Advances in Sciences and Humanities
2018; 4(2): 25-36
http://www.sciencepublishinggroup.com/j/ash
doi: 10.11648/j.ash.20180402.12
ISSN: 2472-0941 (Print); ISSN: 2472-0984 (Online)

Review Article

Quantifying Wellness: Beyond the Dichotomous Choice Between Health and Disease Lies the Road to P6 Medicine

Charles Joseph Kowalski, Adam Joel Mrdjenovich

Health and Behavioral Sciences Institutional Review Board, University of Michigan, Ann Arbor, USA

Email address:
chuckk@umich.edu (C. J. Kowalski)

To cite this article:
Charles Joseph Kowalski, Adam Joel Mrdjenovich. Quantifying Wellness: Beyond the Dichotomous Choice Between Health and Disease Lies the Road to P6 Medicine. *Advances in Sciences and Humanities*. Vol. 4, No. 2, 2018, pp. 25-35. doi: 10.11648/j.ash.20180402.12

Received: May 7, 2018; **Accepted**: July 23, 2018; **Published**: August 18, 2018

Abstract: Systems medicine is the culmination of the progression of the health/disease dichotomy to a continuum from health to disease allowing for measures of disease accumulation that mark an individual's position, i.e., her wellness, along the continuum. Proponents of systems medicine have promised a scientific (non-normative), value-free, holistic measure of "wellness" that will be the cornerstone of P4 (personalized, predictive, preventive and participatory) medicine. While the focus of this paper is on the quantification of wellness, the authors also consider how this metric drives the rest of the P4 program. The authors trace the history of this development in order to appreciate the promises, problems, pitfalls, and perils that accompany this approach. To the 4Ps already in place, the authors add P5 = promissory and P6 = profitable, and find that the road to P6 medicine is paved with neoliberal theories.

Keywords: Health, Disease, Illness, Systems Medicine, Neoliberalism, Biomedicalization, Commodification

1. Introduction

Kowalski and Mrdjenovich advised against indiscriminate dichotomization [1]. They looked at (i) nature vs nurture, and reductionism vs holism, and (ii) several of the ways the scientific pie can be sliced in two pieces, basic vs applied, physical science vs social science, etc., arguing that, in (i), focusing on one or the other of two dichotomous choices often deflects attention from a more fertile intermediate ground where more useful answers might be found, and that, in (ii), a more useful classification scheme than the basic/applied opposition would be based on the nature of the question being asked and the manner in which an answer is sought [2]. Kowalski and Mrdjenovich did not consider the purported health vs disease dichotomy to which the authors now turn our attention. Since the primary interest is in the quantification of wellness, this discussion focuses on those definitions of health/disease that envision the two as extreme points on a continuous scale that will admit of at least the ability to order values along it. The authors begin with a supposed true dichotomous definition of health (and disease), note some of the criticisms that have been raised, and briefly summarize some of the proposed remedies. The authors then focus on those "solutions" admitting of at least an ordinal scale connecting the endpoints, beginning with measures that lead to step-function progressions between health and disease. The authors then study the frequently encountered situation where surrogate markers and/or risk-functions of disease have continuous measurement scales. The next step in this progression is the quantification of wellness, developed for use in P4 medicine, the clinical face of systems medicine, which is itself an offshoot of systems biology. This metric is to be scientific, yet useful in developing individualized treatment plans, and holistic, an all-encompassing summary of what it means to be well.

2. Health vs Disease

The (not simply academic) importance of being able to define health and disease is stressed in [3]. Richman reviews the various attributes that such definitions might possess (e.g., do values play a role?) and describes a number of attempts to provide workable definitions. The authors do not comment on all of these, but begin with an early (1977), widely discussed

definition that has often been used as ground zero for discussions such as ours which states that a system is healthy if it is performing its biological functions well enough to count as typical for its reference class [4]. Specifically, as advanced by Christopher Boorse,

(i) The reference class is a natural class of organisms of uniform functional design, e.g., an age group of a sex of a species.

(ii) A normal function of a part or process within members of the reference class is a statistically typical contribution by it to their individual survival and reproduction.

(iii) A disease is a type of internal state which is either an impairment of normal functional ability or a limitation on functional ability caused by environmental agents.

(iv) Health is the absence of disease.

Item (iv) imposes the dichotomy. Health is seen to be normal functioning, where normality is statistical and functions biological. Boorse is aiming here for a completely theoretical definition of health, one in which values are to play no part, i.e., a non-normative definition of health. The focus is on physiology: Given a normal environment, all of a person's organs need to be functioning normally for that person to be considered healthy. Boorse emphasizes that he is only interested in providing a theoretical, not a clinical, conception of health and disease. This theory is often referred to as the bio-statistical theory of disease, BST.

It didn't take long to recognize that this theoretical definition was of limited use in practical contexts. Indeed, Boorse himself noted that the concept of health as applied in medical practice was somewhat different from the BST, and it is here that he introduced his notion of "illness," "namely, those diseases that have certain normative features reflected in the institutions of medical practice" [5, p. 56], i.e., the diseases treated by licensed physicians.

The World Health Organization (WHO), in 1984, singled out Boorse's item (iv) for direct challenge when it defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." Thus WHO explicitly included mental and social dimensions into the definition, and with the term "well-being" put a positive spin on health, not merely the absence of negativity. Other representative critiques of the BST were given in [6, 7]. In [6], it was shown that Boorse did not succeed in giving a non-normative definition (choosing the appropriate reference classes is value-laden), and in [7] an epidemiologic approach to the study of disease with its attendant risk-of-disease orientation also challenged reference classes, along with the notion of "statistical subnormality," and the normal and pathological as mutually exclusive categories.

These limitations of the BST led to a number of attempts to develop a more encompassing (biopsychosocial) theory of health. The authors separate these into two main categories: those that welcome the addition of normativity and try to "build bridges" between health concepts and disease concepts, and those that try to hang onto a strictly scientific approach, based on the idea of a continuum between two of the extreme values, health and disease.

The authors will have little to say about the first category, except to point out that Fulford [8] explicitly invoked the bridge metaphor in his development which was to span the biological/social divide. Whereas Boorse thought Illness to be a subset of Disease (those diseases that were treated), Fulford adopted the "reverse view," maintaining that Disease is a subset of Illness. For Boorse, one first became diseased, then ill. For Fulford, the natural progression followed the reverse order: something is wrong, so I consult a physician. S/he does some tests and discovers I have such-and-such a disease. Progress in this direction up to 2004 was described and discussed in [3]. Therein and in [9] Kenneth Richman and Andrew Budson developed a theory – called an "embedded instrumentalist" theory – which introduced a distinction between the health of an individual qua organism and the health of an individual qua person. The idea of health qua person is meant to capture positive features of health and is closely related to the notion of quality of life, which brings its own issues regarding measurement [10] and interpretation [11]. In any case, the authors consider the Richman-Budson exposition to be the gold standard of theories of this genre. K. Danner Clauser et al [12] introduced the concept of malady in order to make the definition of "disease" more inclusive, viz., to include problems people have with injuries. Some more recent developments aiming to incorporate health, disease and illness as well as all forms of medical practice are also available [13-15]. These efforts have not succeeded in producing a single, universally accepted criterion for separating health and disease; and interest exploring possibilities remains current. Indeed, a recent issue of Volume 38 of this journal focusses on this question. See Simon et al [16] for an introduction to and summary of this material.

The authors turn attention to the quantification of wellness based on the assumption of the existence of a continuum connecting healthy values to those signifying disease. The reasonableness of this assumption is based on the notion that a strictly dichotomous view is untenable. The authors cite several particularly convincing proponents of this. In the first, Peter Schwartz [17] noted that, in the BST, disease was taken as basically synonymous with dysfunction (item (iii)). The problem, then, if one is to define a dichotomy, is to decide where to "draw the line," i.e., when is there "an impairment of normal functional ability, i.e., a reduction of one or more functional abilities below typical efficiency"? After noting that Boorse had but little to say about this problem, save to conclude the line placement is arbitrary, Schwartz attempts to provide some guidance, introducing the concept of the magnitude of negative consequences imposed by the decreased functional level. This is shown to be useful in several cases, but in general some degree of arbitrariness is unavoidable. This observation supports the notion of a continuum connecting health and disease.

To expound on the parallel between disease and dysfunction in the BST and the observation that arbitrariness cannot always be avoided, we pause to consider a particular context or circumstance; viz. mental illness. Specifically, we contemplate the definition of mental disorder as a

manifestation of dysfunction, and the notion that a given psychological phenomenon should not be classified as a mental disorder unless that phenomenon is a symptom of dysfunction within an individual. The problem, then, if one is to define a dichotomy, is to decide where to "draw the line," i.e., when is there "an impairment of normal functional ability, i.e., a reduction of one or more functional abilities below typical efficiency"? Demarcating the boundary between "normal" and "abnormal" psychological functioning, for example, evokes related questions of how far given behaviors must deviate from "the norm" before those behaviors can be considered pathological; in other words, what is the threshold for diagnosis? Developers of the most recent revision of the Diagnostic and statistical manual of mental disorders [18] were tasked with such questions and issues in reference to the categorical versus dimensional (continuous) approach to diagnosing psychiatric conditions. The categorical approach suggests that mental disorders are discrete entities. Thus, the diagnostic criteria for many of the conditions listed in DSM-5 include cutoffs, such as the requirement that symptoms must be present for at least six months, which can be applied in making determinations about whether an individual "has" or "does not have" a mental disorder. These cutoffs (dichotomies), have been characterized as arbitrary consistent with a more general criticism that the DSM classification system has encroached into normal problems of living. For instance, in previous editions of the DSM, grief experienced over the death of a loved one was considered normal so long as it did not persist beyond two months. A goal of this criterion, known as the bereavement exclusion, was to avoid over-diagnosis; that is, to avoid labeling normal and expected responses to significant loss as clinical depression. As such, clinicians were advised to refrain from diagnosing Major Depressive Disorder (MDD) in patients if their symptoms occurred within the first two months following the death of a loved one. Yet, the significance of the two-month time period was unclear, and possible over-diagnosis was not the only concern. There were also concerns that the bereavement exclusion might lead clinicians to miss major depression when it was present given that grief and major depression can coexist (e.g., the death of a loved one can precipitate a major depressive episode). Thus, the exclusion was ultimately removed from the diagnostic criteria for MDD in DSM-5 and replaced by language to the effect that clinicians must make a careful differential diagnosis in order to facilitate appropriate interventions. This reflected a broader effort to define mental disorders neither expansively leading to unnecessary treatment for everyday problems in living, nor restrictively leading to a denial of treatment for people who could benefit but who do not meet a particular diagnostic threshold [19].

To that end, and in contrast to the categorical approach, dimensional models contend that an exact boundary between normal and abnormal psychological functioning simply does not exist. Said another way, the dimensional approach does not dichotomize; instead, it suggests that mental illness and mental health exist along a continuum such that mental disorders are extreme variants of normal psychological functioning. This has begged the question of whether all or a portion of the DSM could be based on dimensions rather than categories. As an example, we consider the diagnosis of mental retardation, which treats intelligence as a continuous variable (FSIQ < 70), even though there are no discrete breaks that could be used to make a distinction between "normal" and "abnormal" intelligence. An implication is that other mental disorders could be treated in a similar fashion.

Another way of arriving at the validity of a continuous model was given by Elodie Giroux [7]. He looked at health and disease through an epidemiologic lens while maintaining Boorse's theoretical orientation, and showed how analytical (risk-factor) epidemiology raised difficulties for the binary classification of health and disease as mutually exclusive categories, favoring instead a continuous account. He stated (p. 181):

'Risk-based diseases', such as the paradigmatic cases of hypertension and hypercholesterolemia (as used as an indicator of the atherosclerosis process), form a continuum with normal states and thus have an equivocal and unclear status, located somewhere between the normal and the pathological."

He then considered the example of drawing a line between normotension and hypertension:

"In contemporary medical practice, the limit of normality for such a variable does not rely on the normal range, i.e., the population distribution of statistical parameters of blood pressure levels. Rather, it relies on mortality increasing linearly with increased blood pressure, as well as on other economic and therapeutic parameters".

This is clearly a risk-based and value-laden (other economic and therapeutic factors) decision. This line of thinking was reinforced by epidemiologic studies like those held in Framingham MA [20, 21] and Tecumseh MI [22]. Increasingly, the way that diseases such as high blood pressure, high cholesterol, and diabetes[1] are in fact defined is closely related to ideas about modifiable risks [23].

This shift in focus from symptoms and signs of disease to risks of disease resulted in data-base-intensive reliance on modifiable (measurable) risk factors in the definition and diagnosis of disease. Large numbers of patient cases were summarized in statistical tabulations of diseases and physiologic measurements. Correlations were computed and risk factors identified. The relationship between high blood pressure and the development of atherosclerotic diseases resulted in high blood pressure itself becoming a disease state requiring treatment. Jeremy Greene [24] noted that this shift in focus could also be phrased in terms of who was doing the looking: symptoms have immediate subjective significance in defining illness, a first-person voice. Signs, that is pathognomonic indicators of disease such as seen in sclerotic arteries, added a second-person, the physician, dimension to the equation. Now, diseases that may be invisible to both

1 For example, the Health Service at our University does a blood test, called A1C, that that checks blood glucose levels and are used to diagnose prediabetes and diabetes. Normal levels are in the range 4.2 – 5.6%; the pre-diabetic range is 5.7 – 6.4%; and diabetes any level ≥ 6.5%.

patient and physician alike can be diagnosed by those with the proper data base, adding a third-person to the mix. The good news was that this trend could be defended by making the whole process seem more "scientific." "Such numerical definitions of pathology offer a detached, third-person perspective, seemingly independent of both doctor and patient, connected instead to the anonymity of measuring devices and expert committees that define standards, thresholds, and guidelines" [24, p. 8]. The bad news was also noted [24, p. 8-9] quoting Richard C. Cabot who in 1907 warned against indiscriminate use of laboratory medicine: "all that tends to make us build up our diagnosis at a distance from the patient, and without the constant reminders of every side of his case given us by his actual presence before our eyes – all such tendencies, I say, are dangerous."

The authors will consider some of the dangers that arise from adopting detached views that envision patients as points in a p-dimensional space in what is to follow. For the moment, we mention just one such troubling trend. Greene [24, p. 229] showed how the boundaries between normal and abnormal were pushed outward by both pharmaceutical companies and public health advocates so that an increasing number of health states became sufficiently abnormal to warrant treatment. He detailed how this happened for three common ailments, high blood pressure, diabetes, and high cholesterol. And, while Greene did not place exclusive blame on the pharmaceutical industry for the expansion of these boundaries, big pharma surely has an incentive to welcome this trend, as may be seen from the fact that when, in 1984, the guidelines for diagnosing hypertension were lowered from 95 to 90 Hg, this almost doubled the number of Americans considered to be hypertensive and candidates for treatment (p. 77). This is one instance of a process called medicalization, i.e., redefinition of conditions, procedures, behaviors, or characteristics as belonging under medical jurisdiction. The advent of advances in molecular biology has greatly expanded the number of biomarkers we have available to describe disease processes, and resulted in what is called biomedicalization, many examples of which are given by Adele Clarke and colleagues [25].

The authors revisit mental illness in this regard to observe that advertisements and disease awareness campaigns have disseminated the idea that mental disorders can be attributed to fixed biological properties within individuals, and that such disorders represent deviations from "normal" biological functioning [26, 27]. Although such notions were initially applied only to severe mental illnesses, the application has been expanded in recent years. Citing the examples of Binge-Eating Disorder, which is diagnosable in individuals who eat excessively at least 12 times during a three-month period, Frances [28] expressed concern that the DSM-5 would "lower diagnostic thresholds and lead to a higher prevalence of mental disorders" (n.p.).

And, while Greene bends over backwards to note that big pharma is not acting alone in the redefinition of many disease processes, Joseph Dumit [29] is less sacrosanct; he focuses directly on the relationship between big pharma and clinical epistemology. The subtitle of his book, How pharmaceutical companies define our health, accurately describes his subject. He argues that the continual growth in medications, disease categories, costs, and insecurity in the face of risks for impending diseases is due largely to the efforts of the pharmaceutical industry who have carried out clinical studies seen as investments and measure the value of those investments by the size of the market and the profits they will generate. They ask only questions for which the answer is more medicine. As a result, we have a new perception of ourselves as inherently ill and in need of chronic treatment. Esposito and Perez [30] discuss this perception with reference to the mental health arena. Namely, they explore ways in which the very definitions of "normal" and "abnormal" have been informed by interpretations of reality that reflect market considerations, and comment that market society tends to pathologize thoughts and behaviors which deviate from those the market defines as "functional, productive, or desirable" (p. 1).[2] Failure to assimilate typically reinforces the perceived pathology, and the need for chronic treatment confirms personal feelings of doubt and uncertainty. Moncrieff [27] adds, "These feelings are debilitating and they help... to create the dissatisfaction that drives consumerist behavior... A population that feels inadequate is more vulnerable to [consumption]" (p. 302). Esposito and Perez [30] conclude that mental disorders have been "treated as self-contained ailments that can be resolved individually through pharmaceutical drugs, as opposed to being by-products of a market society, where the emphasis on profit/personal gain and competition erodes social bonds and promotes alienation" (p. 3). They caution that "only by opening the reality of a market society to critical evaluation can definitions of sanity/normalcy begin to move beyond sanctified market standards and reflect more fully the richness, diversity, and complexity of human social life" (p. 5).

We have come to "live by the numbers" and "risk factors" and so have but one rational choice: to embrace lifelong commitment to pharmaceutical management. Kaushik Sunder Rajan [31] has also produced a careful study of big pharma's control of clinical epistemology. In particular, what gets considered as health comes to depend on what kinds of experimentation is being done and what kinds of therapies are being developed. "Health is no longer just an embodied, subjective, experiential state of well-being or disease; it can be abstracted and grown, made valuable to capitalist interests" (p. 7). The kind of speculative financial bets that are made in pharmaceutical development are not bets that have anything to do with therapeutic efficacy; they are, rather, bets on market size market penetration, and the potential for market growth. They are bets on therapeutic consumption [31, p. 43].

2 Esposito and Perez [30] put forward that people are considered normal in a market society when they assume personal responsibility for their own circumstances or problems by seeking mental health treatment that would enable them to adjust their attitudes and behaviors to fit with market demands. Individuals who do not subscribe to market reality are regarded as "unproductive" or "irrational", and their behavior might even be attributed to dysfunction or pathology.

In any case, having demonstrated that a strictly dichotomous view of health/disease is untenable in most contexts,[3] the authors proceed to describe and discuss models based on a health/disease continuum. Before delving into the fully continuous model, however, the authors briefly consider an intermediate step that may prove useful in certain situations. Step function models of disease go beyond the dichotomous healthy/diseased classification to a number of ordinal steps along the way. Sara Shostak [34, p. 254; 35] described one such by, "So, you're healthy, now you have hypertension, now you have advanced cardiovascular disease, now you have congestive heart failure, now you're dead." These ordinal-scale models have a long history in clinical medicine [36] and are especially useful when patient-reported-outcome-measures (PROMs) are used, as in a patient grading her pain on a scale from 0 to 10.

Now, one might go beyond the bald statement of "disease" and use molecular biomarkers to indicate disease severity as in saying "you've got one hundred thousand deformed proteins," as opposed to "you've got emphysema." The idea is to go beyond being merely "healthy" or "ill" to use biomarkers as measures of disease accumulation. One would describe gradations of disease by defining "a continuum from health to illness with different quantities of markers of 'disease accumulation' marking an individual's position and movement along the continuum" [34, p. 255]. Thus molecular epidemiologic models of disease replace "step function" models of health and illness with fully normalizing models based on continuous gradients of quantifiable markers of disease. Using biomarkers as measures of disease accumulation, they provide a numerical measure of "wellness," marking an individual's position on the continuum connecting health and disease.

The authors consider next a general proposal for the quantification of wellness that aims for a scientific, holistic measure that will serve as the basis for an approach to clinical medicine that is personalized, predictive, preventive, and participatory. The authors denote the proposed metric by Q (W). Serious concerns can be raised about each of the purported properties of this metric and these are discussed in turn below. The authors first trace the origins of Q (W) to systems biology, in the next section.

3. Systems Biology, Systems Medicine, Systems of Systems, and Networks

Systems biology is the study of biological systems as collections of networks at multiple levels, ranging from the molecular level, through cells, tissues and organisms, to the population level. Systems medicine is the application of systems biology to human disease. In particular, systems medicine is an interdisciplinary field of study that looks at the systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions. Systems medicine draws on systems science and systems biology and considers complex interactions within the human body in light of a patient's genome, behavior and environment. Both systems biology and systems medicine take holistic, quantified approaches to the challenge of biological complexity.

Perhaps the leader in the development P4 medicine[4] as the clinical face of systems medicine has been Leroy Hood and colleagues at the Institute of Systems Biology (ISB), www.systemsbiology.org. They consider the five pillars of systems medicine to be [42]:

Pillar 1: Cutting-edge technologies for generating data regarding multiple dimensions of each person's experience of health and disease;

Pillar 2: A digital infrastructure linking participating discovery science and clinical institutions, as well as patients/consumers;

Pillar 3: Personalized data clouds providing information about multiple dimensions of each individual's unique dynamic experience of health and disease ranging from the molecular to the social. These data will include genetic and phenotypic characteristics, medical history, demographics and other sociometrics;

Pillar 4: New analytic techniques and technologies for deriving actionable knowledge from the data; and

Pillar 5: Systems biology models for understanding the unique health status of each individual in terms of dynamic network states that can be manipulated by cost-effective strategies.

Each individual is seen as comprising and being part of a network of networks. Each individual is represented by a data cloud consisting of billions of data points representing the fully integrated "network of networks" that specifies genetic, molecular, cellular, organ levels and their interconnections, as well as the person's connection to society at large. According to Hood and Flores [38, p. 613], "Systems medicine promises to (1) provide deep insights into disease mechanisms, (2) make blood a diagnostic window for viewing health and disease for the individual, (3) stratify complex diseases into their distinct subtypes for an impedance match against proper drugs, (4) provide new approaches to drug target discovery and (5) generate metrics for assessing wellness. P4 medicine, the clinical face of systems medicine, has two major

3 One last indicator of the difficulty in establishing a health/disease dichotomy may be seen in various attempts to measure these separately. For example, two widely-used and accepted books on measuring health [32] and measuring disease [33] have too many instruments in common to support their separation.

4 Some history on the evolution of the Ps: Systems biology was first seen by Hood et al [37] to enable predictive and preventive medicine that would then lead to personalized medicine. P2 heading to P3 at this point. Hood and Flores [38] raised the ante to P4: Predictive, preventive, personalized and participatory. The addition of participatory is important in that this paves the way for the patient to consumer transition: The individual is held accountable for his/her management of his/her health. Gamma [39] referred to these as 'buzzwords,' and noted that P5 was even within reach: precise, preventive, predictive, personalized, and participatory. Rose [40] recognized the promises of personalized medicine, but also pointed to problems and, even, perils. Another candidate for P5 was promotive, where the optimization of health or wellness is seen as the key to maximizing human potential for each individual [41]. In what follows, we take P5 to be promissory and eventually that P6 = profitable.

objectives: to quantify wellness and to demystify disease."

Quantify. Demystify. Commodify.

These papers, and a number of others emanating from the ISB feature two recurring themes. The first theme consists of two promises: we will quantify wellness and demystify disease. The second is that this is where the money is. Examples of the financial promises: "[A] new science-based 'wellness industry' will emerge over the next 10-15 years that will in time far exceed the size of the healthcare industry. P4 medicine is an area replete with economic opportunities" [38, p 622]. "[T] he wellness industry will be able to capitalize on its ability to improve health outcomes and will become a major source of wealth and economic growth in the 21st century" [42, p. 574]. "[T] here are enormous economic opportunities ahead for all of us" … "any nation that is a leader in the P4 revolution will potentially encounter striking economic opportunities" [43, p. 998]. "[S] timulate innovation and new company formation" [44, p. 1] … "P4 medicine will create enormous wealth for those who adopt it" (p. 13). Here the importance of promises (P5) and profits (P6) are made explicit.

In order to fulfill these promises, "the different levels of information (DNA, RNA, proteins, etc.) must be integrated to understand or capture how the environment has modified the basic digital information of the genome at each level of the biological information hierarchy (DNA, RNA, proteins, interactions, biological networks, cells, individuals and ecologies) and thereby to induce biological responses…the global and dynamic data from the variety of information hierarchies must be integrated and modeled." [45, p. 74]. This is indeed necessary for promise fulfillment, but nowhere in their subsequent published works do Hood or any of his colleagues provide the required models, nor do they even indicate how one might be able to go about integrating the different levels of information and pursuing model development. One might begin to suspect that they view this as proprietary information. Not to be deterred, Vogt et al [41] set out to find some details by studying their patent applications where promises without a roadmap for fulfillment are unlikely to be successful. They found that wellness quantification was tied to gene expression measurement. This connects the digital information of the genome to the next level in the hierarchy, i.e., gene expression is the process by which information from a gene is used in the synthesis of a functional gene product, most usually a protein. Ideally, this would be done by locating the final gene product, i.e., the protein, but it is often more convenient to detect one of the precursors, mRNA (messenger RNA) and to infer gene expression levels from mRNA measures.[5] In any event, having zeroed in on a particular product (we use the generic term molecule), the expression level of each of these is measured, and once having accomplished this, these expression levels are used to construct a health-associated expression region which is taken to define health and against which the position of any individual may be compared in order to determine that person's wellness. The region is a multidimensional region having p-dimensions, where p is the number of molecules considered and there is every reason to believe that p will be large (recall those "billions of data points" in the cloud for each individual). Vogt et al [41, p. 407] illustrate what is involved when p = 3. A three-dimensional ellipsoid represents a health-associated reference expression region. Given (x, y, z) values for another individual we can determine whether or not that individual is healthy and, if not, what molecule (s) are problematic.

The first problem with this approach is immediately evident. We have been promised a scientific, non-normative, value-free metric of wellness, but the health-associated expression region referred to above is determined by the scatter of points in p-dimensional space obtained from a number of individuals selected as exhibiting health. As pointed out by Vogt et al [39, p. 407], the patent states that "One skilled in the art can readily determine desired criteria for the reference population and select individuals fitting the desired criteria." The choices of what criteria to use and which individuals are thought to satisfy them are clearly value-laden. Just as Boorse's reference categories were seen to be normative by Kingma [6] and others, the choice of the reference population here is open to a number of considerations, many of which have but little to do with "science." Of particular concern is the problem of biomedicalization, where the wellness space gets squeezed so as to identify more and more individuals as in need of treatment when market expansion is the only real driver. It also begs the question of why, if those skilled in the art can in fact spot wellness, we need to bypass physicians who have been in this very business for years. When discussing the nature of the human infrastructure needed for creating systems medicine, Hood [44, p. 4] notes that it must encompass widely disparate cross-disciplinary backgrounds, including "biologists, chemists, computer scientists, engineers, physicists, and mathematicians." While this doesn't explicitly rule out physician membership, not prominently including them in this list begs the question of WHY NOT?

Vogt et al [41, p. 409] give three examples (PTSD, bipolar disorder syndrome and chronic Lyme disease) that the ISB has or will work on. These illustrate the problems with providing quantitative correlates to constructs of health and disease that have already been defined normatively.

The above considerations clearly show that Q (W) is not a value-free measure of "wellness." Nor is Q (W) holistic, as claimed. Vogt et al [46] also consider the question: In what sense is P4 medicine holistic? They begin by pointing out that P4 medicine is not holistic in the sense assumed in humanistic medicine, i.e., a stream of medical thought and practice which focuses on the functioning, subjective experience and values of patients as whole persons. Rather, P4 medicine incorporates a technoscientific holism, one that uses ever-more

5 There are a number of methods available to measure gene expression, e.g., Northern blot, Western blot, Fluorescent in situ hybridization, Reverse transcription PCR, DNA microarray, Tiling array, etc. No matter which is used, the result is a number between 0 and 100% with 0% signifying no expression, and 100%, full expression. Whether a high number is good or bad depends on the gene in question, e.g., for an oncogene, 0% would be good.

sophisticated technological means to gather more-and-more data from each particular person that are as all-encompassing or 'global' as possible from each of the systems considered; and then employs novel computer technologies to interpret the interconnections between these systems. This "lets measure everything" approach has a number of problems, perhaps the most vexing is what the authors refer to as the dimensionality problem.

For convenience, as is traditional [47], the authors represent the dimensionality of a multivariate data matrix by Nxp where N is the number of cases and p the number of variables. The existence of the dimensionality problem (but not its solution) was addressed by Hood [36, p. 5] who admitted, "There are networks of intrinsic networks: genetic networks, molecular networks, cellular networks, organ networks, and, finally, the assembly of the networks which operate in the context of the individual. In addition, there are extrinsic social networks that modify our environment. Both intrinsic and extrinsic networks must be taken into account to get the true systems view of disease." Thus, each individual is seen as comprising (N = 1) and being part of (N >> 1) a network of networks where each individual is represented by a data cloud consisting of billions (p) of data points representing the fully integrated "network of networks" that specifies genetic, molecular, cellular, organ levels and their interconnections, as well as the person's connection to society at large. Hood et al [35, p. 992] recognized that the term "personalized medicine" does not reflect the "enormous dimensionality" of the approach and that in order to realize the promises of the method, it will be necessary "to reduce this enormous data dimensionality to simple hypotheses about health and/or disease for each individual." Here the reliance must be on multivariate statistical methods (e.g., factor analysis), but these can be of only limited value in understanding the integration of all these parts into a comprehensible whole. These billions of data points may reduce to mere millions of dimensions (factors), but many of the problems mentioned by Kowalski [47] some 45 years ago are still with us and it will take heroic measures to simplify matters to the extent to which is necessary to affect clinical practice. Only one such heroic attempt was mentioned by Hood [42], viz., to assume these networks are fractal in nature, i.e., all the hierarchical levels of organization are similar in structure. No reason why we might expect homogeneity of network structures is given (or what this structure might look like), but it is clear that this is a very strong (heroic) assumption. One can even question the supposed hierarchical relationship between the levels identified as genetic, molecular, cellular, organ and environmental. Even in the simpler "triple helix" gene-organism-environment situation, Lewontin [48, p. 100] noted that, "the relations of genes, organisms, and environments are reciprocal relations in which all three elements are both causes and effects." Moreover, it opens the door to the dangers of naming the presumed homogeneous structural parts, reifying them, and forgetting that what is reflected here is an assumption, not reality. One can, if this approach is followed, actually commit three of the four of Gould's "oldest issues and errors of our philosophical tradition" all in one felled swoop (c.f. [1]), viz., reductionism, reification, and hierarchy.

One practical problem with statistically parsing a large number (let alone billions) of variables needs to be emphasized. Many of the so-called significant effects will turn out to be false positives. This was discussed by Ibrahim et al [49]. They point to risk of the "incidentalome," that large scale genomic analyses are likely to yield unexpected incidental findings for almost everyone, and take this as a symptom of a dubious quest to gather more-and-more data as a solution to just about any problem confronting us.

Vogt et al [50] also discuss a project undertaken by Hood and colleagues which can be described as follows: The Hundred Person Wellness Project is a 10-month pilot study of 100 'well' individuals where integrated data from whole genome sequencing, gut microbiome, clinical laboratory tests and quantified self-measures from each individual are used to provide actionable results for health coaching with the goal of optimizing wellness and minimizing disease. Vogt et al [50, p. 320] noted

Almost all individuals came to the study with the view that they were (for the most part) well. However, the study exposed for all individuals multiple actionable possibilities that could be acted upon to improve their wellness. This illustrated that most of us have unrealized potential for optimizing our wellness.

There seems to be a problem here. Something is wrong with everyone! All is not well! Actually, this comes as no surprise to Clifton Meador [51], who noted that the last well person was seen 1998 in a shopping mall in Kansas where screening for all known human diseases was offered during the Mid-America Health Fair. Nor would it shock Ibrahim et al [49] who warned that "large scale genomic analyses are likely to yield unexpected incidental findings for almost everyone." This phenomenon was termed the incidentalome by Kohane et al [52] and it was seen to be a serious challenge to genomic medicine. And the genome is but a small part of the entire P4 measurement battery … Nevertheless, the P4 program insists it's not really a problem. There is something wrong with everyone. And this is right where systems medicine wants us to be. It has allowed the medical domain to be extended "beyond the dimension of illness and cure and into the management of normality itself" [53, p. 67]. This move has been placed squarely on the neoliberal doorstep by Imre Bard [54], who documented the transition from restitutio ad integrum to transformatio ad optimum, and the rise of what has been called surveillance medicine, which seeks to constantly monitor health states in order to intervene as early as possible [55]. Everyone is targeted. Everyone is at risk. And "health states" include virtually everything one can think of, as long as there is a market for fixing what "ails" you. The core strategies of the P4 industry are to extend the domain of what we think of as "illness," and to include more-and-more people in the at-risk category. The authors chose but two of the many examples available. Nikolas Rose [56] discussed the strategy of finding people with elevated neurobiological risk

of becoming a perpetrator of aggression or violence; replacing the old "discipline and punish" approach with "screen and intervene." Susan Greenhalgh [57] described how neoliberal principles drove the Chinese government in the making and managing of their 'obesity epidemic.' Following Joseph Dumit [29], she chronicled an instance of where "only diseases representing commercially attractive markets are named and rendered treatable."

P4 Medicine. Promises, problems, perils, and pitfalls

Above the authors have pointed out some problems with the wellness metric proposed by Hood, et al., viz., it is neither value-free nor holistic. This metric is, however, but a piece of P4 medicine, and there are additional problems to be found as discussed in this section. There have been a number of critical reactions to the proponents of P4 medicine. It is convenient to distinguish between those written when the reactions were to the promises being made for the Human Genome Project (HGP), an effort which aimed at many of the goals of P4 medicine, but concentrated on but one system, the genome. This has been called personalized genomic medicine, and the authors refer to this as PGM. It is important to realize that all 4 of the Ps in P4 medicine were meant to apply to PGM [38], and serious concerns were raised about each of these [58, p. 437]. In turn,

> Regarding personalized: If PGM is allowed to buttress reductionist thinking, it risks exacerbating individual and group forms of discrimination;

> Regarding predictive: If PGM slides into medicalizing risk factors, it risks feeding the determinism that encourages stigmatization;

> Regarding preventive: If PGM is carried by the logic of prevention into reproductive settings, it risks resurrecting coercive eugenic practices; and

> Regarding participatory: If PGM serves only to transform social responsibilities for healthcare into individual responsibilities, in may exacerbate healthcare injustices rather than combat them.

The promise of empowerment has made the participatory pill easier to swallow, but Juengst et al [59] have argued that empowerment is a two-edged sword – patient empowerment does not always lead to positive outcomes. They point out that the most vocal of empowerment's advocates have been direct-to-consumer genome scanning companies (see [60] for descriptions of many of these along with their marketing strategies) and these are primarily – if not exclusively – driven by profit motives. See also [61]. And, to these concerns, we must add that participation is a lot of work. For an illustration for what is involved here, see Larry Smarr [62] who seemingly measured and monitored every conceivable health metric then known to man. He separated this measurement battery into three levels. At the highest level were the macro-variables such as nutritional input, exercise, sleep, and stress. The next level included his genome, proteins and metabolic products. The third level was the microbiome metagenome and its proteins and metabolic products. Seems like a full-time job. And expensive. And then there is the problem of analysis and interpretation. Could it be that only a select few will be able to participate?

The Juengst et al papers were written in reaction to the HGP (personalized genomic medicine), not the expansion of the HGP to other biological systems. Flores et al [42, p. 574] thought that system medicine overcame these problems: "For the most part, these concerns are alleviated by eliminating the undue focus on genetics," i.e., measuring everything instead of just the genome solves all of the problems that have been raised. The authors suggest that far from eliminating the problems with the HGP, the resultant increase in dimensionality has raised a number of new challenges. Read from the perspective of the present, the Juengst et al papers ask:" Haven't we been down this road before?" The claims being made by the systems medicine community are eerily similar to those made by the advocates (prominent among them was Leroy Hood) of the HGP over a decade ago. P4 medicine all over again, but this time having gotten over that (now embarrassing) genetic determinism fetish.

Hallam Stevens also reacted to the HGP [63, p. 112]:

"Network science picks out very specific features of biological objects so that its mathematical tools can be applied. This abstraction requires biological networks to be represented in ways that are similar or identical to nonbiological networks. This similarity is then invoked to create and justify explanations and accounts of biological processes on nonbiological terms."

He also pointed out that two levels of abstraction were employed. First, molecules, DNA, RNA, and proteins are represented as mathematical points or nodes. Then "looking at the patterns of connections between say molecules ignores the way (s) in which the interaction occurs, e.g., the timescale or the strength of the interaction. It reduces all this to an edge (line) on a graph. Second, network science depends on the reduction of the networks themselves into quantitative and qualitative mathematical properties, viz., size, density, average degree, diameter, clustering, robustness, and centrality, as well as such notions such as feedforward and feedback" (p. 114). It is seen, then, that network science is based on reduction – it abstracts biological systems into a few key elements and properties. While the network approach does offer us complex, holistic explanations of biological phenomena, it does so using highly reduced models of biological objects. It is in this sense that network science can be seen as reconciling the reductionist and holistic approaches [63], so long thought to be dichotomous [1]. All of these concerns translate without change to the systems medicine version of P4 – except the dimensionality has increased exponentially.

With respect to personalized and patient-centered, Vogt et al [46] argue that systems medicine cannot be completely reconciled with the concept of the patient as a person. They quote one of the most respected proponents of systems biology, Denis Noble, who said "On the one hand, it seems sensible to deal only with what we can observe, measure and understand. This is the pragmatic approach to science. (…) On the other hand, it is laughably presumptuous to suppose that this resolves all questions about life. Clearly, it can't." Thus,

scientific medicine needs to be supplemented with other methods in order to be sensitive to the full range of human capacities, and they suggest that narrative-based medicine and phenomenology (e.g. [64]) are candidates for such complimentary fields of knowing.

It can also be argued that "personalized medicine" is more accurately described as "stratified medicine," personalized being used solely for its rhetorical value. Kohane [65] points out that effective application of personalized medicine requires both an understanding of the individual patient and the subpopulations to which she belongs. Vogt et al [41, p. 412] noted that a patent application submitted by Hood and colleagues from the ISB mentions how the reference population may be stratified into sub-populations according to genetic and other criteria such as diet, drug intake, age, gender, and physiologic states (e.g., exercise, rest, or sleep). This documents how so-called personalized medicine still relies on population-based methods. And, as already noted, stratification criteria will be value-based, and allow biomedicalization to proceed unabated.

4. Discussion

The focus in this paper has been on a measure of wellness, Q (W), that its proponents have described as both scientific (non-normative, value-free, objective) and holistic; one that would serve as the cornerstone of P4 (personalized, predictive, preventive and participatory) medicine. While precious few details concerning the actual structure of Q (W) were provided by its developers, enough could be gleaned from their promised results and patent applications to cast serious doubts on each of characteristics claimed.

The authors recognize, however, that just pointing to the inadequacies of Q (W) will not provide us with a recipe for what should be done next: One needs to offer an alternative, improved course of action to change the current paradigm of measure, measure, and then measure some more. Unfortunately, the authors cannot point to one carefully documented approach that is guaranteed to be a uniform improvement on the systems biology approach in every situation. The authors firmly believe that context is critical in deciding how to attack a given problem, and the most critical aspect of that context is the nature of the problem itself. This does not mean, however, that the authors cannot point to an alternative general approach to the assessment and improvement of wellness that will be sensitive to and able to respond to demands imposed by particular situations. This alternative view is based on our rejection of the stance implicit in Q (W) – that measurement comes first,[6] and questions somehow follow, questions that are limited to whatever it is that can be extracted, precisely or not, from these quantified signals. This ignores sources of information that resist quantification; not because they are unimportant, but only because they cannot be measured with precision. This ordering of priorities has been questioned for a very long time. The authors point to a quote[7] from John Tukey, over 50 years of age (see www.azquotes.com) that captures the spirit of this dissent:

"An approximate answer to the right question is worth a good deal more than an exact answer to an approximate problem."

A more recent version of this attitude in a different context (economics) that zeros in on measure, measure, measure (due to E. J. Mishan, quoted in Porter [66, p. 212]):

"In view of the existing quantomania, one may be forgiven for asserting that there is more to be said for rough estimates of the precise concept than precise estimates of economically irrelevant concepts."

Rather than yielding to quantomania[8], following Levins and Lewontin [67], the authors pursue a more dialectical view of nature: The dialectical world view can be characterized by two basic ideas, (i) things are internally heterogeneous, so there is no least ("fundamental") unit of analysis and (ii) the "correct" decomposition of wholes into parts depends on what aspect of the whole is being investigated. Levins [68] argues for the ontological equality of part and whole and their reciprocal determination. Nothing can be a "part" unless there is a "whole" for it to be a part of … the concepts of "part" and "whole" are dialectically related and reciprocally determine each other's status (p. 131).

To tie these notions to what is going on in P4 medicine's approach to systems analysis, the authors start with the definition of a system used by Richard Levins [68, p. 105] as "an interconnected set of elements that is coherently organized around some purpose. A system is more than the sum of its parts. It can exhibit dynamic, adaptive, goal-seeking, self-preserving and evolutionary behavior." He then set out to contrast systems theory with his favored approach, dialectical materialism. He notes that while the two have many similarities, e.g., systems theory recognizes complexity, interconnection and process, they differ with regard to origins, objectives and theoretical underpinnings, including the models used and their interpretation. The authors do not repeat his arguments here, rather, the authors focus on where P4 medicine differs in these aspects. P4 medicine's origins can be tied to its switch from reliance on the genetic information in the genome to the systems of systems comprising its focus, an individual human being. P4 medicine's recognition of

6 This numerical privileging is based on the notion that it is more 'scientific' to speak in terms of quantities than qualities. Numbers are thought to be impersonal, fair, objective – traits that deflect attention from the real question of whether the number paints a true picture of the phenomenon in question. As put by Porter [66, p. 198], "The impersonality of numbers is at least as crucial for their authority as is the plausibility of their claims to truth."

7 At this same site, you will find several other quotes expressing the same attitude, viz., "It's better to solve the right problem approximately than to solve the wrong problem exactly," "Far better an approximate answer to the right question, which is often vague, than the exact answer to the wrong question, which can always be made precise," and "Be approximately right rather than exactly wrong." This either represents alternative statements of the same, wise council, or the same wise council being applied in different contexts, or both.

8 There is even a (short) definition in Wiktionary, viz., A focus on countable, measurable entities to the exclusion of other factors. A quote from Ida R. Hoos is included: "A kind of quantomania prevails in the assessment of technologies. What cannot be counted simply doesn't count, and so we systematically ignore large and important areas of concern."

complexity can be seen as a direct repudiation of genetic reductionism and the bald biological determinism advocated by so many of the genome sequencing boosters. Emphasis went from "as simple as possible" to "as complex as possible." From the basic building blocks to the entire, integrated structure, including all of the interconnections between its parts. P4 medicine went from a purely reductive stance to a completely holistic one, where holism was taken to be the virtual never-ending series of measurements required to "measure everything."

And, if we were to stop right here, we would indeed have a model worthy of the name "holistic." However, soon as we invoke a systems theory approach, we resume a reductionist stance. Levins [68, p. 105], for example, emphasized that "the 'system' of systems theory is not reality itself but a model of reality, an intellectual construct that grasps some aspects of the reality we want to study, but also differs from that reality in being more manageable and easier to study and alter." (…) "[S] ystems theory starts with the variables as givens. It deals with the problems of selecting variables only in a very limited way … Once variables are selected, they are treated as unitary 'things' whose only property is quantity" (p. 119). This is in line with the remarks of Hallam Stevens cited earlier. Thus, the supposed holism of the P4 approach rests on the adoption of highly reduced models of biological objects.

Models are judged on the basis of such (partly contradictory) things as realism, goodness-of-fit, generality, precision, interpretability, and the ability to predict and control. P4 medicine seeks to predict and control. Levins [68, p 115] argues for a "more complex and non-hierarchical relation between quantitative and qualitative approaches to the world… Quantitative description of a system is not superior to qualitative understanding … We seek practical and theoretical understanding rather than a good fit. Precision and prediction may or may not be useful in this process, but they are not the goals of it."

Finally, consider the objectivity of the wellness metric. Megill [69] distinguishes between four (related but distinguishable) kinds of objectivity: Absolute (representing things as they "really are"), disciplinary (standards of objectivity may vary between disciplines), dialectical, and procedural (aims for impersonal methods of investigation). Dialectical objectivity holds that objects are constituted as objects in the course of an interplay between subject and object. Whereas the other three senses of objectivity eschew subjectivity, dialectical objectivity involves a positive attitude towards subjectivity. This accords well with Longino's [70] notion of "objectivity by degrees" (p. 76-81). The choice of one or another of these attitudes toward objectivity is best determined by the problem being considered [1, 71, 72]. The dialectical approach will not be appropriate, e.g., if concentrating on two viewpoints will exclude consideration of promising alternatives. However, Matthews [73] pointed out that dialectical objectivity is particularly useful in the context of clinical encounters: "The subjective impressions of a physician and the subjective impressions of her patient are equally valid, and the 'objective' therapy is that developed via the dialectical encounter between them (p. 146) … One should endeavor to make the clinical encounter and the process of diagnosis dialogic, with the healer and patient interactively crafting an understanding of the experience of illness" (p. 147). This is a far cry from what happens in P6 medicine, where illness is to be understood from pondering one's position in a very-high-dimensional space relative to the hypersphere of points selected to represent "wellness."

5. Conclusion

These contrasting approaches to the clinical encounter may be seen as contrasting ways of accommodating the competing requirements of scientific and humanistic medicine: Scientific medicine is seen as rooted in the natural sciences and focuses on diseases associated with bodily parts; whereas humanistic medicine focuses on the whole person and not solely on the patient's disease. The successful clinician will accommodate both views, the expectation being that clinicians will treat patients in ways that are not only scientifically valid and evidence-based, but also sensitive to the full range of human capacities, including individual experiences, preferences, needs, and values. P4 medicine seeks to accomplish this merger by moving past the reductionist stance of scientific medicine by incorporating all components of disease complexity: To measure, measure, measure. The dialogic approach respects the inclusion of the physician in the encounter, expecting only that she will (and be given enough time to) ask about the patient's preferences, needs, and values. The authors submit that there is no measurement battery that will provide an adequate substitute.

References

[1] Kowalski, Charles J., and Adam J. Mrdjenovich. 2017. Beware dichotomies. *Perspectives in Biology and Medicine* 59 (4): 517-35.

[2] Ahrens, Edward H., Jr. 1992. The crisis in clinical research: Overcoming institutional obstacles. New York: Oxford University Press.

[3] Richman, Kenneth A. 2004. Ethics and the metaphysics of medicine: Reflections on health and beneficence. Cambridge MA: The MIT Press.

[4] Boorse, Cristopher. 1977. Health as a theoretical concept. *Philosophy of Science* 44: 542-7.

[5] Boorse, Christopher. 1975. On the distinction between health and illness. *Philosophy and Public Affairs* 5: 49-68.

[6] Kingma, Elselijn. 2007. What is it to be healthy? *Analysis* 67: 128-33.

[7] Giroux, Elodie. 2015. Epidemiology and the bio-statistical theory of disease: A challenging perspective. *Theoretical Medicine and Bioethics* 36:175-95.

[8] Fulford, K. W. M. 1993. Praxis makes perfect: Illness as a bridge between biological concepts of disease and social conceptions of health. *Theoretical Medicine* 14: 305-20.

[9] Richman, Kenneth A., and Andrew E. Budson. 2000. Health of organisms and health of persons: An embedded instrumentalist approach. *Theoretical Medicine* 21: 339-54.

[10] Kowalski, Charles, Steven Pennell, and Amiram Vinokur. 2008. Felicitometry: Measuring the 'quality' in quality of life. *Bioethics* 22 (6): 307-13.

[11] Kowalski, Charles J., Jan L. Bernheim, Nancy Adair Birk, and Peter Theuns. 2012. Felicitometrics: interpreting quality of life measurements. *Theoretical Medicine and Bioethics* 33: 207-20.

[12] Clauser, K. Danner, Charles M. Culver, and Bernard Gert. 2004. Malady: A new treatment of disease. In: *Health, Disease and Illness*, eds Arthur L. Caplan, James J. McCartney, and Dominic A. Sisti, 90 – 103. Washington D. C.: Georgetown University Press.

[13] Bircher, Johannes. 2005. Towards a dynamic definition of health and disease. *Medicine, Health Care and Philosophy* 8: 335-41.

[14] Daly, Patrick R. 2009. A theory of health and the healing arts based on the philosophy of Bernard Lonergan. *Theoretical Medicine and Bioethics* 30: 147-60.

[15] Daly, Patrick. 2017. An integral approach to health science and healthcare. *Theoretical Medicine and Bioethics* 38: 15-40.

[16] Simon, Jeremy R., Havi Carel, and Alexander Bird. 2017. Understanding disease and illness. *Theoretical Medicine and Bioethics* 38: 239-44.

[17] Schwartz, Peter H. 2007. Defining dysfunction: Natural selection, design, and drawing a line. *Philosophy of Science* 74 (3): 364-85.

[18] American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

[19] Kupfer, David J., Emily A. Kuhl, and Darrell A. Regier. 2013. DSM-5—The future arrived. *Journal of the American Medical Association* 309: 1691-1692.

[20] Dawber, Thomas Royle. 1980. *The Framingham Study: The epidemiology of atherosclerotic disease*. Cambridge MA: Harvard University Press.

[21] Giroux, Elodie. 2013. The Framingham study and the constitution of a restrictive concept of risk factor. *Social History of Medicine* 26: 94-112.

[22] Epstein, Frederick H., Thomas. Francis, Jr., Norman S. Hayner, Benjamin C. Johnson, Marcus O. Kjelsberg, John A. Napier, Leon E. Ostrander, Jr., Millicent W. Payne, and Horace J. Dodge. 1965. Prevalence of chronic diseases and distribution of selected physiologic variables in a total community, Techumseh, Michigan. *American Journal of Epidemiology* 81 (3): 307-22.

[23] Schwartz, Peter H. 2008. Risk and disease. *Perspectives in Biology and Medicine* 51 (3): 320-34.

[24] Greene, Jeremy A. 2007. *Prescribing by numbers: Drugs and the definition of disease*. Baltimore: Johns Hopkins University Press.

[25] Clarke, Adele E., Laura Mamo, Jennifer Ruth Fosket, Jennifer R. Fishman, and Janet K. Shim, eds. 2010. *Biomedicalization: Technoscience, health, and illness in the U.S*. Durham NC: Duke University Press.

[26] France, Christopher M., Paul H. Lysaker, and Ryan P. Robinson. 2007. The chemical imbalance explanation for depression: Origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice* 38 (4): 411-420.

[27] Moncrieff, Joanna. 2006. Psychiatric drug promotion and the politics of neoliberalism. *British Journal of Psychiatry* 188 (4): 301-302.

[28] Frances, Allen J. 2013. Last plea to DSM 5: Save grief from the drug companies. Available at: www.huffingtonpost.com/allen-frances/saving-grief-from-dsm-5-a_b_2325108.html (Accessed January 30, 2017).

[29] Dumit, Joseph. 2012. Drugs for life: How pharmaceutical companies define our health. Durham NC: Duke University Press.

[30] Esposito, Luigi and Fernando M. Perez. 2014. Neoliberalism and the commodification of mental health. *Humanity & Society* 38 (4): 414-442.

[31] Sunder Rajan, Kaushik. 2017. *Pharmocracy*. Durham NC: Duke University Press.

[32] McDowell, Ian and Claire Newell. 1996. *Measuring health*, 2nd edition. New York: Oxford University Press.

[33] Bowling, Ann. 2001. *Measuring disease*, 2nd edition. Philadelphia PA: Open University Press.

[34] Shostak, Sara. 2010. Marking populations and persons at risk. In: *Biomedicalization: Technoscience, health, and illness in the U.S*., eds. Adele E. Clarke, Jennifer Ruth Fosket, Jennifer R. Fishman, and Janet K. Shim, 242-62. Durham NC: Duke University Press.

[35] Shostak, Sara. 2013. Exposed science: Genes, the environment, and the politics of population health. Berkeley CA: University of California Press.

[36] Feinstein, Alvan R. 1987. *Clinimetrics*. New Haven CT: Yale University Press.

[37] Hood, Leroy, James R. Heath, Michael E. Phelps, and Biaoyang Lin. 2004. Systems biology and new technologies enable predictive and preventive medicine *Science* 306: 640-3.

[38] Hood, Leroy E., and Mauricio Flores. 2012. A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. *New Biotechnology* 29: 613-24.

[39] Gamma, Alex. 2014. He role of genetic information in personalized medicine. *Perspectives in Biology and Medicine* 56 (4): 485-512.

[40] Rose, Nikolas. 2013. Personalized medicine: Promises, problems and perils of a new paradigm for healthcare. *Procedia – Social and Behavioral Sciences* 77: 341-52.

[41] Vogt, Henrik, Bjorn Hofman, and Linn Getz. 2016. Personalized medicine: Evidence of normativity in its quantitative definition of health. *Theoretical Medicine and Bioethics* 37: 401-16.

[42] Flores, Mauricio, Gustavo Glusman, Kristin Brogaard, Nathan D Price, and Leroy Hood. 2013. P4 medicine: How systems medicine will transform the healthcare sector and society. *Personalized Medicine* 10 (6): 565-76.

[43] Hood, Leroy, Rudi Balling, and Charles Auffray. 2012. Revolutionizing medicine in the 21st century through systems approaches. *Biotechnology Journa*l 7: 992-1001.

[44] Hood, Leroy. 2013. Systems biology and P4 medicine: Past, present, and future. RMMJ 2013; 4 (2): e0012. doi:10.5041/RMMJ.10112.

[45] Price, Nathan D., Lucas B. Edelman, Inyoul Lee, Hyuntae Yoo, Daehee Hwang, George Carlson, David J. Galas, James R. Heath, and Leroy Hood. 2009. Systems biology and the emergence of systems medicine. In: *Genomic and personalized medicine*, eds. Huntington F. Willard and Geoffrey S. Ginsburg, 74-85. New York: Academic Press.

[46] Vogt Henrik, Elling Ulvestad, Thor Eirik Eriksen, and Linn Getz. 2014. Getting personal: Can systems medicine integrate scientific and humanistic conceptions of the patient? *Journal of Evaluation in Clinical Practice* 20: 942-52.

[47] Kowalski, Charles J. 1972. A commentary on the use of multivariate statistics in anthropometric research. *American Journal of Physical Anthropology* 36: 119-31.

[48] Lewontin, Richard. 2000. *The Triple Helix: Gene, organism and environment*. Cambridge MA: Harvard University Press.

[49] Ibrahim, Rania, Maria Pasic, and George M. Yousef. 2016. Omics for personalized medicine: defining the current we swim in. *Expert Review of Molecular Diagnostics* 16 (7): 719-22.

[50] Vogt Henrik, Bjorn Hofman, and Linn Getz. 2016. The new holism: P4 medicine and the medicalization of health and life itself. *Medical Health Care and Philosophy* 19: 307-23.

[51] Meador, Clifton K. 1994. The last well person. *NEJM* 330 (6): 440-1.

[52] Kohane, Issac S., Daniel R. Masys, and Russ B. Altman. 2006. The Incidetalome: A threat to genomic medicine. *JAMA* 296 (2): 212-5.

[53] Rose, Nikolas. 1994. Medicine, history and the present. In: *Reassessing Foucault, Power, Medicine, and the Body*, eds. Colin Jones and Roy Porter, 48-72. New York: Routledge.

[54] Bard, Imre. 2012. Pre-empting the threat of human deficiencies. In: *Neoliberalism and Technoscience*, eds. Luigi Pellizzoni and Marja Ylonen, 117-38. Surrey UK: Ashgate Publishing Limited.

[55] Armstrong, David. 1995. The rise of surveillance medicine. *Sociology of Health & Illness* 17 (3): 394-404.

[56] Rose, Nikolas. 2010. Screen and intervene: Governing risky brains. *History of the Human Sciences* 23 (1): 79-105.

[57] Greenhalgh, Susan. 2016. Neoliberal science, Chinese style: Making and managing the 'obesity epidemic.' *Social Studies of Science* 46 (4): 485-510.

[58] Juengst, Eric T., Richard A. Settersten, Jennifer R. Fishman, and Michelle L. McGowan. 2012. After the revolution? Ethical and social challenges in 'personalized genomic medicine.' *Personalized Medicine* 9 (4): 429-39.

[59] Juengst, Eric T., Michael A. Flatt, and Richard A. Settersten. 2012. Personalized genomic medicine and the rhetoric of empowerment. *Hastings Center Report* 42 (5): 34-40.

[60] Nordgren, Anders, and Erik T. Juengst. 2009. Can genomics tell me who I am? Essentialistic rhetoric in direct-to-consumer DNA testing. *New Genetics and Society* 28 (2): 157-72.

[61] Kowalski, Charles J., and Adam J. Mrdjenovich. 2017. Personalized medicine, genomics and enhancement: Monuments to neoliberalism. *American Journal of Clinical and Experimental Medicine* 5 (3): 75-92.

[62] Smarr, Larry. 2012. Quantifying your body: A how-to guide from a systems biology perspective. *Biotechnology Journal* 7: 980-91.

[63] Stevens, Hallam. 2015. Networks: Representations and tools in postgenomics. In: *Postgenomics: Perspectives on biology after the genome*, eds. Sarah S. Richardson and Hallam Stevens, 103-25. Durham NC: Duke University Press.

[64] Gergel, Tania. 2012. Medicine and the individual: Is phenomenology the answer? *Journal of Evaluation in Clinical Practice* 18 (5): 1102-9.

[65] Kohane, Isaac S. 2009. The twin questions of personalized medicine: who are you and whom do you most resemble? *Genome Medicine* 1 (1): 1-3.

[66] Porter, Theodore M. 1994. Objectivity as standardization: The rhetoric of impersonality in measurement, statistics, and cost-benefit analysis. In: *Rethinking Objectivity*, Allan Megill, ed. Durham NC: Duke University Press, pp. 197-237.

[67] Levins, Richard and Richard Lewontin. 1995. *The Dialectical Biologist*. Cambridge MA: Harvard University Press.

[68] Levins, Richard. 2007. Dialectics and systems theory. In: *Biology under the Influence: Dialectical essays on ecology, agriculture, and health*, eds. Richard Lewontin and Richard Levins, 101-24. New York: Monthly Review Press.

[69] Megill, Allan, ed. 1994. *Rethinking Objectivity*. Durham NC: Duke University Press.

[70] Longino, Helen. 1990. Science as Social Knowledge: Values and objectivity in scientific inquiry. Princeton NJ: Princeton University Press.

[71] Kowalski, Charles J., Raymond J. Hutchinson, and Adam J. Mrdjenovich. 2017. The ethics of clinical care and the ethics of clinical research: Yin and yang. *Journal of Medicine and Philosophy* 42: 7-32.

[72] Kowalski, Charles J., and Adam J. Mrdjenovich. 2017. Schemata, CONSORT, and the Salk polio vaccine trial. *Journal of Medicine and Philosophy*, jhx032, http://doi.org/10.1093/jmp/jhx032.

[73] Matthews, J. Rosser. 1995. *Quantification and the Quest for Medical Certainty*. Princeton NJ: Princeton University Press.