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P7 Medicine: Humanizing Systems Medicine

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RESUMEN

A principios del siglo XXI, se introdujo la medicina de sistemas P4 con sus elementos predictivos, preventivos, personalizados y participativos para reemplazar el modelo biomédico tradicional. Los críticos de la medicina P4 afirman que presenta un holismo técnico en lugar del holismo humanista tradicional. Para abordar esta crítica, se propone un modelo médico P7 para humanizar la medicina de sistemas distinguiendo entre dos Ps: la P físico-biomolecular y la P personal, que a menudo se combinan con la P personalizada de la medicina P4. La P personal de la medicina P7 se desarrolla en términos del personalismo tradicional y el nuevo materialismo contemporáneo.

PALABRAS CLAVE: *ómica, medicina personalizada, medicina de precisión, medicina sistémica*.

ABSTRACT

At the beginning of the 21st century, P4 systems medicine with its predictive, preventive, personalized and participatory elements was introduced to replace the traditional biomedical model. Critics of P4 medicine claim that it exhibits technical holism rather than traditional humanistic holism. To address this criticism, a P7 medical model is proposed to humanize systems medicine by demarcating between two Ps: the physical-biomolecular P and the personal P, which are often conflated with the personalized P of P4 medicine. The personal P of P7 medicine is developed in terms of traditional personalism and contemporary new materialism.

KEYWORDS: *Omics, Personalized medicine, Precision medicine, Systems medicine*.

I. INTRODUCTION

During the twentieth century, systems theory, especially as espoused by Ludwig von Bertalanffy (1968), was incorporated into biology, which resulted in the rise of systems biology [Marcum (2009), Trewavas (2006)]. At the start of the twenty-first century, systems medicine emerged from systems biology [Marcum (2020)]. Specifically, Leroy Hood and colleagues introduced a notion of systems medicine called P3

medicine [Hood, *et al.* (2004)]. The first P, predictive, pertains to identifying genetic polymorphisms that are associated with developing particular diseases. The next P is preventive in which pharmacogenetics is utilized to develop preventive drugs – in contrast to therapeutic drugs – that would block the expression of the predicted disease. The final P, personalized, is an outcome of the first two Ps and entails the patient's specific genomic and other biome/omics or digital data for providing therapy tailored for the patient. The next stage in the evolution of P3 medicine was the addition of a fourth P, participatory. As Hood (2013) later elaborates on this P, it involves more than simply passive but rather active participation of the patient. For Hood and colleagues, P4 medicine represents a change from a traditional biomedical approach that is reactive, to a systems medical approach that is proactive [Hood, *et al.* (2012)].

P4 medicine has been embraced but modified within the medical community, particularly with the appearance of P5 and P6 medicine. There are several types of P5 medicine. One type pertains to the addition of a population P to P4 medicine, and it revises each of the other four Ps from an epidemiological perspective [Khoury, *et al.* (2012)]. Another type of P5 medicine includes addition of a political P to P4 medicine, especially in terms of addressing bio-medicolegal injustices through protection of a patient's dignity and values [Ferrara (2017)]. A final type of P5 medicine adds a psycho-cognitive P to P4 medicine [Gorini and Pravettoni (2011), Pravettoni and Triberti (2020)]. Nicola Bragazzi (2013a) has introduced the notion of "psychiatome" to denote this P. Finally, advocates of this P5 medicine have expanded it to include a sixth public P [Bragazzi and Del Puente (2013)]. Bragazzi (2013b) illustrates P6 medicine with the clinical case in which a patient, Salvatore Iaconesi, diagnosed with a brain tumor decides to open his clinical records and story to the public domain to expose the "taboos" and "wall of silence" often surrounding cancer patients.

There are several critics of P4 systems medicine, who raise various objections and concerns [Green and Vogt (2016), Vogt, *et al.* (2014, 2016)]. One of the main criticisms is that the holism which advocates of systems medicine espouse is not the traditional humanistic holism but rather a technical holism. Moreover, in P4 medicine, the patient's integrity, in terms of preferences and values, is not included in the data clouds but such clouds are composed entirely of omics data. The patient *qua* person is not part of the algorithmic framework but rather the patient simply becomes a calculated entity. Rather than being personal, such personalized or systems medicine in the end is impersonal or (de)personal [Hor-

witz, *et al.* (2013)]. In other words, the big data of systems medicine reduces the human face to a virtual or digital face. Another charge against systems medicine is that it is at best a rebranding of traditional medicine and at worst it offers promises that are simply hype and are thereby unattainable or undeliverable [Joyner and Paneth (2019)]. Finally, these criticisms have led Kenneth Weiss (2017) to question whether systems medicine is even possible.

These criticisms, especially depersonalization, need to be addressed if systems medicine is to be implemented successfully into the clinic. Towards that goal, I propose a P7 medicine to humanize systems medicine. The proposed P7 medicine builds off P4-6 medicine not only in terms of including the various Ps proposed thus far, but also with respect to distinguishing between two Ps — the physico-biomolecular P and the personal P. These two Ps are often conflated with the personalized P for other approaches to systems medicine. Importantly, the personal P, which involves the notion of personhood, addresses especially the criticism of P4 medicine as impersonal, in order to configure P7 medicine as personal in a humanistic rather than simply a technical way. Specifically, the personal P is developed in terms of traditional personalism and contemporary new materialism. The seven Ps that compose the proposed systems medicine, which includes both precision and personalized medicine via the personal P, can be divided into two categories. The first category consists of four P-components, physico-biomolecular P or P1, psycho-cognitive P or P2, population-public P or P3, and personal P or P4, along with their associated biomes/omics and systems sciences (see Table, p. 12). The second category of P7 medicine consists of three P-actions, predictive P or P5, participatory P or P6, and preventive P or P7. In the following sections, I first discuss the seven Ps and their relationships to one another, and I finally conclude by briefly identifying the challenges of implementing systems medicine clinically.

II. P-Components

The initial P of P7 medicine is the physico-biomolecular P or P1. It is obtained from data collected through various technologies, including high-throughput sequencing omics and other technologies such as protein microarrays and mass spectrometry, and then analyzed using various computational frameworks [Grainger (2016), Ibrahim, *et al.* (2016)]. The list of omics technologies available is simply staggering [Schneider and Or-

chard (2011)]; however, only a handful of omics are currently relevant clinically. Obviously, the first is genomics or the sequence of the exome or DNA associated with the genome's coding region [Lesk (2017)]. Epigenomics is another useful clinical omics in terms of identifying the impact of DNA methylation, histone modification, and microRNA on gene expression [Carlberg and Molnár (2018)]. Systems genetics is the systems science concerned with both genomics and epigenomics, especially in terms of the flow of information from the genome to the phenome [Civelek and Lusis, (2014)]. Two other important omics for P1 are transcriptomics, which pertains to gene expression with respect to RNA synthesis [Olsen and Christensen (2018)], and proteomics, which involves gene expression in terms of protein synthesis [Twyman (2014)] — both of which are important omics that are vital to systems cell biology [Mast, *et al.* (2014)]. The final two omics of P1 are metabolomics, which refers to the array of metabolites within the cell [Brennan (2019)], and nutrigenomics, which pertains to the impact nutrients have on gene expression [Mathers (2017)]. Systems nutrition represents the systems science for investigating the role of nutrients on gene expression and human health [Kaput, *et al.* (2017)].

A person's physico-biomolecular P represents an integration of the above omics, which involves the interactions of macromolecules, including DNA sequences, RNA transcripts, proteins, and other metabolites, within the cell [Misra, *et al.* (2019)]. An important example of such interactive omics is the integrated personalized omics profiling or iPOP [Snyder (2016)]. Michael Snyder at Stanford University has been involved in championing this approach, particularly since he was the first person to publish his personal iPOP [Snyder (2014)]. Specifically, his iPOP consisted of the analysis of genomic, transcriptomic, proteomic, metabolomic, and autoantibody data obtained from Snyder over a 14-month period. The results from the study revealed a molecular dynamism of the body's physical dimension and even the risk of type 2 diabetes. Although such studies are just beginning, they hold the promise for advancing the physico-biomolecular profile of the individual for systems medicine [Malod-Dognin, *et al.* (2018)].

The next P of P7 medicine is the psycho-cognitive P or P2. As noted earlier, P2 pertains to a person's behavioral or psychological and cognitive profile. Three omics constitute the psycho-cognitive P. The first is connectomics, which involves mapping the brain's neurocircuitry through brain imaging techniques and then correlating the circuitry with behavior [Craddock, *et al.* (2015)]. There are a number of ongoing projects to map the human brain, such as the NIH-funded Human Connec-

tome Project. Systems neuroscience utilizes systems theory to investigate the functions of the neural circuitry obtained from the connectome [Sporns (2016), Yeo and Eickhoff (2016)]. Cognomics is the approach to analyze cognition, as well as consciousness, and includes not only neuroimaging and behavioral testing but also a person's genomics [Barbey (2018), Kotchoubey (2018)]. The Cognomics Initiative of the Donders Institute at Radboud University was launched with the intention of enhancing cognitive abilities through tailoring education according to a person's cognomics profile. Systems psychology involves basic research into human cognition and behavior as well as clinical research in psychological pathologies [Ryzhov (2010)]. For example, "psychomics" has been proposed in which the patient's psychological dimensions, such as perceptions, memory, emotions, and cognition, can be systematized and quantitated [Tretter and Löffler-Stastka (2018)]. Finally, as mentioned above, Bragazzi (2013b) proposed the psychiatome to account for the genomic and behavioral components of psychiatric disorders. And systems psychiatry represents the means for investigating psychiatric disorders through omics technologies, neuroimaging, and behavioral observations [Öngür (2017), Tretter (2018)].

The population-public P or P3 is the next P-component of P7 medicine and pertains not simply to the epidemiological, microbial, and environmental factors that have an impact on the patient's health but also to the public, geographical, social, and cultural factors. Christopher Wild (2005) introduced in the mid-2000s the notion of the exposome to capture the impact these factors have on a person's health risks. Wild emphasized that the exposome complemented the other biomes approaches to assessing potential health risks. In an effort to operationalize the exposome, Wild (2012) identified two chief domains of factors, internal and external. The internal domain consists of the general physiological condition of the body, such as the metabolism or the gut microflora. Although the gut microflora is "external," it is thought to represent another organ of the human body, which constitutes the microbiome [Baquero and Nombela (2012)]. As such, the microbiome is an important component of the internal domain of the exposome, and systems microbiology provides the way to investigate it [Cowan and Smith (2017)].

The next domain of Wild's exposome consists of external factors, which he divides into specific and general external factors. The specific external factors include pollutants, toxins, infectious agents, and personal lifestyle choices, such as smoking as well as drug and alcohol consumption. Systems epidemiology involves using omics technologies to investi-

gate the impact of these factors on individual and public health [Cerdá and Keyes (2019)]. The general external factors include a person's natural or physical environmental, educational, financial, and social or cultural context, which constitutes the envirome [Riggs, *et al.* (2018)]. Consequently, systems ecology pertains to more than simply the investigation of the physical or geographical environment but also the social, cultural, political, and economic landscape [Hörl (2017), Jørgensen (2012)]. Finally, although there are concerns over its operationalization [Peters, *et al.* (2012)], the exposome is a critical component of contemporary medical and epidemiological research and practice [Vermeulen, *et al.* (2020)]. And, the EXPOsOMICS project has been initiated to develop the technology necessary for quantifying the internal and external domains that constitute the exposome [EXPOsOMICS Consortium (2017)].

The personal P or P4 is the final P-component of P7 medicine. From a systems biology perspective, one of the chief biomes is the physiome or physionome [Bassingthwaighte (1995)]. The physiome includes not only the traditionally ordered structure of the various organ systems but also the integration of the various organ systems as a functioning whole, as illustrated in the Physiome Project [Hunter and Borg (2003)]. To that end, systems physiology incorporates systems theory to integrate experimental and theoretical components in terms of computational models, such as the Virtual Physiological Human Project [Hunter (2016), Kitano (2010)]. Besides the normal physiome, P4 also includes the pathome, which consists of interrelated pathological processes in the whole organism [Nam, *et al.* (2014)]. Systems pathology investigates the various morphological and functional histopathological dimensions of the disease process, from the microscopic to the macroscopic, and then integrates them holistically [Costa (2012), Donovan, *et al.* (2010)]. Although the physiome and pathome are important components of P7 medicine, alone they are insufficient and are open to the charge of an impersonal approach that provides technical healthcare only.

To address the impersonalism of systems medicine's dependence on molecular omics and other clinical data, Roy Ziegelstein (2015, 2018), from the Aliki Initiative of the Johns Hopkins Bayview Medical Center, introduced the notion of personome to capture the patient's personal dimensions and characteristics. He defines the personome as "an individual's unique life circumstances that influence disease susceptibility, phenotype, and response to treatment" [Ziegelstein (2015), p. 888]. He goes on to identify five key elements to operationalizing the personome for the clinic. First, the clinician must get to know the patient as an indi-

vidual, particularly with respect to the patient's values. The next element involves incorporating the patient's lifestyle circumstances. The third element addresses the patient's preferences, especially as they concern treatment and possible side effects. The next element is meeting comprehensively the patient's needs, from the physical to the spiritual. The last element is to avoid making assumptions about the patient that might result in biased and harmful healthcare. Finally, he admits that there are significant challenges to implementing the personome into the clinic, but it is "essential in order to appropriately apply an understanding of the patient's genetic and biological individuality to the care of the patient and in that way move from 'no me' to 'know me' in the precision medicine era" [Ziegelstein (2018), p. 5].

Although the personome is a creative approach for addressing the impersonal nature of systems medicine's reliance on omics data, it requires extensive incorporation across the various omics data but in a humanistic fashion to operationalize it for the clinic. To that end, the personal P or P4 represents a network focal hub for integrating and transforming the omics data from P1-3. Full transformation of these Ps, however, requires a robust notion of personhood. The philosophical notion of personalism provides the conceptual foundation for the transformation of the first three Ps into the personal P or P4 [Burgos (2018)]. Personalism, a philosophical movement initiated in the early twentieth century, has been utilized to empower both medical practice and ethics [Beauregard (2018), Marcum (2015)]. Although personhood is a thorny philosophical notion, it can be accounted for ontologically, epistemologically, and ethically — with important implications for clinical practice [Marcum (2016)]. Ontologically, a person is constituted physically, biologically, psychologically, and socially, while epistemologically, a person both perceives and conceives the world, and finally ethically, a person acts in the world for the benefit of oneself and others. The person, then, is a bodily agent, whether clinician or patient, who can create ontologically in terms of beingness and possibilities, epistemologically with respect to knowledge and understanding, and ethically in terms of moral commitments and responsibilities.

Certainly, traditional personalism provides a means for integrating the P1-3 to form P4 of P7 systems medicine, however, the problem arises as to P4's agency — especially in terms of health and illness. Historically, agency qua causation is separate or distinct from the material, for the material is considered passive and inert and relies on external agency for change [Wolfe (2017)]. However, a new materialism locates agency

within the material [Choat (2018), Dolphijn and Tuin (2020)]. Karen Barad calls this agency "agential realism" in which "agency is a matter of intra-acting…doing/being in its intra-activity" [Barad (2007), p. 235]. And intra-acting involves material entanglement that cuts across different scales from the quantal to the cosmic. In other words, agency is part of the material itself and not something conferred on it externally. In causal terms, materiality is not simply necessary but sufficient for processive change and development, whether in terms of autopoiesis or allopoiesis [Hongbao Ma (2005), Meincke (2019)].

Traditional personalism, then, can be yoked to new materialism to forge a new personalism for P7 systems medicine. As noted above, personalism accounts for the nature of human personhood with respect to its ontological, epistemological, and ethical dimensions. The issue, however, is how to integrate these dimensions. New materialism provides a means to that end. Barad frames the human person in terms of an "ethico-onto-epistemological" structure "to mark the inseparability of ontology, epistemology, and ethics" [Barad (2007), p. 409]. The result entails an entanglement for a person's being, knowing, and acting responsibly in the world, which has two important implications for P7 medicine. The first is that P7 medicine. entails a shift from a static and passive notion of personhood to a dynamic and an organic notion. The person is not simply determined by the material either reductionistically or mechanistically; rather, the person emerges holistically from materiality. Thus, the first three Ps are not just integrated to produce P4, but rather they are entangled to create P4; and, in the process they are transformed thereby engendering the unique person — P4. Further, that unique P4 is then able to actualize P6 in a responsible way in terms of participating in the necessary therapy or lifestyle changes to treat or to prevent a particular disease. More importantly, the second implication is in terms of the clinical consultation with respect to entangling intra-actively innovative and novel ontological possibilities, epistemic understanding, and ethical obligations for both the patient and clinician. Through this entangling the ethical infuses both the ontology and epistemology of P7 medicine thereby transforming it into a deeply moral enterprise.

Specifically, the relationship or entanglement of the various P-components of the proposed P7 medicine is critical for delivery of personalized medicine both technically and humanistically. For example, with the transformation of the first three Ps through entanglement to create P4 or the unique person, healthcare delivery need not be stratified in terms of subgroups. Rather, the transformation to P4 involves the

emergence of an individual that constitutes an n = 1 in terms of diagnosis and treatment or prediction and prevention of illnesses or health risks [Van der Greef, *et al.* (2006)]. Given this personal uniqueness, there is no need for general reference classes — although some stratification is possible in terms of the first three Ps, since people do loosely coalesce with respect to physical, psychological, and geographical factors. Moreover, the proposed P7 medicine addresses the criticism that P4 overmedicalizes persons as patients [Vogt, *et al.* (2016)]. Rather than medicalizing persons, P7 medicine prevents persons from being medicalized by predicting health risks and then enlisting a person's participation to prevent them. In this way, P7 medicine reduces the current trend of overmedicalization by preventing disease expression.

Finally, the personal P of P7 medicine incorporates lifestyle science and medicine to integrate, entangle, operationalize, and transform the first three Ps into the personome, especially in terms of systems, personalized, and precision medicine [Egger, et al. (2017), Mechanick and Kushner (2016)]. Specifically, P7 medicine qua lifestyle medicine delivers "the right therapy, for the right person, for the right condition, at the right time" [Kraus (2018), p. 17]. Further, it also provides the means for preventing the disease conditions. In other words, P7 medicine, like P4 medicine, is more proactive than it is reactive [Hood, *et al.* (2012)]. Indeed, many of the lifestyle choices that people make have an impact upon the genome and other biomes that play a critical role in shaping a person's eventual phenome or diseasome [Goh and Choi (2012)]. The goal of P7 medicine is to equip or empower a person to live a long, independent, and healthful life as possible [Gray, *et al.* (2020), Ma, *et al.* (2016)]. Finally, P7 medicine, with its emphasis on lifestyle choices addresses the global surge in noncommunicable and chronic diseases, such as obesity, diabetes, cardiovascular diseases, and cancers, in order to prevent or minimize them [Kushner and Sorensen (2013)].

III. P-ACTIONS

The second category of P7 medicine consists of three P-actions, which represent the activities a person can take to avoid health risks or to treat or manage an existing illness based on the information provided by the P-components. These actions include predicting, P5, possible health risks or diagnosing illnesses and then soliciting the patient's participation, P6, in a program or protocol to prevent, P7, or to treat or man-

age them, thereby maintaining or restoring a person's optimal health. The quality of the information obtained from the P-components is important in terms of the success of the P-actions. For example, the physico-biomolecular P, psycho-cognitive P, and/or population-public P information must be accurate and precise so that possible health risks are predicted or that diagnoses are made with precision and confidence. Also, the information obtained from the P-components, especially the personal P, must be sufficient to forge a bond between the clinician and patient so that the patient trusts the clinician and participates fully in a therapeutic protocol either to prevent a health risk or to treat the illness. If the quality of the information from the P-components is inaccurate or insufficient, then the patient is vulnerable to harm rather than benefit.

The interactions among the three P-actions correspond to a specific relationship, which is important for operationalizing and then implementing P7 medicine. Specifically, the preventive P or P7 emerges from the entanglement of both the predictive P or P5 and the participatory P or P6. Moreover, the three P-actions must be carried out for each of the first three P-components (P1-3) to provide accurate and sufficient information to prevent misleading the clinician and patient as to the best course of action. When P1-3 have been actionized through P5-7, then they are entangled materially to create P4. Once created, P4 is actionized through P5-7 and the patient can be treated in both a personalized and precise manner. In other words, possible health risks are now precisely predicted based on the data and information obtained from the various actionized P-components and the patient can be motivated to participate optimally either in preventing the health risk or in treating or managing the disease. In sum, P7 medicine is a robust type of systems medicine through the entanglement of both the P-components and P-actions and it provides the means for both personalized and precision medicine.

IV. Conclusion

Although systems medicine, as well as personalized and precision medicine, are championed as the future of contemporary medicine, numerous challenges – ranging from the technical to the ethical – face their implementation within the clinic and within the healthcare system in general [Duffy (2016)]. For example, the technical challenges include: 1) developing computational models and bioinformatics infrastructure to integrate omics data to define accurately the clinical phenotype, 2) identi-

fying biomarkers that can predict confidently the patient's future disease condition, 3) assessing the degree of uncertainty of a patient's response to treatment based on omics data, and 4) classifying comorbidities that can have an impact on clinical outcome [Capobianco (2012)]. Ethical issues range from privacy of the patient's omics data to equitable distribution of healthcare resources [Adams and Petersen (2016)]. Another major issue is patient participation, given the technical nature of the omics data, which has an impact on a patient's informed consent [Koenig 2014)]. Given the data's technical nature, can a patient truly make an informed consent?

Although many challenges face the implementation of systems medicine into clinical practice and the healthcare system, one of the major challenges is the incorporation of a traditional humanistic holism rather than simply a technical holism. As argued in this paper, P7 systems medicine represents a framework by which to individualize healthcare in terms of both a traditional humanistic holism and a technical holism with respect to its biological, psychological, and social components. On the one hand, P7 medicine is comparable to the biopsychosocial model of medicine [Engel (1977)]; but, on the other hand, it represents a revision if not an extension of that model. The major difference between the two models is that P7 medicine is not simply the combination of the biological, psychological, and social components but rather it is an entanglement of these components (P1-3 of P7 medicine) from which emerges a unique person or P4. And the patient qua P4 does not represent merely a mechanism that is static and deterministic, but rather the patient is an organism that is dynamic and indeterministic — especially through P6 as participating responsibly in a treatment or prevention plan.

Finally, although P7 systems medicine shares much in common with both personalized medicine and person centered care, it also differs from them [El-Alti, *et al.* (2019)]. With respect to personalized medicine, which emphasizes the genomic and biological dimensions of the patient, P7 medicine integrates the other two important dimensions of the patient, P2 and P3, through the entangling of the P1-3 components to create P4. With respect to person centered care, which emphasizes the humanistic and narrative dimensions of the patient, P7 medicine integrates the P1 dimension of the patient again through the entangling of the P1-3 components to create P4. Consequently, it engenders a picture of the person that is not simply at the center of the clinical encounter but rather the person is one element within the healthcare system. In other words, for the new personalism the best clinical outcome must also in-

clude non-person elements, such as drugs and devices. For P7 medicine, the entangling of both the person and non-person provides a more comprehensive model in which the clinician can caringly tailor healthcare for the individual patient, especially through the three P-actions and particularly through P6 in which the patient and clinician participate responsibly and ethically in guaranteeing the best possible clinical outcome. In sum, P7 medicine provides a unique framework in terms of both the P-components and P-actions from which to integrate the fragmented shards of contemporary medicine to provide the best humanistic healthcare in the twenty-first century.

Table. P7 medicine's P-components, with associated biomes/ omics and systems sciences (see text for details).

P-Components	**Biomes/omics**	**Systems Sciences**
P1 Physico-biomolecular P	Genomics/Epigenomics	Systems genetics
	Transcriptomics/Proteomics	Systems cell biology
	Metabolomics/Nutrigenomics	Systems nutrition
P2 Psycho-cognitive P	Connectomics	Systems neuroscience
	Cognomics	Systems psychology
	Psychiatome	Systems psychiatry
P3 Population-public P	Exposome	Systems epidemiology
	Microbiomics	Systems microbiology
	Envirome	Systems ecology
P4 Personal P	Physiome	Systems physiology
	Pathome	Systems pathology
	Personome	Lifestyle science

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REFERENCES

ADMAS, S.A., and PETERSEN, C. (2016), 'Precision Medicine: Opportunities, Possibilities, and Challenges for Patients and Providers'; *Journal of the American Medical Informatics Association*, vol. 23, pp. 787-90.

BAQUERO, F., and NOMBELA, C. (2012), 'The Microbiome as a Human Organ'; *Clinical Microbiology and Infection*, vol. 18, pp. 2-4.

BARAD, K.M. (2007), *Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning*, Durham, NC, Duke University Press.

BARBEY, A.K. (2018), 'Network Neuroscience Theory of Human Intelligence'; *Trends in Cognitive Sciences*, vol. 22, pp. 8-20.

BASSINGTHWAIGHTE, J.B. (1995), 'Toward Modeling the Human Physionome'; in Sideman, S. and Beyar, R. (eds.), *Molecular and Subcellular Cardiology: Effects of Structure and Function*, New York, Plenum Press, pp. 331-9.

BEAUREGARD, J. (2018), 'Advancing a Personalist Neuroethics'; *National Catholic Bioethics Quarterly*, vol. 18, pp. 269-90.

BERTALANFFY, L. VON, (1968), *General Systems Theory*; rev. edition, New York, G. Braziller.

BRAGAZZI, N.L. (2013a), 'Rethinking Psychiatry with OMICS Science in the Age of Personalized P5 Medicine: Ready for Psychiatome?; *Philosophy, Ethics, and Humanities in Medicine*, vol. 8, p. 4.

____ (2013b), 'From P0 to P6 Medicine, a Model of Highly Participatory, Narrative, Interactive, and "Augmented" Medicine: Some Considerations on Salvatore Iaconesi's Clinical Story'; *Patient Preference and Adherence*, vol. 7, pp. 353-9.

BRAGAZZI, NL and DEL PUENTE, G. (2013), 'Why P6 Medicine Needs Clinical Psychology and a Trans-Cultural Approach', *Health Psychology Research*, vol. 1, p. 5.

BRENNAN, L. (2019), "Metabolomics: A Powerful Tool to Enrich Our Understanding of the Impact of Food on Health'; *Molecular Nutrition & Food Research*, vol. 63, Article no. 1870087.

BURGOS, J.M. (2018), *An Introduction to Personalism*; R.T. Allen, trans., Washington, D.C., The Catholic University Press.

CAPOBIANCO, E. (2012), 'Ten Challenges for Systems Medicine'; *Frontiers in Genetics*, vol. 3, Article no. 193.

CARLBERG, C., and MOLNÁR, F. (2018), *Human Epigenomics*; Singapore, Springer.

CERDÁ, M., and KEYES, K.M. (2019), 'Systems Modeling to Advance the Promise of Data Science in Epidemiology'; *American Journal of Epidemiology*, vol. 188, pp. 862-5.

CHOAT, S. (2018), 'Science, Agency and Ontology: A Historical-Materialist Response to New Materialism'; *Political Studies*, vol. 66, pp. 1027-42.

CIVELEK, M., and LUSIS, A.J. (2014), 'Systems Genetics Approaches to Understand Complex Traits'; *Nature Reviews Genetics*, vol. 15, pp. 34-48.

COSTA, J. (2012), 'Systems Pathology: A Critical Review'; *Molecular Oncology*, vol. 6, pp. 27-32.

COWAN, M.K., and SMITH, H. (2017), *Microbiology: A Systems Approach*; 5th edition, New York, McGraw-Hill.

CRADDOCK, R.C., TUNGARAZA, R.L., and MILHAM, M.P. (2015), 'Connectomics and New Approaches for Analyzing Human Brain Functional Connectivity'; *GigaScience*, vol. 4, Article no. 13.

DOLPHIJN, R., and TUIN, I. VAN DER (2012), *New Materialism: Interviews & Cartographies*; Ann Arbor, MI, Open Humanities Press.

DONOVAN, M., COSTA, J., and CORDON-CARDO, C. (2010), 'From Systems Biology to Systems Pathology: A New Subspecialty in Diagnostic and Personalized Medicine'; *Current Pharmacogenomics and Personalized Medicine*, vol. 8, pp. 108-16.

DUFFY, D.J. (2016), 'Problems, Challenges and Promises: Perspectives on Precision Medicine'; *Briefings in Bioinformatics*, vol. 17, pp. 494-504.

EGGER, G., BINNS, A., ROSSNER, S., and SAGNER, M. (eds.), (2017), *Lifestyle Medicine: Lifestyle the Environment and Preventive Medicine in Health and Disease*; 3rd edition, London, Academic Press.

EL-ALTI, L., SANDMAN, L., and MUNTHE, C. (2019), 'Person Centered Care and Personalized Medicine: Irreconcilable Opposites or Potential Companions?'; *Health Care Analysis*, vol. 27, pp. 45-59.

ENGEL, G.L. (1977), 'The Need for a New Medical Model: A Challenge for Biomedicine'; *Science*, vol. 196, pp. 129–36

EXPOSOMICS CONSORTIUM. (2017), 'The Exposome in Practice: Design of the EXPOSOMICS Project', *International Journal of Hygiene and Environmental Health*, vol. 220, pp. 142-151.

FERRARA, S.D. (2017), 'P5 Medicine and Justice: The Future is Now'; *International Journal of Legal Medicine*, vol. 131, pp. 897-9.

GOH, K.I., and CHOI, I.G. (2012), 'Exploring the Human Diseasome: The Human Disease Network'; *Briefings in Functional Genomics*, vol. 11, pp. 533-42.

GORINI, A., and PRAYETTONI, G. (2011), 'P5 Medicine: A Plus for a Personalized Approach to Oncology'; *Nature Reviews Clinical Oncology*, vol. 8, Article no. 444.

GRAINGER, D. (2016), 'The Multi-Omics Revolution'; *Journal of Precision Medicine*, vol. 2, pp. 81-6.

GRAY, I.D., KROSS, A.R., RENFREW, M.E., and WOOD, P. (2019), 'Precision Medicine in Lifestyle Medicine: The Way of the Future?'; *American Journal of Lifestyle Medicine* vol. 14, pp. 169-86.

GREEN, S., and VOGT, H. (2016), 'Personalizing Medicine: Disease Prevention in Silico and in Socio'; *Humana Mente Journal of Philosophical Studies*, vol. 9, pp. 105-45.

HOOD, L. (2013), 'Systems Biology and P4 Medicine: Past, Present, and Future'; *Rambam Maimonides Medical Journal*, vol. 4, Article no. e0012.

HOOD, L., HEATH, J.R., PHELPS, M.E., and LIN, B. (2004), 'Systems Biology and New Technologies Enable Predictive and Preventive Medicine'; *Science*, vol. 306, pp. 640-3.

HOOD, L., BALLING, R., and AUFFRAY, C. (2012), 'Revolutionizing Medicine in the 21st Century Through Systems Approaches'; *Biotechnology Journal*, vol. 7, pp. 992-1001.

HONGBAO MA, S.C. (2005), 'Nature of Life'; *Life Science Journal*, vol. 2, pp. 7-15.

HÖRL, E. (2017), 'Introduction to General Ecology'; in Burton, J., and E. Hörl, E. (eds.), *General Ecology: The New Ecological Paradigm*; London, Bloomsbury, pp. 1-73.

HORWITZ, R.I., CULLEN, M.R., ABELL, J., and CHRISTIAN, J.B. (2013), '(De)personalized Medicine'; *Science*, vol. 339, pp. 1155-6.

HUNTER, P. (2016), 'The Virtual Physiological Human: The Physiome Project Aims to Develop Reproducible, Multiscale Models for Clinical Practice'; *IEEE Pulse*, vol. 7, pp. 36-42.

HUNTER, P., and BORG, T.K. (2003), 'Integration from Proteins to Organs: The Physiome Project'; *Nature Reviews Molecular Cell Biology*, vol. 4, pp. 237-43.

IBRAHIM, R., PASIC, M., and YOUSEF, G.M. (2016), 'Omics for Personalized Medicine: Defining the Current We Swim In'; *Expert Review of Molecular Diagnostics*, vol. 16, pp. 719-22.

JØRGENSEN, S.E. (2012), *Introduction to Systems Ecology*; Boca Raton, CRC Press.

JOYNER, M.J., and PANETH, N. (2019), 'Promises, Promises, and Precision Medicine'; *Journal of Clinical Investigation*, vol. 129, pp. 946-8.

KAPUT, J., PEROZZI, G., RADONJIC, M., and VIRGILI, F. (2017), 'Propelling the Paradigm Shift from Reductionism to Systems Nutrition'; *Genes & Nutrition*, vol. 1, pp. 1-10.

KHOURY, M.J., GWINN, M.L., GLASGOW, R.E., and KRAMER, B.S. (2012), 'A Population Approach to Precision Medicine'; *American Journal of Preventive Medicine*, vol. 42, pp. 639-45.

KITANO, H. (2010), 'Grand Challenges in Systems Physiology'; *Frontiers in Physiology*, vol. 1, Article no. 3.

KOENIG, B.A. (2014), 'Have We Asked Too Much of Consent?'; *Hastings Center Report*, vol. 44, pp. 33-4.

KOTCHOUBEY, B. (2018), 'Human Consciousness: Where Is It from and What Is It for'; *Frontiers in Psychology*, vol. 9, Article no. 567.

KRAUS, W.E. (2018), 'Personalized Lifestyle medicine'; in Ginsburg, G.S. and Willard, H.F. (eds.), *Genomic and Precision Medicine: Cardiovascular Disease*; 3rd edition, London, Academic Press, pp. 17-26.

LESK, A.M. (2017), *Introduction to Genomics*; 3rd edition, New York, Oxford University Press.

MA, J., ROSAS, L.G., and LY, N. (2016), 'Precision Lifestyle Medicine: A New Frontier in the Science of Behavior Change and Population Health'; *American Journal of Preventive Medicine*, vol. 50, pp. 395-7.

MALOD-DOGNIN, N., PETSCHNIGG, J. and PRZULJ, N. (2018), 'Precision Medicine—A Promising, Yet Challenging Road Lies Ahead'; *Current Opinion in Systems Biology*, vol. 7, pp. 1-7.

MARCUM, J.A. (2009), *Conceptual Foundations of Systems Biology*; New York, Nova Science.

____ (2015), 'Healthcare Personalism: A Prolegomenon'; *European Journal for Person Centered Healthcare*, vol. 3, pp. 228-32.

____ (2016), 'Healthcare Personalism and the Nature of the Person. How Can Personalist Thought Advance the Conceptual Basis of Person-Centered Medicine?'; *European Journal for Person Centered Healthcare*, vol. 4, pp. 409-16.

____ (2020), *From Systems Biology to Systems Medicine*, New York, Nova Science.

MAST, F.D., RATUSHNY, A.V., and AITCHISON, J.D. (2014), 'Systems Cell Biology'; *Journal of Cell Biology*, vol. 206, pp. 695-706.

MATHERS, J.C. (2017), 'Nutrigenomics in the Modern Era'; *Proceedings of the Nutrition Society*, vol. 76, pp. 265-75.

MECHANICK, J.I., and KUSHNER, R.F. (eds.) (2016), *Lifestyle Medicine: A Manual for Clinical Practice*; Cham, CH, Springer.

MEINCKE, A.S. (2019), 'Autopoiesis, Biological Autonomy and the Process View of Life'; *European Journal for Philosophy of Science*, vol. 9, Article no. 5.

MISRA, B.B., LANGEFELD, C., OLIVIER, M., and COX, L.A. (2019), 'Integrated Omics: Tools, Advances and Future Approaches'; *Journal of Molecular Endocrinology*, vol. 62, pp. R21-R45.

OLSEN, R.H., and CHRISTENSEN, H. (2018), 'Transcriptomics'; in Christensen, H. (ed.), *Introduction to Bioinformatics in Microbiology*, Cham, CH, Springer, pp. 177-88.

ÖNGÜR, D. (2017), 'Systems Research in Psychiatric Neuroscience'; *JAMA Psychiatry*, vol. 74, pp. 553-4.

PETERS, A., HOEK, G., and KATSOUYANNI, K. (2012), 'Understanding the Link Between Environmental Exposures and Health: Does the Exposome Promise Too Much?'; *Journal of Epidemiology and Community Health*, vol. 66, pp. 103-5.

PRAVETTONI, G., and TRIBERTI, S. (2020), 'A "P5" Approach to Healthcare and Health Technology'; in Pravettoni, G. and Triberti S. (eds.), *P5 eHealth: An Agenda for the Health Technologies of the Future*, Cham, CH, Springer, pp. 3-17.

RIGGS, D.W., YEAGER, R.A., and BHATNAGA, A. (2018), 'Defining the Human Envirome: An Omics Approach for Assessing the Environmental Risk of Cardiovascular Disease'; *Circulation Research*, vol. 122, pp. 1259-75.

RYZHOV, B.N. (2010), 'The Basis of Systems Psychology', *Systems Psychology and Sociology*, vol. 1, pp. 5-42.

SCHNEIDER, M.V., and ORCHARD, S. (2011), 'Omics Technologies, Data and Bioinformatics Principles'; in Mayer, B. (ed.), *Bioinformatics for Omics Data: Methods and Protocols*, New York: Humana Press, pp. 3-30.

SNYDER, M. (2014), 'iPOP and Its Role in Participatory Medicine'; *Genome Medicine*, vol. 6, Article no. 6.

____ (2016). *Genomics and Personalized Medicine: What Everyone Needs to Know®*; New York, Oxford University Press.

SPORNS, O. (2016), 'Connectome Networks: From Cells to Systems'; in Kennedy, H., Essen, D.C. and Christen, Y. (eds.), *Micro-, Meso-and Macro-Connectomics of the Brain*, Cham, SH, Springer, pp. 107-27.

TRETTER, F. (2018), 'From Mind to Molecules and Back to Mind — Metatheoretical Limits and Options for Systems Neuropsychiatry'; *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 28, Article no. 106325.

TRETTER, F., and LÖFFLER-STASTKA, H. (2018), 'Steps Toward an Integrative Clinical Systems Psychology'; *Frontiers in Psychology*, vol. 9, Article no. 1616.

TREWAVAS, A. (2006), 'A Brief History of Systems Biology'; *Plant Cell*, vol. 18, pp. 2420-30.

TWYMAN, R.M. (2014), *Principles of Proteomics*, 2 edition, New York, Garland Science.

VAN DER GREEF, J., HANKEMEIER, T., and MCBURNEY, R.N. (2006), 'Metabolomics-Based Systems Biology and Personalized Medicine: Moving Towards N = 1 Clinical Trials?', *Pharmacogenomics*, vol. 7, pp. 1087-94.

VERMEULEN, R., SCHYMANSKI, E.L., BARABÁSI, A.L., and MILLER, G.W. (2020), 'The Exposome and Health: Where Chemistry Meets Biology', *Science*, vol. 367. Pp. 392-6.

VOGT, H., ULVESTAD, E., ERIKSEN, T.E., AND GETZ, L. (2014), 'Getting Personal: Can Systems Medicine Integrate Scientific and Humanistic Conceptions of the Patient?'; *Journal of Evaluation in Clinical Practice*, vol. 20, pp. 942-52.

VOGT, H., HOFMANN, B., and GETZ, L. (2016), 'The New Holism: P4 Systems Medicine and the Medicalization of Health and Life Itself', *Medicine, Health Care and Philosophy*, vol. 19, pp. 307-23.

WEISS, K.M. (2017), 'Is Precision Medicine Possible?'; *Issues in Science and Technology*, vol. 34, pp. 37-42.

WILD, C.P. (2005), 'Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology'; *Cancer Epidemiology, Biomarkers & Prevention*, vol. 14, pp. 1847-50.

____ (2012), 'The Exposome: From Concept to Utility'; *International Journal of Epidemiology*, vol. 41, pp. 24-32.

WOLFE, C.T. (2017), 'Materialism New and Old'; *Anthropología Experimental*, vol. 17, pp. 215-24.

YEO, B.T., and EICKHOFF, S.B. (2016), 'Systems Neuroscience: A Modern Map of the Human Cerebral Cortex'; *Nature*, vol. 536, pp. 152-4.

ZIEGELSTEIN, R.C. (2015), 'Personomics'; *JAMA Internal Medicine*, vol. 175, pp. 888-9.

____ (2018), 'Perspectives in Primary Care: Knowing the Patient as a Person in the Precision Medicine Era'; *Annals of Family Medicine*, vol. 16, pp. 4-5.