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Personalized Nutrition and Precision Foodomics as Applicable to Pediatric Services

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ABSTRACT

The impact of nutrition on human health begins before conception and continues throughout life. Pregnancy, childhood and adolescence are critical stages for growth and development. As such, diets during these stages must maintain a balance between environmental sustainability and optimal health outcomes for them. Integrated approaches such as multiOMICS and transomics

represent new trends in child health and Personalized Nutrition (PN). It is the associated individual's genetic, phenotypic, medical, nutritional and other important information, which is intended to pitch specific healthy eating and nutritional guidance as per need. The PN concept involves a deep understanding of the complex molecular interplay between genetic makeup and environmental (exposomal) factors, including nutrition, metabolism and diet, in an individual or group of consumers. Integrated approaches such as multiOMICS and transomics represent new trends in child health and PN. In this review, we examine common conditions in children, such as obesity, type 1 and 2 diabetes mellitus and celiac disease, as well as the actual and potential impact of personalized nutrition protocols in correcting health states.

Keywords: Personalized and precision medicine, Obesity, Type 2 diabetes mellitus, Celiac disease, Multi-omics, Microbiota

1. Introduction

Nutritional disorders have become a major public health issue, requiring increased targeted approaches. Personalized Nutrition (PN) adapted to individual needs has garnered dramatic attention as an effective way to improve nutritional balance and maintain health. With the rapidly evolving fields of OMICS technologies (including genomics and Nutriogenomics), accumulation of genetic variants has been reported to alter the effects of nutritional supplementation, suggesting its indispensable role in the genotype-based PN (Figure 1). Furthermore, the metabolism of nutrients could be improved via advanced genomics, thus paving the way for the transition of conventional generic approach to genotype-based PN. So PN tailors' general population-based nutrition advice to a particular person's needs and preferences while considering unique characteristics like individual lifestyle, socioeconomic status, race or ethnicity, health history, DNA and gender[1,2]. Specific nutritional recommendations begin with a comprehensive nutritious assessment and routine laboratory testing and then move on to more particular OMICS-driven lab testing. Those detailed tests delve into how food and nutrients interact with an individual's personal biology, potentially shedding light on their PN needs.

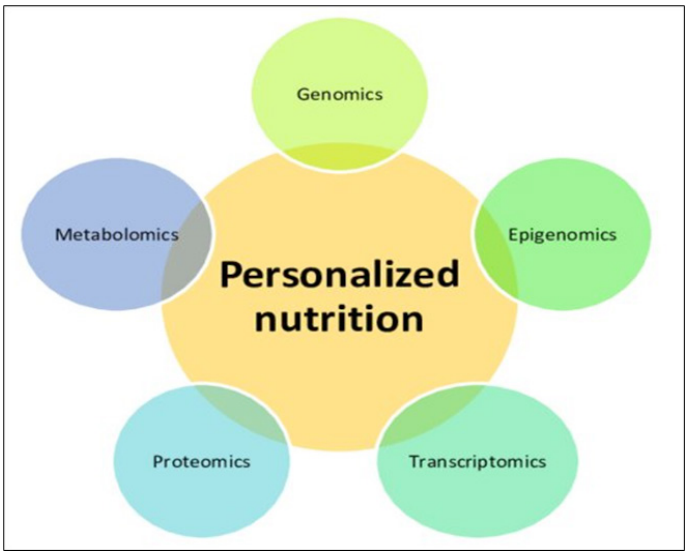

Figure 1: Personalized Nutrition (PN) with a multi-OMICS approach.

Human nutria-OMICS combines food sciences with OMICS focused on the genome of each individual, to take advantage of inter-individuality to promote nutritional strategies that prevent, manage and treat diseases and optimize health. OMICS is therefore essential to develop PN, which will continue to grow in the future[3].

Over recent decades, there has been a notable rise in the prevalence of numerous chronic ailments, such as respiratory, allergies, autoimmune, metabolic and psychiatric disorders, particularly in developed nations. This trend stems from alterations associated with urbanization in lifestyle and exposure to environmental factors, including biodiversity and chemical agents[4]. Increasing exposure to diverse toxicants and pollutants, such as polyaromatic hydrocarbons, microplastics and endocrine disruptors, poses significant threats to immunological and endocrinological balance, either directly or indirectly through their impact on environmental or human microbiomes[5]. Furthermore, the rapid pace of environmental and lifestyle changes has surpassed the immune system's ability to adapt, leading to potential risk factors such as microbial imbalances (gut dysbiosis), chronic immune dysfunction and low-level inflammation, which can predispose individuals to various diseases[6].

Notably, many of these risk factors are hypothesized to be common across multiple Non-Communicable Diseases (NCD). Among the array of noncommunicable diseases, Immune-Mediated Diseases (IMDs) stand out, which present a substantial medical, economic and societal burden due to their escalating prevalence. IMDs are characterized by their prolonged duration and considerable decline in both quality and potential lifespan. These conditions arise from the breakdown of immunological tolerance towards self-antigens (autoantigens) or innocuous environmental anti-gens (e.g., allergens, commensal bacteria), eliciting inflammatory responses and cellular damage. Prominent examples of IMDs include allergic diseases, asthma, Diabetes Mellitus Type 1 (DMT1) and Celiac Disease (CD)[7]. There currently exists no definitive curative intervention for IMDs, except for in certain allergy cases wherein allergen desensitization treatments can mitigate symptoms. Moreover, other therapeutic modalities offer symptomatic relief without providing a permanent resolution or complete mitigation of long-term complications. Since contemporary therapies for IMDs are associated with substantial financial burdens and adverse effects, a gap exists between addressing the prevention of IMDs or the amelioration of its symptoms and more efficacious strategies. Advances in 'OMICS' technologies provide an approach in carrying out personalized treatment, emphasizing its importance in current healthcare[8,9].

Advancing preventive measures require a comprehensive comprehension of disease mechanisms, encompassing pivotal molecules and pathways. As per prevailing consensus, these mechanisms begin to operate during early life stages, including the prenatal period, during which the initial subclinical manifestations of IMDs frequently emerge, coinciding with

the rapid maturation of the immune system from an immature state to its adult state. In this context, the interaction be-tween the indigenous microflora and the child's developing immune system is of particular significance, as they emerge as the most auspicious focal points for preventive interventions. The escalation in the occurrence of IMDs should be attributed solely to genetic predispositions, but environmental factors, encapsulated within the exposome framework exert a valuable influence.

The exposome (Figure 2), typically categorized into three interrelated domains, delineates the non-genetic determinants of disease onset, encompasses environmental stimuli impacting individuals from conception onward. The exposome comprises the general external factors, which encompass socioeconomic, climatic and residential conditions, the specific external factors, which cover pollutants, infectious agents and lifestyle choices and the internal exposome, which include endogenous factors such as the microbiota composition, inflammatory responses, metabolic processes and hormonal balance[10]. Exposomic modulation of early life encompasses factors that can either predispose to or safeguard against diseases. The equilibrium among these exposures, coupled with the host's differential response influenced by genetic and epigenetic factors, ultimately dictates the initiation of disease pathogenesis[11].

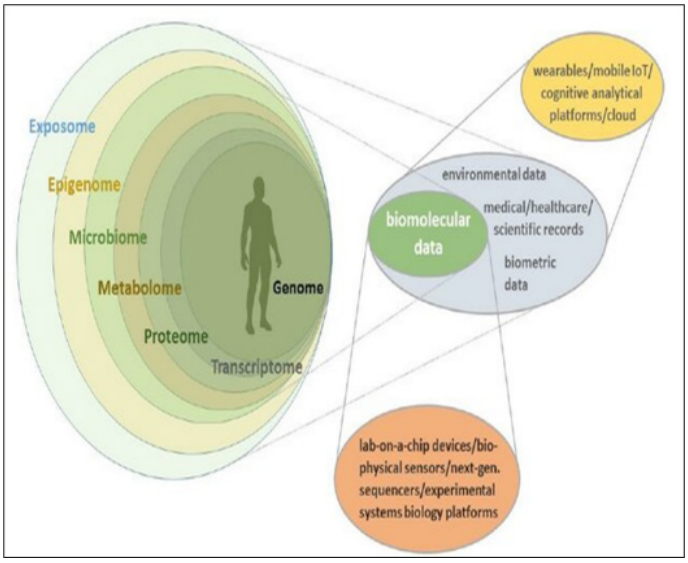

Figure 2: Personalized and Precision Medicine (PPM) contextualizes data from genome to exposome.

While OMICS data is biomolecular by nature, epigenomic and exposomic data also takes environmental, bio-metric and medical metadata sources into account. Even though environmental and biometric data is highly diversified, they are often readily available and can be collected and processed through smart sensor networks that are incorporated into novel mobile platforms such as wearables, smart phones or watches. Such platforms communicate directly to analytical tools for point-of-care monitoring and diagnostics. Furthermore, collecting biomolecular data from intra- and intercellular systems at the genome-to-microbiome scale is a biophysical challenge in the field of systems biology, requiring the design of highly customized tools to detect biomolecules with single particle resolution and single binding sites[12].

2. Shaping the Future of Personalized Nutrition (PN) Through the Resources of Precision Foodomics (PF)

Since dietary habits represent one of the main determinants of health, individually tailored interventions are a promising frontier for nutritional research. The first determinant factor of dietary balance is represented by energy intakes matching individual needs. Metabolomics and Nutrigenomics are other factors that can define individually adapted nutritional needs[13]. An important focus is that personalized dietary advice, specific to everyone, should be more effective in the prevention of chronic diseases than general dietary recommendations. Other PN approaches, while promising in adults and for basic research, are still far from practical application in childhood and pediatrics[14]. Like Personalized and Precision Medicine (PPM), PN refers to the use of unique information about an individual to tailor nutritional interventions, including advice, products and services, to benefit their health, unlike conventional population-based approaches. Furthermore, with OMICS-technologies, Precision Foodomics (PF) and food design, (Information Technology) IT-supporting algorithms, biodata analysis and data technology, PN are increasingly a reality[15,16]. Genomic information has been widely used to tailor PN for certain nutritional supplementations, giving rise to the interdisciplinary science called nutrigenetics and integrating microbiomics and metabolomics[17]. Advances in OMICS-powered tools and related techniques can be applied in nutrition science. In addition, advances in multi-OMICS technology will enable the establishment of objective biomarkers of food intake and health status. These advances include the capabilities to make PN recommendations based on their principles and food design and monitor food intake[18,19].

PPM aims to customize medical practice and healthcare services with a focus on the individual, based on the use of genetic tests, the identification of specific biomarkers and the development of biomarker-guided targeted drugs and nutrients (Figure 3).

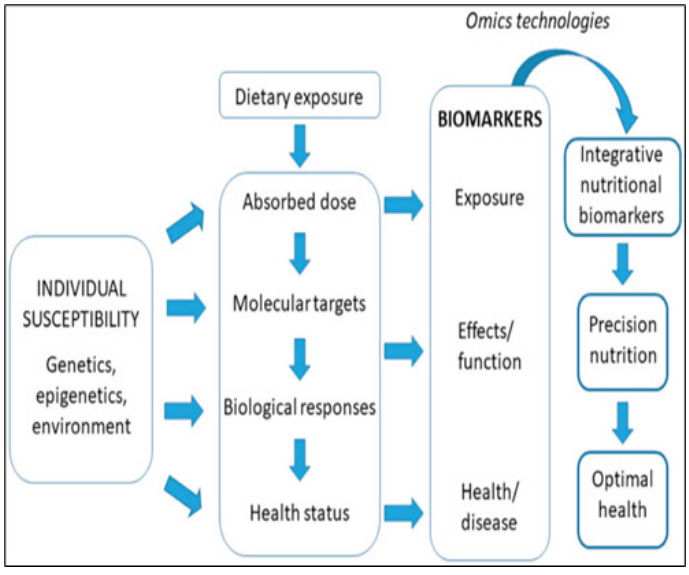

Figure 3: Integrative nutritional biomarkers and their interest in personalized nutrition.

Biomarkers of exposure include markers intended for the assessment of dietary food intake, whereas biomarkers of effect/function are related to target function or biological response. These biomarkers reflect not only the intake but also

the metabolism of nutrients and, possibly, effects on disease processes. Biomarkers of health/disease are biomarkers of main goal and indicative of improved health status and/or reduced risk of disease. Several OMICS factors can affect the individual response to dietary intake and its relation to health status. There is great interest in the development of new types of nutritional biomarkers with an integrative trait, indicative of the intake and effects on the organism, including its relationship with the state of health/disease and omics technologies may play a relevant role[20].

In this context, PF approaches (Figure 4) are becoming essential tools to assess an individual's optimal metabolic space. The latter is crucial to identify specific gene-metabolite, diet-metabolite and gene-diet interactions. Since the gut microbiota is a key player in metabolic homeostasis, a holistic investigation of metagenome-hyperbolome-diet interactions will provide the basis for devel-oping PN-guided functional foods. Therefore, defining food composition in all its chemical and quantitative diversity is critical for data-driven decision making to support PN and PN-driven sustainable diets. In this sense, PF, the application of OMICS-technology to characterize and quantify biomolecules to improve wellbeing, has the potential to elucidate what is in food, how this composition varies across the food system and how diet composition as a set of foods guides outcomes for nutrition, health and sustainability[21].

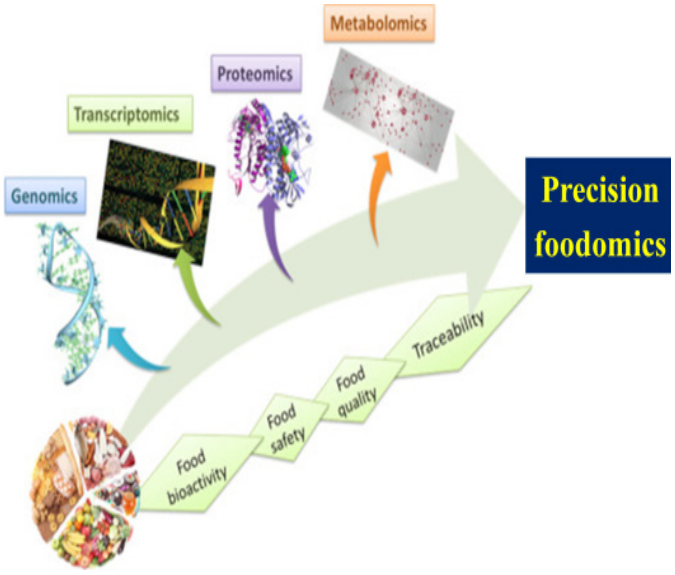

Figure 4: Precision Foodomics (PF) and its applications in Personalized Nutrition (PN).

Precision foodomics investigates food and nutrition fields using the application and integration of advanced OMICS technologies. Numerous studies show the significant potential of PF to enhance food science research, expedite the resolution of food safety issues, improve food quality and traceability and deepen our understanding of the bioactivity of food and its ingredients within the human body at a molecular level[21,22].

In this context, genotype-based nutritional intervention has been evidently useful for people with genetic defects and has helped them effectively improve their health, especially for individuals with metabolic and nutritional disorders[23] (Figure 5). To date, supported by candidate-gene approaches or Genome-Wide Association Studies (GWAS), several Single Nucleotide Polymorphisms (SNPs) have been recognized to have influence over the uptake, distribution, metabolism, excretion and signal transduction of macronutrients and micronutrients[24-26]. Further highlighting some genotypes that identify individuals based on sensitivity to certain nutritional interventions, expanding the understanding of the implementation of PN[27,28].

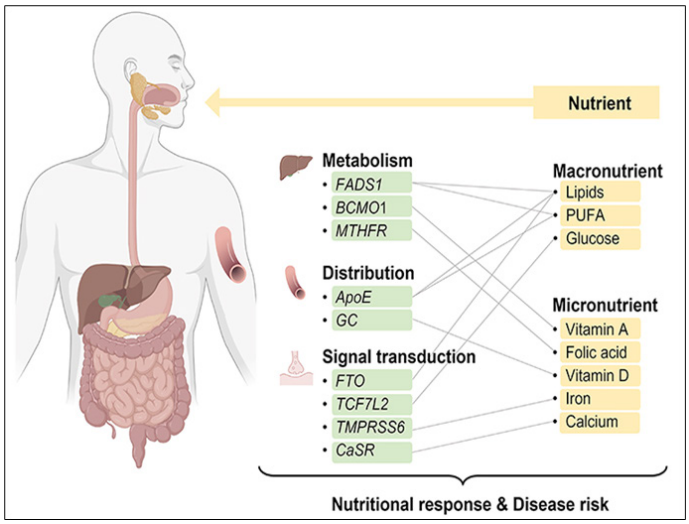

Figure 5: Overview of interactions of nutrients and genes involved in nutritional metabolism, distribution and signal transduction.

The great interest in Personalized and Precision Medicine (PPM) could be explained by the development of biology systems and high-throughput technologies, which are key in many fields of research. Increasing knowledge and interpretation of data from genetic analyses will enhance our understanding of physiological events during health and disease and promote personalized diagnosis and treatment. This type of approach could also be beneficial to reduce the burden of disease by targeting prevention and treatment more effectively by integrating multiple data sources.

Adapted from: Created with BioRender.com[29].

Nutrigenomics, the study of how genes and food components interact, investigates diet-altering disease development by modulating the processes involved in disease onset, progression and severity (Figure 6). Factors affecting chronic diseases development are believed to be mediated by epigenetic mechanisms, heritable and reversible, carry genetic information without changing the nucleotide sequence of the genome and are mediated by maternal and postnatal nutrition. In this context, early post-natal nutrition is a vital determinant of adult health. One mechanism by which postnatal nutrition affects long-term outcome is via developmental programming, which is the modulation of gene expression to impart a short-term advantage accompanied by a long-term cost, achieved through epigenetic modifications of chromatin[30].

Nutrigenomics is a multidisciplinary science that deals with the study of how foods affect our genes, focusing on interactions between the bioactive components of foods and the genome and how individual genetic differences can affect the way we respond to nutrients and other natural compounds in the foods we eat. In addition, it helps us appropriately understand the relationship between human genome, diet, nutrition and health. It includes nutrigenetics and nutrigenomics, which focuses on the consequences of those genetic mutations that can be regulated by diet, based on extensive studies that link specific genetic mutations of individuals with different eating habits[17].

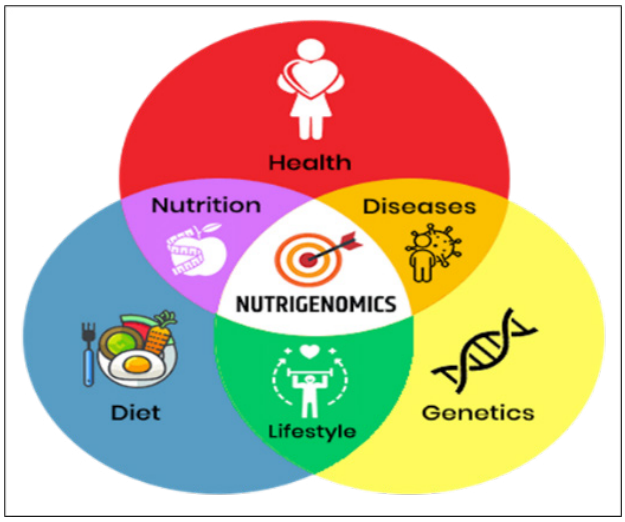

Figure 6: Nutrigenomics: towards Personalized Nutrition (PN).

On the other hand, metabolic programming and metabolic imprinting describe early life events, with impact on later physiological outcomes (Figure 7).

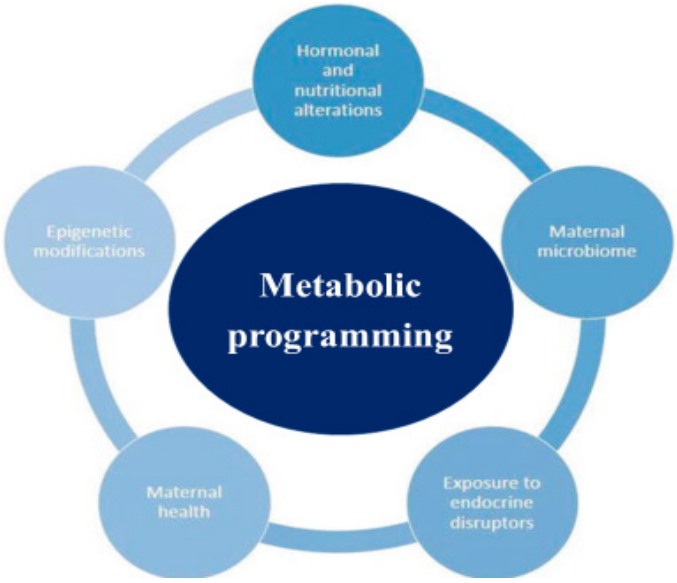

Figure 7: Principal mechanisms linked to metabolic programing: a complex network that affects adult health and disease, including hormonal and nutrition alterations, epigenetic modifications, microbiota and the exposure to endocrine disruptors.

Molecular mechanisms suggest including changes in gene expression, through various avenues, where there is an epigenetic interrelation between certain genes, exposure to environmental factors and biological events. As epigenetic regulation during development changes, the dynamic epigenome has an unstable nature and provides response and adaptation to environmental pressures, including nutritional changes.

Many types of nutritional risks including caloric restriction, macronutrient excess and micronutrient insufficiencies have been shown to induce early life adaptations that produce long-term dysfunction. Several pathways are suggested to support these associations, including epigenetic reprogramming of germ cells. While the mechanisms remain thoroughly investigated, the relationship between nutritional factors in early life and metabolic diseases is clear[31].

Clinical endpoints can be explained mechanistically in terms of epigenetic-mediated gene ex-pression. The predictability of outcomes depends on determining whether causality or association exists in the context of both early dietary exposure and future health parameters. Several health endpoints are affected by metabolic programming/imprinting. These include the link between peri-natal nutrition, nutritional epigenetics and programming early in development and its link to a range of future health risks such as cardiovascular disease (CVD) and diabetes. Both programming and, eventually, reprogramming can become effective tools to improve health through dietary intervention at specific developmental points[32].

Nevertheless, there are limitations of genomics-driven PN when it comes to what we know about the relationships among our eating patterns, persons-at-risk, our genes and how these factors interact with our behavior and our environment. In general, obesity and diabetes are complex and multifaceted diseases. Multiple genetic pathways are known to predispose people to gain weight or have trouble controlling blood sugar. Likewise, these predispositions may act separately or intertwined with lifestyle habits, gut microbiome composition and environment, influencing the risk of developing specific diseases. Therefore, understanding which exposomic, phenotypic and genotypic factors influence response will help interpret the nutrition intervention results and explore such variation in PN provision. To understand these variations, it is necessary to design specific studies that test the influence of these factors[33].

Nutritional status affects all ages and in the pediatric age good nutrition is crucial to achieving adequate growth and development[34]. Nutritional assessment should be an integral part of the care for every patient, especially pediatric patients, the components of which include medical history, nutritional history, nutrigenomic, metagenomics and metabolomic tests of nutritional status. Emphasizing the importance of making accurate measurements using trained personnel and appropriate equipment[35]. Prenatal care and PF-guided PN during the pre-early years of a child's life are crucial factors that define their development. The fetus exposed to undernutrition learn to adapt during pregnancy, leading to "programmed" changes in terms of metabolism and physiology. Nutrigenomics helps prevent acute and chronic effects of malnutrition by providing data that can be used to determine critical genes for metabolic pathways that require micronutrients as cofactors.

In terms of pre-early and early growth and development, the nutritional requirement is high due to rapid physiological growth and functional development. Characterized by an extreme susceptibility to external stimuli in relation to maternal and infant nutritional status that can interfere in the different stages of the development process, generating short and long-term health consequences. Linear growth and brain development are especially affected by insufficient nutrition[36]. In adults, PN personalizes dietary recommendations based on microbiomes. In chronic metabolic and/or nutritional disorders that are often caused by a combination of genetic predispositions and environmental insults, it is essential to "understand the chronic condition" from the NP perspective[37], considering diet and nutrition, nutritional status, dietary patterns, toxins and infections, symptoms and other individual considerations[38].

3. Personalized Nutrition and Clinical Cases

Next, attempting to cover a variety of complex cases such as autoimmunity, hormonal disruption and more, we will explain

the most recent developments in NP and FP in the pediatric age, considering the strengths and limitations of NP-guided clinical practice.

3.1. Obesity in Children

Childhood obesity is a growing concern across global demographics, marked not only by in-creasing prevalence but also by the intensifying severity of cases. This trend is critical in the field of public health. This NCD, a multi-organ disorder, carries substantial morbidity and poses a risk of premature mortality, presenting complications that include dyslipidemia, hypertension, fatty liver disease, psychosocial ramifications, etc. Current treatment guidelines prioritize behavioral and lifestyle interventions, reserving pharmacotherapy and surgical interventions for refractory cases. Although pharmacological innovations are seen in adult obesity, advances in pediatric obesity are much smaller[39].

The incidence of overweight and obese children is constantly increasing every year. In England, in 2019/20, the National Child Measurement Program revealed a prevalence in the children's reception year (ages 4-5) of 9.9%, rising to 21% in year 6 (ages 10 to 11 years). In adults, the prevalence of obesity increased from 14.9% in 1993 to 28.7% in 2017. Obesity-related complications encompass cardiovascular disease, musculoskeletal issues, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, sleep apnea, pubertal disturbances and heightened intracranial pressure. Conditions with an impact on physical and mental well-being, significantly influencing overall quality of life[40].

We must not forget the events in the early stages of life, encompassing the prenatal and child-hood phases, which exert a fundamental influence on long-term health trajectories. Variables such as maternal adiposity, gestational diabetic conditions and infantile feeding practices exert a bearing on a child's susceptibility to obesity in later life. Furthermore, emerging findings suggest that exposure to environmental pollutants, including endocrine disruptors, during critical developmental junctures may contribute to the genesis of obesity and metabolic dysregulation[41].

Childhood obesity is a multifaceted issue influenced by a myriad of factors, including genetic predisposition, environmental conditions, socioeconomic status and behavioral patterns. Genetic elements contribute to an individual's vulnerability to obesity by impacting metabolic functions, appetite regulation and adipose tissue metabolism. However, the surge in childhood obesity rates witnessed in recent years cannot be solely attributed to genetic factors, highlighting the substantial role played by environmental and behavioral determinants[42]. The intricate interplay between genetic predisposition and environmental factors significantly contributes to childhood obesity. Nevertheless, these genetic inclinations interact with environmental variables such as dietary habits, levels of physical activity and socioeconomic circumstances. Children hailing from economically disadvantaged backgrounds, for instance, may encounter challenges accessing nutritious food options and opportunities for engaging in physical activities, thereby predisposing them to obesity[43].

Early intervention in childhood obesity is imperative to preempt the onset of associated complications with this chronic condition, with the possibility of reducing its prevalence in adulthood[44]. Treatment of childhood obesity revolves around lifestyle interventions that emphasize caloric expenditure over intake; however, it is only effective in certain cases. Although pharmacotherapy in the pediatric population has limited data on efficacy and safety, there is potential for it to serve as a beneficial adjunct in the treatment of obesity[45].

3.2. Type 2 diabetes mellitus in children and PN-guided approaches to manage and to prevent the latter

Type 2 Diabetes Mellitus stands as a metabolic disorder characterized by peripheral insulin resistance, culminating in hyperglycemia. Initially perceived as predominantly afflicting adults, T2DM has emerged as a significant pediatric concern, predominantly attributed to lifestyle factors and the escalating rates of childhood obesity. With Type 1 Diabetes Mellitus (T1DM) screening, timely identification and therapeutic intervention in pediatric T2DM is essential to avoid long-term complications, re-quiring the collaborative role of interdisciplinary team members to provide cohesive care and improve outcome in these patients[46]. Long-term sequelae for pediatric T2DM can be severe and often manifesting earlier compared to their adult counterparts. Evidence indicates renal and neurological complications in the decade after diagnosis, including dialysis dependency, limb amputations and visual impairment.

Notably, pediatric T2DM patients exhibit a nearly 40-fold in-creased risk of requiring dialysis compared to non-diabetic peers[47]. Among pediatric chores, approximately one-quarter have hypertension and just over 20% presenting albuminuria. Unlike adults, where T2DM correlates with a notable reduction in life expectancy, data pediatric remains difficult to obtain despite increasing prevalence. Adults with T2DM face escalated susceptibility to diverse complications, including malignancies and non-vascular ailments[48]. Longitudinal prognosis studies of pediatric T2DM remain scarce. The long-term prognosis trajectory in these patients is intrinsically intertwined with compliance with treatment protocols, maintenance of a healthy lifestyle and ongoing medical follow-up. Early detection, comprehensive education and support mechanisms emerge as axes to improve prognosis and reduce the risk of serious complications in pediatric T2DM patients[49].

It is important to mention that conventional glycemic indices, including glucose and HbA1c, harbor limitations that lead to underdiagnosis and suboptimal prognosis in T2DM cohorts. For example, fasting glucose in isolation lacks comprehensive view of the patient's glycemic status. In addition, HbA1c fails to capture transient hyperglycemic fluctuations and is subject to alteration by patient-specific variables, such as underlying medical conditions and ethnic disparities. Currently, glycemic indices such as Glycated Albumin (GA), Fructosamine (FA) and 1,5-anhydroglucitol (1,5-AHG), provide independent clinical insights and augment the prognostic utility of conventional markers. Likewise, the Atherosclerosis Risk in Communities (ARIC) Study framework corroborates the robust association of FA, GA and 1,5-AHG markers with T2DM risk, transcending the predictive capacity of fasting blood glucose and HbA1c metrics.

The discernible moderate correlation and clinical variances between non-traditional markers and conventional indices may be attributed to their heightened sensitivity to postprandial

excursions, contrasting with the protracted glycemic influence encapsulated by HbA1c and the disparate impact of oxidative stress. Given the demands posed by this disease, it is imperative to evaluate blood glucose in the short, medium and long term. Discriminative and synergistic utilization of these tools would lead to accelerated diabetes prevention, early detection and effective treatment[50]. Prevention of obesity in newborns and infants focuses on breastfeeding. The correlation between glucose tolerance at adolescence and presence of breastfeeding is strongly negative[51]. For this reason, scientific societies recommend exclusive breastfeeding for the first 4 to 6 months. Children from 1 year old must eat at the family table. The nutritional recommendations include a varied diet with ample plant-based foods (vegetables, fruits, whole grain products), limited number of foods of animal origin (milk products, meat, fish, eggs) and a low consumption of sugar and sweets, especially beverages with a high sugar content. There is a strong correlation between the development of obesity, the size of meals in puberty and the consumption of unhealthy snacks between meals[52].

The term obese microbiota and lean microbiota was the result of pioneering discovery by Turnbaugh et al[53]. transplanting microbiomes from lean and obese mice into germ-free recipients. Observing a decrease in the relative abundance of Bacteroidetes and an increase in Firmicutes in obesity. The relationship between diet and microbiome may be involved in the development of obesity and may also be part of the solution. The study in which rodents were fed a high fermentable fiber diet demonstrated protection against animal-based diet-induced obesity and associated metabolic defects. The metabolites of microbial fiber fermentation induce the endogenous production of glucagon-like peptide-1 (GLP-1) and GLP-2. GLP-1 has a positive effect on glucose metabolism and GLP-2 promotes the integrity of intestinal epithelial tight junctions. A high-fat, low-fiber diet causes GLP-2-mediated disruption of tight junction integrity, making the intestinal epithelium more susceptible to microbial Lipopolysaccharides (LPS), Trimethylamine (TMA) and other metabolites that contribute to chronic inflammation of the liver and adipose tissue. Contributors to the actual development of conditions associated with metabolic syndrome[54] (Figure 8).

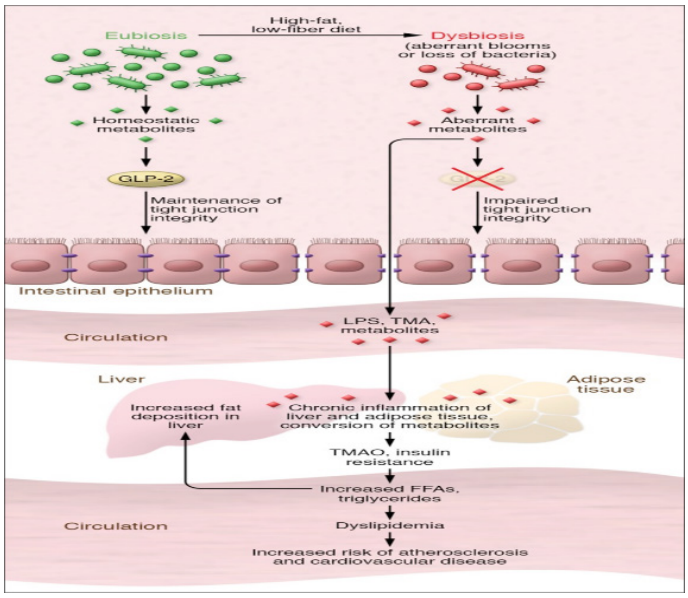

Figure 8: The principle of interaction of the intestinal microbiome with the intestinal epithelial barrier in the development of metabolic diseases.

The intestinal epithelium represents the most regenerative tissue in the human body, located in proximity to the dense and functionally diverse microbial milieu of the microbiome. The intestinal barrier is a dynamic system influenced by the composition of the intestinal microbiome and the activity of intercellular connections, regulated by hormones, dietary components, inflammatory mediators and the enteric nervous system. The gut microbiota structure, dynamics and function result from interactions with environmental and host factors, which jointly influence the communication between the gut and peripheral tissues, thereby contributing to health programming and disease risk. Microbiotas generate a variety of metabolites from dietary products that influence host health and pathophysiological functions. Since gut microbial metabolites are produced near gut epithelium, presumably they have significant impact on gut barrier function and immune responses[55-57].

On the other hand, bariatric surgery is recommended as a treatment of T2DM even in obese children due to its high capacity to improve glycemic control, lipid homeostasis, intestinal and neuronal adaptations, incretin secretion hormones, changes on bile acid levels and nutrient signaling pathways to the gut microbiota[58] (Figure 9).

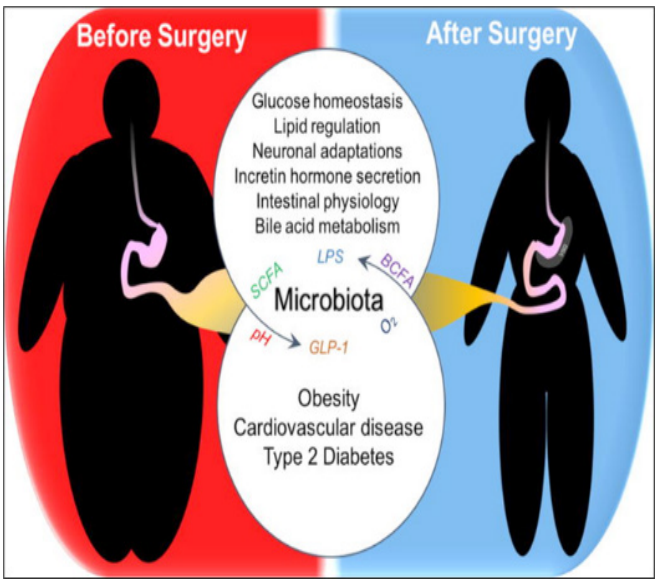

Figure 9: The role of microbiota in outcomes of Vertical Sleeve Gastrectomy (VSG).

Bariatric surgeries like Vertical Sleeve Gastrectomy (VSG) and Roux-en-Y Gastric Bypass (RYGB) cause well-established shifts in the gut microbiota. However, how this contributes to its unique metabolic benefits is poorly understood[59,60].

Even though the richness and diversity of microbiota varied across post-operatively studies, several of them had increased Proteobacteria, specifically genus Escherichia and Bacteroides thetaiotaomicron. Feeding mice B. thetaiotaomicron led to regression of obesity and resistance to weight gain on a high-fat diet. The researchers' hypothesis was that the relationship between this bacterial population and body weight might be related to circulating levels of amino acids and the neuro-transmitter glutamate. Nonetheless, the use of probiotics for 6 months after bariatric surgery did not have a significant positive or protective effect on the recipient's microbiome. In addition, fecal samples are known to represent the microbial environment of the distal colon because it easier to collect and less is known

about the microbial changes after bariatric surgery in the upper gastrointestinal tract. Despite the high density of microbes in the colon, the impact of microbes throughout the gastrointestinal tract, including the small intestine, must be considered[61].

It is known that in obese patients the plasma level of Lipopolysaccharides (LPS), one of the main biomarkers of chronic inflammation and a component of the cell wall of gram-negative bacteria, is elevated. Its elevation in plasma may stimulate the proliferation of adipose tissue precursors and macrophage infiltration, contributing to metabolic diseases. There is evidence that bariatric surgery reduces LPS levels[62]. Most theories focus on Short-Chain Fatty Acids (SCFAs), produced primarily by intestinal bacterial fermentation of fiber and their altered composition after bariatric surgery. It has been suggested that epy increasing levels of certain SCFAs may improve intestinal barrier function, improving insulin signaling[63]. An alternative hypothesis was that changes in gut length or transit time would promote colonization by faster-growing species. Research on the relationship between host genotype, microbiota and metabolic pathways, sensitivity to a high-fat diet and increased insulin secretion has been associated with microbiota with greater expression of Phosphotransferase System (PTS) genes[64]. We expect that patients will soon benefit from microbe-based therapies to improve their weight, glycemia and surgical outcomes, eliminating the need for surgery.

3.3. Type 1 diabetes in children and PN-guided approaches to manage the latter

Type 1 Diabetes Mellitus represents a chronic disorder characterized by the autoimmune destruction of pancreatic beta cells, leading to the inability of the body to produce insulin. Insulin, a pivotal anabolic hormone orchestrates various metabolic processes encompassing glucose, lipid, protein and mineral homeostasis, alongside exerting effects on growth. Consequently, T1DM manifests as a systemic ailment marked by hyperglycemia. Hyperglycemia is caused by both dysfunction and reduction of the β-cells. The range of functional and even morphological insufficiency varies amongst patients. That is the cause of small amounts of stable insulin production in some individuals after T1D manifestation[65]. Extensive investigations underscore the significant contribution of genetic factors to T1DM onset. While T1DM commonly manifests in childhood, elucidating its pathogenesis remains a challenge owing to its multifactorial nature. Although environmental factors, including viral infections, cow's milk proteins and vitamin D3 deficiency, have been proposed as potential triggers in genetically predisposed individuals, definitive causal links remain elusive. Immunological biomarkers such as anti-pancreatic islet cell antibodies, Anti-Glutamate Decarboxylase (GAD) antibodies, anti-insulin antibodies, anti-tyrosine phosphatase antibodies and anti-zinc transporter 8 antibodies underscore the autoimmune nature of T1DM[66].

Gut microbiome barrier Tight Junction (TJ) proteins are regulated by the expression of claudin-2, occluding and cingulin, Zonula Occludens (ZO) proteins. Intestinal permeability depends on the increased levels of zonulin, the production of which is influenced by bacterial colonization. Zonulin reversibly regulates intestinal permeability by modulating TJ. Its serum concentration is high before the onset of clinically evident T1DM[67]. In this context, the role of intestinal microbiota in T1DM etiology has emerged, offering crucial insights into disease pathogenesis and prognostic determinants. Leveraging multi-omics approaches and multicenter sample analyses has revealed a variety of intestinal microbiota implicated in T1DM, providing important insights[68]. This evidence underscores the intricate interplay between intestinal microbiota and insulin dysfunction in T1DM pathogenesis. Moreover, advances in multi-omics and high-throughput sequencing method-ologies have deepened our understanding of T1DM progression, facilitating the translation of re-search insights into clinical practice[69]. Specifically, a GWAS of gut microbiota and T1DM identified one causative bacterial genus, Bifidobacterium. Its high relative abundance was associated with a higher risk of developing T1DM. Likewise, numerous studies have reported a decrease in the Firmicutes/Bacteroidetes ratio in patients with T1DM[70].

Integration of metagenomic and metabolomics approaches in T1DM patients at baseline revealed an increase in the abundance of Clostridiales and Dorea and a decrease in the abundance of Dialister and Akkermansia. Additionally, these patients were characterized by higher levels of iso-butyrate, malonate, Clostridium, Enterobacteriaceae, Clostridiales and Bacteroidales. T1MD patients with higher levels of GAD antibodies had low levels of Roseburia, Faecalibacterium and Alistipes, while patients with normal HbA1c had high levels of purine and pyrimidine intermediates. We expect that specific gut microbial and metabolic profiles may predict the progression and severity of T1DM[71]. Gut microbes have shown multiple pathways for butyrate synthesis, which belongs to SCFAs, such as acetate and propionate, carbohydrate-derived metabolic products of certain bacterial commensals. LPS in food is first converted to acetoacetyl-CoA by glycolysis, which is reduced to butyryl-CoA and then converted to butyrate. Studies have reported a negative correlation between butyrate producers, intestinal permeability and the risk of developing T1DM. In children examined with positive autoantibodies, there was a higher abundance of Bacteroides and a low abundance of butyrate-producing species. Metagenomic studies revealed in T1D patients a significant reduction in the number of butyrate-producing species from Clostridium clusters IV and XIVa, mucin-degrading bacteria - Prevotella and Akkermansia. Treatment with sodium butyrate has also shown to improve insulin resistance[72,73]. Despite evidence of association between loss of butyrate-producing species, gut permeability and T1DM disease progression, attention is lacking to elucidate the precise molecular underpinnings of this process.

Individuals diagnosed with T1DM frequently present with a range of concurrent multi-system autoimmune conditions, encompassing thyroid disorders, parathyroid disorders, Celiac Disease (CD), vitiligo, gastritis, dermatological afflictions and rheumatic ailments. Clinically, it is consistently observed that T1DM patients manifest additional autoimmune disorders, thereby impacting their prognostic trajectory[74]. Celiac Disease (CD) emerges as one of the prevalent autoimmune comorbidities in individuals with T1DM. The prevalence of CD among T1DM patients varies between 3% to 16%, with an average prevalence rate of 8%. While approximately half of CD cases in T1DM may present as asymptomatic, meticulous scrutiny often reveals a diverse array of symptoms indicative of underlying CD pathology. Both T1DM and CD share a common

genetic predisposition, alongside aberrant immune responses within the small intestine, characterized by inflammation and variable degrees of enteropathy[75]. Screening for CD antibodies, particularly tissue transglutaminase antibodies, should be routinely conducted in all T1DM patients at the onset of T1DM diagnosis. Those diagnosed with both conditions necessitate adherence to a gluten-free diet as part of their therapeutic regimen. Moreover, individuals identified as potential CD cases, especially those presenting without symptoms, should be closely monitored while maintaining a diet containing gluten, as a subset may not progress to villous atrophy.

3.4. Celiac Disease in Children and PN-Guided Approaches to Manage the Latter

Celiac Disease (CD) is a multifaceted autoimmune disorder within the spectrum of chronic intestinal diseases, typified by inflammation and structural alterations in the duodenum, accompanied by nausea and diarrhea, in individuals genetically predisposed to exposure to gluten, with triggers a detrimental CD4+ T-cell response towards gluten peptides[76]. Although the immuno-logical underpinnings of CD are well-delineated, the mechanisms orchestrating intestinal restructuring remain largely elusive. However, genomic investigations into this condition have revealed a plethora of genes implicated in interleukin signaling and immune-related pathways. Furthermore, it is important to note that the spectrum of CD manifestations extends beyond the confines of the gastrointestinal tract, raising questions about the potential correlation between CD and neoplastic conditions[77]. Symptoms affecting the intestine are more common in children and may include persistent diarrhea, abdominal discomfort, unintentional weight loss, reduced appetite, inability to grow, abdominal distension, nausea, vomiting and constipation. Despite malnutrition, which is a common sign of CD, being overweight and obesity may also be evident in diagnosis. Studies show that more than half of adult CD patients are obese, while only 15% are obese[78].

In the context of celiac genetics, the sole therapeutic recourse remains adherence to a lifelong Gluten-Free Diet (GFD). This diet should be recommended only after a certain CD diagnosis. Strict adherence to GFD, that is, eliminating gluten-containing grains and derivatives from the diet, usually results in loss of symptoms within days and a rapid weight gain. This means that patients with CDs should avoid wheat-based foods such as bread, pasta, pizza, pastries and processed products[79]. It is also recommended to include gluten-free whole grains such as quinoa, oats and teff, avoiding gluten-free alternatives such as white rice and maize flour. Despite the apparent simplicity-ty, following GFD can be a challenging task, especially in conditions such as schools, restaurants and even at home. Therefore, health professionals play a crucial role in persuading patients to adhere to this diet for life[80].

It is important to note that GFD practices vary across countries due to different diets and may affect the composition of intestinal microbiota. The degree to which people adhere to the GFD and the duration of treatment may affect the abundance of specific bacterial models of the intestine, affecting the metabolism of the intestine microbiota as an adaptive response. Moreover, long-term adherence to GFD leads to two different results in metabolomics: restoring epithelial integrity and creating a more stable intestinal microbial community that is no longer disturbed by dietary changes. For example, a study by Akobeng AK, et al.[81] examined the protective effect of breast milk on the risk of CD, as well as the effect of the duration of natural feeding at the time of the first introduction of gluten-containing foods into the infant's diet on the risk of gluten enteropathy. Breastfeeding at the time of first introduction of gluten-containing foods into the infant's diet was found to statistically significantly reduce the risk of developing CD later in life (OR 0.48; 95% CI 0.40). The authors identified several reasons to justify the protective effect of breast milk: the lower amount of gluten that the child receives given the retention of mother's milk in his diet, the proven preventive effect of natural feeding in relation to intestinal infections. In another study by Radlovic NP, et al.[82] it was found that children who were naturally fed at the time of gluten introduction were diagnosed with CD at a significantly older age. Roman E, et al. [83] also demonstrated in their work that breastfeeding at the time of gluten introduction reduced the risk of CD from 58 to 62%.

Additionally, in a study by Noris JM, et al. [84] the data were obtained that the introduction of gluten to infants 3 months of age or later than 7 months of age statistically significantly increases the risk of developing the disease compared to the period from 4 to 6 months of age. Similar results reported by Stordal K, et al.[85] indicate that among children who were introduced to gluten after 6 months of age, the incidence of CD was significantly higher compared to children who received gluten-containing foods between 4 and 6 months of age. Poole JA, et al. [86] conducted a study including more than 1,600 children and showed that delayed introduction of gluten after 6 months of age increased the incidence of cereal allergy in children. Moreover, the fundamental work in the field of prevention of CD in children was the study of Szajewska H, et al.[87] who analyzed 21 studies, demonstrating that the early feeding (duration of natural feeding and timing of gluten introduction) in general do not radically affect the risk of CD development. At the same time, data from a systematic review did not allow us to exclude the fact that subsequent introduction of gluten into the child's diet leads to a delayed onset of the disease[88].

Currently, early detection and treatment are the most proven methods for secondary prevention of CD in children[75]. The importance of the amount of gluten remains a controversial issue[89]. Nowadays it is unquestionable that it is practically impossible to prevent CD in general as it is a genetically determined disease. This determines the need for physicians to be vigilant regarding children at risk and timely diagnosis of the disease through mass screening before the development of its severe manifest forms. In addition, it is important to note that in both children and adults with CD, a strict gluten-free diet can cause the development of several deficiency conditions, such as: calcium and zinc deficiency, fiber, thiamine, folate[90], as well as vitamin D and calcium deficiency. In a study by Hasret A.C. et al, vitamin and micronutrient levels were evaluated in celiac children on a GFD. The results of serologic screening showed that 40.3% of patients followed a gluten-free diet while 59.7% did not. Children who did not follow the diet had significantly lower vitamin B12, vitamin D, folate, zinc and selenium levels compared to the group of patients who followed the diet. A significantly higher mean serum total IgA level was also found in the group of children without diet adherence. The authors established high efficacy of GFD in relation to the correction

of vitamin and trace element deficiencies and deficiencies[80]. Thus, it is recommended to examine and prescribe treatment for micronutrient deficiencies (iron, calcium, folic acid, vitamin D, vitamin B12) in children with a first diagnosis of CD[91].

Since CD is characterized by the appearance of specific antibodies in the serum, there are several child-specific biomarkers, for example, antibodies to tissue transglutaminase (anti-tTG), anti-bodies to endomysium (EMA) and antibodies to deamidated gliadin peptides (anti-DPG)[92]. Anti-tTG are determined by enzyme immunoassay a method with high sensitivity (98%) and specificity. However, a slight increase in the titter of Anti-tTG is occasionally observed in patients with autoimmune and oncologic diseases, pathology of the liver and cardiovascular system and in children with persistent herpetic infection, widespread atopic dermatitis, bullous epidermolysis[93]. EMA also have tissue transglutaminase as a substrate, located in the intercellular substance the surrounds the smooth muscle elements of the intrinsic lamina of the small intestinal mucosa. It is determined by indirect immunofluorescence using monkey esophageal tissue or human umbilical cord tissue as substrate. The method is semi-quantitative, has high sensitivity and specificity, but requires special equipment and the evaluation of the results of the study is subjective and depends on the qualifications of specialists. Anti-DPG may be a more specific marker of celiac disease than AGA. Nevertheless, anti-DPG are not superior to anti-tTG and EMA in sensitivity and specificity. Anti-DPG can complement the value of serologic diagnosis only in case of an increased titer of anti-tTG[94]. For the rapid diagnosis of CD, rapid tests (POC-tests) have been developed, which allow estimating the level of antibodies to tissue transglutaminase in capillary blood of patients within 10 minutes. This method uses intrinsic transglutaminase in red blood cells as a substrate for antibody detection. Nitric oxide (NOx) and total cysteine (Tcys) are considered as additional markers of celiac disease and are objective indicators of the severity of the pathological process. A NOx/creatinine concentration threshold value of 10 µmol/mmol has been established for patients with acute CD[95].

Another important feature in CD are environmental factors and, above all, the gut microbiota[96]. According to Verdu EF, et al. [97] the gut microbiota plays a complex modulatory role in the hu-man immune response to gluten. Furthermore, based on other researchers, changes in the gut microbiota, along with exposure to dietary gluten and genetic predisposition, are among the most significant factors contributing to the loss of gluten tolerance and increased permeability of the intestinal barrier, thus participating in the pathogenesis of CD[98]. It is important to note that gut bacteria (mainly Firmicutes) can secrete microbial transglutaminase, like human tissue transglutaminase. In addition, microbiomes can directly influence intestinal permeability through the release of the tight contact protein, zonulin[99]. Intestinal dysbiosis occurs both in patients with newly diagnosed celiac disease and in patients receiving a gluten-free diet[100]. Dysbiosis in CD is characterized by a decrease in probiotic (anti-inflammatory) microorganisms (Bifidobacterium spp., Lactobacillus spp., Faecalibacterium prausnitzii), an increase in the number of proinflammatory bacteria such as Bacteroides spp., Escherichia coli, Staphylococcus spp. and others, as well as an increased ratio of Bacteroides fragilis to the content of probiotic butyrate-producing bacterium F Prausnitzii[100]. In children with CD, both total bifidobacteria levels and the abundance of Bifidobacterium longum are decreased[101]. B. bifidum is found more frequently in patients with CD, both adults and children, than in healthy controls, but these differences are not significant in children[102]. Also, elevated levels of E. coli have been found both in patients with active CD and in patients in remission (compared to healthy controls)[103,104].

4. Conclusion

Personalized nutrition is defined as an approach that counts on details of individual characteristics to evolve a package of nutritional counsel, goods or services (Figure 10).

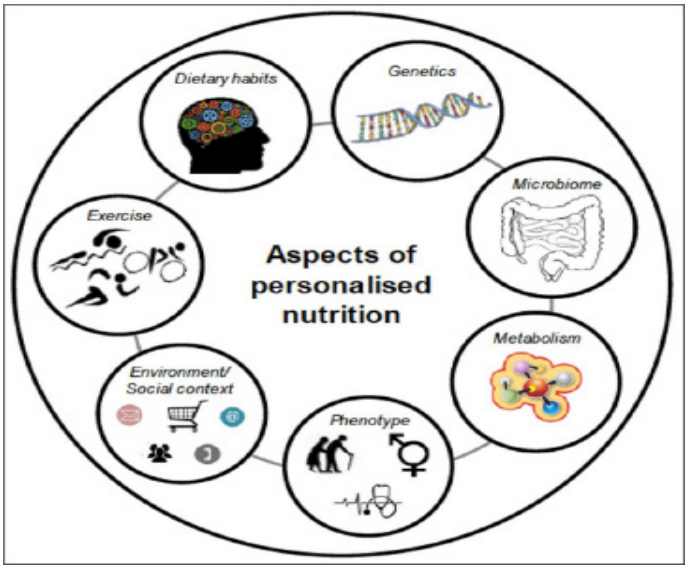

Figure 10: Personal input data elements of Personalized Nutrition (PN) - a package of nutritional features and food, OMICS portfolio, counsel, goods or services.

The unique physiological and genetic characteristics of individuals influence their reactions to different dietary constituents and nutrients. This notion is the foundation of PN. Many disorders are susceptible to the collective influence of multiple genes and environmental interplay, wherein each gene exerts a moderate to modest effect. Furthermore, it is widely accepted that diseases emerge because of the intricate interplay between genetic pre-disposition and external environmental influences. In the context of this specific paradigm, the utilization of advanced "OMICS" technologies, including microbiome analysis, in conjunction with comprehensive phenotyping, has the potential heritable elements and gene-environment interactions.

Comprehensively, PN is the associated individual's genetic, phenotypic, medical, nutritional and other important information, which is intended to pitch specific healthy eating and nutritional guidance as per need. There may be parallel appliances of diet management under PN for healthy people, people at risk and patients. Forthcoming, the fusion of PN, PF and systems biology can bring crucial information about host-microbiome interactions, nutritional-immunology, food microorganisms including pathogens resistance, farm-animal production, etc. or to completely understand the post-harvest phenomena through a universal approach that connects genetic and environmental responses and identifies the fundamental biological networks. Based on this, the NP, by helping to unravel the child's eating patterns in relation to their genetics and nutrition, will be able to offer guidelines to improve their health, providing specific

information according to their unique health or illness needs. Among the benefits of PN-dictated meals, we would prioritize:

- Guide tailored to unique dietary needs.
- Improved health and well-being: by providing PN meals, children receive all the critical nutrients essential for growth and development, contributing to a strong immunity system and a healthy lifestyle.
- Expertise from PN specialists.

Several factors will contribute to the advancement of PN. Firstly, the development of a solid theoretical foundation, including the identification of the most important individual characteristics on which to base personalization. Secondly, evidence of the effectiveness and cost-effectiveness of well-designed intervention and FP studies. Thirdly, the introduction of a regulatory framework designed to protect the public about personalized and private information obtained, giving confidence to health professionals and policy makers. There exist several challenges for PN to continue gaining acceptance, including defining the health-disease continuum, identification of biomarkers, changes in the regulatory landscapes, accessibility and measuring success. Although PN approaches hold promise for public health, more research is needed on the accuracy of dietary intake measurement, utilization and standardization of systems approaches and application and communication of evidence.

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