Applying Precision Medicine to Healthy Living for the Prevention and Treatment of Cardiovascular Disease

Ross Arena , PhD, Cemal Ozemek , PhD, Deepika Laddu , PhD, Tavis Campbell , PhD, Codie R. Rouleau , PhD, Robert Standley , PhD, Samantha Bond , MS, Eulàlia P. Abril , PhD, Andrew P. Hills , PhD, and Carl J. Lavie , MD

Abstract: Healthy living medicine (HLM) is an emerging concept that recognizes the importance of: (1) Moving more and sitting less; (2) Consuming a healthy diet at the appropriate caloric load; (3) Maintaining a healthy body weight; and (4) Not smoking. Suffice to say, HLM should be practiced by all health professionals, prescribing a personalized healthy living polypill to individuals under their care while titrating the dosage for optimal adherence and therapeutic efficacy. Traditionally, HLM, particularly when practiced in the context of physical activity and diet, is commonly viewed as an all-or-none and one-size-fits-all paradigm. As an example, there has been a dichotomous perception to physical activity messaging, where achieving anything less than 150 minutes of moderate-intensity physical activity per day is not beneficial. The same holds true for the all-or-none perception of 5 servings of fruits and vegetables per day; anything less is not beneficial. While these are certainly desirable targets, healthy living practices at levels below current guidelines portend significant health benefits. Precision medicine is defined as "an emerging approach for disease treatment and prevention that takes into account

2018;43:448–483.
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2018.06.001

individual variability in genes, environment, and lifestyle for each person." Much of the focus in precision medicine has been directed toward genomics and only recently has the influence of environment and lifestyle been considered. This review will highlight the importance of HLM directed toward the prevention and treatment of chronic diseases in the context of precision medicine. (Curr Probl Cardiol 2018;43:448–483.)

Introduction

Healthy living medicine (HLM) is an emerging concept that recognizes the importance of: (1) Moving more and sitting less; (2) Consuming a healthy diet at the appropriate caloric load; (3) Maintaining a healthy body weight; and (4) Not smoking.[1,2] It is now well recognized that the practice and delivery of HLM is the primary way to prevent the spectrum of chronic diseases that are currently the leading health concern globally; the incidence and prevalence of cardiovascular disease (CVD) is at the forefront of conditions that require significant attention and a paradigm shift in treatment.[3-5] Ideally, preventing CVD from ever being diagnosed should be the primary goal, which can only be achieved through the practice of HLM. Research has shown that in those individuals who emulate the ideal healthy living (HL) phenotype (ie, achieving or exceeding guideline recommendations for exercise and diet, maintaining a healthy body weight and not smoking), the risk of developing CVD prematurely is reduced by 60% or more.[6-8] Additionally, a recent investigation found that compared to those leading an unhealthy lifestyle, individuals who emulated the ideal HL phenotype extended their life expectancy by, on average, more than 10 years.[9] In those diagnosed with a chronic disease, HLM plays an integral role in improving prognosis and quality of life while reducing health care costs.[10-13] Even for those individuals who do not have an ideal HL phenotype but decide to make some positive changes, such as exercising 2-3 times per week and/or consuming 2-3 servings of fruits and vegetables per day, risk reductions for CVD are still significant and clinically meaningful.[8] Suffice to say, HLM should be practiced by all health professionals, prescribing a personalized healthy living polypill to individuals under their care while titrating the dosage for optimal adherence and therapeutic efficacy.[1,14] Moreover, HL should be encouraged and made easily achievable outside of the traditional health care arena. Public health messaging, communities, schools, and workplaces all play a key role in the practice of

HLM.[15] The more an individual is immersed in a culture of HL, the easier it will be to make healthier choices.

Becoming more physically active and consuming a nutritious diet are two ingredients of HLM that garner a great deal of attention, physical activity (PA) in particular. This is due to the fact that being more physically active and consuming a healthy diet portends significant benefits irrespective of an individual's health status (eg, those who are obese, at risk for a chronic disease, diagnosed with a chronic disease, etc.).[16-19] Traditionally, HLM, when practiced in the context of physical activity and diet, is commonly viewed as an all-or-none and one-size-fits-all paradigm. As an example, there has been a dichotomous perception to physical activity messaging, where achieving anything less than 150 minutes of moderate-intensity physical activity per day is not beneficial.[20] The independent benefits of moving more and sitting less, outside of a structured exercise program, are rarely discussed or publicized.[21,22] The same holds true for the all-or-none perception of 5 servings of fruits and vegetables per day; anything less is not beneficial.[23,24] While these are certainly more desirable levels, participating in physical activity and consuming fruits and vegetables at levels below current guideline recommendations portend significant health benefits.[8,22,25,26] Moreover, it is critical that the population at large recognizes that any type of movement/physical activity is beneficial, both recreational and nonrecreational.[17] In this context, there seems to be a greater degree of flexibility in delivering HLM, allowing for a more individualized approach that has the potential to improve long-term adherence. In other words, the alignment of precision medicine and HLM is warranted.

The National Research Council provided the initial framework for the development and implementation of precision medicine in 2011,[27] and paved the way for President Obama's Precision Medicine Initiative in 2015. This initiative defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." Much of the focus in precision medicine has been directed toward genomics and only recently has the influence of environment and lifestyle been considered. The addition of environmental and lifestyle factors to precision medicine is important because the wealth of randomized clinical trials indicating that a healthy lifestyle, characterized by daily physical activity, maintenance of normal body weight, sound psychological health, a healthy diet, and nonsmoking, lowers the risk and/or prevents development of several chronic diseases, such as diabetes[28] and CVD.[29]

While randomized clinical trials designed to improve healthy living provide valuable information, they are often conducted in very controlled settings outside of "real-world" settings, and the biological responses can be variable due to individual biology, behavior, and environment. To improve compliance with long-term HL practices, the tenets of precision medicine should be embraced by practitioners. As illustrated inFigure 1, there are key treatment and supportive components when striving for precision in HLM that is directed toward improving physical activity patterns, consumption of a healthier diet, achieving/maintaining a healthy body weight, and not smoking. To be optimally effective, the key ingredients of the HL polypill with respect to dosage and composition should be highly individualized. This review will highlight the importance of HLM directed toward the prevention and treatment of chronic diseases in the context of precision medicine.

Precision in Cognitive Behavioral Therapy: The Enteric Coating of the Healthy Living Polypill

Enteric coating, from a pharmacological perspective, is a polymer used to optimize the timing of drug release. In this context, mental health and cognitive behavioral therapy (CBT) can be viewed as the enteric coating of the HL polypill, optimizing the release and efficacy of lifestyle interventions; individuals who are psychologically healthy and counseled using a tailored approach and more likely to adopt HL behaviors. There are 2 fundamental areas in which the study of psychosocial factors can improve precision in HLM. The first involves the assimilation of information on symptoms, behavior, and environment into better understanding individual health and tailoring treatment. The second encompasses understanding how patients, health care providers, and policymakers interact with precision medicine approaches to improve uptake, practice, and policy.

Treatment of Mental Health Conditions Linked to Healthy Living and CVD

Clinically significant associations have been consistently reported between psychological distress and the major modifiable risk factors for CVD, including tobacco use, lack of PA, medication adherence, and unhealthy diet.[30] In addition, several mental health concerns, including depressed mood, anxiety, and hostility are independently associated with the onset and prognosis of CVD.[31-33] For example, rates of major depression are elevated in CVD patients and it is associated with greater morbidity and mortality. Symptoms of major depression predict survival

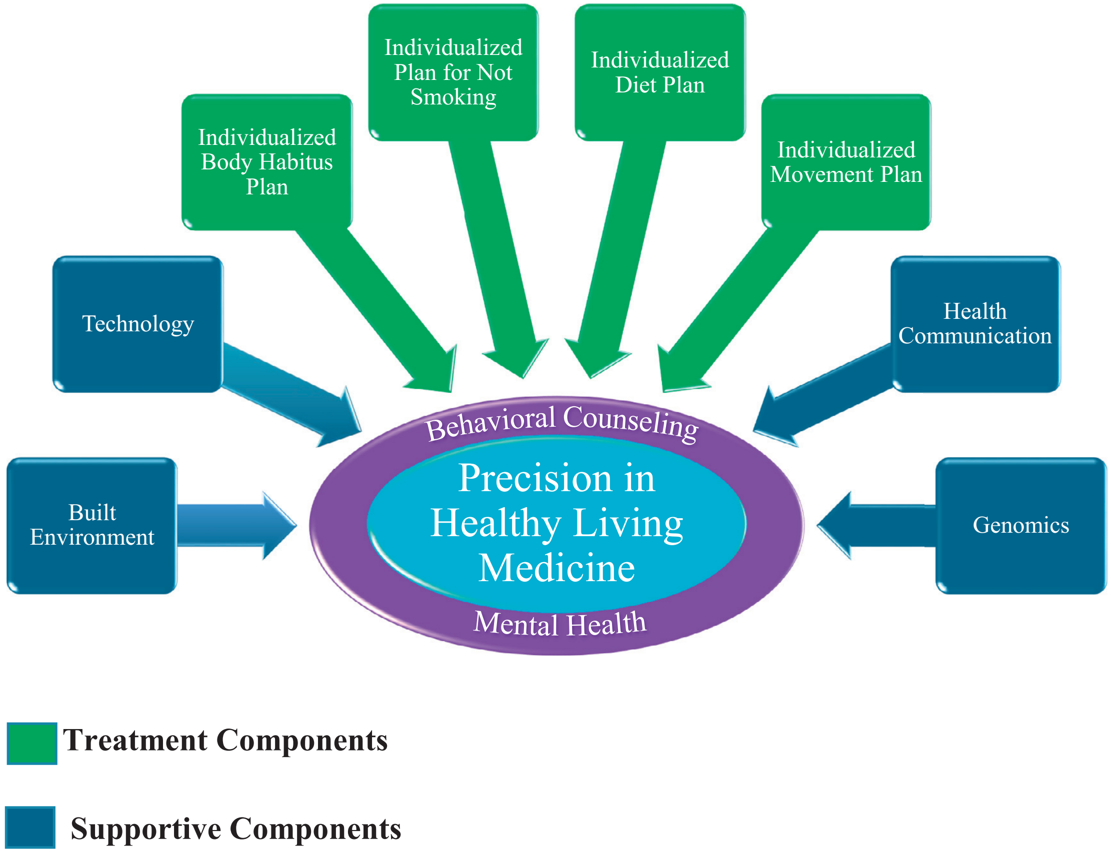

FIG 1. Key treatment and supportive components for precision in healthy living medicine.

postmyocardial infarction and among patients with heart failure and unstable angina, even following adjustment for traditional and nonmodifiable risk factors.[34-36] In addition, a dose-response association has been reported between level of depressed mood and survival over several years.[37] A variety of interventions have been evaluated to treat depressed mood in CVD with exercise, CBT and other psychotherapies, and antidepressant medications all demonstrating some efficacy.[38] Although it remains equivocal whether or not improvements in depressed mood are independently associated with improved cardiovascular outcomes,[30] an arguably larger concern is that the selection of treatment modality lacks empirical justification. From the list of potential talk therapy and antidepressant medication options, it is unclear which is best to treat both depressed mood and reduce CVD risk.[38] This may in part reflect the heterogeneity of symptom patterns and the potential underlying mechanisms inherent in a multifaceted illness like major depressive disorder, which may include low self-esteem, loss of interest in normally enjoyable activities, low energy, pain without a clear cause, and changes in sleep and weight. Precision medicine holds promise for improving outcomes by selecting treatment based on biobehavioral characteristics of symptom clusters. In support of this notion, Dunlop et al[39] used functional magnetic resonance imaging resting-state functional connectivity analyses in 122 depressed patients randomly assigned to 12 weeks of either CBT or antidepressant medication. Connectivity analyses using a bilateral subcallosal cingulate cortex seed demonstrated that resting-state functional connectivity with the subcallosal cingulate cortex and three areas (the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex) was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant medication. Depressed patients who responded to CBT tended to demonstrate stronger patterns of connectivity between frontal areas of the brain (eg, those involved in speaking, planning, and problem solving) with other areas of the brain, while those with lower connectivity responded best to antidepressant medication. While promising, this approach has yielded inconsistent findings in similar investigations[40] and future research using resting-state functional connectivity and other methods identifying depression subtypes is needed to elaborate this preliminary work and extend it to patients with or at risk of CVD. Ultimately, a better understanding of potential pathophysiological mechanisms associated with both depressed mood and CVD will help to determine the best management strategies.

Challenges of Implementing Precision Medicine for the Patient/Provider Interaction

Despite consistent and convincing evidence of clinically meaningful health improvements associated with HL behaviors, in combination with large-scale efforts at promoting health behaviors for the prevention and treatment of CVD, rates of adherence to chronic disease treatment regimens are typically reported to be between 30% and 50%.[41] This modest success of public health and individual efforts to improve risk factors like lack of PA and impoverished diet in order to prevent and treat CVD persists despite widespread improvements in public literacy concerning the benefits of a healthy lifestyle.[42] This may in part reflect the phenomenon of information being necessary but insufficient to motivate health behavior change. For example, it is unlikely that current smokers are unaware of potential health risks but persist in the behavior due to addiction and a variety of perceived benefits. Simply informing patients that they should adopt a particular exercise regimen based on their individual profile and why this can be beneficial is typically ineffective at eliciting successful long-term behavior change.[43] More sophisticated theory-based health behavior change efforts have been met with greater success. For example, the Diabetes Prevention Program, which used a variety of well-established behavior change strategies derived from the social sciences to promote exercise and healthy diet, was associated with a decreased risk of prediabetes progressing to diabetes for several years.[44] In the context of precision in HLM, inadequate adherence and persistence will remain an important challenge. For example, despite clear communication to a patient that a particular behavioral health prescription might be ideal, their individual *preferences* might trump acceptance and there is nothing inherent in the precision medicine approach to address this issue. Further, health literacy becomes a greater challenge for adherence with precision medicine given the lack of ability to convey simple and harmonized public health messaging. Finally, precision medicine will not only provide information regarding who is likely to benefit from a HL intervention, it will also identify who will not respond to treatment, resulting in the potential for patient disillusionment and disengagement with the treatment process. With respect to health care provider adherence with precision medicine prescriptions for HL, there is also a potential for clinical inertia, commonly defined as the failure to initiate or intensify therapy, or a failure to follow clinical practice guidelines.[45] Reasons include the added complexity of synthesizing all of the information inherent in not prescribing a one-size-fits-all approach, as well as the difficulty in communicating individualized courses of treatment to patients.[46] Combined, both patient and provider challenges in successfully implementing precision in HLM into routine care highlight the need for the use of evidence-based health behavior change interventions to be integral to the process. For example, motivational communication represents a coherent set of strategies that have demonstrated efficacy for improving adherence to a range of behavioral health interventions.[47-49] Motivational communication includes evidence-based, patient-centered techniques designed to promote motivation for behavior change, including cognitive-behavioral strategies,[50] motivational interviewing,[51] and/or interventions based on well-established theories of motivation (eg, self-determination theory,[52] social-cognitive theory,[53] theory of planned behavior,[54] and the trans-theoretical model[55]). There is a precedent for this approach with evidence-based guidelines from the United Kingdom (National Institute for Health and Care Excellence [NICE]) including descriptions of how health behavior change interventions can be incorporated as part of standard care.[56] Future work is needed to establish what constitutes competently delivered health behavior change interventions in precision medicine to improve patient health outcomes.

Precision in Healthy Living Medicine: The Key Polypill Ingredients

Precision for Physical Activity and Moving More

Adopting a physically active lifestyle as a primordial or secondary preventative approach to combating chronic diseases has been a cornerstone recommendation endorsed across numerous health organizations.[57-62] Increasing PA is also known to improve cardiorespiratory fitness (CRF), an independent predictor of CVD and all-cause mortality.[63-67] Although PA interventions in sedentary populations lead to group increases in CRF, it is apparent that CRF responses to PA are not uniform across all individuals. Seminal findings from the HERITAGE family study provided robust evidence identifying a wide range (0% to over 50%) of CRF responses to a standard 20-week PA intervention.[68] Further examination of familial responses to PA identified that 47% of the gains in fitness were attributable to heritability.[68] Recent trials have corroborated these observations, highlighting that uniform PA recommendations to increase CRF may not apply for a large proportion of the population.[69] Moreover, individuals already diagnosed with CVD who do not respond to an exercise intervention (ie, improve CRF) demonstrate a worse prognosis compared to those individuals who do respond.[70,71] These findings collectively support a personalized, precision approach to PA interventions, one that focusses on eliciting as high of a CRF response as possible.

In recent years, the notion that accumulating the recommended weekly PA volume of either 150 minutes of moderate intensity or 75 minutes of vigorous intensity would lead to equivalent outcomes has been contested.[72] A growing body of evidence demonstrates that at fixed exercise volumes, higher exercise intensities are associated with greater improvements in CRF and other cardio metabolic risk factors. Ross et al[69] randomized sedentary, middle-aged men and women to perform PA at a: (1) low-amount−low-intensity (~30 minutes at 50% CRF); (2) high-amount−low-intensity (~60 minutes at 50% CRF); or (3) high-amount−high-intensity (~40 minutes at 75% CRF) PA 5 days per week for 24 weeks. By assessing CRF at 4, 8, 16, and 24 weeks, the authors found that the number of nonresponders to the respective PA interventions gradually decreased at each time point. However, at the end of the intervention, 38.5% (15 of 39) of the low-amount−low-intensity cohort, 17.6% (9 of 51) high-amount−low-intensity cohort, and 0% (0 of 31) of the high-amount−high-intensity cohort remained nonresponsive to the intervention. The authors concluded that increasing the amount and/or intensity of exercise significantly reduces or possibly abolishes the number of nonresponders in a sedentary cohort. This suggests that the precision of PA prescriptions to promote gains in CRF may be enhanced by increasing intensity in nonresponders to moderate-intensity PA. Future studies are needed to confirm this by identifying nonresponders and increasing PA quantity and/or intensity.

Although CRF has been established as a highly predictive metric for future CVD and all-cause mortality, protective health effects may still be acquired by engaging in regular PA despite the absence of improvements in CRF. Similar decreases in abdominal obesity, body weight, and enhanced glucose tolerance were noted by Ross et al[73] among PA intervention groups (low-amount−low-intensity; high-amount−low-intensity; and high-amount−high-intensity PA) and were found to be independent of changes in CRF. These findings highlight the importance of a paradigm shift in PA promotion and counseling, one that encourages individuals to move more and sit less. In addition to the benefits of participation in a structured exercise program, decreasing sitting time and taking more steps in a day also portend independent health benefits.[74,75] Evidence indicates that individuals who are at a low level of PA in their daily lives are not aware of the benefits of moving more in general, reporting a narrow view of what types of PA portend health benefits (ie, only vigorous PA).[76] Such a narrow view of the types of movement that are beneficial to one's health may be a barrier (ie, perception that the level of PA needed for health benefits is not attainable) to those who would benefit most—individuals who are currently sedentary.

While the general recommendation of becoming physically active should be endorsed to all individuals for overall health, future efforts will be needed to identify the specific quantity and intensity of PA needed to improve cardiometabolic risk factors. A greater understanding of the specific doses of PA required for accumulating health benefits will add to the level of precision practitioners prescribe structured exercise programs and overall PA recommendations to combat CVD. Given the current state of evidence, all individuals should be encouraged to move more every day; sit less, take more steps, and ideally participate in a regular exercise program.[74] We must also consider an individual's motivations and perceptions with respect to moving more and participating in a regular exercise program.[76,77] The more a movement plan is individualized to align with a person's motivations and interests while working to overcome barriers, both real and perceived, the more likely they will adopt and adhere to a more physically active lifestyle.

Precision for Nutrition

Current national and global dietary recommendations are founded on nutrient-specific reference values developed in efforts to prevent deficiency-related and major chronic disease.[78] While at best, nutrition guidelines are generalizable to populations, an inherent limitation of this "one-size-fits-all" approach is that guidelines do not account for the variable factors between individuals (eg, sex/gender, ethnicity, cultural preferences, life stage, health status, physical activity, etc.) that differentiate nutrition requirements, doses, and responses to nutrients. In efforts to address gaps in current treatment approaches, "precision nutrition," has surfaced in the scientific and public health community, heralding proactive, individualized dietary strategies to promote optimal health and improve overall health trajectory of individuals. The impetus for a personalized nutrition agenda has emerged as a strategy to address interindividual variability responses to dietary intervention recognizing that individual phenotypic responses are presumably modulated by environment (ie, diet), biology, and genetics.[78-80] Thus, a critical pursuit of the precision nutrition initiative has been to develop comprehensive and dynamic nutritional recommendations that take into account the diversity of an individual, as well as the multifactorial and continuously evolving environment to optimize overall health trajectory. Precision nutrition strategies therefore reflect a clear divergence from standardized public health nutrition practices in that they *not only* deliver customized nutrition recommendations but also utilize tailored dietary assessment methods to better inform treatment strategies and refine disease prevention and risk stratification.[81-83] Below we discuss how the "bottom's up approach" applied in precision nutrition, which specifically integrates genetics and various omics platforms with nutrition and dietary characteristics, has led to recent advances in identifying an individual's "nutritional phenotype"[84] and how this translates to metabolic disease risk.

Propelled by advances made in human genome sequencing and genetic technologies, "nutri*genomics*" and "nutri*genetics*" have since emerged as part of the precision nutrition efforts to better understand the overall impact nutrition has on genes, and subsequently the effect that genetic variation has on an individual's response to nutrition interventions.[78] Although inherently different, nutrigenomics and nutrigenomics represent promising opportunities to deliver a "menu" of nutritional requirements that are customized to an individual based on their inherited and acquired genetic background, and changes in genetic characteristics that occur depending on life stage, lifestyle, environment, or in response to dietary preferences and health status.[78] In this regard, there have been a number of advances and adoptions made in high-throughput "omic" technologies enabling researchers to exploit individual genetic and genomic information, and thus provide a more comprehensive evaluation of specific gene−nutrient or gene−nutriome (ie, combination of nutrients) interactions that may potentially modulate disease susceptibility.[78,85] Metabolomics, for example, presents a rapidly growing area of precision nutrition, emerging as a natural consequence to better understand the interindividual diversity in the metabolic response to the same foods, and whether certain food-derived biomarkers (referred to as metabolites) act as mediators, or are causal in the biological pathways that link diet to disease. In essence, metabolomics provide the metabolic "blueprint" of the food and nutrients an individual consumes relative to their whole meal[86] or diet pattern.[87,88] To illustrate this concept, Flogel et al recently identified a network of metabolites known to play a role in fatty acid and carbohydrate metabolism. Further analysis by investigators revealed inverse associations between both metabolite networks and whole grain consumption, but positive associations with obesity, suggesting a mechanistic explanation as to how refined carbohydrates may contribute to the development of impaired glucose metabolism and insulin resistance, and increased oxidative stress and inflammation.[89] Additionally, inverse associations between the metabolite networks of coffee intake and obesity were noted, eluding to possible metabolic pathways that explain the potential protective effects of coffee on obesity development.[89,90] Metabolites of branched chain amino acids have also gained popularity in metabolomics research, with increasing evidence demonstrating their functional role in promoting metabolic changes that contribute to risk of CVD,[91] metabolic syndrome,[92] prediabetes,[93] type-2 diabetes,[91,93,94] and stroke.[95] In this regard, a host of other metabolites has been found to be predictive various metabolic risk phenotypes in response to diet change, including interindividual variation in blood pressure,[88] incident hypertension,[96] and various types of cancers.[97,98]

Recent endeavors in the personalized nutrition agenda have concentrated focus on optimizing the intestinal microflora environment through diet. Since being recognized as an independent risk factor of obesity,[85,99] the gut microbiota has been extensively studied with consistent evidence suggesting distinctions in microbial environments across different dietary habits and pattern backgrounds may unveil critical insights regarding the dietary, genetic, and metabolic potential of the intestinal tract in modulating disease risk and progression.[100] Lower microbial composition and diversity, in particular, have been observed among diets enriched in animal fat and diet patterns characteristic of a westernized diet (eg, high-fat whole milk, sugar-sweetened drinks, higher total energy, and carbohydrate intake), whereas greater microbial diversity has been observed among individuals habitually consuming greater quantities of fibers consumed through fruit, legumes, and vegetables.[101-103] Importantly the microbial benefit elicited from greater plant-based food consumption has been observed even in the backdrop of a conventional, "less-healthy" Westernized dietary pattern, suggesting beneficial regulation of microbial metabolism by the gut in response to habitually practiced—healthier diet behaviors.[104]

Along these lines, specific intestinal metabolites produced via metabolism of red meat have also been correlated to atherosclerosis and CVD pathogenesis,[94,105] providing mechanistic support to previous findings that have linked vegetarian and vegan[106] or Mediterranean diets—which emphasize low red meat consumption,[107] with reduced CVD risk.[27]

As the volume of research investigating the gut microbial ecology continues to increase, so does our understanding of the complex interplay that exists between diet pattern and behavior—genes and the gut microbiome—in modulating individual chronic disease risk. Notwithstanding, preliminary evidence has shown that both composition and diversity of the gut microbiota responds to *short-term* changes in diet, speaking to the importance that the gut microbiome is able to respond rapidly to sudden alterations made in the diet in response to intervention or changes in lifestyle.[102,108] Thus, while gut microbiome profiling is still in its infancy, substantial progress has been made in understanding the pivotal role of the gut microbiota in overall health and disease, and the influence that specific dietary components have in strengthening or perturbing the microbial community.[100] As such, dietary modulation on the gut microbiome has the potential to change an individual's health trajectory and ultimately risk of disease, which may prove to be even stronger than one's genetic makeup alone. Continued advances in gut microbiome research will be fundamental to testing existing nutritional therapeutics, such as probiotics and prebiotics, for the treatment of metabolic conditions.[81] Likewise, integrating gut microbiome profiling with other disciplines of precision nutrition, such as nutritgenetics and metabolomics, provides tremendous potential to identify other nutritional and metabolic targets that will aid in the refinement of disease risk stratification and prevention.

Precision for Weight Loss

Weight loss though lifestyle modification is the primary strategy prescribed to treat obesity and its related comorbidities. Not surprisingly, individual efforts to lose weight are challenged by the temptations rendered in today's obesogenic environment. To this regard, adaptations to more contemporary lifestyles further propagate unhealthy lifestyle behavior practice (eg, increased sedentariness, poor eating behaviors, and sleep deprivation) making excess weight gain inevitable, and further increasing risk of developing metabolic disease. Despite decades worth of obesity-prevention research, there has been limited success showing that, after study completion intentional weight loss continues or is maintained, or any weight regained is minimal. To this regard, challenges in demonstrating long-term effectiveness from dietary interventions have supported the view that individual proneness, and hence genotypes, to obesity, weight loss, and weight regain, along with environment may elicit greater consequence in shaping weight change success and overall metabolic disease risk.[109-111] With the inception of new precision medicine initiatives and recent progress in genome-wide association studies, emerging research has focused on uncapping the genetic determinants of body weight,[109] primarily with respect to genes that regulate energy expenditure regulation, appetite control, lipid metabolism, and adipogenesis.[111,112] Keeping with the theme of "tailored" modification, precision weight-loss approaches have since been developed, underscoring the notion that weight loss prognosis may be more effective for some genotypes than others,[113] and that both genetic makeup and genetic responses to diet (*or* *other lifestyle modifications*) at least partially explain an individual's obesity fate, and hence susceptibility to metabolic disorders.

Given that obesity poses on the greatest risks to metabolic diseases (eg, metabolic syndrome, type-2 diabetes, CVD, etc.), it is no surprise that the interplay between diet and candidate genes predictive of obesity risk (eg, FTO, MC4R, PPARɣ, and MTHFR PLIN1)[85, 114-116] is capable of changing the overall trajectory of specific metabolic traits. To date, several investigations from both observational and randomized control trials, including those from landmark trials, LOOK AHEAD,[117] POUNDS LOST,[109, 118-120] and the Diabetes Prevention Program,[121] among others,[122,123] have confirmed that significant interactions exist between diet and obesity-associated risk genes, and these interactions, in turn, play a critical role in modulating individual's weight loss response to different dietary interventions.[109,111] For example, evidence from two large cohort studies[122,124] indicates carriers of a risk allele on various candidate obesity genes which followed an energy-restrictive high protein diet experienced significantly greater reductions in weight loss, less weight regain,[122] and significant reductions in visceral adipose tissue mass as well as superficial adipose tissue compared to noncarriers and those following a low-protein diet at 6-month. These data suggest a particular genetic effect on overall body fat and fat distribution that may be used to identify individuals who may benefit the most from high-protein diet interventions. In the POUNDS-LOST trial, significant interactions found between carbohydrate intake and a weight-loss allele located on an insulin receptor gene indicate one possible mechanistic explanation as to why carriers of the weight-loss risk genetic variant assigned to a high-carbohydrate, low-fat diet benefited more in terms of greater weight loss and improvements in insulin resistance than those without this genotype.[119] Several other metabolic phenotypes, including hypertension,[125] and metabolic syndrome[120] have similarly been shown to be influenced by the interaction between dietary intervention and metabolic gene variants.[109] In this context, the same obesity-related genetic variants that have been linked to weight loss are believed to be predictive of weight rebound,[113] as evidenced by studies that evaluated weight regain following 6 month,[122] 1-,[117] and 2-year[126,127] evaluations postintervention. Taken together, these findings confirm the existence of a genetic determinant in response to dietary modification for intentional weight loss and body-weight stability as well as prevention of obesity. However, the limited replicability across study findings[109,113,121,123] suggests results are still too premature to include genetic screening in the design of individualized weight-loss prescriptions.[113] Nonetheless, novel insights have been gained regarding the etiology of obesity in response to the individual dietary "environment," and the implications of specific diet−gene interactions in predicting weight loss prognosis. Although still in the preliminary stages, evidence to date has provided a compelling argument for precision-weight loss prescriptions for optimizing individual weight loss efficacy, and protection from disease or disease progression.

Precision for not Smoking

Tobacco use is the leading cause of preventable death worldwide,[128] with more than 480,000 tobacco-related deaths per year in the United States alone.[129] Smoking increases morbidity and mortality from a range of chronic diseases including cancer, heart disease, stroke, and chronic obstructive pulmonary disease.[129] Given these adverse health risks, a common sentiment among healthcare providers is that "it's just common sense" to quit smoking.[130] Contrary to this notion, smoking is far from a simple behavioral choice. Smokers are generally aware of the potential health complications and want to quit,[129,131] but only 3%-5% of quit attempts lead to prolonged abstinence.[132] Although advising patients to quit smoking is considered a critical element of tobacco reduction programs,[133,134] relying solely on advice-giving is likely to be inadequate to promote health behavior change in the majority of cases.[135] This is because the initiation and persistence of smoking are determined by a complex interplay among biological, psychological, and sociocultural factors, including the highly addictive properties of nicotine.[128,136]

A precision medicine approach can be used to develop and implement smoking cessation interventions to match unique characteristics of an individual. For example, the Transtheoretical Model (TTM)[137] has gained popularity since the 1980s as a conceptual framework to match intervention strategies to a patient's level of readiness to quit smoking. The TTM assumes that individuals progress through a sequence of discrete motivational stages in their movement toward behavior change, and also assumes that interventions should emphasize specific processes at each stage.[137] In other words, patient-provider conversations about tobacco cessation should "look different" depending on whether a patient is not ready to quit, is preparing to quit, has achieved continuous abstinence, or is dealing with a relapse. Empirical evidence for the TTM has been mixed, with a 2010 Cochrane Review of 41 trials concluding that TTM-based interventions for smoking cessation, on average, "were neither more nor less effective than their non-stage-based equivalents."[138] Some have also argued that the TTM may inadvertently prompt clinicians to completely avoid intervening with "precontemplators" who are apparently not ready to consider quitting.[139] Despite the need for more high-quality research to clarify inconsistent findings, the TTM model draws attention to the importance of understanding patients' perceptions about tobacco use in an effort to optimize intervention effectiveness.

Attitudes and self-efficacy are two other constructs from mainstream health behavior theories that are frequently used to tailor smoking cessation interventions.[140] The degree to which individuals have favorable evaluations of tobacco use and feel confident in their ability to quit can influence behavioral intentions and the likelihood of successful cessation.[141-143] Individuals report smoking for a variety of reasons including emotion regulation, social approval, weight management, avoidance of withdrawal symptoms, and/or boredom.[144] Understanding individuals' reasons for smoking is important, given that these reasons often serve as barriers to initial quit attempts and long-term abstinence.[145] Several brief interventions, such as motivational interviewing[146,147] and the 5R model,[134] provide guidance on how to enhance self-efficacy and bolster positive attitudes toward quitting among people who are ambivalent about treatment.

Additional examples have been described regarding how to address individualized barriers to smoking cessation. Concern about cessation-induced weight gain, for example, is related to lower intention to quit and poorer cessation outcomes.[148,149] CBT to reduce weight concerns has been demonstrated to improve continuous abstinence when delivered to women concerned about weight gain from a quit attempt.[150] Helping patients develop emotion regulation skills can also support quit attempts in some individuals, as demonstrated by research showing that integrating standard treatment (eg, nicotine replacement therapy) with psychological treatments for patients with psychiatric comorbidity can enhance the likelihood of smoking cessation.[151-153] In addition to addressing individualized concerns about weight or mental health, matching the goals (eg, to quit vs to cut down) and modality (eg, pharmacotherapy, professional support, and "cold turkey") of treatment to patient preferences may enhance motivation to quit.[153-155]

Cultural factors also influence perceptions about the benefits and risks of smoking, and predict individuals' susceptibility to tobacco dependence.[136] There have been efforts to tailor messaging within multifaceted tobacco interventions to Indigenous,[156] Hispanic,[157] and African American[158,159] populations by integrating culturally relevant values, views, spiritual elements, and language. Culture-related differences in tobacco use are influenced not just by cultural norms about the acceptability of tobacco, but also relate to differences in nicotine metabolism, socioeconomic status, and access to tobacco control interventions.[136] For example, Black smokers demonstrate higher levels of serum cotinine than their White or Mexican-American counterparts, suggesting one potential mechanism accounting for their lower success with quitting smoking.[160] With increasing multiculturalism across the world, there is a need for continued research to determine the effectiveness and feasibility of culturally targeted tobacco reduction programs.

A variety of effective medications for tobacco reduction are available to double or triple the likelihood of abstinence,[155] and combining behavioral treatment with pharmacotherapy can produce 25%-30% abstinence rates.[134] Despite advances in smoking cessation treatments, a significant subset of patients does not achieve long-term abstinence, suggesting a need to continue investigating novel methods to identify and treat tobacco use. Biomarkers, such as the α5-α3-α4 nicotinic receptor subunit gene cluster, have been identified as important contributors to nicotine dependence that could guide personalized medicine for smoking cessation.[161] Further, mobile technologies have been used to tailor smoking cessation messaging to individuals' unique patterns of lapse risk factors as they engage in their everyday activities.[162-164] There is no "one-size-fits-all" approach to smoking cessation treatment; individual differences in motivation, nicotine dependence, preferences, biological predilection, and sociocultural characteristics must be considered to optimally address the health burden of tobacco use.

Key Supportive Components for Precision in Healthy Living Medicine

The Built Environment

Simply defined, the built environment includes the major physical spaces, including buildings, streets, homes and infrastructure in which we live, work, receive education, and play.[165] Profound changes to the built environment, particularly over recent generations, have had a significant impact on lifestyle practices of many individuals and populations. In turn, these practices have had serious downstream health consequences. Over time, the major reconfiguration of lifestyle behaviors, including as a function of changes to our built environment, have resulted in dramatic decreases in PA levels across the lifespan, often clustered with other poor behaviors including unhealthy eating practices. Taken together, these primary changes to lifestyle behaviors have been the main drivers of a positive energy balance, predisposition to increased overweight and obesity, and CVD.[166-168] An estimated 1 in 3 adults globally do not meet the minimum weekly PA levels recommended for protective health benefits.[169] This equates to a staggering 1.5 billion adults with the potential to improve their health status and reduce the risks associated with chronic diseases, simply as a function of increasing their PA level.[170]

From a historical perspective, changes to the built environment have coincided with reductions in population PA, including the most common form of activity for people of all ages, walking. Fundamental changes in technology in the built environment, including increased mechanization, urbanization, transportation, and globalization, have been major contributors to the dramatic declines in walking in both the developed and developing world. A primary example is the increased availability of motor cars and other motorized vehicles responsible for displacing active transport for people of all ages. In addition, particularly in urban settings, safety and walkability has been seriously compromised due to increased congestion and attendant pollution, typically associated with an increased reliance on motor vehicles.

In a recent Lancet Series on urban design, transport, and health, Giles-Corti et al[171] identified a set of 8 interventions with the greatest likelihood of encouraging active transport (walking, cycling, and use of public transport). Importantly, if combined these interventions, including pedestrian- and cycling-friendly networks, and desirability of active transport, would assist in healthier and more sustainable urban settings. Evidence suggests that some of the most important causes of numerous global health problems include poor policy and design features of the built environment.[172] For example, chronic disease and injury prevalence is influenced by land use and transport policies through increases in pollution, noise, social isolation, and low levels of PA/sedentary behaviors.[173]

If we agree that the built environment discourages PA and encourages unhealthy eating, urgent attention is required to address the policies and practices that affect the built environment in order to underpin healthy living principles.[165]

Communicative Contexts in Health

Communicative contexts are factors of influence on HL outcomes from a communication perspective. The factors accounted for are the mass media environment, the interpersonal networks of discussion, the social media environment, the technology environment, and the physical environment.

The mass media includes news, social advertising efforts, as well as commercial advertising. For instance, exposure to health news can influence awareness and health literacy, but also attitudes through persuasive elements in the news like framing.[174] Several studies have shown that frames about the causes of obesity (personal vs societal) have consequences for whom individuals perceive to be responsible for the problem, which can influence support for public policies.[175,176] Mass media campaigns have great potential across large populations in curbing undesirable behaviors like consumption of tobacco or high-calorie foodstuffs and producing desirable behaviors such as increasing PA or eating more fruits and vegetables.[177] The back drop of commercial advertising is still omnipresent and its effects are remarkable; for each public service and on TV, there are 400 ads from industry whose share of unhealthy foods is 95%.[178]

Another key communicative context is our interpersonal networks of discussion, also referred to as everyday talk. Everyday talk is both formal and informal, has direct consequences on HL practices and the dissemination of information and values, serves to negotiate meaning and labels about health concerns and defines relationships with healthcare providers.[179] Those effects can be both desirable (eg, we learn that we are not exercising enough) and undesirable (eg, we engage in risky behavior such as smoking).

Recently, interpersonal networks have expanded and merged with mass media with the arrival and diffusion of social networking sites. Social media networks may overlap with interpersonal ones, but they also offer the possibility to interact with strangers as well as distant and local friends or family. Because of its reach and tools to manage privacy and self-presentation, social media can be considered as separate from interpersonal networks of communication. Overall, social media use is heavy among young adults (≈88%) and progressively decreases in older generations,[180] but what is more important is the prevalence of social media in everyday life—∼50% of social media users check these sites several times a day. The effects of social media on health and wellbeing depend on the medium and whether they reflect ongoing campaigns[181,182] or are organically created within the social network.[183]

In addition to affecting HLM outcomes, communicative contexts influence each other—thereby *also* mediating some of the effects on HL. For instance, the literature on food environments has shown that having difficulty accessing healthy foods in one's community negatively affects the consumption of those foods. However, the food environment also has adverse effects on interpersonal discussions of food and nutrition as well as exposure to and reflection of news about the effects of what people eat and drink.[184] These effects, in turn, negatively fuel the decrease in healthy foods consumption, thus creating a vicious cycle. To improve efficacy, HLM requires a multipronged approach in which all these contexts are considered and measured together.

Leveraging Technologic Advances

The use of web-based and mobile health (mHealth; interactive voice response calls, short message service or text messaging, and smartphone applications) platforms continue to expand, providing great opportunities to further refine the delivery of HLM. Current evidence suggests the use of technology has the potential to improve healthy lifestyle patterns such as increasing PA and consuming a healthier diet.[5, 185-188] For example, using a web-, tablet-, or smartphone-based HLM intervention, in conjunction with health coaching, has also been shown to result in significant weight loss in a Medicare cohort at risk for diabetes.[189] As defined by the World Health Organization, mHealth is "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices."[190] Developed in iterations, mHealth platforms target audience-specific behaviors and can change responsively with the needs of both the users and the creators. Where general technology provides open access to information, mHealth can specify content and provide a supportive management system that suggests personalized care and newer, more relevant guidance while reaching a large and continually growing proportion of the global population. In prior studies evaluating mHealth tools within HLM, applications commonly deliver background education, personalized goal setting, and multiple avenues of user motivation.[191-193] However, while these three pieces are vital to each platform and show great potential for HLM results, mHealth tools require well-designed user interfaces and purposes based on satisfactory, comprehendible data to have valid results.[192] Considering low participant cost in addition to the rapid pace of mHealth development, well-designed platforms can transition patients into behavioral changes by including even small opportunities for personalization.

There is also great potential for web-based and mHealth platforms that deliver HLM to incorporate an artificial intelligence (AI) backbone, further enhancing the precision and effectiveness of HL interventions. Targeting multiple behaviors within HLM, AI applications go beyond what traditional educational resources or interventions can do by both giving to and responding to users. This form of reflexive technology design can imply compassion and acknowledgment of a user's lifestyle decisions, affording health professional-controlled patient accountability without the risk of communication influences or excuses on physical difficulty.[194,195] Research into the effectiveness of AI to improve HL characteristics has begun and is showing promising results.[193-196] In the spirit of precision medicine, the use of technology in HLM will not be a one-size-fits-all approach. Individual preferences and available resources must be considered when determining the optimal use of technology in a personalized care plan for HL.

Health care professionals delivering HLM must leverage technology to enhance the number of touchpoints they have with individuals under their care. Technologic advances will occur rapidly and, as such, health care professionals must remain current and titrate their use of technology as more effective platforms emerge. With the emergence and falling prices of wearable technology, publicly available sensory devices can collect real-time health data specific to individual HLM goals. Not only will these devices provide access to many physiological parameters of an individual receiving care, they can also influence the content personalization of smartphone apps and behaviors of responsive AI.[197] Opportunities provided by mHealth development can directly respond to communicative and physical influences surrounding HLM and corresponding outcomes.

How Does Healthy Living Influence Precision Medicine Genomics?

To this point, the primary focus of precision medicine has been on identifying genetic alterations that are associated with various diseases. However, genomic studies have limitations in that they only measure a fraction of the genome, and genes and their products typically do not act alone, but with other genes and proteins in a specific environment.[198] The combination of individual genetic variants with environmental factors creates a highly individualized disease phenotype. Additionally, environmental factors, such as the components of HL, can modify disease risk even when genetic variations are present.[29, 199-201] Understanding the interplay of social and environmental factors with an individual's biology will allow for the development of highly individualized disease phenotypes and ultimately more accurate diagnoses, more rational disease prevention strategies, better treatment selection, and the development of novel therapies.[202]

Several studies have examined the relationship between HL and lowering chronic disease risk in individuals who are genetically prone to developing disease. The Diabetes Prevention Program study[201] and The Finnish Diabetes Prevention Study[200] both recruited individuals with a high risk to develop diabetes and both found that a lifestyle program consisting of diet and exercise counseling reduced diabetes risk by 58%. Additionally, the HL program in the Diabetes Prevention Program study reduced risk significantly more than treatment with metformin (31%).[201] The American Cancer Society (ACS) recommends at least 150 minutes of moderate-intensity PA per week, alcohol intake of ≤1 drink per day, and maintaining a body mass index of ≤25 kg/m^2 for breast cancer prevention.[199] Cloud et al examined the mortality risk of women from the high-risk Breast Cancer Family Registry in New York who adhered to the ACS recommendations.[199] Adherence to all three ACS recommendations was associated with 44%-53% lower mortality in women unaffected with breast cancer at baseline and in women affected with breast cancer at baseline.[199] Lastly, Khera et al examined the extent to which increased genetic risk of coronary artery disease can be offset by a HL.[29] Three prospective cohorts had their genetic risk for coronary artery disease determined and were placed in either a high-, intermediate-, or low-risk category. A favorable lifestyle was defined as meeting at least 3 of the 4 HL factors: (1) no smoking; (2) no obesity; (3) PA at least once weekly; and (4) a healthy diet pattern. Regardless of risk group, a favorable lifestyle was associated with a lower risk of coronary events including a 46% reduction in the high genetic risk group.[29]

Collectively, these four studies highlight how lifestyle and environmental factors impact precision medicine genomics. To achieve the goals of the precision medicine initiative, we must gain a more detailed understanding how genetic risk and treatment responses modify the disease phenotype. Applying "omics" approaches and in-depth phenotyping after HLM interventions will allow for the classification of patients with respect to disease susceptibility, subclass of disease, or the likelihood of a positive or adverse response to a specific therapy and further the precision medicine initiative.

Conclusions

In conclusion, leading a healthy lifestyle is of central importance to both preventing and treating a host of chronic diseases, including CVD. Assisting individual to adopt HL practices is not a one-size-fits-all approach. Any movement toward a healthier behavior portends significant health benefits. As such, employing a precision approach in the prescription of the HL polypill, the key ingredients of which are moving more, consuming a nutritious diet, maintaining a healthy body weight, and not smoking, will enhance adoption and long-term adherence.

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Pursuing a healthy lifestyle is of major importance to both preventing and treating cardiovascular diseases. A healthy life style is not a one-size-fits-all approach. Thus, any type of movement toward a healthier behavior is associated with significant health benefits.

Several perspectives can be taken from this provocative manuscript.

First, the authors put forth the concept of healthy living medicine should be directed toward improving physical activity, consumption of a healthier diet, achieving/maintaining a healthy body weight and not smoking. However, the so called healthy living "polypill" will be effective, if the key ingredients regarding dosage and composition should be highly individualized.

Second, the authors state that healthy living should be encouraged and made easily achievable not only in the medical field but also trough public health messaging, communities, schools, and workplaces.

Third, the authors state that there are several important components for precision in healthy living medicine. These are, the built environment (physical spaces, including buildings, streets, homes and infrastructure), communicative contexts in health (the mass media environment, the interpersonal networks of discussion, the social media environment, the technology environment, and the physical environment) and the influence technologic advances [web-based and mobile health (mHealth; interactive voice response calls, short message service, or text messaging, and smartphone applications)]

Fourth, the authors state that in order to achieve the goals of the precision medicine initiative, we need to understand how genetic risk and treatment responses modify the disease phenotype. They also state that the application of 'omics' approaches and in-depth phenotyping after HLM interventions will allow for the classification of patients with respect to disease vulnerability, as well as the possibility of a positive or adverse response to a specific therapy and improve the precision medicine initiative.

Finally, the application of a precision approach in the prescription of the heathy living will enhance adoption and long-term adherence to treat and prevent cardiovascular diseases.