and novel food products for therapeutic and preventative applications to address the current epidemic of non-communicable chronic diseases.

Further, better understanding of how microbial ecosystems work is expected to lead to the development of simple model communities that will reveal how these ecosystems respond to inputs and changes. That will generate better insights on how the gut microbiome functions at molecular level, and how we can interfere with the microbiome for therapeutic or preventative applications (Ji and Nielsen, 2015). The ultimate goal is to re-programme or re-engineer the microbial communities so that their functioning can be optimised or designed for special purposes.

Standardisation

Comparability of data and studies across each of the many large projects addressing human metagenome research will speed discoveries. This signals the need to achieve a higher level of standardisation, from data formatting to clinical research protocols. A basis for standard operating procedures (SOPs) for the different steps in the development of novel applications based on the functional understanding of the gut microbiomes has been developed by the International Human Microbiome Standards (IHMS) project, which was funded by the EC FP7 programme.[34] IHMS focused on all key aspects from human sample identification, collection and processing to DNA sequence generation and analysis. A final set of 14 SOPs, covering all stages of the process, has been produced by 8 partners of IHMS and 15 contributors across 12 different countries.

Although the use of standard procedure is recognised by all stakeholders active in this field, Brussels Workshop participants also advocated a certain degree of flexibility to improve existing procedures or develop innovative approaches. Standardisation should never form a barrier. The two projects with perhaps the most potential to influence the field, the Human Microbiome Project and the EC IHMS appear to have developed protocols independently. Harmonising these protocols should be considered.

The use of Faecal Microbiota Transplantation (FMT) for therapeutic use – which has been debated for some time and remains controversial – illustrates the critical need for standard protocols in the clinical context. Faecal transplantation has been successfully used as a treatment against *Clostridium difficile* infection (van Nood et al., 2013). Clinical trials to evaluate FMT were stopped prematurely: the treatment was so much more successful than the conventional treatment with antibiotics for the control group that it was considered unethical to continue the control group's treatment.[35] Faecal transplantation has also been reported to be effective against other than intestinal disorders, including metabolic diseases, neuropsychiatric disorders such as Parkinson's disease, multiple sclerosis, myoclonus dystonia, autoimmune diseases, allergic disorders and tumours (Xu et al., 2015).

However, what is not well understood is how faecal transplantation works exactly; what the active species are; how the transplant samples need to be characterised; and how a new stable microbiome can be installed (Smith, Kelly and Alm, 2014). There have been cases, although these are rare, where adverse reactions are seen. Long-term studies are needed to understand which factors determine success and the safety of the treatment.

Again, it is clear that the first requirement is to determine what a healthy intestinal microbial population is, and how it fits best with the recipient host. Work is ongoing to determine what the effective minimal composition is and how samples for FMT can be standardised. Because the mechanistic understanding of what determines successful FMT and standardisation is lacking, it is unclear how FMT should be regulated. In the United States it has been discussed whether stool transplantation has to be regulated as an investigational new drug[36] or as a tissue. At this moment faecal transplantation to treat recurrent *C. difficile* infections can be performed without prior screening of the donor or the faecal sample, while to treat other conditions stool transplantation falls under the regulation of investigational new drugs.

Data sharing challenges

The need for large data and access to it is underlined both by academia and by industry. There is general agreement that access to databases and data deposition in public databases should be promoted. It is clear that this field will benefit from data sharing and for that, standardisation of sample handling and data collection, of storage and of usage is essential. Several of the data infrastructural projects mentioned above make information accessible, but there is a need to connect databases and information sources further. Databases should be accessible across different microbiomes and across different countries and continents.

Often, discussions on data sharing turn to ownership of the data. Some of those participating, mainly from industry, can thus be hesitant to deposit large data sets in public repositories, fearing that this may limit opportunities for product development. Nevertheless, there was consensus among workshop participants that public or private research funds should be spent so that complementary information is generated rather than duplicative datasets**.**

During the OECD Workshop an important observation was made by Jeroen Raes. He approached the big data issues from a somewhat different perspective: “There are – at least on the academic side – no problems concerning data storage and data dissemination. The raw data obtained by European and US academic researchers are accessible and there is sufficient computational infrastructure and power to deal with big data. The main problems are caused by the ethical regulations and lack of financing. It is very difficult to share clinical data across the Atlantic.” This assessment, however, should be taken the context of other work suggesting that data sharing is a problem in academia as well.

In Brussels, a multitude of national microbiome projects raised issues regarding ownership of the data, and procedures for collecting and storing data. International consortia could and should target these difficulties. Such an international approach would also overcome the barrier of scale to reach sufficient critical mass, linked to the fact that different disciplines should be brought together and cross-disciplinary skilled experts need to be trained.

Skills and education

There is broad agreement that moving from mere cataloguing to physical processes and novel applications will require work across a range of disciplines. Microbiologists will have to work with engineers, those in bio-informatics and physicians, as well as experts in all types of omics technologies. This field is increasingly complex and combines expertise in “classical” microbiology with expertise in

many other fields. There is a need for new technology development, engineering, computer modelling and bioinformatics. The future workforce and scientists should be trained to combine these skills so that the field can grow and mature.

In a workshop organised in Brussels on 22 February 2016 by the European Commission, creativity was also mentioned as a major skill requirement to advance this field In addition to technological expertise. Accurate research questions need to be asked that can be solved with the knowledge and technologies available to create better understanding of how microbiomes function.

An interesting example of broadening the public interest and workforce was outlined by Jo Handelsman. Several projects in the United States are running in which undergraduate students are involved in analysing their own microbiota while keeping track of their diet.[37][38] This has created more interest than any other educational programme in the field could have achieved. It enlarges the potential workforce and encourages undergraduates to engage in science. This approach too is part of the NMI described above.

Crowdsourcing and citizen science

Public engagement in research projects is strongly indicative of the huge public interest in developments in this field. The American Gut is one of the largest crowd source citizen science projects in the country.[39] Since October 2015, the initiative has raised over USD 1 million from over 6 500 participants. The project allows the building of large public data sets and informs participants about their own body's microbes. It also collects data on diet and alcohol consumption or on health conditions such as autism or intestinal problems of the participants, in order to match such information with the microbial ecosystems in individuals. All information is anonymised and made freely available for research all over the world. The project has expanded to Europe through the British Gut project,[40] and is calling for similar projects to be started in other countries, in order to develop comparative data.

Although there is consensus on the added value of public engagement, during the OECD Workshop it was observed that care must be taken, because self-declaration of participants is not always reliable. In addition, samples collection, storage and handling are very important for extracting correct information; this is not easy to control with voluntary participants. The availability of a stringent logistical system is essential to reduce loss of efforts.

Funding issues: Public funding and return on investment

Industry, as well as academic partners, is calling for public-private partnerships to stimulate the translation of scientific knowledge into new products and treatments.[41] Several such partnerships in this field have already been set up.[42] More funding than currently allocated is required to support the high costs of metagenomics and other omics technologies. Costs are often too high to build larger cohorts. The use of smaller cohorts leads to limited validity of the results and a larger loss of budget in the end, as analyses need to be reproduced according to statistically relevant orders of magnitude.

Given the budgetary constraints of public bodies, the system seems to have reached its limits. One of the issues that may be discussed is whether it is possible to develop models out of the box to support public-private research projects. Possibilities for creating business models in which public-sponsored research creates a return on investment should be analysed. Such mechanisms may be at the expense of the profit margins of large industries, but would support further research in large global consortia. Such mechanisms may hold implications for intellectual property, and may need to bring food and pharmaceutical companies on board to join forces.

For companies to develop a new portfolio, next to costs considerations there are concerns about intellectual property rights. Industry representatives believe that the existing intellectual property regime for data is of too short a duration to adequately incentivise private research and development. Analysis is needed to determine whether level of protection is above or below optimal, given the massive amount of data needed, its complexity, and the cost related to the research. On top of that, the fact that a great deal of data is created in large consortia, stored in shared databases, and funded from public and private sources in some cases raises issues of data ownership.

The regulatory framework

Pivotal to delivering innovative applications targeting the gut microbiome is the regulatory framework, which needs to follow recent developments to facilitate market creation and uptake for and by society. Indeed, it is a consumer's imperative that if new products – whether they be new foods or new medicines – are efficacious, innovative and safe, they should get to the market as fast as possible. The regulatory framework should guarantee that health claims are evidence based, relying on a solid science base to protect the consumer against false expectations generated by products that have not been thoroughly tested. A solid regulatory framework will also create an enabling environment for public and private R&D investments to support better public health and economic outcomes. A number of challenges are presented in this context.

More harmonisation

The fact that regulations differ among countries and continents constitutes a significant complication. A good overview of the different regulations in the United States, the European Union, Canada, Japan, Australia, Russia, India, China, Korea, Malaysia, Africa and countries in the Pacific Rim is given in *Nutraceutical and Functional Food Regulations in the United States and Around the World, Second Edition* (Bagchi, 2014). Another resources is the nutrition, health and disease edition of Regulatory Focus (August 2016) discerning 'New Food Regulatory Paradigms: The Right Paths for Nutrition, Health and Disease Management' (Hall, 2016), covering as well 'Medical Food/Food for Special Medical Purposes (FSMP): Global Regulatory Challenges and Opportunities.' (Ruthsatz and Morck, 2016) to improve the role of nutrition in support of optimal care for patients and presenting the international regulatory framework.

Although the European Union and the United States, while different, serve as benchmark models, companies putting products on the market act with a global perspective. That brings its own challenges and hurdles because of the differences around the globe in the regulatory and policy frameworks.

To ensure the building of innovative solutions based on understanding of the interactions of gut microbiome and food for better health, it will be useful to harmonise the terminology used and to agree on how health claims should be analysed. The fact that different jurisdictions are using different terminologies and regulation creates confusion among consumers. For example, according to the European regulation, "probiotics" refers to a health claim and hence it cannot be used without prior approval. On the other hand, "probiotics" is defined by the FAO and WHO as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (2001) (Schlundt, 2001).

Different regulations also use different terms referring to food, food additives and ingredients, food with associated health claims, food for dietary management and food for special medical purposes. Terminologies such as nutraceutical or functional food are not well defined and not used in the regulatory reference documents. Rather, they remain popular terms in laymen publications.

To stimulate international discussion and harmonisation at the global level when it comes to standards, procedures, policies and regulations, the OECD can offer a forum and use its convening power to advance the discussion. To address shortcomings in the regulatory frameworks, a dialogue among the regulators is greatly needed. Therefore, the gathering in the Brussels Workshop was highly appreciated, and participants called for more such opportunities bringing scientist from academia and industry together with regulators and policy makers.

Regulating health claims on foods: the case of Europe

With respect to health claims for new food products or new dietary approaches for therapeutic uses, there is a strong need for validated biomarkers to test and support the claims with respect to safety and efficacy. The current frameworks need to be challenged to install workable and transparent evaluation procedures and ensure that health claims are not misleading.

The European Union is one of the most extensively regulated areas in this matter. Health claims for food, including food supplements, are covered by the Nutrition and Health Claim Regulation (NHCR) (Regulation EC No. 1924/2006).[43] Despite intensive research efforts, health claims that modulate the gut microbiome so far have had very little success in obtaining approval in Europe. The only product on the market today is yoghurt or fermented milk that improves lactose digestion in individuals who have difficulties digesting lactose. In order to bear the claim, yoghurt or fermented milk should contain a defined minimum concentration of live starter microorganisms (*Lactobacillus delbrueckii bulgaricus* and *Streptococcus thermophilus*).

During the Brussels workshop, Dr. Yolanda Sanz from the Spanish Council for Scientific Research (IATA-CSIC) gave an overview of the recent work by the Panel on Dietetic Products, Nutrition and Allergies (NDA) from the European Food Safety Authority (EFSA), of which she is a member. Nutrition and health claims for food products are only allowed when listed on a so-called positive list. The European Commission bases its approvals on EFSA positive opinions as conclusions from scientifically substantiated dossiers submitted. The scientific assessment follows the highest scientific standards, with the purpose of protecting consumers while ensuring fair competitiveness and innovation. The assessment focuses on three criteria:

- The food or the food constituent, which is the subject of the claim, should be sufficiently characterised.
- The claimed effect should be defined and the health benefit should be demonstrated.
- The cause/effect relationship between the intake of the food and the claimed effect should be proved. This claimed effect reaches the consumer through the food label or other communication forms.

The health claims are addressed in three articles of the regulation:

- article 13.1 on health claims based on generally accepted scientific evidence
- article 13.5 on health claims based on newly developed scientific and/or proprietary data
- article 14 on health claims on reduction of disease risk or referring to children’s development and health.

The NDA Panel has evaluated over 570 scientific opinions since the regulation entered into force. Out of 421 applications related to Art. 13.1, only 10% received a favourable outcome. Under the other two articles, 155 applications were submitted; of these only 7 received a favourable outcome. The analysis of the NDA panel revealed that in 80% of the submitted claims the food constituent to which the claims were attributed was insufficiently characterised – the main reason for the unfavourable opinion. In addition, the beneficial effect often is defined as gut health, which is too broad: effects should be specific, measurable and beneficial. In some cases effects were indeed measurable, but a beneficial effect was not demonstrated.

A certain degree of creativity is needed to develop studies in a gradient between health and disease, as food cannot be used to prevent or treat diseases or used as a diagnostic. Some of the studies forming the basis of a health claim for a food product were set up with the primary goal of treating or preventing diseases, but the active factor involved could not be shown. Moreover, according to the EFSA guidelines, health benefit claims should be demonstrated in a healthy population and not be used to treat a patient population. Sometimes this goes against professional guidelines such as from the World Gastroenterology Organisation, which has guidelines for the use of pre- and probiotics for digestive health and treatment of intestinal diseases, published in 2011.[44] The WGO guidelines and claims invoked or embodied in the European EFSA regulations.

The work of the NDA panel helped to improve communication and dialogue with stakeholders. New guidance documents on the regulations were published in January 2016 after several public consultations; these provide examples of favourable opinions that can be used to design studies and reports (EFSA Panel on Dietetic Products, Nutrition and Allergies [NDA], 2016a, b). EFSA principles are updated on:

- general scientific guidance for stakeholders on health claim applications
- guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic micro-organisms.

The guidance updates include the use of new molecular tools according to state of the art technologies (such as multilocus sequence typing, optical mapping and whole genome sequencing). In addition, commensal indigenous human bacteria now can be considered as novel foods, although Regulation EU 2015/2283 on the safety and taxonomy of these organisms equally applies.

Furthermore, the NDA guidance documents provide more clarity on appropriate outcome variables, and explain procedures for the validation of questionnaires. It gives advice on the duration of the interventions and emphasises the importance of bringing biological plausibility mechanisms forward. The updated guidance document advises further on the appropriate study population, the design of the study, and how to deal with risk factors like LDL-cholesterol and blood pressure; also, the presence of toxic pathogens or toxins can now be used as risk factors.

Dr. Sanz also emphasised the stop-clock procedure that is used when the claim file needs to go back to applicants. The main weaknesses relate not to the claimed effect and the target population, nor to the characterisation of the food constituents, but to the design of studies, the statistical analysis and the reporting. Dr. Sanz strongly recommended that applicants designing studies carefully read the previous and updated EFSA guidelines and guidance documents as well as previous scientific opinions. And while these furnish scientific advice, at the same time it should be realised that every claim is unique and the guidance documents cannot take all methods, claimed effects, outcomes, etc. into account. The guidance documents should be interpreted as helping future applicants understand the rationale of the principles applied, rather than be considered a source of magic recipes.

A food-drug continuum

Another of the major challenges is that the difference between food and drug becomes a blur when food is used for therapeutic purposes. According to Dr. Manfred Ruthsatz, Global Head of Regulatory Advocacy at Nestlé Health Science in Switzerland, there is a food-drug continuum that creates grey zones for which existing regulatory frameworks may need to be reconsidered. The regulation is complex and addresses different stakeholders with different targets and constraints.

The fact that food cannot legally claim to treat diseases poses an important obstacle to health claims based on recent insights. Regulatory frameworks ensuring safe and effective food and drugs are based on the traditional pharmaceutical industry model. The traditional nutrition model falls under the food regulation, but it is increasingly clear that nutrition as a preventative approach may be a new way to address non-communicable diseases.

Nutrition can bring affordable, cost-effective healthcare solutions to patients and society, and although the existing regulations are largely sufficient, the grey zones mentioned need to addressed. Food as treatment or a preventive approach currently is not taken into account; the regulation is not adapted for the food-drug continuum where new evidence is fast emerging but where some uncertainty remains related to the quality and amount of evidence that is required. Dr. Manfred Ruthsatz explained that the guiding principle for product regulation should be intended use, be it for the consumer or the patient. In cases of doubt, drug legislation typically should prevail, after case-by-case assessment and under consideration of all product characteristics.

Health claims associated with food are approved only for the intended use of the food ensuring the claim. In this case efficacy needs to be validated and safety risks need to be addressed, even though these components are naturally present in food. In general, it is expected that the dose of active substances should be significantly higher than what is usually consumed as part of daily food, in order to be considered a product with therapeutic effect and not just healthy for the diet.

Recent insights indicate that the microbial composition can be modulated by dietary interventions and can be used in this way for therapeutic purposes. It is generally believed that food products are safer than chemically synthesised drugs, although emerging examples show the opposite: some bacterial (lactic, bifido-, bacillary) dietary supplements naturally contain the genes of antibiotic resistance. While such a resistance can be a desirable trait, as bacterial probiotics help restore gut microflora during the treatment with antibiotics, the transfer of genes of antibiotic resistance to pathogenic bacteria may provide serious clinical threats (Wong et al., 2015; Topcuoglu et al., 2015). The regulatory framework should ensure the safety of food products used for therapeutic interventions, and at that point it may be more appropriate to use the drug regulations.

Additionally, food products are processed in the body by the gut microbiota, and can lead to the delivery of a number of active metabolites that may in turn produce physiological effects on the body, as outlined above. The current status of knowledge does not allow tracing out these complex transformational events, and therefore represents a major burden for clinical and regulatory approval systems in terms of safety.

Health or disease?

Preventing or treatment of disease is considered the legally defined domain of medicines. Typically safer for its usage than medicines, nutrition is considered by healthcare professionals sometimes as the most appropriate and safest ‘therapy’, e.g. in pediatric Crohn’s disease (Ruemmele et al., ECCO/ESPGHAN Consensus Guidelines, 2014). Further examples for nutrition and disease management

include severe cow's milk allergy, or inborn errors of metabolism, e.g. Phenylketonuria (PKU), yet the term prevention or therapy is not permitted.

According to Dr. Ruthsatz, current regulation requires adaptation for disease prevention or diagnostics with regards to food products. The concept of disease prevention should be revisited, as prevention can indeed be beneficial in terms of both health and healthcare costs. In many cases, it is not clear when disease prevention is considered as medicine, and when it is merely part of nutrition or lifestyle. With that same reasoning it is difficult to define where health and homeostasis ends and disease begins, especially with omics technologies leading to new and early diagnosis even before symptoms are visible. How will regulators define these concepts when claims are going to be made for products focusing on early intervention, early diagnosis and prevention? What level of evidence is required to demonstrate effects? What level of acceptable uncertainty as to not mislead the consumer or patient? It should therefore also be questioned whether the different approaches to diagnostics for lifestyle monitoring or health purposes are relevant, as devices promoting a healthy lifestyle will contribute to better health in general.

Food or chemical?

Regulation needs sufficient flexibility, which is lacking at this moment. Some products switch categories from nutrition to drug or chemical, depending on the intended use and dosage. In some cases, different regulations will then apply for the same product. For example, vitamin C is switched from nutrition to drug or chemical, depending on the amounts implicated. Different regulation then applies, although it is chemically the same molecule.

Another example outlined by Dr. Ruthsatz during the workshop was the fact that enteral and parenteral nutrition, while related principles, fall under different regulatory frameworks. Both forms of medical nutrition are used to address malnutrition in vulnerable patients. Enteral nutrition is administered via the gastrointestinal tract, hence considered to be more 'physiological'; parenteral nutrition is administered into the veins. Enteral nutrition is regulated under the general EU food framework (Foods for Special Medical Purposes or FSMP), while parenteral nutrition is part of the pharmaceutical regulatory landscape. In practice, it is crucial to raise awareness, increase the implementation of the guidance given by professional healthcare organisations to their members to use the most appropriate solution for their patients. (For a full discussion see Gill'ard, Green and Smit, 2013).

Developing innovative products and solutions require deciding on the specific regulatory category early on in development. Each regulated product category has specific compliance requirements that change for basically the same product, different rules in terms of analytics, clinical research, production, environment, etc. apply. Switching from food to drug or vice versa has severe implications for production, as category specific stringent requirements of good laboratory and manufacturing practices must apply to ensure quality. Embarking on production of a food under drug Chemistry, Manufacturing, Controls regulation (CMC) is very time-consuming and expensive, and may even require building a new facility to comply with all the production requirements.[45]

The challenges are further illustrated by the fact that a food will be considered a drug according to the US legislation and guidance when clinical disease endpoints are used. However, nutrient cocktails typically will contain 40 active ingredients, making a dose-response analysis for each component, as required for drugs, very difficult. Medical food additionally legally requires demonstrating the distinctive nutrition requirement for a given disease (Giordano et al, 2016), quasi the patho-mechanism of action, while this is not required for drug approval.

In Europe, food supplements and nutrition and health claims legislation cover products intended for normal healthy population, while the European legislation also considers the Regulation on Food for

Specific Groups which includes the Food for Special Medical Purposes (FSMP; Commission directive 1999/21/EC). A revision of this framework took effect in July 2016 and is meant to simplify and improve the application of rules and the protection of consumers.[46] FSMP is only for patients who have specific disease-related nutritional requirements. Any food that claims to have a pharmacological effect is no longer considered a food, but is considered a drug by function; that has significant implications for, among others, development and production costs, as explained earlier. This could deter innovation.

The messages from the workshop indicated that the focus should be on quality and safety, not on categorisation of the health claim. Regulations and policies should be simplified, and – very importantly – post-marketing surveillance, which is common practice in the pharmaceutical industry, could be used to increase the evidence base of certain products.

Time for a dialogue

Although there is a real need to modify the regulatory framework to fit with new challenges and opportunities, this is a long-term process. Food and drug regulatory frameworks need to be better matched to make innovative solutions for dietary disease management possible. One of the first requisites is the harmonisation of the definitions and terminology used in the various regulations, in addition to agreement on how health claims should be analysed. Classifications need to converge and common standards and endpoints have to be introduced as an easier approach to opening up some of the regulatory barriers. Innovation should become a core principle that is fostered in new regulations. Active discussion is currently ongoing in the European Commission on how to achieve this.

In summary, regulations and regulatory processes should be science based, predictable, clear, transparent and efficient; they should include precise timetables, be enforceable, and facilitate the free movement of goods and innovation. To achieve this, concerted action is required among the different stakeholders, from scientists/nutritionists, regulators, policy makers, patients and NGOs to the payers, as reimbursement is indeed a powerful incentive to stimulate innovation in this field. When it comes to preventive approaches, that may not seem evident.

ENDNOTES

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