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Making preventive medicine more personalized: implications for exercise-related research

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Abstract

Objective—This commentary offers a discussion of the need to consider behavioral interventions such as physical exercise as integral components of personalized medicine.

Methods—We discuss the concept of personalized medicine and review existing evidence of variability in response to exercise training.

Results—We argue that increased understanding is needed regarding sources of variability in exercise responsiveness, and that such understanding should lead to more tailored, often multi-modal interventions.

Conclusion—Studies of personalized medicine to date have primarily investigated heterogeneity in drug responsiveness; we believe it is time to begin considering preventive strategies such as exercise within a broader scope of personalized care.

Keywords

Personalized Medicine; Physical Activity; Non-responder; Genomics; Phenomics

Perspective on personalized medicine

The early 21st century has witnessed a steady push by scientists, industry officials, and government officials to make medicine more personalized. (Ginsburg and Willard, 2009, Hamburg and Collins, 2010) In 2007, the U.S. Congress passed the Genomic and Personalized Medicine Act with the intent of advancing this new field of medicine. (Obama, 2007) The same year, future President Barack Obama emphasized the importance of the act stating that “in no area of research is the promise greater than in the field of personalized medicine.” The global goal of personalized medicine is to use each patient’s unique genetic and environmental characteristics to design optimal healthcare strategies. The Institute of Medicine has also highlighted the importance of personalized medicine by stating that

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Conflict of Interest

The authors have no conflict of interest to disclose.

“patients and providers are increasingly seeking evidence not only from representative populations, but also from relevant subgroups. Increasing emphasis on patient-level attributes that may modify the balance of benefits or harms can lead to more personalized medicine, reducing the pressure to try alternatives found to be ineffective in similar subgroups.”(Institute of Medicine, 2009)

Indeed, researchers have made great strides in making medicine more personalized through the study of pharmacogenomics – a field of inquiry that explores the impact of genomic variability on drug responsiveness. Pharmacogenetic studies have provided key insights responsible for identifying individuals who respond either adversely or superbly, or who are non-responsive to certain drugs based on their genetic makeup (reviewed in (Wang, et al, 2011). For example, pharmacogenetic studies of the anticoagulant warfarin have identified two genes – CYP2C9 and VKORC1 – that influence the drug’s metabolism and together account for 30% to 40% of the total variation in the appropriate warfarin dose. (Manolopoulos, et al, 2010) Findings such as these have made and will continue to make a marked impact on the health and well-being of patients. Yet something is missing.

The concept of personal medicine should not refer simply to drug prescription but to all aspects of medicine. To date, few data exist regarding the extent and source of heterogeneity in responsiveness to preventive strategies such as physical exercise.¹ Indeed, exercise is a powerful intervention with positive implications for a wide-variety of medical conditions including cardiovascular disease, diabetes mellitus, cancer, respiratory diseases, osteoarthritis, and osteoporosis. Yet despite the breadth of utility of exercise and that the concept of heterogeneity in exercise responsiveness was proposed nearly three decades ago, (Bouchard, 1983) information remains limited regarding individualized health responses to this important behavioral intervention.

Variability in Response to Exercise

That is not to say that data are completely unavailable. Evidence has long existed to indicate individuals vary in their responsiveness to chronic exercise training. For instance, two well-controlled studies conducted nearly twenty years ago indicated a mean increase in maximal oxygen consumption (VO_{2max}) of approximately 25% in response to aerobic training programs.(Bouchard, 1995,Kohrt, et al, 1991) However, despite similar levels of adherence, the range of VO_{2max} change was 0–100% in persons aged 17–29 years and 0–58% in persons aged 60–71 years. Indeed, no change compared to a two-fold increase is quite a dramatic difference in response to the same exercise stimulus. Likewise, Hubal and colleagues (Hubal, et al, 2005) previously reported that among 585 individuals who performed 12 weeks of progressive resistance training, maximal strength of the elbow flexors increased between 0–250% with significant variation existing among both males and females. This variability has been explored by some in recent years by categorizing individuals as either “responders” or “non-responders” to an exercise training program, although more appropriate terminology – i.e. “high- and low-sensitivity” – has been proposed.(Booth and Laye, 2010) This distinction is important because the responder/non-responder nomenclature may be misleading; since, for any given physiological construct, responses to exercise are likely not binary but rather graded in nature.(Sisson, et al, 2009) Moreover, these responses likely depend on multiple factors including the chosen outcomes, study population, and exercise stimulus (i.e. mode, frequency, duration, etc.)

¹It should be noted here that we are largely referring to heterogeneity that exists despite similar levels of adherence to a given training regimen. While poor adherence is a well-known factor in determining exercise responsiveness, our brief discussion here will focus more on more nascent areas of research.

While descriptive data such as these are important, they are merely a first step. These data identify the fact that variability exists in physiological responses to exercise, but the evidence available for making exercise prescriptions personalized remains insufficient. To date, few studies have been conducted with the express purpose of identifying the factors responsible for variability in exercise responses. To the authors' knowledge, only two studies to date – the HERITAGE family study (Bouchard, et al, 1995) and the FAMuSS (Functional single nucleotide polymorphisms associated with muscle size and strength) study – have been conducted with the express purpose of broadly and comprehensively addressing the causes of heterogeneity in responsiveness to exercise training. (Thompson, et al, 2004) These studies and many other candidate gene studies have provided key data regarding the genomic contribution to exercise responsiveness. However, two key components of personalized medicine remain relatively unexplored.

First, future studies are needed which employ outcome measures that can be utilized clinically. This approach is critical to increasing physician involvement in the prescription of exercise programs. Certainly the chosen outcomes will depend on each study's given hypothesis and design, but the goal should be to consider outcomes that are both predictive of adverse health outcomes and feasible in a clinic setting. For example, Cleveland recently called for walking speed to be utilized as a screening tool for older patients going into cardiac surgery due to its high prognostic capacity, high reproducibility, and extraordinary cost-effectiveness. (Cleveland, 2010) Second, data are still lacking regarding the contribution of phenotypic characteristics such as body composition, disease status, and medication usage to training adaptations. These factors are each an important component of the exposome, a concept defined as the measure of all exposures of an individual in a lifetime and how those exposures relate to health.² Indeed, a more comprehensive understanding of how one's unique characteristics interact with their unique environment would greatly contribute to research in this area. Subsequently, the need for exquisitely detailed phenotyping is just as, if not more, important than obtaining large-scale genetic data. (Bilder, et al, 2009)

Intervention development

However, the identification of sources of variability is only one step in moving the field toward a meaningful change in practice (Figure 1). The primary aim of personalized medicine is to develop and tailor interventions to treat an individual or population subgroup in the most appropriate manner. Thus any data gathered regarding sources of variability in exercise responsiveness should be used to identify alternative and/or adjuvant therapies appropriate depending on the targeted patient(s) and intended outcome. Potential adjuvant therapies include nutritional, pharmaceutical, and manual therapies (e.g. massage or intermittent compression) that could maximize the benefit of exercise to members of a particular subgroup. In a recent editorial related to exercise training in heart failure patients, Kitzman highlighted the potential utility of a multimodal approach stating that “research studies that strive to isolate the effects of exercise training alone likely underestimate the full range of potential benefits.” (Kitzman, 2011) Randomized controlled trials support this point by showing that dietary restriction significantly enhances the effects of exercise on the physical function of obese and overweight older adults. (Villareal, et al, 2011, Messier, et al, 2004, Anton, et al, 2011, Rejeski, et al, 2011) These studies highlight the potential synergistic effects of multimodal interventions. Notably, these particular interventions were tailored specifically for older adults who are obese as dietary restriction is contraindicated for non-obese seniors. (Miller and Wolfe, 2008) It should be noted that several other examples exist to highlight the potential utility of such tailored, multi-modal interventions, but a comprehensive review is beyond the editorial limits of this commentary.

²See (<http://www.cdc.gov/niosh/topics/exposome/>)

Moving forward

Studies of personalized medicine published to date have been primarily concerned with understanding heterogeneity in drug responsiveness. However – it is, in the opinion of the authors, time to begin considering preventive strategies such as exercise within a broader scope of personalized care. To achieve this goal, more information is needed regarding the source of heterogeneity in responses to exercise. Such knowledge will assist in identifying potentially efficacious adjuvants for particular population sub-groups. Large long-term randomized controlled trials, such as the ongoing LIFE Study,(Fielding, et al, 2011) will have sufficient power and scope to identify the phenotypic, genotypic, health-related, environmental and behavioral factors that may enhance the effects of exercise. Furthermore, a broader physiological understanding of factors influencing responses to exercise will inform the conduct of clinical trials designed to test these strategies and increase their probability of success. We look forward to seeing personalized strategies being applied to preventive health interventions such that the field of personalized medicine may expand beyond pharmacogenomics. However, extensive future research is needed to make this vision a reality.

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Highlights

- Research regarding personalized medicine should extend beyond pharmacogenomics
- Preventive health strategies, e.g. exercise, need to be more personalized
- Improved understanding is needed regarding variability in exercise responsiveness
- Multi-modal interventions are needed to maximize benefits of exercise

Figure 1.
Opportunities for moving exercise-related research toward personalized medicine.