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Precision Medicine in Lifestyle Medicine: The Way of the Future?

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ANALYTIC REVIEW

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Precision Medicine in Lifestyle Medicine: The Way of the Future?

Abstract: *Precision medicine has captured the imagination of the medical community with visions of therapies precisely targeted to the specific individual's genetic, biological, social, and environmental profile. However, in practice it has become synonymous with genomic medicine. As such its successes have been limited, with poor predictive or clinical value for the majority of people. It adds little to lifestyle medicine, other than in establishing why a healthy lifestyle is effective in combatting chronic disease. The challenge of lifestyle medicine remains getting people to actually adopt, sustain, and naturalize a healthy lifestyle, and this will require an approach that treats the patient as a person with individual needs and providing them with suitable types of support. The future of lifestyle medicine is holistic and person-centered rather than technological.*

Keywords: precision medicine; genomics; epigenetics; microbiome; caloric restriction; genetic risk score; individual support; social connectedness

While "precision medicine" has been described as an approach that integrates individual differences in lifestyle, environment, and biology, in actual practice it is simply a rebranding of genomic medicine. Genomics dominates in almost all research papers pertaining to precision medicine with the underlying assumption that, at its root, disease primarily results from genetics. As we shall see, the use of the term "precision" is aspirational and prematurely hopeful rather than descriptive. Even when the alternative term "personalized medicine" is used it primarily refers to determining what subgroup an individual belongs to rather than to medicine that considers the personhood and individuality of the patient.[1]

Lifestyle medicine, while recognizing that genes may predispose to various diseases, nonetheless postulates, based on overwhelming evidence, that most chronic disease results from lifestyle factors. So, the question is, "Should the future of lifestyle be centered on genetics or on lifestyle as the core factor for everyone in remaining disease-free and independent as long as possible? Should it be technological or holistic and humanistic?"

Lifestyle medicine has 3 simple goals for the individual: to remain healthy as long as possible, to remain independent as long as possible, and to live as long as possible. In other words, the 3 things we are working against are disease, dependency, and death. Notably, we are always working against time since the longer an unhealthy lifestyle is left unchecked, the shorter the time until one or more of these 3 possibilities will be realized. Ideally, we do not want to simply increase life span; we want to increase health span[2] and compress morbidity.[3-5]

Lifestyle medicine has 3 simple goals for the individual: to remain healthy as long as possible, to remain independent as long as possible, and to live as long as possible.

Genomic medicine is still in its infancy and currently the preponderance of evidence favors the lifestyle approach. Thousands of studies demonstrate not

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only that poor lifestyle increases the risk of chronic disease but that healthy lifestyle changes can reduce the risk of chronic disease, in some cases slowing or even reversing its progression.

There are 3 areas in which precision medicine could potentially be of value to lifestyle medicine:

- Establishing a causal basis for the known effectiveness of lifestyle recommendations
- Earlier identification of risk, with a motivating effect for adopting lifestyle changes at an earlier age
- Individualizing lifestyle recommendations to deal with differences in response

How Genomic Medicine Helps Explain the Effectiveness of Lifestyle Medicine

In recent decades, advances in genomics have helped explain precisely why lifestyle changes work.

The first discovery was epigenetic change and gene methylation in the mid-1970s.[6] While it had been earlier recognized that every human cell contains the same genetic material, the question was how cells were able to differentiate during embryogenesis and how genes were able to be either expressed or silenced. This resulted in the discovery of heritable epigenetic changes and finally epigenetic changes as a result of diet and exercise. In turn this provided insight into how inflammation and oxidative stress could affect gene expression and provided a pathway to underpinning lifestyle medicine with fundamental science. Interest in this area has grown substantially since 2006. We now know that what is important is the complex interplay within the whole genome, with genes being turned on and off in response to cellular exposures to chemical gradients and physiological stressors.[7]

The second discovery was that of the human gut biome.[8] Although the significance of the microbiome was first suspected in the mid-1980s,[9] the advent of new genomic technologies in the 21st century made it possible to identify thousands of distinct species and families of bacteria populating the human gut. For the first time it was possible to see the effects of diet, exercise, and probiotics on the ecology of the gut and to see the effect of microbiomic diversity and composition on risk of chronic disease, including certain infectious diseases. Interest in this area has been rapidly increasing since 2013.

The third discovery was the effect of various forms of caloric restriction (CR),[10,11] including fasting-mimicking diets[12] and time-restricted feeding,[13] on gene expression,[14] on the composition and function of gut microbiota,[15] and via differential stress response on cancerous cells.[16,17] CR has been found to have benefits for autophagy induction (necessary to destroy dysfunctional cellular components),[18-20] which has potential impacts on increasing healthy longevity.[21,22] Interestingly, aspirin has been found to display similar features to CR.[23] It has been hypothesized that moderate intermittent stressors, like CR, may mobilize body systems to work more effectively.[24] Whereas the benefits of fasting had been proclaimed for more than 2000 years, the underlying mechanisms have only been placed on a firm scientific footing within the last 10 years.

Paradoxically, these discoveries diminish the importance of pure genetics as an explanatory factor in disease. Epigenetic change and microbiome composition and function are driven by diet and physical activity, which along with CR, are largely a matter of choice rather than genetic determinism. Studies of monozygotic twins who are genetically identical but disease-discordant have found epigenetic[25,26] and microbiomic differences,[27-29] which strongly suggest that lifestyle and environment may largely override genetics, at least for some diseases. Two further discoveries complicate the genetic picture: microchimerism and somatic mosaicism. In microchimerism, a woman's body may contain fetal cells and alien genetic material from her child, which persist for decades in different tissues with the potential for both beneficial and adverse effects.[30,31] Somatic mosaicism is the occurrence of genetically distinct populations of cells within an individual due primarily to mutations during embryogenesis and to mutations during cell division over the course of a lifetime,[32-34] which may accumulate with ageing.[35]

In the face of epigenetics, microbiomics, microchimerism, and somatic mosaicism, the search for risky genes for chronic disease, rather than being a cost-saving fast track to accelerated medical progress, may instead turn out to be an expensive blind alley. As one review of the progress of genomic medicine put it, "Soccer is the sport of the future in America . . . and it always will be."[36] Claims made for precision medicine, which always appear to be just over the horizon, may well fall into the same category.[37]

While genomic medicine has had some successes in relation to targeting drugs and gene therapies for some rare genetic variants[38] and therapies for some cancers,[39] in general the results have been mixed.[40] Even diseases such as cancers may be 70% to 90% non-genomic in genesis,[41,42] which suggests it would be better to promote prevention than cure.

Animal experimentation has revealed effects of diet and activity, and specific dietary components that also demonstrably apply to humans. An extreme case is that of intermittent CR, which demonstrably increases longevity in species as diverse as yeast, nematodes, mice, and humans.[43] If human genetic diversity were a key factor in chronic disease, animal models would be almost worthless. Changes in disease patterns when East Asian or indigenous peoples[44] adopt a Western lifestyle, as well as the increases in chronic diseases since the second half of the 20th century,[45] strongly suggest that chronic disease is primarily non-genetic in origin.

The Success of Lifestyle Medicine in the Absence of Genetic Information

The theoretical basis of lifestyle medicine has changed significantly over the past decade. Cholesterol has reduced importance as a risk factor for cardiovascular disease (CVD),[46-49] with more emphasis on chronic inflammation[50,51] (or metaflammation[52]) and oxidative stress[53] and the interaction between the two[54] (which have been referred to as oxy-flammation[55] or as an oxidative-inflammatory cascade[56]) as key factors in the genesis of chronic diseases in general and in their complications.[57,58] In the context of aging-related disease, this has been referred to as "inflammaging."[59-62]

What integrates many aspects of a healthy lifestyle is mitochondrial dynamics and its relationship with inflammation, oxidative stress, and chronic disease.[63-65] Poor lifestyle may cause mitochondrial dysregulation and dysfunction,[66] while exercise[67-69] and caloric restriction[70] may improve mitochondrial function. Mitochondrial function has also been identified as a potential target for mitigating the effects of age-related chronic disease.[71,72] It has been hypothesized that cancers, rather than being caused by somatic mutation, may be caused by or promoted by mitochondrial dysfunction (based in part on the role of mitochondrial cell signaling on apoptosis).[73-78] If true, this would help explain how a healthy lifestyle reduces cancer risk.

Epigenetic mechanisms show that genes are not destiny. Instead, there is an interplay between genetic and lifestyle factors, both prenatal and over the life course, influencing gene expression and the potential for a given disease to become a reality.[79] The ecology of the human gut and the makeup of the species with which it is populated also demonstrably play a role in human health.[80] Lifestyle factors mediate the composition of and changes in gut flora, which in turn affect the risk of chronic disease. The microbiome also appears to be independent of host genetics[81] but is affected by both diet[82,83] and activity,[84] independently of one another.[85]

Last, there is now greater emphasis on activity generally rather than just exercise as a key factor in maintaining a lifetime of health, with a role in reducing oxidative stress.[86,87] Physical inactivity has been linked to multiple chronic diseases including coronary artery disease, type 2 diabetes (T2D), various cancers, mental illness, and dementia.[88-95] Conversely, increasing physical activity may assist in secondary prevention or reversal of such diseases[96] and reduce mortality in survivors of breast, bowel, and prostate cancers[97] as well as increase brain volumes and improve memory in older adults,[98] reduce depressive symptoms and the risk of relapse in depression sufferers.[99-101] The latter is particularly important given the massive increase in anti-depressant use in the West and the association between anti-depressant use and increased risk of CVD.[102] Yet between 2001 and 2015, physical inactivity rose from 27% to 37% in developed countries, placing a further 10% of the population at risk.[103]

In summary, we now have a more complex theoretical base for looking at chronic disease and a clearer perspective on the relative importance of different lifestyle factors, much of it derived from population and clinical studies or cell and molecular biology, rather than genetics. One complication in many studies is that lifestyle behaviors tend to cluster. People with a healthy diet also tend to be less likely to smoke and more likely to be physically active; those with a less healthy diet and in particular those who eat the most meat tend to have an less healthy lifestyle overall.[104] A study that only looks at one lifestyle factor risks confounding from other unmeasured lifestyle factors. This in itself highlights the need for a holistic approach.

The power of the lifestyle approach is that despite the changes in how we explain chronic disease and its prevention, the theoretical changes have simply served to reinforce the same recommendations while providing ever deeper explanations for their effectiveness.

Major studies over the past few years have reinforced existing recommendations[105-107] but also provided some surprises. A major Canadian study,[108] centered on 4 lifestyle factors (smoking, alcohol consumption, physical activity, and diet), found that those who had a healthy lifestyle in relation to all 4 factors could have a life expectancy up to 18 years longer than those who scored poorly on all 4 factors. Most surprisingly, the reduction in life expectancy as a result of physical inactivity was just as high as the reduction from smoking, and both were twice as high as the effect of diet with minimal reduction in life expectancy from excessive alcohol consumption. A study of the risk factors for being metabolically obese normal-weight,[109] using factor analysis, found not 1 but 2 different dietary approaches that reduced this risk: a "healthy" approach (high in fruit, vegetables, and low-fat dairy) and a "prudent" approach (high in fish and whole grains, low in refined grains, sweets, sugars, boiled potatoes, and cured meats), as well as 2 diets that increased the risk, designated as "fat, meat, and alcohol" and "coca cola, hard cheese, and French fries." Thus, within the lifestyle paradigm there is still room for diversity both in how people stay healthy as well as how they become chronically ill. Two recent studies have found that a healthy lifestyle significantly reduces the risk of CVD and diabetes for both those who are genetically at risk and the general population.[110,111]

Michael Pollan's advice, "Eat Food. Not too much. Mostly Plants,"[112] is supported by a growing body of research. Predominantly plant-based dietary patterns, both vegetarian and Mediterranean, are associated with increased longevity and significant reductions in risk of chronic disease.[113-116] Several small studies have even found evidence that broad-based intensive interventions, which include such dietary patterns, may slow and even reverse various chronic diseases, including coronary artery disease[117-120]

and age-related cognitive impairment.[121,122] Community-based programs that encourage such eating patterns demonstrably result in significant reductions in risk factors for coronary artery disease among program participants, often within a very short period of time.[123,124] Eating less red meat significantly reduces risk of type 2 diabetes,[125] while predominantly plant-based eating[126,127] may markedly improve glycemic control, reduce medication use, and potentially reverse complications.[128-131]

Would Knowing Genetic Risk Make a Difference?

In unpacking this question, there are 3 issues to consider: "knowing," "risk," and "make a difference."

On the question of "knowing," genomics produces ambiguous evidence at best for chronic disease (as opposed to rare genetic syndromes) and at worst spurious associations. One example is the association of over a thousand genes with educational attainment.[132] Social disadvantage may be associated with race, so racial differences in gene frequency could spuriously suggest a causative association between genes and education level, health, or economic achievement. One example of such a racial difference is the APOE4 gene, which is found in 25% to 40% of indigenous people across the world, while only found in around 12% of non-indigenous people.[133]

A core concept in genomics is gene penetrance, the likelihood that carrying one or more copies of genes associated with a disease will actually result in that disease.[134] However, genomic research involves populations in which the majority of people lead an unhealthy lifestyle. Thus, estimates of gene penetrance are contaminated by the effects of the gene-lifestyle interaction.[135] With as much as 80% of chronic disease attributable to lifestyle,[136] this interaction is likely to be significant. A large part of gene penetrance may be explicable purely in terms of lifestyle and actual absolute risk from such genetic risks may be grossly overestimated. Genetic risk may largely be vulnerability to the effects of an unhealthy lifestyle. Estimates of gene penetrance also require some matching between genes and diagnosed disease; however, the rate of medical misdiagnosis may be as high as 10% to 15%,[137] significantly adding to the uncertainty of any association found.

Some recent studies suggest that genetic risk is readily modifiable by lifestyle change. A large study found that women who were in the highest decile for nonmodifiable risk of breast cancer but who had low BMI, did not drink or smoke, and did not use menopausal hormone therapy had risks comparable to an average woman in the general population.[138] Similarly, individuals in the top quintile of genetic risk for incident coronary events who had at least 3 of 4 healthy lifestyle factors (no smoking, BMI <30, physical activity at least once weekly, and a healthy diet) had a 46% lower relative risk of coronary events compared with those with a less favorable lifestyle.[139] In both cases, even a moderately healthy lifestyle significantly reduced genetic risk. A study of genetic risk versus lifestyle factors in relation to colorectal cancer found that lifestyle factors had more weight than the genetic score.[140] Other studies have further shown that lifestyle factors account for most of the risk in relation to CVD.[141]

A systematic review of the FTO genotype (a variant related to increased risk of obesity) and weight loss found that carriers responded equally well to weight-loss interventions as noncarriers.[142] Another study, the DIETFITS study,[143] looked at a low-carbohydrate and a low-fat diet to identify any difference in outcomes within groups as a result of genetic differences or in insulin dynamics. But the study found that at 12 months there was no significant difference in outcome and neither of the potential predisposing factors could identify which diet was better for whom.

This sampling of studies demonstrates that whatever the future may hold in relation to teasing out gene-disease links, a healthy lifestyle must still play the major role in mitigating risk. An unwarranted emphasis on genetic factors may simply dilute the message that taking responsibility for positive lifestyle behaviors may prevent, delay, or attenuate most premature disease. It may focus too much on individual genetic risk at the expense of the lifestyle risks that everyone faces.

The second aspect of genetic risk is to what extent it is a meaningful concept. It has been estimated that an individual may carry hundreds of genes associated with increased risk of various diseases[144,145] for which they will never display any sign. So, what does it mean to say that the genes carry a risk? If each person has a unique genetic profile of several hundred variants associated with disease, how could this inform any clinical decision? Given that most people are healthy most of the time as are those around them, to what extent would this simply undermine genetic risk as a factor to be considered?[146]

A person may carry a gene associated with increased risk for a disease without any familial history of the disease. They (and/or their family) may also possess one or more genes that modify or nullify the effect of the first gene such that their risk of that disease is effectively nil.[147] Not only genetics but familial patterns of disease may be important,[148] and even then, the impact of shared lifestyle and environmental exposures cannot be dismissed. Complicating matters further, a SNP (single nucleotide polymorphism) protecting against one disease may be a risk factor for another disease.[149] The danger in acting on such perceived risks is a higher likelihood of overtreatment or treatment of unclear value,[150] carrying with it risks of its own.

Finally, would knowing genetic risks make a difference? In many cases, the answer is no.

Several studies have shown that being advised of an increased genetic risk does not result in any significant change in health behaviors.[151,152] Nor does being diagnosed and treated for hypertension,[153,154] coronary heart disease,[155] type 2 diabetes,[156-159] or

chronic disease generally.[155] A study of college athletes found that being advised of increased genetic risk of poor recovery from traumatic brain injury would not affect their playing behavior.[160]

Even surviving cancer makes little difference to adopting a healthy lifestyle.[161-165] This is of particular concern given that cancer survivors are much more likely to suffer from comorbid chronic disease than the general population even where their lifestyle behaviors are the same.[166,167] There is growing evidence that cancer treatments themselves significantly increase the risk of subsequent CVD.[168,169] Adopting a healthy lifestyle may increase the likelihood of disease-free survival[170,171] with higher levels of physical activity reducing the specific risk of CVD.[172,173] The effect of chemo- and radiotherapy as cancer treatments on risk of CVD is itself a warning that technological approaches to health care (such as gene therapy) may have unforeseen adverse health consequences downstream.

With substantial evidence that knowing the risk of one disease does not motivate many people to change their behavior, what could we then expect of being advised of genetic risk of a hundred or more diseases? Would this be motivating, overwhelming, or simply unbelievable? Responses are likely to range from fatalism, panic, and tunnel vision to incredulity, leading to either inaction or to overreaction and unnecessary preemptive treatment. All of these responses could be dysfunctional, especially when making healthy lifestyle changes could provide broad-spectrum protection against almost all of these risks.

Carrying a gene that increases risk of one disease does not reduce risks of other diseases. A narrow focus on the one genetic risk may simply shift the risk to such other diseases instead. A meta-analysis by the Cochrane Collaboration on cancer screening found that "the trials with adequate randomization did not find an effect of screening on total cancer mortality, including breast cancer, after 10 years . . . or on all-cause mortality after 13 years."[174]

Why Do Not People Adopt Healthy Lifestyle Behaviors?

We tend to make unjustified assumptions about human behavior including the assumptions that people are rational/irrational or that all people need is more information to motivate change.[175] However, we sometimes overlook the fact that, for many people, chronic disease has low saliency and low perceived risk,[176,177] both of which may need to be addressed if healthy lifestyle is to be promoted. There are at least 4 barriers to healthy people adopting a healthier lifestyle.

First, for much of its course, chronic disease is essentially invisible to other people. We do not know what medications the people around us may be taking for a chronic disease, and it is only when such a disease reaches a critical point such as requiring dialysis, or amputation or other surgery, or where a person visibly deteriorates or needs mobility or other functional aids that we actually see evidence of chronic disease. This may lead many people to underestimate the risk. In 2014-2015, a massive 50% of Australians reported having at least 1 of 8 chronic diseases.[178] Yet in the mass media, there is virtual silence regarding the prevalence such diseases. Paradoxically, those at highest risk of chronic disease may perceive their risk to be low.[179]

Second, the normalization of obesity may reduce motivation to do anything about weight gain.[180,181] While stigmatization of obesity is counterproductive[182] and obese people may need additional emotional support for health behavior change,[183] the validation of obesity by movements such as the "fat acceptance movement" potentially undermines public health efforts to combat obesity and its health consequences, by encouraging complacency and inaction.

Third, based on age-specific mortality rates for Australia, 90% of people in Western countries now live to at least the age of 65,[184] 85% to the age of 70, and 80% to the age of 75. So, while people are working, they are unlikely to see significant levels of mortality in coworkers or their age-cohort and would tend to associate chronic disease with aging, without drawing the connection between morbidity/mortality and the cumulative effect of lifestyle behaviors. When age-specific causes of death are considered for people under 45, the main causes are suicide and accidents, which in themselves do not directly relate to factors such as diet or activity levels.

Finally, the very success of modern medicine in stabilizing chronic diseases (without actually curing them) may reduce the perceived threat. Coupled with social safety nets for subsidized health care and disability payments in many Western countries, reduction in the perceived risk of unhealthy behaviors may lead to more rather than less unhealthy behavior, the so-called "Fence Paradox,"[185] due to the reduced costs involved to the individual.[186] One such example is HIV prophylaxis and treatment.[187-189]

Can Genetic Risk Actually Be Predicted With Precision?

A number of recent studies claim to be able to predict risk of CVD with accuracy as great as or better than conventional clinical measures. One study[190] generated a genetic risk score (GRS) based on 49310 SNPs (single nucleotide polymorphisms); however, when applied to new data gave inconsistent results for different populations (Finnish vs British), with no overlap in 95% confidence intervals for odds ratios for the 2 populations. A second study[191] used 1.7 million genetic variants to generate a genetic risk score, but only gave a marginal improvement over clinical measures. (Interestingly another study using only 31 variants yielded comparable accuracy,[192] suggesting that almost all of the 1.7 million variants were redundant.) Both of the studies using

large numbers of variants appear to have a number of methodological issues, including the assumption that including more variants of lower demonstrated association with CVD risk will somehow improve accuracy rather than simply adding noise.

But the greatest deficit in such studies is the lack of consideration of the false negative rate, the false positive rate, or specificity,[193-195] any of which could have serious consequences[196] for those whom a model predicts of being at high risk. Such models may result in overtesting, overdiagnosis, and overtreatment. In the process, more people will join the ranks of the "worried well," anxious about a disease they will never get, hypervigilant for any associated symptoms, and perhaps less alert to symptoms of the genesis of an actual unrelated disease. There are already indications that some genetic associations may be spurious with the same SNP showing increased risk in some populations but not others.[197-199] Some researchers argue for a more rigorous approach to determining causality[200] and a greater focus on biological mechanisms,[201] with one recent survey even casting doubt on whether extensive genetic data will ever be useful for making reliable causal inferences.[202] In many studies, rather than all of the SNPs being verified as present, they are imputed algorithmically. In the UK Biobank of around 500 000 people, used in many studies, around 805 000 genetic markers have been collected that by imputation are increased to 95 million variants.[203] Such high levels of imputation raise reasonable concerns about the results of such research.

The human genome is incredibly variable with the 1000 Genomes Project finding more than 88 million variants in just 2504 individuals.[204] Such vast numbers of genetic variants or SNPs can only be accommodated into existing statistical methods by aggregating them and then stratifying the aggregated values, automatically resulting in loss of information.[205] Different genes may promote heart disease via different pathways, for example, by increasing endogenous cholesterol or by moderating lipid metabolism, anti-inflammatory processes, or antioxidant defenses. But the grab-bag approach of throwing them all into a homogeneous category means that even if risk is established from the GRS it provides no guidance as to how it should be mitigated and thus has to fall back on blanket treatments, which could be ineffective for the gene variant the individual actually has. Unless the functional role of a SNP is established and how that function relates to increased risk of CVD, it may simply be a chance artefact of testing thousands or millions of variants. Extending a predictive model beyond a few dozen variants may not result in increased predictive power.[206,207] One study that looked at the clinically confirmed severity of coronary artery disease and genotype data imputed to 2.5 million SNPs was only able to confirm a single, already known, locus as a risk for severity of coronary artery disease.[208]

Genomic prediction probably will not markedly improve in the future simply because the most common variants with moderate to high association with chronic disease have already been identified,[209] that is, the low-hanging fruit have already been picked.[210] As Fröhlich and coauthors state,

> The lack of impact on clinical practice can largely be attributed to insufficient performance of predictive models, difficulties to interpret complex model predictions, and lack of validation via prospective clinical trials that demonstrate a clear benefit compared to the standard of care.[211]

A recent study, using only 48 SNPs, identified from genome-wide association studies, found that GRS and diet were independently associated with risk of T2D and concluded that everyone regardless of genetic risk would benefit from favorable food choices.[212] Identifying increased genetic risk of CVD, T2D, or cancer would not significantly change recommendations for a healthy lifestyle. The massive increase in chronic disease since the mid-20th century has been driven, not by a massive change in the genetic make-up of the population but by changes in lifestyle and environmental exposures.

What Is the Future of Lifestyle Medicine?

Lifestyle medicine ultimately aims to make a healthy lifestyle the norm rather than the exception. This means finding better strategies to promote a healthy lifestyle, helping individuals adopt and sustain such a lifestyle, and combatting the detrimental effects of an obesogenic environment. The maximum gains to be made in reducing chronic disease still lie in a focus on improving health behaviors for people generally rather than a focus on outliers, simply because of the high prevalence of unhealthy lifestyles.

At the risk of seeming Luddite, the future of lifestyle medicine is humanistic rather than technological. It needs to focus on how more people can be induced to adopt a healthy lifestyle and how such a lifestyle can be sustained and become habitual.[213] Whereas limited frequency health behaviors such as vaccinations and screening are relatively easy to promote, a healthy lifestyle requires repeated-occurrence health behaviors and continued abstention from unhealthy behaviors across the entire lifespan,[214] a much tougher proposition.

The obesogenic environment is a continuing, if not rising, problem (with digital technology a contributor toward increased obesity).[215] An analogous approach may need to be taken to unhealthy foods as has been successfully taken with smoking, including things such as banning advertising and promotion of unhealthy foods aimed at children, increasing sales taxes on unhealthy food items, or subsidies on fruit and vegetables to increase their affordability.[216] However, we still need to make a distinction between the environment as a stimulus and individual responsibility for what people do in response to that stimulus. If individuals are not ultimately responsible for their own health behaviors, health promotion becomes irrelevant. Environmental

triggers alone do not cause unhealthy lifestyles. On a more positive note, there is some evidence that healthy behaviors may be becoming more prevalent at least in the Asia-Pacific region (including Australia and New Zealand).[217]

Another area on which lifestyle medicine needs to focus is making better use of "teachable moments," particularly those times where a patient is advised of a risk or diagnosis[218-220] or where they have been successfully treated but face increased risk of co-morbidity.

Increasing our effectiveness in helping individuals sustain healthy behaviors requires acknowledging the ways in which they differ in the kinds of messages that they find sufficiently persuasive to result in action,[221,222] in the misinformation and misperceptions they may have,[223] in how they differ in their motivations[224] and in their ability to implement and sustain changes, and in how their social environment can support or undermine change.

Lifestyle medicine also needs to more deeply explore how mental health risks may be reduced via health behavioral change.[225] This is of increasing concern given the huge increase in the rate of anti-depressant use in Western societies. Finally, we may need to embrace ideas that have historically been considered to lie within the ambit of spirituality, with numerous studies finding positive associations between religious participation and physical and mental health[226-228] as well as associations with particular components of religious attitudes such as generosity.[196,229]

Lifestyle medicine's future may ultimately lie in individualizing support so that adopted lifestyle behaviors become permanent rather than transient.

Individualizing Support

There are several excellent resources dealing in detail with individualizing exercise recommendations for chronic disease.[230-234] In addition, Minich and Bland's coverage of issues relating to special dietary considerations is also wide-ranging.[235] So, the issues concerning physical aspects of lifestyle will be covered only briefly here, followed by further discussion about personalization of lifestyle medicine in 3 areas: social connectedness, psychological skills and support, and basic practical skills.

Exercise and Activity

For physical activity, the most critical aspect is to start with activities that lie within the individual's capabilities but which serve to extend those capabilities over time. This is particularly necessary where individuals suffer from chronic diseases, which may cause dysfunction at the cellular level, but which may improve over time with diet and activity. Individuals differ in response to exercise depending on the intensity, frequency, duration, and modality, as well as on the timing and composition of meals,[236] so exercise needs to be tailored to the individual[237] to elicit the best response for that person.[238] For some people, exercise (not activity) may lead to adverse effects on blood pressure, high-density lipoprotein cholesterol or other biomarkers or symptoms[239] so a more gradual approach, with more biometric monitoring, could be warranted for such individuals.

There is some evidence of nonresponse to particular kinds of exercise for some people,[240] which could mean experimenting to see what works best at a given time for a given individual at a particular stage of chronic disease.[241-243] Compensatory behavior, such as increased eating or reduced activity, may negate any benefits,[244-246] so this may also need to be addressed.

While there is evidence that personalized exercise prescription may enhance response,[237] at this point the specific use of genetic information to inform exercise prescription may be premature. A 2017 review of genetic testing for exercise prescription and injury prevention found that "the predictive value of such tests is too low to warrant clinical application."[247] A systematic review of VO_2-max trainability found that of 97 genes identified as possible predictors only 13 were reproduced in more than 2 studies and that heterogeneity in the studies limited the conclusions that could be drawn.[248] The META-PREDICT study, which involved developing predictors, based largely on genetics, for the health benefits of exercise for individuals appears to have quietly died following its final report in 2016.[249]

Individuals vary considerably in their affective response to exercise intensity. Most people have a positive response to moderate-intensity exercise while having an aversive response to higher intensities.[250] Additionally, people who have more positive feelings about exercise are more likely to engage in it.[250] So for an individual to continue to want to exercise they need to feel good as a result of the exercise,[251,252] and it needs to be set at a level that best balances effectiveness and affective response, with an initial focus on increasing enjoyment of physical activity.[253] Taking individual differences into account is crucial for effective physical activity interventions.[254]

Nutrition

The effects of some nutrients may differ in people with different gene variants, although the evidence is often mixed. While increased requirements for certain micronutrients have been established beyond doubt for some people (eg, folate for pregnant women to prevent neural tube defects and anencephaly),[255] most findings that relate genetics to nutrient requirements find either small effect sizes or conflicting evidence for the direction of the effect. For example, an examination of genetic variations and zinc requirements[256] concluded that "the data extracted confirmed a connection between genetics and zinc requirements, although the direction and magnitude of the dietary modification for carriers of specific genotypes could not be defined."

In 3 studies (all by the same researchers) of interaction of DHA with the APOE4 gene (a risk factor for Alzheimer's disease [AD]),[257] one study found limited transfer of DHA to cerebrospinal fluid,[258] another study using a different measurement method found increased brain-uptake of DHA for the same gene,[259] while a third study

suggested that high-dose DHA in early stages of AD dementia could decrease prevalence in APOE4 carriers.[260] Other studies have found improved cognitive function with fish oil supplementation only in APOE4 carriers[261] or conversely no benefit only for APOE4 carriers.[262] The bottom line is that we simply do not know what the interaction is, if any.

One difficulty in linking micronutrients with chronic disease is that if an individual has a high-energy, nutrient-poor diet, then, rather than nutritional deficiency being the cause of the disease (eg, obesity), both the disease and nutritional deficiency may be attributable to diet quality. Accurately measuring nutrient intake and nutritional needs for micronutrients for individuals is extremely challenging,[263] so rather than focusing on specific nutrients, the safest approach is a varied diet of healthy foods,[264] adjusting for particular food sensitivities. However, including unhealthy foods in a varied diet may actually increase risk of abdominal obesity and T2D.[265]

Social Connectedness

Social isolation and loneliness have been recognized as detrimental to health for more than 30 years.[266] Growing numbers of people report social isolation or loneliness, while others experience dysfunctional or undermining relationships that can also be detrimental to health or the success of a lifestyle medicine intervention.[267] Negative social experiences correlate with poorer health behaviors[268] while loneliness tends to be associated with poorer social skills.[269] Conversely, support from family, friends, or workmates may all contribute to a person making and sustaining healthy lifestyle changes.[270] Belonging to a cohesive, stable, and homogeneous community may in itself have positive health benefits (the so-called Roseto Effect[271]), something that modernity seems to have undermined. Blue Zones notably involve groups who, whether by reason of ethnicity, isolation, or religious participation, constitute such cohesive communities.

Addressing social isolation may be a core factor in improving lifestyle behaviors, whether this involves helping people to improve social skills or facilitating participation in a stable social group. Face-to-face support groups[272] that persist beyond the intervention and peer mentoring/support (the buddy system)[273-275] may be effective means of both supporting behavior change and reducing the negative impact of social isolation by providing new social ties and support, other than that of a paid health professional. They can also be more cost-effective,[276] an important consideration in an era of skyrocketing health costs.

Social skills training and opportunities to practice these growing skills may help overcome some of the more detrimental emotional effects of loneliness that for some underpin dysfunctional health behaviors. Finally, the health benefits of volunteering[277,278] may in part lie in increased social contact with less focus on self and could form part of a lifestyle intervention for people lacking social support.

Psychological Factors

Individual psychological differences may affect their capacity to adopt and sustain healthy lifestyle behaviors. How people deal with failure[279] may influence abandonment of health behaviors, and it is possible that similar strategies for dealing with relapse could be utilized as for addiction.[280] One possible future research direction may be how individuals deal with micro-temporal factors such as temporal and situational cues, as well as transient thoughts and feelings.[214] Individuals also differ on multiple dimensions on how they approach goal setting and achievement,[281] so finding the best approach for the individual may be essential for long-term success. One key strategy may be planning in advance how to deal with obstacles or setbacks[282] and using implementation intentions, which has shown promise in terms of reducing meat consumption[283] and increasing physical activity.[284] Individuals may have chronic diseases as a result of past self-regulatory failure and may need training in a range of skills such as planning, mental contrasting, distracting, and reframing.[285] Motivational interviewing and health coaching have proven effective in assisting individuals in meeting their health goals[286-288] and may help individuals build self-efficacy.

For individuals with multiple comorbidities, regimen factors,[289] burden of treatment,[290] and patient capacity[291] may all need to be considered in deciding what approach to take with promoting lifestyle changes for individuals who may already be struggling to cope. An approach known as "minimally disruptive medicine" may be needed.[292] In some cases, implementing small changes may be the best approach to take[293] with a focus on progress rather than perfection.

Skills Training

For many individuals, just knowing what they should be eating is not enough, they need to be given the skills to put those recommendations into practice. In order to be able to eat healthily, an individual may need to learn basic cooking and shopping skills and strategies. Teaching basic cooking skills has been shown to encourage healthy eating,[294-297] with home-cooked meals associated with better dietary quality.[298] Community interventions to improve cooking skills have been shown to increase food literacy,[299] while incorporating cooking demonstrations and opportunities to taste healthier foods as part of a health promotion program could help encourage healthier eating.[300] Using a grocery list when shopping is also associated with a healthier diet among high risk adults[301] and healthy shopping tours are being increasingly offered by health organizations.

Conclusion

Precision or genomic medicine is not the enemy.[302] There may be some scope for cross-fertilization between the 2 specializations. For individuals who conscientiously adopt a healthy lifestyle but show no improvement in biomarkers,

genetic research could help identify whether there is a genetic explanation or whether there is some previously unknown lifestyle or environmental factor that needs to be considered. Conversely longitudinal research on populations who live a healthy lifestyle could help sharpen estimates of gene penetrance paving the way to better predictive models. Such research could possibly even help identify new lifestyle factors by looking at differences in outcome between genetically similar people following the same healthy lifestyle.

However, chronic disease is simply not the primary target for a genetic approach and extending it to the broad mass of people at low genetic risk is overkill. Precision medicine is best targeted at gene therapy for gene variants with proven etiology, identifying genetic factors in variations in drug effectiveness and identifying high penetrance genes for disease screening.[209] Primary genetic research may also identify links between diseases and the functions of genes and gene networks that may lead to novel insights into the genesis of disease.[303,304]

While this article has identified technical barriers to a genuinely "precision" medicine, there are also numerous ethical issues[305-307] and regulatory protections that would need to be ironed out should such an approach become the dominant paradigm.[308] These include things such as informed consent, continued ownership of one's own genetic information[309] and the right to have it destroyed, privacy (especially in an era where data leaks are so common and where depersonalized data can be re-personalized[310]), genetic discrimination, the right to refuse genetic testing, and the potential for future abuse by governments.[311] Precision medicine has been described as "drowning in a regulatory soup."[312] The demand for ever bigger genomic data sets and ever more personal medical information with which to match it, combined with the rush by governments to accommodate these demands, is likely to lead to fundamental human rights and freedoms being overridden. There are already calls for every newborn to be genetically sequenced[313] with the consequent medicalization of life.

None of these concerns apply to lifestyle medicine.

We currently seem to be at the "Peak of Inflated Expectations,"[314] and it may be some years before the limited utility of precision medicine is recognized and that projected cost savings are illusory.[315] The financial resources being allocated, for what is effectively a promissory note, may ultimately divert resources from the more acute problem: How can we persuade most people to adopt a healthy lifestyle?[316]

Lifestyle medicine now possesses a much deeper scientific foundation but the actual recommendations have not markedly changed as a result. The fundamental problem for lifestyle medicine remains: How people can be motivated to adopt, sustain, and ultimately naturalize a healthy lifestyle. Rather than delving ever more deeply into physical mechanisms, instead we need to look at the psychological and social factors that either encourage or obstruct healthy lifestyle behaviors. Interventions need to be personalized to the individual and their embodied experience of the world. This does not necessarily mean changing what we recommend, but it does mean changing how we support the individual in their efforts to live healthier.

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Trial Registration

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