Preventive medicine

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1. INTRODUCTION

Modern medicine is moving towards treating the cause rather than the symptoms of disease. P4 medicine, being predictive, personalized, preventive and participatory, is expected to become the main approach in disease management in the next decade. Understanding the molecular and genetic changes behind disease development and using prevention strategies is the key to quality healthcare. There are many challenges on the path from idea to execution, and finding ways to overcome these challenges is a task assigned to members of the healthcare community. Focusing on the causes will enable earlier medical intervention, and ultimately prevent the disease from occurring completely or delay its onset and progression. Successfully implementing prevention strategies will not only benefit the medical system itself, but more importantly the patients' quality of life (Hood and Friend, 2011).

PAST	PRESENT	FUTURE
Intuition Medicine	Evidence-based Medicine	Precision Medicine
Signs and Symptoms	Clinical Trials	Algorithms

Table 1: Precision medicine is changing the way we approach healthcare (adapted from Gameiro et al., 2018).

Precision medicine relies on changes in concentration of multiple molecular markers or molecular profiles to characterize a patient's status and make a therapeutic decision. Finding the signal in the noise presents a significant technical challenge, so assays usually measure concentrations of a small number of molecules with available reagents. With molecular profiling and proteomic analysis, multiple proteins can be characterized as biomarkers and clinically evaluated. This improves accuracy, time needed for diagnosis and identification of

new therapeutic targets. If a genetic predisposition for disease is discovered, preventive strategies can be tailored to the patient in a timely manner (Prodan Žitnik et al., 2018).

It is important to differentiate between prediction and prevention. In summary, predictive medicine analyzes an individual's genome sequences and its influence on molecular, cellular and phenotypic characteristics. It is important to provide a baseline measurement that can be defined as healthy, to identify any changes that can ultimately lead to disease. Several laboratory procedures are used to predict disease development, such as whole-genome sequencing or liquid biopsy, but more technical advancements are needed to implement them into routine medical practice. Prevention can be carried out on an individual or population basis, one example being public health campaigns. In certain areas such as mental health, scientists prefer prevention-oriented approaches rather than those prediction-oriented. The goal is to avoid categorizing patients and statistical predictions, as comparisons between patients and institutions can sometimes lack meaning. The focus should instead be on collaborative planning towards life-saving preventive actions.

The risk factors for many of the leading causes of death can be controlled. An unbalanced diet, physical inactivity and tobacco use prominently contribute to the development of chronic disease. By educating healthcare professionals, the knowledge is also extended to their patients. Patients should be motivated to take action to improve their health, which significantly raises their chances of having a long and productive life. Recent findings suggest promoting healthy behaviors should begin in early childhood, perhaps even in the prenatal period, to achieve lasting results (Hood and Friend, 2011).

Patients and healthcare consumers are seemingly determined to improve the management of their own health using the internet and social networking tools to gather information. Wearable fitness trackers and mobile fitness applications have become increasingly prevalent in modern society, providing important healthcare information and potentially increasing physical activity rates. Patient engagement and interest will ultimately enable the transformation of the healthcare system from reactive to P4, alongside the advancements in education and technology. The P4 healthcare system will be successfully implemented when lifestyle data from self-monitoring (nutrition, activity level, sleep pattern) is consistently integrated with data generated by medical institutions (Flores et al., 2013).

1.1. Levels of prevention

Preventive healthcare strategies include primary, secondary and tertiary prevention levels, aimed at susceptible individuals or populations. Primary prevention focuses on preventing disease development altogether or increasing the body's natural resistance. This can be done by immunization, maintaining a healthy diet and developing daily exercise routines. Food is often considered as the main tool in preventive healthcare, but unhealthy habits such as tobacco and alcohol use should not be ignored either. Due to recent scientific advancements, genetic testing can be used to diagnose hereditary conditions and individuals with an increased risk of developing a specific disease.

In patients with subclinical disease, pathologic changes are present without any clinical symptoms or with vague symptom presentation. Secondary prevention includes methods to detect these latent diseases and prevent disease progression in asymptomatic individuals. Treatment of hypertension is a good example, as early detection and proper management can stop complications (in the form of cardiovascular diseases) from developing. Another example is cancer screening, because cancer is unfortunately hard to predict or completely prevent as specific biomarkers are still being discovered. After the onset of disease, tertiary prevention strategies are used to reduce pain, damage and complications. Examples include various surgical procedures, rehabilitation and medication. Rehabilitation must be mental, physical and social to allow the patients to continue with their normal daily life as much as possible. Unfortunately, as preventive medicine continues to develop so does the risk of excessive medicalization. A new concept of quaternary prevention was therefore created to protect patients from unnecessary clinical interventions and propose ethically acceptable alternatives (Kisling and M Das, 2021).

In 1978, primordial prevention was introduced as an additional preventive strategy. It goes beyond the concept of primary prevention by intervening with the appearance of risk factors. Primordial prevention is often aimed at children to discourage them from adopting harmful lifestyles and minimize risk exposure. In conditions with high prevalence, such as hypertension, primordial prevention is rarely used in research or clinical care. More focus should be given to strategies for maintaining blood pressure in the ideal range, which are directed towards reducing childhood obesity, avoiding excessive salt consumption, increasing fruit intake, limiting screen time and promoting healthy sleep habits. Intervention approaches

include individual and mass education, along with a strong focus on social, economic and environmental conditions. High-risk patients should be clinically monitored while changes are introduced to public health policies, school programs and community services to reinforce primordial prevention (Falkner and Lurbe, 2020). A rather controversial approach is health related food and drink taxes introduced in various countries, mainly focusing on items containing artificial sweeteners (Smith et al., 2018).

1.2. Translational research

In the last few decades of the 20th century, considerable advances in fundamental biomedical research were achieved. However, obstacles between applied, clinical and basic research have not disappeared, but on the contrary, became more significant than ever before. These challenges catalyzed the implementation of the initiative named “translational science”. Created at the beginning of the 21st century, this new concept has since been embraced by many respected institutions and individuals. Translational science connects public scientific institutions, the academic biomedical community, and the industry. It has resulted from the necessity for more effective discovery of new therapeutic options and medicines, along with the need for the creation of stronger links between fundamental research and practice, particularly the clinical one. Fundamental scientific discoveries on the molecular or cellular level are typically made in research laboratories. To contribute to improving human health and healthcare, basic research has to be translated from the laboratory to clinical and subsequently industrial practice level. This will enable the connection between research and application to become more efficient and productive.

Requirements and the complexity of drug discovery and clinical research continue to increase each year due to regulatory demands and increased costs of production. Therefore, the new concept of translational research has been created to provide new means for developing and implementing novel therapeutic options, and subsequently reduce disease progression and morbidity. This approach represents the foundation of translational medicine developed by the support of specifically skilled professionals. These scientists can connect fundamental scientific discoveries with clinical research, and translate clinical trial results to clinical and industrial practice by utilizing results and data collected from different sources. The purpose of all these

initiatives is to facilitate the process of turning early discoveries into drugs and medical devices, improve the overall patient care, and enhance preventive measures.

The translational research approach can be applied in many areas of biological/biotechnological science and medicine. Particular use has been found in developing specific, targeted ("smart") therapies, broad public health measures and activities for the prevention of chronic degenerative diseases, notably metabolic disorders. Implementation of such activities requires academic institutions, hospitals, industry, and regulatory agencies that issue licenses for the marketing, distribution, and sales of drugs to collaborate and invest in expanding knowledge and skills. New initiatives in healthcare today are based on the so-called P4 principles and translational science is expected to play a key role in the introduction of personalized, tailored therapy. However, implementation of specific procedures and successful interaction of existing knowledge requires large multi- and trans-disciplinary teams of experts who know how to apply the tools they have at their disposal. To meet this objective, improvements in the education system for young physicians and researchers must be made. Academic medical institutions should strive to promote translational and clinical research, among both students and experts in their respective field, and grant it a higher priority in funding.

By combining translational science and the P4 approach, the vast majority of industrial applications, scientific knowledge and emerging technical innovations can be directly utilized to develop sustainable human welfare. Basic research can provide innovative drugs, technology and biomedical equipment, while clinical researchers can create knowledge about the nature and progression of a disease that can drive basic research. Without translational and clinically oriented research healthcare would stagnate. Translational research will improve communication and feedback between researchers and medical workers, and simultaneously offer multiple benefits for the end user – patient (Čikeš et al., 2012).

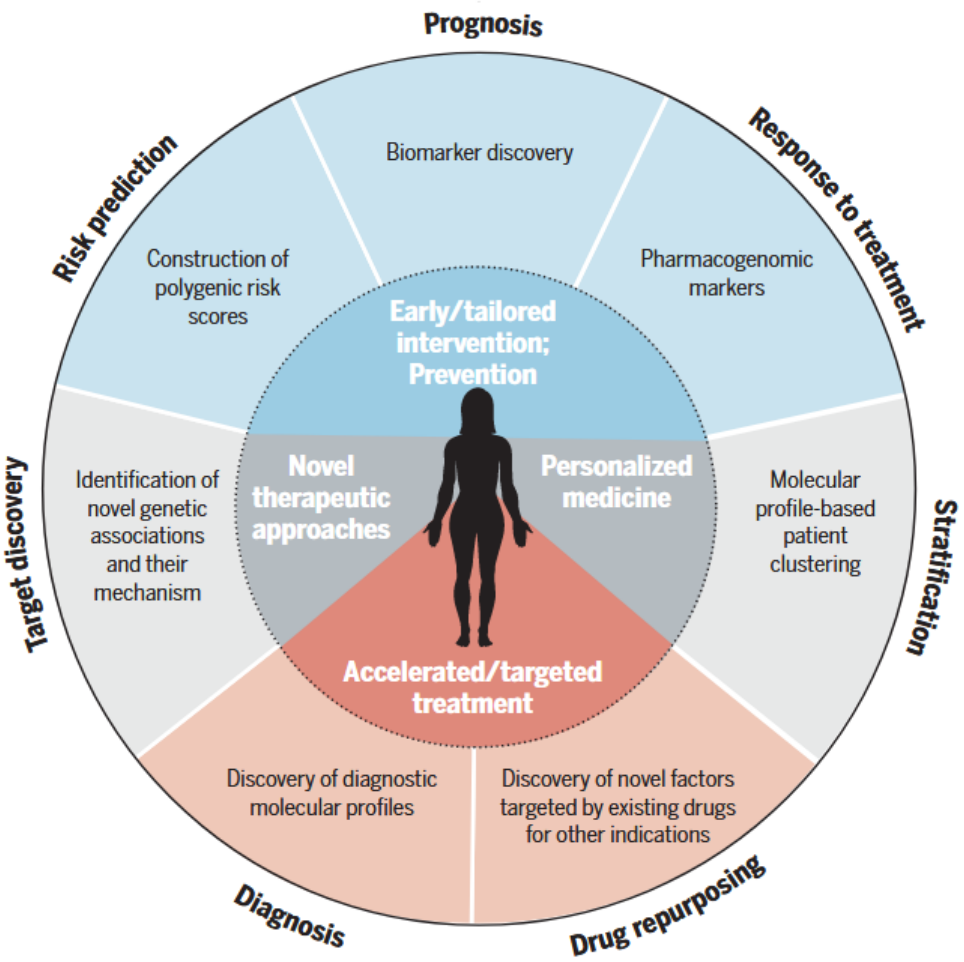

Figure 1: A diagram displaying how discoveries made through genetic and genomic research can be applied in a clinical setting. Potential improvements to the human health are listed in the inner circle. To achieve successful translation, scientists will need to focus on functional interpretation instead of just identifying associations between sequence variants and phenotypes for common complex diseases (adapted from Zeggini et al., 2019).

2. OBJECTIVES

P4 is an evolving, innovative approach in medicine. The digital revolution provided the tools necessary for the development of new computational models, which can be used to understand the interaction between an individual's genetic makeup and the environment. These models can potentially both demystify disease and define what it means to be healthy. Both young and experienced healthcare professionals should be aware of emerging technologies so new procedures can be seamlessly introduced to routine clinical practice.

As diverse medical data begins to accumulate, patients with diseases such as breast cancer or Crohn's disease will be more accurately classified into subgroups based on different reactions to drugs, disease risks, molecular and cellular origins. Connecting specific deviations in biological networks to diseases will provide new drug targets for the pharmaceutical industry. If the target population is precisely stratified and smaller in number, drugs will be cheaper to develop and more effective. Laboratory medicine will undergo change in the near future as well with the introduction of automation, biosensors, microchips, genomics and proteomics. The diagnostic procedures are already becoming more patient-centered and there is growing demand for direct-to-consumer testing (for example, saliva collection kits for genetic testing). A more personalized approach can facilitate the introduction of reference intervals specific for that patient, which can redefine values that are considered pathological in analytes with high between-subject biological variations (Flores et al., 2013; Greaves et al., 2019).

Although research and technology seems to progress rapidly in contrast to clinical practice, it's important to emphasize that patients' needs and satisfaction should be the main driving force of precision medicine. The aim of this thesis is to clarify the importance of lifestyle in maintaining overall wellness, and focus on the impact of nutrition, physical and mental activity on different health conditions. Obesity, hypertension, inflammatory bowel disease, diabetes and subsequent complications are all examples of chronic diseases whose onset and/or progression can potentially be prevented by modifying individual behavior. As the global burden of chronic diseases is on the rise, engagement of both medical professionals and patients has become a necessity to decrease pressure on the healthcare system.

3. MATERIALS AND METHODS

Information cited in this thesis was gathered from various systematic reviews and publications found by searching the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar databases from March to August, 2021. The keywords “P4 medicine”, “preventive medicine”, “personalized medicine”, “prevention strategies” and “translational medicine” were used to provide material that will serve as an introduction to the subject. In the subsequent chapters, “Western diet”, “Mediterranean diet”, “lifestyle medicine”, “microbiota or microbiome”, “probiotics and prebiotics”, “gender medicine”, “RRI” and “dissemination” were used as keywords, along with names of several chronic conditions. All of the referenced articles and books were written and published between 2005 and 2021, with an emphasis on most recent publications.

4. DISCUSSION

4.1. Extrinsic factors and related conditions

"You are what you eat" is a phrase commonly found in the media today. Nutrition plays an important role in all public health campaigns for chronic disease prevention. Chronic diseases are also known as noncommunicable diseases (NCDs), meaning they are not passed from person to person. Most common NCDs are diabetes, cardiovascular diseases and respiratory system diseases. Western diet, and its globalization, is associated with the development of chronic diseases. Fast food is becoming disturbingly prevalent in today's society, with quick and cheap snacks full of strong flavors available at every corner. As NCDs account for about 70% of deaths across the globe, prevention and management is a major health concern. About 10 million people die annually due to cardiovascular incidents, 913 000 from cancer and almost 339 000 from type 2 diabetes (Afshin et al., 2019). The Western diet is associated with an increased intake of animal food, saturated and trans-fat. Another major component are refined foods such as snacks, carbonated drinks and meals with a high glycemic index. There is a prominent deficiency in micronutrients and a high intake of salt (Fedacko et al., 2019).

Negative changes in diet as well as lifestyle promote the production of reactive oxygen species (ROS), hyperinsulinemia and insulin resistance, low-grade inflammation, sympathetic nervous system and renin-angiotensin system (RAS) dysfunction. Recent studies suggest these significant metabolic distortions are the major cause of degenerative diseases (Kopp, 2019). A single dietary element cannot cause chronic disease, contrary to the belief of some scientists and health experts. Excessive consumption of modern foods causes the metabolites to interact in a complex way, eventually resulting in various health conditions. Some researchers suggest the primary cause of chronic diseases is the collision of our ancient genome with modern life conditions and food introduced in recent human history (Cordain et al., 2005).

4.1.1. Nutrition

Food will never be as effective as drugs or medication, and relieve pain like a painkilling tablet. However, proper nutrition can be a powerful ally in preventing and recovering from diseases, maintaining physical and mental balance. Recent systematic reviews suggest that poor dietary habits are responsible for more deaths globally than any other factors, including tobacco use. Data suggest 1 out of 5 deaths is linked to unhealthy eating habits, characterized by a deficit of valuable nutrients. The contrasting behavior of dieting obsession is also taking its toll, mostly resulting in eating disorders such as anorexia nervosa, and nutritional deficiencies in children or even pets.

Nutritional requirements are very individual and depend on a variety of factors such as physiological condition, age, biochemical and hematological findings, lifestyle, physical and mental activities. Food intake is also associated with positive or negative events, sometimes called “emotional eating”. Some people turn to food to cope with difficult situations and feelings of despair, loneliness or boredom. Food is also a vital part of socializing, whether it’s dinner dates, birthdays or family holidays.

In recent years, there is a big emphasis on the macrobiotic diet, particularly among severely ill patients. The diet was first described by a Japanese physician, and it is defined by a low intake of overall calories and saturated fats, while being rich in plant fibers, minerals and complex carbohydrates. Eating in-season, locally grown, organic food is recommended as a part of the macrobiotic diet, but it’s also present as a popular dietary advice.

The vegetarian diet is gaining popularity as well, whether it’s because of religious rules, or ecological, ethical and philosophical reasons. The main features of this diet are restricted foods of animal origin, reduced total fat content, saturated fatty acids and cholesterol. Numerous studies have shown that the vegetarian diet lowers the risk of type 2 diabetes, malignancies, vascular and degenerative diseases. This can be explained by the increased intake of fruits and vegetables rich in antioxidant, fiber and mineral content. It is important to note that more restrictive vegetarians – vegans have a higher incidence of calcium, vitamin D and vitamin B12 deficiencies. Amino acids, zinc and iron levels should also be monitored, especially in children. Sources of protein should be carefully selected to ensure adequate daily intake of all nine essential amino acids and avoid any nutritional deficiencies, along with their complications.

Amino acids are the building blocks of proteins, which are large, complex molecules that play many critical roles in all living organisms. Recommended daily intake for healthy adults is 0,8-1,0 grams per kilogram of bodyweight, but athletes and professional bodybuilders may require more protein to build muscle mass. High protein/low carb or ketogenic diets can be used as a potential treatment for various disorders such as Alzheimer's disease, Parkinson's disease and glaucoma. However, side effects may include acidosis, gastrointestinal disturbances and reduced appetite so patients following the ketogenic diet should be supervised. People with a family history of kidney stones and kidney diseases should also proceed with caution, as the high animal food content in this diet may worsen their condition. The ketogenic diet is growing in popularity due to its weight loss effects, and it's important for health enthusiasts to consider both the risks and rewards before deciding on any major changes in their dietary habits.

The dietary pattern originated in the Mediterranean region is the so-called Mediterranean diet. It is said to improve overall health status and control non-communicable diseases. Evidence based studies suggest the Mediterranean diet reduces the risk of coronary heart disease and some forms of cancer, mainly gastrointestinal, prostate and breast cancer. This diet also lowers the levels of inflammatory markers such as CRP, fibrinogen, homocysteine and LDL cholesterol, in turn improving the outcome of chronic inflammatory diseases.

Figure 2: A graphic depiction of the Mediterranean diet suggesting how frequent certain foods and beverages should be consumed. Nuts and olive oil are a source of monounsaturated fatty acids, while fish is a source of polyunsaturated fatty acids. Both have been associated with reduced inflammatory signaling, whereas complex carbohydrates have an important role in maintaining eubiosis (www.cleaneatingmag.com).

It is important to note that isolating single nutrients from the Mediterranean diet won't have the same benefits as a whole-diet approach and general lifestyle change. The addition of olive oil to meals, for example, will most likely have a positive effect on cardiovascular health and inflammation. Unfortunately for most, simultaneously consuming refined foods associated with the Western diet will most likely counteract these benefits. Therefore, the best culinary interventions should include a collection of healthy nutrients instead of specific foods, with an emphasis on consistency and long-term adherence to the Mediterranean diet (Parish et al., 2011).

Precision nutrition is achieved by studying large quantities of metabolic and health data, also called big data. It includes information such as genes, transcripts, proteins, metabolites and microbiome composition. Urban living and modern diet is causing a rise in food allergies. Proper diagnostic procedures and metabolic biomarkers are needed to prevent patients from seeking alternative treatment and avoid unnecessary elimination diets. A promising, non-invasive procedure called liquid biopsy has received immense attention during the past decade. It involves analyzing biomarkers circulating in fluids, such as the blood, for diagnostic screening, therapy response and outcome prediction. Since the procedure requires a sample of the peripheral blood, scientists hope it will ultimately replace standard tissue biopsy and minimize its complications (bleeding, pain and infections). Liquid biopsy is currently used in cancer research given that peripheral blood can contain circulating tumor cells and circulating tumor DNA, but it also contains a variety of human and bacterial metabolites. By analyzing these markers, the molecular profile of the disease can be established, allowing medical professionals to adjust prevention strategies and treatment to better suit their patients. This will benefit both the patients with aggressive and non-aggressive diseases (Verbanac et al., 2019; Widmer et al., 2015).

4.1.2. Precision medicine in obesity

Obesity is a growing medical and socioeconomic problem, associated with numerous physical and mental conditions. People are generally classified as obese when their body mass index (BMI) is over 30 kg/m2, while individuals within the range of 25-30 kg/m2 are considered overweight. According to the WHO, worldwide obesity has nearly tripled since 1975 and is no longer only a cosmetic concern. The simple explanation for the rise of obesity is increased consumption of high-calorie, high-fat food and sedentary lifestyle (office jobs, convenient means of transportation, lack of exercise). Overweight individuals have a higher risk of developing various chronic and degenerative conditions, increased susceptibility to infection and higher mortality rates.

The main role of adipose tissue is energy storage in the form of lipids, but it is also a major endocrine organ and has immunomodulatory functions. Fat tissue can induce insulin resistance, development of metabolic syndrome and inflammation, which is why obesity is considered a chronic inflammatory disease. Another important component of obesity is the gut

microbiota, since it affects energy production from food, provides low-grade inflammation and influences fatty tissue composition. Short-chain fatty acids (SCFAs) produced by microbes balance the homeostasis of the gut, improve the strength of the intestinal barrier and reduce inflammation. According to research, dietary supplementation with butyrate can decrease insulin resistance by increasing mitochondrial function and energy consumption. SCFAs are also able to reduce appetite directly by interacting with specific receptors for energy sensing, which regulate intestinal function through hormone secretion. Obesity is managed with controlled weight loss, which can be achieved by following a balanced diet, modulating microbiota diversity with probiotics and prebiotics, pharmacological and surgical treatments.

Numerous studies have confirmed supplementation with probiotics and prebiotics can improve gut bacteria composition, offering promising opportunities for prevention and treatment of obesity. Probiotics can inhibit insulin resistance, prevent weight gain and body fat (specifically visceral fat), reduce the number of lipopolysaccharide-producing bacteria and subsequent inflammation. The information on prebiotics as functional food and their effect on human metabolism is scarce, but several studies have reported an increase in microbial diversity and improved leptin resistance after the consumption of cocoa flavanols, dark chocolate and lycopene (Aoun et al., 2020). To improve the survival and implantation of live microbial dietary supplements, pro- and prebiotics have been combined into synbiotics, but differences in bacterial carbohydrate utilization patterns across different strains and species present a challenge in further development (Pandey et al., 2015).

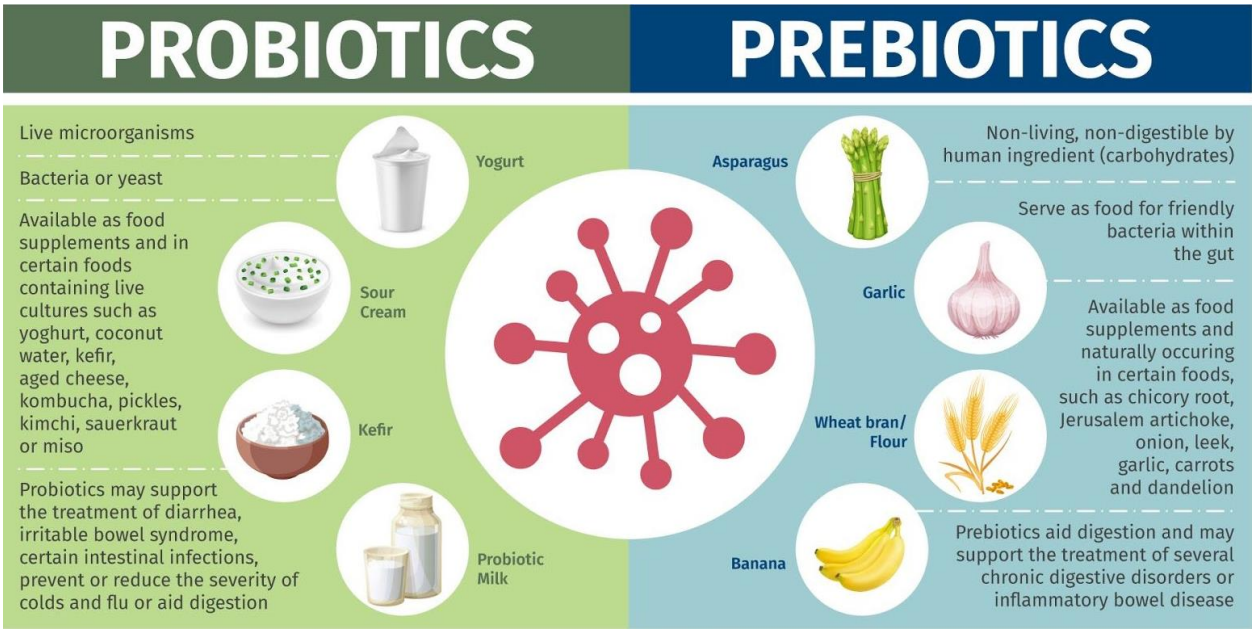

Figure 3: Probiotics and prebiotics may promote immune mechanisms inside and outside the gut, help regulate the gut motility, and act as anti-inflammatory compounds. Supplementation is used alongside pharmacotherapy in various digestive disorders to improve the gut's microbial composition and preserve its stability (thedempsterclinic.com).

A list of potential genes for obesity-related traits can be found in the Human Obesity Gene Map, and in the last update (2005), 127 candidates were described. Genetic factors explain roughly 40% of the variation in BMI, as they influence appetite, resting energy expenditure, thermogenesis and lean body mass. Resting energy expenditure (REE), also called resting metabolic rate (RMR), should not be confused with basal metabolic rate (BMR) measured in the morning, under strict conditions to avoid the thermic effect of food and daily activities. REE is therefore a better indicator of daily energy requirements, and the results are utilized in long-term weight management and calorie intake planning (Katz, 2017).

However, while genetic factors raise susceptibility to obesity, high prevalence in both developed and developing countries in the last century suggests there are risk factors beyond genetics. This includes socioeconomic and environmental factors, most of which are modifiable by individual behavior and response to everyday health challenges. According to studies, food availability, parental obesity, smoking, exposure to endocrine-disrupting chemicals and antibiotics at an early age, gestational diabetes and multiple other elements can influence the development of obesity. Pregnancy is an important preventive avenue where nutrition education and weight gain monitoring can ensure the child has an optimal start and doesn’t suffer

repercussions later in life. Since obesity is a complex issue, interventions are needed both on an individual and community level, including industry, agriculture and public health sector, to provide substantial education, prevention and treatment (Hruby and Hu, 2015).

4.1.3. Precision medicine in hypertension

Hypertension is often regarded as the most important preventable risk factor for cardiovascular disease and premature death. The definition of hypertension, or high blood pressure, has changed over time and the cutoff value is currently 140/90 mmHg. When a patient's blood pressure exceeds this level, they receive a diagnosis of hypertension and consequent treatment. Most common intervention is pharmaceutical therapy, including various drugs such as angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers, thiazide diuretics and beta-blockers. However, only one-third of hypertensive patients achieve the target blood pressure. This is a widespread and pressing problem, as hypertension increases the risk of cardiovascular disease more than smoking or hypercholesterolemia. In simple terms, as the blood vessels become stiffer and narrower, there is a higher possibility of blood clot formation and ischemic stroke.

A major mechanism for development of hypertension is total peripheral vascular resistance. This happens due to endothelial dysfunction, increased vascular tone and vascular structural remodeling. Complex interaction of genes and environmental factors have large effects on blood pressure, including aging, diet and various health conditions such as insulin resistance. The lack of consistent drug therapy response can be attributed to genetic polymorphisms or poor adherence. Even in compliant patients, the response to drugs might still be inadequate. Factors that contribute to this are comorbidities (obesity, diabetes, chronic kidney disease), salt sensitivity, excessive alcohol consumption, sleep apnea and various others. Genetic or molecular markers can be used to personalize hypertension management, such as measuring renin levels in patients using ACEI or diuretics. As there are multiple biological and non-biological factors that need to be included in both prevention and disease management, it is evident why hypertension is a major candidate for precision medicine (Padmanabhan and Touyz, 2016).

4.1.4. Precision medicine in diabetic kidney disease

Diabetes and its complications are one of the major public health concerns worldwide, with a significant impact on life expectancy and national economies. While type 1 diabetes prevention remains a challenge even though the incidence is slowly rising each year, type 2 accounts for over 90% of all cases of diagnosed diabetes and its onset can be prevented or delayed by modifying diet, physical activity and weight gain. Brisk insulin release after food ingestion, storage in the form of adipose tissue and low calorie burn rate offered an evolutionary advantage during times of famine. In modern times, these responses present a challenge due to nutritional abundance, leading to hyperinsulinemia, obesity, insulin resistance and ultimately diabetes after β–cell failure.

Diabetic kidney disease is among the most dangerous complications of diabetes mellitus. It affects nearly one-third of patients with diabetes and increases cardiovascular risk. Multiple approaches are used to prevent or delay the onset of diabetic kidney disease, as well as slow its progression. The disease is characterized by "silent" changes in blood flow, increased glomerular filtration rate and structural changes in the glomerular membrane. The first noticeable sign is usually microalbuminuria, due to the diabetes-related damage to nephrons and leakage of proteins into the urine. Prolonged periods of hyperglycemia can be directly toxic to cells due to increased generation of reactive oxygen radicals, or induce inflammatory cell activation and growth factor release because of glycation. Progressive renal damage is marked by macroalbuminuria, reduced glomerular filtration rate and ultimately the need for renal replacement therapy. However, in some patients the disease doesn't progress through stages.

As cardiovascular risk is already increased in the early stages of diabetic kidney disease, reliable detection could lead to successful prevention. Microalbuminuria remains the universal biomarker for early detection, as well as prediction and therapy response. If the patient's disease progresses rapidly despite preventive therapy, it's important to recognize these patients and offer them novel or experimental drug therapy. Research suggests primary prevention is possible, as angiotensin receptor blockers have been proved to delay the onset of microalbuminuria. Given that not every patient with diabetes will develop kidney disease, clinicians should avoid exposing two-thirds of patients to unnecessary drug treatment. Only high risk patients should be identified and monitored for any signs of disease progression, as

they are ideal candidates for preventive strategies. Therefore, precision medicine is the best approach to diabetic kidney disease (Currie et al., 2016).

4.1.5. The role of lifestyle in preventive medicine

People tend to think life-changing advances in medicine include expensive, state-of-the-art equipment, and comprehensive lifestyle changes seem too simple to make a powerful difference. On the contrary, plenty of scientific and medical literature suggests daily habits and practices significantly affect both short-term and long-term quality of life. Regular physical activity, maintaining appropriate body weight, following healthy dietary patterns and avoiding tobacco use is vital in prevention and treatment of metabolic disorders, and is included in clinical guidelines for various conditions. Some studies suggest over 80% manifestations of cardiovascular diseases and diabetes could be prevented by adopting positive lifestyle practices. Focusing on overall wellbeing and mental health is a personal choice, and while it's not an immediate fix, it's an important step towards a more fulfilling life.

Physical activity has been demonstrated to reduce risk of obesity, metabolic syndrome, cardiovascular incidents, type 2 diabetes and even certain types of cancer. Furthermore, regular aerobic and/or resistance exercise can have a positive impact on the central nervous system, improving brain health, cognition and sleep patterns, while reducing anxiety and depression. Vulnerable populations such as children or elders can also benefit from physical activity, as it increases mental alertness, and minimizes the risk of fall-related injuries by improving balance and joint mobility. Physical activity during pregnancy can decrease the likelihood of excessive weight gain and the onset of gestational diabetes. However, engaging in physical activity without a clear goal in mind may affect the patient's motivation, and it's important to monitor the improvement in LDL, HDL, blood pressure and mobility to encourage patients to continue working.

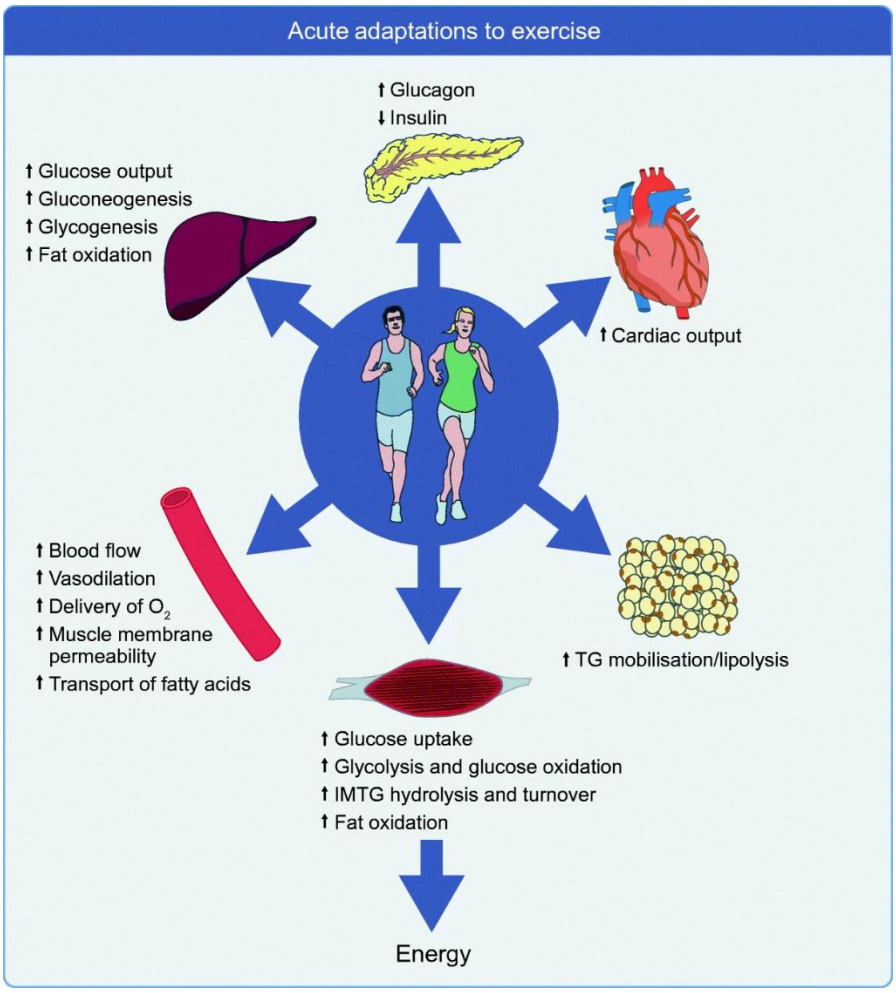

Figure 4: Both acute and regular exercise affect the metabolic rate and whole-body insulin sensitivity. Muscle contraction and energy expenditure promote the secretion of signaling molecules myokines, which have an effect on skeletal muscle mass and multiple endocrine organs. The minimal volume of physical activity required to produce significant structural, functional and metabolic adaptations is still being investigated (adapted from Thyfault and Bergouignan, 2020).

Multiple sources indicate that cigarette smoking significantly contributes to the development of chronic diseases, including cancer, diabetes and cardiovascular incidents. In the early 20th century, smoking and its related complications were more prevalent in men than women. This ratio has remained unchanged in developing countries, but rising smoking prevalence among females can be observed in developed countries in the present day. However, women still smoke fewer cigarettes per day and have lower nicotine dependence, presumably due to faster nicotine metabolism. This can affect smoking cessation pharmacotherapy with nicotine replacement products and possibly clarify lower quit rates in female smokers. It’s also

important to consider the risk factors of secondhand smoke, as it contains numerous carcinogens that may linger in indoor environments, potentially harming both human and animal health (pets).

Cancer is a group of more than 100 diseases involving uncontrolled cell growth with a wide range of etiologies. Though cancer was previously regarded as an inevitable consequence of aging, researchers have since identified potential environmental carcinogens, genetic mutations and habits that increase the risk of developing a particular type of cancer. Lifestyle interventions can play an important role in the prevention of cancer and benefit the patients currently in therapy or cancer survivors. There appears to be a strong link between obesity and cancer. The metabolic activity of adipose tissue can promote inflammation and insulin resistance, creating an environment for cancer cell growth, maintenance and progression. Physical activity has the potential to reduce levels of reproductive hormones (including their metabolites) and increase concentrations of hormone-binding globulin proteins, decreasing the risk of tumors in the reproductive system. Exercise can modify the response to leptin, a hormone secreted by the adipose tissue responsible for appetite control and energy expenditure, typically by reducing overall body fat (Bouassida et al., 2006). The combination of exercise and nutritional patterns can alter microbiome composition (increased quantity of Bifidobacterium and Lactobacillus phylum, improved Bacteroidetes-Firmicutes ratio) and intestinal mobility, decreasing the contact time between pathogens and GIT mucosa layer. These processes provide a biological link between physical activity and lower risk of colon cancer.

Stress is another risk factor for chronic disease development, affecting roughly one third of the population. Acute, life-threatening cardiovascular events and several social problems are associated with stress, affecting the wellbeing of both adults and children. The stress response is caused by the stimulation of the sympathetic nervous system, increasing heart and respiratory rate, blood supply to the muscles, body temperature and cognitive activity. Certain levels of stress might be protective, but chronic stress can decrease performance at work or home and have long-lasting health consequences. The demand for psychological therapy is increasing in modern society, and promoting positive psychology concepts and using stretching, meditation and relaxation techniques may help reduce stress in everyday life (Rippe, 2018).

4.2. Intrinsic factors and related conditions

4.2.1. Metabolism, caloric restriction and aging

In 1935 an American biochemist and nutritionist discovered that the restriction of calories without malnutrition can prolong lifespan in mice. After the initial report, early research has mostly focused on diseases and disorders caused by aging rather than the aging process itself. It was believed that caloric restriction (CR) slowed disease progression through passive mechanisms (lower rate of aging), instead of altering metabolic pathways. Recent studies suggest the mitochondria has an important role in age-related disorders, such as diabetes, cancer and neurodegenerative disease.

Intermittent fasting and protein restriction, as dietary interventions, have a well-known impact on health and resistance to stress, but the effects of CR on longevity are still unprecedented. Gene expression studies show that aging is coordinated across tissues, despite the difference in cell types and molecular patterns. CR increases mitochondrial energy metabolism and protein synthesis, while decreasing inflammatory and immune pathways via gene regulation. Body composition is also affected by CR, with a noteworthy impact on adipose tissue. There is an increase in adiponectin, a peptide hormone that promotes fatty-acid oxidation, and enhances insulin sensitivity in combination with leptin. Many of the factors affected by CR are energy sensors and nutrient sensors, including kinase and deacetylase enzymes which regulate post-translational modifications, cell signaling and metabolic balance. The stimuli can range from nutrient signaling to metabolic status indicator molecules, like reactive oxygen species, NAD or ATP. All these signaling pathways are interconnected, and this ensures a coordinated cellular response.

The effects of CR have been tested on rodents and monkeys in long-term studies with positive results. Serum risk factors and adipose tissue mass decreased, while insulin sensitivity and longevity increased across all species. There have been short-term studies on people, but compliance was a major issue and it is believed that CR will never gain wide popularity. Unfortunately, this also limits the possibility of rigorous scientific testing of the impacts of CR on human lifespan. There is, however, the opportunity to translate CR to human health in a clinical setting (Anderson and Weindruch, 2012).

4.2.2. Microbiota

When discussing overall health and nutrition, the role of microbiota cannot be dismissed. The microbial communities in the human gut and their impact on human health and disease are among the most exciting new areas of research today. However, after antibiotic treatment or enteric infection, microbiota structure may not completely recover. The estimated number of microorganisms colonizing the gastrointestinal (GI) tract is over 10^{14}, with at least 1000 different species of bacteria. The microbiota is involved in several functions that benefit the host, such as strengthening gut integrity, digestion of carbohydrates, vitamin synthesis, protection against pathogens, mucosa-associated immunity and drug metabolism. In case of altered microbial composition, also known as dysbiosis, these mechanisms can be disrupted and have a negative impact on the host's health. Gut microorganisms and greatly affected by dietary intake during the entire lifetime. While microbiota does respond to changes in the consumption of dietary fat or fiber, the levels of bacteria return to their baseline if the intervention is discontinued.

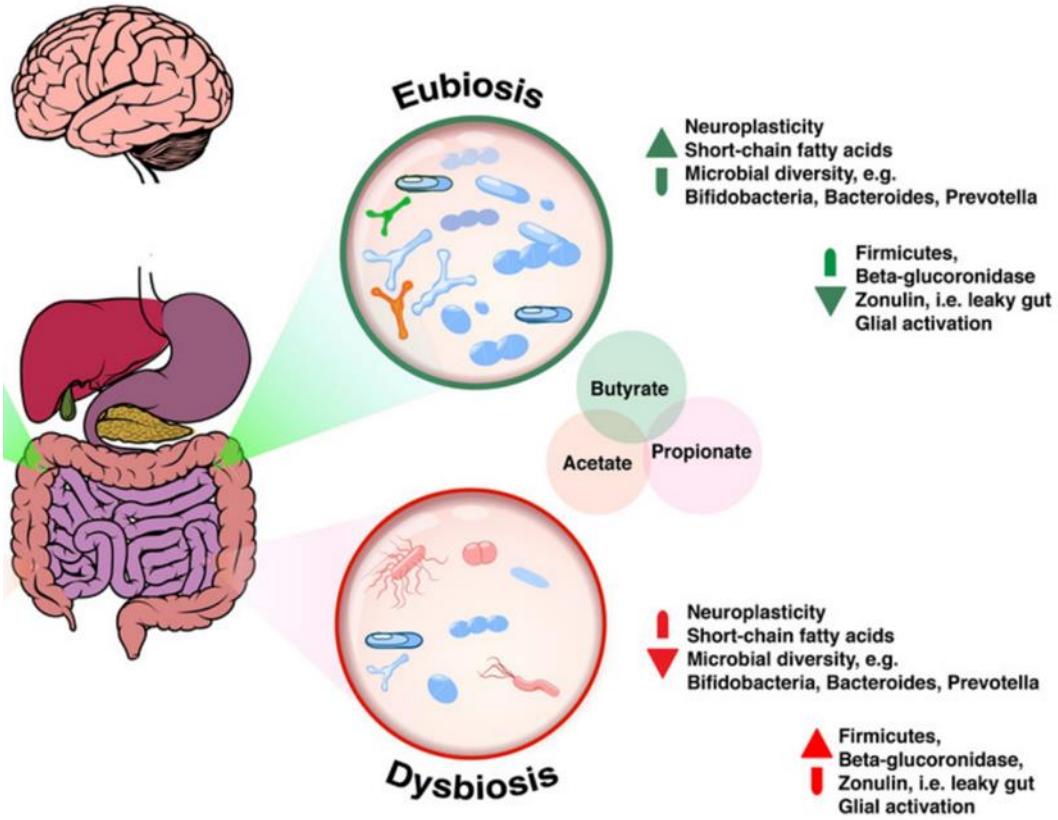

Figure 5: Mediterranean-style diet rich in fresh foods promotes eubiosis, while a diet rich in ultra-processed foods promotes dysbiosis (adapted from Toribio-Mateas, 2018).

Main theories suggest the GI system is rapidly colonized after birth, and changes during different stages of life or antibiotic treatment. When children are over 2 years old, their microbial composition, diversity and capabilities resemble those in adults. Even though different regions of the GI system have different microbial composition, in healthy individuals 90% of the total bacteria belong to Bacteroidetes and Firmicutes phylum. The remaining 10% includes Proteobacteria, Verrucomicrobia and Actinobacteria. Human microbiota is dominated by bacteria, but commensal populations of viruses, fungi, archaea and protists are present, as well. These non-bacterial microorganisms and their interaction with the host's immune system have not been as extensively studied as bacterial microbiota. Even after the introduction of culture-independent next-generation sequencing techniques (NGS), there are still limitations for identification and characterization of fungal components of microbiota. The majority of research is focused on the effects of intestinal fungi on gastrointestinal diseases and results have shown that increased levels of anti-Saccharomyces cerevisiae antibodies (ASCA) are a reliable diagnostic and prognostic biomarker for Crohn's disease.

Bacteriophages have the potential to become a therapeutic option for treating IBD due to their effect on maintaining a healthy intestinal environment. The gut virome population is dominated by bacteriophages (bacterial viruses), which contribute to virulence factors and antibiotic resistance as they outnumber the commensal bacteria. Eukaryotic virome is established through environmental exposure and provides beneficial effects to the host, despite viruses being generally considered as pathogens or opportunistic pathogens by most people. Moreover, the majority of intestinal archaea are methane-producing organisms involved in metabolic processes of the entire microbiota. A unique feature of archaea is their ability to respire hydrogen which inhibits bacterial energy production when present in high concentrations. Similar to viruses, most of the commonly encountered intestinal parasites are considered pathogenic, but certain groups have evolved to cause minimal harm and adopted a commensal lifestyle (Matijašić et al., 2020).

To survive in the gut, microorganisms have to exhibit certain phenotypic traits. As their main source of energy are carbohydrates, this includes processes like fermentation and sulphate reduction. Short-chain fatty acids (SCFAs) are the most important energy source for healthy colonocytes (epithelial cells of the colon), with butyrate, propionate and acetate as the main fatty acids. Sources of SCFAs include butter, cheese, human breast milk and fiber. The best investigated SCFA is butyrate, known for its anti-inflammatory and anticancer properties (Klement and Pazienza, 2019; Thursby and Juge, 2017).

Additionally, the gut microbiota can actively digest and utilize several biological polyphenols. The beneficial effects of dietary polyphenols have been the subject of many studies in the last two decades, and these compounds are often considered as an excellent source of prebiotics alongside fermentable fibers. A list of food and beverages rich in polyphenols includes apples, grapefruit, kiwi, green tea and red wine. The majority of plant polyphenols are present in the form of glycosides, which are cleaved (hydrolyzed) by intestinal microbiota and used as an energy source. Released glycans have greater bioavailability than their precursors and were found to modify the quantity of bacteria in favor of Bacteroidetes and suppress the growth of pathogenic bacteria. Polyphenols and their metabolites modulate various cell signaling pathways and contribute to the maintenance of optimal concentrations of cellular biomarkers related to oxidative stress. By regulating local and systemic low-grade inflammatory response, the intake of dietary polyphenols directly or indirectly reduces the risk of developing a chronic disease such as inflammatory bowel disease or cancer (Aravind et al., 2021; Verbanac et al., 2014).

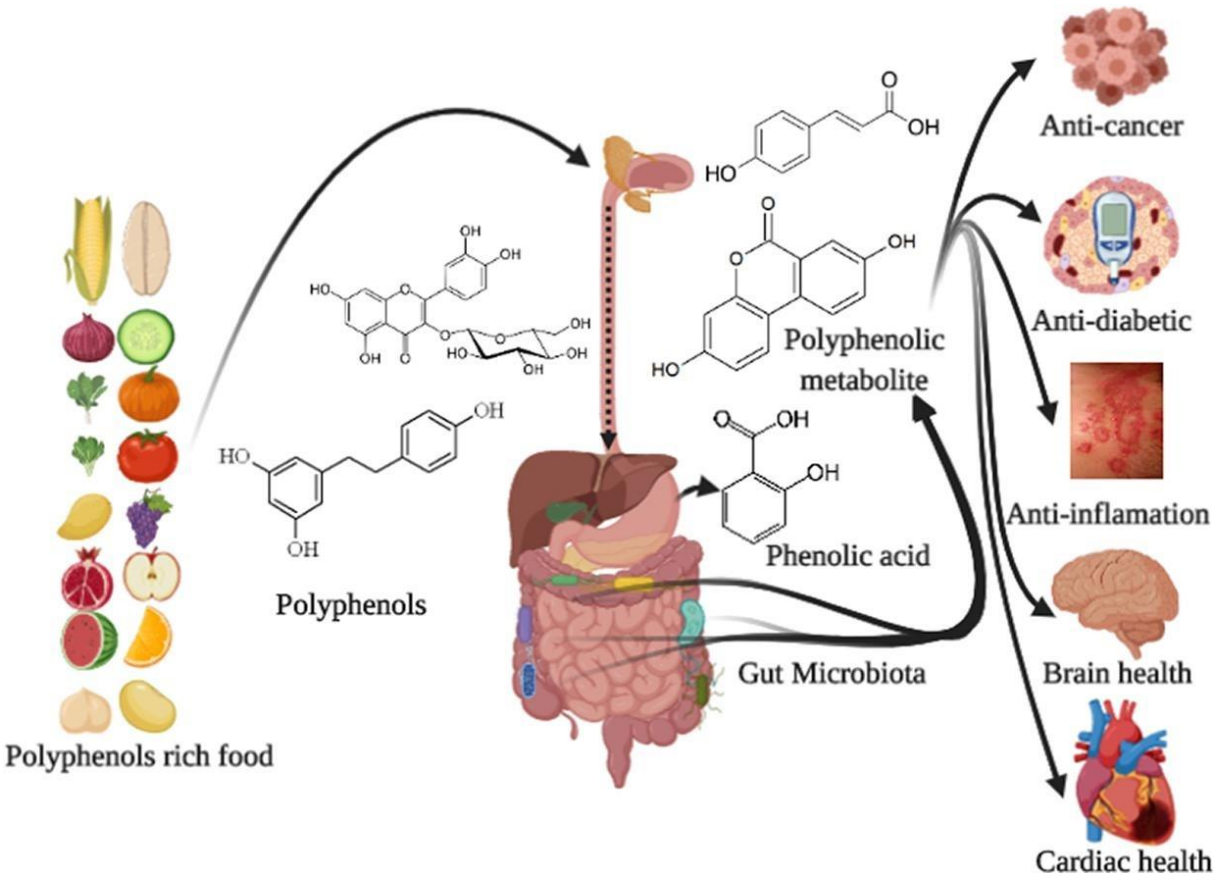

Figure 6: An illustration of the effects of dietary polyphenols on the gut microbiota and health benefits to the host (adapted from Aravind et al., 2021).

Microorganisms colonize various body environments outside the gastrointestinal tract, such as the skin, nose, mouth, genital and urogenital tract. Urinary tract infections, also known as UTIs, are among the most common bacterial infections and represent a significant burden on the healthcare system as treatment often contributes to antibiotic resistance. A wide range of pathogens can cause an UTI, usually originating from the gastrointestinal tract, but latest studies suggest there is an interplay between intestinal, vaginal and urinary microbiota. Uropathogenic Escherichia coli is responsible for over 80% of infections and increased prevalence of the bacteria in the gut can precede bacteriuria and uncomplicated or recurrent UTIs. The vaginal microbiome is seen as healthy when it's dominated by Lactobacillus species and maintaining a low pH environment, but uropathogenic bacteria can establish a vaginal intracellular reservoir if levels of protective bacteria decrease. Urinary tract has its own unique distribution of the main bacterial species, so modifying the ratio of beneficial and pathogenic species presents a challenge. However, it is worth noticing that the majority were previously isolated from either gut or vaginal microbiota. Gut microbiota dysbiosis treatment provides a promising strategy in prevention and treatment of UTIs, alongside precision antimicrobial drugs and UTI vaccines. Administration of commercially available oral or intravaginal probiotic products has provided mixed results in reducing the risk of recurrent infections (Meštrović et al., 2020).

4.2.3. Gut microbiome and inflammatory bowel disease (IBD)

Inflammatory bowel disease, abbreviated as IBD, is a group of chronic inflammatory conditions of the gastrointestinal tract. The two main clinical types are ulcerative colitis and Crohn's disease. Ulcerative colitis is limited to the colon, while Crohn's disease can affect any part of the GI tract. While early research was focused on the immune dysregulation and genetic susceptibility to IBD, recent technological advancements can study the influence of diet and microbial exposure. High-throughput microbial sequencing and anaerobic bacterial culturing techniques are necessary to identify bacterial strains in the GI system, instead of standard culture-based tests. By analyzing microbial distribution and their metabolic activity, potential IBD biomarkers can be identified earlier in the diagnostic process, allowing patients to be stratified more precisely and treated with more efficient therapeutic options.

There is a notable difference between microbial diversity in IBD and healthy individuals. The number of bacteria that belong to Proteobacteria phylum increases, while the

number of Firmicutes decreases. This change in bacterial composition can have direct effect on disease progression as some bacteria in Firmicutes phylum, particularly *Faecalibacterium prausnitzii*, secrete factors that counterbalance intestinal inflammation. Several strains of bacteria also effectively induce regulatory T-cells in the colon to suppress inflammation, while the interaction between Th1 and Th17 has a pro-inflammatory effect (Viladomiu and Longman, 2017).

Macronutrients have a major impact on gastrointestinal health since, through eating and digesting, we nourish our gut microbiota, which influences its diversity. Although a disrupted microbial equilibrium can have many causes, such as infectious pathogens and/or use of antibiotics, the role of our daily food and lifestyle is invaluable. Research suggests bacterial composition can change after only two weeks of high-fat, low-fiber Western diet. An example is proliferation of *Fusobacterium nucleatum*, which is an invasive species prevalent in both IBD and colorectal cancer. Disturbed microbiota balance can cause various disorders including functional intestine disorders, inflammatory bowel diseases, and other immune-mediated diseases, such as celiac disease and specific allergies. Over the years, metabolic conditions, such as type 2 diabetes, and recently even behavioral disorders, such as autism and depression, were reported to be linked to gut microbial imbalances (Klement and Pazienza, 2019). At the same time, a diet rich in olive oil, vegetables, salads and fruits, rich sources of bio- and polyphenols has proven to be beneficial in maintaining health. The same applies to fermented dairy products containing pro- and prebiotics.

Recent literature proposes various dietary approaches to regulate nutrient deficiencies and the severity of IBD as alternatives to complement pharmacological treatments. Exclusive enteral nutrition (EEN) is a specialized liquid formula that was found to be effective in pediatric patients with Crohn's disease and increase their quality of life by promoting mucosal healing, weight gain and vitamin D absorption. Over the years, several diets restricting the intake of complex carbohydrates and processed sugars have become popular with IBD patients, most notably the low-FODMAP diet. The main downside of these dietary interventions is the reduction in overall caloric intake in patients who are already at risk of malnutrition. To produce favorable therapeutic response, researchers suggest using dietary interventions alongside supplements like pro-, pre- and synbiotics or more advanced options like fecal microbiota transplantation (FMT) and treatments with helminths ova (based on the "hygiene hypothesis", the prevalence of autoimmune disorders is reversely correlated to human exposure to childhood pathogens) (Matijašić et al., 2016).

4.2.4. Gender medicine

There are several studies that use the term “gender” and some use “sex” to indicate men and women, which can cause confusion. The term sex refers to biological and physical characteristics, while gender usually refers to behaviors, roles, expectations and activities within socially constructed norms. However, it should be noted that sex and gender work together and both affect health. Sex and gender can cause different pharmacological responses, which depend on various factors such as molecular structure, social factors and environmental stress (Mauvais-Jarvis et al., 2020).

There is a difference in how frequently men and women use the healthcare system. Women receive less total joint arthroplasty, despite osteoarthritis being more prevalent in women. Women also receive less treatment for end-stage kidney disease and younger women with acute coronary syndrome don’t have the same access to healthcare compared to men with the same condition. There is a disparity in emergency recognition of ST-elevation myocardial infarction in women, with delayed reperfusion leading to higher mortality (Franconi and Campesi, 2017). The mortality rate is lower in women treated by female physicians or when female colleagues are present in medical teams. However, women themselves often underestimate their risk of cardiovascular incidents, seeking clinical consultation and treatment later than men. This might be due to different presentations of myocardial infarction in women, who are more likely to experience pain between the shoulder blades, shortness of breath, nausea and vomiting alongside chest pain. On the other hand, men are more likely to develop obstructive coronary artery disease of larger vessels. Racial and ethnical aspects affect healthcare as well, and people of African-American or Hispanic origin receive poorer quality treatment on average.

There are several differences between men and women in medicine, neuroscience and sociology. Sex and gender affect a wide range of physiological functions, creating differences in cardiovascular and immune systems, as well as many others. Women seem to have a higher prevalence of neurological disorders, including depression and Alzheimer’s disease. Immune response to viral infection is stronger in women, and estrogen receptor signaling could be the potential cause and therapeutic target. Estrogen has an anti-inflammatory effect on endothelial and immune cells, causing women’s hearts to develop less inflammation under stress, while testosterone induces cardiac tissue remodeling resulting in more fibrosis. Hypertension is less

common with premenopausal women, but increases after the age of 60 and even surpasses the incidence seen in older men (Pettengale, 2017).

Stroke as a cause of death is more common in women than men, mostly due to the fact that women live longer. Ischemic stroke is the most prevalent type, while women are more susceptible to hemorrhagic stroke. Men have a higher incidence of stroke in childhood and early adulthood, but stroke rates increase in women after middle-age due to obesity, adverse lipid profiles, diabetes, contraceptive use and hypertensive disorders of pregnancy like pre-eclampsia. Aspirin is recognized as a drug in primary prevention of stroke and is considered more effective in men than women. Unfortunately, thrombolysis and thrombectomy as acute ischemic stroke therapies are not often performed on women due to age and fragility, despite the possible benefits.

Cancer has a slightly higher prevalence in men, in all races and at all ages. Survival rates are lower for men across multiple cancer types, even after adjustment for risk factors such as dietary habits, smoking and alcohol consumption. Sex-specific cancer biology indicates a predisposition of male astrocytes to malignant transformation and subsequent development of glioblastoma, while aggressive phenotypes of hepatocellular carcinoma can be linked to stimulatory effects of androgens. Future cancer treatment and therapy will require sex-specific and gender-specific approaches, as metabolic regulation and cellular nutrient partitioning is different in men and women, affecting approaches like ketogenic diet and glutaminase inhibition. In men with advanced melanomas and non-small cell lung carcinoma, immune checkpoint inhibitors are considered to improve survival compared to women with the same conditions.

Women are twice as likely to develop chronic obstructive pulmonary disease at a younger age with less tobacco exposure and chronic bronchitis, while emphysema has similar prevalence in both men and women. There is a high possibility of misdiagnosis in younger women, who also disproportionately suffer from comorbidities such as anxiety and depression. Asthma is more prevalent in boys before puberty, but from puberty onwards more women have asthma. During therapy, it should be taken into account that estrogens increase asthmatic inflammation while androgens reduce it, and bronchodilators for women should target M2 muscarinic receptors as their expression in the lungs of female patients is higher.

During the prediabetic phase, impaired glucose tolerance (postprandial) is more prevalent in women, while impaired fasting glucose is more prevalent in men. Though the

absolute rates of cardiovascular disease are higher in men, women with type 2 diabetes can have more advanced atherosclerosis and severe consequences (ischemic heart disease, stroke, dementia). However, hypertension and diabetes are the most common causes of chronic kidney disease in men, and the majority of patients undergoing dialysis are men. Other important disabling disorders with high prevalence in men include Parkinson's disease and autism spectrum disorders, whereas autoimmune diseases, migraines and eating disorders are more common in women. In addition, it's alarming how working-age men have high premature mortality, probably due to poor lifestyle choices and being socially conditioned to neglect pain, therefore missing routine checks which results in higher hospital admission rates (Mauvais-Jarvis et al., 2020).

There appears to be a difference in physicians' preventive practices according to both professionals' and patient's gender. Overall, men receive preventive care more often than women, but the physicians delivering preventive practices are predominantly female. This positive influence of female physicians in the area of prevention has several sociological explanations. Women in the medical world may want to follow specific guidelines, record their practices and express concern about consequences, as obedience and efficiency is promoted throughout their education. Nevertheless, preventive care disproportionately favors male patients, while recent studies demonstrated diabetes as a cardiovascular risk factor and smoking as a risk factor for lung cancer have more negative effects on women. Whether male patients receive more preventive care due to epidemiologic evidence or because they are considered less informed and less aware of risks is open to debate. The approach to prevention and patients' risky behavior is rarely gender neutral, affecting medical activities (Delpech et al., 2020).

Clinical trials are problematic since, historically, women have been excluded from medical research to protect them and their future offspring. Despite the fact that, on average, women consume more drugs than men, the patients involved in clinical trials are mostly men. The results from such studies are sometimes applied to women without prior critique, leading to errors in drug administration and injury. Pharmacokinetics are also different in men and women. Men have lower gastric pH, faster renal function, more muscle tissue and water, while women have slower gastric and enteric mobility, slower renal function and a higher amount of adipose tissue. Sex hormones modulate all pharmacokinetic parameters, and drug doses have to be adjusted for pregnant, premenopausal and postmenopausal women.

Adherence to therapy is problematic for both men and women, as approximately 50% of chronic patients don't take their medication as prescribed. Compliance is worse in individuals

with lower socio-economic status and patients taking multiple drugs. Lifestyle also influences drug response, as dietary habits are different between sexes, and women are more vulnerable to the toxic effects of alcohol and tobacco use. Alcohol and nicotine have different metabolic pathways between sexes, and both can modify pharmacokinetic parameters and safety profiles of drugs. Unfortunately, there is still not enough evidence-based knowledge on how sex and gender influences therapy, and more precise sex-based and gender-based approach is needed in the future (Franconi and Campesi, 2017).

4.3. Preventive medicine in the landscape of responsible research and innovation (RRI)

Responsible research and innovation (RRI) is a science policy framework, emerging around the year 2010 and appreciating support by the European Commission. Although various slightly different definitions of RRI exist, its aim is to ensure that research purpose, development process and research outcomes are acceptable, sustainable and desirable for the environment and society. The support for the implementation of key aspects of RRI is growing in the community. However, established research and innovation practices often resist the change necessary for the full implementation of the RRI principles. It is challenging to present RRI principles incorporating wider stakeholder groups and publicly funded research as a benefit to private companies. Regardless, innovation should never prioritize increasing profit for the company above the interest of their consumers (Stahl et al., 2017). One of the recent innovations following this principle are telemedical, continuous diabetes monitoring systems, which offer precise, real-time information to both patients and their physicians. This case study demonstrates that the integration of RRI principles benefits multiple stakeholders, including health insurance and medical technology companies. The development of telemedical devices and open access services enables early screening, prevention and intervention for diabetic patients, which helps avoid consequences of severe glucose level fluctuations, especially in children or elderly (Karsten, 2018).

There are different ways in which the adoption of RRI can enhance company performance and employee satisfaction. Applying RRI principles could improve communication with stakeholders, including customers, to ensure the company's final product or service would meet societal and regulatory expectations and requirements. Companies and their employees carry different responsibilities and follow practices which may or may not align well with RRI. This could be evaluated systematically with maturity models, allowing companies to engage with RRI, receive feedback and target areas in need of improvement.

Research ethics is another component of RRI, protecting human and animal participants from harm and misuse. Informed consent and confidentiality of medical and genetic data is an important concept in research ethics, alongside controversial topics such as the involvement of children or the use of human embryonic stem cells. Besides ethical standards, RRI implies

gender equality, open access publication and science education. When implementing RRI into the education system, college students should be encouraged to interact with an audience as scientists, practicing their communication skills and reflecting on potential social benefits of their future research. A more challenging and ambitious goal is including the general public in the scientific discourse, in the hope of receiving a more favorable response to research projects (Demers-Payette et al., 2016). Research topics are therefore chosen to reflect the current social concerns, including greater challenges like water and food production or aging societies.

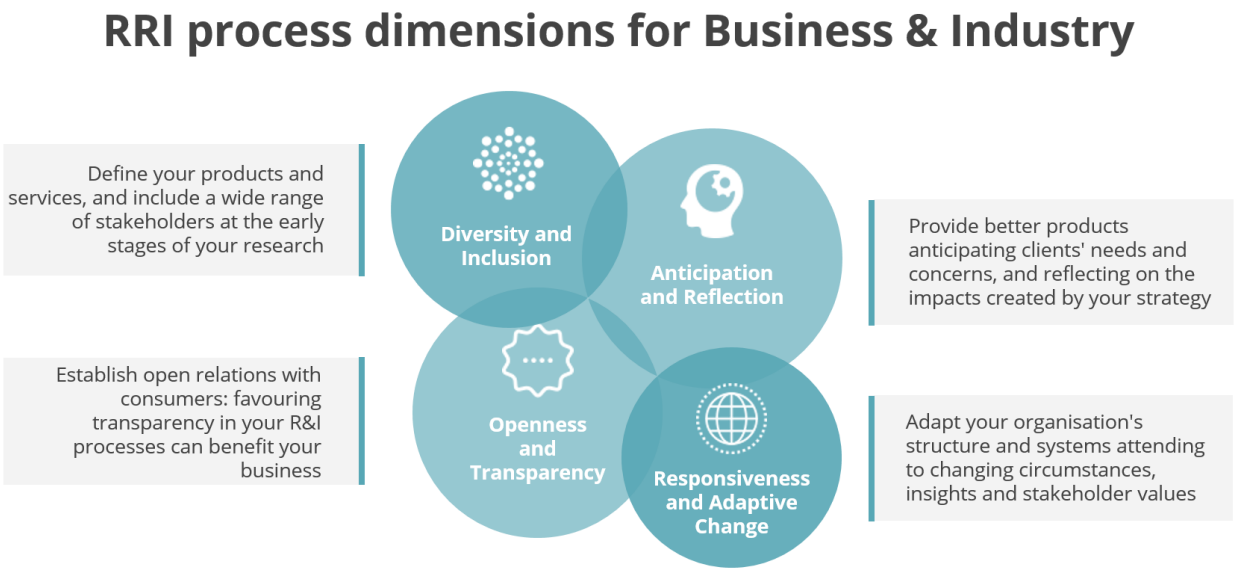

Figure 7: An overview of the principles of responsible research (rri-tools.eu)

Anticipation, engagement, reflection and responsiveness are important activities in the RRI process. Scientists should be able to anticipate the impact of research and technology on society and approach the matter in alternative ways if deemed necessary, even without public participation. When introducing new procedures or technologies into society, such as genetically modified organisms (GMO), it is important to judge the present social conditions rather than focus on potential future benefits. The introduction of GMO could either strengthen or undermine the confidence of local farmers in the global food industry and have a lasting impact on compliance. However, responsible research has to find a balance between following reliable scientific information, serving people's aspirations and correcting expectations (Carrier and Irzik, 2019).

Preventive medicine is a new form of healthcare and simultaneously an innovative form of clinical research (Silva et al., 2018), and therefore includes anticipation, engagement, reflection and responsiveness. Due to the variability in the patient population, it is to be expected that new treatments may be ineffective or cause adverse reactions in some patients. This risk assessment and issues beyond compliance are part of the anticipation activities. Surveys suggest a high percentage of people are willing to participate in medical research studies focused on specific conditions, particularly cancer, heart disease, addiction and depression (Nass et al., 2009). Participants' and users' satisfaction is vital in determining whether RRI activities are effective and by prioritizing social benefits during development, companies can ensure that their products or services are received more positively and accessible to more patients. Reflection and responsiveness activities include improving the final product either voluntarily or through user feedback. When developing mobile health applications, user engagement can be identified through data mining and quality issues can be modified to facilitate longer use, consequently providing better health outcomes. However, it is important to preserve transparency about how the patient's data is used through the informed consent process (Stahl et al., 2017).

Some of the producers of new medical devices and pharmaceutical products, fail to appropriately consider end-users during their development process, so social and environmental consequences are assessed only after the product is fully developed. Introducing the concept of responsible medical innovation can offer solutions to current challenges in the healthcare system. RRI strategies should seek to anticipate and minimize potential risks, while remaining flexible towards associated opportunities. Dissemination of new medical technology must also be evaluated as it can impact human resources and patients, creating new therapeutic targets and the need for further medical training (Demers-Payette et al., 2016).

4.3.1. The value of dissemination in the research process and practice

Dissemination and implementation (D&I) theories and models provide a systematic way to understand and utilize evidence-based approaches in healthcare and education. Dissemination is the act or process of distributing evidence-based interventions to a target audience, leading to widespread use. Theories provide a systemic way of interpreting events or behaviors, while frameworks are strategic or action-planning models, and both help interventions focus on behavioral change. Incorporating theories and frameworks in D&I research ensures interpretability of study findings and implementation of strategies in real-world practice. The work in D&I originated in various industries and disciplines several decades ago, but has since found its place in medicine, public health and psychology. Tobacco control programs and school-based drug use prevention programs are notable examples of translation from research to practice, displaying mixed results.

Models used in D&I science are different from the simple dissemination at the end of the research study, with a press release or peer review. Different designs affect whether models can be used by researchers or clinicians, communities and organizations or on a national level. Broad models have loosely defined concepts and allow more flexibility with D&I activities, while operational models provide detailed guidance for each step of D&I research processes. Researchers can opt to use an existing model and adapt it accordingly, or develop an original model which addresses a gap in the current literature. Factors such as social status, geography, language and culture should be considered when adapting models to specific populations or settings, along with technological resources needed for distributing knowledge (high-speed internet, digital literacy). Modifications like wording, timeline or cultural preferences can be made without hesitation, but core elements and communication models should not be compromised without substantial evidence (Tabak et al., 2012).

Dissemination is considered an important tool in disease prevention and improving public health, since research products are not consistently applied to practice despite funding and staff effort. Insight from researchers and practitioners suggests important, but simple competencies are missing from D&I science training. Research findings should be disseminated beyond academic communities, through compelling ideas tailored for practice and written in simple language. There is a high demand for communicating results through social media, press releases and marketing, with various options such as online video broadcasts and open lab days.

To enable productive discussion of emerging policy issues, scientific communities and industry stakeholders should be motivated to empathize and improve communication and active listening skills. Partners and practitioners should be able to build lasting partnerships to ensure full implementation, with regards to the priorities of various stakeholders (economic companies, patient groups) (Tabak et al., 2017). Dissemination between generators of evidence and public health practitioners is an ongoing challenge, with a major barrier being the lack of access to journals (Brownson et al., 2018).

Evidence-based programs and interventions should offer flexible adaptation and sustainability. During the research process, young scientists should be trained in qualitative research methods, data analysis and data collection in realistic settings. Interdisciplinary teams should be built to enable diffusion of innovation and related theories, as well as offer new perspectives. Teams make fewer mistakes than individuals and complete objectives more rapidly, increasing performance. This practice will ensure that research is productive and relevant throughout all stages, which is an important concept in the education of trainees and students.

Some of the challenges that need to be addressed in future research are the lack of consistency in terminology, as well as the evaluation of constructs included in models and intervention efforts. Innovative dissemination implicates going beyond traditional academic journals and conference presentations, actively educating the population about research findings. Scientists who are less versed in D&I research and practitioners can benefit from the knowledge D&I science provides as well, allowing them to provide the best care to their participants and patients (Tabak et al., 2012). Researchers' dissemination efforts are often motivated by their department, employer or funder, while reporting to an audience outside the scientific community holds a non-monetary, subjective value (social recognition, reputation). Scientists should not be driven solely by grants and funding, but their intellectual curiosity as well. Encouraging these subjective exchange values can improve the dissemination process and provide multiple benefits for society (Beck et al., 2019).

Cancer prevention and control initiatives are a great example of areas in need of improvement. There is a large gap between evidence and practice on a global scale, with approximately 60% of overall cancer deaths occurring in developing countries annually. This data can be applied to breast cancer cases, and interventions are needed to raise awareness and promote education, early detection and treatment quality. D&I frameworks are an especially relevant tool in enhancing the effectiveness of cancer control programs, as they provide

information on factors that influence implementation success and quantitative metrics. To improve breast cancer care in developing countries, it is important to assess local providers' knowledge on diagnosis and treatment, along with general community awareness through surveys or interviews. The results are shared with a diverse stakeholder group, including patient representatives and leading oncology departments, whose role is to identify and adapt the approach with most benefits for patients in the region. D&I also offer tools to evaluate potential implementation outcomes, so financial barriers don't affect the success of healthcare interventions and clinicians are provided with proper education to implement new programs. D&I research adopts a different approach from clinical or epidemiologic research, addressing local context and stakeholder perspectives to ensure interventions are not only theoretically useful, but acceptable, cost-effective and sustainable. To minimize global disparity in cancer mortality, future research should be aimed at identifying interventions to ensure easy access and effectiveness of prevention, diagnosis and treatment programs in developing countries and their local communities (Rositch et al., 2020).

4.4. Potential challenges for the implementation of preventive and precision medicine

As the total population and the percentage of the aged population increases, so does the strain on the healthcare system. New platforms need to be developed to allow for deeper collaboration of physicians, laboratory specialists, nurses and pharmacists. This will enhance the quality of healthcare and patient satisfaction, as clinical teams will be more focused on patient outcomes rather than bureaucracy (Greaves et al., 2019). However, larger amounts of data needed for the personalized approach increase the demand for healthcare administration staff who can organize incoming data from self-monitoring and data generated in a clinical setting. There is growing unease about the potential misuse of emerging technological capabilities and reducing patients' identities to their genetic backgrounds (Flores et al., 2013). The quality of entered data and patient privacy are legitimate issues as well.

Some scientists have expressed their concerns about the economic impact of precision medicine. Innovative technologies come with additional cost of reagents, continuous education of pathologists and data storage costs. Nevertheless, some argue that a medical test which can be performed cheaply, but doesn't influence patient care presents a waste for the whole healthcare system. Targeted therapy is expensive, but cost-effectiveness of treatment is increased by identifying patients who will most likely respond favorably and whose survival will be improved. Some studies show precision medicine can reduce inpatient hospitalizations and emergency department visits. Additionally, preventive interventions and lifestyle changes can reduce costs associated with treatment, thus allowing resources to be allocated to patients In need of expensive therapy (Doble, 2016).

5. CONCLUSION(S)

- P4 (predictive, preventive, personalized, participatory) medicine is soon expected to become the main approach in chronic disease management. Introducing the practice of preventive medicine will enable earlier medical intervention and completely prevent or delay disease onset and progression.
- Preventive healthcare strategies can be primordial, primary, secondary, tertiary or even quaternary depending on the patient's age, presence of risk factors and diagnosis. After the onset of disease, preventive strategies can be utilized to improve the patient's quality of life, avoid complications and decrease the possibility of excessive medicalization.
- The concept of translational research ensures models or products developed by researchers reach clinical and industrial practice levels.
- Noncommunicable diseases (NCDs) present a financial burden for both the healthcare system and global economy. An increase in the prevalence of metabolic disorders and low-grade inflammation can be attributed to the rising prevalence of the Western diet and lack of human genetic adaptation.
- The Mediterranean diet is viewed favorably by many researchers interested in preventive cardiovascular medicine. Unlike the vegetarian or keto diet, the Mediterranean diet does not exclude specific food items or limit calories which improves patient adherence.
- Obesity, hypertension and diabetic kidney disease are major candidates for precision medicine because multiple biological and non-biological factors need to be considered for effective prevention or disease management. In some patients, limiting tobacco use and improving physical activity, nutrition and mental health can reduce the incidence of chronic disease by 80%.
- Short-chain fatty acids (SCFAs) and polyphenols are an invaluable energy source for gut microbiota and have been known for their anti-inflammatory and antioxidative properties. Intestinal, genital and urogenital tract can either represent a reservoir of pathogenic bacteria or play a protective role against various inflammatory conditions such as IBD or UTI.

- Caloric restriction without malnutrition has the potential to increase longevity and improve general health. Supplementation with pro-, pre- and synbiotics can improve gut bacteria composition. Microbiome-directed therapy is still evolving and databases for reliable identification are still being generated, particularly for non-bacterial microorganisms.
- Women seem to have a higher prevalence of autoimmune diseases, Alzheimer's disease and eating disorders, whereas cancer, Parkinson's disease and autism spectrum disorders are more common in men. Additionally, male patients seem to receive more preventive care, while female physicians seem to deliver preventive care more consistently.
- Responsible research and innovation (RRI) models evaluate the objectives and consequences of technological innovation during the development process. Creating a partnership between publicly funded research, private companies and large stakeholder groups is necessary to ensure there is a balance between consumer (patient) satisfaction and commercial impact, instead of profit being the main focus.
- Dissemination and implementation (D&I) frameworks can enhance disease control in developing countries. By addressing local providers' and stakeholders' perspectives, theory-based interventions can be successfully applied to clinical practice, and remain useful, sustainable and cost-effective in the future.
- The use of advanced technology and continuous medical education will not transform healthcare from reactive to P4 if the patients are not interested in managing personal health and willing to provide lifestyle data. Protecting patients' and consumers' personal data is one of many challenges of modern society, and it cannot be avoided without stalling scientific and technological progress altogether.

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7. SAŽETAK/SUMMARY

7.1. Sažetak

U kliničkoj praksi se relativno nedavno počelo pridavati više pozornost uzrocima bolesti nego simptomima, dok znanost i tehnologija napreduju puno brže. P4 medicina predstavlja originalan pristup liječenju te obuhvaća procese predikcije, prevencije, personalizacije i participacije. Koncept prevencije može se primijeniti na razini pojedinca ili šire populacije, s ciljem promjene životnih navika koje dovode do razvoja kroničnih degenerativnih bolesti. Na globalnoj razini pristupi prevenciji su raznoliki, od javnozdravstvenih kampanja i edukativnih nastavnih programa do povećanja poreza na pojedine proizvode.

Dob, spol, metabolizam, razina fizičke aktivnosti i stresa te način prehrane bi se trebali uzimati u obzir pri određivanju preventivnih opcija prilagođenih pacijentovim navikama, dijagnozi i terapiji. Dostupnost brze hrane i rasprostranjenost zapadnjačkog načina prehrane predstavlja značajni rizik za razvoj hipertenzije, otpornosti na inzulin i pretilosti. Unos hrane utječe na sastav crijevne mikrobiote i može poticati razvoj patogenih vrsta, a posljedice se mogu odraziti na druge organske sustave (urogenitalni sustav, živčani sustav itd.).

Uspješno uvođenje koncepta prevencije i novih terapijskih mogućnosti u kliničku praksu ovisi o kvaliteti procesa translacije i diseminacije, koji bi se trebali prilagoditi financijskim i obrazovnim mogućnostima ciljane populacije. Novi pristupi zdravstvu trebali bi omogućiti pružanje najbolje moguće skrbi pacijentima te im poboljšati kvalitetu i duljinu života, a ne težiti povećanju profita i marketingu. Uvođenje koncepta preventivne medicine predstavlja etički, društveni, ekonomski i akademski izazov, ali može višestruko doprinijeti unaprjeđenju zdravstvenog sustava.

7.2. Summary

Clinical practice has recently started progressing towards treating the cause instead of symptoms of disease, while research and technology are moving more rapidly. P4 medicine is an innovative approach to healthcare, encompassing prediction, prevention, personalization and participation. Prevention strategies can be applied to individual patients or the larger population, targeting lifestyle choices that increase the risk of developing chronic diseases. Worldwide the approaches vary depending on the country, from public health campaigns and school-based programs to higher health taxes.

Various factors like age, gender and metabolism, physical activity levels, stress and nutrition should be considered in the process of prevention, diagnosis and treatment. The abundance of fast food and the widespread Western diet present a major risk factor for hypertension, insulin resistance and obesity.

Dietary intake affects gut microbial composition and potentially promotes the growth of pathogenic species, which can have long lasting consequences for multiple organ systems (urogenital tract, nervous system, etc.). Successful implementation of preventive strategies and therapeutic options developed by researchers depends on the quality of translation and dissemination, so patients and clinicians aren’t limited by financial and academic barriers.

New initiatives should focus on optimal patient care, improved survival and quality of life instead of profit and marketing. Introducing preventive medicine to routine clinical practice presents an ethical, social, economic and intellectual challenge, but has the potential to transform healthcare for the better.

8. ABBREVIATIONS

ACEIs - angiotensin converting enzyme inhibitors

ASCA - anti-Saccharomyces cerevisiae antibodies

ATP - adenosine triphosphate

BMI - body mass index

BMR - basal metabolic rate

CR – caloric restriction

CRP – C-reactive protein

D&I - dissemination and implementation

DNA - deoxyribonucleic acid

FODMAP – fermentable oligosaccharides, disaccharides, monosaccharides, and polyols

FMT - fecal microbiota transplantation

GIT – gastrointestinal tract

GMO - genetically modified organisms

HDL - high-density lipoprotein

IBD – inflammatory bowel disease

LDL - low-density lipoprotein

NAD - nicotinamide adenine dinucleotide

NCD - noncommunicable disease

NGS - next-generation sequencing techniques

RAS - renin-angiotensin system

REE - resting energy expenditure, also known as resting metabolic rate (RMR)

ROS - reactive oxygen species

RRI – responsible research and innovation

SCFAs - short-chain fatty acids

UTI – urinary tract infection

WHO - World Health Organization

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PREVENTIVNA MEDICINA

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PREVENTIVE MEDICINE

Iva Ušić

SUMMARY

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