# IMPLEMENTATION ACTION PLAN

# (2020-2025)

# FOR THE ITALIAN MICROBIOME INITIATIVE

## INTRODUCTION

Microbiomes are complex communities of Bacteria, Archaea, Eukarya and viruses found in humans, plants, and animals as well as in terrestrial and marine environments that provide benefits to the planet as a whole. Microbiomes are highly dynamic, changeable and adaptable systems.

Ongoing studies have highlighted that microbiomes, with their varying structure and dynamics across the food system (from soils and marine habitats to plants, animals and foods) can have both direct and indirect effects on human and environmental health, in addition to their obvious impact on food quality, safety and sustainability.

New research and innovation (R&I) are required to fully clarify the interplay between microbiome-host and microbiome-environment, in order to design microbiome-based interventions to promote human and animal health as well as a healthier, safer and more productive and sustainable food system. Actions addressed to exploit the existing knowhow at the industrial level should also be promoted and sustained. Indeed, companies of the pharma and agri-food sectors are certainly among those already exploring the potential of the microbiome for the development of novel drugs, supplements, foods, pharma foods, feed and fertilizers enriched with ingredients, including live microorganisms, which can positively modulate human, animal, plants, soil and marine microbiomes.

The EU Commission invested about € 600 M to improve knowledge and technology on such priorities during the last 5 years and more than € 1.4 Billion during the last 12 years, via FP7 and Horizon2020 framework programs. USA and some EU Countries including Italy[1] have launched a national Microbiome Initiative.

Italy is playing a minor role in such emerging field, mostly because of the high fragmentation and poor coordination of its qualified expertise, infrastructures and actors available in the different areas of microbiome translational research. Italian researchers are present in a large number of prominent international publications and in about 30 FP7 and Horizon2020 projects funded in the microbiome domains. However, such EU projects are only 5% of those funded by the two framework programs and Italy is coordinating only 6 of them. Italy also possesses relevant and complementary infrastructures in the health and in the main domains of the food systems, but it is missing others and has difficulties in maintaining/updating/renewing the existing ones. Finally, the country counts prominent national industries in the biotech, pharma, food and agriculture domains interested in the microbiome opportunities, but they are not engaged to effectively and responsibly contribute to the exploitation of the Italian research knowhow.

To reverse such a scenario, the Italian National Committee for Biosafety, Biotechnology and Life Sciences (CNBBSV) of the Presidency of Council of Ministers launched a national microbiome

[1] http://cnbbsv.palazzochigi.it/media/1859/microbioma-2019.pdf

program/initiative in 2019[2]. It is now imperative to promote a national Implementation Action Plan (IT Microbiome IAP, 2020-2025) for boosting innovation on human, animal, plant and food microbiomes in the coming 5 years, addressed to:

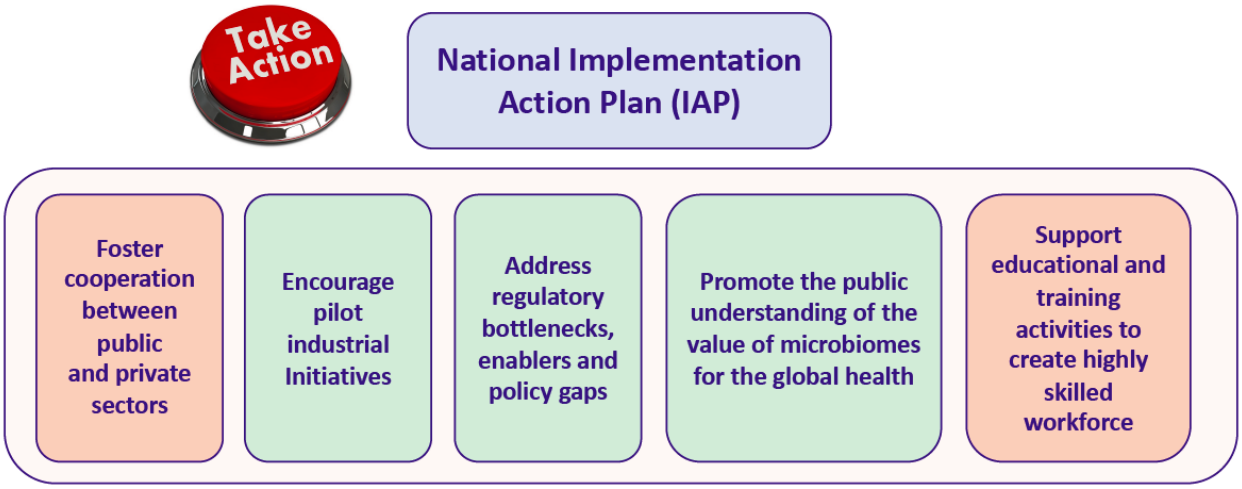
a) foster cooperation between public and private sectors, in close cooperation with the Italian Health and Agri-food technology clusters (ALISEI and CLAN, respectively), to maximize the leverage effects investments in R&I and knowhow transfer;

b) support pilot industrial initiatives and consequent actions to de-risk of the investment for investors;

c) address regulatory bottlenecks, enablers, and policy gaps associated with such actions;

d) promote the public understanding of the value of microbiomes for the global health, and

e) support educational and training activities to create highly skilled workforce in the exploitation of microbiome knowhow in health and food system domains.




## OBJECTIVES OF THE IMPLEMENTATION ACTION PLAN

The present **Implementation Action Plan (IAP)** translates the above needs into distinct actions, to ensure an operational roll-out of the microbiome potential across Italian pharma and food systems in the coming 5 years. It is set up and promoted by the CNBBSV of the Presidency of Council of Ministers with the involvement of experts from the public institutions and industries, as represented by the national technology clusters ALISEI e CLAN. The present IAP will be presented in a dedicated event hosted by the Presidency of Council of Ministers in the second semester of 2020, and then opened to inputs from all national stakeholder interested in being involved in its implementation. CNBBSV will then promote it towards national, European and international governments and R&I

[2] http://cnbbsv.palazzochigi.it/it/materie-di-competenza/bioeconomia/iniziativa-nazionale-microbioma/

organizations and will hold a public forum on it every year, to stimulate research/industry/primary producers/education and citizen communities to share their needs and suggestions, then used for the annual IAP improvement and implementation. Finally, the CNBBSV will interact with other microbiome-related initiatives active in the other EU Member States to facilitate the exchange of best implementation actions and practices, enhance inter-country cooperation and joint actions, promote the overall implementation of microbiome priorities in Europe.

## STRATEGIC ACTIONS PLANNED

The Italian Microbiome IAP 2020-2025 **identified some operational actions under 3 broad headings**:


- **Promote the development and implementation of policies, standards, labels, financial instruments and emerging market-based actions for a more efficient exploitation of the national know how on microbiome in the human and animal health, pharma and food system domains;**
- **Launch of national industrial pilot actions on both domains of pharma and food systems;**
- **Promote education, training, skills upgrading and entrepreneurships in the same domains**.

## 1. Develop/implement policies, standards, labels, financial instruments and emerging market-based actions for a more effective exploitation of the national know how on microbiome in the health and food system domains

The **recommended actions** are to:

a) Develop and promote standards and related labelling, for conventional microbiome-related products;
b) Encourage the European Union to harmonize EU legal framework establishing the conditions for a strain to be considered as probiotic, or a positive list of individual strains which have a probiotic status to avoid inadequate protection of consumers and doctors, especially when probiotics are aimed at the dietary management of serious conditions.
c) Design a mobile exhibition to showcase on the role of microbiome in the human health and disease, including communicable and noncommunicable diseases, such as obesity, type-2 diabetes, cardiovascular diseases, neurological disorders, metabolic syndrome, eating disorders. Public fora on microbiome and health will be organized through webinars, workshops and conferences.
d) Promote an entrepreneurial mind-set and culture for the Microbiome through dedicated actions as well as open Innovation initiatives to accelerate a scale-up of innovative solutions in the field developed by start-up and SMEs;
e) Promote/sustain the establishment of tailored partnerships among farmers, bioremediation industries, wastewater/biowaste exploiting companies, etc. and microbiome scientists and experts to develop and then validate on the full scale microbiome-based approaches to optimize and improve efficiency, stability and reproducibility of the full scale soil, sediment and wastewater processing and biowaste exploitation processes/technologies;
f) Encourage the provision of tailor-made finances in the microbiome exploitation area by raising awareness in investors (e.g. banks, “business angels”, insurers, pension funds, investment funds, crowdfunding schemes) to encourage them to include microbiome opportunities as part of their investment strategies;
g) Promote microbiome potential in the wide domains of the pharma and food systems in the frame of national and regional Smart Specialization Strategies, by mobilizing structural funds addressed to the microbiome potential implementation at local level;
   Act to increase the EU financial support to the sector, in line with the recommendations of the European Investment Bank, to improve access-to-finance of projects, by helping them to improve their bankability and investment-readiness, structuring their financing and liaising with private investors.

## 2. Planned pilot industrial actions in the microbiome domains of pharma and food systems

Several of the priorities identified in the Italian Microbiome initiative vision document[3] are of primary interest for the Italian pharma and agri-food public private partnerships belonging to/mobilized by the ALISEI and CLAN national Technology Clusters. They are ready to launch industrial actions at different Technology readiness levels (TRL), along the following priorities.

### 2.1 Production of Next generation probiotics

Advances in microbiome science have broadened the scope for the development of probiotics, next generation probiotics and Live Biotherapeutic Products (LBPs), including live bacteria as single strain or consortia, donor-derived fecal microbiota for transplantation (FMT), and genetically modified bacterial strains. However, progress in understanding the specificity and the therapeutic potential of LBPs has been limited by the still insufficient characterization of their functional mechanism and the absence of reliable biomarkers of their efficacy. The identification of next generation probiotics and LBPs capable to modulate microbiome dysbiosis and restore healthy profiles and functionality could provide new candidates for the development of safe and efficacious treatments in several nutritional and therapeutic areas (Figure 1).

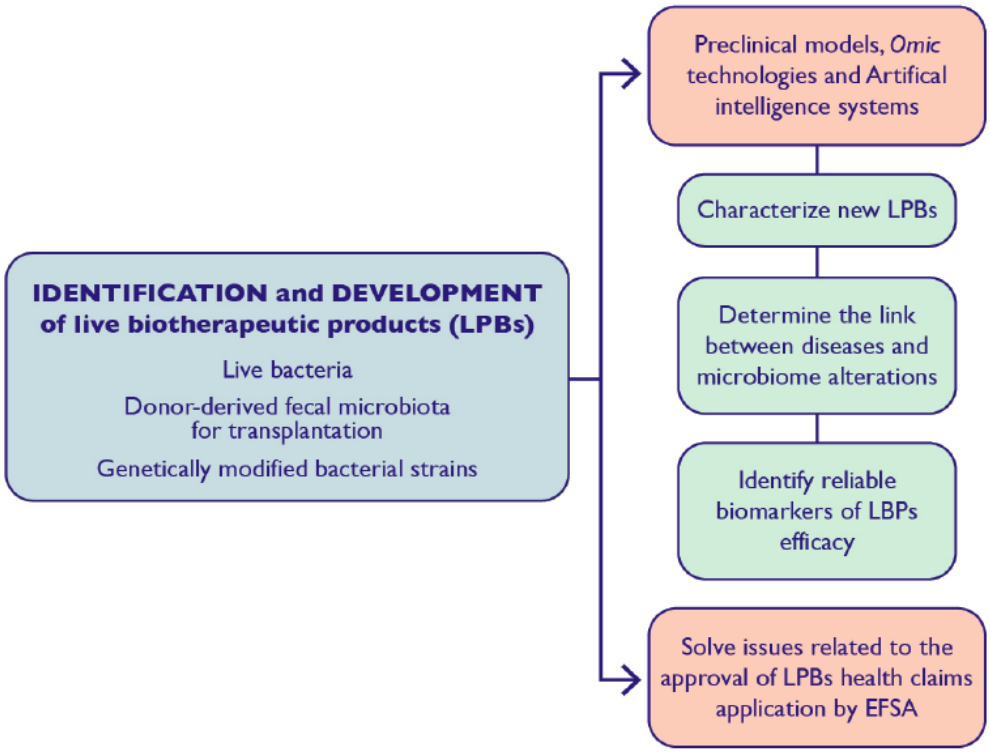



**Figure 1.** *The identification of LBPs could provide new candidates for the development of safe and efficacious treatments in multiple therapeutic areas*

[3] http://cnbbsv.palazzochigi.it/media/1859/microbioma-2019.pdf

The planned actions are addressed to:

→ Develop preclinical models, *omic* technologies and artificial intelligence systems to a) characterize new LBPs as potential drug candidates, by investigating their efficacy/safety profile and potential clinical benefit, b) determine the link between the diseases and the related microbiome alterations, then identify LBPs that can restore the healthy microbiome status, and c) analyze microbiome data from healthy subjects and patients/animal to identify reliable biomarkers of LBP efficacy (TRL3)

→ Promote approval of probiotics health claims applications by EFSA.
Based on the current regulation, the documentation for substantiation of health claims for probiotics is too complex and challenging. Some probiotics claims have been judged as not eligible as they pertained to treatment of pathological situations. A real challenge is posed by the requirement of the EU regulation where the health claims are clearly targeted for general healthy population. Such a requirement poses specific issues on human and animals intervention studies.

## 2.2 Probiotic formulation for human gut microbiota eubiosis and host health

Gut microbiota dysbiosis, due to intestinal illnesses (irritable bowel syndrome, celiac disease, and inflammatory bowel disease) and extra-intestinal illnesses (obesity, metabolic disorders, cardiovascular syndromes, allergy, and asthma), are often treated with the administration of probiotics, prebiotics, and synbiotics. Currently used probiotics include lactic acid bacteria, bifidobacteria, enterococci, the yeast *Saccharomyces boulardii*, dairy propionibacteria, *Bacillus* spp., and the Gram-negative *Escherichia coli* strain Nissle 1917. However, since the cooperative nature of microbiomes, therapies based on multi-probiotics application should be developed, as they could ensure stronger and long-lasting rebalancing effects. The planned actions are to:

→ Demonstrate, by means of omics approaches, that bacterial consortia can better treat human gut microbiota dysbiosis, and identification of the most effective consortia, to formulate oral multi-probiotics combinations resistant to the gastric environment and able to ensure a more efficient microbiota modulation (TRL 4).

→ Address and overcome regulatory issues; many claims are related to the increase of the proportion of health promoting bacteria in the gut, so sustaining beneficial health effects. However, EFSA does not consider such changes in intestinal bacteria as generally agreed benefit, requiring further evidence associated with beneficial outcomes. So far, increasing the numbers of any groups of microorganisms, including well established health promoting groups, is not considered by itself a beneficial physiological effect (Figure 2).

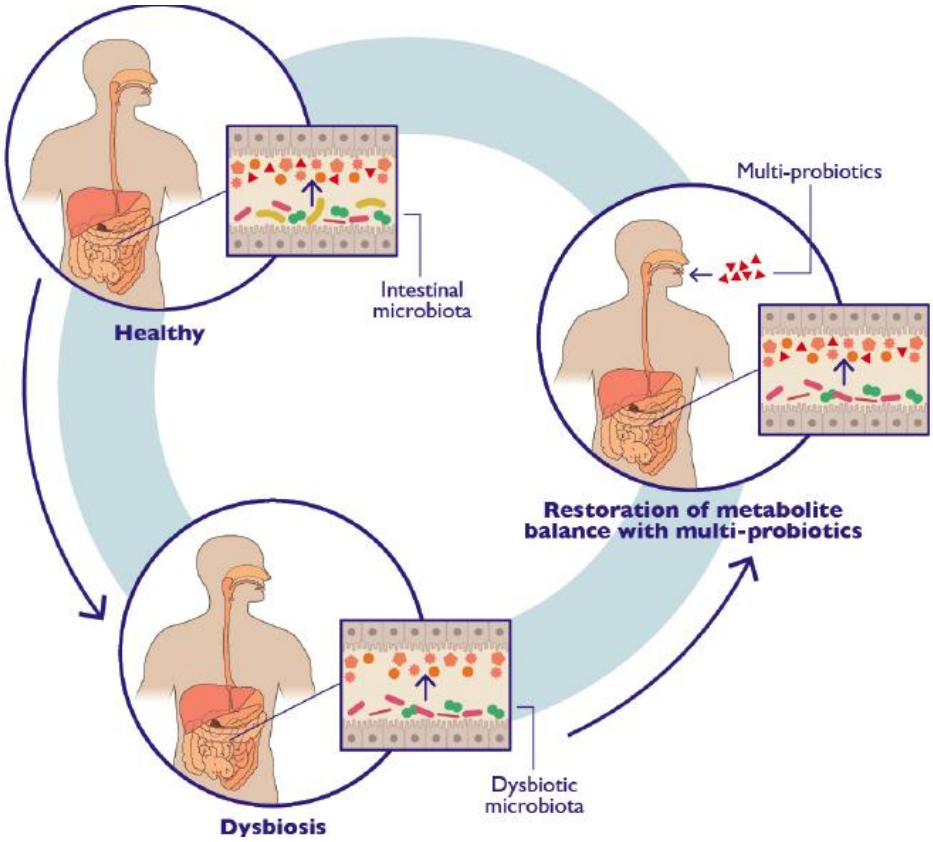



**Figure 2**. *Therapies based on multi-probiotics application could ensure a stronger and long-lasting rebalancing effects*

In a globalized world, the existing regulatory positions for probiotics are not consistent across all jurisdictions (EFSA, FDA). (North American regulations are much more lenient on claims and countries such as China, South Korea & USA have the biggest markets and high consumer demands for probiotics). The planned Actions are to:

→ **Strengthen the EFSA engagement with relevant stakeholders so that all parties have a clear understanding of precisely what documentation is required for approval of probiotics (and next generation probiotics) for commercial sale.** Over 350 probiotic claims have been filed covering claims to support healthy gut microbiota, decreased digestive transit time, support of the immune system, defense against pathogens, oral health etc., and to date, EFSA has rejected them all. The main reasons why EFSA has been rejecting all the health claims are: issues with the study design and statistical analysis; the claim was not sufficiently defined; the food was not sufficiently characterized; not enough evidence was provided to prove the claim and establish a cause & effect relationship. These problems could be overcome via pre-application meetings of applicants with EFSA to discuss study designs and endpoint would be very useful.

## 2.3 Exploit knowledge on Microbiome and drug metabolism

With the effort to tailor therapy providing the best response and highest safety profile, the inter-individual's variability plays a significant role in the drug responses. Growing evidence indicates the

human microbiome might play a role in this variability; however, the molecular mechanisms mostly remain unknown. Moreover, the study of the drug-microbiome interaction, which can be of high relevance also for non-antibiotic drugs, such as CNS and anti-inflammatory drugs, is not systematically performed throughout the drug development phases nor in the post marketing studies. An additional challenge is to consider the possible role of the drug formulation. The acquisition of knowledge on drug-microbiome interactions, including a quali-quantitative understanding of the physiological, chemical, and microbial factors, could allow to explain interpersonal variability in drug response and provide new solutions for personalized medical treatments. Other priorities are to identify the effects of gut, oral, skin and vaginal microbiota on drug metabolism by means of both *in vitro* studies and clinical trials. This would allow to develop tailored personalized treatments. The planned actions are (TRL 3):

→ Collection of microbiome samples (gut, oral, vagina, skin) from human clinical trials, including longitudinal and cross-sectional studies throughout the drug development phases, including the post marketing studies;

→ Analysis of efficacy and ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) data, along with multi-omics and microbiological studies aimed to detect potential correlations with the microbiome fingerprint;

→ In vitro screening of active principles and drug formulations using fecal samples or selected bacterial strains for the study of microbiome-drug interactions.

## 2.4 Exploit the knowledge on microbiome and metabolism of nutraceuticals and xenobiotics

Diet and/or dietary supplements as well as non-digestible dietary compounds, including plant secondary phytochemicals (mainly polyphenols and fibers) and living microorganisms (probiotics), are modulating gut microbiota and in turn the health status of the host. Edible-plant derived high and low-molecular weight polyphenols (EPDPs) represent an emerging group of bioactive compounds that seems to prevent diseases by properly interacting with intestinal microbiota (Figure 3).

In particular, the intestinal microbiota seems to regulate the metabolism and bioavailability of EPDPs, while EPDPs regulated the microbiome metabolism and its effects. Rigorous preclinical and clinical validation of these evidences are necessary in order to: a) enlarge the knowledge of the ability of EPDPs and their post-fermentation metabolites to influence microbiota diversity and substantiate the relationship between the double-faced EPDPs–microbiota interaction with clinical pharmacokinetics and efficacy, and b) pave the way to the setting up of a validated portfolio of nutraceutical products which can represent a relevant added value for the consumer care area.

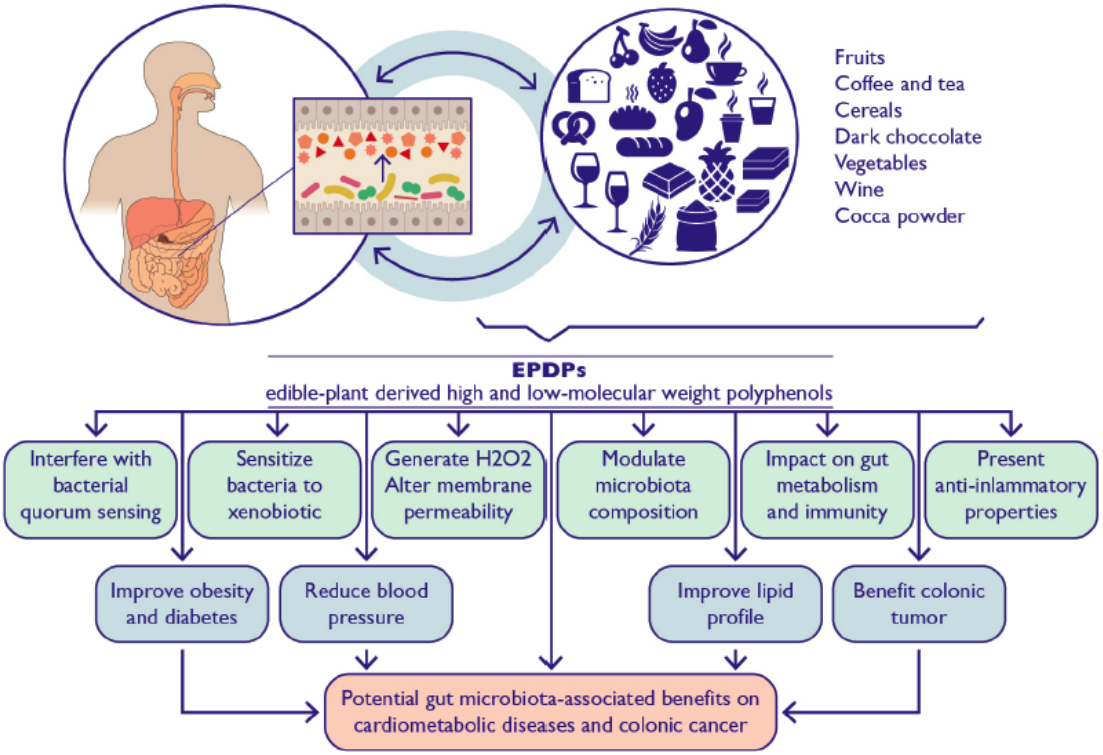



**Figure 3.** *Ability of EPDPs and their post-fermentation metabolites to influence microbiota diversity*

The planned actions are (TRL 4):

→ Perform Standardized test of well characterized extracts, obtained from previously identified edible plants, in simulated human gut microbiota models to study the fermentation and the biotransformation of the standardized extracts and the metabolomic profiling of products.

→ Compare standardized extracts and their fermentation metabolites for their ability to a) impact on cross the intestinal barrier, b) interact with probiotics, c) affect the microbiota diversity and d) impact on cellular activation and epigenetics.

→ Set-up formulation technologies for optimizing intestinal targeting and distribution of major polyphenols. Pilot pharmacokinetic studies in human volunteers with plasma, urinary and fecal metabolomic profiling and pilot proof-of-concept (POC) clinical studies on targeted area of interest (metabolic, cardiovascular, CNS, neurodegenerative, etc.)

## 2.5 Exploit knowledge on microbiome and prevention and progression of some pathologies

**2.5.1** While the microbiome is considered as a unique fingerprint for each individual, its study generally requires a large amount of data and huge numbers of samples because of many sources of variability (individuals, sample collection, storage, analyses). Thus, the study of microbiome in some populations, particularly in patients suffering from rare diseases, constitutes a big challenge. Furthermore, while a large body of evidence indicates a correlation between disturbances in the

microbiota–gut–brain axis and progression of several neurological and psychiatric disorders (e.g., eating disorders, depression, schizophrenia, Autism Spectrum Disorders (ASD), Fragile X Syndrome (FXS), Epileptic Encephalopathies (EE)), specific data on the microbiome profile, also at different stages of disease, are still lacking. Recently, lung microbial misplacement has been recognized playing a role in Acute Respiratory Distress Syndrome with a potential actionable factor in respiratory failure in SARS-CoV-2 infection. The identification of specific microbiome patterns in the long-term disease progression could allow to identify biomarkers to define specific stages and foster the scientific rationale for innovative therapeutic approaches. The actions planned are (TRL 3):

→ Systematic collection and analysis of clinical data, microbiome samples and metabolites over the time (including long-term measurements), at different stages of disease progression and in patients under treatment.

→ Setting of specific models, including in silico and in vivo approaches, to study the microbiome changes during disease progression.

To fully realize the potential of microbiome-based products to prevent or cure disease in humans, the effort of nutritional and pharmaceutical developers must evolve from the basic research area into translational work leading to product development and commercialization. To this purpose, the main requirements are: well-characterized product candidates, well-designed development plans (including clinical studies with relevant end-points), and well-defined target product profiles. The action planned is (TRL 3):

→ Development of new microbiome-based products either as novel foods, to be used as ingredients for innovative food supplements and foods for special medical purposes, or drugs, following the guidelines and the recommendations of the competent regulatory bodies for nutraceuticals and pharmaceuticals (EFSA, EMA).

**2.5.2** The small intestine is the largest part of the immune system and a central hub of the body's network of lymphatic vessels. Immune cells from around the body circulate via these lymphatic vessels through the tissues of the small intestine where they are conditioned by exposure to the many antigens and immunomodulatory agents that continuously pass through. These conditions can then impact disease and health at all sites of the body. Microbiome plays a key role in the immune homeostasis, particularly in the small intestine. Here the action planned is (TRL 3):

→ Identify new classes of oral biologics (individual strains or association of microbes) acting on small intestinal axis and able to contrast Neurological and Psychiatric diseases, Chronic respiratory diseases, Cardiovascular diseases, Diabetes, Autoimmune diseases.

**2.5.3** The complexity and the variability of human gut microbiota still represent major challenges for the development of new therapeutic approaches in the modulation of multiple neurochemical pathways via microbiota therapeutics (MT). More information on the role of the metabolism products of the microbiota (postbiotics) in the regulation of neuro-immuno-endocrine function is needed to pave the way to the development of future treatments/new drug candidates for central nervous system (CNS) disorders and neurodegenerative diseases with high unmet medical need. The actions here are (TRL: 3):

→ New investigations on the role of the metabolism products of the microbiota in the regulation of neuro-immuno-endocrine function

→ Development of future treatments/new drug candidates for central nervous system (CNS) disorders and neurodegenerative diseases.

## 2.6 Exploit the nexus Microbiome, Enteral Nutrition and Special Nutrition

Some Food for Special Medical Purposes (FSMP), in particular those for oral nutritional supplements and artificial enteral nutrition, are not sufficiently recognized as relevant for their non-pharmacological therapeutic role. While companies working on them are investing consistently on producing clinical evidences, at the same time they have not the possibility of investing in randomized, double-blind clinical studies to demonstrate efficacy and tolerability with the same effort/level of quality of pharma companies. The planned actions are to (TRL 4):

→ Create new know how on how the microbiota restores with and without interference of nutrition;

→ Develop targeted approaches with probiotics or other nutritional solutions, to restore the microbiota and prevent inflammation and infection during a patient's recovery, allowing therapeutic diets helping drugs to be more effective in their therapeutic role.

## 2.7 Exploit the role of microbiomes in the carbon fixation and nutrients availability in soils, sediments and water

Italy, with an 8.38% annual loss of soil in arable land, is the second country with the highest average rate of soil degradation in the European Union. The storage of organic carbon in soil (SOC), through the increase of soils organic matter (SOM) and its assimilation via native soil microbiomes, can contribute to the restoration of fertility and productivity of terrestrial ecosystems, supporting eco-systemic services derived from soil such as its quality, water filtration, erosion control, nutrient cycle, healthy habitat for organisms. Biofertilizers as well as biobased products which don't accumulate in soil, high quality compostand biochar, like those obtained from the treatment of urban, agricultural and biobased industry biowastes, including the organic fraction of municipal solid waste (OFMSW), sewage sludge, etc. can be used as effective and low-cost sources of organic carbon for the soil and permit reducing the quantity of organic waste sent to disposal with consequent environmental benefits (Figure 4). This requires an extremely efficient separate collection systems, based on the use of bioplastics and compostable materials for the collection of organic waste, and efficient treatment according to the advanced circular bioeconomy models, as well as aligned regulatory and administrative indications and technical training actions for public and private stakeholders involved in the sector.

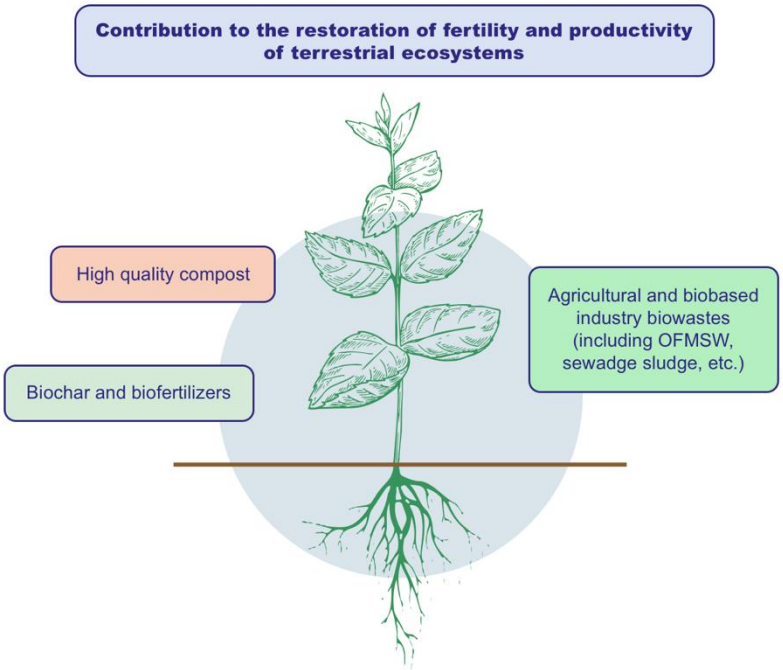



**Figure 4**. *Elements that can be used as effective and low-cost sources of organic carbon for the soil and permit reducing the quantity of organic waste sent to disposal with consequent environmental benefits*

The actions planned are:

→ Promote actions addressed to increase the soil organic matter through the addition of compost, biochar, biodegradable in soil mulch and biofertilizers and sequential stimulation and monitoring of native microbiomes;

→ Assess the average impacts of biobased products which don't accumulate in soil, compost, biochar and biofertilizers on the microbiota of major types of soils under actual site conditions and how the applied organic matter can be processed (TRL 4);

→ Promote the conversion of biological matrices of urban, agricultural and industrial origin (including OFMSW, sewage sludge, lignocellulosic materials and waste cellulose and other biowaste) into biobased products which don't accumulate in soil, high quality compost, biochar and biofertilizers by reducing the quantity of waste sent to disposal (TRL 8).

## 2.8 Exploit the role of microbiome on the sustainable animal production, health and welfare with reduced use/replacement of antimicrobials

**2.8.1** New approaches to the production of food of animal origin need to respond to many different issues. Animal welfare and health, environmental impact, sustainability, and food safety are major and interconnected strategic challenges. The identification of probiotics or bioactive compound targeted to reduce productive inefficiencies like greenhouse gases (GHGs) emission and nitrogen excretion by improving animal efficiency concur in reducing the environmental pollution, protecting

soil and water resources and reduce the soil utilization dedicate to crop production for animal feed. The actions planned are:

→ Extensive characterization of microbiome from different animal species, production systems, body sites, including longitudinal and cross-sectional studies throughout the development of eubiotic substances (TRL 3).
→ Development of models and relationship between diet composition and animal welfare, intestinal health, feed conversion, GHGs and nitrogen excretion (TRL 4);
→ Development of diagnostic tools and biological markers able to monitor *in vivo* response to different management, feed composition, pre and probiotics supplementation (TRL 3);
→ Animal derived food and charcutier need a better knowledge about microbiome to establish positive microbiota, to reduce additives and preservatives, ensuring an improvement in durability and shelf-life. (TRL 3)

**2.8.2** Awareness of living in a globalized world, where animal and human health are strictly linked, requires a "One Health" approach (Figure 5). The composition of microbiome of all living beings is related to the development of many diseases and metabolic disorders. In the post-antibiotic era, we need to gather tools and better knowledge on how microbiome composition prevents infection by dangerous pathogens. More knowledge on this can permit to improve animal welfare and health, as well as to reduce the need of antimicrobials use, restoring the antimicrobial sensitivity in a "One Health" approach, allowing to improve the feed efficiency reducing the environmental impact.

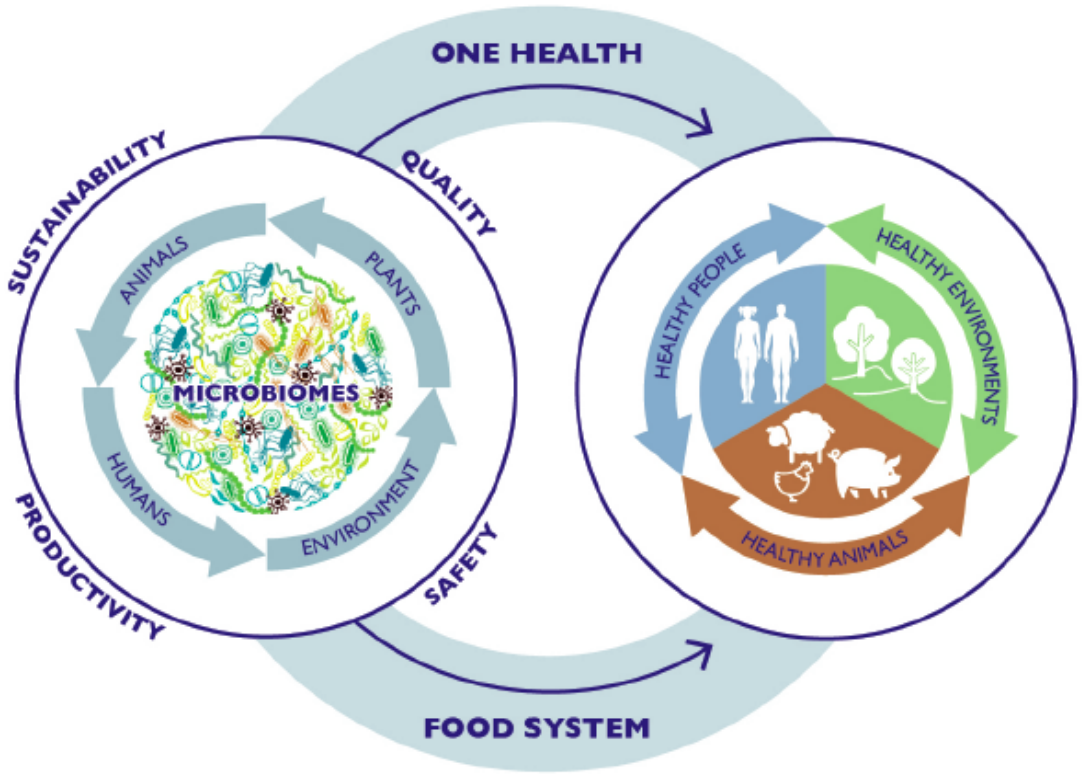



**Figure 5**. *"One Health" Approach*

Animal industry is minimizing the use of antibiotics for the treatment of bacterial diseases. Animal share the need already highlighted for human at the points 2.2, 2.4 and 2.5. Indeed, probiotics, prebiotics and bioactive molecules like essential oils are used as feed additive to improve gut functionality, hence reducing the probability of infectious diseases. However, there is a substantial lack of know-how on microbiome functions of different animal species and on their grow-out phases and in the different parts of the gastro-intestinal tract. This adversely affect the targeting of nutritional interventions. Further, there is the need of new effective candidate bioactive compounds, bacterial strains as well as microbial consortia; then, a dedicated dossier for each of them is asked by the European legislation and therefore information on their safety and the quality aspects, impacts on growth performance and feed efficiency, as well as on immune response or inflammatory status, will be required. Finally, more information on the connection among specific production systems, host and its microbiome are required, even in the framework of the urgent need to develop non-antibiotic therapeutics effective to treat the diseases. These actions would result in improved animal health, welfare and production efficiency along with a reduction of the risk of generation and spread of antimicrobial resistance as well as food borne pathogens and zoonoses. The actions planned are to:

→ Set up of specific models, including in silico, *ex vivo* and *in vivo* approaches, to study the microbiome changes during disease progression (TRL 4)

→ Develop feed additives targeted to increase the natural resistance of the animals against pathogens (TRL 4)

→ Develop non-antibiotic therapeutics to treat specific animal diseases (TRL 3)

→ Define the rules for the authorization of the non-antibiotic therapeutics, in order to promote the industrial investments on this cutting-edge research field.

**2.8.3** Impact of the crops-endogenous microbiota and mycobiota in the quality of the silage.

Silage production has a great zootechnical and economic importance in Italy; many traditional DOP Italian cheeses are produced using milk obtained from animals fed with silage, and the majority of the beef cattle are nourished with silage mixtures (mainly obtained from fermented corn and alfalfa). Appropriate systematic studies should be undertaken on the silage microbiota and mycobiota, to study relationship with desirable/undesirable fermentation profiles, growth of pathogenic microorganisms and, especially, production of mycotoxins, with the objective to increase the nutritional quality, the security and the safety of the silage.

## 2.9 Exploit the role of microbiome on the vegetal primary production and antibiotics replacement

In the direction of a sustainable agriculture, a systematic isolation, identification, and characterization of Italian plant- and soil-associated microbes should be performed. The definition of an "healthy soil/culture-specific microbiota" that can engage in each micro-environment an intimate and unique association with healthy plants, can permit to sustainably increase in the quality and yield of crops, and to decrease the need of pesticides and chemical fertilizers.

Plant microbiomes support the plant's nutrition, health and resistance to biotic and abiotic stress. These microbiomes are highly diversified and deliver key ecological functions favoring plant primary production, including fruits. It is therefore relevant to identify specific inocula able to increase the resilience, environmental sustainability, productivity and quality of products of the major crops of industrial interest and to test them on the large scale. The planned actions are to:

→ Develop and test "biofertilizing agents", able to increase the root systems, making it able to adsorb more rapidly a wider number of nutrients (TRL 5);
→ Develop and test "bioactivators agents", able to create in the rhizosphere enabling conditions for the plant assimilation of nutrients (TRL 4);
→ Develop and test "BioProtecting agents" able to reduce the competition/adverse effects of pathogenic fungi and insects on plant growth (TRL 3).

## 2.10 Exploit the role of microbiome in the production of food and beverage

Italy is ready to produce food formulations supporting health promoting microbiomes in humans and to produce healthier foods via microbiome exploitation in the food processing. Milk powder formulations for babies and children (stages 1, stage 2 and stage 3) with ingredients able to enrich the more suitable microbiome for the selected target population, can be produced on large volume for the country but also for China, South Korea, Saudi Arabia, Algeria etc, with interesting foreseen revenues. At the same time, tailor made modified vegetable raw materials, as pulse and/or cereals, can be obtained by means of specific and innovative fermentation processes, based on tailored microbiome exploitation. Other examples are finished baked goods, that, according to the current legislation, can only be prepared via natural yeast (known as sourdough, also named as "mother yeast"). The tailored fermented products normally display excellent organoleptic features, improved preservability, digestibility, nutritional characteristics and lower preparation costs. The actions planned are to:

→ Set up of other powder formulations for babies and children with ingredients supporting the positive development of the microbiome in selected target population (TRL 4);

→ Identify new raw materials with higher potential to improve the nutritional properties of confectionery products by fermentome processing. These new raw ingredients might be used as bulking in the partial sugar substitution or in the animal raw materials substitution, to reduce the environmental impact or to produce vegetarian-vegan products (TRL 4);

→ Identify a specific and proprietary sourdough to be used for baked good production, in order to maximize production efficiency and to get the best performing product in term of sensorial properties (TRL 7);

→ Develop some confectionery products with different quantity/quality of "fibers and/or antioxidants", able to induce positive functional effects on the microbiota characteristics and then on the human health (TRL 6);

→ Develop and standardize specific biomarkers to measure all core health parameters of the products (TRL 4).

## 2.11 Determine and contrast mycotoxins effects on Microbiome.

Mycotoxins represent a serious threat to human and animal health. In Europe, the most relevant source of contamination of mycotoxins are foods or feeds based on cereals (including rice, wheat, maize and barley), nuts, fruits, silage, milk and dairy products predominantly imported.

→ The impacts of long-term exposure to low-dosage mycotoxins (a condition that regrettably occurs in the average European diet) on the human and animal intestinal microbiota composition and metabolic activity should be experimentally evaluated in animals and in human populations to correlate the chronic exposition to some mycotoxins to specific dismicrobisms/pathologies (in human and animals), or decrease of productivity (in animals).

## 2.12 Exploit microbiome on the environmental biotechnology applications

In the last decades, several biological processes for the clean-up of polluted soils, sediments and wastewaters and for the valorization of biowaste have been developed and applied on the full scale and the field. These are mainly based on the creation of the environmental conditions able to sustain the growth and biodegradation activity of indigenous specialized microbes (biostimulation) and/or the addition of tailored exogenous pollutant degrading microorganisms (bioaugmentation). However, such promising techniques, as cheaper, simpler and more environmentally and socially friendly than any physical-chemical approaches suitable for the same processes, are often limited in robustness, efficiency and performance reproducibility due the lack of an efficient control over time and space of the biological activity of the indigenous active microbes. Indeed, the latter act in the contaminated matrix as part of ultra-complex microbiomes, that are subject to spatial and temporal variability in response to the environmental perturbations and establish multidimensional networks of microbe-microbe interactions. Thus, to improve the performance, reproducibility and robustness of bioremediation/conversion technologies mentioned, the following actions are planned (TRL 4-8):

→Promote/sustain the creation of tailored partnerships among farmers, bioremediation industries, wastewater/biowaste exploiting companies involved in full scale/field application and scientists/experts of microbiome characterization and exploitation;

→Develop and adopt an evidence-based, model-informed microbiome management approach to efficiently control the soil/sediment/wastewater/biowaste microbiome structure and functions, and to develop microbiome-based approaches to optimize and improve efficiency, stability and reproducibility of the full scale processes/practices/technologies.

## 3. Promote awareness, education, training and skills across microbiome-related domains

The recommended actions are:

a. Set up a microbiome portal to gather basic information, R&I projects and industrial actions on microbiome in the pharma and food systems. The portal will take the form of a website intended for the general public and a trade audience;
b. Encourage the organization of "open days" in companies active in pharma and food systems, by facilitating direct discussions between company managers and project promoters on the one hand, and the general public and consumers on the other, thus facilitating the microbiome based products acceptance by society;
c. Conduct technical information campaigns in association with the main Italian and European scientific societies to disseminate the importance of microbiome-based medicine, primary production and processing of food products and the opportunities they offer;
d. Introduce the microbiome concepts both in high school education and in specialist vocational life sciences courses (schools of agronomy, schools of medicine, medical specialization schools, chemistry, pharmacy and biology courses, agricultural teaching, school education);

e. Disseminate the microbiome concept in initial and continuous training courses, Summer Schools, Continuing Professional Development Modules, Satellite Workshops etc;
f. Support the inclusion of microbiome and the pharma and food system concepts inside academic Health and Bioeconomy-related Bachelors' degrees, Masters' degrees and PhD programs.

## ACTORS INVOLVED

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Presidenza del Consiglio dei Ministri

CNBBSV

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