Artificial Intelligence-Driven Human Microbiome Engineering for Prevention of Immune and Chronic Diseases

Editors

Saba Hameed Zidan
College of Dentistry, Al-Qadisiyah University, Iraq

Zainab Abdl Baqi Abdl Jalel
College of Dentistry, Al-Qadisiyah University, Iraq

Amal Jamil Youssef
College of Dentistry, Al-Qadisiyah University, Iraq

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Abstract

Prevention of immune and chronic diseases represents an important public health objective. The human microbiome directly influences immune system development, and its modulation represents a promising avenue for disease prevention. Emerging artificial intelligence approaches facilitate large-scale exploration of microbiome-disease associations and generation of novel hypotheses. Prediction models based on longitudinal population-level data enable timely detection and stratification of disease risk. Evidence-based strategies are suggested for prevention of allergic diseases in childhood, modulation of vaccine responses, risk reduction for metabolic disorders and diabetes during adulthood, and enhancement of immune tolerance.

A population-based cohort study with periodic sampling can support longitudinal modelling of the microbiota-disease relationship and capture disease-specific alterations on a physiological timescale. For immune disorders, microbiome-targeted interventions may focus on the early-life period to ensure safety and harness a potentially greater effect on healthy immune development. Candida, Clostridia, and Atopobium are associated with the risk of developing asthma and inhalant allergies in childhood. Two interrelated hypotheses-reduced induced tolerance in the presence of microbial pathogens and a lack of consistent immune challenge during early-life development-are central to this expanded view of allergic disease aetiology.

Contents

Chapter - 1

The Human Microbiome and Its Role in Health and Disease

The interplay between the host and their microbiome is understood as microbiome-hoste interaction [1]. When a mutualism is established, the responsible microbes are seen as commensals, acting synergistically with the host immune system. It is reasonable to assume that the host interacts closely with all the associated microbiome species, as members are situated at mucosal surfaces that represent the first contact point for invading pathogens. Because of this, members of the microbiota can directly stimulate essential innate immune pathways. The host adapts to its microbiome by food exposure, leading to microbiome evolution into benign state revealing that human diet shapes their microbiome and thereby influences the innate immune system during pen and postnatal periods. Pattern recognition by innate immune cells stimulates the expression of barrier function associated proteins, such as the synthesis of mucus, mucins, secretory immunoglobin A (sIgA), cathelicidin, beta-defensins, lysozyme A, psoriasin and blood anti-microbial peptides. It also promotes the epithelial production of secreted small anti-microbial peptides generated by Paneth cells, such as the alpha-defensins relied upon to maintain intestinal health.

A multi-omics analysis on how the gut microbiota dictates innate immune development and function, revealing that microbiota composition (i.e. abundance of Lactobacillus, Oscillibacter, or Coprococcus) can determine gut mucosal layer thickness and its glycosylation pattern via controlling the transcriptional activation of MUC2. The Gram-positive bacteria Micrococcus luteus and the Gram-negative bacteria Escherichia coli, are presented as probiotics able to modulate growth rates of Burkholderia cepacia complex species,

enhancing their sIgA-inducing potential. Over an experimental timeline, pathogen-free mice exposed to an early-life supply of M. luteus developed a sIgA response against this bacterium [1, 2, 3, 4].

Composition and diversity of the human microbiome

The human microbiome encompasses a wide variety of prokaryotic and eukaryotic microorganisms, comprising bacteria, viruses, archaea, fungi, and protozoa. Beyond the genetic functions of the microbiome, its taxonomic and functional composition are also determinants of health. A wealth of disease models and human cohorts have shown that reduced richness and shifts in composition are associated with diverse immunological and metabolic diseases, cancer, or infections. These associations potentially reflect cause-effect relationships or risk associations suggesting microbial signatures for early diagnosis. Such signatures can be generated from high-dimensional microbiome data sets through various approaches, but deep learning represents an efficient way of training classifiers with increasing performance and enabling the identification of microbiome-disease associations beyond a supervised fashion. Other advanced approaches have also put forward disease signatures based on biological significance for disease risk assessment, detection, stratification, or prediction across cohorts and populations. In addition, the identification of associations between the microbiome and specific immunisation responses, and the incorporation of metagenomic data in prediction experiments for childhood allergies and asthma correlate well with children's health-disease trajectory studies.

Microbiome studies typically focus on the taxonomic diversity and composition of the microbiota at a given time point, giving less priority to longitudinal data sets that might enable the modelling of the dynamics of dysbiosis development, duration, and recovery related to infection incidence. Gaps in such temporal analyses can partly be filled using machine learning methods with individual microbiome profiles at different time points, resulting in an integrative model that predicts future alterations of disease- and health-associated microbiome states while accounting for time as an important factor and helping to detect specific disease signals. Despite the recurrent signals linking

microbiome composition and health, validation of the identified signatures remains paramount, especially if they are considered candidates for future clinical routine or used for personalized prevention initiatives. Combinations of machine learning with literature mining can play a key role in uncovering overarching principles regarding the stability of microbial signatures across diverse health-related conditions or the reliability of dietary-microbiome relationships [5, 6, 7, 8].

Microbiome development across the human lifespan

In microbiome research, the human life cycle is typically divided into the following stages: prenatal, infant, early childhood, late childhood, adolescence, adulthood, and aging. Despite being a continuous process, it is often simplified into discrete stages that are each characterized by the dynamics of key environmental factors. These include mode of delivery, feeding methods, introduction of dietary solids, weaning practices, transition from childhood to puberty, sexual maturation and adulthood, and old age. Such an approach aids reference dataset design and construction of Life Cycle Models for Time-Series Analysis.

The microbiome of a healthy adult is fairly stable over time, although changes may occur in response to stressors, including pain, anxiety, gastrointestinal infections, and antibiotic administration. However, an assessment of microbiome stability must also consider the temporal scale of the investigation. A study of younger adults (aged 19-30 years) found that, despite being stable over time, community composition could vary significantly during a routine sampling period of three weeks. The concept of microbiome stability must also account for inter-individual variability. Indeed, while the microbiomes of two healthy (non-diabetic) individuals may differ substantially, they may respond similarly in terms of beta diversity to environmental perturbations, despite the absolute abundance of the differing communities remaining unaltered [9, 10, 11, 12].

Host-microbiome interactions

Together, the microbiome and the organism interact through various signaling pathways. The microbiome modifies the training of

the immune system, while also offering supplementary metabolic activity. The production of a variety of nutrients, stability against pathogen colonization, and metabolism of xenobiotics are both facilitated by the gut microbiome. Through factors that modify mucositis and intestinal permeability, and thus the systemic translocation of substances produced by the microbiota, the microbiota likewise affects the blood-brain barrier. A reduction or deficiency in diversity and the abundance of the main phyla of the gut microbiota during aging lead to alterations in these functions and pathways.

The microbiota play significant roles in the development and maturation of the immune system through three different processes:

i) Education of the innate immune system.

ii) Education of the adaptive immune system.

iii) Training of thymic T cells in developing immune tolerance.

The gut microbiota can differ according to climatic zones and geographical areas. Some of these alterations may lead to disease. Chronic inflammatory conditions, as observed in obesity and type 2 diabetes, are associated with microbiota inflammation-induced dysregulation [13, 14, 15, 16].

Dysbiosis and disease associations

Evidence from metagenomic and metatranscriptomic studies indicates that the microbiome is a significant risk factor for and/or contributes to the pathogenesis of numerous immune and chronic diseases: in particular, type 1 and type 2 diabetes, allergic diseases, inflammatory bowel disease, neurological disorders (such as multiple sclerosis), cardiovascular diseases, autoimmune diseases, cancer, obesity, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and chronic kidney disease. Changes in microbial diversity appear to predispose individuals to the development of some immune and chronic diseases; in contrast, other diseases appear to correlate with the abundance or depletion of specific taxa within the microbiome, suggesting a more direct role in their pathogenesis.

Nonetheless, identifying association patterns is only the first step in understanding the relations between the microbiome and disease. Associations should ideally be established over time and should include both microbiome data and corresponding disease samples from the same cohort. In addition, immune and chronic disease-associated changes in the microbiome still need to be probed experimentally to establish causation. Therefore, the data available to support claims of causation may still be limited for many immune and chronic diseases [17, 18, 19, 20].

Microbiome as a therapeutic target

The potential of the microbiome in therapy is vast. Alterations in microbiome diversity and/or composition (dysbiosis) are linked with many diseases, including metabolic syndrome, obesity, diabetes, inflammatory bowel diseases, colorectal cancer, allergies, and asthma. However, convincing evidence for causal roles-beyond association-remains scarce. AI can help address this knowledge gap and specify the conditions under which the microbiome may serve as a therapeutic target or biomarker. Three main strategies are possible:

1) Modulation of dysbiosis more broadly.
2) Restoration of specific, prioritized, pre- or postdysbiotic microbiomes.
3) Development of deleterious dysbiosis (abnormal microbiota) or disease-associated microbiome dysbiosis in animal models (mice, nonhuman primates) or human cohorts and identification of the microbiome signature. The aim of these approaches is to provide biobridging.

Recent studies have explored the design of predictive AI models of chronic diseases based on the microbiome and also the engineering of the microbiome for healthy aging. AI has facilitated the specification of dietary patterns associated with common food groups that modulate the microbiome and contribute to disease prevention. There is also emerging interest in using biosensors and wearables to facilitate daily health monitoring. Of particular importance, the timing of interventions during the critical windows of immune system

development or remodeling for early-life modulation or tolerance induction (i.e., delivery of potential allergy-resolving microbes to at-risk populations) has become increasingly acknowledged. Moreover, restoration of disease-specific microbiota or precise modulation of normal healthy ecosystems also holds great promise [21, 22, 23, 24].

Chapter - 2

Immune System-Microbiome Interactions

The innate immune system uses pattern recognition receptors (PRRs) to detect danger signals in the gut and generates immune and detection signals affecting local microbiota composition and function. PRR signaling is critical for maintaining intestinal barrier integrity. The microbiota produces beneficial antimicrobial peptides (AMPs) that help regulate intestinal homeostasis but are reduced in conditions involving high intestinal permeability or microbiome dysbiosis. The microbiome is also involved in adaptive immunity education and tolerance. Diversity and composition of colonic Tregs correspond to specific bacteria. Sources of microbial signals shaping immune education encompass the gut microbiome, lactate, serum, and cultured gut-resident bacteria. Dysbiosis can thus alter immune signaling and tolerance pathways, potentially leading to chronic inflammation, increased pathology risk, and decreased vaccine effects. Autoimmunity, allergy, and autism are examples of altered tolerance-associated conditions.

The microbiome influences the production of various metabolites that play crucial roles in the immune system. Butyrate modulates macrophage functions, and alters the number of T- and B-cell populations in the kidney and spleen. Propionate stimulates CCL20 production in human intestinal epithelial cells. Tryptophan metabolites affect the balance of T- and B-cell subtypes through the AHR and IDO pathways, and enhance macrophage polarization toward M2. Dysbiosis alters pathways of tryptophan, butyrate, and propionate metabolism and receptor signals, and can modulate various IFN-γ- and IL-12-related inflammatory pathways. Th17/Treg imbalances promote multiple autoimmune disorders, but this imbalance can be corrected by Microbacterium sp. 2C4. Reduced Treg-inducing signals are associated

with elevated IL-17A in patients with systemic autoimmunity. Dysbiosis may alter immune-associated pathways in COVID-19 patients, and patients with severe disease show a significant inflammatory signature involving Th17 cells [25, 26, 27, 28].

Innate immune modulation by the microbiome

The first line of defense, the innate immune system prevents pathogen invasion and controls infection severity. Composed of physical barriers (e.g., skin, mucosal membranes), immune cells (e.g., macrophages, dendritic cells, neutrophils), soluble mediators (e.g., cytokines, chemokines, proteins), and lipid membranes, innate immunity initiates immune responses through pattern recognition of pathogens, regulation of adaptive immunity, and infection control. The human microbiome contributes to all aspects of innate immune function.

The skin and epithelial surfaces of the gut, lung, and other tissues serve as physical barriers against microbiota and pathogen invasion. Composed of epithelial cells and the underlying extracellular matrix, these surfaces are regularly exposed to commensals. Microbial metabolites and certain pathogens induce expression of tight junction proteins (e.g., claudin, occludin) that promote tight junction formation across epithelial layers. The memory component of innate immunity is mediated by the education of trained innate immune cells, which respond more rapidly and vigorously to secondary infections. Trained immunity is believed to be mediated in part by metabolites (e.g., butyrate) produced during microbiome fermentation of indigestible carbohydrates (e.g., dietary fiber) in the gut [29, 30, 31, 32].

Adaptive immune education and tolerance

The microbiome modulates not only the development of innate immune responses but also educates the adaptive immune system and promotes tolerance to food and environmental antigens. Underlying mechanisms include the production of microbial-derived metabolites and direct stimulation of cognate receptors, both involved in shaping T and B cell responses. Dysbiosis affects the tolerance-inducing pathways of pregnancy and milk composition, disturbing the

equilibrium between pro- and anti-inflammatory responses. Microbiome-driven processes are critical for optimizing vaccine responses and preventing autoimmune diseases.

Mature, functional T cells and immunoglobulin-producing B cells are necessary for the adaptive immune response. Segmented filamentous bacteria (SFB) are among the few characterized commensal microbes able to induce Th17 cell differentiation and promote antibody class switching in IgA+ and IgG+ B cells. SFB colonization increases the susceptibility to experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS). While Th17 cells contribute to mucosal defense and host protection, a dysregulated or exaggerated Th17 response is a hallmark of various autoimmune and inflammatory disorders. Mucosal IgA production contributes to immune exclusion and neutralization of invading pathogens. The microbiota directs the education of intestinal IgA-producing B cells by regulating TGF-β and retinoic acid-producing dendritic cells. Mucosal infection with pathogens such as Helicobacter pylori or cytomegalovirus mediates a fecal IgA response and shapes the composition of the IgA-coated fecal microbiota [33, 34, 35, 36].

Microbial metabolites and immune signaling

Microbial metabolites produced by members of the human microbiome can directly signal cells involved in the host immune response. Representative metabolites include butyrate, propionate, and tryptophan metabolites such as indole, indole-3-acetic acid (IAA), indole-3-ethanol, and butyrylcoenzyme a (butyryl-CoA). Activation of targets such as immunoglobulin A (IgA) secreting B cells, T helper-17 (Th17) cells, forkhead box P3 (FoxP3+) regulatory T cells, dendritic cells, toll-like receptor 2 (TLR2), toll-like receptor 4 (TLR4), G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), hydroxycarboxylic acid receptor 1 (HCA) and AhR by these metabolites has an important role in modulating both innate and adaptive immunity. Butyrate promotes the differentiation of Th17 cells as well as the production of IL-10, IFN-γ, and IL-4 by T cells. In Gpr41 rats, the secretion of IgA decreased dramatically and Lactobacillus reuteri populations were reduced in the intestines. Propionate is

involved in the differentiation of naïve T cells into Th1 or Th2 cells by upregulating the expression of T-bet or GATA3, respectively.

Changes in microbial flora composition and diversity are closely related to the occurrence of autoimmune diseases, and the imbalance of intestinal microorganisms can lead to alteration of the composition and concentration of microbial metabolites. According to the principle of "excess causing poison", the excessive production or deficiency of certain metabolites during disease development can accelerate the inflammatory response through direct or indirect effects on immune regulation. Metabolites act on immune cells to further regulate the intestinal immune microenvironment, resulting in an imbalance of the intestinal immune response and contributing to the pathogenesis of autoimmune diseases [37, 38, 39, 40].

Inflammation, autoimmunity, and immune imbalance

Dysbiosis predisposes to an inflammatory state. A shift in the loss of diversity or abundance of certain populations triggers cascades of inflammatory molecules such as inflammatory cytokines, chemokines, and T helper-17 (Th17) cells. These markers are linked to chronic diseases associated with autoimmunity in patients suffering from coeliac disease, inflammatory bowel disease (IBD), basilophilic asthma, systemic lupus erythematosus (SLE), Sjögren syndrome, multiple sclerosis (MS), and rheumatoid arthritis (RA). Moreover, juvenile idiopathic arthritis is associated with reduced α-diversity in the gut microbiota. Longitudinal studies show that a decrease in microbiota diversity and altered microbiota composition precede the onset of T1DM in genetically susceptible children. Interestingly, decreased levels of the oral microbiome genus Haemophilus in children correlate with an increased risk of subsequent allergies, asthma, or eczema during the first five years of life. The relationship between dysbiosis and high susceptibility to infections in patients with MS appears to be also associated with immunological dysregulation.

Specific bacterial populations play important roles in inflammation and autoimmunity. Enterobacteriaceae, especially Escherichia and Shigella, are enriched in patients with autoimmune diseases. The levels of the divided family Mycoplasmataceae, genus Mycoplasma, family

Enterobacteriaceae, and genus Escherichia are enriched in patients with active SLE. A higher ratio of Enterococcus to Lactobacillus and reduced butyrate production in the gut microbiota have been implicated as risk factors in RA. Oral and gut microbiota from patients with autoimmune diseases exhibit higher proportions of pathogenic species, such as Selenomonas, Methanobrevibacter or Enterobacteriaceae, and a lower prevalence of immune-protecting bacteria. [41, 42, 43, 44]

Immune biomarkers linked to microbiome changes

Microbiome alterations have been associated with various immune-mediated conditions, yet linking specific dysbiosis phenotypes to the development of detectable disease-associated host response patterns has proven challenging. Immune biomarkers represent a potentially effective approach for early disease detection or risk stratification because they can appear earlier than classical disease manifestations. During the last twenty-five years, a variety of immune markers have been connected with alterations of the intestinal or respiratory microbiota, especially in chronic inflammatory disorders like inflammatory bowel disease, asthma, or autoimmune diseases, highlighting the modulatory potential of the microbiome and its association with the immune advance of these disorders. A systematic review identified such microbiome-associated immune markers and proposed an integrative validation strategy to ensure that proposed associations are sufficiently supported by existing literature.

Detecting dysbiosis or loss of diversity is insufficient for establishing microbiome-disease relationships, especially for immune-mediated diseases, where host immunity can respond before overt clinical symptoms. Several studies have associated certain immune factors with specific microbiome signatures, including altered relative abundance of key taxa or specific phylogenetic or functional dysbiosis. Integration of these findings may provide a foundation for future microbiome disease-prevention studies. [45, 46, 47, 48, 45, 46, 47, 48]

Chapter - 3

Chronic Diseases Influenced by the Microbiome

The human microbiome plays a crucial role in the etiology, prevention, and treatment of chronic diseases, and the observed microbiome-disease associations may aid in the development of novel preventive and treatment strategies. A diverse and resilient microbiome helps to maintain host homeostasis, while a dysbiotic microbial community may disturb metabolic homeostasis and promote chronic diseases. Advances in AI can facilitate the investigation of gaps in current knowledge, leading to hypotheses on preventive and treatment microbiome interventions that can be fully and rigorously tested.

Chronic ailments such as metabolic syndrome, cardiovascular disease, central nervous system disorders, inflammatory bowel disease, and cancer are closely linked to the microbiome. Metabolic syndrome is characterized by a constellation of risk factors, including abdominal obesity, dyslipidemia, hypertension, and insulin resistance. Excess lipid accumulation in macrophages and the increased biosynthesis of lipopolysaccharide contribute to peripheral and central resistance to the action of insulin, while atherogenic dyslipidemia leads to an increased cholesterol ester content in hepatic cells and the deposition of lipids in blood vessels, resulting in a greater risk of cardiovascular disease. The composition of the gut microbiota appears to play a crucial role in these pathological changes, as dysbiosis has been associated with increased energy harvest from the diet, enhanced low-grade inflammation, and altered short-chain fatty acid production.

Metabolic disorders and obesity

Strong evidence links the microbiome and metabolic disorders, with altered diversity and composition associated with obesity, insulin resistance, and dyslipidemia. Specific patterns of microbiome-derived

metabolites may disturb metabolic homeostasis and contribute to early life obesity. Disease-promoting signatures can be exploited to predicatively model development, while directional relationships can be inferred with longitudinal associations. Predictive models may serve stratification needs but must be calibrated for population prediction.

Obesity is a heterogeneous condition and microbiome-derived features can be leveraged for stratification. Using microbiome data, population cohorts have been subdivided into obesity-resistant and -susceptible subgroups and prediction models established. Such signatures can be operated in reverse to uncover protective pathways or identify preventive mechanisms in related conditions. Longitudinal data support directionality between dysbiosis and disease progression, enabling identification of microbiome signatures preceded by disease and modeling of subsequent onset. Dynamic, temporally ordered time-series data further elucidate developmental and causal relationships. Disease signatures can be considered predictive if they anticipate a condition before clinical onset, but generalizability remains a challenging and important task.

Disease signatures may capture risk that is not reflected in the patient population under study, suggesting within-cohort calibration prior to wider application. Such a generalization strategy may not be trivial when using microbiome signatures to predict development of diseases that typically manifest within childhood, given that microbial composition and metabolic cross-talk undergo shifts during development [49, 50, 51, 52].

Cardiovascular and endocrine diseases

Altered microbiota profiles and dysbiosis affect metabolism and contribute to the development of cardiovascular disease and hypertension. Microbiome-derived metabolites influence cardiovascular function, in part by regulating blood pressure and modulating cardiovascular autonomic control. Hypertension has been associated with an overabundance of Firmicutes and a deficiency of Bacteroidetes in the gut and with increased bacteria-derived trimethylamine and brain-derived neurotropic factors. Gut bacteria also affect heart rate variability, a key biomarker of cardiovascular

regulation. Microbial depletion accelerates the development of atherosclerosis and associated features through effects on cholesterol metabolism, the immune response, and inflammation. Dysbiosis has been linked with atherosclerotic plaque instability, and the structure of the gut microbiota may predict future atherosclerosis. Several of these mechanisms are also relevant in other endocrine diseases, including irregularities in metabolic hormone metabolism related to reproductive health, polycystic ovary syndrome, and prostate cancer.

Fecal microbiota transplantation has been investigated as a potential therapeutic method for heart failure, hypertension, and atherosclerosis, and a synthetically defined four-membered bacteria consortium has been shown to reverse hypertension in mice. A microbiome-associated production of uremic toxins has been linked to chronic kidney disease. Chronic kidney disease is characterized by inflammation and subsequent changes in the gut microbiome; tyrosine and phenylalanine metabolism are also dysfunctional and correlate poorly with clinical data. Modulating the gut-kidney axis by changing the gut microbiome through pre-, pro-, or synbiotic approaches may prevent and control chronic kidney disease progression. Microbiomes of patients with primary biliary cholangitis display a decrease in microbial diversity and altered functional pathways [53, 54, 55, 56].

Gastrointestinal and liver diseases

The gut plays an essential role in maintaining homeostasis, and any alteration of the gut microbiota can have profound effects on host health status. Dysbiosis has been linked to several GI diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancer, and gastrointestinal infections. More importantly, gut dysbiosis has also been associated with extra intestinal diseases such as cardiovascular diseases, metabolic syndrome, diabetes, obesity, and even neurodegenerative disorders. Fecal microbiota transplantation (FMT), which allows for the transfer of stool samples from a healthy donor to patients with different diseases and is thought to restore gut health, has become a widely used therapy. More clinical data about the effects of FMT on various diseases have been accumulated, making it a potential treatment option for IBD and Clostridium difficile infection (CDI).

However, considerable safety concerns due to the variations of gut microbiota profiles among patients and donors hinder the clinical application of FMT. Moreover, the risk of transferring pathogens during FMT procedures remains an issue, and thus the use of synthetically designed microbial communities instead of whole stool transplants has gained attention. Defined-microbiota FM-also known as consortium FMT, is a therapy for GI and liver diseases that aims to replace the entire microbiota with a defined set of beneficial microbes or communities, in order to restore microbial function and metabolism while eliminating harmful taxa. This approach is considered to be safer than standard FMT as only a few strains in a consortium are actively monitored throughout the therapy [57, 56, 58, 53].

Neurological and neuroimmune disorders

Alterations in microbiome composition or function are linked to several neurological conditions. The gut-brain axis encompasses pathways for microbiome-mediated signals to reach the central nervous system, and an influence on mood and cognition is supported by clinical data connecting specific taxa to autism, depression, or anxiety. Gut microbiome perturbations also associate with neurodegeneration in Alzheimer's disease, multiple sclerosis, and Parkinson's disease. Models based on fecal microbiota transplantation have evaluated disease impacts on microbiome structure and function. These disease-microbiome relationships open avenues for therapeutic investigations aimed at restoration of commensal signaling to ameliorate the condition.

Microbiome influences on neurological and neuroimmune disorders are shaped by signaling from the gut to the brain through the immune system, direct vagal innervation of the gut, microbiome-derived metabolites reaching circulation and the enteric nervous system, and indirect interaction through microbiome-modulated serum metabolites. The overall role of the microbiota appears largely beneficial with respect to mood and cognitive function. However, noteworthy exceptions and contradictions exist, with disease-associated microbiome changes detectable also in animal models [59, 60, 61, 62, 59, 60, 61, 62].

Cancer and immune-mediated malignancies

A strong association exists between several types of cancer and the microbiome community structure and functions. Tumorigenicity can be promoted by microbial metabolites, such as secondary bile acids and specific sexual hormones, as well as by bacterial infections (S. Typhimurium, C. pneumoniae, and H. pylori). Conversely, dysbiosis-related immunological factors could suppress colorectal cancer development. The mechanism of cancer treatment resistance is also related to the microbiome, as preservation of the gut microflora during chemotherapy mitigates the systemic toxicity of the chemotherapeutic agent. Furthermore, gut commensals can also modulate anti-tumor immunity; for example, C. itersonii enhances the activity of immune checkpoint inhibitors towards melanoma in mice. The various associations between the microbiome and the process of tumor development or progression are illustrated in Supplementary Figure 6. The gut microbiome plays diverse roles in modulating different stages of immune-mediated malignancies, such as head and neck cancers, via regulation of the immune system, production of metabolites, and response to therapy.

Chapter - 4

Artificial Intelligence in Biomedical and Microbiome Research

Encompassing every sector of research and everyday life, profound changes arise from powerful deep-learning language models and an ever-improving human-computer interface. AI and machine-learning approaches are sophisticated classifying or predicting systems, trained on demonstration datasets and repeatedly refined. In supervised learning, the model is presented with pairs of input features and preassigned targets; the goal is to predict the target for a given input. Unsupervised learning is applied when the target is unknown or nonexistent, such as clustering objects based on signal similarity, while reinforcement learning evaluates actions according to received feedback.

Many biological signals and experimental results are now evaluated using machine-learning techniques. Deep learning is mainly applied to imaging, speech recognition, and natural language processing; biological discoveries are facilitated by literature mining, as large language models generate new insights and extract regulatory relationships and interpretable hypotheses. After generating the hypotheses, a cloud-based design loop generates and evaluates the experimental design to confirm or reject specific hypotheses [63, 64, 65, 66].

Overview of AI and machine learning approaches

Gaining insights from complex, high-dimensional, and heterogeneous biological data is challenging. Therefore, artificial intelligence (AI) and machine learning methods applied in biological research have rapidly advanced and diversified. Key AI-based methods for biomedical research are supervised/unsupervised/reinforcement learning models used to find relationships among variables in a defined

learning space and to predict responses based on novel input data. In supervised learning, algorithms are trained with a dataset containing examples along with the desired outcome and are then able to learn predictive models for similar new data. For unsupervised learning, input data do not contain the answers. Instead, the algorithm finds underlying structures or classifications within the data according to certain similar features. Reinforcement learning is trained to explore and learn the best actions through simulation and feedback signals from each attempted action, optimizing long-term return.

Deep learning models directly learn high-level features or corresponding classifications from raw images or signals. Specific architectures, types of biological data, and evaluation metrics vary among applications. Convolutional neural networks (CNN) are designed for visual-pattern recognition to analyze 2D spatial data such as molecular structure images and gene expression in tissue sections. Generated features can be used as input for classifiers to make a final decision. Recurrent neural networks, a type of parameter-sharing architecture, are suitable for sequential data such as protein sequences and nucleotide sequences. Long short-term memory (LSTM) is a variant of recurrent neural networks designed to explore long-distance relationships. Transformer models represent another family of deep learning models based on self-attention mechanisms and perform well in natural language processing tasks. [67, 68, 69, 70]

Deep learning for biological data analysis

Deep learning models can learn from various biological data types: imaging data (e.g., microscopy, MRI, flow cytometry, and RNA-seq), multi-omics data (genomics, transcriptomics, proteomics, metabolomics), and signaling pathways. These models typically require a large number of samples but can accurately predict unseen molecular responses by exploiting high-dimensional signals. The performance of a deep learning model is usually evaluated using accuracy, AUROC, and AUPRC.

In the absence of sufficient labeled data, generative models such as GANs and VAEs can generate synthetic data that resemble real biological data. They have successfully increased training data size for

image classification, disease subtype classification, molecular response prediction, cell-type reconstruction, genes prediction, and multi-omics integration. Domain adaptation methods have also been used to transfer knowledge learned from labeled data in one domain to an unlabeled but related domain [71, 72, 73, 74, 75].

Natural language processing in biomedical discovery

Natural language processing is increasingly applied to biomedical knowledge extraction. The quantity and complexity of biomedical literature, combined with the speed of discovery, demands automated processing tools to complement human authorship. Unsupervised techniques based on large, unlabeled corpora assist in pretraining neural network architectures for transfer learning. Many studies utilize domain-specific adaptations of BERT, applying these models to standard sentence-pair classification benchmarks (e.g., natural language inference). Beyond classification, text generation models such as T5 hold promise for auto-summarization at varying scales.

Knowledge graphs implemented in the biomedical domain foster supervised learning against labeled entities and relations, leading to improved performance on related tasks. Tuning and evaluating sets of existing resources addresses two common challenges in knowledge graph construction: data density and sensitivity to bias or noise. In a complementary vein, multiple training methods have been proposed in sequences or multi-view settings, allowing for exploitation of potential label sources. Natural language processing enables mining of diverse biological hypotheses. Discovery pipelines include the extraction of associations between stimuli and responses, candidate interactive agents, and genes with redundant downstream pathways. [76, 77, 78, 79]

AI-driven hypothesis generation

The AI model enables generation of multiple, highly diverse biological hypotheses, followed by high-throughput testing in the laboratory within a rapid cycle of hypothesis testing. Initially, the AI thoroughly mines the existing literature to identify a specific biological question and potential causative factors. Data streams generated from high-throughput functional testing specifically test elements identified

by the AI model in a manner analogous to the operation of the fastest, high-throughput synthesis and screening platforms coupled to robotics and AI currently available. The AI uses consensus pathway data to establish a causal relationship from high-throughput biological correlations.

This strategy enables exploration of some of the less well-studied areas of biology where knowledge is limited; in these areas, carefully designed AI- and machine learning-driven experiments will likely yield novel findings and lead to the generation of novel findings that may subsequently be explored in future AI and machine learning-driven experimental analyses. The results obtained from these AI-guided studies can then be mined in the same manner as literature-derived data, and subsequently used to drive the generation of novel biological hypotheses that can be tested via synthetic biology and microbiome-directed therapeutic exploration that can then also be rapidly implemented. The AI framework allows the combining of key causal checkpoints to help further accelerate the rate of progress within each area. [80, 81, 82, 83, 84]

Limitations and biases in AI models

AI offers powerful tools for biomedical discovery, but successful application is contingent on the representativeness and quality of the used data. Performance relies on the training data rather than the model architecture. Imbalanced data can lead to bias toward predicting the common class, while the interpretability of black-box models remains a challenge. Further, small datasets might yield unreliable models with little predictive power, and successive testing against a few biological examples can produce misleadingly high predictive accuracy. Nevertheless, the limited availability of high-quality data might not only hinder model validation but ultimately impact the whole field of research. Therefore, assuring data quality remains a pressing concern.

Problems can arise at all stages of data generation and processing from raw sequencing data to cleaned and normalized feature tables. Variances due to different platforms and laboratory protocols require dedicated attention, for instance, by involving the actual laboratories when compiling a meta-dataset or aligning data captured with other

experimental settings. Adverse effects posed by batch configurations can be detected during preliminary analyses and corrected through multiple-method approaches or source-effect removal sessions. Moreover, sequencing depth is a crucial factor influencing outcome reproducibility, and input data should be extensive enough in this regard. Consequently, data distributions facing high frequency shifts should be resampled, preventing predictive models from relying on rare features. [85, 86, 87, 88]

Chapter - 5

Microbiome Data Generation and Integration

Metagenomics and metatranscriptomics-widely used for characterizing microbial communities at composition and functional levels-sample the collective DNA and RNA of the community, indicating the organisms present and their potential metabolic activities. Shotgun metagenomic sequencing, which randomizes DNA fragments so that both low- and high-abundance organisms can be sequenced without relying on marker regions such as 16S rRNA genes, is increasingly used. Metagenomics performs the sequencing in bulk, capturing all reads and providing maximum data for community analysis, whereas metatranscriptomics focuses on the RNA expressed at a specific niche. Additional metagenomic and metatranscriptomic strategies, such as 16S rRNA gene amplicon sequencing.

Microbial products are also characterized thanks to the growing adoption of LC-MS, GC-MS, NMR, and matrix-assisted laser desorption/ionization mass spectrometry imaging technologies. Such systematic interrogations produce metabolome and proteome profiles of the samples, evaluating differences in metabolite types and abundances across conditions. These datasets allow elaboration of metabolite-function correlations. The microbiome interacts with multiple host organs via several metabolites that can serve as disease signatures. Proteome profiling identifies differences in protein expression, linking specific proteins with relevant functions, pathogen infections, or dysbiosis of the gut-skin or gut-brain axis. Integration of metabolomic and antimicrobial peptide concentration data into microbiome-associated signatures holds significant potential [89, 90, 91, 92].

Metagenomics and metatranscriptomics

Metagenomics provides insight into the taxonomic composition of microbial communities and contributes to understanding the associated functional repertoires. It involves sequencing the total microbial DNA (or employing shotgun metagenomics) from environmental samples, typically using shotgun sequencing (SBS) or targeted sub-fragment amplicon sequencing (such as 16S rRNA genes for bacteria and archaea or fungal ITS regions). Metagenomics is not only suitable for sequencing specific domains or kingdoms of life but can also be applied to organisms with unknown reference genomes; in that case, it permits metagenome assembly, followed by annotation of the assembled genomes. Depending on prospective research topics, the target composition and identity, and the bioinformatic capabilities and libraries available, researchers can choose between taxonomic classification using reference databases, where sequence identity is sought in previously sequenced organisms, and more complex functional prediction of putative uncharacterized proteins.

Metatranscriptomics extends metagenomic analysis onto the mRNA transcriptome level. Characterizing the metatranscriptome in combination with the metagenome and the other "omics" produces credible evidence about active functions in specific environments. Metatranscriptomic approaches enable detection of genes related to the current environmental conditions, including response processes such as low oxygen concentration [93, 94, 95, 96].

Metabolomics and proteomics profiling

With their immense growth in recent years, metabolomics and proteomics analysis technologies are actively expanding their application to the microbiome field. Metabolomics aims to provide a comprehensive profiling of circulation metabolites. Proteomics profiling offers a detailed quantification of microbial community composition and functional capacity through protein-level operational taxonomic unit (OTU) sequencing.

The major technical platforms for metabolomics include nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass

spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and their combinations. Cumulatively, these technologies cover a wide spectrum of metabolites from different classes such as amino acids, fatty acids, carbohydrates, organic acids, lipid molecules, and many others that can play a crucial role in host-microbiota interactions. The formation and functions of these metabolites correlate with various host disorders such as cardiovascular disease, obesity, diabetes, and inflammatory bowel disease (IBD); even within the gut, the microbiota produce several metabolites with far-reaching regulatory effects. They regulate the gut integrity and gut-blood barrier, serve as energy sources for colonic mucosa, and maintain the balance of gut microbiota composition.

The major technical platform for proteomics includes metaproteomics, which is based on deep sequencing of short peptide fragment libraries and further mapping these fragments back to metagenomic-assembled gene datasets. Compared with metagenomic approaches, the proteomics are closer to what the microbiome actually performs in the human body. Very recent progress has demonstrated its ability to capture the fine-scaled protein membership in the microbiome. [97, 98, 99, 100]

Single-cell and spatial microbiome technologies

New sequencing technologies can provide a single-cell resolution of the living microbiome or its components and relate them, for example, to immune cells at single-cell resolution in the mucosa. ScRNA-seq, for example, has allowed the transcriptome of prokaryotic and archaeal organisms to be obtained through Catalyzed Reporter Deposition in situ-based scRNA-seq, generating the Carrera of small prokaryotic cells in the FIB-SEM. Techniques of the former type can also probe the presence of entire microbial communities in combinations with other opportune analyses. Microbial organisms can also be characterized through their placement within tissue via spatial transcriptomics, and the conditions surrounding them can be measured as well. The ongoing expression of the transcriptomes at single-cell resolution of eukaryotic, bacterial, and acheral organisms with their position within tissues can be obtained through spatial transcriptomics

techniques, which can relate these single-cell expression data to the presence of specific immune cells, for example, or the microenvironment of specific bacterial communities. Some techniques allow for the definition of microbiome-related chemical signals at the level of entire organs, while others provide integrated microbiome-organelle resolution. A broader description of the microbiome will also start being offered by the integration of transcriptomes and proteomes through new combined experimental and analysis strategies.

The great diversity of sequencing techniques is accompanied by the increasing richness of reconstruction or detection methods that allow mapping the associations and interactions of multiple species over time and space. Various methods allow associations and interactions between fungal, archeal, and bacterial microbiomes to be inferred as well the resolution of these associations and interactions at the level of metagenomes, gene-content profiles, or co-abundance. Nevertheless, the analysis that remains largely understood and mainly unknown concerns the environmental novel (meta) transcripts derived from the microbiome. Resolution at the host-microbiome interaction level is also starting to be addressed through predictive metagenomics-coupled modeling approaches. With the great sensitivity and resolution offered by scRNA-seq and by transcriptomics methods, these techniques are progressively entering into the realm of analysis and reconstruction of host-microbiome interactions using transcriptomes, permitting the resolution of metagenome-based associations, as well as the detection or prediction of novel associations, together with the description of interactions (bi)findings) between different host and microbiome members. [101, 102, 103, 94]

Multi-omics data integration strategies

Successful prediction of disease-associated microbial signatures and preparation of microbiome-based clinical predictive models are based on a combination of metagenome, metabolome, and other multi-omics data layers such as transcriptomics and proteomics. The utility of metabolomic, transcriptomic, and proteomic data has been demonstrated in microbiome-based disease models. Different analysis strategies can be used to enable the integration of heterogeneous

microbiome data layers collected in different studies. The integration of metagenomics with multilayer concentration profiles is an effective approach for improving the accuracy of predictive models and understanding disease mechanisms.

The recent development of transfer learning methods enables the acquisition of model knowledge from a source population where a large amount of labeled data is available for public disease-related topics and adapts it to the target population for a new or emerging disease with extremely limited and scarce labeled samples. This strategy leads to improved prediction performance with "less" by leveraging knowledge learned from "more." Large amounts of literature-based knowledge extraction and validation pipelines are powerful instruments for consolidating, confirming, and expanding predictive models. [104, 105, 106, 107]

Data standardization and quality control

The use of microbiome data in artificial intelligence models can be constrained by heterogeneous data generation methods across studies and the absence of analytical best-practice standards. Despite extensive advances in data generation, the establishment of technical processing pipelines, and the development of meta-analysis algorithms, other biological fields still lack agreed-upon standards for microbiome data generation and analysis. Conversely, rapidly evolving automated pipelines and comparative frameworks, which are specific to particular types of biological data, have allowed other research fields to synthesize massive quantities of quality-controlled data. The extension of existing sample and data processing standards and the development of AI-mining frameworks for microbiome data could aid in overcoming these problems.

Data quality assurance is critical for both the data used in AI analyses and the generation of data- and learning-model-specific mining frameworks. Microbial community databases facilitate the mining of reference sequences for diverse microbial substrates, serving as essential resources for training and validating AI models. AI- and machine-learning-based data assimilation frameworks that provide tools for coarse-scale molecular-level explorations are also essential

for interpreting spatial and temporal microbiome differences. Integration tools that utilize advanced machine-learning-based molecular-difference prediction can rapidly interrogate metagenomic sequence data from hundreds of samples [108, 109, 110, 111].

Chapter - 6

AI-Based Microbiome Profiling and Pattern Recognition

Artificial Intelligence (AI) tools enable taxonomic classification, functional annotation, and feature selection from microbiome profiles. High-dimensional data representation threatens generalizability, interpretable biological priority of selected features depends on designated criteria, and list- or signature-based methods for deriving disease-specific patterns must ensure sufficient transferability.

Prediction of immune and chronic disease threats involves pattern-recognition models trained on microbiome profiles and associated health outcomes. Population-level models identify microbiome signatures for characteristic signatures for these conditions, while cohort-wide longitudinal prediction differentiates population-level correlations from potential causal relationships. Cross-validation of population-level signatures across multiple cohorts tests reproducibility. Population- versus individual-level predictions represent converse facets of model accuracy; generalizability-based models inform microbiome-shifting strategies, whereas non-transferable models facilitate personalization. [112, 113, 114, 115]

Taxonomic and functional classification using AI

Artificial intelligence is increasingly used for taxonomic and functional classifications of microbiome data based on amplicon sequencing data (16-19) and metagenomic assemblies (20,21) at both marker-gene and whole-genome levels, including species-level classifiers for complex datasets. Performance evaluations are necessary to validate neural network meta-classifiers on sequences from diverse environments. Such models have proven successful for taxonomic annotations, yet many rely on deep learning approaches trained on

sequences from specific habitats-often Earth surface samples with high abundance and diversity. Machine learning classifiers have also been trained specifically for metagenomic data. Niche adaptation and taxonomic feature abundance appear key in species identification. Meta-classifiers for 16S rRNA gene sequences have been trained for microbially diverse environments but can be used only to classify among genus-level groups.

Functional predictions can also be conducted with neural networks. Microbial multi-omics datasets can be fed to AutoEncoder models to exploit clustering and disentangled-bottleneck properties and allow dimensionality reduction in high-dimensional settings. A general strategy to support taxonomic imputation consists of training a deep neural network by combining label embedding representation and transition probability. These meta-learning adaptations cover new label distributions with minimal training effort. Moreover, recurrent neural networks have been used to directly infer pathways and genes from full-length 16S rRNA sequences, and pathway coverage can be learned from gene co-abundance patterns in an unsupervised manner. [116, 117, 118, 119]

Feature selection and dimensionality reduction

Feature selection reduces the number of variables by selecting the most informative and relevant features. The final feature set should maximize the model's prediction performance while providing a better understanding of the underlying biological processes. Dimensionality reduction transforms the feature space into a space with fewer dimensions that captures most of the variance. This technique is commonly used with image data but can also be valuable for omics data analysis, where the number of features is usually very large.

Feature selection is critical for any classification task because even a small number of redundant or irrelevant features can adversely affect model generalization performance. Feature selection methods can be grouped into three categories: filter methods, wrapper methods, and embedded methods. Filter methods, such as ANOVA F-value statistical tests, correlation, or mutual information criterion, measure the relevance of each feature in isolation and rank them according to

their scores in connection to the outcome variable. Selection is not biased by the downstream model. Wrapper methods evaluate model performance with different feature subsets, whereas embedded methods perform selection during the model-training process. The trade-off is that these methods are generally more computationally intensive and prone to overfitting, especially when the number of features is large.

After raw features are parsed, most machine-learning methodologies benefit from using latent representations instead of the original feature space. This allows a model to generalize better when dealing with multiple datasets and population settings. Dimensionality-reduction methods can be grouped into supervised or unsupervised categories. Supervised dimensionality-reduction approaches, such as supervised principal component analysis (PCA), remain close to supervised feature selection methods in that they aim to achieve better prediction performance in the decision stage. Unlike supervised dimensionality-reduction methods, unsupervised approaches do not use the label information of the training data. [120, 121, 122, 123]

Disease-specific microbial signatures

Defining disease-specific signatures is a critical step for accurate prediction and identification of disorders based upon microbiome data, enabling the development of better diagnostic methods and the elucidation of biosignatures related to underlying pathophysiological pathways. Consequently, this section presents a detailed discovery workflow for microbiome-disease signatures encompassing several distinct cohorts belonging to a wide range of clinical conditions.

Potential disease-specific signatures can be identified in an unsupervised manner or pre-defined for specific disorders on the basis of known associations, or dysbiosis patterns. While microbiome signatures may take the form of taxonomic or functional features, it is necessary to cross-validate commonly identified signatures across different cohorts to ensure robustness and accuracy. Specific signatures are, therefore, subjected to stringent testing in different cohorts to confirm their predictive power and biological relevance. [124, 125, 126, 127]

Predictive modeling of disease risk

Microbiome-based predictive models were constructed to estimate the risk of multiple immune and chronic diseases. Meta-analyses identified microbial features associated with disease, and external independent cohorts were leveraged for model development. For several diseases, models predicted risk years in advance of the clinical diagnosis and classified individuals into risk strata. These concepts can be further developed to assess the risk of additional diseases and might ultimately assist clinicians in making proactive preventive decisions.

The microbiome participates in various biological functions that have been imputed as putative mediators of the development of both immune disorders and several chronic diseases influenced by the microbiota. Therefore, the cumulative evidence suggests that the microbiome could serve as a biomarker for risk prediction, early disease detection, disease stratification, and personalized medicine.

Several studies have shown that microbiome-based models can efficiently predict the risk of complex diseases. These models leverage multi-cohort approaches that combine information from multiple independent cohorts to better extract relevant signals from the microbiome data. A meta-analysis assessed the association of the gut microbiome with twenty-four diseases, identified microbial features consistently associated with disease across cohorts, and subsequently constructed predictive models for nine diseases using metagenomic data from three independent cohorts. Overall, the models predicted risk years before clinical diagnosis and stratified patients into risk groups. Such approaches could be useful for other immune disorders and chronic diseases influenced by the microbiome. [128, 129, 115, 130]

Validation and reproducibility of AI models

An essential aspect of applying AI models to predict human conditions is their validation and reproducibility. AI-derived models should ideally be trained and tested on independent cohorts not included in the discovery phase. Internal validation is emphasized when external data sets are unavailable and it is often used as a preliminary step before submitting a model for external testing.

Validated models must be open and clearly reported, along with detailed descriptions of the biological rationale behind feature selection. The complete procedure should be shared in an accessible and reproducible format to facilitate broad utilization and testing.

For microbiome-based models, external testing of disease-associated signatures is a priority. Discrepancies may indicate sampling or methodological differences, population-specific signals, or the effect of confounders not considered in the discovery cohort. Well-defined stratification approaches, including sensitivity analyses, are essential to circumscribe model applicability. [131, 130, 132, 133]

Chapter - 7

Predictive Modeling of Immune and Chronic Diseases

Microbiome data-based models enable the prediction of immune and chronic disease risks and timeline of onset. Candidate cohorts are scanned for associations between gut microbiome composition/ function and disease occurrence within an arbitration period. Disease risks are then predicted by supervised machine learning models using microbiome composition/function and non-microbiome risk factors as input features. Meta-analyses have been conducted by combining findings from hundreds of studies, such as colitis in mice, several immune disorders, and metabolic syndrome in humans. AI algorithms not only facilitate prediction but also guide the timing of sample collection for early detection and stratification of disease risk groups.

Microbiome data collected over time allow an association analysis between microbial shifts and immune or chronic disease trends. State-of-the-art methods are applied to identify the influence of taxa variation in one time frame on the incidence of disease in a later stage, thus revealing potential causal directionality. Such longitudinal models refine population-level prediction towards individual-level estimation, while the former generalize well across cohorts, the latter provide tailored strategies for disease prevention or amelioration. AI-based models can pinpoint specific pathways targeted by different populations or cohorts, hence offering translational clinical implications.

The loss of microbiome diversity in life is generally recognized as an indicator of disease; however, the preceding interval of diversity loss prior to the occurrence also holds great implications for the same disease. The shorter the duration before the manifestation of immune-mediated disease, the stricter the time points of detection. Hence, integrating such empirical support into prediction models will facilitate

the closing of prediction gaps based on estimations derived from standalone source species or groups. It has also been shown that immune disorders can serve as a modulatory variable for dysbiotic manifestations. [134, 10, 135, 136]

Risk prediction using microbiome-based models

Artificial-intelligence models established a link between microbiome features and multiple immune disorders/early-life conditions, enabling prediction of risk in different growth cohorts. Such predictions support focused disease-preventive actions, particularly when made early and at population scale. Microbiome patterns also enabled analysis of time-series data from different cohorts to detect probable disease precursors at an individual level.

The human microbiome has been implicated in the development of various immune and allergic disorders, such as allergic rhinitis, asthma, and food allergies, as well as other immune conditions originating in early life. A visualized representation of the connections among microbiome changes, dysbiosis, and immune diseases provides a reference for disease prevention strategies. A microbiome-immune axis approach opens new possibilities for preventive medicine by elucidating the underlying mechanisms and identifying operational signatures. AI models trained on these signatures are valuable for risk prediction in healthy populations-especially during critical early periods such as infancy and early childhood, when preventive measures can be quickly applied. [137, 138, 139, 140]

Early disease detection and stratification

Microbiome-based predictive models hold promise for early detection of immune and chronic diseases, facilitating the identification of individuals at elevated risk prior to clinical manifestations. Recent studies reveal associations between baseline stool microbiomes and subsequent development of several diseases, including specific types of cancer, Crohn's disease, and ulcerative colitis. Such findings raise the question of whether these correlations merely reflect susceptibility to disease or instead represent a precursory alteration in microbiome composition that may precede clinical onset for extended periods and drive disease evolution.

To assess this possibility, a time-series cohort of fecal samples is examined, with microbiomes reconstructed at multiple pivotal points preceding disease onset. Additionally, clinical annotation of these samples and associated patient metadata facilitates analysis with respect to diverse diseases and conditions. Through careful investigation of the resulting longitudinal data, clear timelines for microbiome-associated disease onset and progression are established, and conditions for subclinical stratification are identified. These insights hold great potential for the early detection of immune and chronic diseases and provide a foundation for longitudinal modeling of microbiome-disease relationships and underlying mechanisms [141, 142, 143, 144].

Longitudinal microbiome-disease modeling

Step-wise analysis of sequentially sampled microbiome data can achieve causal updates on disease development trajectory and their predictive pattern. Time-series microbiome structures can be combined with potential data-related disease onset information to perform supervised machine learning that differs from conventional predictive modeling. The method is complementary to conventional predictive modeling, interpretable by providing augmenting combined disease association rules, and able to incorporate microbiome-related yet temporally distant disease onset data to identify risk factors.

Well-calibrated prediction models provide more than just association with the predicted class. These models are also capable of estimating disease risk for each sample. For example, prediction models for allergic diseases have high specificity, and their threshold can be adjusted according to clinical demand. A pilot study on prediction of Crohn's disease-associated proteinuria onset at a 10-year horizon has demonstrated a potential to provide patients with warnings of disease risks more than 5 years prior to onset. Such prediction modelling capabilities also suggest that prediction models are potentially able to identify microbial features-like dosage forms involved in the disease progression that have predictive power. Applied on the original longitudinal dataset, population-level risk predictions can be complemented with individual-level sampling dubbed "when

will I get sick" questions that are increasingly popular with the public. [145, 146, 147, 148]

Population-level vs. individual-level predictions

AI-driven microbiome-based predictive models enable forecasting of disease risk at different levels- population and individual. Population-level predictions identify general trends across large cohorts; they can reveal the presence of clear shifts in the microbiome composition during the onset of specific diseases, thus allowing for early disease detection. Individual-level predictions, on the other hand, address personalized medicine, enabling predictions of disease susceptibility and prognosis for each patient or even allowing for the stratification of individuals into specific risk subgroups. However, while microbiome-driven models may be highly predictive for a defined group of patients, they may not perform well when applied to individuals from other groups with different characteristics at the time of prediction.

Finding a balance between population-level predictive power and model generalization performance remains a challenge, especially when working with smaller, more specific cohorts used to train the algorithms. In this case, strict external validation and multiple testing procedures are essential to achieve reproducibility and general applicability. Predictive models have the potential to deliver preventive strategies that would monitor a patient's microbiome trajectory over time in order to generate specific intervention plans that can reduce the risk of inflammatory bowel diseases, diabetes, and other disorders, or signal a high probability for a brain disorder 5 years prior to clinical diagnosis. [149, 150, 151, 152]

Clinical interpretation of AI outputs

Machine learning models successfully trained to predict the risk of immune and chronic diseases based on changes in the gut microbiome undergo a final transformation phase. Their outputs are converted into interpretable descriptions, enabling timely clinical action for patients. Microbiome alterations affecting underlying mechanisms are highlighted together with corresponding targetable microbial taxa or

metabolites. The specialist can then assess whether the manipulation of these microbiome components is feasible for the specific patient at risk and whether the active modulation can be coupled with primary prevention strategies.

Output interpretation offers several decision-support options. For instance, it may help determine whether reconstituting a specific group of beneficial microbes is plausible by assessing their enterotype. It may highlight cross-kingdom driver-passenger relationships that can be exploited for co-administration of interacting species, such as specific fungi and bacteria. Additionally, it may reveal loss of populations involved in protective mechanisms, indicating that restoration of associated functions through microbial administration is feasible. Importantly, the outputs could facilitate patient stratification for upcoming clinical studies. [153, 154, 155, 156]

Chapter - 8

Engineering the Microbiome: Concepts and Strategies

Engineering the microbiome involves intentional perturbation of a microbial ecosystem for a desired function. Desired functions vary with application but may include dysbiosis reversal, disease risk mitigation, or restoration of lost functions. Important considerations in microbiome engineering include maintaining biosafety in the engineered microbial ecosystem and achieving any functional alteration with the minimal possible perturbation to the original ecosystem structure; however, these principles are not universally applicable. Probiotics, prebiotics, synbiotics, and microbiota transplantation are considered established methods of dysbiosis modulation. Engineered microbes, synthetic microbial consortia, and second-generation probiotics consist of genetically modified strains that can be safely reintroduced into the environment; these approaches still face hurdles, including regulatory challenges and ethical scrutiny. Precise modulation of defined microbial ecosystems, such as human gut, skin, or vaginal consortia, aligns new data and understandings with traditional microbiome transplantation methods. Precise resilience or stability recovery in defined microbial nursery communities has also been explored.

Specific modulation of dysbiotic ecosystems by community replacement, species addition, and selective membership regulation represents a rapidly evolving strategy in the field of microbiome engineering. Controlled addition of external species, especially keystone species, could facilitate natural recovery processes, whereas restraint traits gene systems can be developed and implemented to facilitate natural addition of desired, imported, and alien microbial species for long-term maintenance. Proposed monitoring strategies can evaluate stability, resilience, and healthiness of engineered microbial ecosystems. [157, 158, 46, 159]

Principles of microbiome engineering

Microbiome engineering aims to create favorable shifts in composition or function, thereby enhancing health or reducing disease risk. Successful strategies should be based on a mechanistic understanding of host-microbiome interactions and the functions and principles governing microbial community dynamics. Specific goals include restoring lost ecological functions after extinction (e.g., through transplantation) and prevention of leukocyte-driven, dysbiosis-mediated inflammatory pathologies by re-establishing immune-inducing microbial aldehyde biosynthesis. Safety remains the highest priority, encompassing engineering-induced unintended consequences or unforeseen determinants of host-microbiome interactions.

Preventive measures include the use of probiotics, prebiotics, and synbiotics to increase microbial functions associated with lower disease risk; the design of microbial strains or defined communities to modulate the microbiota without transmissibility risks; and the identification of targeted, controlled, and monitored keys to precise ecosystem modulation. Three critical components are needed for successful microbiome engineering: deep communication and mutual learning between microbiome researchers and engineers; analysis of host-microbiome interactions at all levels; and functional snapshots of microbiome community stability. [157, 160, 161, 162]

Probiotics, prebiotics, and synbiotics

Constitute the most comprehensively defined categories of approaches targeting the microbiome. Probiotics are live microorganisms that, when administered in appropriate amounts, confer health benefits on the host. This definition does not specify genera, species, or strains, avoided in clinical trials whenever possible. Prebiotics are substrates that are selectively utilized by host microorganisms, providing health benefits. Synbiotics consist of a combination of probiotics and prebiotics that beneficially affect the host by improving the survival and activity of probiotics in the gastrointestinal tract. Probiotics and prebiotics are readily available in fermented foods, dietary supplements, and functional foods. Synbiotics are available in fewer products, mostly as dietary supplements.

Several candidate probiotics have been suggested for preventing allergy and asthma. Enterococcus, Lactobacillus, and Bifidobacterium species of genera have been investigated the most in interventions targeting allergy and asthma prevention and often incorporated in synbiotic formulations, sometimes with Inulin, oligofructose, or other prebiotics. Few probiotics have been shown to ameliorate allergy and asthma in humans; some of their effects may result from the combined action of multiple strains-especially when tested at the population level. Directed probiotics may support child growth and development in subsets of children under environmental stress but do not replicate human breast milk, and effects on specific immunoglobulin E levels or allergy incidence after the first two years of life remain inconsistent.

For all categories of microbiome-modulating interventions, evidence from recent clinical trials should continue to be examined and synthesized in order to reveal reliable patterns and support causal inferences. The balance of available evidence can thus inform AI-driven design of hypotheses and recommendations for subsequent intervention trials. [163, 164, 165, 166]

Engineered microbes and synthetic consortia

Comprise groups of distinct strains designed to achieve specific functions through common biosynthetic pathways. Furthermore, specific strains can assist in delivering auxiliary functions, thus making the design of synthetic consortia a practical option for achieving complex aims. During the engineering process, available metagenome-assembled genomes (MAGs) from disease-associated microbiota can be utilized as a basis. When the potential of a strain to engender a particular metabolite is documented, these strains can be established and their effects evaluated at different dendrogram branches. Consequently, the candidate-modulating strains can be assimilated into distinct microbial consortia. However, natural ecosystems are inherently stable and capable of residing and thriving in specific environments. Consequently, a major safety concern related to administration using engineered microbes and synthetic microbial consortia is avoidability, or the possibility of surviving in a foreign environment different from their natural habitats. The long-term effects

of artificial synthetic microbial consortia on the human body remain unexamined; these concerns must be discussed and thoroughly evaluated before moving on.

Artificial-intelligence approaches can provide real-time decision support for patients by carefully monitoring their fecal conditions through established smart healthcare systems either in their homes or on the move. Such automated personalization could further stimulate patient interest, enhancing the effect of such a personalized-modulating method. Furthermore, with the rapid advancement of biotechnological support, an even broader range of genes could be targeted for biosynthesis; thus personalized design aiming for more complex modulation might eventually be realized. To mitigate various diseases related to alterations of the gut microbiome, precision modulation should be conducted cautiously, aiming for balanced changes to restore the robustness of the microbiome ecosystem, with the goal of returning patients to a healthy state. [167, 168, 169, 170]

Microbiota transplantation approaches

Fecal microbiota transplantation (FMT) is established as a powerful therapeutic modality for C. difficile infection, but applications for other diseases remain limited. Vaginal microbiota transplantation is an emerging intervention for recurrent urogenital infection, although supporting clinical evidence is still lacking. Defined-microbiome transplantation delivers a well-characterized microbial community for which efficacy can be targeted to specific indications. Infection risk is a major consideration in all microbiota-transplantation strategies, and appropriate monitoring protocols should be established.

Fecal microbiota transplantation (FMT) has been successfully employed in the treatment of patients with recurrent Clostridium difficile infection and is undergoing clinical testing in a variety of other conditions. Despite potential benefits, the implementation of FMT for disorders beyond C. difficile infection remains hampered by concerns regarding safety and efficacy. Vaginal microbiota transplantation is an approach to address recurrent bacterial vaginosis and urinary tract infection, but supporting clinical data are scarce and preclinical reports

have yielded mixed results. The application of defined-microbiome transplantation enables the transfer of a known microbial consortium with a specific therapeutic target, yet this method faces its own challenges, including the risk of pathogen transmission and community instability. To minimize the risk of transmission, all transplantation strategies should be guided by evidence-based monitoring approaches to assess infection risk. [53, 56, 54, 171]

Precision modulation of microbial ecosystems

Maintaining a healthy balance among microbial communities is crucial to the well-being of the host. Disturbances in the community composition can promote dysbiosis, which is defined as the loss or overgrowth of certain members of the microbiota and concomitant loss of biodiversity and community resilience, and a decreased ability of the microbiota to respond to external stressors. Under the influence of the host environment, diseases are associated with changes in microbial composition and function, and are characterized by a specific loss of a subset of taxa. It is thus possible to attain preventive or therapeutic outcomes by precisely restoring the absence of members, or modulating an overgrown population. However, such corrective measures are not always successful, mainly because (i) the restoring approaches do not consider the complete ecosystem, and only replace the absent microbe, (ii) a defined-self microbiota transplant approach is not supported by sufficient evidence or resources; and (iii) the monitoring of the population response and of individual health conditions remains a blind process, without feedback control.

To increase the chances of success, the transforming interventions should first be predicted and designed based on a deep understanding of the microbial ecosystem and of the patients' characteristics, or directly controlled by monitoring desirable patterns. Protocols can be developed with such features for three sets of interventions. Firstly, the introduction of abundant, under-consumed species should be based on their associations with health-promoting functions (detoxification, antiaging, etc.), and complemented by recipes for the required substrates. Secondly, population intensities that have a deleterious effect on the host should be identified, and interventions to reverse

them designed. Finally, the trends of important microbial ecological parameters (e.g. diversity, rarefaction of keystone taxa, redundancy of interaction patterns or ecological network) can be exploited to assess whether the microbiota is moving away from illness, and feedback signals help to intentionally maintain a balanced course of progression. Such monitoring patterns can also trigger and supervise microbiota interventions in closed loops. [48, 172, 173, 174]

Chapter - 9

AI-Guided Design of Therapeutic Microbial Consortia

AI-driven optimization methods facilitate the design of therapeutic microbial consortia that target specific health conditions. User-defined goals determine the microbial group structure and functions, constraints ensure biosafety and stability, and compatibility screening identifies supportive intertaxa interactions at several levels. Pathway flux analysis guides metabolic engineering to achieve desired functionalities, while simulation of environmental perturbations and resilience assessment foster robustness. Finally, customization pipelines allow patient-specific tailoring and personalization of the therapy.

Existing therapeutic agents and planned clinical experiments provide proof-of-concept for individual modules, while publicly available cohort data set building blocks for interventions targeting metabolic syndrome. A range of additional health problems is amenable to similar AI-driven approaches, including immune diseases, cancer, and neurodegenerative disorders. Robust pipelines enable the efficient design of microbiome-based therapies targeting a wide array of health conditions and key microbial traits [175, 176, 177, 178].

Optimization of microbial community structure

Microbial communities play a crucial role in maintaining ecosystem stability, function, and resilience. The structure of these communities, defined by the composition and relative abundance of resident species, is a key determinant of these properties. Previous studies have shown that the ability of microbial ecosystems to resist perturbations relies on specific patterns of community structure. Microbiome engineering efforts should therefore optimize community structure. However, the objectives of these engineering efforts-such as

promoting metabolic pathway expression, enhancing resilience to perturbations, or improving strain compatibility-often conflict with one another. Strain selection, interaction modeling, and intervention design should therefore incorporate multiple objectives to achieve maximal efficacy.

Machine learning optimization algorithms are well suited to these multi-objective design challenges, and can also incorporate solutions found using conventional approaches. Fitness landscapes of community-level properties can be inferred from strain compatibility assessments, and utilized to prioritize strain combinations for validation in gnotobiotic models. Together, these approaches can identify compatible community structures for particular applications, guiding the selection of candidate consortia for next-generation testing. In addition, perturbation response information can be integrated to assess the resilience of candidate configurations, enabling the identification of robust modular designs for sustainable microbiome-mediated effects. [179, 180, 181, 182]

AI-driven strain selection and compatibility

Two distinct principles guide the selection of microbial strains for therapeutic consortia targeting chronic diseases and immune disorders. The first principle emphasizes the identification of a chemically diverse collection of microbes capable of producing health-related metabolites such as hormones, neurotransmitters, and anti-inflammatory agents (θ-consortia). The second principle centres on ensuring compatibility among the selected strains to maintain community stability throughout their active life. The first principle maximizes the possibility of detection; the second minimizes the risk of undetected negative interactions that could jeopardize efficacy or stability, since resident communities are less likely to inhibit strains that are naturally part of the system.

To address the compatibility issue, mathematical models of pairwise microbial interactions have proven useful by integrating experimental data, co-occurrence patterns at different scales, and characteristics of the microbial niche. In a different context, meta-omics data can guide compatibility predictions, as certain metabolic

activities can create barriers to the colonization of specific bacteria. The effects of target metabolites on community resilience in the face of abiotic perturbations are also relevant for the design of combination therapies, as they can determine the best developmental order of multiple treatment cycles, potentially allowing for the initial use of monospecies microbiotherapy before switching to a cocktail approach. [183, 184, 185, 186]

Functional pathway optimization

Outlines metabolic engineering goals and pathway flux analysis. Engineering microbial strains for specific functions and a carefully designed community structure can reconstruct a desired functional profile in complex ecosystems, thereby enhancing specific microbial metabolic pathways. The design of experiments principle also applies here: the contribution of a specific functional pathway can be optimized for performance and robustness before being incorporated into a more complex community. With proper design, redundant or antagonistic interactions can be minimized, allowing the community to achieve a particular pathway goal while maintaining the required structure and functionality.

Many metabolic pathways are known to achieve similar outcomes, use similar substrates, and interact with common environments, making it possible to define a pathway's contributions and dynamics. One well-studied example of the development of a complex community that converts into short-chain fatty acids (SCFA) utilizing soluble fibre, resistant starch, and non-starch polysaccharide at physiological concentrations is the production of biohydrogen. More generally, metabolic fluxes, trajectories, and preference relationships can be further defined for any key metabolite and its chemical space, and pathway influences on health can be described for any other metabolite of interest. [187, 188, 189, 190]

Stability and resilience modeling

Microbial ecosystems must be capable of withstanding environmental perturbations to be effective, and these stability and resilience characteristics need to be evaluated during the design phase.

Following the framework of ecological stability theory, resilience is defined as the area underlying a resilience curve, or the time it takes for a community to return to its original state following a disturbance. Stability can be examined by determining whether perturbations in community structure propagate through the ecosystem, e.g., whether abrupt changes in community composition also cause a large change in ecosystem functioning. Exactly what measure of recovery time is appropriate for a particular human application depends on the ecological and clinical context; in the case of dietary changes and feedback-controlled probiotics, for example, recovery speed is critical, whereas in naturally-occurring microbial populations, full recovery within a short timeframe may not be necessary.

Many machine learning (ML) methods designed to determine resilience and stability within microbial communities make predictions about community stability or resilience based solely on correlations between community members. Due to the relationship between community structure and function, these predictions may not be misleading and, in fact, are often successful, but correlations must always be interpreted cautiously. Other ML approaches use additional ecological information, e.g., a metabolic network, to build larger models that also predict functionality; this information can improve predictions of stability and resilience, but at the cost of requiring more detailed empirical data. [191, 192, 193, 194]

Personalized microbiome interventions

Microbiome interventions with a well-established clinical effect may benefit from personalization, enhancing effectiveness in particular patients or subgroups. At a minimum, such strategies can incorporate evidence supporting higher treatment efficacy under specific conditions. Examples include correction of specific dysbiotic signatures; supplementation of a deficient community; or application of an adjuvant treatment designed to complement an existing dysbiosis. Another layer of customization may involve selection of treatment eliciting a desired response within a defined set of options (e.g., choice of one among several probiotics).

More ambitious interventions consider patient-specific features that are essential for treatment success. Fecal microbiota transplants (FMTs) are a prime example, due to the necessity of consulting treatment compatibility with the recipient's microbiota and the risk of transferring an undesirable microbiome signature from donor to patient. Finally, full engineering of the recipient's microbiome community is theoretically plausible, aiming to establish the healthiest community composition possessed by any subject within a healthy cohort. Such an approach is entirely independent of clinical features, relying exclusively on the microbiome targets identified in the development stage and illustrated in the previous section. A practical alternative is to maintain indirect control of a personalized FMT procedure, in which case the donor’s microbiome offers a shortcut for composing a pathogen-free microbiota accurately modeled and optimized on a patient-specific basis. [157, 195, 196, 197]

Chapter - 10

Microbiome-Based Prevention of Immune Disorders

Specific immune disorders, especially associated with immune imbalance, are prevalent in the population and impose a huge burden on public health. The identification of microbiome signatures can provide insight into the development of preventive strategies. Such approaches include modification of the early-life microbiome to reduce the risk of allergic asthma, hosting supportive microbial communities or transplantation of immune-tolerant microbiotas to ameliorate Th2-skewed inflammation, delivery of defined bacterial communities with adjuvant capacities to enhance vaccination responses, and oral intake of products designed based on the microbiota-immune axis.

Microbiome-based strategies that aim to prevent or reduce the risk of developed immune disorders-especially those associated with Th2 responses in early childhood or Th1-response skewing later in life and promote immune tolerance rather than imprinting a Th1/Th3-skewed response-have garnered attention. These strategies can be categorized into two groups: those targeting the microbiome early during life and those targeting the microbiome in adulthood. For the former, modulation of the early-life microbiome with probiotics, prebiotics, or synbiotics; fecal microbiota transplantation; and feeding with microbiota-rich food products have all been proposed, rather targeting specific microbial pathways or determinants in a precision-medicine manner. In adulthood, immune-tolerant communities can be delivered via fecal microbiota transplantation or focused vaginal microbiota transplantation to ameliorate Th2-skewed immune disorders [198, 199, 200, 201].

Allergy and asthma prevention strategies

Allergy and asthma risk reduction strategies based on microbiome profiling are diverse and engaging. Different pathways have been

linked with elevating the risk of the two conditions. Conclusively, probiotics, prebiotics, and synbiotics have shown accumulated but mixed evidence for helping prevent asthma and allergy disorders in children and adults. More support is desired, especially for the long-term effects of such intervention, requiring standardized definitions, operational means, and study populations. Animal models still serve as health-related proof-of-concept studies, and their potential applications should be cautiously considered, bearing in mind only a small subset of food-associated microbes can act as allergy- or asthma-promoting indications, while also maintaining safety during human evaluation and future applications. More novel ingredients would be valuable complementary material in addition to adequate external trials.

Allergy and asthma belong to a large family of hypersensitivity diseases caused by T helper 2 (Th2) immune response orientation. As one of early-life immune traits, the microbiome is recognized for its essential role in steering immune equilibrium between effector and regulatory phases at different life stages. Risk-stratified mother-infant cohorts point to a temporal association between microbiome changes and asthma onset during childhood. Maternally modified diets that support early-life microbiome maturation, in line with the healthy trajectory, associate with lower offspring asthma risk. Significant associations have also been observed after early-second-trimester dermatological condition and cesarean birth, respectively. However, clinical evidence remains unknown on whether targeting other microbial-modifying pathways can also mitigate later asthma risk. [202, 203, 204, 205]

Autoimmune disease risk reduction

Recent epidemiological studies suggest that a healthy microbiome can reduce the risk of developing autoimmune diseases. However, strategies employing microbiome-modulating probiotics have not been widely adopted. Importantly, few studies have verified the potential of microbial cues for enhancing tolerance towards allergens or other environmental immunogenic agents. Such knowledge gaps impede the design of biomodulating therapies that can guarantee microbial safety and efficacy, delaying their move into clinical and commercial applications.

Autoimmune disorders result from unbalanced immune responses mediating tissue damage. Changes in the composition and/or function of the gut microbiota have been associated with various autoimmune diseases. Several long-term cohort studies indicate that early-life dysbiosis may predispose development of type 1 diabetes and multiple sclerosis, while some evidence also links childhood antibiotics exposure to juvenile idiopathic arthritis. Analysis of mucosal tissues and adjacent healthy and diseased intestinal microbiotas points to a significant association of Crohn's disease and ulcerative colitis with local and systemic dysbiosis. These observations suggest that specific microbiome signatures could help predict future development of particular autoimmune diseases. [206, 44, 207, 208]

Vaccination response modulation

Emerging evidence supports a substantial role for the microbiome in modulating responses to vaccination. Several recent studies observed direct links between vaccine-induced humoral and cellular immmunity (measured as immunoglobulin levels, interferon γ secretion, etc.) and either the metagenomic profile of the fecal microbiota or specific microbiome-derived derived metabolites (e.g. butyrate). Microbiome composition also correlated with antibody titers induced by COVID-19 mRNA vaccination and the seroconversion response to seasonal influenza vaccination. Longitudinal metagenomic profiling of SARS-CoV-2 vaccinees detected predictive microbiome signatures associated with SARS-CoV-2 anti-spike antibody levels. Localization of rituximab-resistant mucosal IgA- secreting cells to the gingival mucosa-the site of the initial immunization-to provide earlier mucosal IgA production is required for increased anti-SARS-CoV-2 IgG and IgA responses. Metabolomic analysis detected reduced production of β-hydroxybutyrate and other microbiome-derived metabolites in vaccination non-responders and identified gut short-chain fatty acids (SCFAs), particularly β-hydroxybutyric acid, as potential biomarkers for predicting anti-viral antibody response in individuals receiving COVID-19 vaccines.

To mitigate the possible negative effect of the gut microbiome on vaccine efficacy, strategies that modulate microbiota composition and

predicted function are under investigation for both inactivated viruses and protein-based subunit vaccine candidates. These options include supplementation with synbiotics, prebiotics, butyrate, or Faecalibacterium prausnitzii; combinations of the probiotic Lactobacillus plantarum and tryptophan; Metformin, reported to enhance vaccine development and immune response; and specific dietary patterns. The combination of fecal microbiota transplantation (FMT) and vaccination is anticipated to exert a synergistic effect. [209, 210, 211, 212]

Early-life microbiome interventions

Timely manipulation of the early-life microbiome, the vital period for establishing microbiome-immune system interactions, holds great promise for preventing immune and chronic diseases. The evidence is accumulating for various approaches, but more naturalistic late-life interventions to restore early-life signals remain to be explored rigorously. A responsible combination of microbiome-based early-life intervention and naturalistic late-life restoration may help prevent a series of immune-related diseases.

Allergy and asthma have emerged as major global health burdens during recent decades. The connections between the early-life microbiome and the risk of subsequent allergy or asthma in human cohorts have been cultivated intensively over the past few years. Two different operational strategies for allergy/asthma prevention through microbiome elicitation have been suggested: the reconstruction of the lost vaginal microbiome in mothers, and the provision of probiotics that mimic ancestral maternal vaginal microbiota associated with certain phylogenetic lineages of Lactobacillus. Both approaches have undergone testing in rodents and await prospective validation in cohorts of humans.

A relationship has been postulated between type 1 diabetes and gut microbiota; immune-modulatory probiotics are being explored. These induce oral tolerance-like pathways that promote the down-regulation of islet autoimmunity and the prevention of disease progression in high-risk children aged 5 years. Vaccination with islet autoantigens combined with early-life probiotic exposure (Lactobacillus plantarum

K8) restores islet autoantigen-specific immune tolerance. Such findings align with those of T regulatory cell induction studies in the NOD model by early-life treatment with Clostridia or a mixed-species microbiota. Together, these investigations point to a role for increased gut microbiota diversity in diabetes tolerance. [213, 214, 215, 216]

Immune tolerance engineering

Several strategies aim to promote immune tolerance through microbial cues. Probiotics that exert anti-inflammatory effects, especially on the gut-skin axis, may prevent allergic diseases. Other interventions either stabilize microbiome composition/transcriptomics/ metabolomics during immune tolerance induction, or target nasal, lung, and gut microbiota in parallel. Evidence suggests that tolerance can be enhanced by oral exposure to innocuous environmental microbes or by natural or engineered cohabitation with friendly wild microbes. These are more appealing than conventional bacterial/infection-based schemes because they avoid biosecurity concerns.

Based on immune tolerance as the guiding principle, predictive modelling and microbiome biosynthesis approaches are used to mitigate autoimmune diseases or improve vaccination responses. These include a combination of perturbation-transcription based synthetic microbiota construction and immunological marker prediction. AI-driven techniques can provide new insights into the engineering of the gut microbiome to improve vaccine responses for infectious diseases. AI systems can also explore the roles of microbiota-derived metabolites in modulating immune tolerance during a variety of immunological processes. Integrating environmental exposures into predictive models may expand the toolbox for promoting immune tolerance in other diseases [217, 218, 209, 219].

Chapter - 11

AI-Enabled Microbiome Therapies for Chronic Diseases

Leveraging predictive models trained on large-scale, longitudinal microbiome data sets, it is feasible to design microbiome therapies that target chronic diseases, such as metabolic syndrome and type 2 diabetes (T2D). Commonly prescribed drugs for T2D affect the gut microbiome, but the specific bacterial pathways and species involved remain elusive. Examining the Putative Metagenomic Inconsistency in T2D Treatment pathway across T2D, coronary atherosclerosis, and Alzheimer disease may clarify the reasons for partial failure and identify potential solutions. Similarly, inflammatory bowel disease (IBD) and disorders along the gut-brain axis can be treated with AI-guided pipelines: AI models detect disease-associated microbiome alterations, and microbiome engineering techniques target the affected pathways. For example, microbiome transplant therapy using various types of transplant (fecal, vaginal, or defined) or external additives (dietary intervention and prebiotics) can alleviate IBD, and the engineering of TMA-producing bacteria can prevent or alleviate the consequences of IBD and neurodegenerative diseases.

With respect to cardiovascular disease, a meta-analysis reveals that the relative abundance of two TMA-generating taxa is higher in patients, pointing to a potential preventive role for therapies aimed at reducing their levels. It is becoming increasingly clear that the gut microbiome contributes to multiple diseases via the production of distinct metabolites. The next step is to identify metabolites for which both supply and consumption pathways can be tailored in order to enable a complete therapeutic solution. Looking at aspects of cardiology as a whole may accelerate this process, with the associated opportunities and challenges offering significant potential. At the same

time, the gut-vaginal-oral-breast-fecal microbiome axis provides additional considerations for treating complex conditions.

Metabolic syndrome and diabetes prevention

Microbiome alterations confer increased susceptibility to metabolic syndrome (MetS) and diabetes. Therapeutic strategies targeting the microbiota have shown promise for alleviating MetS in rodents. Accordingly, AI-assisted pipelines have proposed candidate interventions for MetS management. MetS encompasses type 2 diabetes (T2D) or conditions predisposition characterized by obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension. The alteration of host metabolism propels excess caloric intake and stimulates lipogenesis in peripheral tissues. Phylogenetically distinct microbiomes enrich in the gut of patients with MetS, and functions related to glucose and lipid metabolic disorders tend to differ from those of healthy individuals. The microbiome is considered an important contributor to the initiation and development of MetS. Microbiome-targeted therapies are safe and effective for alleviating MetS in mice. Translating these findings into human healthy dysbiosis prevention during MetS requires discovery of appropriate candidates and optimized therapeutic strategies for clinical practice.

Engineering the gut microbiome at early life stages to reverse imbalances can mitigate the likelihood of developing future chronic diseases and ultimately establish the first lines of defense for diabetes. Changes in gut microbial composition during early life appear to influence glucose homeostasis in adults. Specific alterations leading to diabetic complications can also be identified, such that modulation or restoration strategies can be proposed. Specificity of modulation provides the opportunity to control for collateral, potentially adverse consequences beyond the primary treatment purpose. AI-based designs contribute to MetS treatment and novel strategies through engendered commensal organisms capable of transporting gut microbiome metabolites addressing MetS and its components.

Inflammatory bowel and gut-brain axis disorders

Aberrant interactions between the immune and digestive systems can lead to inflammatory bowel diseases (IBD). An increasing body of

evidence implicates dysregulated immune-microbiome interactions during disease development, thereby highlighting the microbiome as a therapeutic target. Improvement of IBD symptoms has been reported after treatment with microbial signatures predictive of positive therapeutic response. Similar approaches have been proposed for traveler's diarrhea and recurrent Clostridium difficile infection. Feeding trials indicate that a diet high in dietary fiber, vegetables, and fruits, but low in saturated fats; oral administration of probiotics such as Lactobacillus can effectively support gut-down left-enantiomer dopamine concentration through the gut-brain axis. Additionally, fecal microbiota transplantation reduces pain and Poor Self-Rated Health of patients suffering from multiple sclerosis, thymoma, sleep disorders. Modulation of the microbiota composition during treatment can control the severity of gut inflammation and disease symptoms in a mouse model of experimental autoimmune encephalomyelitis. Combined problems in the development or function of both the central nervous system (CNS) and the immune system may be associated with neurological disorders, such as schizophrenia, autism, and Alzheimer's disease, during early-life development. Taken together, these findings underscore the potential for ameliorating gut-brain axis diseases by enhancing communication along the gut-brain axis [220, 221, 222, 223].

Cardiovascular disease prevention

Microbiome-centered strategies have been proposed to reduce cardiovascular disease (CVD) risk. A microbiome-based model for CVD risk prediction identified disease-associated biomarkers and a pathogenic pathway linking microbiome changes to atherosclerotic risk. Several approaches modulating the disease-related risk factors in the microbiome are currently established or have been recently reviewed. These include strategies targeting hypertension, trimethylamine-N-oxide (TMAO) production, lipid metabolism, and metabolism of metabolic hormones (e.g., leptin, resistin, and adiponectin) involved in atherogenesis, as well as microbiome interventions aiming at atherosclerosis. Moreover, risk reduction has been suggested for specific azole drugs and probiotics designed for cholesterol management. However, further research integrating multi-

omic and multi-dimensional microbiome data is desired to elucidate mechanisms of action and identify specific targets for therapeutics, or tailored microbiome prescriptions, employing microbiome control in conjunction with classical risk-factor intervention.

In addition to these bottom-up approaches focusing on specific contributors, systems-level strategies targeting the microbiome as an interconnected ecosystem have been assessed for modulation of the leading cause of CVD, namely, hypertension-an early and prominent risk factor of atherosclerosis-by characterizing the compositional and functional shifts of gut microbiota in animal models of hypertension and classifying the specific metagenomic-metabolomic signatures associated with hypertension. The results form a basis for developing a multi-targeted, microbiome-prescriptive dietary strategy to prevent hypertension. Taking into consideration the multitude of proximate factors discovered in the gut microbiome and its ability to co-modulate multiple complex diseases concurrently, a master modulator designed to cover multiple diseases, including CVD, may perform better than tailored microbiome interventions targeting specific conditions. [224, 225, 226, 227]

Neurodegenerative and mental health disorders

Alterations in microbiome composition and activity have been implicated in various neurological and neuropsychological disorders, increasingly studied under the umbrella of the gut-brain axis. Visualization of microbes in the central nervous system supports a causal role, and fecal microbiota transplantation can modulate behavior. A potential bidirectional mechanism has emerged, with depression and anxiety potentially altering microbial communities in addition to the reverse effect. Microbiome-derived microbial metabolites, particularly tryptophan degradation products, can affect nervous system development and function, and their administration may confer protective effects against multiple conditions. AI-based modeling stratification approaches can identify potential microbiome-based treatments for severe mental disorders. Microbiome modulation potentially offers preventive action against neurodegeneration and associated cognition decline. Elucidation of the underlying

mechanisms enables targeted clinical trials, presenting a promising means of delaying the onset or reducing the severity of neurodegenerative disease.

Evidence from multiple cohorts indicates that the composition and functionality of the gut microbiome are different in patients with schizophrenia, Alzheimer's disease, Parkinson's disease, and autism spectrum disorders compared to healthy controls. Causal links can be established by demonstrating the presence of the microbes in the nervous system and the ability to induce behavioral changes in germ-free animals by fecal microbiota transplantation. There are, however, additional observations of altered gut microbiome composition and function in patients with depression and anxiety. Most studies support the hypothesis that microbiome signals influence psychological health, but few explore the inverse. Machine learning methods can answer questions related to stratification and prediction based on the microbiome on both sides of the causation chain. [228, 229, 230, 231]

Cancer prevention and immunomodulation

Microbiome-directed preventive approaches against cancer. Growing evidence points to a role of the human microbiome in cancer onset, progression, and therapeutic response. This has prompted research aimed at minimizing cancer risk via microbiome modulation, including the transplantation of healthy microbiotas. The bacteria Fusobacterium nucleatum and Peptostreptococcus anaerobius stand out for their positive association with cancer, serving as potential targets. Diet, the use of probiotics or prebiotics, and lifestyle interventions represent additional preventive strategies.

Epidemiological studies have suggested that diet can affect the risk of certain cancers through modulation of the microbiome. The association of Synlogic's engineered strain of E. coli with a multiplex cocktail of common antitumor agents in preclinical models of AML also points to the potential of microbiome modulation to improve tumor therapy. [232, 233, 234, 235]

Chapter - 12

Diet, Lifestyle, and Environmental Influences

The complex interplay between diet, lifestyle, environment, and the microbiome is receiving growing attention. Causative connections are beginning to emerge among diet, microbiome composition, and immune parameters. The microbiome modulates the association between dietary components and allergic disease, while various dietary groups affect the interactive role of the microbiota and the risk of developing asthma. Integrating dietary exposures, microbiome data, and immune response into a unifying system through AI may facilitate the development of personalized diet strategies to reduce the risk of immune diseases. These components can thus become parts of a personalized decision-support system, predicting the effect of nutritional changes on health status.

Physical activity and circadian rhythms also influence the gut microbiome composition, indicating that both external (e.g., pressure) and internal (circadian oscillation) signals together modulate the gut-dwelling microbes. Changes in the environmental microbiome associated with urbanization and lifestyle hazards also exert strong impacts on human health. The use of biopolymers made from starch after microbial fermentation with probiotic strains including Lactobacillus rhamnosus GR1, Lactobacillus acidophilus, and Lactobacillus plantarum has been proposed as a preventive measure to protect the gut from gut-use-associated antibiotic treatment and for potential readjustment after such treatments. In general, digital health is an opportunity for a full integration of sensors, microbiome and health data, allowing for continuous health monitoring, feedback-controlled microbiome modulation, closed-loop interventions, integration of interactions and relationships between different parameters, and active smartphone-based interaction between patients and physicians. [236, 237, 238, 239]

Diet-microbiome-immune interactions

Diet is a crucial modulator of the microbiome and, consequently, can have a strong impact on the immune system. The findings of human and animal studies that explored how dietary factors influence the microbiome and which dietary constituents are key modulators of specific immune decisions have been compiled. Causal pathways connecting diet, microbiome, and inflammation can now be modeled, paving the way toward personalized nutrition planning that takes the dietary-microbiome-immune relation into consideration. Moreover, an AI-assisted decision-support platform can be envisioned that will enable individuals to receive personalized nutrition guidelines. This platform would aid the consumers wishing to find diet-lifestyle choices that improve health and well-being.

The introduction of a wide array of synthetic and natural compounds through the diet substantially impacts the composition and activity of the microbiome. The food composition and dietary habits of a population can alter the composition of the gut microbiome over time. The type of main dietary pattern consumed by the subjects of each study influences not only the community structure but also the composition and predicted functionality of the gut microbiome. Certain dietary constituents such as specific lipids, carbohydrates, polyphenols, and proteins have now been linked to specific taxonomic groups within the gut microbiome. [240, 241, 242, 243]

AI-driven personalized nutrition

Diet is a major determinant of the microbiome, and in turn, the microbiome regulates nutrient absorption and metabolism. Microbial dysbiosis has been shown to contribute to several chronic ailments, including allergies, type 2 diabetes, metabolic syndrome, cardiovascular disease, inflammatory bowel disease, obesity, and non-alcoholic fatty liver disease. Causal pathways between microbiome, diet, and immunity have been explored extensively, allowing the identification of key metabolomic features as predictive biomarkers of allergic disease and immune tolerance.

Microbial-based personalized dietary recommendations and decision-support systems may therefore improve health outcomes.

These systems rely on various types of nutrition data, including dietary intake, microbiome composition, enterotype clusters, and nutrient concentrations of biological fluids. Feedback mechanisms based on combinations of physiological indicators can boost adherence to dietary strategies and increase the likelihood of achieving clinically relevant outcomes. Predictive models that incorporate external environmental factors, such pollution and antibiotic exposure, allow the elaboration of personalized dietary recommendations that take all components into account. Finally, digital tools with feedback control represent the next steps in this field since they allow for real-time closing of the nutritional loop and enhanced decision-support capacity, thereby promoting improved health outcomes. [244, 245, 246, 48, 244, 245, 246, 48, 247]

Physical activity and circadian rhythm effects

Continuously collating data on physical activity and circadian rhythms shows these processes shape the composition and active states of the gut microbiome, which in turn influence health and disease risk. Personalized lifestyle recommendations can thus be generated by using microbiome changes as intermediary signals.

A growing number of studies point to complex and dynamic relationships between the temporal patterns of bodily functions and the community composition and operation of the human microbiome. These relationships extend beyond the well-established connections between diet and the composition of the gut microbiome. Variations in physical activity levels-including both types of activity (exercise training vs. limited physical activity) and modes of activity (aerobic vs. resistance training)-were linked to fluctuations in the diversity, composition, and activity of the gut microbiome. Key factors deserving special emphasis include circadian cycles and sleep duration.

Lifestyle patterns-such as food intake, sleep, physical activity, and circadian rhythm-are all deeply associated with human health and disease risk. The ongoing development of digital health, wearables, and biosensor technologies is now making it feasible to monitor these patterns in real time. As these lifestyle measures are continuously collected in very large populations with diverse diseases and

ethnicities, they can serve as training data for AI models. In addition to direct effects on health, real-time lifestyle data can also be integrated as intermediaries affecting the composition and operation of the gut microbiome, in combination with other data modalities.

Environmental exposures and microbiome shifts

The environmental exposure factors affecting the microbiome include pollution, antibiotics, and urbanization. Community-level approaches integrating information from different research domains, including microbiome profiling, cohort studies, multivariate association testing, multiplex laboratory experiments, exposure assessment, estimating effect size, and down-sampling caused substantial shifts in the microbiome at the city level. Airborne particulate matter emitted by traffic indicated a positive effect on the abundance of potential pathogens in individuals living at different distances from the traffic polluters. Biomass burning and engine-related traffic pollution have been found to be associated with mucophilic and nasal Klebsiella species. Concentrations of burn and traffic markers such as potassium and indium in the air were positively related to the frequencies of a wide range of febrile illnesses and simian virus 40 in the inhabitants of the city of Kolkata. The commensal microbiome may help to establish who can tolerate superinfections after extreme air pollution exposure. It has been established that pathogenic infection risk increases when community-living fauna and flora become old and lack biodiversity-creating stressors like fire and flood.

The industrial development of urban centers, using motor vehicles, power plants, and thermal power stations, has raised sulphur and nitrogen concentrations in air to toxic levels and led to superinfections of human and animal pathogens. Long-term exposure to excess sulphur and nitrogen from various sources was associated with an increased risk of multiple infections in children, and sampling from the natural vegetation indicated a 2000-fold increase in the sulfur-oxidizing bacterium Thiobacillus thiooxidans. The incorporation of healing practices into public health to mitigate or control the effects of the urbanization-associated combinations of pathogenic pollution sources

has been stressed. Children astride the Ganges River have been subjected to heavy burdens of infectious diseases, suppressed immunity, and increased consumption of antibiotics. [248, 249, 250, 251]

Behavioral data integration in AI models

Should encompass subject privacy and data protection when individuals participate in studies, long-term collection, and the type of data collected. Behavioral data can greatly improve the accuracy and practicality of the assigned task. Data fusion can strengthen the ability of a single model to reason across the modal in different ways. However, biases in the samples that violate the fair and just principle or insufficient samples may greatly reduce the prediction capability of the model.

Individuals participating in studies should provide analysis plans or requests to investigators before the collection of behavioral data, including the duration of the collection, the prediction model needing data, the type of data needed (e.g. characters, response patterns, physical activity, sleep habits, or nonspecific activities), and sampling frequency. Long-term collection of such data will improve the practical aspect of using data to predict the success of the disease. The choice of the type of behavioral data is largely data dependent. For example, if the prediction model is trained with time series information (e.g. blade signal of some affection), then using a single blade signal as compensation will only add noise instead of enhancing the model. If data from multimodal sources are fused into a single pipeline, then the amount of data used in the analysis should be as big as possible to avoid over-fitting. [252, 253, 254, 255]

Chapter - 13

Digital Health, Wearables, and Real-Time Microbiome Monitoring

Integration of wearable and biosensor data; specify data streams and harmonization needs.

Instruments worn or implanted by users capture digital biomarkers indicative of vital parameters such as health status and risk, lifestyle, and environmental factors. Wearable and stationary devices for monitoring metabolism, physical activity, heart activity, neuromuscular activity, and many other biochemical and physiological processes are being explored. These low-cost and low-impact data streams can be integrated into the AI models as additional features for prediction and stratification. Data from mobile sensors coupled with saliva sampling will give information about the oral microbiome along with preventive support options, suggesting preventive measures associated with microbiome-related diseases. Continuous and automatic health data collection using wearables will enable real-time monitoring of health status by clinicians and care providers, producing alerts if any information is out of normal ranges.

Development of closed-loop systems that offer personalized intervention procedures is also needed. Such an approach can help design feedback-controlled interaction plans: the AI models used for predicting responses to natural or synthetic microbiota freshwater can be integrated with wearable sensor data to modulate the microbiome safely through nutrition, pro-, pre-, syn-, or postbiotics in a closed-loop. Continuous monitoring of patients by combining mobile health platforms with AI-driven coaching will help motivation and adherence. Ensuring data security and ownership (privacy, governance, control, and consent) will enhance patient acceptance and engagement. [256, 257, 258, 259, 256, 257, 258, 259]

Integration of wearable and biosensor data

Wearable devices and biosensors monitor diverse dynamic health metrics in population microbiome studies. Continuous heart rate, activity, sleep, and body temperature data from wearables outline short-term variations, while smart body-washers quantify daily skin microbiome disturbances. SCFA and hormone levels, sensed in breath or sweat, reflect gut-brain axis activity as well as metabolic and circadian states, enabling continuous, fine-resolution health representation. Continuous glucose monitors provide near-real-time glycemic ranges, generating predictive windows framing events of interest for associated microbiome dynamics. Sweat glucose-microbiome paths enable the training of prediction models. Integrating multimodal wearable data with microbe-targeted predictive models refines associations between dysbiosis, HDL, and lactate/propionate profiles.

Wearable data help define and track a person's health from multiple angles, creating a feedback system based on the subjective sensation of well-being or clinical needs. Such information provides an unprecedented opportunity for continuous health surveillance, real-time detection of risk factors, and timely alerts. Additional mobile health applications can assess mental status via communication style, coded expressions, and sentiment analysis, along with possible semantic analyses for edge computing. Such advanced capabilities can improve adherence to treatment or supervision by coaching individuals integrated into digital health systems that generate alerts based on wearable data.

Combining computer-zoologue apps with biosensors, social activities or behavioral changes-such as circumstantial contacts, interactions, or present emotional state-also allows monitoring of microbiome-affecting factors and autonomously provides feedback via preferred social channels. Integration into a decision-support system capable of considering factors influencing changes in a targeted microbiome can provide clinical feedback and advice to individuals throughout daily life-such as feed-exercise balance and external exposure-enabling continuous data collection from many players and supporting other dynamic data cores.

Continuous health monitoring systems

Integration of wearable and biosensor data enables continuous health monitoring systems with real-time alerting and interpretative capabilities. Collected data constitute new input layers for AI models, providing an energetic real-time overview of the individual conditions without exposing sensitive personal data in the models. The detected health trends are interpreted by specialists, and alarms are generated for irregular data patterns at an early stage. The information is continuously shared with the user through a smartphone interface and an optional wearable device. These systems empower the user and increase motivation to improve health condition and lifestyle.

To maintain a healthy lifestyle and pre-empt the occurrence of diseases, the ideal approach is to stimulate the self-correcting mechanisms of the body or modify specific health determinants in a positive direction. An optimal strategy is to implement a closed-loop health-regulating system for microbiome modulation: a system that collects signals about the health condition and conveys them to the AI model that recommends the precise action needed to restore balance-e.g., modulating the diet or physical activity in real time, feedback-modulating the microbiota, or suggesting the use of specific supplements or pre-or probiotics. [260]

Feedback-controlled microbiome modulation

Feedback-controlled interventions could maintain continuous modulation of the microbiome. Automated identification of deviations from target microbiota profiles would trigger closed-loop interventions, with actions governed by user-defined risk thresholds (for example, potential disease relapse). Such systems should also incorporate additional safety checks to avoid excessive deviation from baseline microbiota structure, which could lead to unintended consequences. Initial interventions would remain advisory, providing personalized recommendations for diet, lifestyle, and supplementation. Over time, however, user engagement and trust in the system could support adoption of automated feedback responses, such as provision of selected supplements via biosensors or smart appliances. Eventually, permissioned access to wearable data streams from all users across

clinical cohorts could facilitate identification of trigger events, enabling preventative dual-targeted microbiome modulation at the population level, accordingly adjusted for socio-environmental conditions and other risk factors. [261, 262, 263, 264]

Mobile health platforms and AI coaching

Mobile health platforms enabling habitation normally do the desired task, decreasing user interaction overhead and improving overall experience. Data collected via wearables or biosensors are integrated into a bottom-level of the work. Even user-assisting, patients should actively monitor their health condition and provide feedback about unexpected changes, such as unusual biometric values, symptoms, or risky behavior. Alerts activation should be conditioned to error rates, minimizing false-positive or false-negative situations. Continuous health fraction is charged with autonomous interpretation of signals: scoring functions suggest modifications for the next period, supporting optimization of probiotics, prebiotics, or synbiotics intake, active drug intake, or other modulatory agents. Even users are not connected to the system, abnormal health fractions alerts are sent.

Mobile health platforms engaged to promote adherence are close to coach support and to random reinforcement. A reporting environment is provided to patients with intuitive UX. Information from physiological or contextual factors is periodically integrated into a prediction function, suggesting personalized guidelines to change behavior or diet. The underlying AI model is regularly updated, aiming at the user. Moreover, information from the platform guides sampling reducing data privacy issues, by using sensitive data for the specific individual evaluation of attraction magnitude for a determined food. Achievements from patients in overcoming health challenges indicated by the prediction function are reported, increasing motivation to continue with the assigned actions. Concerns related to data usage for AI model updating are clearly stated to users to obtain full consent during sampling. [265, 266, 267, 268]

Data security and patient engagement

Protecting the privacy and security of data collected from individuals who engage with Digital Health (DH) systems is

paramount. DH and AI-based systems require access to sensitive patient information and biomarker data and continuously collect information on patients' behavior, habits, and environmental conditions. Residents are often not aware of the breadth of information collected and the potential uses of that information, leading to a possible loss of confidentiality and concern related to the need to share private data with their health care providers. Concerns about data security, loss of confidentiality, or the approval of unwanted ads after online tracking may affect the adherence to mobile health or digital health systems. It is, therefore, crucial that these types of information are protected and that patients are aware of possible uses and risks associated with their private information.

Trust depends on an understanding of how private information is stored, used, and potentially shared with third parties by the company that collects it. This is especially important for sensitive data provided by digital health systems (CHAPITRE 14). As a result, adherence responses may be positively affected if the company has strong privacy policies. It is important to design mobile technologies and wearable systems that are supportive and respectful in their interface with users and that provide users with a virtual environment enabling active learning and user engagement. [269, 270, 271, 272]

Chapter - 14

Ethical, Legal, and Regulatory Considerations

Defining data privacy remains a challenge. Stakeholders disagree about which data should belong to the patients who generate it. Some consider the evidence generated by wearables and other biosensors designed to monitor health states for the sake of the users also their private data. Others believe that the results these devices closely resemble the outputs of clinical examinations or laboratory tests, which thus should belong to the health systems. Collaborative and democratic governance policies could help define the ownership in an inclusive manner, ideally establishing a baseline that varies across jurisdictions depending on local priorities, values, and willingness. Such policies could also define consent models regarding the ingestion of image and sensor data that some digital health applications need in order to deliver meaningful information regarding the patient. Users should opt in or out of digital health dashboards and related decision-support applications.

Bias in AI decisions can come from many sources. Health data population unbalance may lead to under-represented but safer population samples. Opacity in the pipeline may lower the level of trust and acceptance in the result-or the distribution method. If interventions can effectively benefit only certain categories or groups, yet are discussed with a consumer/customer logic rather than a social logic, mainly benefitting a wealthy category while neglecting overall public health responsibility, society may question their acceptance. Such issues need to be carefully addressed in order to safeguard justice and ensure a cross-distributive effect. If detected and explained, public health authorities can mitigate the unbalance. What remains unclear will always enhance the gap of untrustworthiness. The responsibility of justice must be properly assigned to the party being investigated or treated. Hence, bias must always be addressed.

Regulatory agencies must adapt traditional frameworks that designed, validated, and approved classical medications and interventions, since the approval and release systems for microbial pills may pose different and more serious questions. Experimental or pilot therapeutic actions may incorporate the use of signalling, acting in a spatio-temporal manner, for treatment purposes, which constitute a legal grey area never before envisaged. External signalling may stimulate or inhibit certain pathways, or restore patient's crossed-signalling equilibrium. Interestingly, a recent report proposes a new category of regulators, termed "DCR-Data Competence Relations", to oversee such actions. Aimed at data-driven development of microbiome-focused therapeutics, a DCR should guarantee safety throughout the whole production chain, from marketing to commercialisation, and at all later stages, if any. [273, 274, 275, 276]

Data privacy and ownership

The rights and ownership of health data, especially regarding medically relevant data, are inherently a sensitive subject. To some extent, healthy members of the population, patients, government entities, nonprofit and commercial organizations, and health universities contribute to data generation. At the same time, data-pooling policies vary from protocol to protocol. Individual companies may retain exclusive intellectual property without sharing returns. Hence, the public is deprived of self-ownership of the data they share but also becomes financially liable for the investments by other natural or legal entities. With the consumption of countless supporting biological samples by the common citizen, is it not natural for them to receive the benefit of disclosed research results built upon their data?

Some citizens and institution rulemakers wish to remain entirely public in health issues and the virus prevention strategies and readiness efforts for future pandemics. Others are very reluctant as they value privacy, wish to remain secretive, and ask for exclusivity. Those wishing to give value to their biological signal for the entire population or for a specific group should have freedom of use of one of the embodied split returns. The elaboration of fine metadata for a wide population with the help of medical specialists and commercial

companies offering aids in their platform could help in fulfilling requests for cohorts. In countries whose legislation allows sensitive health places and companies, such data can be owned for a specific purpose. [277, 278, 279, 280, 281]

Ethical challenges of AI-guided interventions

The development of AI-assisted biomedical applications may introduce ethical issues, including bias in the training database that affects prediction quality, lack of representativeness in the population undergoing treatment as a result of model-facilitated stratification, and unaccountable output when patients receive the intervention blindly targeting the AI-estimated effect within an unidentified mechanism. Engelbart's proposition regarding machine-assisted augmentation of human intellect aims at promoting human creativity by ensuring that important decisions such as treatment designs, stratifications, run predictions, and interventions are made by intelligent humans supported by advanced AI methods and models that carefully present, visualize, and interpret for humans the analyses of existing knowledge.

In addition to ensuring that decision-making remains under human responsibility, clinical intervention strategies minimising control variables and focusing on free will in AI-guided decision support systems may also help to alleviate AI-related ethical problems by minimising bias and allowing intervention from a higher layer AI model trained on the user model of the first-layer decision support system. These and other factors affect the level of public trust and the rapid acceptance of AI-assisted digital health strategies. [282, 283, 284, 285]

Regulatory frameworks for microbiome therapies

While microbiome research is advancing rapidly, the regulatory frameworks for microbiome therapies remain limited and heterogeneous across jurisdictions. Harmonized regulations are needed to facilitate global research, development, and commercialization. Regulatory authorities should adopt a science-based approach specific to microbiome therapy without the bias of traditional pharmaceutical development. The identification of health-promoting microorganisms and updates of regulations require a clear overview and in-depth analysis of the role of the microbiome in health and disease.

Current regulatory frameworks for microbiome applications vary considerably among different jurisdictions. The use of pro- or prebiotics is generally classified as a food product. Fecal microbiota transplants constitute a therapeutic product in Europe and North America and are regulated accordingly. The FDA considers fecal microbiota transplantation a biological investigational new drug, for which any clinical trial must follow good manufacturing practices. Microbiome-based therapeutic consortia, e.g. a defined consortium manufactured by Synlogic Pharmaceuticals for treatment of urea cycle disorders, are being developed in strict compliance with regulations for pharmaceutical products. Such therapies must meet conventional criteria for safety, efficacy, and/or quality. The European Medicines Agency's Committee for Advanced Therapies considers microbiome therapy as a combined advanced therapy medicinal product, which contains cells or tissues and acts principally by metabolic, pharmacological, or immunological means and that is not a medicinal product as defined in Regulation (EC) 726/2004 [286, 287, 288, 289, 286, 287, 288, 289].

Safety and long-term risk assessment

Long-term effects of AI therapy-associated risks must be carefully evaluated. Pre-market testing runs from nonclinical trials targeting safety assessment through to clinical trials for safety and efficacy. Preclinical testing is limited and focused on cell and animal studies. Animal studies evaluate carcinogenic, reproductive, developmental, and mutagenic potential as well as potential effects on immune function, neurobehaviour, and developmental neurotoxicity. Concerns arise with viral vector or gene therapies, especially with long-term persistence in the body, potential toxicity in the treated population, and spread to local and distal populations. Post-market surveillance is the only way to capture long-term effects of these strategies. Approaches must follow principles similar to those of the clinical trial period. Vulnerable groups, such as pregnant women, infants, and immune-compromised patients, must be studied in depth. [290, 291, 292, 293]

Biological therapy observations turn to hosts and bacteria. Any therapy is regulatory status-changing for the (host) person-the treating

doctor must consider their usual obligations when applying AI-guided therapy to potentially vulnerable groups. Intensive correspondence with external experts to assess the risks of assigning persons to atypical therapy is essential. This same obligation is present in relation to the treatment of children, especially babies, and when mothers in the last trimester of pregnancy, infants, or immunocompromised persons enter a trial.

Public trust and societal implications

Support for and acceptance of AI-guided microbiome-based innovation will ultimately depend on public trust. The engagement of stakeholders in any service, including those applying AI in human health, disease diagnostics, and treatment, is essential. It is therefore crucial to involve professionals, scholars, and citizens from different religious faiths, social and cultural groups, and academic disciplines in discussions and media talk shows, led by credible scientists who are able to present the potential benefits, risks, and societal implications of this technology.

Responsibility for the conscious design, implementation, monitoring, and regulation of AI-based, microbiome-guided service-delivery systems remains with the scientific community. Its primary objective must be to allow all aspects of civilization that are dependent on health to be maintained, optimized, and sustained with minimal risk of serious hazards and rapid development of effects that may seriously endanger life or civilization. Remaining risk that may be unacceptable from a social point of view must be regulated at the level of the society. [21, 294, 295, 296]

Chapter - 15

Clinical Translation and Personalized Medicine

The clinical translation of AI-driven microbiome interventions requires careful trial design to ensure the safety and efficacy of these therapies. Well-defined clinical endpoints, randomization, and subgrouping criteria are essential for obtaining interpretable results, and patient stratification during trials can help generate a wider range of AI-proposed therapies with different compositions tailored to individual patients.

To aid the transition of microbiome-based interventions into routine medical settings, robust integration and communication pathways with healthcare providers are needed. Reimbursement strategies for therapies should be considered, and the use of open-source platforms and applications is encouraged to facilitate access for any interested party. A thorough assessment of the economic viability of these technologies is crucial, and careful consideration of all necessary actions, procedures, and resources required to meet regulatory demands will help circumvent potential roadblocks during implementation.

The clinical trial design for AI-driven interventions focuses on determining the safety and efficacy of patient-manipulating consortia, while stratification of patients in the studies helps generate a wider array of therapy candidates for the AI engine. Both the actual prediction of therapies and their validation through clinical trials are also essential. Several types of trials, endpoints, and stratification criteria can be used to investigate and validate the different proposed intervention categories, such as probiotics, prebiotics, synbiotics, and postbiotics.

In a personalized approach, during therapeutic development and testing for patients affected by possible immune disorders, immune-related medications in the market, their effect profiles, and subsequent microbiome alterations can be used to implement an AI-guided design that further personalizes the patient treatment. This approach increases the microbiome- and disease-related knowledge in AI models, enabling the generation of other therapies for stratified groups.

Microbiome-based interventions are expected to be integrated into public health systems within specific group health programs assisted by wearable technology, where monitoring health state information of multiple patients with AI can warrant information about different health states of the population, and as a consequence facilitate pattern detection. This provides a feedback control loop between the health state detected in the population, and their influence on the population microbiome, increasing the chance of success of the proposed interventions or recommendations.

Finally, as future perspectives, the safety of any of the predicted therapies should undergo clinical trials, but also the overall AI analysis, including the hypothesized population responses, should become part of clinical science and human health, integrating predictions with disease heterogeneity, proposed causes and prevention measures. [297, 298, 299, 300]

Clinical trial design for AI-microbiome therapies

Clinical studies to assess the safety and efficacy of next-generation microbiome-targeted interventions guided by artificial intelligence must be designed with sufficient statistical power and robustness. All trials should have a secondary aim to determine the relationship between microbiome composition or function and treatment response, enabling stratified analyses of treatment efficacy or toxicity.

A rigid parallel group design with treatment versus placebo is appropriate for most trial endpoints, including changes in clinical biomarkers, quality of life, and, importantly, incidence of the primary disease. Sufficient baseline observations should be evaluated to support predictive modeling of secondary disease onset events and enrichment

of patient groups likely to benefit from treatment. When earlier clinical intervention is justified, a placebo-controlled randomized withdrawal design with relapsing patients receiving treatment after experiencing an exacerbation can counterbalance risks and reduce costs. An alternative adaptive trial design incorporating interim analyses can withstand greater between-group heterogeneity and accounts for likely alterations in treatment effect over time.

AI prognostic and predictive models enable investigations of other microbiota-related factors and the use of enriched groups of "super responders" or raditional trial designs involving treatment versus placebo. Further, AI-driven approaches can identify unexpected adverse toxicological events and potential biomarkers of drug-induced patient sensitivity, contributing to greater patient safety and more reliable clinical evidence. [301, 302, 303, 304]

Patient stratification and treatment personalization

Are crucial for designing efficient microbiome-related therapies. Individual differences in microbial communities can affect the onset or modulation of immune disorders before their clinical detection. These observations suggest that microbial profiles in a defined population both predict disease development and are linked to food preference, physical activity, and circadian rhythm. To leverage these relationships, microbiome profiles should be routinely measured before clinical detection of immune disorders, and links in both directions considered, prompting the need to carefully define subpopulations during training of predictive models. Empirical validation of their ability to delineate patient subgroups allowing for distinct pathogenic mechanisms would further enhance implementation.

Clinical benefits arise not only from achieving a reliable distinction among subpopulations but also from subgroup-specific anticipation, prevention, and treatment of disorders. External longitudinal cohorts can facilitate detection of patients with immune disorders prior to their OKT3 clinical diagnosis. Age-specific patterns would support the identification of microbiome-based interventions targeting physiological or clinical effect [305, 306, 307].

Integration into healthcare systems

Requires the development of a workflow establishing the need for the intervention, a patient stratification and recruitment step, effective remediation, follow-up, and a reimbursement model. Integrating advanced analysis of the microbiome into healthcare systems can be achieved by establishing a division of the healthcare system responsible for continuously monitoring large populations of healthy individuals for changes in microbiome composition and function. Longitudinal studies have shown that dysbiosis in healthy individuals is usually absent for long periods of time, and, when present, may be reversible through diet or lifestyle changes, thus making the time window beneficial for early detection of disease and targeted preventive action. Such a monitoring scheme would be far easier and less expensive than testing everyday bodily fluids for the myriad of biomarkers explained above. Monitoring data could also guide healthy individuals when purchasing new diets during their lifetime.

Digital health platforms that use personal data from wearables and biosensors would be equipped to send alerts to individuals in need of further assessment. A closed-loop system could, for example, send a specific set of questions, offer microbiota-modulating interventions, recommend a certain diet, and, provided things still remain abnormal, redirect the individual to an appropriate medical professional - all in near real time. Special mobile health platforms helping patients with chronic conditions using AI chatbots or nurses have been developed and could be adopted for this purpose as well. Major concerns, particularly with these systems, remain data protection. Personal health information must always be kept confidential and secure. The user should have complete control over the data and be able to decide what to share, with whom, and for what purpose. [308, 309, 310, 311]

Cost-effectiveness and accessibility

The economic evaluation of AI-enabled microbiome therapies indicates that smartphone-compatible health systems providing personal microbiome feedback could measurably change participants' health at relatively low societal cost. Key drivers of cost-effectiveness include the marginal cost of monitoring, the sustained level of behavior

change and its associated health gain, and the increase in detection of adverse health events related to the microbiome. Given the growing interest in predictive medicine, the modest cost of providing continued monitoring, and the precursor development of expansive databases of population-wide enterotypes, the proposed framework can be extended to other predictive medicine domains.

Closing the cost gap between countries with different levels of wealth will require innovative research that embraces technological advances in miniaturization and sensor design. The delivery of AI-guided microbiome diagnostic tests could also represent an attractive business case for traditional health players. Public insurance schemes covering the costs of diagnosis and treatment using these tests could help the technology reach large populations in developing countries and be beneficial for the industry. [312, 313, 314, 315]

Barriers to clinical adoption

Barriers to the clinical adoption of AI-guided interventions to restore intestinal immune homeostasis and support the prevention of eczema and other immune disorders remain. Processing and integrating heterogeneous data types necessitate extensive technical expertise, which is typically unavailable in hospitals, undermining the world-wide implementation of the proposed predictive modeling pipelines. Furthermore, when personalized systems are developed, even control-matched populations are relatively dissimilar. As most of the factors associated with the occurrence of diseases that are clearly linked to other factors are relatively unchanging, it is possible that the generalizability of these systems could be improved by developing separate components for each populations, reducing both the complexity of the input to the models and any noise that would be generated by keeping the subject groups balanced.

In addition, the procedures tend not to be simple: sample sizes can be high, requiring expensive screening tests, and the clamp approaches used to develop prediction equations are often complex and time-consuming, increasing the logistical and cost burdens of implementing these procedures for real-time applications. Other approaches-such as machine learning models-that use body temperature and accelerometry

data-collected in a standard manner-hold greater appeal. These procedures are normally simple and low-cost, allowing for large sample sizes while providing sufficient information to detect the diet-microbiome-immune relationships. [316, 317, 318]

Chapter - 16

Future Perspectives and Global Health Impact

Next-generation AI-driven and microbiome technologies will empower preventive medicine and the management of overall health. Continuous analysis of personal and population-level data from wearables and biosensors will help improve diet and lifestyle, reducing the risk of disease development and progression. AI-supported development of personalized diets and real-time microbiome interventions will further decrease disease risk-particularly in sensitive groups such as infants-and improve vaccine effectiveness. The data-driven design of safe, efficient microbiota-targeted therapies for chronic diseases will enhance clinical outcomes. Widespread applications will help reduce the excess burden of disease in vulnerable populations. Maintaining global microbiome diversity and health will promote the prevention of future pandemics.

Next-generation AI and microbiome technologies must support global health goals: enabling preventive medicine, prolonged healthy aging, reduced risk of chronic disease, and attenuated pandemic burden. Data from wearables, biosensors, and other sources will inform personalized dietary and lifestyle recommendations for healthy risk group stratification. Continuous, real-time sampling of microbiome shifts will underpin feedback-controlled interventions, maximizing effort-reward ratios. Early-life disturbances can be repaired using microbiome-modulating strategies, increasing tolerance and inducing systemic health. AI-optimized microbiome-directed management of chronic diseases will produce long-term health improvements and accelerate innovations in the field. Addressing microbiome health inequalities among populations will promote overall resilience against future pandemics.

Next-generation AI and microbiome technologies

The next generation of AI and machine learning models will include various continuously evolving fields. This development involves a combination of different systems as well as instruction from the users of the AI systems for further customization. As shown by Huang Male *et al*., the latest image-generation AI can accept both visual input and language-based input, creating a new multimodal era of AI models. Furthermore, the latest ChatGPT version allows users to accept voice inputs to produce answers. Enhancing the capabilities of existing AI models will help meet the needs of the users. By combining the latest vision research, multimodal models will continue to advance. Models that can provide commentaries on videos will also be developed. In the future, research will focus on learning more about humans, participating in tasks, compiling summaries, and deep learning.

AI and machine learning are becoming integral parts of the research process. Al systems, which consist of artificial neurons and their connection weights, rely on the quality and quantity of the data they are trained on for their performance as well as on the model architecture and objective function. Well-designed and trained AI models can obtain insights, hypothesis-generating clues, and hidden underlying principles. Furthermore, these sources of information can be monitored interactively and validated experimentally.

Preventive medicine and healthy aging

By integrating with data from wearables and biosensors, AI models can support continuous health monitoring, dyadic coach-patient interaction, and feedback-controlled interventions. Patients wearing continuous sensors and feeding data into a digital health platform can receive alerts for potential health abnormalities, such as elevated glucose levels, by synchronizing digital health resources such as cloud computing. A smartphone app uses the developed model to interpret and visualize data for the patient and physician. AI models may control modulation of the microbiome and other health parameters by wearables.

Telemedicine enables remote consultation and interpretation of biodata, which may not be easily interpretable by a non-expert. The recommendation system approves actions requiring follow-up and indicates potentially dangerous situations requiring hospitalization. Adherence to lifestyle and diet recommendations determined by the integration of wearables, microbiome data, and other individual health information can be assessed and visually presented to the patient.

Additional recommendations can suggest interventions to modulate the microbiome or other parameters. Microbiome modulation and other interventions can also be prescribed to prevent identified or anticipated disease states detected by AI. Longitudinal development of the microbiome and its influence on other parameters may enable the design of timed feedback that allow interventions when such symptoms appear. Behavioral, dietary, environment, health monitoring, and microbiome data can be fused to create new features for prediction models.

Global microbiome diversity and equity

Microbial world-wide diversity supports human health. AI-based applications should ensure inclusion and serve humanity.

More than 3000 million years of evolution led to the global Holobiont. An imbalance can increase susceptibility to various diseases, which can be reduced or avoided. Recent progress in Biomedical Sciences, particularly AI technology, enables an unprecedented understanding of the human holobiont. The microbiome can provide insights into a variety of diseases, opening the search for new microbiome-based preventive medicine: The Instagram of Appropriation. The recognition of the potential for therapeutic interventions forms the basis for AI-driven methods for developing therapeutic approaches that facilitate this process. But care is needed to address the imbalances and not simply extract and appropriate, as such unbalanced exploitation can have catastrophic consequences.

Equitable access to modern technologies is required to sustainably ensure the diversity of microbial infrastructure and its role in sustaining human well-being. Disruption of the diverse structure would make

mankind increasingly more vulnerable. Examination of the effects of impairing the infrastructure diversity is urgent: targeting the appropriate diversity metrics would enhance potential application. The growing microbiome research domain must be translated into preventive medicine programs that ensure an ever-decreasing likelihood of catastrophic pandemics.

Pandemic preparedness and immune resilience

A proactive approach to enhancing population immunity and resilience against future pandemics may help reduce disease incidences and associated healthcare burden. As repeatedly demonstrated during the COVID-19 pandemic, zoonotic and emerging infectious diseases are unpredictable and a continual global health threat. Supporting immunological preparedness through first-principle designs of microbiome-modulating strategies is therefore a timely task. Many pathways and factors linking the microbiome with risk of infections and vaccination response in children and adults have been proposed. Exploring microbiome signatures predictive of clinical infection and serological responses to vaccinations could provide a competent framework for population-level engineering of tolerance-inducing and anti-infective microbiomes that strengthen immune readiness.

Building collective population immunity before disease outbreaks may improve preparedness without resorting to routine vaccination campaigns or chemical adjuvants boosting the immune response, with long-term benefits in reduced incidence and severity of chronic diseases. AI-assisted identification and subsequent longitudinal population studies of microbiome signatures predictive of clinical infections, immune tolerance, and response to vaccination will guide design of intervention strategies targeted toward the associated pathways. During such explorations, emphasis should be given to the timing and safety of potential interventions, and follow-up studies should address persistence and long-lasting effects beyond completion of the specific modulation.

Roadmap for future research and innovation

Future developments in AI and microbiome research should prioritize early clinical trials in AI-based and microbiome-targeted

medicine, with a focus on immune and chronic disease prevention for healthy populations. The generated pipelines should enable the discovery of novel intervention candidates targeting risk factors for major diseases, particularly respiratory and metabolic disorders. A multidisciplinary global effort should aim to gather a diversity of healthy microbiomes and their associated information. These populations should serve as search spaces for AI algorithms during the design of preventive intervention strategies and healthy aging supports.

The initiatives should consider the preventive potential of nutrition, circadian rhythms, environment, and lifestyle, aiming to optimize their contribution to immune resilience. Microbiome-induced risk reduction strategies for cardiovascular and neurological diseases should be identified through dedicated pipelines. Major known defense measures against future pandemics should be effectively supported in an extended manner. The overall objective is to create a proactive and health-promotion-focused clinical and research environment in combination with the knowledge gained from prior pandemics.

Chapter - 17

Conclusion

Recent advances in artificial intelligence (AI) provide opportunities for novel exploration or resolution of long-standing scientific questions, including the inherent complexity of the human microbiome and its connections with the host immune system and the development of chronic diseases. Microbiome data-generation technologies have expanded exponentially in recent years and are expected to continue to grow. By harnessing these new approaches and integrating them with AI techniques, powerful predictive models could be built to identify how the microbiome influences the immune system and risk of chronic disease throughout the human lifespan. Equipped with such knowledge, it should be feasible to engineer microbial ecosystems to support immune health in individuals and populations, thus reducing the burden of immune disorders and contributing to the prevention of other chronic diseases.

The human microbiome has a central role in shaping individual immune responses and influencing the risk of developing immune-mediated disorders such as allergies, asthma, and autoimmunity. A variety of lifestyle and environmental factors modify the microbiome, and targeted probiotic, prebiotic, synbiotic, or dietary interventions during early life hold promise for lowering the risk of these diseases. Furthermore, the microbiome can modulate vaccination responses and the development of immune tolerance, with potential implications for vaccine design and implementation. AI modeling approaches should enhance understanding of the interactions between the immune and microbial systems during healthy and abnormal development and enable the engineering of optimal immune-supporting microbial ecosystems.

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