

ISSUES PAPER ON “**THE MICROBIOME, DIET AND HEALTH: ASSESSING GAPS IN
SCIENCE AND INNOVATION**”

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Introduction

1. Public health is facing major challenges caused by the increasing incidence of complex diseases. The underlying cause of disease, 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 lacking. Often these diseases are linked to changing demographics and modified diet among other factors. While the role of nutrition in health is common knowledge, recent scientific studies are linking food to an array of health conditions in new ways that can begin even before birth and can influence the development of complex pathologies (Gluckman *et al.*, 2008).²
2. Increasing scientific evidence has identified human gut microbiome as a key biological interface between human genetics and environmental conditions influenced by nutrition. Imbalance of the gut microbiome has been associated with increasing risk of a number of diseases and has been suggested to be even a determining factor in neuropsychological pathologies although a causal role is not always clear (Hanage, 2014; Mayer *et al.*, 2014; Sun and Chang, 2014).
3. Better understanding of the complex interplay of diet, nutrition and the microbiome could lead to positive health and economic outcomes through the development of innovative and cost efficient diagnostics, preventative measures, and treatments for complex diseases linked to nutrition and health status. Indeed, at the same time as the microbial ecosystems in the human gut are becoming better understood, increasing efforts are being made to understand the impact of the different food products on the composition and functioning of microbial communities.
4. Better understanding of the microbiome could also stimulate the production and consumption of healthier food. There is a trend towards the production of food products that claim to have a positive effect on human health. The food industry is gearing up towards the development of personalised diets and specific food for specific target groups. These products may operate through influencing the gut microbiome.
5. While the food industry has clearly stated interests in these recent developments, the pharmaceutical industry and several innovative biotechnology companies have also identified the human microbiome as a potential target to address chronic diseases. Although the scientific insights in the field are growing fast, large challenges remain in terms of developing an evidentiary base, standardisation and acceptance of harmonised regulatory frameworks.
6. Before such approaches are adopted in the clinical environment, there is a need to demonstrate the causal role of the microbiome in diseases and methods need to be developed for diagnoses and treatment. Some have argued that health professionals need to be better educated in this new field that implies a paradigm shift in which the human microbiome is a functional part of the human body and has an essential

² www.who.int/dietphysicalactivity/publications/trs916/summary/en/

role for health.³ Furthermore, acceptance by health professionals and consumers relies on a solid regulatory framework, which is unsatisfactory in some cases. Not only do regulations differ across countries, but there is also confusion on the terminologies used.

7. Through a series of panels, this workshop will address gaps and barriers for this field to move forward. The workshop seeks to promote understanding across relevant scientific, regulatory, and commercial communities and contribute to an innovative sector and preventative medicine based on targeting the gut microbiome.

NCDs are the most important cause of death

8. It is now known that the human gut microbiome plays an important role in many if not most non-communicable diseases (NCDs), including in neurological diseases, although the causal relationship and mechanisms causing diseases are still not well understood. (Hanage, 2014; Mayer *et al.*, 2014; Sun and Chang, 2014). Given the burden of these diseases, the potential benefit of developing therapies or preventative approaches based on knowledge of the microbiome is enormous.

9. Public health is facing huge challenges caused by the rise of complex diseases, linked to changing demographics. Non-communicable diseases (NCDs) comprise 63% of the major cause of global deaths.⁴ 25% of people dying from NCDs are younger than 60 years old. The burden of NCDs on health care systems is further illustrated by the fact that NCDs are causing 48% of healthy life years lost, while for other diseases, this is only 40%. According to a study by 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).

10. NCDs are chronic diseases that are treated with lengthy and expensive treatments. There are important economic advantages if NCDs are prevented, not only for the healthcare systems, but also in support of healthy people actively participating in society and economies and thereby reducing poverty in general. According to WHO, reducing the risks on NCDs would reduce CVD and diabetes by 75%, while cancers could be reduced by 40%.⁵

11. The burden of NCDs and the threat they pose on progress towards the Sustainability Development Goals were considered so significant that the United Nations called in 2011 upon the second and most recent UN high level Health meeting on NCDs to take action. NCDs are known to be negatively influenced by bad habits such as lack of physical activity, tobacco and alcohol abuse but also by unhealthy diets. Poverty is also closely linked to NCDs. Not surprisingly, most NCD-related deaths are in low and middle income countries, and while the highest economic burden is in high income countries the costs in middle income countries in particular are likely to grow significantly together with their economies. Malnutrition costs the

³ <http://bioimmersion.com/blog/the-human-microbiome-paradigm-shift/;www.nytimes.com/2013/05/19/magazine/say-hello-to-the-100-trillion-bacteria-that-make-up-your-microbiome.html>

⁴ The major NCDs are cardiovascular diseases, cancers, respiratory diseases and diabetes or metabolic syndrome related to increasing incidence of obesity. Very often also neurological diseases are considered, especially as the burden of ageing related dementia is exponentially increasing. It is indeed expected that due to the increasing average age of the global population and the increase of the population as such, also the burden of NCDs will further increase.

⁵ www.who.int/features/factfiles/noncommunicable_diseases/facts/en/index9.html

global economy USD 3.5 trillion per year according to FAO, of which under-nutrition accounts for about two thirds of the costs and obesity related diseases for the rest. The costs are mainly due to loss of productivity and healthcare expenditures.⁶

The human microbiome

12. The human microbiome can be defined as the combination of all microbial genomes that live in and on the human body in symbiosis or as commensal. The communities of such microbial organisms are jointly called microbiota and consist of bacteria, archaea, fungi, viruses and unicellular organisms. In fact, the microbial population that is hosted by our bodies is ten times larger than the number of body cells in a human. While not all organisms of the microbiota can be isolated and grown individually, they can be characterised through their genome and are hence referred to as the microbiome.

13. New technologies have enabled the characterisation of the complete human microbiome, without the need of isolating, purifying single species organisms and growing them in pure cultures. It is only since the availability of omics technologies that organisms can be characterised as part of the community. Moreover, a combination of omics technologies now make it possible for microbiomes to be characterised not only in a descriptive way based on the identification of their genomes, but also to generate insight on the functioning of the microbiome.

14. Different symbiotic or commensal microbial populations are found in the mouth, on the skin, vaginal or in the gastrointestinal tract, which is the densest one and contains the highest biodiversity. The gut microbial population consists of over 1 000 species, good for about 1.5 kg. More importantly, the gut microbiome adds to our body 21 to 27 times the number of genes.

The gut microbiome: a functional organ, an interface between human genetics and diet

15. As accumulating scientific evidence indicates, the 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 in function of external factors (Evans *et al.*, 2013). But the gut microbiome is not a homogeneous and 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 between those ecosystems is needed.

16. Given that NCDs are globally the largest cause of death and the gut microbiome has recently been shown to be implicated in many NCDs, using new insights addressing the gut microbiome for better health and wellbeing opens high expectation for the development of novel applications or treatments based on microbiome-targeted interventions of which the society in general and healthcare systems in particular could benefit from (Dietert and Dietert, 2015).

⁶ www.fao.org/zhc/detail-events/en/c/238389/

Recent advances: Different enterotypes linked to diet and disease

17. In 2012 the first results from large research efforts that were started early in the millennium were published. It became clear that globally the human gut microbiomes can be classified in distinct so-called enterotypes, comparable to blood types (Arumugam *et al.*, 2011).

18. Three enterotypes have been characterised despite the diversity of the microbial population that inhabits the gut. Each of these enterotypes 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 described earlier (Yong, 2012, Knights *et al.*, 2014). These enterotypes are not linked to ethnic backgrounds, age, weight or gender albeit 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, even neurological diseases, although the causal relationship still needs to be proven (Schreiner *et al.*, 2015). In addition, it was shown that short term dietary changes change the microbial composition, although not the enterotype, which is determined by long term dietary patterns (Wu *et al.*, 2011; David *et al.*, 2014).

19. For a long time it has been known that gut bacterial ecosystems are essential in food digestion for providing enzymes for the production of vitamins and essential amino-acids not produced by normal human cells. Now it was found that, for example, enterotype 1 favours the production of vitamin B7, while enterotype 2 favours the production of vitamin B1.

20. Based on these findings, it is hypothesised that diets may be tailored on an individual basis to meet personal requirements.⁷ For specified target groups, specific diets may work as a preventative medicine approach. In addition, studies are ongoing to define diets to treat certain diseases (Bushman *et al.*, 16 August 2013).⁸

Development of new therapies targeting the gut microbiome

21. New insights generated over the last years on the role and functioning of gut microbiomes create expectations for novel treatments based on microbiome targeted interventions or contributing to preventative medicine, which might help to keep healthcare systems sustainable.

22. That a healthy intestinal microbial population is essential is demonstrated convincingly with fecal transplantation as a treatment for recurrent *Clostridium difficile* infection. This infection causes severe diarrhoea that occurs in patients after antibiotics treatment that also has detrimental effect on the normal gut flora (van Nood *et al.*, 2013). Clinical trials were stopped prematurely because the treatment was so significantly more successful as compared to the patient group treated in a more conventional way with antibiotics that it was considered unethical to continue with the conventionally treated control group.⁹ How fecal transplantation works exactly, and what the active species are or how the transplant samples need to be

⁷ www.nytimes.com/2011/04/21/science/21gut.html?_r=0

⁸ www.nestlenutrition-institute.org/resources/library/Free/workshop/NNIW77/Documents/Diet,%20Gut%20Enterotypes%20and%20Health%20Is%20There%20a%20Link.pdf

⁹ www.wired.com/2013/01/fecal-clinical-trial/

characterised is not well understood however (Smith *et al.*, 2014). While it is known that side effects are very rare, long term studies are needed to see if adverse effects develop after stool transplantation.

23. It is also not clear whether this treatment is useful for other intestinal diseases. As its working mechanism is not fully understood, standardisation of the samples is lacking and regulation is still unclear. In the US it has been discussed whether stool transplantation has to be regulated as an investigational new drug¹⁰ or as a tissue. At this moment faecal transplantation to treat recurrent *C. difficile* infections can be done without prior screening of the donor and faecal sample while to treat other conditions stool transplantation falls under the regulation of investigational new drugs.

24. Other interventions attempt to modulate the intestinal flora through nutrition. Recently it was shown that the gut flora of undernourished children is different from that of well-nourished ones (Blanton *et al.*, 2016). The former microbiota are immature and when transplanted in germ free mice transmit the phenotypes associated to undernourishment, such as growth impairment. 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 sialated oligosaccharides, which are present at 20 times higher levels in human breast milk as compared to in bovine milk, when added to the diet of model organisms that were colonised with gut flora from undernourished children, induced a beneficial effect on growth and metabolism, through acting on the microbiota. These findings open speculation of developing relatively easy and cheap treatments of undernourished children, which may help a lot in the poorest areas of the world.

25. Other studies demonstrated that the gut microbiota of obese human and mice is different from those of normal mice.¹⁷ Moreover, the gut flora from obese mice induce greater increase of body fat when transplanted in the gut of germfree mice than when transplanted with the flora from lean counterparts. In humans it was shown that the gut flora show lower bacterial diversity in obese individuals when compared to the lean individual of twin pairs. Also, differences in metabolic pathways and microbial genes were observed (Turnbaugh *et al.*, 2009).

26. That gut microbial composition is determined at least in part by what we eat is becoming accepted, although not understood how this is achieved (David *et al.*, 2014). Long term and wide studies are needed to start understanding the mechanism of which food components are active and which microbial species have an active role in metabolising or producing such active compounds. The science will have to deepen to go from descriptive analysis to functional analysis to start understanding how the gut microbiome functions as an integral organ in our bodies.

27. Moreover, it was recently shown 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 large study indicating that personalised diet is possible and that it can alter the microbiome.

28. It is becoming clear how the microbiome is functioning as a virtual organ that has an essential role in general health. The scientific challenge to start understanding how microbiomes work and how the gut microbiome is responding to what we eat can only be achieved through large collaborative efforts.

¹⁰ https://en.wikipedia.org/wiki/Investigational_New_Drug

Large consortia and initiatives

29. The characterisation of the complete human microbiome was one of the next big challenges after the finalisation of the human genome project. The availability of novel high-throughput omics technologies now for the first time made it possible to characterise complete microbial communities without isolation and pure culturing of individual species.

30. In 2008 the Human Microbiome Project was launched by NIH.¹¹ In the same year also the International Human Microbiome Consortium was launched with support of the European Horizon 2020 Framework Programme.¹² The final goals of both large collaborative efforts were to characterise the human microbiome and analyse its role in human health and disease.

International Human Microbiome Consortium

31. In 2008, after a series of meetings that started in 2005, scientists launched the International Human Microbiome Consortium to share data related to the human microbiome and make data freely available to the global scientific community to create a better understanding of the role of microbes in health and disease. The database also includes information from the other major initiatives, such as the NIH Human Microbiome Project, and MetaHIT (Metagenomics of the Human Intestinal Tract) – the EC funded initiative under the seventh framework programme. Other contributors included the Commonwealth Scientific and Industrial Research Organisation (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 according to the policies of the consortium. Members now include also France, Japan, Gambia, Korea and Ireland. The consortium aims to harmonise the work focused on the human microbiome and co-ordinate activities and policies of international groups.

NIH Microbiome Project

32. The first phase of the NIH Microbiome Project 2007-2012 was one of the major international efforts to characterise the human microbiome and analyse its role in health by using omics technologies. The project not only focused on cataloguing bacterial genes, but also developed new tools for computational analysis and focused on ethical issues. In its second phase from 2013-2015, with a budget of USD 22,1 million, the programme focused on the better understanding of the human microbiome's role in health and disease.¹³

33. 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 in how host-microbiota interactions can modulate specific host phenotypes related to obesity, digestive and liver diseases and the role of the microbiome in nutrition.¹⁴

¹¹ <http://hmpdacc.org/overview/about.php>

¹² www.human-microbiome.org/index.php?id=25

¹³ www.genomeweb.com/nih-awards-22m-human-microbiome-projects-second-phase

¹⁴ www.genomeweb.com/research-funding/nih-earmarks-15m-fund-human-microbiomeresearch-projects

MetaHIT

34. MetaHIT had similar goals and was active between 2008 and 2012 with a budget of over EUR 21 million, of which more than half was supplied by the seventh framework programme of the European Commission. The consortium involved more than 50 researchers from 8 countries, including China and 14 research and industrial institutions. The project generated a catalogue of 3.3 million bacterial genes (Qin *et al.*, 2010), and described the three enterotypes (Wu *et al.*, 2011). Insights from this project opened perspectives for early detection of chronic diseases, and opens ways to personalised or stratified medicine and the development of nutrition that help cure certain diseases.

35. An assessment of the US microbiome research that was published in January 2016, indicated that between 2012 and 2014 already USD 922 million was spent on microbiome research in the US. Over 59% of the budget was covered by the NIH.

Recent calls for a new international initiative

36. Although huge efforts are ongoing in many countries, US scientists recently called for a harmonised effort to address microbiomes or microbial ecosystems in general and push the transition from description to causality and engineering (Alivisatos *et al.*, 2015). Such a Unified Microbial Initiative (UMI) should be an interdisciplinary platform to develop and advance tools that will lead to better understanding of how the microbial organisms interact with each other and with their hosts. This call was echoed by scientists from Germany, China, and the US emphasising the need for an international initiative or International Microbiome Initiative (IMI), rather than a national US one to ensure standardised approaches and to bring cohesion among the many different microbiome projects (Dubilier *et al.*, 2015).

37. The fact that there is a multitude of many different national microbiome projects raises issues with ownership of the data, and procedures of collecting and storage of data. It is clear that the sharing of data is of major importance and hence standardisation of data and procedures are absolute necessities. An International Microbiome Initiative (IMI) would help overcome a lot of these difficulties. Such an international approach would also overcome the barrier of scale to reach sufficient critical mass in the different disciplines that should be brought together. Indeed, further development in this field needs a cross disciplinary expertise by bringing together microbiologists, bioinformatici, engineers, health professionals, molecular biologists and experts in the different omics technologies.

European Initiatives

38. In 2013 a project dedicated to the human gut microbiome was started under the Seventh Framework Programme of the European Commission.¹⁵ MyNewGut is a five year project with an estimated total cost of over EUR 13 million for which it received a budget of almost EUR 9 million.¹⁶ The goal of this project is to generate a better understanding of how the gut microbiome influences our health, how it is functioning and how it is influenced by diet.

¹⁵ www.mynewgut.eu/home

¹⁶ http://cordis.europa.eu/project/rcn/111044_en.html

39. The Joint Programming Initiative on Healthy Diet for Healthy Lives (JPI HDHL) has also started working on the microbiome.¹⁷ In joint programming initiatives, national R&D programmes are bundled to address global societal challenges that single states cannot address individually. To achieve the goals a Strategic Research Agenda is developed. In JPI HDHL 25 countries joined forces to address as one of their goals, chronic diseases that are linked to poor diet. Recently a call was launched for proposals on research projects addressing intestinal microbiomics to increase knowledge on how diet affects the gut microbiota and how this in its turn affects human health and development of NCDs. A budget of over EUR 7 million was awarded to six projects that started in March 2016.

Ireland

40. In addition to the large multinational efforts, in several countries large national initiatives are being supported. The Alimentary Pharmacobiotic Center (APC) Microbiome Institute, is the Irish research institute for diet, medicine and the microbiome.¹⁸ The APC Microbiome Institute was established in 2003 as a partnership between University College Cork and Teagasc, the Agriculture and Food Development Authority and is hosted at the University of Cork. It is set up as a public-private partnership that brings industry partners together with academic and other public partners. The APC Microbiome Institute is governing a EUR 70 million budget from the Science Foundation Ireland and industry funding across 2013-2019.¹⁹ The work of the institute is focussing on microbiome research and development new therapies for chronic debilitating gastrointestinal disorders. Ireland focused very early on the gut microbiome. In 2008-2013 the Irish government supported ELDERMET, a Metagenomics of the Elderly programme. ELDERMET is a unique metagenomics project that aimed to understand the relationship between diet, gut flora and health in over-65 year olds. The goal behind it is to improve health and wellbeing through controlling the gut flora by diet.

Canada

41. Canada also hosts major programmes developed by the government.²⁰ In 2008, the Canadian Institutes of Health (CIHR) provided CAD 500 000 to award projects with a single grant of up to 100 000 for one year. The CIHR Institute of Nutrition, Metabolism and Diabetes engaged to fund 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), INMD, and the CIHR Ethics Office. In total 12 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. Their goal is to create better understanding of the human microbiome and translate this into an understanding of how the micro-organisms in the human body affect both the normal healthy and disease states.

42. 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 from 2010 until 2012.

¹⁷ www.healthydietforhealthylife.eu/index.php

¹⁸ www.ucc.ie/en/

¹⁹ www.sfi.ie/investments-achievements/sfi-research-centres/apc.html

²⁰ www.cihr-irsc.gc.ca/e/39941.html

France

43. In France, the Metagenopolis programme 2013-2017 is a public-private demonstration project that received a budget of EUR 19 million to develop microbiome-based therapeutic products.²¹

Belgium

44. In 2013, the Flemish government in Belgium allocated a budget of EUR 700K to support an ambitious Flemish Gut Flora project in the VIB lab of Jeroen Raes.²² The aim of this project is to do longitudinal studies of a wide population. The public was called to donate stool samples through the dense network of pharmacist. The project created a lot of interest and sympathy from the public and reached by April 2016 over 5000 people contributing samples in this way, of which close to 4000 samples have been characterised already. In addition, to stool samples, the project also collects general information of life style, health, quality of life and general wellbeing, dietary habits as well as on the genetic background, including family comparisons and links this information to the characterised stool samples.

45. Although the importance of this project is acknowledged, it remains difficult to gather sufficient funding for such a large scale project. The total running cost of this project is estimated around 1,5 to two million Euro and should be continued over long times. In addition, international collaboration is needed to improve statistical relevance of the results of such studies. It has been realised that access to and collaboration with multinational cohorts is not easy, very often because of reasons of privacy.

The United Kingdom

46. Due to open in 2018, the Quadram Institute (QI)²³ will integrate research teams from the Institute of Food Research (IFR) and the University of East Anglia (UEA)'s Faculty of Science and Norwich Medical School with the Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH) gastrointestinal endoscopy facility. There is a strong microbiome focus in the Institute's science vision going forwards. The initial multi-million pound investment for the Quadram Institute is being provided by the Biotechnology and Biological Sciences Research Council (BBSRC) together with IFR, NNUH and UEA.

Crowdsourcing and Citizen Science

47. Interesting developments are taking place with public engagements in research projects, indicating the large public interest in developments in this field. The American Gut is one of the largest crowd source citizen science projects.²⁴ Since October 2015, the initiative 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

²¹ www.inra-transfert.fr/fr/focus-sur/104-2-demonstrateurs/314-mgps-metagenopolis

²² www.vib.be/nl/mens-en-gezondheid/darmflora-project/Pages/default.aspx

²³ <http://quadram.ac.uk/>

²⁴ <http://americangut.org/>

own body's microbes. The project also collects data on diet and alcohol consumption or health conditions such as autism or intestinal problems of the participants to associate such information with the microbial ecosystems in individuals. All information is anonymised and made freely available for research all over the world.

48. The American Gut project has expanded to Europe through the British Gut project.²⁵ The organisation is calling for similar projects to be started in other countries. This unique approach will give the insight required in different populations, using different diets.

Industry and the microbiome

In food industries

49. Consumer healthcare offers promising growth opportunities for which pharmaceutical companies are starting to compete for market share with consumer good companies. The importance of food for health was already underlined in ancient Greece as Hippocrates stated "Let food be thy medicine and medicine be thy food". Also in many traditional cultures the role of food for better health is part of traditional approaches against certain conditions. Not surprisingly, an important segment of the food industry focuses on production and development of healthy nutrition. 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. Large budgets are invested in the research departments of these companies.

50. 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 does fundamental research for the understanding of health and disease and for developing science-based nutritional solutions for the maintenance of health. The Nestlé Institute for Health Sciences hosts 160 scientists and collaborators from around the world. One of the research lines focuses on the better understanding of the human gut microbiome.

51. Also Danone is investing significantly in research to develop specialised food products for special target groups, such as babies or the elderly. In 2013 Nutricia Research Utrecht in the Utrecht Science Park was inaugurated – it is intended to be the main development hub of the group in this field and currently employs 400 people.²⁶

In pharmaceutical industries

52. The fact that the human microbiome strongly influences our health opens new avenues towards a new type of medicine. Indeed, addressing a disease through interfering with the microbiome is a previously unexpected approach and goes beyond the idea of healthy food as a preventative measure as an insurance 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. The new developments have not been ignored by pharmaceutical companies.

²⁵ <http://britishgut.org/>

²⁶ www.nutriciaresearch.com/location/utrecht

53. Janssen Research and Development, LCC one of the Janssen Pharmaceutical Companies of Johnson and Johnson launched in the beginning of 2015 the Janssen Human Microbiome Institute (JHMI).²⁷ Janssen Pharmaceutical companies have been experimenting with open innovation for several years and the JHMI will also operate by fostering external collaborations through anchor research centres in the U.S. (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, at the different Janssen R&D sites both in Europe (Beerse, Belgium) and throughout the U.S. and engage the external community from both academic centres and biotechnology companies.²⁸

54. 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 focussing in this area. Launched in March 2016, Johnson & Johnson Innovation, JLINX will provide access to infrastructure, venture capital and investment, and expertise to accelerate innovation and build businesses.

55. Analogous open innovation platforms and research partnerships are set up by other pharmaceutical companies such as GlaxoSmithKline PLC,²⁹ Pfizer Inc.³⁰ or Dupont.³¹ 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 provided analysis of on a market survey undertaken in July and August 2014.³² It identified 23 microbiome companies and 12 microbiome-related deals, of which five involve the participation of big pharma. The Janssen Biotech unit was 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 is justified. It is expected that the microbiome work will provide major contributions to healthcare. Two-thirds of the respondents believe that big pharma will be very actively involved in further developments in this field over the next decade.

56. A 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 included four partnerships between small companies and big pharma. The online survey was expanded to 119 individuals, of which less than half worked in industry and more than half in academia. Nearly half of the respondents expect that new personalised biotherapeutics will become very important in the future. Two-thirds expect that in the next two years the industry efforts in the field will increase. The market potential is growing very fast and is projected to reach USD 294 million in 2019 and further rise to USD 658 million by 2023. June 2015 saw the first IPO in the microbiome environment and is expected to lead to the development

²⁷ www.jnj.com/news/all/Janssen-Launches-Three-New-Research-Platforms-Focused-on-Redefining-Healthcare

²⁸ <https://talk.jnjinnovation.com/article/gutsy-idea-human-microbiome#sthash.oEVxxDNG.dpuf>

²⁹ <http://intbio.ncl.ac.uk/?projects=gsk-gut-microbiome>

³⁰ www.lightstonevc.com/sites/all/files/press/Big%20Pharma%20Embraces%20Microbiome%20Research.pdf

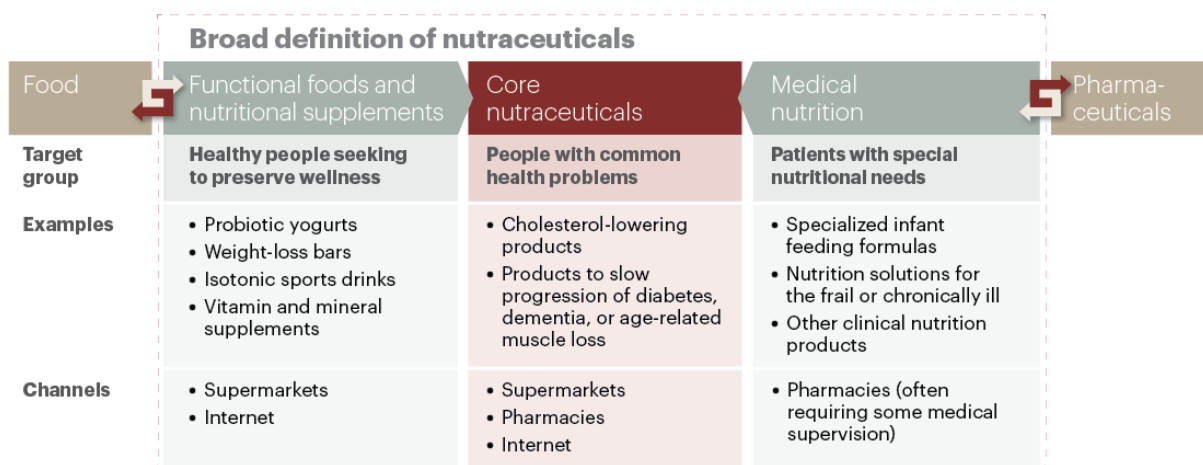
³¹ www.genomeweb.com/business-news/dupont-inks-deal-acquire-microbiome-firm-taxon

³² www.insightpharmareports.com/Human-Microbiome-2016-Report/

of a first drug targeting the gut microbiome to treat *Clostridium difficile* infections. The IPO collected over USD 130 million, half of which from Nestlé.³³

57. According to an analysis by AT Kearney, the so-called “nutraceuticals” market is gaining increasing size and importance (Fig. 1).³⁴ Nutraceuticals take a position between food and medical nutrition. In their analysis, annual sales were approximately USD 150 billion in 2015, corresponding to about one fifth of the size of the global pharmaceutical industry turnover, when narrowly defining nutraceuticals (i.e. not including infant nutrition, food intolerance products, diabetes control, medical nutrition and 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 few years (Fig. 2).

Figure 1 Nutraceuticals play in the continuum between food and pharmaceuticals



Source: A.T. Kearney analysis

Source: www.atkearney.com/health/ideas-insights/featured-article/-/asset_publisher/4rTTGHNzeaaK/content/nutraceuticals-the-front-line-of-the-battle-for-consumer-health/10192

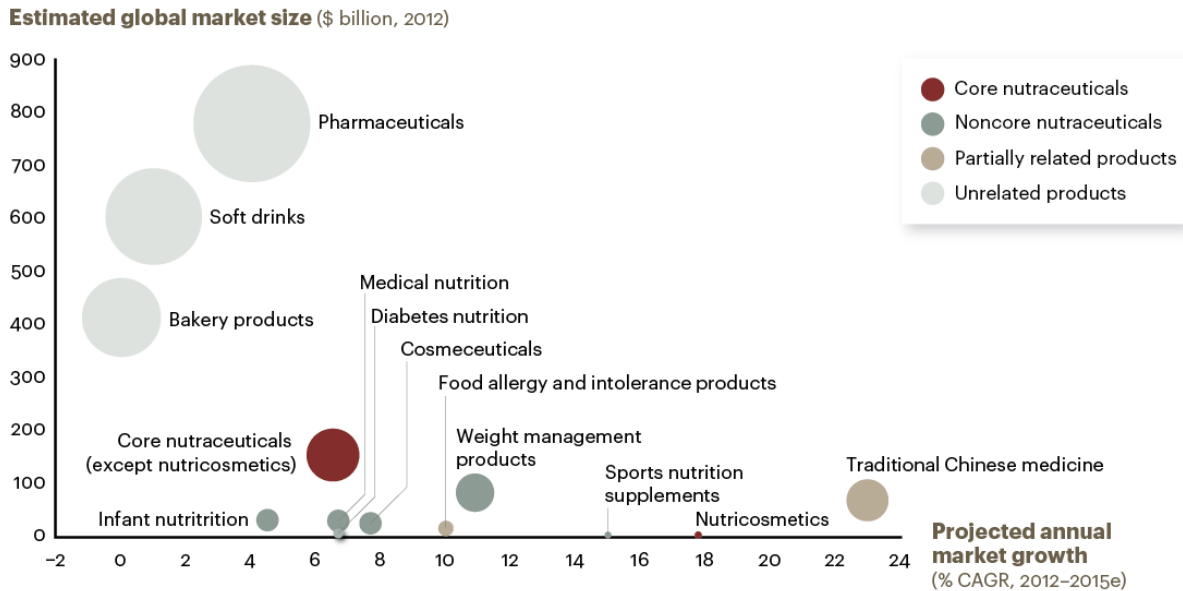
58. It was reasoned that the growth rate could be much stronger if a solid regulatory framework were in place, so as to guarantee medical credibility. Medical credibility is the crucial factor to increase acceptance by consumers and health professionals.

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

³³ www.xconomy.com/boston/2015/06/25/on-eve-of-seres-ipo-a-rival-nonprofit-microbiome-treatment-expands/

³⁴ www.atkearney.com/documents/10192/4306155/Winning+the+Battle+for+Consumer+Healthcare+-+Nutraceuticals.pdf/e4c67b42-cb4b-436a-b50d-7b35c0508b95

Figure 2 Nutraceutical market size and projected growth



Note: Bubble area represents projected market size in 2015.

Sources: 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; A.T. Kearney analysis

Source: www.atkearney.com/health/ideas-insights/featured-article/-/asset_publisher/4rTTGHNzeaaK/content/nutraceuticals-the-front-line-of-the-battle-for-consumer-health/10192

Highlighting policy issues for the workshop

60. The goal of the workshop is to stimulate discussion on policies that can foster innovation based on new insights of how the human microbiome, and the gut microbiome in particular, is functioning. It is expected that this field will help to decrease NCDs and therefore contribute to sustainable healthcare systems. Innovations based on better understanding of how the intestinal microbiome functions and regulates our health and how it is impacted by what we eat are expected also to support preventative medicine and better wellbeing in general. For this field to follow the pace of new scientific insights and translate these to innovative applications, however, there is a need for policy action at the national and international level. This section reviews some key points to consider as policy is developed.

Issues to be considered

- Need for basic research
- Need for translational research
- Need for clinical research and population studies
- Need for cross-disciplinary research (skills and training)
- Need for strengthening research collaborations (Large research consortia versus small dedicated projects)
- Need for access to and sharing of data (big data infrastructure needs)
- Need for standardisation of material collection and storage
- Need for standardisation of research procedures

61. Given the expectations of the new insights on the human microbiota and the high complexity of the system, there is a strong argument for more thorough research and large population studies. In a Google+ Hangout discussion on “A Microbial Manifesto”³⁵ that was hosted by the Kavli foundation in January 2016, experts agreed that although there is already a lot of data, much more data is needed. Not only more, but data should also be delivered faster, cheaper and with higher accuracy. Understanding how microbial ecosystems work is a huge challenge. It is clear that this field will benefit from data sharing and for that standardisation of sample handling and data collection, storage and usage are essential. Given that the challenges of data sharing are well known, how can they be overcome in this arena?

62. New and better algorithms and new ways of computing are also necessary to improve and accelerate the processing and interpretation of the data. Many genes are still unknown or mis-annotated. On top of that only 2% of the metabolites produced by a typical microbial community correspond to known structures and of these only a small fraction are on known biochemical pathways.

63. Better understanding of how microbial ecosystems work is expected to lead to the development of simple model communities to learn how these ecosystems respond to inputs and changes. This 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.

64. To make the transition from mere cataloguing to mechanistic insight and further translate towards novel applications there is a need to work across disciplines and bring microbiologists together with engineers, bio-informatics, and experts in all types of omics technologies as well as with biochemists, molecular biologists, medical doctors and so on. In addition to technological expertise, the need for creativity was also mentioned as a challenge at a workshop that was organised in Brussels on 22 February 2016 by the

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www.kavlifoundation.org/science-spotlights/spotlight-live-microbial-manifesto-transcript#.Vw5HmfmlTmE

European Commission.³⁶ 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.

65. It is likely that better understanding of the functioning of the intestinal microbiome will contribute to the development of science-based preventative and stratified medicine. As many NCDs seem to be linked to (malfunctioning of) the gut microbiome, innovative interventions based on better understanding of the microbial ecosystem could significantly reduce healthcare costs while adding to a more general qualitative health improvement.

66. Given the huge challenges ahead and the major costs associated to them, there is a call to strengthen research collaboration. Although there is a significant shared enthusiasm to set up large international consortia, some contest the need for additional overarching consortia and instead advocate the return to 'boutique science', questioning the added value of large research collaborative efforts. In any case, new research projects should address well formulated research questions and encourage hypothesis driven science, rather than mere tool development and cataloguing. Sometimes smaller competing research projects may lend themselves better to bringing people with the right skills together to address well formulated research questions. There is also a fear of channelling too much funding into a limited number of projects at the expense of others.³⁷

67. Public-private partnerships may help to ensure innovative applications in this field; these arrangements may require particular attention to be paid to open access and use of the data generated.

Regulatory Issues

Issues to be considered

- Need for high quality data and their critical mass to build evidence to support emerging regulatory frameworks
- Need for definitions that specify the human gut microbiota in its normal and pathological status
- Need for definitions of nutrition-based products that may have therapeutic effects
- Need for a regulatory framework to ensure safety, quality and efficacy of novel applications that target the gut microbiome for better health (public acceptance – health professionals)
- Measuring impact of emerging regulatory frameworks on public health and business viability
- Address novel business and collaborative models that are best suitable for industry (food and pharma companies)

68. Pivotal to delivering new solutions based on innovative foods is the regulatory framework, which needs to follow recent developments and insights to allow appropriate new applications to become available for society. The regulatory framework should guarantee the solidity of the science base and that health claims are evidence based. The consumer should be protected against false expectations generated by products that

³⁶ Author participation

³⁷ <http://blog.mothur.org/2015/10/29/Initial-reactions/>

have not been thoroughly tested. A solid regulatory framework will 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.

69. One of these challenges is that the difference between food and drug becomes a blur when food is used for therapeutic purposes. There is a food-drug continuum in which there are grey zones for which existing regulatory frameworks may need to be readdressed. The regulation is complex and addresses different stakeholders with different targets and constraints. Although not the same, the regulatory frameworks in Europe and the US today serve as the references.

70. The fact that the regulations differ amongst countries and continents poses an extra complication. A good overview of the different regulations in the US, the EU, 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). The different regulations also use different terms referring to food, food additives and ingredients, food with health claims associated to it, 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 reference regulatory environments; they rather remain popular terms in laymen publications.

71. To ensure building innovative solutions based on the understanding of the interactions of gut microbiome and food for better health it will be crucial to harmonise the terminology used and to agree on how health claims should be analysed. An international agreement on such harmonisation is highly desirable.

72. 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).³⁸ Nutrition and health claims are only allowed when listed on a so-called positive list. Health claims only receive approval from the European Commission following an EFSA opinion upon a submission of the scientifically substantiated dossier. This also accounts for claims in the reduction of disease risks associated to foods. One of the major obstacles for health claims associated to foods to receive a positive EFSA opinion is that the cause and effect relationship should be demonstrated through randomised clinical trials. Very often the information and evidence to support a health claim is considered insufficient due to the lack of strong evidence and not fully characterised ingredients. Of the 44 000 health claims that were submitted since the NHCR regulation until mid-2012, only 222 health claims were approved.³⁹ For a number of claims, the approval is still pending.

73. One of the issues that needs to be taken into account is that food supplements and nutrition and health claims legislation cover products intended for a normal healthy population. 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 will take effect on July 2016 and is meant to simplify and improve the application of rules and better protection of consumers.⁴⁰⁴¹ FSMP are only for patients who have specific disease-related nutritional limitations and thus exclude foods with curative or preventative impact. Any food that claims a pharmacological effect is no longer considered

³⁸ http://ec.europa.eu/food/safety/labelling_nutrition/claims/index_en.htm

³⁹ www.eubusiness.com/topics/food/nuhclaims-guide

⁴⁰ http://ec.europa.eu/food/safety/labelling_nutrition/special_groups_food/index_en.htm

⁴¹ http://ec.europa.eu/food/safety/labelling_nutrition/special_groups_food/medical/index_en.htm

a food, but is considered a drug by function. This also has further implications on, amongst others, the production costs given that such products need to meet pharmaceutical quality manufacturing requirements.

74. Recent insights indicate that the microbial composition can be modulated by dietary interventions and in this way can be used for therapeutic purposes. It is generally believed that food products are safer than chemically synthesised drugs, although emerging examples shows 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 it may then be more appropriate to use drug regulations.

75. Additionally, the novel foods/diets are processed in the body through; inter alia, the gut microbiota. Such a transformation definitely leads to the delivery of a number of active metabolites that may exert, in turn, physiological effects on the body. The current status of knowledge does not allow tracing out these complex transformational events and therefore represent a high burden for clinical and regulatory approval systems in terms of safety. Current frameworks need to be assessed to ensure they are reliably evaluating whether new food products/diets are safe and efficient (including through validated biomarkers) so that health claims do not mislead consumers.

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

77. Safety and efficacy of products can only be tested in clinical trials, which is another major source of elevated costs in drug development. On top of that the business models and profit margins of food companies and pharmaceutical companies are very different. The main fear is that these elevated costs may pose a significant barrier to the development of novel food or food products for therapeutic uses.

Funding issues: Public funding and return on investment

Issues to be considered

- How can science policy leverage public and private sources of money through partnerships?
- Can new forms of public-private partnerships be established, and what will be there conditions and terms?
- How to ensure a return on investment for public research funding?

78. Industry as well as academic partners are calling for public-private partnerships to stimulate the translation of scientific knowledge into new products and treatments (see above).⁴² Several such partnerships

in this field have already been set up.⁴³ Given the budgetary constraints of public bodies, the system seems to have reached its limits. One of the issues that could be discussed in the frame of this workshop is whether “out of the box” models can be developed to support public-private research projects.

The Workshop

79. The workshop on 'The Microbiome, Diet and Health: Assessing Gaps in Science and Innovation' is intended to spur reflection on current scientific insights and expected trends in the field leading to innovative applications for the benefit of society. Experts have been asked to comment on possible policy gaps and barriers and to reflect on how innovation in this field could be stimulated. It is expected that a better understanding of how the microbiome is influenced by diet and thereby regulates health will benefit public and enhance the sustainability of health care systems. In addition, the role of industry and interaction between food and pharmaceutical industries is likely to lead to new growth potential.

80. The workshop will be introduced by a keynote presentation. Three thematic sessions will outline scientific and regulatory issues. A concluding panel discussion will summarise outcomes of the previous sessions and indicate where policy actions are needed to address barriers and support the development of innovative applications based on new insights in this field.

Thematic session 1: Human Gut Microbiome: Potential for Healthier Foods and Health Innovation?

81. Session one of the workshop will cover the most recent advances in our understanding of human microbiota and its role for human health; how it functions, how it is influenced by diet and how it may be a new target for therapeutic interventions. The session will highlight current trends and the status of research and sketch how this is expected to evolve in the future in stratified and preventative medicine through dietary applications.

82. Presentations and discussions in this session will focus on the following key questions:

- What are the current scientific advances and the main expectations and impacts?
- What are the main drivers and barriers to development and uptake of therapeutic interventions based on the understanding of the link between microbiome and health and the role of diet that influences this link?
- How close we are to controlling the microbiome through innovative dietary interventions in preventative medicine?

Thematic session 2: Personalised Diet and New Foods

83. The second thematic session will focus on the development of food products to which positive health effects are assigned and personalised diets, and evaluate the state of the scientific evidence to support health claims currently being made. Foods with health claims or personalised diets are expected not only to

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www.nutriciaresearch.com/partnering/public-private-partnerships/

contribute to preventative medicine, but may also be used to combat diseases, including neurological diseases.

84. Although evidence is accumulating that food and dietary strategies may function through influencing the gut microbiome, the causal effect of diet on the gut microbiome needs to be scientifically substantiated. Eventually, novel developments are expected to lead to the development of personalised diets based on personal gut microbiome configuration; however, continued scientific research is needed to bolster efforts to develop dietary based therapeutic interventions or preventative medicine.

85. Session two of the workshop will address the following key questions:

- What typologies do we have to describe different kinds of “new foods” and are these adequate for the purposes of policy?
- Do we have food products with associated health claims/ diets with proven efficacy?
- Are the current efficacy evaluation models for probiotics, food products with health claims and personalised diet sufficient?

Thematic session 3: Regulatory and Enabling frameworks

86. Session three of the workshop aims to identify regulatory frameworks and policies needed to support the uptake of novel foods or diets with health beneficial effects so as to improve public health and wellbeing. In so doing, the session hopes to address the needs for the food and/ or pharmaceutical industries to develop new foods with health benefits and to bring these to the market. One important issue is whether these novel entities need to be regulated like drugs. The food industry may have to collaborate more closely with the pharmaceutical industry should it need clinical testing on large populations to demonstrate the health claims of novel foods or food products with health claims assigned to them, since this specific expertise lies with the pharmaceutical industry. Complex clinical studies that are used to test efficacy and safety, however, will significantly increase the costs of development of such new food products, while the safety issues may be less critical than for drugs. A second major aim of the session is to better understand the nature of regulatory diversity across countries in efforts to promote greater standardisation. The current regulatory frameworks in place will be outlined and experts are asked to outline where existing barriers should and could be removed.

87. In thematic session 3 the following key questions will be addressed:

- What regulatory or enabling frameworks are in place or needed to stimulate developments towards preventative diet-based medicine while ensuring the claims are correct and based on solid scientific evidence?
- How can barriers for innovative development in this field be avoided or taken down?
- When novel foods and diet can improve health outcomes, how can we stimulate their uptake by the public?

Concluding session on policy opportunities - Panel discussion

88. The concluding session will identify policy needs and opportunities based on the conclusions and main messages from the previous sessions. The concluding session will start with a short presentation on the main findings of the earlier thematic sessions by the workshop rapporteur. After that, a panel discussion between policy makers (OECD, EC, EFSA,...) and industry and researchers will focus on legislation, regulation, ethical issues, communication (raising awareness on healthy food, clear communication on food labelling) and the need for a systems approach in policy making in this area.

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