Title:

Quantum Biophysical Semeiotics Constitutions play a central Role in Single Patient Based Medicine

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Abstract

Background
The 'Single Patient Based Medicine' is the medicine based on the accurate knowledge of structure and function of biological systems in a single patient, and its nonlinear dynamics, the final result of the complex interaction between the environment and its genotype, expressed by maternal inherited constitutions, are studied both from physical and psychological points of view, with the aid of Quantum Biophysical Semeiotics (QBS).

Method
QBS theory has a trans-disciplinar approach due to the contribute of several sciences such as chemistry, biology, biophysics, applied mathematics, genetics, genomics, and the recent disciplines of deterministic chaos and quantum physics. QBS diagnosis is based on the ancient clinical method of 'Auscultatory Percussion', which permits a wide study of reflexes' auscultation, by means of the common stethoscope, as the body is appropriately stimulated.

Results
The stimuli are used to induce consistent behaviour in precise and well defined biological systems of the human body, thus giving local qualitative and quantitative information on the state of health or disease, whether potential, being developed but not yet evident by usual clinical trial, effective or even in the chronic phase.

Conclusions
This integrated vision favors a refined diagnosis in any stage of the most severe human disease, both from a clinical and pre-clinical point of view, so allowing an efficient primary and pre-primary health prevention.

Keywords: *Single Patient Based Medicine, primary prevention, stethoscope, bed-side diagnosis, mitochondrial dysfunction, microcirculation, genetic alteration, mtDNA, Inherited Real Risk.*

Overview

The concept of health proposed in 1948 by the World Health Organization (WHO), i.e., a state of complete physical, psychological and social wellness, and not just the absence of disease, is becoming a reference for the development of a new model of medicine centered not only on disease but also on health. The role of the physician as promoter of the health, and not only of diseases solver, is recognized. This paradigm shift is certainly a direct result of genetic and genomics research from which doctors still expect "huge advances in the ability to diagnose diseases on the basis of genotype, to identify conditions of increased risk related to the presence of susceptibility genes and to identify the best treatment for the specific health problem of a particular patient"[1].

These results really are slow to achieve for various reasons, including the absence of a previous rational selection, on a massive scale, of individuals at real risk of more frequent and severe human disease. The contribution of Evidence Based Medicine (EBM) is remarkable in the diagnostic and therapy, but there are difficulties in transferring on the single patient the large trials collected data, scientifically elaborated from a statistical point of view. Moreover, the EBM does not provide clinical information about single patient's bio-systems' structure and function. These customized information, unique and unrepeatable, have a primary importance for the attending physician and / or the researcher, at any given time. As the EBM does not adapt to the individual characteristics and priorities of the single patient, it becomes a form of potentially harmful reductionism.

In the Human Genome Project few genes responsible for rare monogenic diseases, such as cystic fibrosis [2] and Huntington's disease [3], have been identified so far. The very wasteful study of the mutated genes is hampered from achieving its objectives, due to the fact that only a small proportion of disease is monogenetic. For instance, issues relating to heredity in type 2 diabetes mellitus (T2DM) are very complex. The disease has a polygenic nature, and the phenotype of a patient with T2DM, in addition to environmental factors, involves at least three, perhaps even tens of different genetic variations. The current concept of pre-diabetes is a realistic foundation for the prediction and prevention of T2DM. A multi-factorial, multi-marker approach based on understanding of new patho-physiological factors of T2DM, tout-lines a "map" of pre-diabetes physiology. Predictive genetics is limited by the interpretation of genetic predisposition and individualization of the level of risk [4]. There is no doubt that T2DM pathogenesis interpretation calls for co-operation with clinicians [5].

Additionally, the products' activity of normal genes is prevented by pathological proteins. Mutations in these genes determine the disease with high but indefinable probability. However, there are many other genes (susceptibility genes) that may increase the risk of developing a disease [6]. These susceptibility genes essentially have the meaning of "risk factors". Genomics does not allows to know, for example, the real seat breast cancer risk in a woman with mutated BRCA1 and BRCA2, neither in the presence of EMSY protein. In the presence of mutated genes whether the disease has begun, and the precise site of onset of the disease remains to be discovered [7].

Moreover, today's medicine classifies diseases on the basis of their clinical manifestations. However, we recall that different diseases in relation to the cause and pathogenesis may present with similar signs and symptoms: diseases classification based just on symptoms and signs (i.e., the phenotype) has a certain meaning when treatment is only symptomatic, but it becomes a limit when therapy acts on the causes and pathogenesis of the disease.

Other open problems are the crisis of the doctor-patient relationship and the difficulty in the use of research results in daily practice activities. It is necessary to restore the doctor-patient relationship, adapting it to the current cultural situation. It is desirable that the physician could have a global, holistic, complete vision of the patient's health care. Physicians should perfectly know the psycho-physical structure of the single patients who addresses them.

Predictive diagnostics is considered as the basis for targeted preventive measures and consequent development of individualized treatment approaches. Of paramount importance is the

communication among professionals – medical doctors, biotechnologists, computer scientists, healthcare providers, policy-makers, educators – who are involved in the paradigm change from curative to predictive medicine. This is a new philosophy in healthcare and the platform for personalized patient's treatment, which is truly the medicine of future [8].
Genomics, proteomics, metabolomics, and bioinformatics are giving impetus to the development of this radically new health care area--preventive, predictive, and personalized medicine (PPPM) [9]. Predictive genomic medicine has the potential to shift medicine from a primarily population- or cohort-based activity to one that instead uses individual susceptibility, prognostic, and pharmacogenetic profiles to maximize the efficacy and minimize the iatrogenic effects of medical interventions [10].
The established molecular heterogeneity of human diseases requires the development of new paradigms for the design and analysis of randomized clinical trials as a reliable basis for predictive medicine [11]. More integrated and complex approaches going - beyond the simplistic idea of "one gene, one disease" are needed. For example, considering the genomic biomarkers in predictive medicine, although ten million single nucleotide polymorphisms have been identified to date, the majority of them do not appear to have a relationship with risk of development of pathogenic processes in the human body. Future developments are oriented on integrative systems of genomic risk markers [12]. Moreover, recent studies of predictive medicine still does not clarify and define the right border and the relationships between genetic causes and risk factors in the evaluation of susceptibility to diseases with a genetic component such as, i.e., breast cancer [13].
Interestingly, recent studies include a new customized holistic vision of the human subject, considering the uniqueness and complexity of each individual in a trans-disciplinary approach with the aid of disciplines such as mathematics applied to non-linear systems (neural networks, fuzzy logics, deterministic chaos), taking into account that between health and disease there is a largely unexplored and nuanced intermediate zone [14], pre-clinical stages, pre-metabolic, of certain diseases, but the pure mathematical-statistical approach does not seem to be easily extended upon a large scale.
The above mentioned open questions try to be faced by a new medical discipline that is called Quantum-Biophysical Semeiotics (QBS), based on auscultatory percussion or better reflex diagnostic auscultatory percussion [15]. A refined diagnostic methods, made possible by the QBS, the definition of the many QBS constitutions and pre-metabolic syndrome, classical and variant, which may follow them and move to the metabolic syndrome, have encouraged the founding of the Single Patient Based Medicine (SPBM) [16] introduced in the following chapter.

Single Patient Based Medicine

QBS theory provides an effective clinical method, reliable and not expensive [15]. It allowed to discover the many constitutions [17], basis of the SPBM, which plays an essential role in predictive medicine. With the aid of QBS, physicians can achieve a more correct diagnosis of the most frequent degenerative disease, particularly in the complete absence of clinical phenomenology: for example, it is estimated that there are about one-third of unaware diabetics, in consequence of the failure of clinical symptoms. QBS addresses this problem by using a different approach. Instead of investigating the mutated genes, QBS studies structure and function of biological systems, from the birth, allowing to recognize the many QBS constitutions and to monitor their possible pathological slow evolution over time. This monitoring permits, at the need, in a timely manner, an appropriate primary and pre-primary prevention. This original "Weltanschauung" in medicine led to the SPBM founding.
The Single Patient Based Medicine (SPBM), as defined by one of the authors [16], is the medicine based on the accurate knowledge of structure and function of biological systems in a single patient, the final result of the complex interaction between the environment and its genotype, expressed by QBS constitutions, studied both from the physical and psychological points of view, with the help of Quantum Biophysical Semeiotics (QBS).

Among the 5 key points of EBM there is the one related to the transfer in clinical practice of the conclusions drawn from the results: this is the locus of the action of the SPBM. The SPBM is a valuable tool in the diagnosis, therapy, research, primary prevention on a massive scale and in achieving the transfer of knowledge obtained with the EBM to the single patient. The predictive medicine, justified and made more effective by SPBM, allows to predict any change in the health status of a single subject, studied and objectively monitored both from the point of view of the simple predisposition to the disease and in its slow pathological evolution, lasting years or decades, starting from the very initial stages of the disease.

The role of the SPBM is essential In primary prevention of the most frequent and severe human diseases: not all individuals may be affected, i.e., by type 2 diabetes mellitus (T2DM) or cancer, but only those showing well defined (mtDNA) genetic alteration mostly transmitted through the mother [18]. QBS constitutions are one of the pillars on which the SPBM rests. QBS constitutions are the "conditio sine qua non" of the occurrence of the most frequent and severe human diseases such as T2DM, cancer and heart disease. In fact, according to QBS experimental and clinical evidences, without QBS constitutions, all the related environmental risk factors are innocent bystanders [19].

In reality, there are not diseases but sick persons, and each of them is an individuality. Only the perfect knowledge of QBS constitutions, of the way of being and functioning of the various parenchyma and its microvessels, may allow the physicians to best use all the possible benefits offered by EBM. In this way, the SPBM completes EBM in achieving optimum results in clinical diagnostics, in therapy and therapeutic monitoring of the single patient. The intent is favor a collaboration and interaction between EBM and SPBM. They can integrate and complement each other with great benefits for everyone: patients, doctors and National Health Services.

Quantum Biophysical Semeiotics: an introduction

QBS is a new discipline in medical field and an extension of the classical medical semeiotics. It is a scientific trans-disciplinary approach that is based on the "Congenital Acidosic Enzyme-Metabolic Histangiopathy" (CAEMH) [18], a unique mitochondrial cytopathy that is present at birth and subject to medical therapy. The presence of intense CAEMH in a well-defined area (e.g., myocardium) is due to gene mutations in both nDNA and mtDNA. At the base of all these alterations there are both parenchymal and microvascular inherited alterations (nDNA and mtDNA), which parallel the former, according to the theory of Angiobiopathy, that completes Tischendorf's Angiobiotopy theory [15], i.e., genome's information are simultaneously transmitted both to parenchyma and related microvessels. In fact, all complex gene mutations parallel biological system dysfunctions [20], because, to be significant, whatever gene mutation has to bring about well-defined biological system functional modification, we can now study by means of a stethoscope. This is the basis for one or more QBS constitutions [17], i.e., Oncological Terrain [15], which could bring about their respective Inherited Real Risks (IRR) [15, 21], i.e., IRR of breast cancer [7]. QBS constitutions [16,17], diagnosable since birth, represents the genotype of QBS approach: they are the inherited congenital ground or terrain of well defined potential diseases clinically hidden, which can last several years before appearing, in the slow transformation process from potential (pre-metabolic syndrome, pre-clinical stages) to effective pathology (metabolic syndrome).The contribution of these modifications to the relative pattern of any syndrome, based always on genetic or inborn errors – CAEMH - is different from patient to patient and during the disorder's evolution. For instance, in case of diabetic syndrome, insulin-secretion increases silently for years or decades, before appearing T2DM. This is a pre-clinical stage [5] that is not detectable through usual clinical tests. QBS approach allows to assess, through a bed-side evaluation, the existence of the pre-metabolic syndrome [22], that can last for years or decades, pre-clinical stage of the disease still potential or on training (evolution to pathology, pre-morbid state or gray area), so allowing an effective prevention. QBS method permits the clinical and pre-clinical diagnosis of the most severe diseases, which is achieved in the easier way through the 'Auscultatory Percussion' of the stomach [15, 23]. The patho-physiology of QBS reflexes is based upon local microvascular conditions. In

case of genetic alteration of both DNAs, intense CAEMH, maternally-inherited QBS constitutions evolving to the IRR of the related disease, i.e., T2DM [5], cancer [7], CAD [24], Alzheimer's Disease [25], lithiasis [26], there is a typical, inherited microcirculatory remodeling of related microvessels. This is worsened by well-known environmental risk factors, caused by vasomotility and vasomotion impairments (e.g., functional imperfections) and structural obstructions, due to the newborn, pathological Endoarteriolar Blocking Devices (EBDs), discovered by one of the authors, and Arteriovenous Anastomosis (AVA) [15, 21]. The local biological activity, examined with the aid of QBS signs, results significantly abnormal, allowing to assess the IRR of pathology at an individual level. This information complements testing for mutations of disease susceptibility genes or for their diminished expression; it is an adding value for a more precise and refined diagnosis. QBS diagnosis is based on the method of 'Auscultatory Percussion', through which by means of the common stethoscope, it is possible to listen to the signs that the body gives us when appropriately stimulated. The stimuli are used to induce consistent behaviour in precise and well defined biological systems of the human body, thus giving local qualitative and quantitative information on the state of health or disease, however potential, being developed but not yet evident by usual clinical trial, effective or even in chronic phase. QBS theory provides very detailed case studies (on more than 100.000 patients) based on the latency time, duration, and intensity of the reflexes, which play a central role in such a clinical method, that can be used both for diagnostic purposes and for therapeutic advices, because it is able to measure the microcirculatory activity and its complex behavior, whose nonlinear dynamics, as measured by statistic invariants typical of deterministic chaos and fractals, i.e., fractal dimension measure, have significant interpretation and importance for clinical and pre-clinical diagnosis and therapeutic monitoring [26] before and after each preventive treatment, in order to understand the effectiveness of remedies, so orienting and monitoring any choice according with biological activities modifications and improvements, allowing a proper primary and pre-primary prevention. Several studies [28, 29] agree that nonlinear complexity appears to degrade in characteristic ways with aging and disease, reducing the adaptive capacity of the individual. QBS experimental and clinical evidences confirm that chaotic complex dynamics, typical of physiological bio-systems' behaviors, slowly decrease to simpler dynamics as well as, i.e., a QBS constitution progressively evolves to the IRR of pathology, and the overt disease [30].

Method: Diagnosis of Quantum Biophysical Semeiotics Constitutions

The physician, skilled in QBS, should answer exactly the following question: what QBS constitutions [17] are present in the single patient and what is their severity? From QBS point of view, the basis of SPBM, one must know and be able to recognize quantitatively, at the bed-side, all the QBS constitutions at the time described, eventually present in the single patient, the 'Real Risk' of the most serious diseases in relation to the precise location and severity of the same risk, etc. With the aid of SPBM [16], it is easy to address and quickly implement a deeper diagnostic procedure, to prescribe a customized preventive therapy, to conduct an objective therapeutic monitoring and to achieve more correct prognosis integrating the customized information with EBM scientific data. This approach can foster major economies and a rationalization of costs for public health services with clear and easily deductible benefits.

Notoriously, the first act of the therapeutic process concerns the diagnosis, which should always precede any kind of treatment. An example of a QBS diagnostics, with the aid of SPBM, in case of acute pain in the right upper quadrant of single patient is as follows: a) history; b) QBS Constitutions diagnosis [17]; c) assessment of the Metabolic Syndrome, both classic and variant [15,22]; d) evaluation of antibody synthesis conditions [15]; e) evaluation of QBS inflammation's signs, i.e, RESH [15,31], acute phase proteins [15], circulating immune-compressed [15], prolactin elevation [15], etc.

In this chapter we introduce the easiest way to diagnose the presence or absence of any QBS constitution. In well-defined circumstances biological systems dynamics highlight the phenomena

of non-locality, similar to those of entanglement between particles in quantum physics [18, 32]. In particular, through the 'Auscultatory Percussion' of the stomach, by means of an intense stimulation of the investigated organ's trigger points, if the 'Gastric Aspecific Reflex' (GAR) appears simultaneously (the stomach expands simultaneously to the intense digital pressure), then there is the presence of the related QBS constitution, otherwise there is not. By this way we can assess the presence, or not, of any QBS constitution of any subject from the moment of birth. In table 1 the different QBS constitutions, and the related trigger points are summarized. The intensity of trigger-points digital stimulation can quantitatively vary depending on the information requested by the physician, both from a quantity and quality point of view.

QBS CONSTITUTIONS	TRIGGER POINTS	POSITIVE CONSTITUTION
Artrosic Constitution	Sinovium or skin of the back of the hand. Digital pressure	Simultaneous reflex
Atherosclerotic Constitution	Artery (brachial, femoral, carotid, etc.). Digital pressure	Simultaneous reflex
Diabetic Constitution	Sixth dermatome (skin projection of the pancreas). Pinching of the skin	Simultaneous reflex
Dislipidemic Constitution	Abdomen, Subcutaneous Region. Pinching of the skin	Simultaneous reflex
Gouty Constitution	Headset pavilion. Compression between two fingers of bent helix	Simultaneous reflex
Hypertensive Constitution	Biceps or any skeletal muscle. digital pressure	Simultaneous reflex
Lithiasic Constitution	Gall bladder under the costal arch (VII Thoracic dermatome). Pinching of the skin	Simultaneous reflex
Osteoporotic Constitution	Lumbar vertebra. Digital pressure	Simultaneous reflex
Oncological Constitution	Skin projection of the epiphysis or GH - SRH. Digital pressure	Simultaneous reflex
Reumatic Constitution	Sinovium or skin of the back of the hand. Digital pressure	Simultaneous reflex
Inherited Real Risk of CAD	Any point of precordium. Digital pressure	Simultaneous reflex
Inherited Real Risk of neurodegenerative disease	The pre-frontal area. Digital pressure	Simultaneous reflex
Inherited Real Risk of "Eye" disease	Eyeball. Digital pressure	Simultaneous reflex
Inherited Real Risk of gastrointestinal disease	Just above the jugular notch, along the midline of the neck. Digital pressure	Simultaneous reflex
Inherited Real Risk of nephropathy	Lateral abdominal region. Skin projection of a kidney. Pinching of the skin	Simultaneous reflex

Table 1. Diagnosis of QBS Constitutions

In case of slight or mean intensity digital pressure on the skin projection area of the investigated parenchyma, we induce a sufficient flow of matter-energy-information so inducing bio-systems nonlinear dynamics as those of dissipative systems far from equilibrium investigated by Prigogine [33], whose complex behavior is rich of quality information, quantitatively defined by the laws and statistic invariants of deterministic chaos [34]. These are the cases respectively of QBS ureteral reflexes (slight intensity stimulation) revealing the microcirculatory dynamics (microvessels

function and structure) tool of Clinical Microangiology [35] and, i.e., QBS gastric reflexes (mean intensity stimulation), for a deeper investigation of related parenchyma conditions in case of any positive QBS constitution [15, 17, 21].
In case of intense digital pressure on the trigger points of the investigated parenchyma, we are provoking a strong obstruction of the matter-energy-information flow, so that the above mentioned dissipative bio-systems - with positive entropy - so far created, tend to become conservative. Notoriously, conservative systems do not allow complex dynamics and complex equilibrium, i.e. strange attractors typical of deterministic chaos, so we can get a poorer information and simpler equilibrium due to a zero entropy. This is the case of the signs revealing the QBS Constitutions, giving a very simple information, 0/1 type, but of a primary importance for diagnosis and therapeutical monitoring, suggesting and inducing physicians to a deeper investigation, so allowing an effective primary and pre-primary prevention. Really, simultaneous QBS signs, are a recent discover due to the fact that their sense and meaning is finally revealed by a transdisciplinar approach, i.e., the precious contribution of quantum entanglement phenomena in physics [36], the recent observations of biological entanglement [32] and the experimental evidences of the wave genomics [37].
In presence of any QBS Constitution, the physicians must refine the diagnosis making an investigation more focused on the correct localization and severity of the underlying clinical disorder, if the pathology is in progress, or of its Inherited Real Risk, if there is one or more. In fact, a QBS Constitution, i.e., Oncological Terrain [15, 17], can be present from the moment of birth, but the IRR of any cancer can last several decades before appearing or they cannot appear at all along the life. This is achieved through a deeper QBS diagnosis of the specific signs, i.e., IRR of type 2 diabetes mellitus [5], Coronary Artery Disease [24], breast cancer [7], Alzheimer's Disease [25].

Results: QBS Primary and Pre-primary Prevention

QBS tools are useful both for diagnostic purposes and for therapeutic advices. QBS diagnosis, corroborated by more than 100,000 clinical and experimental evidences over the last five decades, allows a primary and pre-primary prevention providing additional information complementary to those usually collected according with Official Protocols. QBS therapeutical monitoring allows to measure the microcirculatory activity before and after each preventive treatment, in order to understand the effectiveness of remedies. In case of IRR of any degenerative disease - CAEMH and QBS Constitution-dependent - preventive treatments [38,39] are suggested to stimulates the activity of mitochondria respiratory chain by acting on metabolism, but also improving it, as far as to normalize mitochondrial and tissue oxygenation, expression of the normal activity of mitochondrial oxidative phosphorylation. By this way tissue oxygenation and mitochondrial activity improve, mitochondria run well, but the genetic alteration of mit-DNA still remains: CAEMH, QBS Constitutions and IRR are yet positive, but the IRR becomes 'residual'. By the way, recent experimental evidences show the chance of an efficient pre-primary prevention with recursive effects [40] able to reverse the genetic alteration of mit-DNA and CAEMH. In particular, we successfully tested a quantum therapy based on millimeter waves with Extremely High Frequencies (EHF), for the pre-primary prevention of CAD [41] and other degenerative diseases, such as Type 2 Diabetes Mellitus [38] and cancer [39].

Conclusions

The SPBM allows a prior rational selection, on a massive scale, of individuals at real risk of the most frequent and severe human diseases, a goal that can only be reached by using an effective clinical method, reliable and not expensive, such as that offered by the QBS approach, which can play an essential role in predictive medicine. Such predictive medicine, enriched by QBS informative contribute, permits to achieve the best results with lower and more sustainable costs for National Health Service (NHS). This is possible only if the genotype of all individuals, from a biological point of view, is early recognized, possibly from birth, and secondly, adequate preventive

measures are implemented just in the subjects so far rationally selected, positive for one or more QBS constitutions, revealing the possible future risk of any of the most common and severe human disease, i.e., type 2 diabetes mellitus, dyslipidaemia, hypertension, glaucoma, gout, osteoporosis, gallstones, malignant tumors. The application of this theory on a large scale, permits health care costs savings, free resources for research, primary prevention, and really efficient preventive therapies, finally addressed on rationally selected individuals therapeutically monitored by perfectly appropriate clinical controls distributed over time, as needed.

List of abbreviations

AVA stands for Arteriovenous Anastomosis
CAEMH stands for Congenital Acidosic Enzyme-Metabolic Histangiopathy
CAD stands for Coronary Artery Disease
EBM stands for Evidenced Based Medicine
EDBs stands for Endoarteriolar Blocking Devices
IRR stands for Inherited Real Risk
mtDNA stands for mitochondrial DNA
nDNA stands for nuclear DNA
NHS stands for National Health Service
PPPM stands for Preventive, Predictive, and Personalized Medicine
QBS stands for Quantum Biophysical Semeiotics
SPBM stands for Single Patient Based Medicine
T2DM stands for Type 2 Diabetes Mellitus
WHO stands for World Health Organization

Conflicts of Interest

None

Authors Contributions

Sergio Stagnaro has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. He has given final approval of the version to be published.
Simone Caramel has been involved in drafting the manuscript or revising it critically for important intellectual content.

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