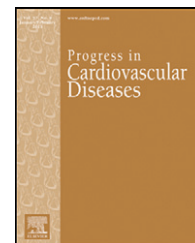


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# The P4 Health Spectrum – A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan

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## ABSTRACT

Chronic diseases (i.e., noncommunicable diseases), mainly cardiovascular disease, cancer, respiratory diseases and type-2-diabetes, are now the leading cause of death, disability and diminished quality of life on the planet. Moreover, these diseases are also a major financial burden worldwide, significantly impacting the economy of many countries. Healthcare systems and medicine have progressively improved upon the ability to address infectious diseases and react to adverse health events through both surgical interventions and pharmacology; we have become efficient in delivering reactive care (i.e., initiating interventions once an individual is on the verge of or has actually suffered a negative health event). However, with slowly progressing and often 'silent' chronic diseases now being the main cause of illness, healthcare and medicine must evolve into a proactive

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system, moving away from a merely reactive approach to care. Minimal interactions among the specialists and limited information to the general practitioner and to the individual receiving care lead to a fragmented health approach, non-concerted prescriptions, a scattered follow-up and a suboptimal cost-effectiveness ratio. A new approach in medicine that is predictive, preventive, personalized and participatory, which we label here as “P4” holds great promise to reduce the burden of chronic diseases by harnessing technology and an increasingly better understanding of environment-biology interactions, evidence-based interventions and the underlying mechanisms of chronic diseases. In this concept paper, we propose a ‘P4 Health Continuum’ model as a framework to promote and facilitate multi-stakeholder collaboration with an orchestrated common language and an integrated care model to increase the healthspan.

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Chronic diseases, otherwise known as noncommunicable diseases (NCDs), represent the major global health problem of the 21st century.<sup>1–4</sup> The major chronic diseases listed by World Health Organization (WHO) are cardiovascular disease (CVD), cancer, chronic respiratory diseases and diabetes mellitus (DM); neurodegenerative disorders are also a significant concern. Chronic diseases are the world’s leading cause of health burden and mortality and are continuing to increase in both incidence and prevalence.<sup>1,4,5</sup> Moreover, chronic diseases are a major cause of poverty and hinder economic

development.<sup>6</sup> Chronic diseases share common risks including socio-economic factors, cluster in co-morbidities and are intertwined with aging.<sup>4,7</sup> The challenge for chronic diseases in the 21st century is to deal with their complexity and the often ‘silent’ transition from health to disease with a late onset of symptoms which can delay treatment and interventions and to shift towards prevention.

Fortunately, the majority of chronic diseases can be prevented or delayed until significantly later in life through interventions such as adoption of a healthy lifestyle

### Abbreviations and Acronyms

BP = Blood pressure
CVD = Cardiovascular disease
DM = Diabetes mellitus
LCHD = Life course health development
NCD = Noncommunicable disease
PA = Physical activity
P4 = Preventive, predictive, personalized and participatory
P4H = P4 Health
QoL = Quality of life
WHO = World Health Organization

throughout the lifespan resulting in an extended healthspan (i.e., the duration of one's life spent in a state of wellness, free of disease).<sup>8–12</sup> Monitoring and maintaining normal values for key health metrics, such as blood pressure (BP), lipids, and blood glucose also play a primary role in reducing chronic disease risk.<sup>5</sup> Moreover, as we gain a better understanding of genomics and more importantly the interaction be-

tween genomics, lifestyle, personal experiences of adversity and the social and physical environment, the ability to predict risk and prevent chronic disease will be further improved.<sup>13–15</sup>

As such, powerful mechanisms to combat the chronic disease crisis are currently present and continue to evolve. However, a new healthcare delivery model is needed to implement these mechanisms effectively. For example, Halfon and Hochstein<sup>16</sup> introduced the Life Course Health Development (LCHD) concept that describes “how health trajectories develop over an individual's lifetime due to positive and negative experiences and how this knowledge can guide new approaches to policy and research.” One important issue is that early life adversity from poverty, abuse and neglect has long lasting influences on health and contributes disproportionately to the health care burden.<sup>17</sup>

An approach in medicine that is preventive, predictive, personalized and participatory (P4)<sup>18–25</sup> holds great promise to reduce the burden of chronic diseases by harnessing technology and an increasingly better understanding of human interaction, evidence-based interventions and the underlying mechanisms of chronic diseases. Current chronic disease management is characterized by the addition of interventions and recommendations made by the various medical specialists involved. Minimal interactions among specialists and limited information to the general practitioner and patient lead to a fragmented health approach, non-concerted and sometimes ineffective interventions, a scattered follow-up and a suboptimal cost-effectiveness ratio.<sup>26,27</sup> The amalgamation of P4 medicine with other prevailing concepts and principles has the potential to reinvent healthcare.<sup>28</sup> In the current concept paper, we propose the P4 Health (P4H) continuum model, which embraces and expands upon the concepts of P4 medicine,<sup>24</sup> as a framework to promote and facilitate pro-active collaborations with a common orchestrated language and integrated care model. This framework draws upon a number of concepts that have been previously established,<sup>25,29–33</sup> brought together in a way that augments the potential impact.

## The P4H continuum model

There is broad agreement that the current framework used to guide healthcare and chronic disease management is largely ineffective. As such, there is a need to re-conceptualize the paradigm to focus on wellness and the prevention of chronic disease and associated risk factors first and foremost. The concept of wellness, an optimal state of health, is a paradigm-changing concept for transforming healthcare. In the future, healthcare must shift its focus to promoting a state of wellness, from the individual to population level, as well as following wellness to disease transitions and learning how to reverse common diseases at their earliest possible stage. Within the coming years, we predict that the ability to better define true human wellness will be further refined through advancements in numerous scientific fields including blood biomarkers. In instances where risk factors or an actual chronic disease diagnosis has manifested, the focus must shift to aggressively return an individual to a state of health and wellness. Moreover, there is wide agreement that the stakeholders involved and the interventions and programming needed to combat chronic disease must expand and embrace a multisector approach.<sup>32</sup> Fig 1 illustrates the P4H continuum model; the two central components of this model are *Stages of Health* and *Levels of Intervention*. The remaining sections describe core components of the P4H continuum model, illustrated in Fig 1, in detail.

### Stages of health

The chronic disease trajectory and the transition from health to a chronic disease can be divided into four primary stages, based on the model of allostasis and allostatic load and overload.<sup>34</sup> Allostasis is the active process of adaptation to daily experiences, good or bad, and allostatic load and overload refer to the cumulative change in brain and body that, when an individual experiences “toxic stress”, both psychologically and physiologically and lacks control, dysregulation of the mediators that normally promote adaptation and pathophysiology ensues, leading to disease. Negative health behaviors related to a stressful lifestyle contribute to allostatic load and overload. In this scheme, initially, an individual moves from health, Stage A, to detectable signs, or biological expression, Stage B, where early disease precursors and dysfunctions can be detected but the individual is unaware of them and does not have any symptoms, which is common in clinical medicine. From Stage B, chronic diseases usually progress slowly, the individual showing symptoms, and clinical expression Stage C is the point at which traditional reactive health care is initiated. Despite advancements in interventions, many individuals with symptoms will make the transition to confirmed chronic disease, Stage D, where traditional healthcare is continued and up-titrated with pharmacotherapy, surgery and other interventions used to manage the chronic disease. Once reaching Stage D and a chronic disease diagnosis is confirmed, some degree of permanent physiologic damage/dysfunction (i.e., allostatic overload) is likely. For example, ischemic damage

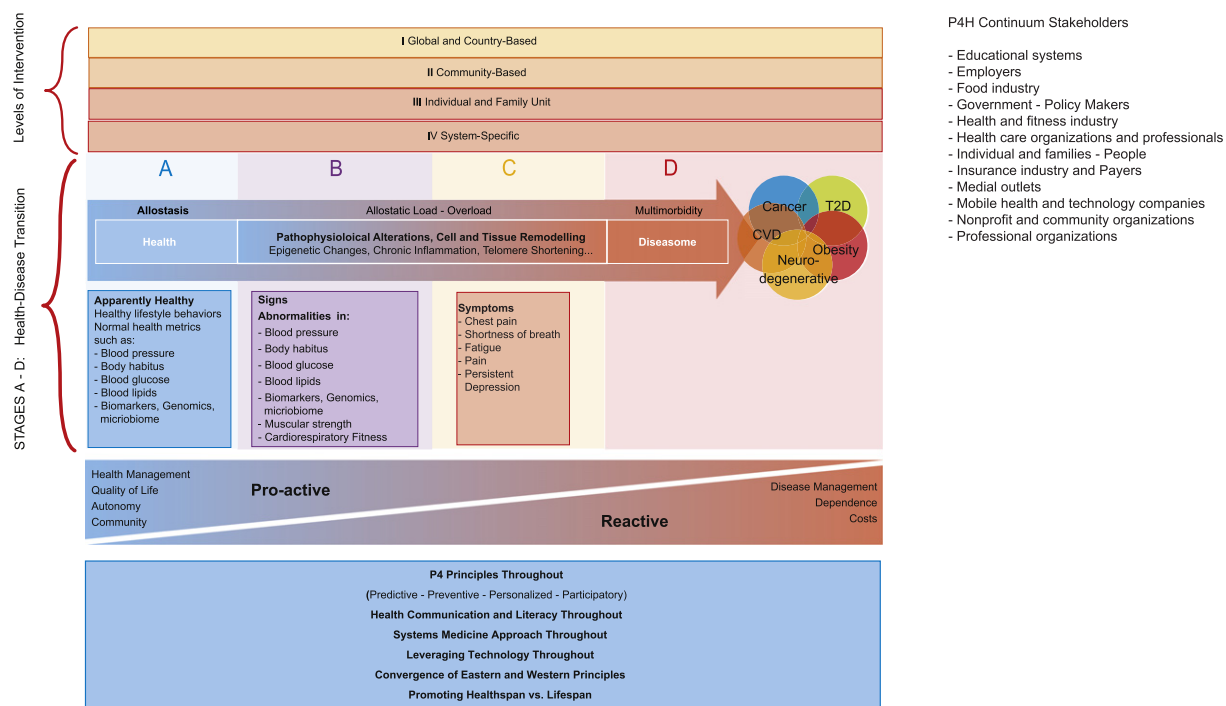


Fig 1 – The P4H continuum model.

after a myocardial infarction or stroke, cancer and other chronic diseases will leave permanent damage and dysfunctions that, in the current reactive health care system, usually requires lifelong treatment and management. Even so, in those who aggressively attempt to improve core components of their health, an individual with a chronic disease diagnosis has the potential to significantly improve their prognosis, clinical status and quality of life (QoL). Type II diabetes is a classic example of development through these stages, eventually leading to an irrevocable stage. However, intervention and lifestyle management at Stage B or C has the potential to reverse this disease process. The following passages describe the stages of health illustrated in Fig 1 in greater detail.

*Stage A: Apparently healthy and avoiding the accumulation of stressors*

Stage A (i.e., allostasis) indicates an individual is in apparently good health and wellness. Individuals in Stage A emulate healthy lifestyle characteristics [i.e., regular physical activity (PA), no tobacco use, nutritious diet, no harmful alcohol use] and possess key health measures within the normal range (i.e., blood glucose, BP, blood lipids and body habitus). It is during this stage that individuals are able to “adapt to potential threats to their survival and changes in their environment (often referred to as “stressors”) in order to maintain homeostasis and promote survival.”<sup>35</sup> The term ‘apparently’ healthy is used because at this time we do not have the tools at hand to determine levels of poor health beyond the presence of clinical risk factors. There is however research progress in identifying more granular risk categories (stages of accelerated aging and early disease risk) in the absence of clinical biomarkers. Such genomics and other

detailed biological, clinical, environmental and molecular assessments are currently not readily available for assessment for the general public. As our ability to perform detailed molecular assessments for a larger percentage of the population evolves, the characterization and definition of apparent health in Stage A will become refined and more precise. Movement in this direction has begun with precision medicine initiatives moving forward.<sup>13,18,36-38</sup> Large, dense, dynamic, personalized data clouds, such as the one being generated by the 100 K wellness project,<sup>39</sup> are specific examples of a movement towards precision medicine. These efforts are creating the framework for “scientific wellness,”<sup>40</sup> where millions of data points, from DNA, blood, saliva, the microbiome and lifestyle, among others, will be used to exponentially refine how an individual’s health is managed and optimized.

Unfortunately, those who emulate Stage A health comprise a very small percentage of the current global population.<sup>5,8,9</sup> Moreover, most individuals are immersed in a world that is far from what can be characterized as health-promoting. In a sense, this poor health environment (e.g., limited access to nutritious food, a physically inactive environment and limited effective social network interactions, etc.) is a communicable condition. That is to say the poor health characteristics of an environment can be transmitted to an individual.<sup>41-43</sup> We thus have created a world where the ability of an individual to remain in Stage A is increasingly difficult. A global health goal must be directed towards substantially increasing the percentage of the population that remains in Stage A health, providing an inoculation from unhealthy environments.

Chronic diseases share a common cluster of environmental and lifestyle risk factors or stressors (e.g., physical

inactivity, poor nutrition, psychosocial distress, excess body mass, indoor and outdoor air and sound pollution, tobacco, inadequate sleep, excess stress, etc.).<sup>4,5,44</sup> Socio-economic determinants, especially poverty, also influence the generation, severity and management of chronic diseases.<sup>6,45</sup> It is usually a constant exposure to these stressors and poor health behaviors that underlie the journey towards allostatic overload and resulting chronic disease. Negative stressors, or distress, are complexly associated with sustained local and systemic inflammation as well as a host of other dysfunctions.<sup>46,47</sup> These stressors can begin early in life reflecting effects of abuse, neglect and poverty, with significant negative health implications during adulthood that contribute disproportionately to the healthcare burden.<sup>48,49</sup> Children exposed to adverse childhood experiences (i.e., psychosocial, socioeconomic disadvantage, maltreatment and social isolation) are at increased risk for depression, increased systemic inflammation and clustered metabolic derangements in adulthood.<sup>50</sup> The cause of a complex set of disorders such as chronic diseases cannot be pinpointed to a single origin; rather, a highly complex interacting network of many mediators and factors that interact on different levels over time and space is involved.<sup>21,47,51,52</sup> It is also important to note that biological systems work in a non-linear way, with the brain as the central organ of adaptation or maladaptation.<sup>53</sup> And with progression along the chronic disease trajectories that is cumulative and does not follow a specific timeframe, becoming a unique personalized experience for each individual requiring personalized care.<sup>54</sup>

Certain factors can increase resilience against stressors and maintain an individual in Stage A; healthy nutrition and physical activity can reduce the risk of cancer and CVD<sup>55,56</sup>; contemplative practices can modulate interception to attenuate affective and psychosomatic disorders<sup>57</sup> and reduce perceived stress and neurogenic inflammatory response.<sup>58</sup> Meaning and purpose in life and social connectedness also promote better health.<sup>59</sup> Telomeres provide an example of how these factors can impact the rate of biological aging in the absence of disease. Most of these positive lifestyle resiliency factors have been related to longer telomere length. Further, a positive lifestyle appears to protect telomere shortening when under psychological stress.<sup>60,61</sup>

Given the right data and aids with interpretation, such preventive activities can be effectively personalized to the individual (e.g., providing feedback through monitoring).<sup>62</sup> Beyond a healthy lifestyle, there is still much work to be done with how pharmaceutical or other interventions could potentially increase resilience towards outside stressors and prevent diseases. It is important to remember that a certain amount of positive stress (i.e., eustress) is necessary to maintain health; physical exercise and caloric reduction result in eustress, leading to positive biological adaptations.<sup>47,63,64</sup>

Moving from Stage A (i.e., allostasis) to the beginning of a pre-chronic diseaseome,<sup>5</sup> Stage B (i.e., allostatic load), is usually of slow progression and often unnoticed by the individual undergoing this transition. We have studied a prion-based mouse model for neurodegeneration with brain transcriptome analyses of 10 time points across the entire neurodegenerative process and demonstrated that 4 major biological networks become successively disease perturbed –

and one can from these networks follow beautifully the progression of the disease. The course of the disease lasts 22 weeks, the first clinical signs appear at 18 weeks and the first disease-perturbed network is seen at 7 weeks – long before any clinical signs.<sup>65</sup> As stressors accumulate and an individual manifests a greater number of unhealthy lifestyle characteristics, the signs of chronic disease risk that define Stage B become imminent. This accumulation of stressors and a failure of biologic resiliency, or *allostatic load*, may be defined as the Stage A–B transition.

#### *Stage B: The emergence of chronic disease signs*

The intertwined multitude of stressors most individuals are exposed to in Stage A lead to complex phenotypes that eventually manifest as clinical and biologic signs.<sup>33</sup> Stage B marks the initiation of detectable phenomena associated with increased chronic disease risk. Traditional signs include elevated BP, dyslipidemia, and elevated blood glucose.<sup>7</sup> Measures of chronic inflammation<sup>66,67</sup> have emerged as important signs for chronic disease risk as well, and allostatic load battery that has predictive value for later disease brings together measurements of primary and secondary mediators of allostasis that can be scored and presented in different ways.<sup>68–70</sup> In fact, the fields of genomics, epigenetics, transcriptomics, proteomics, metabolomics and gut microbiome analyses related to chronic disease risk prediction are continuing to evolve and future discovery will refine the identification of individuals in Stage B with these parameters.<sup>36,71,72</sup> It is important to note the ‘omics’ are usually thought of as providing a disease signature but they may be even more valuable in the transition from Stage A to Stage B, before there are clear underlying signs of allostatic load and clinical biomarkers of disease. Moreover, the importance of a lower than sex/age predicted level in cardiorespiratory fitness and muscle strength/endurance are important predictors of future chronic disease risk and adverse events.<sup>73–78</sup> Excess body mass, particularly visceral fat, is also a significant predictor of chronic disease risk and associated adverse events.<sup>5,79–81</sup> Even so, exercise performance and body habitus, while recognized as important markers of health and prognosis, are traditionally not viewed as “signs” of chronic disease risk. We are proposing a paradigm shift in this mindset and recommend below-normal exercise performance and excess body mass be treated as signs of increased chronic disease risk and, when present, allow an individual to be classified as Stage B. Fig 1 lists examples of Stage B signs that hold significance. This list of signs is kept broadly defined and not intended to be exhaustive but rather an account of general themes as research into the optimal combination of signs for identifying risk will continue to evolve. Moreover, depending on resources, health professionals may not be able to perform an exhaustive assessment of signs and, in such instances, should perform assessments using the means they have available. A great deal of information related to an individual’s health, chronic disease risk and prognosis can be gained from signs associated with traditional health behaviors and key metrics (e.g., physical activity, dietary patterns, BP, lipids, blood glucose, body habitus and tobacco use).<sup>7,82</sup>

Early dysfunctions and chronic disease pre-cursors as signs of allostatic load are often overlooked in the traditional health care setting. Individuals with the classic initial signs of chronic disease risk such as high BP, blood glucose and dyslipidemia as well as recently discovered signs such as telomere length shortening and changes in the gut microbiome usually do not go along with functional impairment in daily life. Moreover, diminished exercise performance is also usually undetected in the general population – a situation that could be significantly impacted going forward by integrating data from the growing set of digital health devices in the marketplace. This underperformance in exercise is partly due to the fact that a large percentage of the population, particularly those at greatest risk for one or more chronic diseases, leads a sedentary lifestyle, avoiding levels of exertion that would likely manifest an exertional Stage B sign (e.g., diminished cardiorespiratory fitness and muscle strength/endorurance).

Complex dynamical systems, such as human beings, can have tipping points at which a sudden shift to a contrasting dynamical regime may occur. Although predicting such critical points before they are reached is currently difficult, work in different scientific fields is now suggesting the existence of generic early-warning signals.<sup>83–85</sup> Dynamical network biomarker theory (i.e., driver network) was recently used to describe upstream, tissue-specific, critical transitions in the liver, adipose tissue and muscle that lead to the development and progression of type 2 DM.<sup>86</sup> The monitoring of such early warning signals can help predict the state of disease progression and the occurrence of abrupt transitions to a worsening state of health.

Individuals in Stage B, if engaged, would benefit greatly from a pro-active, preventive approach with the goal of eliminating signs and returning an individual to Stage A. At this stage, a particularly important opportunity emerges for the health professional to assess the individual's understanding of health information, assist them in appraising and applying critical thinking, and identify obstacles or motivations for the patient to make lifestyle changes. Possible assessment may be dictated by the individual's level of education and language acquisition. Open ended questions that lead to discourse analysis may elucidate and encourage the individual's critical thinking skills. Simple narrative collection will shed light on the individual's motivations and goals for their own health. A variety of media may be used to ensure the patient understands the health information through text, visual aids, and verbal cues.

Since most individuals are either unaware of their downhill movement from health towards a chronic disease or unwilling to take steps to reverse this trajectory, they are unlikely to take preventive, proactive measures, such as lifestyle modifications or biological or pharmaceutical interventions.<sup>38,39,87</sup> Emerging efforts seek to empower individuals with knowledge to optimize wellness and reverse this trajectory.<sup>39,40</sup> It will be very important to bring this educational approach to science education – so that young adults will already be exposed to these modern insights. It is helpful to view this early health monitoring, psychoeducation, and counseling, as critical as early immunizations. The knowledge

and motivation can immunize young people from continuing down the silent path of chronic disease.

In the absence of such, individuals continue to progress along the Stage B portion of the continuum; a cluster of signs both silent and those becoming increasingly apparent worsen in severity. After a variable time period, which may take decades, Stage B signs will give way to Stage C symptoms (i.e., progressing allostatic load).

#### *Stage C: The emergence of chronic disease symptoms*

The manifestation of chronic disease symptoms is a common entry point for individuals into today's traditional reactive healthcare system. For example, dyspnea occurring within the range of exertional capacity needed for activities of daily living (e.g., climbing a flight of stairs) is a Stage C symptom. Persistent depression should also be viewed as a symptom that elevates chronic disease risk.<sup>88,89</sup> While an official chronic disease diagnosis has not yet been made, significant pathophysiologic dysfunction is likely well established. Moreover, unhealthy lifestyle characteristics and abnormalities in key health measures are, in the vast majority of cases, also well established in Stage C and now compounded by outwardly apparent symptoms. *In the traditional reactive healthcare system, the symptoms are oftentimes treated without addressing the poorly understood underlying causes and mechanisms that are at the root of the dysfunction, which are in large part unhealthy lifestyle behaviors.* In this sense, this healthcare approach perpetuates the reactive cycle. Symptoms become temporarily alleviated as the level of dysfunction persists and progressively worsens as do the unhealthy lifestyle behaviors, giving rise to subsequent symptomatic episodes and progressive biological damage. At this point, the transition for the eventual diagnosis of a chronic disease and transition to Stage D (i.e., allostatic overload) is extremely high.<sup>5,90</sup>

#### *Stage D: Confirmed chronic disease diagnosis*

Once a chronic disease is diagnosed (e.g., ICD-coded) the treatment approach becomes more aggressive and is the defining moment of the reactive health care model. Treating a full blown chronic disease, such as coronary artery disease or cancer, requires expensive and often invasive interventions. As in Stage C, underlying causes and mechanisms of the diagnosed chronic disease are not addressed. The reactive health care model is focused on stabilizing the individual in a hospital setting and ameliorating acutely elevated symptoms. Over the last several decades, we have become very efficient in this model as indicated by the decrease in annual CVD mortality rates.<sup>5</sup> Even so, very little is done to address the root cause of these conditions. Even at this stage, environmental and lifestyle risk factors, which if modified substantially improve prognosis and quality of life,<sup>91</sup> are usually not addressed. As such, dysfunction continues to spiral downward and symptoms worsen with morbidity and premature mortality and increasing health care costs as the end result. While this does not have to be the case, once reaching Stage D, individuals commonly reside at this stage of health for the remainder of their lives, with a coexisting and compounding cluster of Stage B and C signs and symptoms, respectively. Moreover, many individuals are diagnosed with more than

one chronic disease (i.e., multimorbidity). In truth, a number of chronic diseases may be capable of reversal from Stage D (or even Stage C) back to Stage A (or B).

*Health stages: Where you have been, where you are now*

Health Stages A–D should not be viewed as unidirectional or stationary, progressing from apparent health to chronic disease with no hope of reversal. A wealth of information clearly demonstrates improving health behaviors and key health metrics significantly improve an individual's future health trajectory.<sup>91–93</sup> An individual who has been diagnosed with a chronic disease, but aggressively improves health metrics and lifestyle behaviors, may ameliorate all Stage C symptoms and Stage B signs. In this case, the individual who was diagnosed with a chronic disease (i.e., where they have been) is now demonstrating traits consistent with Stage A health (i.e., where they are). Viewing the stages of health in this manner allows individuals to understand the importance of improving health metrics and lifestyle behaviors irrespective of baseline health status. Through active participation, P4 medicine strives to prevent: 1) the first event/diagnosis from occurring; and 2) subsequent events from occurring when a personalized predictive diagnosis has already been made. Both goals are equally important in the P4H continuum, ensuring appropriate care is given to individuals in all stages of health.

### Levels of intervention

Moving towards a modern, pro-active health care system, different levels of intervention must be clearly defined and the list of stakeholders invested in the implementation of the P4H continuum model must be expanded. Health and well-being depend on a complex fabric of systems that are constantly interacting and shaping human biology, behavior and the environment, particularly with respect to lifestyle characteristics and chronic disease. The following sections describe the four intervention levels in the P4H continuum model, as illustrated in Fig 1.

#### Level I: Global and country-based interventions

Global and country population strategies, otherwise defined as public health, strive to improve the health of a large population and reduce the chronic disease burden. The World Health Organization is the prime example of a global organization that has a strong focus in this area, as demonstrated by its initiatives, publications related to chronic disease and goals for improvement.<sup>4</sup> National governments are also focused on strategies to improve the health of their populations as it relates to chronic disease.<sup>3,94–98</sup> Global and whole-country public health organizations as well as national/federal governments play a vital role in Level I interventions through numerous avenues including: 1) health-promoting legislative policies; 2) financial investment in health-promoting initiatives and research; and 3) policy reports and recommendations. The WHO has put forth a “health in all policies” initiative, encouraging governments to consider the impact of population health for all legislations implemented. This framework is defined as “an approach to public policies across sectors that systematically

takes in account the health implications of decisions, seeks synergies, and avoids harmful health impacts, in order to improve population health and health equity.”<sup>99,100</sup> An approach such as this helps governments to consider Level I health interventions in all actions it takes.

#### Level II: Community-based interventions

Despite public health efforts and laws, health-changing behaviors are primarily shared across local communities and the environment within them. Despite being categorized as chronic NCDs, to a degree, follow a network pattern. This has been shown with obesity and lifestyle-related chronic disease risk behaviors. Communities and social networks influence lifestyle patterns and behavior in a significant way.<sup>41–43,101–103</sup> Level II interventions focus on creating an environment where individuals are immersed in a healthy lifestyle environment and readily available access to: 1) nutritious and affordable food; 2) opportunities for PA and contemplative practice; 3) a smoke free environment; 4) information and resources on how to maintain health and prevent chronic disease; and 5) health care systems that promote preventive medicine and healthy lifestyle behaviors. There are numerous examples on how to promote healthy lifestyle choices where individuals live, work, and attend school.<sup>32,102,104–111</sup> Most of them have not met with outstanding success – and we have to learn how to persuade individuals to change their misguided or ill-informed health trajectories towards wellness.<sup>62</sup> There are also numerous opportunities for healthcare systems within a community to practice preventive medicine and embrace healthy lifestyle interventions.<sup>112</sup>

#### Level III: Individual and family unit interventions

Ultimately, the delivery of preventive medicine and healthy lifestyle interventions must reach and be embraced by a given individual – that is, it must be participatory.<sup>20</sup> In addition to the ultimate goal of Level I and II interventions reaching the individual, Level III interventions continue the P4H continuum care plan via face-to-face interactions with health professionals (e.g., physician, nurse, dietician, exercise scientist, pharmacist, behavioral counselor, physical therapist, community health worker, wellness coaches, etc.). Level III interventions are directed at the individual as a whole and thus healthy lifestyle interventions are a primary focus. To be effective in delivering Level III healthy lifestyle interventions, we must rethink the education of the health professions to ensure all disciplines receive the necessary education and training to effectively provide PA, weight loss, dietary or smoking cessation care plans.<sup>113</sup>

This opens the opportunity for new career trajectories in the health care professions (i.e., professional wellness coaches). Healthy lifestyle is a universal medicine that should be provided by all health professions speaking a universal language. Health professionals delivering Level III interventions greatly benefit from effective Level I and II interventions. If the individual receiving guidance from a health professional is immersed in a healthy environment and made well aware of the importance of healthy lifestyle through population/community messaging campaigns, the ability and likelihood to follow the plan of care are substantially

improved. Level III interventions, delivered by a broad array of health professionals, must be expanded beyond the traditional walls of the healthcare system (i.e., hospital and outpatient clinics). In particular, to optimally prevent chronic disease, there should be a strong focus on delivering Level III interventions in community settings; school systems, the workplace, public parks and libraries, grocery stores, pharmacies, in addition to traditional outpatient clinics and hospitals, are all appropriate settings for Level III interventions.<sup>32,91,111,114</sup> In this way, Level III interventions reach individuals in all stages of health. Level III interventions must also include the immediate family unit surrounding the individual receiving care. Adoption of and compliance with Level III interventions are optimized if those closest to a given individual become invested and believe in the care plan.<sup>32,115</sup> In essence, the primary “clinic” of Level III interventions is in an individual’s home.

#### Level IV: System-specific interventions

Levels I–III interventions focus on the whole individual, promoting participation in a healthy lifestyle. Level IV interventions are system-specific, targeting a specific physiologic system within an individual that demonstrates abnormal function or chronic disease. Examples include: 1) pharmacologic interventions for hypertension, dyslipidemia or elevated blood glucose and 2) surgery for cancer or CVD. At this moment, Level IV interventions comprise the majority of care delivered in the current reactive healthcare system; most individuals currently receiving Level IV interventions are in Stage C and D health, receiving generalized care based on current scientific evidence. We are recognizing this generalized downstream (i.e., Stage C and D) approach is not optimal. The National Institutes of Health (NIH) has defined precision medicine as “treatment and prevention that take into account individual variability in genes, environment, and lifestyle for each person.”<sup>116</sup> As precision medicine advances,<sup>13,18,117</sup> opportunities to deliver Level IV interventions to individuals in Stage A and B health will evolve and improve the ability to deliver P4 medicine.

#### All levels of intervention for all stages of health

Given the previously described *where you have been* – *where you are now* framework, all levels of intervention are essential to all health stages. No matter what health stage an individual enters the P4H continuum model, the primary objective is to prevent future chronic disease diagnoses and adverse events, ameliorate symptoms and signs when present, and improve lifestyle behaviors. In this context, all intervention levels should be delivered at all stages of health.

#### Stakeholders and guiding principles of the P4H continuum

The right-side and lower panels of the P4H continuum illustrated in Fig 1 highlight stakeholders and overarching guiding principles for the model and are described in the following sections.

#### The collaborative multistakeholder model

To realize the full vision of the P4H continuum model, the stakeholder’s involved in the future preventive, proactive,

healthy lifestyle healthcare system must be expanded. Moreover, to make the impact needed in preventing and treating chronic disease, strong collaborations are required among stakeholders.<sup>32</sup> The formation of multistakeholder groups, with representatives from all sectors must be invested in preventive medicine and healthy lifestyle interventions. These groups, formed within communities, should create innovative programming that is locally applicable and effective. Preventive medicine and healthy lifestyle interventions should not be viewed as a one-size-fits-all approach. The non-hierarchical multistakeholder model outlined in a U.S. – European policy statement<sup>32</sup> is an integral component of the P4H continuum model and allows for full implementation of all levels of intervention across all stages of health.

## P4 principles throughout

Clearly the reactive health care model that currently exists is suboptimal, requiring a paradigm shift to improve global to individual health and address the current challenges we face with chronic disease and associated risk factors. We need a new approach, focusing on care that is preventive, predictive, personalized and participatory (P4) as core principles of the P4H continuum model. Table 1 lists key factors to consider in delivering P4 medicine and subsequent sections describe key attributes.

### Predictive

Predicting dysfunctions and detecting disease pre-cursors at Stage B allows for pro-active interventions to address the underlying mechanisms before symptoms occur. Predictive medicine is essential to the preventive framework; when a risk factor phenotype manifests, predicting an increased likelihood for adverse events, all efforts should be taken to eliminate these risk factors, returning the individual to an optimal state of health. This will require a broad array of health care professionals to take a more active role in addressing and interacting with ‘healthy individuals,’ without signs or symptoms, to detect the risk of emerging dysfunctions, preventing a progression in stage of health at a minimum and ideally facilitating a regression (i.e., back to Stage A).

A biomarker is an indicator of a biological state, or the past or present existence of a particular type of organism. It is not necessarily a genomic or post-genomic one. Blood lipids are a risk factor for CVD.<sup>118</sup> However, for many diseases (including cancer), clinically useful biomarkers are just beginning to appear and are not yet wide spread.<sup>119,120</sup> For example, a 13 protein blood panel that has the ability to distinguish benign from neoplastic lung nodules has recently been developed; this simple expediency can save the healthcare system \$3.5 billion a year in avoiding unnecessary surgeries. This is now an available CLIA approved test.<sup>120</sup> Future systems biology research will help to discover new biomolecular networks and biomarkers for disease prediction and monitoring. Biomarkers of pharmacogenomics and targets will also be of interest to improve bio-pharmaceutical interventions.



**Table 1 – P4 concepts of chronic disease severity, activity, control and responsiveness.****Severity**

Loss of function in the target organs induced by disease. It is important to highlight that severity may vary over time and needs to be regularly re-evaluated, in particular since the population is aging. Notably, temporal fluctuations of disease markers may provide a diagnostic or phenotypic signal by themselves.

**Activity**

Level of biological process activation that drives disease progression. This is a fundamental concept that needs to be clearly separated from “severity” because treatment strategies are different. Hence, whereas treatment of disease activity aims at stopping and/or reducing the progression of the disease, thus eventually avoiding the occurrence of severe disease, treatment of severity aims at palliating the impact of the disease on the patient’s health status. Current management of chronic diseases focuses on treatment of severity but neglects treatment of activity because of the lack of validated activity biomarkers.

**Control**

Degree to which therapy goals are currently met such as glycemic control in diabetes. The lack of validated biomarkers of disease activity limits their use in most chronic diseases.

**Responsiveness**

Ease with which control is achieved by therapy. Adherence to therapy is a key component of responsiveness and should also be monitored.

**Source:**

Bousquet J, Jorgensen C, Dauzat M, Cesario A, Camuzat T, Bourret R, Best N, Anto JM, Abecassis F, Aubas P, Avignon A, Badin M, Bedbrook A, Blain H, Bourdin A, Bringer J, Camu W, Cayla G, Costa DJ, Courtet P, Cristol JP, Demoly P, de la Coussaye JE, Fesler P, Gouzi F, Gris JC, Guillot B, Hayot M, Jeandel C, Jonquet O, Journot L, Lehmann S, Mathieu G, Morel J, Ninot G, Pelissier J, Picot MC, Radier-Pontal F, Robine JM, Rodier M, Roubille F, Sultan A, Wojtuszczyz A, Auffray C, Balling R, Barbara C, Cambon-Thomsen A, Chavannes NH, Chuchalin A, Crooks G, Dedeu A, Fabbri LM, Garcia-Aymerich J, Hajjam J, Melo Gomes E, Palkonen S, Piette F, Pison C, Price D, Samolinski B, Schunemann HJ, Sterk PJ, Yiallourous P, Roca J, Van de Perre P and Mercier J. Systems medicine approaches for the definition of complex phenotypes in chronic diseases and aging. From concept to implementation and policies. *Current pharmaceutical design*. 2014;20:5928–44.

Currently, ‘classic’ biomarkers’ such as blood lipids, blood glucose and C-reactive protein remain at the core of predicting diseases. The next generation of biomarkers will increase the precision of identifying dysfunctions, ideally early in the process. However, given the complex interaction of the different systems and biomarkers inside the human body, a systems-based approach is needed to make better sense of the overall biomarker profile instead of looking at individual markers, such as cholesterol in isolation.<sup>117,120–122</sup> Such an approach has begun in the field of aging, where, in young “healthy” people, an algorithm of biomarkers predicts the pace of aging and early decline vs single markers.<sup>11</sup>

**Preventive**

It is obvious that preventing chronic disease is the preferred approach moving forward. Functional and physiologic health decline in parallel with advancing age and/or manifestation of chronic disease and co-morbidity.<sup>123</sup> Aging currently is

associated with increases in the likelihood of dysfunctions, chronic diseases and co-morbidities, thereby confounding their effects on health and well-being. Quality of life, autonomy and life expectancy are greatly reduced as the individual progresses rightward along the continuum (i.e., Stage A to D). The slope of the decline in functional and physiologic health can be dramatically attenuated through a preventive approach. Health care costs are highest at Stage C and D where Level IV interventions are primarily utilized. Preventing diseases as early as possible requires a deeper understanding of chronic disease pathogenesis, which comes from employing systems medicine approaches that identify relevant disease-perturbed networks,<sup>65</sup> and the influence of risk factors as well as potential protective factors. Ideally, preventing disease in Stage A ensures risk factors for chronic disease never manifest (i.e., primordial prevention). If this avoidance were achieved, Stage A would become a true stage of health and wellness/well-being as opposed to a doorway to Stage B and beyond. While primordial prevention should be the ultimate goal, primary and secondary preventions are also integral components; regardless of age or health status, preventive medicine is highly effective and valuable (i.e., where you have been – where you are now). An overarching goal for the P4H continuum should be, when individuals cared for in this model, are asked “where they are now?”, their response is Stage A.

**Personalized**

Medicine has traditionally made generalized assumptions regarding the individual receiving care without an appreciation of the complexities of human biology and its unique interaction with the surrounding environment. Such a generalized approach has led to suboptimal outcomes for a large percentage of individuals receiving care. Research is beginning to illustrate the importance of personalized medicine. For example, personalized nutrition research has revealed highly inter-individual responses to standardized meals, illustrating the importance of not taking a one-size-fits-all approach.<sup>124</sup> The response to physical exercise and psychological stress is also highly variable and depends on individual genetic profiles and lifestyles.<sup>125,126</sup> Moreover, chronic disease risk in general has a genetic component that is highly individual.<sup>15,119</sup> The approach to certain chronic diseases such as cancer is already moving towards a more personalized approach based on individual phenotyping and molecular targeting.<sup>119</sup>

Health care is also beginning to fully appreciate the ‘non-responder’ phenomenon, diving into clinical trials, where statistically significant P values have traditionally denoted interventional success, and identified individuals where treatment was ineffective.<sup>125,126</sup> This distinction between individual responses is the essence of the personalized approach, identifying the non-responder phenotype and creating individualized interventions that break past that barrier. Personalized medicine will need to find ways to provide user-friendly, secure and efficient ICT-systems to manage the highly diverse, complex and distributed data of the individual patient across the entire P4-health continuum. This

**Table 2 – The five pillars of P4 medicine.****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 from deriving actionable knowledge from the data.

**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

will empower the individual to take ownership on his/her own data and at the same time support the growth of a public health knowledge environment where the community benefits from the information gathered on its individual members.

### Participatory

Medicine has a longstanding tradition of a top-down approach. This approach might have been useful during times where infectious diseases and acute injuries were the main health concerns. But with chronic diseases now being the primary health crisis, a new approach is needed that involves the individual receiving care, and his/her family, as primary stakeholders.<sup>20,32,115,127</sup> The individual ultimately has to be part of the preventive and predictive approach in order to be successful.<sup>62</sup> Involving the individual in personalized treatment and preventive interventions and improved data collection through self-tracking will be important factors. To achieve this goal, we have to gain a much better understanding of an individual's "health literacy." The WHO defines health literacy as, "people's knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgements and take decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve QoL during the life course."<sup>128</sup> Having an understanding of an individual's literacy is of paramount importance to the participatory component of P4 medicine. Through every stage, efforts should be made to assess individual's motivations and competencies to maintain or return to a healthy state. Moreover, aligning the multidirectional flow of health information, between the individual, health professionals and all stakeholders immersed within the surrounding environment, is essential to all stages of health and all levels of intervention. Successful and truly participatory approaches with a long lasting and sustainable impact will be a major challenge and easier said than done. We will need to obtain a much better understanding about the identity, the motives

and the abilities of the various stakeholders within the P4-health continuum. Clark et al.<sup>129</sup> have described a framework for crafting usable knowledge for a sustainable development that takes into account stakeholder collaboration, social learning, knowledge governance and researcher training. Although developed primarily in the context of climate or ecosystems, the principles and lessons learned might very well be applied to the upcoming transformations in health care.

### Leveraging technology

The use of technology to continually engage individuals in preventive medicine and healthy lifestyle messaging, information and interventions is vital moving forward.<sup>37,38,130</sup> Health-focused platforms continue to emerge and evidence demonstrating the meaningful impact of technology-based healthy lifestyle interventions is continually growing.<sup>131–134</sup> There is particular value potential in utilizing the smartphone platform for continual engagement centered on preventive medicine and healthy lifestyle messaging and interventions.<sup>135</sup> Moreover, the use of well-designed technologic platforms has the potential to create individually tailored public health messaging. All stakeholders involved in the P4H continuum model should utilize technology to expand the reach and impact of initiatives and interventions. With advances in technology, there may even be a role for characterizing levels of robust health (vs. disease risk) in Stage A, which both add a motivational goal to strive for as well as add further leverage to the ability to measure and promote prevention.

### Systems medicine and the complexity of chronic diseases

An old Indian story talks about a group of blind men coming across an elephant. Each of the blind men touched a different part of the elephant and gave a description of what he believed an elephant was. The first person touched the elephant's trunk and claimed the elephant to be a snake. The second person touched the elephant's leg and declared the elephant to be a tree trunk. Then the last person came forward, touched the elephant's ear and positively identified the elephant to be a sail. Based on the blind men's confined level of interaction with the elephant, their observations made sense. However, if they had collaborated and studied the elephant globally, its true structure would have become apparent.

Understanding systems as complex as the human body has to involve interactive collaboration between specialists from different fields. For many years, biologists have been studying specific proteins and molecular networks individually, describing local interactions and perturbations in detail. Indeed, understanding the individual components is an important first step, but, to truly understand complex biological systems, an integrated approach must be taken. Therefore, a common, orchestrated language that allows specialists to speak and communicate with ease should be standard in training curricula, or a specialist trained in communicating between specialties should be included

**Table 3 – Paradigm shifts from reactive to proactive medicine.**

Reactive Medicine	Proactive P4 Medicine
Reactive symptoms based response	Proactive and preventive
Cross-sectional disease management	Pre-symptomatic biomarker response
Few measurements, limited diagnostic and prognostic value	Lifespan Health Management
Organ-centric	Many measurements, high resolution diagnostic and prognostic value
Disease-centric	Systems-biology
Symptom focused therapy	Person-centric
Top-down	Based on needs, personal requirements and biological variability
	Disease mechanism focused therapy/interventions
	Individual and health professional as a team

whenever possible. Further, a variety of data at all relevant levels of cellular organization with clinical and individual reported disease markers have to be integrated using the power of computational and mathematical modeling, to enable the understanding of the mechanisms, prediction, prevention and treatment of disease.<sup>121</sup>

Modern medicine has to take into account that the human biological system is a collection of networks at multiple levels, ranging from the molecular level, through cells, tissues and organisms, to the population level. Years of research have generated detailed information about the components of the complex systems that characterize ecosystems, life, organisms, genes, and cells; this knowledge has begun to fuse into greater understanding of how all those components work together as systems.<sup>121,124</sup>

P4 and systems medicine take global, integrated and quantified approaches to the challenge of biological complexity. Systems medicine uses high throughput technologies – such as DNA and RNA sequencing – to produce global data sets tracking multiple dimensions of dynamic network interactions to better predict and prevent chronic disease.<sup>15,71</sup> Enormous amounts of data obtained by tracking multiple biological networks are integrated to create a comprehensive understanding of human biology. For example, with this information scientists can begin to understand how an individual's genetic makeup and environment together produce health and disease.<sup>14,37,38,64,136</sup> Modern medicine requires a new infrastructure described in Table 2 as the 'five pillars' of systems-based P4 medicine.

### Convergence of principles from Eastern and Western medicine

Eastern medicine, like P4 medicine and systems medicine, considers human biological systems as a cohesive whole. Eastern medicine also considers the human body as a holistic entity of harmonious organs and approaches health from this framework. Eastern medicine principles are mainly derived from Chinese and Indian cultures, with long-term practical experience in the prevention, diagnosis and treatment of chronic diseases.

### Principles of Chinese medicine and its role in the P4H continuum

Traditional Chinese medicine has evolved over thousands of years and represents one of the oldest paradigms of

translational medicine in the world.<sup>137</sup> Chinese traditional medicine considers the human body as an open organism operating in a continuous biological and mental exchange process with the outside environment; human health is maintained by the balance between *Yin* and *Yang* that respectively represents two opposing factors in nature.<sup>138</sup> The diagnosis and stages of health (i.e., Stage A), risk (i.e., Stages B–C) and disease (i.e., Stage D) are established based on signs and symptoms, physical and psychological status of an individual and environmental factors that may modify homeostasis of the human body. The therapeutic approaches of chronic diseases include: 1) a primary medical prescription that targets the causative abnormality or the main symptom; 2) other remedies for treating secondary disorders or symptoms that enhance the efficacy of the primary intervention; and 3) eliminate toxicity associated with the primary medical prescription or pathogenic factors from the external environment. In the P4H continuum model, the *Yin* and *Yang* view on human health could be further considered for staging chronic disease trajectory and the transition from health to a chronic disease, as well as intervention strategies directed towards optimizing health stage through modulating the balanced points at physical and psychological levels.<sup>139</sup> Currently, in China, traditional Eastern medicine has been integrated into the country-, community-, family-, and individual-based healthcare system, which serves as a complement to modern Western medicine. In the era of modern P4 medicine, Eastern medicine could enhance chronic disease prevention and management through its view of the integration of complex systems of the human body, psychological stresses, lifestyle patterns and the environment in an optimal cost-effective manner.

### Principles of Indian medicine (Ayurveda) and its role in the P4H continuum

Ayurveda basically means “knowledge (Veda)” of “life (Ayur).” Ayurveda is an ancient system of personalized medicine documented and practiced in India since 1500 B. C.<sup>140</sup> Today, Ayurveda not only plays a key role in Asian health care systems but is also increasingly recognized in the European and North American model.<sup>141</sup>

A unique aspect of Ayurveda is the comprehensive understanding of the biological basis of human individuality through *Prakriti* (literally meaning basic nature or the healthy state – Stage A). According to Ayurveda, an individual is born with a specific *Prakriti* that not only determines an

individual's overall phenotype but also predicts the susceptibility to diseases and responsiveness to extrinsic and intrinsic environments.<sup>140</sup> Assessment of the disease state (Vikriti) and treatment in the Ayurveda system depend on “where you were and where you are now” with respect to an individual's own Prakriti and how far enhancement of specific Dosha has occurred to create imbalance leading to a state of Vikriti (i.e., Stages B–D). Ayurvedic medicine treats individuals holistically in combination of medicine, diet and lifestyle management (yoga and other exercises) with the goal of returning to one's original state of Prakriti (i.e., Stage A). In this context, Ayurvedic system of medicine draws several parallels to the prevailing concepts of P4 medicine.

Over the last decade, major efforts have been initiated in India to establish the molecular correlation with specific Prakriti. These efforts in translating the concepts of P4 medicine and establishing the relationship of phenotypic classification of Ayurveda with modern genomic analysis has led to the convergence of two disciplines and emergence of the new field of Ayurgenomics.<sup>142–144</sup> Attempts are being made to correlate differences in epigenetic markers (DNA methylation) with various Prakriti phenotypes<sup>145</sup> along with Genome-Wide SNP Analysis as correlates of Ayurveda Prakriti.<sup>146</sup>

### The P4H continuum: Impacts from population to cellular health

The key benefits of the P4H continuum model, from the population to cellular level, include the following examples: 1) prevent the occurrence of chronic diseases and associated risk factors by implementing effective interventions at all levels; 2) detect and predict disease at an early stage, when it can be controlled and reversed effectively; 3) stratify individuals into refined specific disease phenotypes, enabling the selection of optimal therapies; 4) reduce adverse drug reactions through the early assessment of individual drug responses; 5) improve the selection of new biochemical targets for interventions; and 6) shift the emphasis in medicine from reactive to proactive prevention and from disease to health, including enhancing wellness in disease-free individuals. Table 3 describes the key paradigm shifts from a reactive to proactive P4H continuum model. The authors of this concept paper are proposing the model described herein become the framework for combating the chronic disease crisis we currently face.

### Conclusion

To address chronic diseases globally and in their totality, and in order to reduce their burden and societal impact, *medicine has to evolve from a reactive to a proactive system*, the latter of which is committed to a healthy aging process (i.e., lengthening the healthspan). It is proposed that chronic diseases should be viewed as a single expression (i.e., chronic diseaseome) with common risk factors and themes. Efforts to make healthcare more predictive, preventive, personalized and participatory (i.e., P4 medicine) will greatly improve health and well-being across the health continuum. The

introduction of a systems-approach, continually capitalizing on the most recent technologic advances as well as the requirement of more interdisciplinary work, requires an orchestrated language to help researchers, healthcare professionals and stakeholders across a multitude of sectors to collaborate as efficiently as possible. We can also use systems approaches to understand the most common morbidities and why they are related and how to simultaneously reverse these shared conditions. The authors of this concept paper hope that the model proposed herein helps to spur the needed paradigm shift, with a focus on maintaining allostasis, wellness and prolonging the healthspan.

### Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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