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COMITATO NAZIONALE PER LA BIOSICUREZZA,
LE BIOTECNOLOGIE E LE SCIENZE DELLA VITA

IL PRESIDENTE

CONCEPT PAPER

ITALIAN MICROBIOME INITIATIVE FOR IMPROVED HUMAN HEALTH AND AGRI-FOOD PRODUCTION

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1. Summary

Microbiomes inhabit humans, plants, animals and terrestrial and marine environments, and provide benefits to the whole planet and its populating organisms. Due to their astonishing metabolic potential, microbiomes occupy a central position in the “One Health” framework, contributing to human health in a new integrated and holistic view, which includes biomedical systems, terrestrial and marine primary production, feed and food production and nutrition.

Many different research projects in recent years have delivered new knowledge on associations between the microbiome and a wide range of human diseases. Now we are translating the data and knowledge to define balanced healthy conditions and to prevent and treat diseases through the development of personalised approaches and clinical tools. In parallel, ongoing studies are demonstrating that microbiomes structures and dynamics across the different actors of the food systems (from soils and marine habitats, to plants, animals and the deriving foods) can directly and indirectly affect human microbiomes and health, besides an obvious impact in terms of food quality, safety and sustainability.

Innovative technologies are providing us with more detail about the microbes with which we are living in symbiosis. In this context, a multi-disciplinary approach integrating these technologies allows to retrieve more information about the human being, the plant or the animal. From available studies, the microbiomes are emerging as very dynamic, changing, and adaptable systems. Future research needs are to fully clarify the interplay between microbiome and environment, nutrition and host variables.

The European Commission funded to date 216 projects as part of FP7 and H2020 with about €500 M to advance knowledge on such priorities (Hadrich, Front Genet, 2018). However, Italy played and is playing a minor role in such an EU prominent effort. Indeed, despite of the prominent expertises of the Italian researchers in the field of human microbiome and virome (at preclinical and clinical levels), microbiomes in foods, plants, terrestrial and aquatic animals, and their relations with the human gut microbiome and health, their actions are largely fragmented and thus often with social and economical impacts lower than they could be. This is mostly due to the fact that Italy, differently from other EU countries, does not have any national funded programme on microbiome and thus, microbiome knowledge production and exploitation is not a key priority in the “national plan for research” and in the strategic R&I agendas of the Italian Technology Clusters.

This asks for a coordinated action, a national initiative addressed to: a) establish a national network of experts and of public and private actors working in the sector, to share existing national data, knowledge, infrastructures, capacities in the area of human, animal and plant microbiome; b) foster cooperation between public and private sectors, also in close cooperation with the Italian Technology Clusters Health and Agrofood, for maximizing the leverage effects of public and private investments; c) plan and implement joint R&I and policy actions at regional and national levels, by creating more investments in R&I and spin offs/start-ups, and facilitate their interconnection with international networks to promote applicability of microbiome know-how as well as best practices, standards and consistent protocols; d) promote researcher careers, training and mobility, and in general the development of skills in the different microbioma domains; and e) exchange knowledge across the scientific and political community and ensure an efficient use of the available resources, while advocating public understanding of the value of microbiomes for the human, plant, animal and planetary health.

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2. Introduction

Complex microbial ecosystems, collectively referred to as microbiomes, inhabit and interact with living organisms - human, plant and animal – and have co-evolved with them a range of symbiotic relationships, including mutualism, with ultimate beneficial outcomes for the host. Due to their astonishing metabolic potential, microbiomes have a key role for human, plant, animal and, ultimately, planetary health, and occupy a central position in the “One Health” framework, contributing to human health in a new integrated and holistic view.

Among these microbial ecosystems, the most explored to date is undoubtedly the human gut microbiome, which refers to the large ensemble of microbes hosted in our gastrointestinal tract - as numerous as human cells -, including components from all three domains of life, i.e. Bacteria, Archaea and Eukarya, and their viruses. In constant and extensive interaction with the host at the intestinal mucosal surface, this microbial community plays fundamental roles in several aspects of our physiology, instrumental to the maintenance of metabolic and immunological homeostasis. Intestinal microorganisms are involved in the bioconversion of dietary components, leading to the production of a wide and diverse range of bioactive small molecules, including short-chain fatty acids (SCFAs), vitamins, amino acid metabolites, neurotransmitters and phytoestrogens, with major impacts on host nutrition, immune functionality, endocrine system, central nervous system function and protection against pathogen colonization (Tilg and Moschen, *Gastroenterology* 2015; Sonnenburg and Bäckhed, *Nature* 2016). In particular, the crosstalk between the gut microbiome and the immune system is widely recognized to be critical to human health (Honda and Littman, *Nature* 2016; Thaïss *et al.*, *Nature* 2016). Similarly, the gut microbiota is considered as a forgotten endocrine organ, acting as an endogenous circadian organizer, and an integral component of central nervous system, with an ultimate capacity to modulate our behavior and contribute to the pathophysiology of neurological disorders (Neuman *et al.*, *FEMS Microbiol Rev* 2015; Sharon *et al.*, *Cell* 2016; Thaïss *et al.*, *Cell* 2016). The individual gut microbiome may also affect the detoxification of xenobiotics, including drugs, with potentially important repercussions on the metabolism and thus the pharmacokinetics of several pharmaceuticals (Spanogiannopoulos *et al.*, *Nat Rev Microbiol* 2016).

The intestinal microbial communities are inherently dynamic, capable of fluctuating between different “eubiotic” configurations over time, closely linked to the person’s life path, still keeping a mutualistic relationship with the human host, essential to maintaining in turn homeostasis and health (Halfvarson *et al.*, *Nat Microbiol* 2017). However, when challenged with certain endogenous and/or environmental stressors, the gut microbiota may considerably shift in composition and function, resulting in a “dysbiotic” profile that compromises the mutualism, eventually triggering or consolidating a disease state.

Mounting evidence supports a role of the gut microbiome in a number of disorders, at both enteric and systemic levels, ranging from gastrointestinal to metabolic, hepatic, autoimmune, respiratory, cardiovascular, neurological, and even oncologic diseases, often referred to as Non Communicable Diseases (NCDs) (Lynch and Pedersen, *N Engl J Med* 2016). Microbiome-disease associations typically involve the loss of beneficial, health-associated microbes (mostly producers of SCFAs), the bloom of opportunistic pathogens, or a broad restructuring of the gut microbial ecosystem, with clinically relevant, if not life-threatening, consequences (Duvallat *et al.*, *Nat Commun* 2017). Based on recent, extensive surveys and meta-analyses exploring the human gut microbiome variation in health and disease, even microbiome dysbioses are highly personalized and follow distinctive temporal changes, whose understanding may help guide more knowledge-based personalized intervention strategies (Zaneveld *et al.*, *Nat Microbiol* 2017; Koskella *et al.*, *Nat Ecol Evol* 2017). Furthermore, the loss

102 of the microbiota-host equilibrium may contribute to the onset of “pre-disease” states (pre-
103 diabetes, pre-hypertension, etc.) and thus play a part into the inflation of NCDs (van de Guchte
104 M *et al.*, Microbiome 2018).

105 Studies characterizing the gut microbiome in thousands of people, in parallel with covariates
106 assessing health status, diet, lifestyle, medication, biomedical parameters and genetics
107 (Falony *et al.*, Science 2016, Wang *et al.*, Nature Genetics 2016; Rothschild *et al.*, Nature
108 2017), demonstrated that these determinants explain only a limited fraction of the total gut
109 microbiome variation and that we are still missing important covariates when assessing
110 drivers of microbiome variation. According to this vision, innovative and neglected drivers of
111 human gut microbiome variation could be searched in the frame of the One Health Theory,
112 including covariates in animal and environmental domains, which have never been explored,
113 going beyond the mere biomedical system. For instance, microbiomes structures and
114 dynamics across the different actors of the food systems (i.e. soil, sediments, plant/animal,
115 feed, food, farm, processing, workers and consumers) can directly and indirectly affect human
116 microbiomes in a plenty of ways. Indeed, the soil/rhizosphere microbiome mediates the cycle
117 of carbon and other nutrients, the maintenance of soil fertility and soil carbon sequestration,
118 and sustains plant growth. These activities have direct and indirect effects on plant as well as
119 animal growth and health in terrestrial and marine ecosystems and, therefore, affect the
120 quantity, quality and sustainability of primary production (Amundson *et al.*, Science 2015),
121 and food processing, and, in turn, the final impacts on human health.

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123 In parallel to the bacterial counterpart, on which the overwhelming majority of current
124 microbiome knowledge is based, viruses are receiving increasing attention because they have
125 been found to fill a variety of ecological niches within their host. Virome interactions with the
126 host can no longer be encompassed by a view of viruses as pathogens. In particular, members
127 of the eukaryotic virome that chronically infect mammals, including humans, have been found
128 to exert significant effects on host physiology beyond the simple paradigm of invasion and
129 tissue destruction (Foxman *et al.*, Nat Rev Microbiol 2011; Stelekati *et al.*, Cell Host Microbe
130 2012; Virgin *et al.*, Cell 2009).

131
132 Unlike some other EU countries, Italy does not have any national microbiome program
133 supported by national grants. Despite of this, Italian researchers are actively working on
134 human microbiome, in different body districts, in preclinical and clinical studies to
135 characterize its role in physiological and pathological conditions, in infants, children, adults
136 and elderly. Others are involved in studying the human virome, and others are investigating
137 the microbiome of soil and sediments, terrestrial and aquatic plants and animals, foods, and
138 their relations with human gut microbiome and health. Although such a number of relevant
139 expertises and prominent scientists active in the field, they are largely fragmented limiting the
140 potential of impact on the international microbiome know-how and its exploitation, and this
141 asks for a urgent need for a national coordinated action.

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3. Expertise, infrastructures and industrial sectors involved in microbiome-based knowledge exploitation

3.1 Microbiome Facilities and Expertise rely on genomic-based analyses, resources and support necessary to characterize and study microbiomes, including:

1. Advanced technological platforms for the phylogenetic and functional characterization of microbiomes, including **next-generation sequencing (NGS) platforms** based on Miseq, NextSeq and HiSeq (Illumina) as well as Ion Torrent PGM (Life Technologies) and PacBio (Pacific BioSciences), that allow researchers to:

- rapidly sequence whole microbial genomes and metagenomes, instrumental in providing an overview of microbiome functional capacities;

- utilize RNA sequencing (RNA-Seq) for metatranscriptomics analysis.

2. **Quantitative Real-Time PCR platforms** for quantification of nucleic acids in many different applications, for Gene Expression, Genotyping, Copy Number Variation, MicroRNA, Pathogen Detection, etc.

3. **Proteomics platforms** to quantify meta-proteomes and specific metabolic pathways.

4. **Metabolomics platforms: LC-MS/MS Quantum Access MAX triple quadrupole mass spectrometer** coupled to U-HPLC and **NMR 600 Hz** for host/microbiome metabolomic profiling, quantification of microbiome metabolites and co-metabolites, measurement of trace-level environmental or food contaminants, or detection of specific biomarkers.

5. **OmniLog® Phenotype Microarray** for genotype-phenotype characterization of microbes, as well as for determining optimal conditions for cellular growth, sporulation and germination, production of secondary metabolites, or enzymatic activities in cell lines.

6. **Simulator of the Human Intestinal Microbial Ecosystem (SHIME®)** to *in vitro* mimics the human gastrointestinal digestion. SHIME is one of the few gut models that mimics the entire gastrointestinal tract incorporating stomach, small intestine and different colon regions.

7. **Animal Facilities** to perform studies in animal models (e.g. mice and rats). Authorized facilities to perform specific challenge models in controlled conditions and infrastructures to produce germ-free and specific pathogen-free animals are available, as well as animal facilities to implement small and mid scale farming animal (e.g. pigs, poultry, dairy cows and goats) trials, and experimental tanks for aquaculture studies.

8. **Databases and bioinformatics pipelines** necessary for the microbiome metataxonomic and metagenomics data analysis, and **multidimensional statistics approaches** for the integration among microbiome datasets and host phenotyping, as well as environmental metadata, in a perspective of systems biology.

9. **Human & animal model phenotyping:** body composition analysis (dual-energy X-ray absorptiometry, bioimpedance analysis, air displacement plethysmography), energy expenditure evaluation (indirect calorimetry, movement actigraphy), energy and nutrient intake (eating pattern and behaviour evaluation), functional assessment (handgrip and leg-extension strength tests, sub-maximal exercise test, physical performance battery).

3.2. Italian involvement in EU projects and networks

Following an overview of a selection of past and running collaborative EU projects dealing with nutrition, microbiome and host health – human, animal and plant- in which Italian researchers participated or are currently joining.

The Italian contribution to the microbiome in nutrition and host health can be represented by the following EU projects:

- 195 • Consortium "New dietary strategies addressing the specific needs of elderly population for
 196 a healthy ageing in Europe" (**NU-AGE**); Collaborative Project targeted to develop elderly-
 197 tailored prototypes of functional foods and to improve traditional foods.
 198 https://cordis.europa.eu/result/rcn/155983_it.html; COORDINATION
- 199 • Consortium "European network on the factors affecting the gastro- intestinal microbial
 200 balance and the impact on the health status of pigs" (**PiGutNet**); Collaborative Project
 201 targeted to study genome/metabolome-wide association and to provide a road map to
 202 increase pig resistance against GIT infections. COST Action FA1401,
 203 <http://www.pigutnet.eu/> COORDINATION
- 204 • Consortium "Ecology from farm to Fork of microbial drug resistance and transmission"
 205 (**EFFORT**); Collaborative Project targeted to a special group (such as SMEs);
 206 https://cordis.europa.eu/project/rcn/111140_it.html
- 207 • Consortium "Reducing egg susceptibility to contaminations in avian production in Europe "
 208 (**RESCAPE**); Collaborative Project targeted for food quality and safety - Disease risk for
 209 consumers from alternative and enriched cage laying hen systems;
 210 https://cordis.europa.eu/project/rcn/80032_it.html
- 211 • Consortium " European animal disease genomics network of excellence for animal health
 212 and food safety" (**EADGENE**); Collaborative Project targeted for strengthening the
 213 implementation of durable integration in FP6 Networks of Excellence;
 214 https://cordis.europa.eu/project/rcn/74158_en.html
- 215 • Consortium "Interplay of microbiota and gut function in the developing pig – Innovative
 216 avenues towards sustainable animal production" (**INTERPLAY**); Collaborative Project
 217 targeted for improving production animal health and food safety through investigating the
 218 gut function of farm animals, the gastro-intestinal microflora and their interactions;
 219 https://cordis.europa.eu/project/rcn/92294_en.html
- 220 • Consortium "Connecting the animal genome, gastrointestinal microbiomes and nutrition to
 221 improve digestion efficiency and the environmental impacts of ruminant livestock
 222 production" (**RUMINOMICS**); Collaborative Project targeted to develop models and tools to
 223 enable the livestock industry to decrease environmental damage from methane and
 224 nitrogen emissions, and to improve efficiency of feed utilisation;
 225 https://cordis.europa.eu/project/rcn/101163_it.html
- 226 • Consortium " The role of intestinal microflora in non-alcoholic fatty liver disease (NAFLD)"
 227 (**FLORINASH**); Collaborative Project targeted to address the role of intestinal microflora
 228 activity in the pathogenesis of NAFLD;
 229 https://cordis.europa.eu/project/rcn/93672_en.html
- 230 • Consortium "New E-Services for a dietary approach to the elderly" (**RISTOMED**);
 231 Collaborative Project targeted to solve the common problem of delivering innovative
 232 nutraceuticals for the control and prevention of the age-related diseases;
 233 https://cordis.europa.eu/project/rcn/92439_en.html COORDINATION
- 234 • Consortium "Metagenomics of the Human Intestinal tract" (**METAHIT**); Collaborative
 235 Project targeted to establish associations between the genes of the human intestinal
 236 microbiota and our health and disease;
 237 https://cordis.europa.eu/project/rcn/87834_en.html
- 238 • Consortium "Microbiome Influence on Energy balance and Brain Development-Function
 239 Put into Action to Tackle Diet-related Diseases and Behavior" (**MyNewGut**); Collaborative
 240 Project targeted to develop new approaches to prevent diet-related diseases and
 241 behavioural disorders through lifestyle changes, intake of pro- and prebiotics and semi-
 242 personalised and innovative food products;
 243 https://cordis.europa.eu/project/rcn/111044_it.html
- 244

245 *The Italian contribution to the microbiome in the food processing can be represented by the*
246 *following EU projects:*

- 247 • Consortium "Controlling Microbiomes Circulations for Better Food Systems" (**CIRCLES**);
248 Collaborative Project targeted to discover, translate and communicate innovative,
249 microbiome-based applications to enhance food system performances and their
250 sustainability; H2020-SFS-2018-2020 COORDINATION
- 251 • Consortium "Biotransformation of brewers' spent grain: increased functionality for novel
252 food applications" (**FUNBREW**); Collaborative Project targeted to establish bioprocessing
253 technologies for the synthesis in situ of functional compounds in BSG, such as
254 exopolysaccharides (EPS) and antioxidants COST ACTION 2017.
255 [https://tuhat.helsinki.fi/portal/en/projects/biotransformation-o\(ea2896e5-a08a-4cd4-](https://tuhat.helsinki.fi/portal/en/projects/biotransformation-o(ea2896e5-a08a-4cd4-a131-ddc6faf52098).html)
256 [a131-ddc6faf52098\).html](https://tuhat.helsinki.fi/portal/en/projects/biotransformation-o(ea2896e5-a08a-4cd4-a131-ddc6faf52098).html)
- 257 • Consortium "Inflammatory Bowel Disease: a EU-NZ integrated approach for characterizing
258 its molecular multifactorial mechanisms" (**REINFORCE**); Collaborative Project targeted to
259 lead to a high degree of novelty in IBD training by allowing to build up a new profile of
260 researcher able to tackle the different aspects of IBD; FP7- PEOPLE.
261 https://cordis.europa.eu/result/rcn/165580_en.html
- 262 • Consortium "Novel multifunctional plant protein ingredients with bioprocessing"
263 (**BIOPROT**); Collaborative Project targeted to reinforce the scientific cooperation between
264 EU member and associated states in order to maximise the contribution of research to the
265 development of more sustainable food systems; FP7-ERANET-2011-RTD.
266 [https://www.era-learn.eu/network-information/networks/susfood/1st-joint-call-for-](https://www.era-learn.eu/network-information/networks/susfood/1st-joint-call-for-proposals/novel-multifunctional-plant-protein-ingredients-with-bioprocessing)
267 [proposals/novel-multifunctional-plant-protein-ingredients-with-bioprocessing](https://www.era-learn.eu/network-information/networks/susfood/1st-joint-call-for-proposals/novel-multifunctional-plant-protein-ingredients-with-bioprocessing)
- 268 • Consortium "Innovative biotechnological solutions for the production of new bakery
269 functional foods" (**Bake4Fun**); Collaborative Project targeted to responds to the needs of
270 food SMEs of innovating food formulations and technologies to overcome the negative
271 effect of iron fortification of bakery products; FP7-SME-2013.
272 https://cordis.europa.eu/project/rcn/110204_it.html

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274 *The Italian contribution to the microbiome in soils, sediments and rhizosphere knowhow can be*
275 *represented by the following EU projects:*

- 276 • Consortium "Unravelling and exploiting Mediterranean Sea microbial diversity and ecology
277 for xenobiotics' and pollutants' clean up" (**ULIXES**); Collaborative Project targeted to
278 approaches towards bioremediation of the Mediterranean Sea by exploring its microbial
279 diversity – SICA; FP7 https://cordis.europa.eu/project/rcn/97824_it.html
280 COORDINATION
- 281 • Consortium "Marine Microorganisms: Cultivation Methods for Improving their
282 Biotechnological Applications" (**MACUMBA**); Collaborative Project targeted to improve the
283 isolation rate and growth efficiency of marine microorganisms from conventional and
284 extreme habitats and the use of automated high throughput procedures; FP7
285 https://cordis.europa.eu/project/rcn/104389_it.html
- 286 • Consortium "Industrial Applications of Marine Enzymes: Innovative screening and
287 expression platforms to discover and use the functional protein diversity from the sea"
288 (**INMARE**); Collaborative Project targeted to streamline the pathways of discovery and
289 industrial applications of new marine enzymes and bioactives for targeted production of
290 fine chemicals, drugs and in environmental clean-up applications; H2020
291 https://cordis.europa.eu/project/rcn/193292_it.html
- 292 • Consortium "Marine Microbial Biodiversity, Bioinformatics and Biotechnology" (**MICRO**
293 **B3**); Collaborative Project targeted to develop innovative bioinformatic approaches to
294 make large-scale data on marine viral, bacteria; archaeal and protists genomes and

- 295 metagenomes accessible for marine ecosystems biology; to define new targets for
296 biotechnological applications; FP7 https://cordis.europa.eu/project/rcn/101555_en.html
297 • Consortium "Increasing Value and Flow in the Marine Biodiscovery Pipeline"
298 (PHARMASEA); Collaborative Project targeted to produce new products with desirable
299 characteristics for development by the SME partners in three accessible market sectors,
300 health (infection, inflammation, CNS diseases), personal care and nutrition; FP7
301 https://cordis.europa.eu/project/rcn/104338_it.html
302 • Consortium "Development Of innovative Tools for understanding marine biodiversity and
303 assessing good Environmental Status" (DEVOTES); Collaborative Project targeted to
304 develop/test/validate innovative integrative modelling tools to further strengthen our
305 understanding of ecosystem and biodiversity changes; FP7
306 https://cordis.europa.eu/project/rcn/105613_en.html
307 • Consortium "Biotechnology from desert microbial extremophiles for supporting
308 agriculture research potential in Tunisia and Southern Europe" (BIODESERT) FP7 regpot
309 https://cordis.europa.eu/project/rcn/93561_en.html
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311 **3.3 Industrial sectors involved in microbiome-based knowledge exploitation.**

312 The generated knowledge around microbiome is now attracting the interest of several
313 industries that need to be engaged to effectively and responsibly apply this new knowledge.
314 The National Technology Clusters CLAN (Agri-Food) and ALISEI (Life Sciences) are sustaining
315 initiatives to open ways to modify the microbiomes and develop microbiome-based
316 applications.
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318 *Biotechnological industry*

319 Several companies, sprouted up in recent years, aim at developing new therapies that
320 alter the microbiome for the benefit of human health. For instance, probiotics and
321 prebiotics have become a quite widespread consumption recently, and they are routinely
322 included in foods, drinks and supplements.

323 *Pharmaceutical industry*

- 324 • Developing alternative intervention measures (prophylaxis/prevention or treatment) to
325 limit anti-microbial use has a high translational potential. The development and the
326 validation of modulators of host immunity and/or of microbial ecosystems, feed
327 additives or novel molecules, are key targets of research for the industry. Collaboration
328 between sectors could open new perspectives for the exploitation of residual bioactive
329 compounds as well as by-products of the agro-industry.
- 330 • The identification of biomarkers to reclassify the co-morbidities on mechanisms and
331 companion to therapeutic strategies is one of the expected major results of microbiome
332 research. New identified and validated biomarkers will greatly facilitate the
333 management of metabolic diseases and of those co-morbidities by providing new
334 possibilities for diagnostics, predictions and qualified strategic therapies, and thus pave
335 the way for a new direction in clinical research on new targets.

336 *Food industry*

337 We are observing alterations in how and what we eat (processed foods with longer shelf
338 lives, more "ready-to-eat" items, the evolving dominance of snacking, etc.), experiencing
339 rapid expansion of human population and great challenges related to sustainable
340 agriculture. The combination of these forces is creating a need for sustained innovation in
341 identifying affordable new food sources and new highly nutritious foods. Studies of
342 microbiomes could provide efforts to integrate agricultural policies and practices, food
343 production and distribution, and nutritional recommendations for consumers
344 representing different ages, lifestyles, geographies, and states of health.

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Agro industry: primary production

Developing new products for agriculture, indeed plant and animal microbiome manipulation, represents a potential alternative for sustainable food production through modulating growth, development, pathogen defense, nutrient acquisitions and stress resistance.

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4. Vision: state-of-the-art of knowledge, needs and actions for boosting the sector in Italy

4.1- Knowledge and impacts

4.1.1. Microbiome and human health

Among the microbiomes colonizing different body districts (nose, mouth, throat, skin vagina, urethra, intestine), the gut microbiome is the most studied. Endowed with an immense gene catalogue, exceeding the human one nearly 500 times, the intestinal microbiome exerts a profound influence on human physiology and metabolism. Indeed, gut microorganisms complement several gaps in human metabolic pathways, producing essential vitamins (mainly those of the B group), and affording the extraction of energy from otherwise indigestible carbohydrates (i.e. dietary fiber), thus playing a major role in host energy balance and nutrition. Intestinal microbes are also involved in the bioconversion of dietary components with major impacts on immune functionality and metabolic homeostasis (Tilg and Moschen, *Gastroenterology* 2015; Sonnenburg and Bäckhed, *Nature* 2016). Hence, it is not unexpected that several metabolic disorders, including obesity, type 2 diabetes and non-alcoholic fatty liver disease, are associated with microbiome dysbiosis, with an altered pattern of bacterial taxa and microbiota-derived biomolecules that may contribute to promote or further aggravate disease processes (Hartstra *et al.*, *Diabetes Care* 2015; Tripathi *et al.*, *Nat Rev Gastroenterol Hepatol* 2018). For example, the dysregulation of the microbiota-host co-metabolism of bile acids can contribute to compromised glucose homeostasis, impaired liver and pancreatic function, and adipose tissue inflammation (Wahlström *et al.*, *Cell Metab* 2016). High-fat low-fiber Western diets are indeed repeatedly shown to affect the gut microbiota structure with downstream detrimental effects on intestinal permeability, lipid accumulation, and inflammatory state (Jena *et al.*, *FASEB J* 2018). In contrast, adherence to a Mediterranean-style diet, characterized by increased intake of fiber-rich food, is known to beneficially modulate host-microbiome interactions, helping preventing a number of diseases (De Filippis *et al.*, *Gut* 2016). However, there is a need to better investigate the health-promoting features of the gut microbiome as shaped by the Mediterranean diet.

In parallel to diet, recent evidence is also supporting a role of physical activity in the modulation of microbiomes, with important repercussions on metabolism (Cronin *et al.*, *mSystems* 2018; Greenhill *et al.*, *Nat Rev Endocrinol* 2018).

In the context of metabolic disorders, metagenomics analysis in Italian obese subjects revealed specific signatures related to metabolic traits. An interplay between increased proteobacteria and phenylacetic acid, a microbial metabolite that interferes with branched chain aminoacid catabolism, has been demonstrated (Hoyles *et al.*, *Nature Medicine* 2018). Derangements in microbial tryptophan metabolism with a specific induction of kynurenine and reduction in indoles are related in the same subjects to glucose intolerance (Laurans *et al.*, *Nature Medicine* 2018).

The gut microbiota is widely recognized as an integral component of the human immune system, finely calibrating both innate and adaptive immune responses throughout life. The intimate interplay between gut microbes and mucosal immune cells has been shown to be crucial for the maintenance of immune homeostasis and especially for the education of the immune system during infancy (Honda and Littman, *Nature* 2016; Thaïss *et al.*, *Nature* 2016). Indeed, specific alterations of the gut microbiome in the first months of life, a critical time window for the child's long-term health, have been found to be associated with the development of allergy and other immunological/metabolic disorders later in life (Arrieta *et al.*, *Sci Transl Med* 2015; Cox *et al.*, *Cell* 2014). Regardless of age, disruption of the delicate balance of commensal bacteria (i.e. dysbiosis) may lead to impaired local and systemic

403 immune responses, with breakdown of mucosal barriers, translocation of gut bacteria
404 beneath the epithelium, and alterations of the cytokine milieu and T cell ratio towards an
405 inflammatory phenotype, thus eliciting a profound inflammatory state both locally and
406 systemically (Gopalakrishnan *et al.*, Cancer Cell 2018). This is the case of several NCDs that
407 share inflammation as a common basis, including inflammatory bowel disease and irritable
408 bowel syndrome, and other disorders with a strong immunological component, i.e. when the
409 host can no longer control commensal bacteria (as in autoimmune diseases – e.g. type I
410 diabetes and rheumatoid arthritis) and/or may allow pathogen invasion and infection (as in
411 immunosuppressive diseases – e.g. in patients with HIV infection or undergoing
412 hematopoietic stem cell transplantation for hematological malignancies) (Lynch and
413 Pedersen, N Engl J Med 2016; Zaneveld *et al.*, Nat Microbiol 2017).
414 Accumulating data on the bidirectional gut-brain axis are also supporting a role of the
415 intestinal microbiome in the regulation of anxiety, cognition, pain and behavior, and its
416 possible contribution to the pathophysiology of central nervous system disorders, as multiple
417 sclerosis and autism spectrum disorders (Sharon *et al.*, Cell 2016).
418 In addition, the functional output of the gut microbiome, including SCFAs and aminoacids, and
419 the microbiome capacity to alter the bioavailability especially of aromatic and branched chain
420 aminoacids confirm the existence of a gut-muscle communication pathway and seem to be
421 involved in the mechanisms leading to the development of sarcopenia and sarcopenic obesity
422 (Picca *et al.*, Mediators Inflamm 2018; Ticinesi *et al.*, Nutrients 2017; Inglis *et al.*, Curr
423 Osteoporosi Rep 2015).

424

425 **4.1.2 The human gut microbiome and disease prevention and therapy**

426 There is urgent need to translate the gut microbiome data and knowledge generated in recent
427 years into concrete actions. In particular, the growing body of literature on the transition of
428 the human gut microbiota from health to disease will help design knowledge-based,
429 personalized intervention strategies to manipulate the intestinal microbial community
430 towards a more “favorable” profile, for enhanced therapeutic responses. Strategies will
431 include: i) dietary interventions, as a simple, safe and accessible adjunct to current therapies;
432 ii) administration of bacterial consortia or “designer probiotics”, rationally selected based on
433 the increasing understanding of the complex syntrophic connections between microbiota
434 components and the peculiar dysbiosis to be addressed; iii) approaches of fecal microbiota
435 transplantation, as the most direct means of manipulation of an altered gut microbiome.
436 Future research will have to take into account the inherent variability of the gut microbiome,
437 monitoring the individual trajectory over time, in eubiotic and dysbiotic states. Similarly,
438 novel, microbiome-specific end-points must be implemented to assess the efficacy of a
439 probiotic therapy. Indeed, it is now a matter of fact that the success of a probiotic course
440 depends on the supported recovery of an eubiotic microbiome state and, therefore, on the
441 probiotics capacity to re-direct the individual dysbiotic trajectory in the frame of the
442 physiological fluctuation (“the healthy plane of variation” – Halfvarson *et al.*, Nat Microbiol
443 2017; Zaneveld *et al.*, Nat Microbiol 2017). Carrying out a re-analysis of the gut microbiome at
444 the end of probiotics interventions will thus be mandatory to evaluate their efficacy in terms
445 of recovery of a healthy microbiome configuration. Finally, the new approaches of
446 culturomics, aimed at cultivating all the components of the human gut microbiome by use of
447 optimized, selective and/or enrichment culture conditions coupled to metagenomics
448 identification, are expanding the current narrow range of probiotics available to consumers,
449 by revealing other organisms as providers of new and more effective probiotic functions, i.e.
450 the “next-generation probiotics” (O’Toole *et al.*, Nat Microbiol 2017; Kim *et al.*, Crit Rev Food
451 Sci Nutr 2018). As an example, the bacteria *Christensenella* and *Faecalibacterium prausnitzii*
452 showed increased anti-inflammatory potential compared to the more traditional
453 bifidobacteria and lactobacilli, and the species *Akkermansia muciniphila* has promising

454 application for the treatment of obesity. Furthermore, human microbiomes are receiving
455 significant attention given their influence on cancer therapy, with several recent studies
456 demonstrating the existence of a “more favorable” gut microbiome configuration predictive of
457 a positive long-term response, and strongly suggesting that manipulating the gut microbiota
458 could be an important adjunct to current anti-cancer therapeutic strategies for improved
459 responses, circumventing primary resistances and disease recurrences (Gopalakrishnan *et al.*,
460 *Cancer Cell* 2018).

461 On the other hand, despite the many advances in metagenomics we have witnessed in recent
462 years, the human gut microbiome still harbors a large amount of uncharacterized functional
463 diversity, with an immense potential for the discovery of new health-promoting biological
464 molecules. Such molecules could represent innovative medicinal chemistry possibilities
465 towards the identification of novel drug candidates, targets, and more in general innovative
466 ways for the treatment of unmet medical needs. Microbiota-derived metabolites are indeed
467 emerging as promising starting hit compounds to modulate human targets, hence triggering
468 certain pharmacological responses. Robust campaigns of metagenome-based microbiome
469 bioprospecting, synergizing different and complementary approaches, such as functional
470 omics, systems medicine, *in silico* drug discovery, target fishing and quantum biomolecular
471 modeling, must thus be given priority to implement innovative, precision intervention
472 strategies for specific steering of the gut microbiome contribution to human health. At the
473 same time, the increasing knowledge of the microbiome impact on pharmacokinetics and thus
474 on the individual response to pharmaceuticals, is instrumental to the implementation of
475 specific approaches of rational drug design, aimed at removing or modifying chemical and
476 functional groups known to be subjected to microbial metabolism in the gut, for increased
477 bioavailability and decreased toxicity of drugs. Research in this direction will be essential to
478 define the best intervention strategies based on the individual gut microbiome functional
479 layout, for more precise, knowledge-based and cost-effective drug utilization.

481 **4.1.3. Soils, sediments and sustainable agriculture and food processing**

482 *Relevance of primary production and food processing for the Italian Economy.* In 2016, the
483 value of arable, fodder and tree crop productions in Italy has been approximately 27 billion
484 Euro. It contributes to half of the value of all agriculture, silviculture and fishery sectors
485 (CREA, 2017 [https://www.crea.gov.it/wp-content/uploads/2017/03/Itaconta-2016-x-](https://www.crea.gov.it/wp-content/uploads/2017/03/Itaconta-2016-x-WEB.pdf?x99213)
486 [WEB.pdf?x99213](https://www.crea.gov.it/wp-content/uploads/2017/03/Itaconta-2016-x-WEB.pdf?x99213); the Italian Bioeconomy strategy
487 [http://www.agenziacoesione.gov.it/opencms/export/sites/dps/it/documentazione/S3/Bioe-](http://www.agenziacoesione.gov.it/opencms/export/sites/dps/it/documentazione/S3/Bioeconomy/BIT_v4_ENG_LUGLIO_2017.pdf)
488 [conomy/BIT_v4_ENG_LUGLIO_2017.pdf](http://www.agenziacoesione.gov.it/opencms/export/sites/dps/it/documentazione/S3/Bioeconomy/BIT_v4_ENG_LUGLIO_2017.pdf)). Italy is a leading country in Europe for the high
489 quality certified agri-food products. Since 2013 the export for the agri-food sector increased
490 from 33 to 41 billion Euro. The demand for Italian high quality agri-food products is
491 increasing both in Europe and outside the continent. Farmers, especially those producing high
492 quality products, pay increasing attention to sustainable solutions that adopt microbial-based
493 fertilizing, plant growth-promoting, plant bio-conditioning and biocontrol products (Bashan
494 *et al.*, *Plant Soil* 2014; Bashan *et al.*, *Biol Fertil Soils* 2016). This interest is markedly
495 supported by the ongoing growth of organic farming in Europe and worldwide. In 2015, the
496 organic farming product market in Europe was of 29.8 billion Euro, with an increase of 13%
497 with respect to the previous year. Italy is among the ten biggest world producers of organic
498 products and is the second one in Europe, after Spain, for the surface area destined to organic
499 farming. In 2016, the Italian organic farming surface area increased by 20% with respect to
500 2015, with 3.5% of the total world organic farming surface area (1.8 M hectares) and 14.5% of
501 the national surface being destined to agriculture (CREA, 2017 [https://www.crea.gov.it/wp-](https://www.crea.gov.it/wp-content/uploads/2017/03/Itaconta-2016-x-WEB.pdf?x99213)
502 [content/uploads/2017/03/Itaconta-2016-x-WEB.pdf?x99213](https://www.crea.gov.it/wp-content/uploads/2017/03/Itaconta-2016-x-WEB.pdf?x99213)).

503 In line with the above primary production context, the Italian food industry in 2017 had a
504 turnover of 137 billion Euro (approximately 32 billion Euro from the export), 385,000

505 employees and 58,000 companies. The food industry is the second largest manufacturing
506 sector in Italy, and the third in Europe, behind Germany and France (Italian Bioeconomy
507 strategy
508 http://www.agenziacoesione.gov.it/opencms/export/sites/dps/it/documentazione/S3/Bioeconomy/BIT_v4_ENG_LUGLIO_2017.pdf). The 18th census of the Italian Ministry of
509 Agricultural, Food and Forestry Policies (GU Serie Generale n. 57 del 09-03-2018 - Suppl.
510 Ordinario n. 11) lists more than 4,800 traditional foods and beverages, which are the main
511 pillars of the regional economies. Italy is the leading European country for foods and
512 beverages, which have a legal status of recognition. Indeed, 294 foods have the status of DOP,
513 IGP or STG, and 523 wines those of DOCG, DOC or IGT. As declared by UNESCO, the
514 Mediterranean Diet, mainly based on traditional foods and beverages, is an Intangible Cultural
515 Heritage of Humanity.

516
517
518 *Microbiome relevance in the terrestrial primary production.* The soil/rhizosphere microbiome
519 mediates the cycle of carbon and other nutrients, the maintenance of soil fertility and soil
520 carbon sequestration, and sustains plant growth. All these activities have direct and indirect
521 effects on plant and animal health in terrestrial ecosystems and, therefore, affect the quantity,
522 quality and sustainability of primary production (Amundson *et al.*, Science 2015). Because of
523 the large soil heterogeneity and the fluctuating environmental conditions across microbial
524 habitats (e.g., rhizosphere, preferential water flow paths, animal burrows, intra-aggregate and
525 inter-aggregate environments), there is not a “typical soil microbiome” and the relative
526 abundances of the major bacterial and archaeal taxa vary considerably within few centimetres
527 of a spatial scale (Fierer *et al.*, Nat Rev Microbiol 2017). To date, the functions of soil microbes
528 are largely unknown. The available data suggest that the soil microbiota represents a complex
529 and dynamic ecological community able to interact with animals and plants, thus influencing
530 their physiology, health status, production efficiency and behaviour. Microbiomes associated
531 with plant rhizosphere and tissues in the root system and the other plant organs are
532 determinants of the host fitness. They support plant nutrition, health and resistance to biotic
533 and abiotic stresses. Such microbiomes are highly diversified and provide a plant-
534 independent secondary genome that delivers key ecological functionalities, which favor the
535 plant host fitness (Rosenberg, Zilber-Rosenberg, MBio 2016). Because of these interactions,
536 the soil and plant microbiota plays a key role on the quality and safety of plant primary
537 production, including fruits, and related processed foods (Gilbert *et al.*, Proc Natl Acad Sci USA
538 2014; Marasco *et al.*, Microbiome 2018). Italian researchers actively worked on the microbial
539 resource from desert and arid environments for the alleviation of abiotic plant stresses.
540 The microbiome profile and functions in food-producing animals have been investigated on a
541 number of species. The expectancies here are to exploit microbiota knowledge for facilitating
542 the transition of the livestock production from a system strongly oriented to maximize the
543 productivity to one more efficient, less dependent on the use of antibiotic and consequently
544 more sustainable for the environment and for the society. Even if the different species seem to
545 partially share their microbiota (Milani *et al.*, ISME 2017), monogastric (e.g. pigs, chicken),
546 ruminant (e.g. dairy cows, sheep) and lagomorph (e.g. rabbits) represent well distinguished
547 ecosystems co-evolved with their peculiar microbiota and characterized by specie-specific
548 enterotype. This is due to their peculiar feed preferences (e.g., herbivorous *vs* omnivorous)
549 and feeding behaviors. Several studies on rumen microbiota (Wallace *et al.* BMC Genomics
550 2015; Ben Shabat *et al.* ISME J 2016) have dealt with the evident symbiosis between rumen
551 microbiota and ruminants, and with the role of some microbial species for the greenhouse
552 gases production. Conversely, in pigs and poultry data are quite scarce and no exhaustive
553 dataset evidenced a consistent relationship between gut microbiome and animal phenotypes
554 (Stanley *et al.*, Appl Microbiol Biotechnol 2014; Yuliaxis Ramayo-Caldas *et al.*, ISME J 2016).

555 However, the available data suggest that the livestock microbiota is a relevant determinant
556 for the final health status, production efficiency and behaviour of animals.

557

558 *Relevance of microbiome in the marine primary production.* Fish is an invaluable source of
559 food, nutrition, income and livelihoods. World per capita fish supply reached 20 kg in 2014,
560 thanks to the growth in aquaculture, which now provides half of all fish for human
561 consumption (FAO 2016). Microbial communities dominating sediment and marine water
562 ecosystems are numerically, taxonomically and functionally diverse. They are the primary
563 contributors to marine/ocean biogeochemical cycles and thus the drivers of other trophic
564 levels, including aquatic animals production and health (Moran, Science 2015). The marine
565 microbiome responds to many natural and anthropogenic environmental pressures (Bourlat
566 *et al.*, Mar Pollut Bull 2013; Goodwin *et al.*, Front Mar Sci 2017; Buttigieg *et al.*, Curr Opin
567 Microbiol 2018) and it has been proposed as an ecosystem indicator to assess the quality and
568 productivity of seawater and sediments (Nogales *et al.*, FEMS Microbiol Rev 2011).

569 A limited number of studies are investigating the role of the microbiome in fish health,
570 physiology, ecology, and behaviour. Pioneer molecular studies describe the functional
571 diversity of seabream microbiome (Xing *et al.*, FEMS Microbiol Ecol 2013; Ni *et al.*, FEMS
572 Microbiol Ecol 2014), its role in the developmental stages of fish (Califano *et al.*, Front
573 Microbiol 2017) and how the nutrition impacts on the gut microbiome and, in turn, on the fish
574 growth and efficiency (Parma *et al.*, Anim Feed Sci Tech 2016; Piazzon *et al.*, Microbiome
575 2017).

576 Aquaculture in open-sea fish cages plays a key role for the future growth of aquaculture, due
577 to increasing competition for land and water, and the growing market demand for high-
578 quality fish products. Main issues is the benthic organic enrichment caused by solid waste in
579 the form of faeces and feed settling on the seabed, that in enclosed and semi-enclosed coastal
580 environments may lead to eutrophication problems (Price *et al.*, Aquacult Environ Interact,
581 2015; Ballester-Moltó *et al.*, Mar Environ Res 2017). Ultimately, the loss of marine
582 environmental quality also affects aquaculture fish quality and productivity. Bioremediation
583 technologies can be employed to prevent/mitigate such consequences.

584

585 *Relevance of microbiome in the food processing and nutrition.* Microbes occurring in food and
586 beverages are key elements of their ultimate quality, authenticity, nutritional properties,
587 safety and preservation. The microbial fermentation represents the most natural, sustainable,
588 low-cost, functional and friendly biotechnology to obtain foods and beverages with improved
589 shelf life, safety, nutritional, functional and organoleptic properties, and health-promoting
590 potential (Macori and Cottar, Curr Opin 2018; Filannino *et al.*, Curr Opin Biotechnol 2018).
591 Currently, the most intriguing and promising perspective in food processing is the
592 establishment, assembly and shaping of the microbiome, which play fundamental roles in any
593 food matrix ranging from fermentation, contamination and spoilage (Gobbetti *et al.*, Curr Opin
594 Biotechnol 2017). A coherent and novel view dealing with the management of the microbiome
595 in foods and beverages must consider not individual players and their food-related
596 performance but the overall community. Most of the scientific evidences have suggested that
597 fermented foods should be included in the national dietary recommendations (Chilton *et al.*
598 Nutrients 2015) because they are sources of biotypes used as probiotics and because of the
599 ability of microbes to synthesize bioactive or bioavailable metabolites/compounds.

600

601 **4.2- Constrains, needs and opportunities for R&I and policies**

602

603 **4.2.1 Microbiome and host health**

604 *Expanding microbiome research to other body sites*

605 Although the gut microbiota represents the largest and most complex microbial community
606 associated with the host, other body sites, such as mouth, skin, urogenital and respiratory
607 tracts harbor their specific microbial consortium intimately related with several
608 physiological functions and often involved in conditioning host health at local or systemic
609 level. During the development, the host microbiome follows a body site-specific trajectory,
610 and each body site develops a specific “biogeography”.

611 **The oral microbiota** is considered one of the most complex and variable host-associated
612 microbial community. Such complexity depends on the great number of distinct niches
613 present in the oral cavity (Xu *et al.*, Environ Microbiol 2015) while its composition is
614 characterized by a huge inter-personal diversity and temporal variability (Hall *et al.*, NPJ
615 Biofilms Microbiomes 2017). The finely-tuned ecosystem in the oral cavity can shift to a
616 dysbiotic profile with loss of community balance or diversity and a single or few species
617 predominating. To date, different studies have shown a relationship between the changes
618 in the oral microbiota composition and host health not only with respect to pathologies
619 strictly associated to oral cavity (Kilian *et al.*, Br Dent J 2016), but even to systemic diseases
620 (Jia *et al.*, Br Dent J 2018).

621 **The skin** is another body site harboring a myriad of microbial communities residing on the
622 tissue surface, as well as in hair follicles and sebaceous glands (Belkaid and Segre, Science
623 2014). It has been demonstrated that skin-resident microbes control the expression of
624 various innate immune factors (Gallo *et al.*, Nat Rev Immunol 2012), limit pathogenic
625 microbial invasion and reinforce its own stability and containment (Belkaid and Segre,
626 Science 2014). Despite the increasing amount of data, the specific contribution of skin
627 resident microbes to the host health needs further investigation.

628 **The vaginal microbiome** has a certain degree of stability and can be classified into discrete
629 states during disease. Individual species of *Lactobacillus* as well as diverse additional
630 anaerobic taxa tend to dominate the vaginal microbiota in asymptomatic subjects (Ma *et al.*,
631 *Annu Rev Microbiol* 2012). The lactobacilli are believed to benefit the host by lowering vaginal pH and
632 reducing allochthonous microbial colonization or pathogen invasion. Variation of microbial
633 composition does occur over days to weeks within an individual subject (Ravel *et al.*,
634 *Microbiome* 2013).

635 **The respiratory tract** is a complex organ system that spans from the nostrils to the lung
636 alveoli showing a succession of ecological niches with distinct but related bacterial
637 communities. To date, the knowledge about composition and function of such microbial
638 community is still limited, if compared to other host microbiomes. The anterior nares harbor
639 a relatively simple microbiota (Zhou *et al.*, Genome Biol. 2014), in contrast to the
640 nasopharyngeal microbiota, which is more complex and dynamic, undergoing important
641 changes over time (Perez-Losada *et al.*, PLoS One 2017) and constituting a well-know
642 reservoir for potential pathogens able to cause respiratory tract infections. The healthy lung
643 sterility paradigm has repeatedly been challenged since the introduction of culture-
644 independent techniques (Dickson *et al.*, Lancet Respir Med 2014; Taylor and Wesselingh, Cell
645 Microbiol 2016). From a functional point of view, the microbiota associated to the respiratory
646 tract might play an important role in maintaining the homeostasis of respiratory function,
647 acting as a gatekeeper that provides resistance to colonization by respiratory pathogens and
648 probably shaping local immunity (Man *et al.*, Nature Reviews Microbiology 2017).

649
650 *Virome*

651
652 The term “virome” has been coined to describe the total collection of viruses in a given organ
653 and, usually, at a single time point. The virome encompasses a sort of viral “flora” that
654 includes bacteriophages, endogenous retroviruses, eukaryotic viruses either orphan of
655 disease or capable of causing acute and self-limiting, persistent, and latent infections (Virgin

656 *et al.*, Cell 2009; Focosi *et al.*, Clin Microbiol Infect 2016). Characterizing the virome is a key
657 point to study disease transmission across human, wildlife and domestic animals, which are a
658 growing risk for public and veterinary health (Miller *et al.*, Sci Rep 2017; Olival *et al.*, Nature
659 2017). Bat and rodents have been recognized as main reservoirs for emerging viral
660 transmission cross-species (Han *et al.*, Science 2015; Luis *et al.*, Proceedings of the Royal
661 Society B, 2013); for this reason, their virome characterization is one of the objectives of the
662 global virome project, which aims to describe the majority of currently unknown viruses
663 (Carroll *et al.*, Science 2018). However, a defined link of viral transmission between wildlife
664 reservoirs and livestock animal remains poor or restricted to specific viruses (Zhou *et al.*,
665 Nature 2018).

666 The characterization and the role of human and animal virome in health and disease is largely
667 unknown. Once thought to be present during a disease, viruses have been demonstrated to be
668 present in the host in healthy conditions and in various sites. Indeed, the recent application of
669 metagenomics approaches for the characterization of the human and livestock virome,
670 allowed to identify a consistent number of unknown viruses in host healthy conditions (Shan
671 *et al.*, J Virol 2011; Lima *et al.*, J Gen Virol 2017; Day *et al.*, Virol J 2010). However, further
672 studies are needed to expand and confirm the livestock virome characterization.

673 Furthermore, increasing evidence demonstrates that virome fluctuations, interaction with
674 host, changes of bacterial microbiome, and environmental factors exert profound effects on
675 virome composition and host physiology (Freer *et al.*, Curr Med Chem 2017; Freer *et al.*, Front
676 Microbiol 2018, Hurwitz *et al.*, ISME J 2015; Anderson *et al.*, Microbiome 2017). Among
677 environmental factors, modulation of livestock gut and ruminal virome using different diets
678 can open new perspectives for the livestock farming by improving host's health and
679 productivity, but until now only few studies restricted to ruminants have investigated this
680 opportunity (Anderson *et al.*, Microbiome 2017).

681 It has been recently suggested that monitoring intra-host dynamics of human virome is a
682 promising and innovative area of research for identifying new biomarkers predicting an
683 ailment or helping physicians in the management of diseased subjects (De Vlaminc *et al.*, Cell
684 2013; Carding *et al.*, Aliment Pharmacol Ther 2017; Legoff *et al.*, Nat Med 2017; Albert *et al.*, J
685 Clin Virol 2017; Focosi *et al.*, J Gen Virol 2015; Focosi *et al.*, J Infect Dis 2014). For livestock
686 animals, no investigation in potential biomarkers for diseases has been proposed yet and
687 could represent a new research field. It is therefore crucial and, seen the technologies at
688 disposal today, quite timely to investigate composition and evolution of virome in depth and
689 on a wide scale, to increase our knowledge on its composition, fluctuation and its symbiotic
690 relation with the host microbiome. Characterization of intra- and inter-host viral diversity
691 may also result in remarkable advancement in knowledge of variations of virome composition
692 in the host health, as well as in definition of novel markers to monitor well-being conditions
693 and predict disease onset and progression.

694 695 *Mycobiome*

696
697 The microbial species of the intestinal microbiome are present at varying abundance levels,
698 which results in microorganisms that are predominantly found and other, less common, being
699 overlooked. These rare components include fungi, i.e. yeasts and molds, or the "mycobiome".
700 The few available studies have consistently shown, in healthy individuals, a community of low
701 biodiversity, dominated by yeasts (mainly *Saccharomyces* but also *Malassezia* and *Candida*)
702 and characterized by high variability between and within individuals over time. The
703 composition of the gut mycobiome has been found to be closely related to eating habits and
704 lifestyle, as well as to the bacterial component of the microbiota, which can modulate the
705 fungal fraction by direct or indirect interactions, through the modulation of the host immune
706 system (Nash *et al.*, Microbiome 2017).

707 The human intestinal mycobiome is receiving increased research attention because it can act
708 as a reservoir of opportunistic pathogens and therefore represent a risk factor for many
709 diseases, both gastrointestinal and systemic, especially when the mucosal barrier is
710 compromised (Iliev and Leonardi, Nat Rev Immunol 2017). In particular, alterations of the
711 fungal community have been found in the context of inflammatory bowel disease, colorectal
712 adenomas, post-operative complications, *Clostridium difficile* infection, obesity, type 1
713 diabetes and various types of disorders in immunocompromised individuals (such as
714 hematological and infectious diseases). The analysis of the gut mycobiome could be of
715 relevance for women, especially pregnant and lactating, when the control of fungal infections
716 is important not only for their wellbeing but also for that of their child, and for premature and
717 underweight neonates. In addition, antibiotic treatments can considerably increase the risk of
718 imbalance in the mycobiome, thus contributing to the onset of specific mycoses (Huseyin *et*
719 *al.*, FEMS Microbiol Rev 2017).

720 The mycobiome in livestock animals is considered a new field of research. Few studies have
721 examined the fungal community in animals, including bat (Li *et al.*, Current Microbiology
722 2018), mouse, pig (Donovan *et al.*, PLOS ONE 2018), and ruminants (Dias *et al.*, Front
723 Microbiol 2017; Ishaq *et al.*, Front Microbiol 2017), while from our knowledge, no consistent
724 information about yeast and moulds is available. In the same way, the role of the fungal
725 community on livestock disease is still poorly studied and is mainly focused on ruminants
726 with regard to clinical mastitis (Wen *et al.*, Adv Microbiol 2018) and sub-acute ruminal
727 acidosis (Ishaq *et al.*, Front Microbiol 2017).

728 Furthermore, despite a large number of yeasts have been used as probiotics with a positive
729 effect on livestock animals (Hatoum *et al.*, Front Microbiol 2012), a lack of information on
730 their effect on intestinal and ruminal mycobiome, as well the interaction with the microbial
731 community is still present. The fungal community in livestock has been specifically studied in
732 relation with the animal waste (Heaney *et al.*, Sci Total Environ 2015) or in relation with
733 farms air quality for humans (Kumari *et al.*, Sci Rep 2016).

734

735 *Culturome research*

736

737 A bottleneck of microbiome research is the difficulty to be translated into laboratory models
738 for experimental verification. This discrepancy is mainly due to the difficulty of *in vitro*
739 culturing the majority of bacteria and reproduce intermicrobial and microbe-host interactions
740 in the laboratory. Out of ca. 1 million bacterial species existing on the Earth, just over 7,000
741 bacterial species have so far been validly classified (<http://www.bacterio.net/>). Starting from
742 11 bacterial phyla (the highest-level division within the bacterial kingdom) described in the
743 '80s, the number of phyla of bacteria identified through metagenomic analyses has grown to
744 more than 80, the majority of which have no cultured representatives (Schloss *et al.*, MBio
745 2016). "Unculturability" is not an intrinsic feature of these bacteria, but simply implies that
746 our culturing techniques are currently unable to support their laboratory growth. Therefore,
747 "unculturable" does not mean "impossible to be cultured" but, rather, implies that we lack
748 critical information on the biology of these species, and this offers challenges but also
749 opportunities (Lagier *et al.*, Clin Microbiol Rev 2015). Indeed, the study of "unculturable"
750 bacteria can provide the chance to investigate the molecular aspects behind recalcitrant
751 growth, allowing to improve our repertoire of microbiological techniques and to gain access
752 to previously hidden metabolic diversity, that will ultimately provide new natural products
753 and reveal factors that contribute to ecological balance, nutrient cycles and/or host health.
754 The last decade has seen the development of several effective techniques for culturing these
755 organisms. These "**culturomics**" approaches include (i) co-culturing with other (growth-
756 promoting) bacteria, which has also revealed the molecular mechanisms of these beneficial
757 effects, (ii) bringing culture media and systems directly into the environment, to allow the *in*

758 *situ* cultivation of novel species, and (iii) microscale cultivation in specific devices, which
759 increased the rate of isolation of “unculturable” bacteria by removing the competition with
760 bacteria sharing the same ecological niche. With a large pool of new bacterial isolates
761 potentially available for functional studies, it will be possible to elucidate the role of these
762 highly diverse organisms in nature. Building of modern strain storage infrastructures
763 (“biobanking”) will be an essential step to preserve our asset of bacterial strain diversity
764 (Bolan *et al.*, EMBO Rep 2016). More importantly, successful cultivation of these novel
765 bacterial species could have profound effects on human health. Regarding drug discovery,
766 screening of novel isolates could lead to the identification of new natural compounds that may
767 finally support the antibiotic (and drug) discovery pipeline, which has almost collapsed in the
768 last decades. Moreover, culturomics approaches will allow to: explore the close interactions
769 between individual species and the host; understand the dynamic relationships between the
770 different components of ecosystems; study the interactions between mutualistic bacteria,
771 pathogens and host cells; identify the strain-level diversity among individuals, as well as the
772 status of ecosystems in different tissues and body districts; elucidate the role of different
773 strains in colonization resistance as an important step in the development of prebiotics and
774 probiotics (Lagier *et al.*, Nat Rev Microbiol 2018). Thus, in line with the One Health initiative,
775 sustaining current and future “culturomics” efforts is expected to offer multiple benefits for
776 health, ecology, and science.

777

778 *Resistome research*

779

780 Antibiotic resistance (AR) is alarmingly increasing worldwide due to the indiscriminate use of
781 antibiotics in human and veterinary medicine, farming and agriculture (O'Neill, AMR Report
782 2014). Surveillance data show that Italy has a primacy in Europe, reporting a worryingly high
783 frequency of AR in both human and veterinary infections (ECDC; 2017; EFSA J, 2018). AR is
784 natural in bacteria and as old as the naturally-produced antibiotics, for the simple reason that
785 antibiotic-producing microorganisms must protect themselves against their own antibiotics
786 in order to avoid suicide (Davies and Davies, Microbiol Mol Biol Rev 2010). All known
787 bacterial pathogens have rapidly developed resistance to one or more antimicrobial
788 molecules, suggesting the presence of a pre-existing pool of AR genes in ‘natural’ reservoirs,
789 and their transferability among microorganisms sharing the same habitat (Allen *et al.*, Nat Rev
790 Microbiol 2010). Although the downsides of AR are mainly clinical, this problem is not
791 restricted to the clinic and should be addressed considering that the resistance gene flow is
792 “from” and “to” natural environments, in line with the One Health initiative. Most of the
793 antibiotics given to humans are used in the household, and eventually end up in the sewage.
794 More important, the use of antibiotics in agriculture and aquaculture practices leads to a
795 significant increase of AR, and to an accumulation of antibiotic-resistance genes (ARGs) in
796 bacteria (Hu *et al.*, Front Med 2017). The environment is therefore the original source of AR,
797 and the reservoir of ARGs that constitute the antibiotic **resistome** (i.e. the collection of ARGs
798 in a specific bacterium or ecological niche). To prevent diffusion of ARGs in the clinic, it is
799 necessary on one hand to raise the public awareness of the problem of AR, and on the other
800 hand, to track reservoirs of resistance to impede the dissemination of environmental ARGs
801 (Laxminarayan *et al.*, Lancet Infect Dis 2013). The recent development of High-Throughput
802 Sequencing (HTS) tools that enable the culture-independent study of diverse environmental
803 microbial communities, has led to a relatively rapid growth of catalogue of ARGs (Wright, Nat
804 Rev Microbiol 2007). However, HTS studies are often descriptive and need to be
805 complemented by functional metagenomic approaches to experimentally ascribe resistance
806 functions to genes not previously identified as resistance determinants, or to discover
807 resistance genes with novel sequences. Cryptic ARGs, i.e. those genes which are present but
808 not expressed, as well as ARG precursors which encode for proteins conferring low-level

809 resistance, i.e. capable of binding or modifying antibiotics with low affinity or specificity
810 should be identified by means of new algorithms, bioinformatic tools, and appropriate
811 databases. Cryptic genes and ARG precursors are probably the most dangerous resistance
812 determinants to next generation antibiotics, since they are a still unexplored source of new
813 resistance mechanisms (Hu *et al.*, Front Med 2017; Garmedia *et al.*, Clin Microbiol Infect
814 2012). For future resistome studies, AR database harmonization, validation and accessibility
815 are mandatory actions.

816 As research into AR expands, a proactive approach to the AR identification and surveillance,
817 as well as to the antibiotic therapy development should be adopted. The antimicrobial
818 development pipeline should include screens for existing environmental resistance threats to
819 new drugs before they spread.

820 Starting from the wide use of antibiotics in 1950s as therapeutics, prophylactic, metaphylactic
821 and growth promoters (AGPs), and most recently with the ban of the use of the AGPs in
822 Europe (since 2006) and the limitation in the uses of colistin (since 2015), the livestock
823 production has always been a central subject of attention with regard to the occurrence and
824 diffusion of AR (Hu *et al.*, Front Med 2017; Marshall and Levy, Clin Microbiol Rev 2011). The
825 spread of ARGs may occur through the animal handlers, the food chain and farm effluents
826 (Forsberg *et al.*, Science 2012; McEachran *et al.*, Environ Health Perspect 2015; Noyes *et al.*,
827 Sci Rep 2016).

828 However, despite the amount of evidences, the role played by livestock in the resistome
829 dispersal is still a matter of debate. In this context, the phylogenetic study of the “resistomes”
830 is important to define the boundaries of the ecological continuum of ARGs and to clarify the
831 role of livestock environment as ecological corridor within these gene flows.

832

833 **4.2.2 Soils and sediments, Sustainable agriculture, and food processing**

834 *Microbiome in the terrestrial primary production*

835

836 Due to the large heterogeneity of soil and environmental conditions across habitats and the
837 lack of knowledge on soil microbe functions, the identification of specific links between **soil**
838 **microbiome** composition and its functional capabilities is difficult. At the same time, it is
839 difficult to predict the rates of a given biogeochemical processes that might influence plants
840 growth and nutrition properties. Here it is not enough the use of simple indices such as
841 bacterial-to-fungal ratios or phylum-level abundances, and thus the field needs to move
842 beyond simple descriptions of community diversity to identify patterns in their complexity
843 and to recognize when that complexity is important. While genomic data are rapidly
844 accumulating for the vast majority of undescribed soil microbial taxa, the gaps in our
845 understanding of their functional attributes is relevant. Further, the cultivation of many soil
846 microbial taxa – particularly slow-growing ones – remains a difficult task, and this is
847 adversely affecting the assessment of environmental tolerances, gene annotations,
848 quantification of enzyme kinetics, and identify novel antibiotics or probiotics. Strategies that
849 use genomic data to identify conditions for the effective cultivation and isolation of not-easy-
850 to-grow microorganisms are sought.

851 There is a big knowledge gap also in the role and functions of the microbiome associated to
852 plants. It is now evident that plants adopt mechanisms for addressing the specificity of
853 microbial recruitment in the roots from soil and hence in the rest of the plant organs (Lebeis
854 *et al.*, Science 2015) and that microorganisms provide the alleviation of stresses in the plant
855 [Cherif *et al.*, Environ Microbiol Rep 2015) by means of specific mechanisms (Vigani *et al.*,
856 Environ Microbiol 2018). However, the understanding of such mechanisms is in its infancy
857 and requires an increased effort to clarify the factors regulating the plant microbiome
858 association and their relations with the agriculture ecosystems. Another area in which we
859 need to know more is the microbiome contribution to the adaptation of the plant host to

860 abiotic stresses like the ongoing climate changes (East, Nature 2013), heat waves, soil salinity,
861 flooding events, nutritional imbalances and biotic stresses. Here we know that microbiome
862 components influence the modulation of the plant hormone homeostasis and the architecture
863 of the plant root system favoring the plant response to the soil water and the nutrient
864 provision but more evidence-based knowledge are necessary. Further, the impact of the
865 plant-associated microbiome on the quality of plant products is a virtually non-explored issue,
866 while it is conceptually considered that the microbiome may exert effects on the quality of the
867 fruit and the related products. Finally, the inheritability of the microbiome through the
868 reproductive forms of the plants, the seeds, is emerging as an aspect not yet covered by
869 sufficient research.

870 In the field of **animal microbiome**, the factor affecting the host microbiota and cross-talk
871 between the animals system and microbiota need to be deeply studied. A limiting factor for
872 the progress in the knowledge is the absence of specific databases. Reference gene catalogues
873 of the pig gut and rumen microbiome were published in 2016 and 2018, respectively (Xiao *et al.*,
874 *Nat Microbiol* 2016; Seshadri *et al.*, *Nature Biotechnol* 2018), while for poultry it is under
875 definition. The application of innovative metagenomics approaches (e.g. ITS-based
876 sequencing; Terabase sequencing and quantitative metagenomics, etc.) and the definition of
877 *longitudinal studies* able to characterize the gut microbiome included virome at different
878 production stages and synergistically associate it with a wide number of hot descriptors (e.g.,
879 metabolome) is essential to define a *National database of animal microbiome/virome*. This
880 resource would significantly will speed up the identification of biological predictors as well as
881 the identification of new beneficial microbes (new probiotics) able to improve the natural
882 resistance of the animals against pathogen infections as well to ameliorate feed efficiency of
883 the animals in terms of nutrient utilization and consequently reducing the production cost
884 and the environmental impact of the livestock productions. Further, it is of utmost importance
885 to define a strategy to predict and investigate the biological functions of gut microbiome
886 molecules in different conditions as when different dietary strategies are used (e.g. high vs
887 low dietary protein; different sources of fibre) or in optimal and sub-optimal health status, as
888 well as to reveal key molecules resulting from co-regulated microbiota–host pathways as
889 potential therapeutic targets, in line with the EU strategy for replacing some of the antibiotics
890 currently used in livestock with new therapeutic molecules. Finally, it would be strategic to
891 develop a national strategy for the definition, classification and exploitation of the
892 biodiversity that characterizes the Italian productions, as an opportunity to disclose peculiar
893 microbiome and its applications to improve the national production systems. Equally,
894 studying the integrated biological systems of each species is essential to pave the way to
895 manipulate the animal microbiome to improve animal health, feed efficiency, food quality and
896 food safety and security.

897
898 *Microbiome in the marine primary production.* Marine habitats microbiome is corelated with
899 the health and productivity of the marine ecosystems. Holistic evaluation of such relationship
900 requires complex, community-level insight integrating taxonomic and functional information
901 spanned temporally and spatially. In addition, a more comprehensive characterization of the
902 genetic pool of the marine microbiome and a broader use of functional genes as indicators is
903 needed to target a wider range of processes that shape the composition of microbial
904 communities and to predict more reliably the impacts on the local bacterioplankton
905 production, diversity and abundance and in turn on the health status of fishes and other
906 marine organisms. More efforts should be made for better assessing the role of marine
907 diversified and active community members in the final seawater biosphere and primary
908 production.

909 The unravelling of intricate host-microbe symbioses and the identification of core
910 microbiome functions would be key steps for the understanding and the exploitation of

911 microbiome potential in fish culture and marine vertebrate health (Tarnecki AM *et al.*, J Appl
912 Microbiol 2017). Further, exploiting the microbial communities inhabiting and interacting
913 fishery to improve its productivity, quality, safety and sustainability has been proposed as one
914 of the strategies underpinning the disruptive changes of the sector. However, a better
915 comprehension of the microbiome role in fish biology will allow to implement and validate
916 informed actions to improve the fish microbiome by means of an integrative usage of
917 probiotics, prebiotics and feed supplements. The timing of actions needs to be calibrated to
918 obtain better performances in terms of improved fish health and food chain
919 productivity/quality. Actions targeting the fish microbiome must be integrated with
920 interventions targeting microbiomes from wastewaters and sediments, increasing the overall
921 environmental sustainability of the food system together with a better food quality,
922 productivity and safety.

923 The *in situ* stimulation of indigenous marine bacteria from the marine microbiomes (also
924 including microbiomes from holobionts marine organisms, such as fishes, shellfish, corals,
925 sponge, among others), able to degrade a wide range of natural organic compounds (e.g.,
926 lipids, proteins and carbohydrates) constitutes an innovative and promising approach. In this
927 scenario, the microbiomes of wild specimens of the fish models, shellfish, corals, sponge will
928 be used both as a bioindicators of the environmental health and, parallel, as a new sources for
929 next generation applications of blue-technology approaches, such as the bioprospecting of
930 marine microbiomes with biodegrading potential and their use in microbiome bio-activators
931 to enhance degradation of organic matter, mitigating the environmental impact and
932 improving sustainability.

933
934 *Microbiome in the food production and nutrition.* In foods and beverages, even minor
935 alterations to species/biotypes diversity or numbers may result in significantly different
936 products and variations in safety, nutritional, functional, shelf life and organoleptic
937 properties. Therefore, a microbiome composition with temporal and spatial stability and
938 resilience results in consistent fermentations and process conditions that are necessary to
939 produce high quality foods and beverages. The establishment, assembly and shaping of the
940 core microbiome in foods and beverages is only possible through an extraordinary access to
941 complementary genetic information based on omics techniques that reveal the overall
942 composition and functionality. Omics based approaches provide detailed insights into the
943 food microbiome and its relationship on the overall quality attributes. This will reveal not
944 only the genomic essence of a microbiome but also whether a food manufacturing facility eco-
945 niche will influence the core microbiome and whether the overall core microbiome forge the
946 food manufacture. Omics platforms dedicated to the establishment, assembly and shaping of
947 the food core microbiome will represent fundamental tools for getting improved and
948 standardized protocols for the manufacture of foods and beverages, aiming at the
949 biotechnological transfer to small and medium enterprises. The role of food microbiome on
950 health and the progression to chronic degenerative diseases need to be better investigated by
951 also including the contribution of overall lifestyle and of the eating pattern in the final
952 outcomes. This implies that the microbiome resulting from the whole eating pattern must be
953 studied and this, in turn, requires new approaches for the data collection and analysis.

954 955 **4.3 Actions required for boosting the microbiome applications in Italy**

956
957 Among the major research needs in the sector, we have that of standardizing the approaches
958 used for analyzing microbiomes as results reproducibility is often a critical issue. In
959 particular, there is the need of improved and standardized methods for the i) experimental
960 design, ii) choice of molecular analysis technology, iii) data analysis and the integration of
961 multiple omics data sets. This is essential for minimize noise and bias, allowing more

962 definitive conclusions on the impacts of the gut microbiome in human health but also for
963 more robust, reliable and concrete microbiome-tailored applications in both the clinic sector
964 and the whole food system.

965
966 Further, Italy needs improved technological tools for the characterization of microbiomes.
967 While the depiction of microbiome compositional structure can be afforded by cost-effective
968 16S rRNA (for bacterial component) or ITS-based (for fungi) sequencing, for the
969 comprehension of the microbiome functionality, metagenomics, metatranscriptomics and
970 metabolomics approaches are mandatory and they are asking for terabase sequencing and
971 quantitative metagenomics, with the first allowing to explode the phylogenetic resolution
972 down to the strain level and the second providing a new quantitative dimension to the
973 microbiome variation. Microbiome studies are also asking for robust data banking,
974 bioinformatics and multidimensional statistics as well as for new infrastructures, repositories
975 and tools for microbiome data storage, organization, sharing and extraction and utilization of
976 specific information from microbiome studies across the globe.

977
978 In addition, the national studies and applications of the microbiome in the health sector
979 would remarkably benefit from the establishment of a national network of experts and
980 research centers able to:

- 981 • collect and provide data on the baseline microbiota profiling of Italian healthy subjects in
982 different body districts, different ages and lifestyles;
- 983 • identify new microbiome biomarkers for disease and dedicated diagnostic tools;
- 984 • develop new therapeutic approaches tackling microbiomes;
- 985 • set up metagenomics/metabolomics-based medicinal chemistry campaigns;
- 986 • to identify neglected lifestyle, dietary and environmental drivers of dysbiosis;
- 987 • build a comprehensive demographic databases (dataset) obtained by processing samples
988 with homogenized methods and standardized parameters for biostatistics;
- 989 • define, characterize and provide data on nutritional protocols and physical activity
990 programs able to improve the microbiota profile;
- 991 • to assess Mediterranean diet factors promoting a healthy microbiome structure;
- 992 • standardize the storage of microbiota profiling data, to be made available to the
993 community of clinicians, microbiologists and omics microbiota scientists;
- 994 • analyze the whole host virome, to characterize yet undefined viruses and their role in
995 determining the host immunological status;
- 996 • assess the impact of probiotic formulation on gut microbiota eubiosis and host health;
- 997 • to characterize next generation probiotics;
- 998 • evaluate nutritional properties in novel food and in traditional foods according to changes
999 induced on gut microbiota taxa and/or functions;
- 1000 • analyze the role of microbiome in the drug metabolism, efficacy and side effects;
- 1001 • further investigate the impact of microbiomes on cancer immunotherapy.

1002
1003 The leadership of Italy in the implementation of a microbiome-based terrestrial and aquatic
1004 primary production and in the valorization in the frame of the food system should be based on
1005 the country natural capital peculiarities and the higher added value crops and livestock
1006 products, and foods. Key actions for boosting knowledge, technological developments and
1007 technology transfer in the priority areas are:

- 1008 • Development of research-driven understanding and applications of soil/marine
1009 sediment/water plant and animal associated microbiome systems in the protection of
1010 national primary production from nutritional, biotic and abiotic stresses and in the

1011 improvement of the sustainability, quality and nutritional and healthy properties of its
1012 products and deriving food and feed;
1013 • Assessment of the role of plant, livestock, fish and food-associated microbiomes in the
1014 definition of the typicality of Italian primary productions and foods, and as promoters of
1015 Italian microbiome eubiotic structures, for the promotion of their added value on
1016 international markets.

1017
1018 The creation of a national network of experts and of infrastructures mentioned above would
1019 remarkable contribute to interconnect the different pillars of the microbioma food system and
1020 to exploit its whole potential and national specificities.

1021
1022 Finally, for implementing the microbiome know how and potential in Italy, is also essential to:
1023 • consolidate relationships between reserachers/research infrastructures and national and
1024 international companies, essential for to effective transfer of available knowledge and
1025 value creation;
1026 • Create awareness amongst citizens on the importance and the opportunities of a
1027 microbiome-based medicine, primary production and food products;
1028 • Educate, train as well as support researcher careers and mobility, and the development of
1029 skills in relevant sectors of microbiome to ensure the necessary highly qualified
1030 workforce capable of underpinning an advanced and robust microbiome based knowhow,
1031 and industry.

1032

1033
1034 **5. Conclusion**
1035

1036 Research on the microbiome has delivered many interesting basic findings and advanced
1037 technologies, enabling this discipline to become a beacon of hope with great potential and
1038 many possibilities in Europe and in many other Continents. The European Commission
1039 funded to date 216 projects as part of FP7 and H2020 to advance knowledge on such
1040 priorities but Italy has played and it is playing a minor role in such an action. This is mostly
1041 due to the lack of coordination among the prominent national scientists and institutes
1042 working in the sector and of initiatives integrating and jointly exploiting their expertises and
1043 infrastructure.

1044
1045 The present initiative is asking for a national joint action addressed to: a) establish a national
1046 network of prominent experts and of public and private actors working in the different domains of
1047 microbioma (human microbiome and virome, at the preclinical and clinical levels, and
1048 microbiome in foods, plants, terrestrial and aquatic animals) to share their data, knowledge,
1049 infrastructures and capacities; b) foster their cooperation with the private sectors, also in
1050 close cooperation with the Italian Technology Clusters Health and Agrofood; c) develop a joint
1051 R&I and policy strategic agenda and implementation action plan addressed to create more
1052 national investments in R&I and spin offs/start-ups in the sector, and as well as better
1053 interconnecting the Italian microbioma community with international networks promoting
1054 microbioma R&I priorities and applicability, best practices, standards and consistent
1055 protocols; d) promote researcher careers, training and mobility, and in general the
1056 development of skills in the different microbioma domains; and e) exchange knowledge
1057 across the scientific and political community and ensure an efficient use of the available
1058 resources, while advocating public understanding of the value of microbiomes for the human,
1059 plant, animal and planetary health.

1060 This initiative should also contribute to promote the microbioma knowhow and potential in
1061 the Mediterranean area, also through the cooperation with the PRIMA
1062 (<https://ec.europa.eu/research/environment/index.cfm?pg=prima>) and the BLUEMED
1063 (<http://www.blued-med-initiative.eu/>) initiatives, both coordinated by Italy, for a more
1064 sustainable and productive growth of Bioeconomy in the region, wider social cohesion and
1065 greater political stability in the area.

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