Perspective on the future use of genomics in exercise prescription

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The study of the importance of genomic factors in the responses and adaptations of health-related traits to exercise stimuli has increased dramatically over the past 10 years (3, 25). One rationale underlying the work is that by understanding the genomic factors (e.g., DNA sequence variants) important for the responses of various phenotypes to exercise interventions, clinicians will one day be able to "individualize" exercise prescription, much as genomics is being considered for inclusion in typical medical care. Although the future use of genomic information in general medical treatment is not certain (8, 11, 22), a unique concern for the use of genomics in exercise prescription is whether such use is reasonable given the existing recommendations that all individuals perform regular exercise. With physical activity known to be important across a wide variety of systems with impacts on overall morbidity and mortality, how can genomic factors be used to improve our ability to administer exercise interventions? This Viewpoint seeks to address some of these issues, although it will not address the important idea that genomic studies will meaningfully contribute to identifying important physiological pathways (7, 16) underlying exercise responses and adaptations.

That genomic factors are important to the responses and adaptations of a variety of phenotypes to exercise stimuli has been shown in multiple studies and strides have been made in identifying specific contributing genes (3, 25). As any exercise scientist can argue, however, exercise training is a potent means of improving a wide range of health-related phenotypes; in effect, it acts as an across-systems, synergistic stimulus that tends to improve virtually all such phenotypes (31). But this consensus about the importance of exercise as a general therapeutic tool argues against the importance of genomic screening for exercise prescription: if exercise is useful as a therapy training: a genomic profile consistent with 1) a positive adaptation of a phenotype; 2) no adaptation (i.e., nonresponder); or 3) a negative or adverse adaptation.

In scenario 1, the individual’s genomic profile is consistent with a positive response to an exercise intervention, making it likely that non-lifestyle therapies (e.g., medication) can be substantially reduced from the treatment plan. Scenario 1 provides minimal rationale for genomic screening, as lifestyle factors should already be the first line of prescription regardless of genotype, although this does not appear to be typical for most physicians (9, 10). Whether genomic information would provide a motivating factor for participation and adherence is an open question (20, 21).

In scenarios 2 and 3 we see improved rationale for the use of genomic screening. In scenario 2, a nonresponse of the target phenotype to a typical exercise prescription, healthcare providers would have the advantage of being able to target non-exercise therapies (e.g., diet, medication) for the phenotype of interest at the outset of treatment. The incorporation of exercise into the treatment plan would still be expected, as it will provide numerous benefits for other non-targeted phenotypes and no apparent negative risk for the target phenotype. In scenario 3, we see an important deviation, one not often considered within the exercise science community: a genomic profile consistent with an adverse response of the target phenotype to exercise. In this case, exercise prescription early in this patient’s care could result in an adverse effect on the phenotype, thus delaying or worsening the desired outcome.

Scenario 3 is arguably controversial and the author makes the important point that exercise prescription is delayed, not ignored. The key point is that in this scenario, exercise presents an increased risk. The delay of exercise treatment in favor of other interventions would provide the highest level of care, with a later introduction of carefully monitored exercise for its more general health benefits. The emphasis for both scenarios 2 and 3 is on a particular target or at-risk phenotype. In fact, while an individual may have a negative response to exercise for one phenotype, there is little evidence to suggest that other phenotypes will show similar negative responses for that person, as has been seen in data from HERITAGE (24) and other large cohorts (personal communication, J. Hagberg).

Much work remains before determining the utility of the proposed use of genomic screening for scenarios 2 and 3. One argument is that the number of susceptible people will be small. Depending on the definition of neutral and negative responses, as many as 45% of individuals may fall into scenarios 2 and 3 (as is seen in Fig. 1), although smaller fractions are more likely. If even only a small fraction of individuals (5–15%) has an adverse response of a target phenotype to an exercise intervention, then there is considerable rationale for delaying such a prescription until that phenotype is stabilized. In no way is this an
Fig. 1. Individual data points, ordered along the X-axis, for the adaptation of various glucose metabolism variables to 20 wk of aerobic exercise training in the HERITAGE Family Study (5). A: insulin sensitivity ($\mathcal{S}_i$; mean: 10% increase); B: acute insulin response to glucose (AIR$_g$ mean: 3% decrease); C: glucose effectiveness ($\mathcal{S}_g$; mean: 11% increase); and D: glucose disappearance index (Kg; mean: 3% increase). A number of subjects in all figures show adverse adaptations to the exercise stimulus (indicated by a minus sign on each figure). The subjects are 596 healthy men and women with average age ~35 yr (range 17–65 yr) who were previously sedentary. The training program gradually progressed to an intensity of 75% of initial VO$_2$peak, which was maintained for the final 6 wk. Reprinted with permission from The American Diabetes Association (5).

argument against the use of exercise as a standard of care, but rather for the careful incorporation of such prescription to maximize treatment for specific individuals.

Another key issue is whether the specific genomic factors that contribute to various phenotypes will have large or small effects, as well as being commonly carried in a population (23). Although debate continues in the genomics community, common genomic factors with major impact are predicted to be identified for complex disease phenotypes (32). More importantly, complex combinations of genomic and environmental factors will ultimately contribute the larger, clinically significant influences on a particular trait, and identifying those combinations is the goal. Of course, if neutral or negative phenotype responses can only be predicted by complex interactions of many genomic and environmental factors with small independent effects, the likelihood of clinical utility will be small. Those traits with less-complex genomic etiologies or major contributing genes, perhaps “intermediate traits” such as biomarkers, will emerge as stronger targets for future clinical use. That different types of exercise prescription [e.g., modes (aerobic vs. strength training), intensities, frequencies, etc.] will undoubtedly have different interactive effects with genomic factors will further complicate this work. In addition, existing studies of phenotype variability have been performed primarily in healthy individuals, while genomic screening for exercise prescription implies targeted risk analysis in diseased individuals. Whether the extensive response and adaptation variability seen in healthy populations to exercise training will translate to diseased populations has not been fully tested, although existing data indicate similar variability between healthy and diseased humans (6, 18).

In presenting evidence for the potential importance of genomic factors in exercise prescription, we must not neglect the overwhelming evidence for the importance of environmental factors in disease prevention and treatment. Clearly, population-wide behavioral and lifestyle measures to improve disease risk have the greatest ability to improve public health. That said, genomic factors do contribute to individual disease risk across a number of traits and use of such information is already being used as a means of improving individual patient outcomes in some areas (14, 15). So, while there are many obstacles yet to surmount before genomic medicine becomes a reality (8, 11, 22), we can anticipate that future screening for genomic factors predicted to result in an adverse response of an at-risk phenotype to exercise prescription can improve treatment in susceptible patients. Preliminary findings in the areas of exercise and insulin sensitivity (5, 28, 29) and exercise and obesity (12, 26) suggest that such genomic factors are being identified. While we await additional discoveries, exercise should certainly remain the first line of prescription for the many phenotypes positively impacted by this important treatment; however, we can recognize that this standard of care is not optimal for some patients and envision the future application of genomic information to improve and individualize exercise prescription.

REFERENCES
