REVIEW
The future: genes, physical activity and health

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Abstract
The assigned title for the Lindhard presentation was to examine the future of genes, physical activity and health. The current review is a summary of this presentation. Caution is expressed that technology is improving so rapidly that a future view is limited to a few years as opposed to the 100 years passing since Lindhard’s achievements. The near futuristic opportunities and challenges for four major topic topics are reviewed here. Concerns are expressed over current usage of the terms ‘control’ group and ‘non-responders’ in exercise research. Our view is that ‘control’ needs to be differentiated between its usage for treatments of exercise to restore natural functions in individuals with less than healthy levels of physical activity and the inherited genome’s expectation for physical activity levels to maintain normal function. For the second discussed topic, it is proposed that the term ‘non-responders’ should be replaced by the term ‘low sensitivity’ as there may be no such human who is a non-responder to every exercise adaptation. The third futuristic topic is exercise prescription as envisioned for individualized medicine. However, numerous limitations and challenges exist to truly optimal exercise medicine at the level of one individual. Finally, preventative physical activity medicine is discussed. Physical activity as a therapy now exists to prevent most of the chronic diseases. The future needs to understand the molecular basis for how the body becomes dysfunctional when its level of physical activity does not match the norm of physical activity that selected our inherited genome.

Keywords  control group, exercise, individualized medicine, non-responders, preventive medicine.

Physical inactivity increases the risk of breast cancer, colon cancer, coronary heart disease, hypertension, osteoporosis, stroke and type 2 diabetes by 31%, 41%, 45%, 30%, 59%, 60% and 50% respectively (Katzmarzyk & Janssen 2004). These conclusive epidemiological data now lead to the requirement to show causality. To prove causality, it is necessary to find the molecules and pathways that initiate the link between physical inactivity and chronic diseases. Indeed, using molecular approaches is an unquestioned approach in medicine. The theme of a series of articles in Nature Reviews Molecular and Cell Biology is ‘Understanding of molecular and cellular basis of diseases is vital for dissecting the mechanisms of disease pathogenesis and for designing appropriate and effective treatments’. Previously when the molecular pathways underlying health issues concerning tobacco and asbestos were determined, major changes in U.S. public health policy...
occurred. Additionally, uncovering the molecular pathways by which exercise exerts beneficial effects will allow pharmaceuticals to more accurately focus research into the development of drugs aimed at problems where there is no known existing effective treatment such as physical exercise. Four concerns in tackling such issues in the context of physical activity will be discussed next; they are – control group, responders/non-responders, personalized medicine and preventive medicine.

A future need is to have designation of the control group with physical activity levels most closely approximating the levels under which selective pressures established optimal gene function for survival.

Physiology is the study of normal function. Therefore, to define what normal homeostatic levels functions were evolutionarily selected, the choice of the proper animal/human model is critical. Sedentary humans undertake about 25% of the activity expenditure of free-ranging mammals (Hayes et al. 2005). No debate exists that metabolic adaptations associated with exercise training of sedentary are ‘healthier’ (Fig. 1). However, our simple premise is that sedentary behaviour is not the normal physical activity level. Understanding normal physiology is fundamental to understanding the pathology of chronic diseases. The normal physical activity level is the amount of physical activity obligatory for survival in a self-sufficient environment where each individual or small groups of individuals are responsible for gathering their own food, making their own shelter and providing their own defence. The adaptations to this level of physical activity then resulted in the genetic programme leading to normal physiology. So the question can be asked, why is the sedentary level of physical activity then designated as normal physiology by the majority of biologists? By designating sedentary as normal, physical inactivity in daily living does not exist and thus exercise prevents chronic diseases through mechanisms other than countering physical inactivity. This flawed logic can lead to dramatic errors in interpretation and design of experiments. For instance, with current efforts to define the function of ~100000 proteins (including modifications of the same protein), the question as to whether protein function in sedentary animals is the same as the function of a protein in physical active animals is crucial for interpretation of the data. From molecular biologists to applied clinical exercise scientists, a shift to the designation of an appropriate normal for physical activity is necessary for better-designed and more valid designations of gene function in future studies.

In addition to its conflict with the medical dogma calling the physically inactive sedentary group as control (Booth & Lees 2006), such designation is inconsistent with our ancestral genetic selection. Human ancestors had to be more physically active than today’s sedentary control group in order to find food and offer defences (Cordain et al. 1998). For instance, it is believed that endurance running played a critical role in the evolution of genus homo, with persistence hunting (before the advent of hunting weapons) providing the appropriate nutrition for the unique evolution of hominids (Bramble & Lieberman 2004). Thus, those who were unable to perform the high levels of physical activity to partake in persistence hunts were more likely to have their gene pools extinguished before reproductive age. We have proposed that this high amount of physical activity shaped the ‘normal’ function of metabolic and strength genes. The amount of physical activity required for ancestral normal functions of genes is largely absent today. Thus, we believe the lack of physical activity in our environment interacting with our genes is largely responsible for the development of chronic metabolic diseases and sarcopenia in modern humans. This is in part due to the extremely successful engineering of physical activity out of our environment. Unfortunately, humans have not been successful in engineering genes that remove the physical activity requirement out of our genome. Indeed, Francis Collins, one of two individuals to first sequence the human genome, wrote,

However, the best opportunity to reduce risk in genetically susceptible people for the foreseeable future will not be to re-engineer their genes, but to modify their environment. (Schwartz & Collins 2007)

Thus, using sedentary animals as the control is more akin to the sociological norm than to the genetic or health norm.

A future need is to understand the nuance that adopting the pharmaceutical approach to designate the control group as not receiving the intervention contrasts
with the physiological/pathological approach that the control group is the healthiest.

The purpose of this section is to use accepted definitions to clarify the misuse of the term ‘control’. First, we will discuss definitions for normal and abnormal. Physiology is defined as studies of the normal mechanical, physical and biochemical processes of animals and plants (Anonymous 2005). Pathology is defined as the anatomic and physiological deviations from the normal that constitute disease or characterize a particular disease (Anonymous 2007). Disease is defined as an impairment of the normal state of the living animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions and is a response to environmental factors (such as malnutrition, industrial hazards or climate), to specific infective agents (such as worms, bacteria or viruses), to inherent defects of the organism (such as genetic anomalies) or to combinations of these factors (Anonymous 2007). Pharmaceutical is defined as a substance used in the diagnosis, treatment or prevention of disease and for restoring, correcting or modifying organic functions (Anonymous 2008). Thus, the goal of prescribing a drug is to make you healthier and return the body to normal mechanical, physical and biochemical processes. Likewise, prescription of exercise returns the body to normal mechanical, physical and biochemical processes. In this sense, then, prescribing drugs or exercise is a treatment, and thus neither would be traditionally thought of as a control group. Both treatments make the body healthier. While the above is non-controversial, application of usage of the term ‘control group’ to the above is controversial.

We next introduce current dogma that labels the sicker population as ‘control’. Conventions in the medical literature are to designate those not taking drugs as the ‘control’ group to compare to the treatment group taking drugs. We contend that such designations are pharmacological nomenclature rather than genomic nomenclature. Likewise, sedentary, not exercising, subjects are conventionally designated as the ‘control’ group in comparison with experimental subjects in the ‘exercise’ group. Unfortunately this leads to the assumption that the less than healthy sedentary subjects serving as ‘controls’ also have normal physiology. Obviously in relation to the definitions paragraph above, such designation is wrong. While drugs are not natural molecules in the body, and thus did not shape selection of the human genome throughout evolution, physical activity did. In our opinion, it is a misconception and misleading to imply that the sicker sedentary group is both physiologically and genomically normal. One approach to address this problem would be to include the adjective ‘sick’ or ‘sedentary’ control vs. ‘healthy’ or ‘active’ control to distinguish between the physical activity levels of the non-intervention group.

This discussion was initiated by a recent American College of Sports Medicine campaign entitled ‘Exercise is Medicine’ to encourage increased exercise for better health. Our interpretation is that ‘Exercise is Medicine’ is a U.S. cultural expression attempting to express the importance of exercise. In U.S. culture, short advertising phrases have been adopted by others to sell an idea; whether it is to vote for a political candidate or to alter lifestyle, such as, ‘Buckle up America’ is used to encourage seat use. The scientific implications of ‘Exercise is Medicine’ is consistent with our proposal to return physical activity levels for optimal health to those levels that selected our genes for optimal homeostasis of body function and capacity when humans had to be self-sufficient. We wholeheartedly support the ‘Exercise is Medicine’ campaign.

However, three-word advertising slogans cannot capture totally accurate scientific fact; thus, providing scientific misunderstanding. One interpretation of ‘Exercise is Medicine’ is that the phrase is analogous to ‘Drugs as Medicine’; both being treatments to establish improved health. However, they differ in that the lack of a drug was not the initial cause of the sickness whereas the lack of exercise was most often a contributing initial cause of most chronic diseases. Thus, drugs may use mechanisms that bypass the molecular cause of chronic disease to restore normal physiology, whereas increases in physical activity prevent activation of pathological processes and restore normal physiological function. Finally, we contend ‘Exercise is Medicine’ is a cultural U.S. advertisement necessary to relate the relative importance to doctors that the prescription of exercise is just as important as a drug prescription.

A future need is to delineate the molecular basis for why specific phenotypes do not respond to exercise training.

Subject variability in magnitude of adaptive response to exercise training

A major future challenge will be addressing the wide range of the magnitude in the percentage/absolute change of a given physiological adaptation to an identical exercise intervention. For instance in the HERITAGE study, a range of 0–100% increase in VO2max occurred in sedentary subjects undergoing a progressive aerobic exercise training programme of three times a week at a final heart rate that was 75% of their initial VO2max for 50 min day−1 for 15–20 weeks (Bouchard et al. 1999). Other experiments have shown a similar heterogeneity (mean 24%, range 0–58% increase) in VO2max adaptation to similar exercise interventions (Kohrt et al. 1991). Other adaptations to training such as heart rate at low work loads, improvements in blood pressure and improvements in insulin
sensitivity in diabetic patients all have variable magnitudes in responses to exercise training among subjects in the same study (Bouchard & Rankinen 2001, Fritz et al. 2006). Interestingly, the genetics have been calculated to contribute 48% of this variable response in VO$_{2\text{max}}$ (Bouchard et al. 1999), implying non-genetic causes for the other half of the variation. Existence of a significant environmental component to gene expression is consistent with the necessary ability of species to adapt to new environments as Darwin originally conceived. If all members of a species had no responsive genes to the environment, that species would more likely be extinguished by any major change in the environment. Such variability in responding to the changes in environment may have offered selective advantages for survival during evolution and could offer selective advantages in future. Understanding the interaction between the variability in the genome and variability of the environment is a future area fundamental to understanding complex biological processes.

The problem of extrapolation from single phenotype to all exercise-inducible phenotypes

Often studies focus on a single phenotype, representing an integrated process, that is heterogenous in response to exercise in a group of subjects. While this is a practical consideration and limitation of such studies, some interpretations employ the term ‘non-responder’. Use of this term implies that because one complex adaptation does not occur, no exercise adaptations will occur out of the hundreds of other non-determined potential adaptations to that exercise type. However, such interpretations are invalid, and in principle flawed, without proof that the hundreds of other remaining adaptations also do not change. Given that exercise is polygenic within a given organ and affects multiple organ systems, there are likely other undetermined adaptations that do respond to exercise. A proof of principle is that Vollard et al. (2009) recently showed that the group of subjects who did not increase VO$_{2\text{max}}$ in response to aerobic exercise did show improvements in oxidative enzyme activities in muscle. Importantly, while VO$_{2\text{max}}$ was correlated with performance both before and after the training intervention, the percentage change in VO$_{2\text{max}}$ with training was not associated with the intervention’s change in physical performance. This indicates improved performance must have occurred through alternative adaptations to changes in VO$_{2\text{max}}$ in those having low sensitivity in increases in VO$_{2\text{max}}$ in response to endurance-type training. Thus, failure to improve one specific phenotype is not reason enough to cease or fail to recommend or prescribe exercise because VO$_{2\text{max}}$ does not increase, as suggested by some. Regardless, future studies need to determine whether the genetic programme that leads to the non-responsiveness of one phenotype by one type of training extends to other types of training. For example, will an individual who has low sensitivity to improved insulin sensitivity by endurance-type training have improved insulin sensitivity as a result of resistance-type training?

It is more difficult to prove the negative than to prove the positive

The generalized term ‘non-responder’ is misleading as it implies that no exercise-induced adaptations occur. With thousands of biochemical adaptations to exercise (multiple cell types, multiple exercise types, multiple thresholds for significant change, multiple interactions among adaptations), it is foolhardy to extrapolate from one adaptation and claim exercise should not be prescribed as one exercise scientist once told NIH. The proper response in 2009 is that there is no such thing as a ‘non-responder’; there is just heterogeneity of responses to the same stimulus. Maybe a more appropriate terminology would be ‘high sensitivity’ and ‘low sensitivity’.

Is responsiveness binary or graded in nature in response to exercise?

The idea that adaption to exercise is more of a graded than binary nature has indeed already been tested. Sisson et al. (2009) increased the exercise prescription by threefold, and the percentage of VO$_{2\text{max}}$ non-responders dropped from 43% to 15%. Thus, the implication that some people either respond or fail to respond in a binary fashion is incorrect. Indeed, in the case of VO$_{2\text{max}}$, the more correct interpretation is that there is heterogeneity or a variation in the ‘sensitivity’ of response to a similar stress, and not a failure to respond by all exercise adaptations. It may be that the increased exercise merely increases expression of the same pathways that fail to respond to the lower level or exercise. Alternatively entirely different pathways that create redundancy in most physiological phenotypes may be activated. Clearly, future studies are needed that attempt to characterize where the genetic control expressions responsible for a range of sensitivities to a range of exercise adaptations are needed.

Pharmaceutical application to isolated low-sensitivity adaptations to exercise and to those physically unable to exercise

A future challenge is how to improve a specific response of individuals who are low-sensitivity responders to exercise for the measured exercise adaptation, which is
a clinically relevant problem. An analogous situation exists in patients non-responsive to pharmaceuticals. In this case the dose of the drug might be increased, if no adverse side effects are present. In a similar manner the dose of exercise could be increased to provide a stronger stimulus. However, this approach might be unfeasible in the elderly or extremely physically impaired, and alternative treatments that use pharmaceuticals may be necessary. In the case of the patient not being able to exercise, a drug that may counter some of the inactivity effects is ethically correct because the individual cannot exercise. However, implying that healthy individuals could stop exercising and not miss all health benefits because of the inappropriate usage of the term ‘exercise mimetic’ is, at least in our opinion, a serious ethical concern (Narkar et al. 2008). Furthermore, clearly it is, at least in our opinion, both false and unethical to call a chemical an exercise mimetic when it also produces a side effect(s) negative to health unlike exercise.

**Combinations of exercise and pills**

Examples exist where animals are non-responsive to pharmaceuticals. However, the same pharmaceutical in combination with exercise may provide synergistic adaptations to improve otherwise non-responsive adaptations. For example in mice, an oral PPARδ agonist does not improve run time to exhaustion unless the mouse is also exercising (Narkar et al. 2008). Alternatively, pharmaceuticals may be beneficial through increasing the amount of exercise patients with low sensitivity to a needed adaptation to exercise can undergo. For example, while steroids, alone, result in modest improvements in strength, steroids in combination with resistance exercise greatly enhance strength. However, negative health effects of anabolic steroids and their usage by those able to exercise has been ruled illegal by most governments. As exercise physiologists, future research in identifying the molecular adaptations responsible for the heterogeneity of responses should provide greater insight into how exercise can be used even in ‘non-responsive’ patients.

*A future need is to improve the scientific basis of exercise prescription. Individualized medicine will occur, but will it be the end game?*

**Variants**

The enormity of the genetic and environmental variants needed to optimally prescribe individualized exercise prescriptions suggests caution.

**Gene variants**

With the genetic revolution of the last decade, an increasing appreciation is occurring – individual genetic differences in genes that contribute to the risk and development of chronic diseases. Such genetic variation can encompass, but is not limited to, single nucleotide polymorphisms, haplotypes, microsatellites or simple sequence repeats, insertion and/or deletion and copy number variations, and aneuploidy. All the aforementioned variations involve changes in DNA sequences. Additional variation is introduced by epigenetics variation where the DNA sequence remains unchanged, but the gene expression and phenotype differ because of changes in histones or DNA methylation, adding another level of complexity to gene–environment interactions.

**Environmental variants**

Environmental components interact with predisposing genes to modify disease risk. Certainly within a given population, the heterogeneity in response to environmental factors (pharmaceuticals, nutrition or exercise) is a major hurdle to developing efficacious treatments for the masses.

**Subject variants**

Understanding how the environmental variants interact with the genetic variants is necessary to understand variation between subjects. For example, a huge future challenge will be taking the known variation in exercise response coupled with variants from whole-genome sequencing to develop individualized or personalized medicine/treatments. These treatments would predict the best drug/nutrition/exercise intervention based on whether the patient has a specific set of gene variants. Currently there are several examples the practical applications of this in terms of exercise and gene variants exist. For instance the β3 adrenergic receptor, which is predominantly expressed in adipose tissue, can have either an Arg or a Trp at amino acid64 in its sequence. Women with an Arg at amino acid64 lose less weight than women with a Trp amino acid at this position in response to a low-calorie diet and exercise intervention (Yoshida et al. 1995, Sakane et al. 1997). Another gene variant that results in differential weight loss with exercise is found in UCP1. The GA SNP genotype in UCP1 results in greater weight loss in response to diet and exercise intervention than the GG SNP genotype (Kogure et al. 1998). Interestingly, when the GG SNP in UCP1 is combined with an Arg at amino acid64 in the β3 adrenergic receptor, even less weight is lost with the intervention (Kogure et al. 1998). This example highlights the potential complexity of how epistatic interactions between multiple differing genotypes may affect a single phenotype when applied to personalized medicine.
When developing future personalized exercise recommendations several challenges/limitations currently exist. Much of the difficulty will be establishing a cause and effect that is clinically relevant to allow specific exercise prescriptions. There are several reasons for such difficulties. Most clinical interventions involving exercise also contain a diet component making it difficult to separate out diet vs. exercise interactions. Thus, specific prescriptions pertaining to just diet or exercise may be less effective. In addition to the nutrition–exercise interaction, age–exercise and gender–exercise interactions are also present, adding yet more variables in the clinical application of personalized medicine. Additional non-genetic factors related to compliance must be considered as to what exercise to prescribe from the genetic exercise map. Compliance to exercise prescription can be influenced by safety, religious or cultural practices, number of jobs, child care, weather, vacations, travel, etc. An important limitation to ‘optimizing’ personalized medicine to perfection is the limitation of the lack of an appropriate control for each individual. Each individual cannot serve as their own control (i.e. live their life twice with two different exercise prescriptions for life), nor will two individuals, other than the small fraction of the human population that is monozygous twins, have identical polygenic characteristics for chronic diseases and exercise/inactivity sensitivities.

While clearly exercise affects multiple organ systems (Laye et al. 2009), the polygenic effects of exercise likely express in different ways in different organs, and even differently in the same cell type in different organs. Thus, while molecular pathways can be fairly easily characterized in skeletal muscle, doing so in other human tissues such as the liver or hypothalamus in large clinical studies is a practical impossibility at this time. As a result, the proper prescription of exercise for improved coronary perivascular fat, liver or hypothalamus health is going to be an estimate at best. A potential limiting factor on the optimal accuracy of exercise prescription is the dependency of genetic prescription for exercise from blood or skeletal muscle DNA without being able to determine biochemical/molecular adaptations in the human genome in organs/tissues not accessible. As mentioned earlier, heterogeneity in the sensitivity for adaptation will exist among the thousands of adaptations to exercise. For example, while exercise may not affect VO2max, it may stress blood flow, improving endothelial vasodilation. Furthermore, while genetic variants clearly play a role in disease development, it is likely that other regulatory mechanisms that regulate gene expression, such as microRNA, siRNA or epigenetics, contain individual variations that contribute to individual responses to exercise (Kahn & Fraga 2009). Luckily, these problems provide plenty of opportunities for exercise scientists to play a prominent role in moving the field of individualized medicine closer to a clinical reality.

How individualized will individual medicine prescriptions be?

The database for exercise prescription likely needs to include ~6 billion individuals in the world × age of individual × gender of individual × number of chronic diseases × number of polygenes involved in a given disease × number of variants in each polygene for a given disease × number of organ systems in a given disease × number of exercise types × number of polygenes involved in a given exercise type × number of variants in each polygene for a given exercise type × number of organ systems in a given exercise type. Clearly, this is improbable, and thus determining the feasibility of population, group or family-based ‘individualized’ prescriptions is necessary, rather than individualized for each of the 6 billion humans.

A future need is to delineate the molecular and systemic basis for how physical fitness and activity are one of the most powerful preventers of chronic disease.

Primary, secondary and tertiary prevention of chronic diseases are defined as reducing incidence by eliminating causative agents, detecting and correcting preclinical symptoms before overt clinical disease occur, and reducing complications and morbidities of clinical disease respectively. Here, discussion will be limited to type 2 diabetes. Conclusive epidemiological evidence exists for primary and secondary prevention of type 2 diabetes. In an outstanding review, Hu et al. (2007) summarize three types of studies on the prevalence of type 2 diabetes – prospective physical activity, prospective physical fitness and clinical trials. Prospective primary prevention studies have investigated physical activity and cardiovascular fitness. Sedentary groups have increased type 2 diabetes prevalence ranging from 1.2–2.5 times, with most of the studies showing a 1.4- to 2.5-fold increase, compared with the enhanced physical activity during commuting, leisure time or daily life (reviewed in Hu et al. 2007).

Lower cardiovascular fitness is associated with higher risk of type 2 diabetes. Poor physical fitness was reported in 1996 to be a very early feature in the development of type 2 diabetes in Swedish men (Eriksson & Lindgarde 1996). For instance, maximal O2 uptake of <25.8 mL kg−1 min−1 had five times the prevalence of type 2 diabetes than for those >36 mL kg−1 min−1 in Finnish men (Lynch et al. 1996). Similarly, the lowest quartile of cardiovascular fitness had 4.3–6.1 times higher incidence of type 2 diabetes after 22 years from a starting age of 40–59-year-old Norwegian men (Bjornholt et al. 2001).
Likewise, the low fitness group (20% of U.S. male subjects) at baseline had a 1.9-fold risk for impaired fasting glucose and a 3.7-fold risk for diabetes compared with those in the high fitness group (40% of men) (Wei et al. 2000). Another group of U.S. men and women with low fitness (<20th percentile) were three to sixfold more likely to develop diabetes, hypertension and the metabolic syndrome than participants with high fitness (≥60th percentile) (Carnethon et al. 2003). Finally in a male Japanese cohort, the lowest quartile of cardiovascular fitness had four times the prevalence of type 2 diabetes than the top quartile (Sawada et al. 2003). Interestingly, these studies suggest that increased fitness is more effective than increased physical activity in preventing type 2 diabetes. So while genetics (naturally higher cardiovascular fitness) protects against type 2 diabetes, physical inactivity lowers cardiovascular fitness. Those individuals with low cardiovascular fitness can still lower their risk of type 2 diabetes by avoiding physical inactivity. A challenge exists not to discourage those with low cardiovascular fitness to give up and not exercise because they are told that they have not inherited the ‘exercise genes’.

The epidemiology data are convincing for an associative link between lack of physical fitness and type 2 diabetes. So why would molecular links from physical inactivity to type 2 diabetes be needed? A convincing answer is of two parts. First, despite the convincing association between either low cardiovascular fitness and sedentary lifestyle and higher prevalence of type 2 diabetes, future predictions are for a major increase in prevalence. Worldwide the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al. 2004). In the United States, the 2004 prediction that one in three births will have diabetes in their lifetime (Narayan et al. 2003) was readjusted only 2 years later from 39 million in 2050 to 48.3 million cases of diagnosed cases of diabetes (Narayan et al. 2006). In Europe the DECODE study of 13 countries estimates the prevalence of diabetes will reach 25% and 45% in old men and women respectively (DECODE Study Group 2003). Second, predeance exists for molecular links positively influencing public health policy. Molecular links between an environmental agent (smoking and asbestos) and a molecule that increases cell proliferation and cancer resulted in regulatory changes affecting behavioural change. Importantly, this is compelling evidence that molecular links can lead/initiate corrective healthcare policies.

**Conclusion**

The existence of new scientific technologies opens doors for future research opportunities by those credentialled with an understanding of the complexities of the body’s adaptive responses to exercise and physical activity. Major challenges exist to understand the molecular relationships between our inherited genome and physical inactivity, designating what is meant by ‘control’ group, how to prescribe exercise to low-sensitivity responders, optimizing the accuracy of personalized medicine and placing greater emphasis on primary preventive medicine rather than on curative medicine.

**Conflict of interest**

There is no conflict of interest.

**References**


