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From Nutrigenomics to Microbiomics: New Interpretations

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ABSTRACT

In this work we analyze the current interpretations based on the studies of Nutrigenomic and Microbiomics, according to which, at the base of many pathological and dysmetabolic manifestations, there would be or variations of single nucleotide polymorphisms (Snps), in the Nutrigenomic vision, or changes of the normal gut microbiota, in the Microbiomic conception. In particular, we analyze critically, the singular pathogenic coincidence, which for the same pathologies calls into question or Snps mutations or the presence of specific modifications of the Microbiota. Other possible causes of observed diseases are thus neglected. On the basis of the literature examined, we present a different interpretation of pathogenic causes.

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Introduction

Nutrigenomics and Microbiomics are two disciplines born for several years, they have developed exponentially independently of each other, and have produced an impressive number of publications and scientific research. Their study is aimed at the discovery of the pathogenic causes of numerous diseases, using methods of investigation and very different approaches. The Nutrigenomic attributes to the genetic variations of single nucleotides (Single Nucleotide Polymorphisms -Snps) the root cause of the diseases, while the Microbiomic attributes the cause to the alterations of the Microbiota (which is the set of microorganisms that populate our organic apparatuses, especially the intestine).

The two research branches to date have identified and described an incredible number of polymorphic variants and bacterial strains, which would be cause of many diseases. All the merits of these discoveries must be recognized to them, but what is surprising is that the two disciplines attribute to the same diseases, but just the same, the different pathogenic causes object of their investigation. Then we find that, for example, at the origin of cardiovascular diseases, there is, according to the Nutrigenomic, the mutation of a single nucleotide and while for the Microbiomics the cause is to be attributed to the presence of abnormal bacterial strains [1-12].

Those who wish to use nutrition science for the prevention or treatment of dysmetabolic problems would thus face a methodological dilemma as to which is the best approach to adopt to customize the diet, Nutrigenomics or Microbiomics?

In this work we will examine the postulates of the two lines of research, to try to offer a different interpretation of the phenomena related to the causes of certain diseases.

Nutrigenomic, Nutrigenetic and Microbiomic

Nutrigenomic, Nutrigenetic provide the strategies to study how components of the diet interact with genes, and their products, to alter phenotype and, conversely, how genes and their products metabolize these constituents into nutrients, and bioactive compounds, with a common ultimate goal to optimize health through the personalization of diet. At the same time provide powerful approaches to unravel the complex relationship between nutritional molecules, genetic polymorphisms, and the biological system as a whole [1].

So according to these disciplines, through the study of genetic polymorphism and mapping of genes it is possible to identify foods that can have positive or negative effects on our health, helping us to protect the organism.

SNPs and prediction of effects

Differences between two SNPs nucleotide sequences are used to evaluate their effects at the level of gene expression, as the different types of mutations can have very different effects. Predicting the effects of a mutation at the level of phenotypic expression is a complex process, in which all factors involved in the process and their mutual interactions must be taken into account. In the following table 1 are highlighted examples of correlation between SNPs and cardiovascular diseases.

Table 1: Nutrigenetic analysis of SNPs within some CVD -related genes

CVD Risk Factor	Gene	SNPs	Genotype
Lipids	APOAI	-75G→A	GA
Lipids	APOC3	3175C→G	GG
Lipids	APOE	ε2, ε3, ε4	2, 3
Lipids	CETP	279G→A	GG
Blood pressure	ACE	Ins/Del	ID
Blood pressure	AGT	-6C→A	AA
Infammation	IL1B	-511C→T	TT
Inflammation	IL6	-174G→C	GC
Methylation (folate)	MTHFR	677C→T	TT
Methylation (B12)	TCN2	776C→T	CT

CVD – cardiovascular diseases - SNPs -Single Nucleotide Polymorphisms

Gene expression is the process by which the instructions in our DNA are converted into a functional product that will help determine the specific characteristics of our body. However, there is no direct relationship between genes – and a functional product as stated by the "central dogma of Biology ". We know that in the long run from the gene to its phenotypic effect there are numerous intermediate stages that can profoundly change the final result. This path is the subject of study of Epigenetics.

Epigenetics studies which and how many factors are involved in the final formation of the functional product. These factors are the following: Fig.1

DNA Methylation: DNA methylation works by adding a chemical group to DNA. Typically, this group is added to specific places on the DNA, where it blocks the proteins that attach to DNA to "read" the gene.

Histone modification: DNA wraps around proteins called histones. DNA wrapped tightly around histones cannot be accessed by proteins that "read" the gene.

Non-coding RNA: Your DNA is used as instructions for making coding and non-coding RNA.

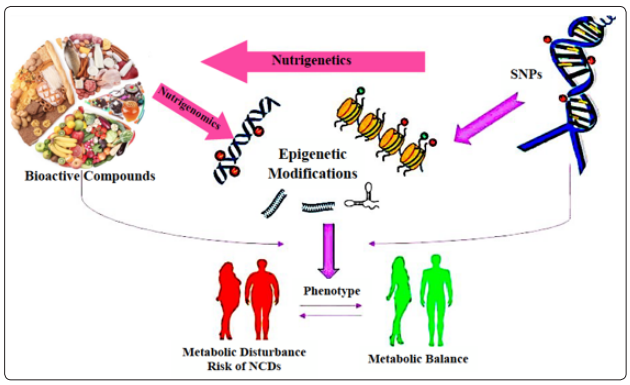

Figure 1: Interactions among genes, diet and human health

While Microbiomics has a mainly *bacteria-centric approach*: "***It must be stressed that to date research on gut microbiota is very bacteria-centric***" [7]. Because it attributes to specific "dysbiosis" of the intestinal flora, called *Microbiome*, the cause of numerous metabolic and chronic degenerative diseases, the list of which is constantly growing.

So the Microbiomics with the use of advanced sequencing technologies, defined *Metagenomics*, allows:

1) The detection of genetic set of bacterial population present in the gut, known as *Microbiota*, and

2) the restoration of homeostatic balance, with the implantation of specific bacterial strains, named *Probiotics* [7].

Metagenomic genetic analysis consists of DNA sequencing and the study of the ribosomal operon, in particular of the RNA 16S gene present in the Microbiome [7-8].

Materials and Methods

That genetic mutations are responsible for many diseases is sure, just as it is sure that some pathogenic bacteria cause gastroenteric infections. But for what inexplicable coincidence divergent polymorphisms or intestinal dysbiosis can cause the same identical pathologies?

An amletic doubt assails us, on which of the two interpretations is correct.

Here are some examples from the literature in support of the different pathogenic interpretations Table 2: The detailed analysis of altered polymorphisms and bacterial strains taken into account by the numerous existing studies, would be a difficult task, we report below only some bibliographical references to demonstrate our thesis.

NUTRIGENOMIC, NUTRIGENETIC REFERENCES
Diet, genetic polymorphisms and pathologies

Autors	Associated Diseases	References
Tanya Agurs-Collins et al	Obesity	13
Francis C. Lau et al	Obesity	14
Hélène Choquet and David Meyre	Obesity	15
Hélène Choquet and David Meyre	Obesity	16
Lu Qi et al	Obesity	17
Sihua Peng et al	Obesity	19
J.A. Silvester	Celiac Disease	20
Michael V Holmes et al	Cardiovascular disease	21
Koichi Miyaki	Cardiovascular disease	22
So-Young Lee et al	Cardiovascular disease	23
International Consortium for Blood Pressure Genome-Wide Association Studies.	Cardiovascular disease	24
Lifton RP , et al	Cardiovascular disease	25
Newton-Cheh C, et al.	Cardiovascular disease	26
Go VL, Butrum	Cancer	27
Anderle P,	Cancer	28

MICROBIOM , METAGENOMIC REFERENCES
Microbiom Variations and pathologies

Autors	Associated Diseases	References
Katerina Kotzampassi, Et Al	Obesity	39
Vanessa K. Ridaura,Et Al	Obesity	40
Jonas Halfvarson et al	Inflammation Bowel disease	41
Ludovica F.Buttó, DirkHaller	Intestinal inflammation	42
Yolanda Sanz ,et Al	Microbioma and metabolic Disease	43
Jiaqian Qi et al	Cardiovascular disease	35
Weifei Zhu et al	Cardiovascular disease	36
Xinmin S. Li et al	Cardiovascular disease	37
Takeshi Kitai and W.H. Wilson Tang	Cardiovascular disease	38
Zahra Eslami-S , et al Anderle P,	Cancer	44
Joao B. Xavier et al	Cancer	45
Vancheswaran Gopalakrishnan et al	Cancer	46
Debra Lynch Kelly et al	Cancer	47

Table 2: Coincidence in pathogenic interpretations for some diseases between Nutrigenomic and Microbiomics

Diet, genetic polymorphisms and pathologies

While acknowledging the importance and mutual influence of the environment, diet and microbiota as a whole, Fig.2, however the various researchers of this discipline, give the alteration of the intestinal microbiome a primary role on the state of health or disease of patients [12].

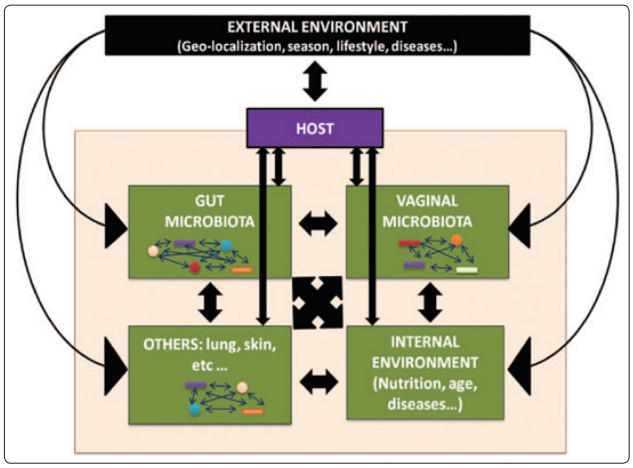

Figure 2: The human microbiome conceptualized as a dynamic ecological community

Starting from these assumptions, the use of faeces transplantation containing particular microbial strains, to rebalance and correct intestinal dysbiosis, is even postulated [13-15].

This method has been the subject of many ethical and scientific criticisms.

Discussion

All living organisms , from viruses to human , are in constant relationship with their environment and necessarily adapt to it , is a matter of survival, failure to adaptation leads to the extinction of the species. The most basic living species, such as bacteria, fungi and viruses, reproduce at a faster rate and adapt rapidly to their environment, with the known mechanism of mutation and selection. Therefore it is quite natural to find various microbial species (bacteria, fungi, viruses, etc.) that we have defined as a whole Microbiota, in the intestine and in other apparatuses of different people [7-12]. Fig.3 The GI epithelium is critically located at the interface between the body and environment, it incorporates an array of strategies to facilitate peaceful communication between luminal contents, including nutrients and microbes and the mucosal renewal system, thereby preserving its tissue homeostasis.

Luminal nutrient also stimulates intestinal mucosal growth indirectly by releasing gut hormones from the distal small intestine, colon and pancreas. In addition, adaptive changes in small intestinal mucosal mass are generally associated with parallel changes in segmental absorptive function, but the magnitude of induction of individual transport processes can be selectively affected by the specific nature of the nutrients within the lumen.

Luminal factors include a variety of nutrients, secretions, and other essential components in the diet or produced in the lumen of the GI tract that have been known to function physiologically to stimulate gut mucosal growth. A large body of evidence has accumulated and strongly suggests that luminal factors are the principal stimulus for GI growth.

The GI mucosa is in continuous contact with prokaryotic symbionts. Until recently, it has been recognized that microbes present in the lumen of gut affect GI health and functions including the regulation of the GI mucosal growth. The epithelial cells lining the intestine function to keep bacteria from invading the body, but they also have mutually beneficial relationship with these intestinal flora, which regulate a wide variety of physiological functions of the gut.

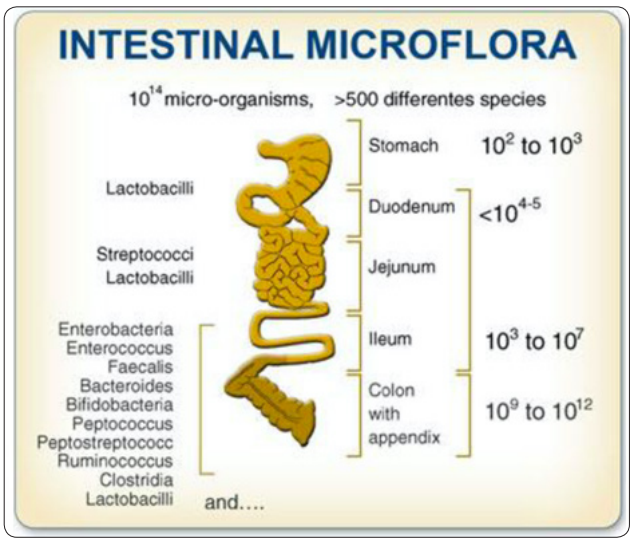

Figure 3: Distribution of bacterial species in the human intestine

We also know that the microbiota changes in relation to changing dietary habits and in the lifetime of the individual, Fig.4.

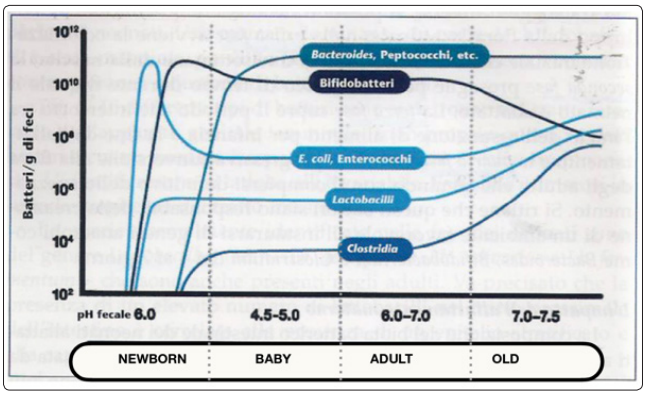

Figure 4: Variation of intestinal bacterial composition with age

Attributing to a certain cause, recognizable and measurable the origin of diseases, such as the presence of a particular set of bacteria, is a loophole that satisfies our scientific ego, even if the causality link is certainly not demonstrable. The only causal relationship demonstrated by traditional microbiology is between pathogenic bacteria and the infectious diseases produced by them. The following is a synopsis of the criticism of the setting of the causal role of the microbiome for many diseases:

Causality has not been established between changes in gut microbiome structure and function and markers of human health.
• It is not established if dysbiosis is a cause, consequence, or both of changes in human gut epithelial function and disease.
• Microbiome communities are highly individualized, show a high degree of interindividual variation to perturbation, and tend to be stable over years.
• The complexity of microbiome-host interactions requires a comprehensive, multidisciplinary research agenda to elucidate relationships between gut microbiome and host health.
• Biomarkers and/or surrogate indicators of host function and pathogenic processes based on the microbiome need to be determined, along with normal ranges, and validated.
• Future studies measuring responses to an exposure or intervention need to combine validated microbiome-related biomarkers and surrogate indicators with multiomics characterization of the microbiome.
• Because of human gut microbiome dynamics, static genetic sampling misses important short- and long-term microbiome-related changes to host health, so future studies should be powered to account for inter- and interindividual variation and should use repeated measures within individuals.

Effect of Industrial Additives on Health

In the last hundred years we have witnessed a profound change in the eating habits of human populations and a consequent increase in degenerative diseases. While in past centuries food production was of the "short chain" type, from harvesting, hunting, or fishing food to direct consumption. Today's nutrient intake has profoundly changed in quantity and quality, and the production of food on an industrial scale has profoundly transformed the biological and nutritional characteristics of our daily food Fig. 5.

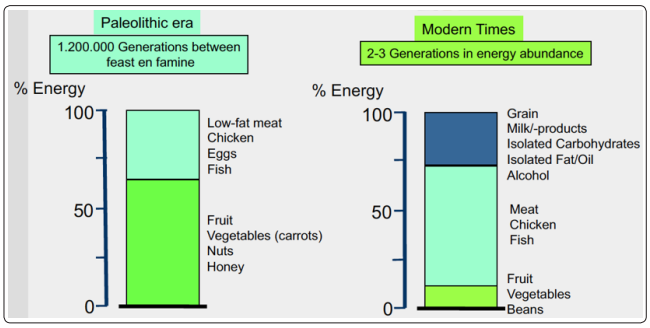

Figure 5: Nutrient intake in different ages

Today, the various vegetable and animal foods we eat are subject to numerous technological treatments. Apart from the so-called "organic" foods (for which we have some doubts about their authenticity) all the others are subjected to procedures that serve to ensure their stability and safety, and therefore have very little natural. Thus during the production of intensive crops of cereals, fruits and vegetables there is a wide use of fungicides, pesticides , while for animal breeding, antibiotics, hormones, pesticides are used . And also for packaged foods (***ready to eat products***) use of coloring substances, preservatives, emulsifiers, thickeners, in addition to even contain bacterial contaminants and toxins. We find all these substances directly in our diet [16-21].

We are faced with a food alteration and transformation that has no precedent, so much so that we can consider them as potential "biological weapons" that, added to environmental pollution, have an immeasurable and unpredictable impact on our health Table 3 [22].

Additivo	% di utilizzo
Aromi	63.5
Vitamine	6.9
Agenti emulsionanti	5
Sostanze tamponanti	3.5
Agenti chelanti	2.6
Coloranti	2.1
Conservanti	1.8
Stabilizzanti	1.8
Antiossidanti	1.7
Dolcificanti	0.4
Altri …	10.8

Table 3: Use of food additives in the United States

What is the direct and indirect effect that all these substances produce on our health?
The trials reported rarely examine the possible effects of the pollutants and additives mentioned above and which certainly play an important role in the determinism of the pathologies studied [2].

Food Additives and Food Intolerances

Another aspect that concerns an extraordinarily widespread phenomenon in industrialized countries, is represented by food intolerance and obesity, which are taking on the size of a real pandemic plagiarism. Also in this case the Nutrigenomic and the Microbiomic give an interpretation in key of polymorphic or of the Microflora variations in order to describe the phenomenon. In addition to gastrointestinal intolerances and diseases of recognized

genetic origin, there are others that have a different cause, are those produced by the additives used in the production of foods that we have mentioned previously [23-25].

In fact, what has changed in the modern diet compared to that of previous centuries?
The nutrients are the same but the contribution of the various substances has changed with the diet -Fig.5- and the mode of production and transformation of the foods, introduced from the industry, with the uncontrolled use of the additives of various nature along the productive chain. Let's try to describe what impact these substances have on the biological and nutritional quality of food and on our health [26,27].

Additives act directly by modifying the chemical structure of many nutrients, for example proteins, they can undergo structural alterations and denaturation, or some metals that have a pro-oxidant activity and produce free radicals that modify the lipid structure and irreversibly damage the cell membranes of enterocytes. While the presence of methyl groups changes the DNA (*methylation*) which has an "epigenetic" effect that modifies protein or enzyme synthesis; *emulsifiers* alter tight junctions at the intestinal level, with "leaky gut" effect. The list could continue. The consequence of these alterations is that nutrients aren't recognized as natural by our organism, but are treated as "aliens" towards which to activate an immune defense process. This is the heavy tribute that we have paid for production of food on an industrial scale for the exclusive benefit of the multinationals food.

Environmental chemicals and intestinal microorganisms might interact in different ways:

- Gut microorganisms themselves can metabolise a variety of environmental chemicals;
- Microbiota can metabolise environmental chemicals after their conjugation by the liver;
- Environmental chemicals can interfere with the composition of the intestinal microbiota;
- Environmental chemicals can interfere with metabolic activity of the microbiota, with potentially deleterious consequences for the host;
- Microbiota can regulate host genes involved in chemical metabolism.

Food Addiction, Eating Addiction and Eating Disorder
To complete the discussion of the treatment of food produced by industry, we need to address the debated and controversial issue of food addiction. Food is a vital biological necessity and is one of the most complete and complex sensory stimulation systems with olfactory, visual, tactile, and gustatory stimuli that act simultaneously on different nerve centers and reward physiological needs [28].

Extensive literature has shown that the food industry makes extensive use of ultra-processed foods (ultra-processed foods, UPS) which are distinguished by the presence of food additives and processed ingredients, which are not used in the home kitchen, such as casein, whey, gluten, hydrogenated oils hydrolyzed proteins, modified starches, invert sugar, etc.. [*]

Junk food, coincides with the category of food, boot food and drinks, ultra-processed, for the presence of ingredients unknown to the kitchens at home (e.g. palm oil) and excess fat and saturated fat, added sugar and/or salt lead to completely unbalanced nutritional profiles. And it is precisely for this reason that junk food is also identified with the acronym HFSS (High in Fats, Sugar and Sodium).

[*] The agri-food industry is the leading manufacturing sector in the EU (with over EUR 1 trillion in turnover, 30 billion in trade surplus, 4.24 million in employment [28]. The interests at stake, inevitably, are carried forward by opposing sides on different sides. Large industrial groups vs. Smes, production chains vs. GDO, North vs. Southern Europe, balanced foods vs. indulgence foods (or junk-food, depending on your views).

The close link between eating ultra-processed foods and its association with food addiction has been documented [29,31]. The vicious link between sugar, fat and salt deliberately added to foods that could instead be made with balanced nutritional profiles serves to obtain an artificial 'palatability' to which addiction and compulsive consumption are associated. The identification of foods that can be associated with addiction is very important for the proper treatment and prevention of childhood obesity, which continues to be one of the world's largest health problems [32]. A heated debate is ongoing between advocates of processed food addiction and advocates of compulsive behavior in food consumption, to explain the pandemic explosion of obesity. Apart from the pathogenic conception of obesity according to the Nutrigenomic and Microbiomic discussed earlier, it is quite clear, that even admitting that at the origin of obesity there is a compulsive and dysphoric behavior of the obese subject, access to highly palatable food, artificially produced by the food industry, can only encourage and aggravate the tendency to overeating. This is another very important aspect of understanding the origin and causality of obesity and dysmetabolic diseases.

Critical Review and Limits of Nutrigenomics/Microbiomics Interpretation
It is known for many centuries the reciprocal and mutual activity exercised between the living and their environment and how this activity constantly modifies the living and their environment in the search for a constant homeostatic balance. In the human organism there are several ecosystems in which there are numerous microbial species that we call *Microbiota*, which have an important biological role for many vital functions and to maintain the state of health. Equally important are the changes that occur constantly in the various ecosystems for the normal activity and metabolic cellular turnover necessary for the growth and proper functioning of our organism. All these transformations undergo the influence of genetic factors (*Epigenetic*), of the Microbiome, diet and microenvironment (ecosystem), the latter represents the theater where all factors come into play. Fig.6 The closer the link between the different species that coexist in the same environment, the greater the influence they exert on each other, and, reciprocally, the effect that these biological entities determine on the surrounding environment [34].

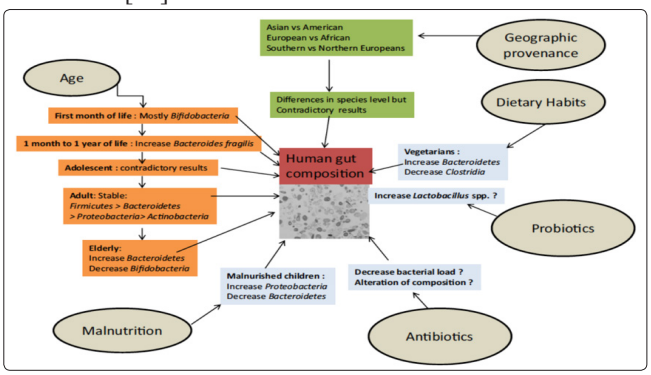

Figure 6: The influence of external factors determining the composition of the human gut microbiota

The content of the intestinal lumen is a complex ecosystem in which coexist products of digestion, mucus, enterocytes of cleavage of the mucosa, numerous microorganisms, and pollutants of various origins. It is in this cauldron that all the interactions between the various effectors take place that lead to the result of equilibrium or to the dysbiosis of our intestines.

The Nutrigenomic investigates only the variations of the genetic polymorphisms, the Microbiomic studies only the modifications of the intestinal Microbiome, in the research of their effects on the health conditions. Both overlook the results of mutual research and variations that occur in the intestinal environment [35-50].

Conclusion

Undoubtedly the study of the Microbiome and the Nutrigenomic, can make a fundamental contribution to the knowledge of the conditions that favor the state of well-being or the onset of diseases, particularly if they combine their efforts and their research with the common objective of improving our living conditions.

From the union of these two disciplines we will surely have great advantages and useful resources to fully and objectively discover the interactions between the diet, Genetics, the Microbiome and the lifestyle and the overall effects that these produce on our current and future health.

What I consider hardly sustainable is to attribute to the variability of polymorphisms or microbiome, individually considered, the state of well-being or disease that were ascribed to them. In the light of the above, I propose to reconsider the pathogenetic role of all factors that have a direct or indirect link with different diseases, and use a holistic approach that takes into account their effect on both the change of the microbiome, both on genetic variations [51-63].

We want to close with the words of the Italian Bioethics Committee: "*At present, research on the biological basis of complex characters remains essentially the subject of study, as predictive or susceptible tests, with some rare exceptions, are currently not clinically applied. On the other hand, a scenario is increasingly taking shape in which the most common diseases are determined by the cumulative effect of genes whose single effect confers a very modest risk of disease (with very low "penetrance") but equally relevant when associated with many if not plenty of other*"

Joint Group CNB-CNBBSV, NATIONAL BIOETHICS COMMITTEE NATIONAL BIOSAFETY, BIOTECHNOLOGY AND LIFE SCIENCES, GENETIC SUSCEPTIBILITY TESTING AND PERSONALIZED MEDICINE, 15 July 2010 -Page 17

Disclosure

The authors report no conflicts of interest in this work.

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