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on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Clinical Cardiology, and Council on Nutrition, Physical Activity and Metabolism

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The Importance of Cardiorespiratory Fitness in the United States: The Need for a National Registry A Policy Statement From the American Heart Association

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Association Advocacy Coordinating Committee, Council on Clinical Cardiology, and Council
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The recent 2012 update of the Heart Disease and Stroke Statistics from the American Heart Association (AHA) emphasizes the continuing burden of cardiovascular disease (CVD) in the United States, with a prevalence of CVD nearing 40% in those approaching 60 years of age and exceeding 70% in older ages.¹ Direct and indirect costs of CVD in the United States exceeded \$300 billion in 2008, and the projected total costs of CVD in 2015 and 2030 are more than \$500 billion and nearly \$1200 billion, respectively.² Recently, the AHA developed year 2020 impact goals to achieve ideal cardiovascular health, which is influenced greatly by key health behaviors of being physically active, maintaining appropriate dietary habits, and not smoking.³ The obesity epidemic in the United States has been a substantial contributor to the CVD burden, with current estimates of obesity prevalence being ≈20% in US children and adolescents and >33% in adults 20 to 74 years of age. It is well accepted that for most people, obesity is a direct outcome of an energy-rich diet, lack of sufficient physical activity (PA), or both. Another consequence of both obesity and insufficient PA is a reduction in cardiorespiratory (or aerobic) fitness (CRF) levels. Collectively, this evidence emphasizes that an individual's health behaviors have a major role in the prevention of CVD, which is of critical importance in the United States and worldwide from a medical and economic perspective.

Increasing attention is being given to the importance of PA and physical fitness (PF), both muscular fitness and especially

CRF, for decreasing chronic diseases, promoting overall cardiovascular and general health, improving quality of life, and delaying CVD and mortality in the US population.^{4,5} Clearly, PF and CRF in particular are an underpinning for academic achievement, job productivity, and overall maintenance of cardiovascular and general health, among other things.^{6,7}

Given the staggering physical burden of CVD, considerable attention has been directed at the major risk factors for CVD, particularly coronary heart disease (CHD), including inadequate PA, obesity, hypertension, dyslipidemia, and smoking, as well as type 2 diabetes mellitus.¹ Although substantial efforts have been directed at eliminating or reducing these CVD risk factors, the importance of CRF has often been neglected in the equation of major CHD and CVD risk, despite the fact that it appears to be one of the most important correlates of overall health status and a potent predictor of an individual's future risk of CVD.^{4,7} Besides being perhaps the strongest predictor for CVD and total mortality,^{4,6-9} CRF is also strongly associated with other important health and functional outcomes, including depression and dementia, and their related mortality risks,¹⁰⁻¹³ as well as mortality rates attributable to various cancers, especially of the breast and colon/digestive tract.^{14,15}

Although CRF is recognized as an important marker of both functional ability and cardiovascular health, it is currently the only major risk factor that is not routinely and regularly assessed in either the general or specialized clinical

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setting. Health behaviors and risk factors believed to be most important have been documented and tracked through federally funded programs (eg, the National Health and Nutrition Examination Survey [NHANES]); however, the acquisition of data regarding CRF has been relatively weak and extremely limited. Given the importance of CRF, a compelling need exists to better define both normative and criterion-based CRF standards.

Currently, there is no formal multicenter CRF database that provides a sufficiently representative sample of the US population that can be used to accurately interpret CRF measures. The largest and most commonly used reference set for CRF classification is from the Cooper Institute (Dallas, TX), which began in approximately 1970 and includes data relating to $\approx 45\,000$ men and 15 000 women.¹⁶ From these data, CRF appears to be one of the strongest risk factors for CVD and all-cause mortality, and high levels of CRF largely negate the adverse effects of traditional CHD risk factors, even in patients with multiple CHD risk factors (ie, overweightness/obesity, metabolic syndrome/type 2 diabetes mellitus, and hypertension).^{17–23} In most circumstances, patients with these major CHD risk factors and high CRF have lower mortality than patients without these CHD risk factors but with low CRF. In addition, an individual's decline in CRF level predicted the development of hypertension, hypercholesterolemia, and metabolic syndrome,²⁴ as well as all-cause and CVD mortality, in the Aerobics Center Longitudinal Study cohort.²⁵ Although this data set has contributed a wealth of research findings demonstrating the importance of CRF, there are a number of factors that limit its broader use. These limitations include the relatively small sample size; the homogeneity of the patient population studied, with patients being predominately non-Hispanic whites, well-educated, and middle- to upper-class; and the use of predicted metabolic equivalents (METs) from treadmill time, speed, and grade as opposed to direct measurement through ventilatory expired gases. Additionally, the current Cooper Institute data, as published in the American College of Sports Medicine guidelines,¹⁶ do not provide information regarding differences related to body composition or other commonly available clinical measures. Thus, there is a compelling need for a national CRF database with an increased sample size; more diverse characteristics, including populations from various regions, ethnicities, racial backgrounds, socioeconomic classes, educational backgrounds, and cultural diversity; and a more robust group of ancillary exercise test variables.

The purpose of the present policy statement is to outline the importance of broadening the assessment of CRF and to provide the rationale for the development of a national adult CRF registry that would be representative of the entire US population. Additionally, this statement will outline how a national CRF database could enhance the value of CRF assessment in the US population and across environments, including the clinical setting and the workplace, as well as in the general public, to better inform our national policy efforts on PA, fitness, and health.

Importance of CRF

Over the past 2 decades, a considerable amount of data has been published demonstrating the importance of CRF in predicting risk for adverse health outcomes.^{4,26,27} In some of these

studies, CRF was a stronger predictor of adverse outcomes than traditional risk factors such as hypertension, smoking, obesity, hyperlipidemia, and type 2 diabetes mellitus. In addition, CRF has been shown to be a more powerful predictor of risk than other exercise test variables, including ST-segment depression, symptoms, and hemodynamic responses,^{9,28–32} a fact not broadly appreciated by the clinical medical community.^{33,34} Moreover, the lower levels of CRF in these studies did not appear to be associated with subclinical disease. A number of recent studies have expressed CRF in the context of survival benefit per MET; each 1-MET increase (a relatively small increment achievable by most individuals) is associated with large (10%–25%) improvements in survival. Despite these observations, the importance of CRF in the risk paradigm has historically received inadequate attention in cardiovascular medicine because of the tendency to focus on the ST segment and the potential need for revascularization.^{34,35}

Blair et al¹⁷ performed a seminal study with the Aerobics Center Longitudinal Study cohort in which CRF was assessed by treadmill performance in $>13\,000$ asymptomatic subjects who were followed up for 110 482 person-years (an average of >8 years per subject) for all-cause mortality. Age-adjusted mortality rates were lowest (18.6 per 10 000 person-years) among the most fit men and highest (64.0 per 10 000 person-years) among the least fit men, with the corresponding rates among women being 8.5 and 39.5 per 10 000 person-years, respectively. These findings closely parallel an earlier report among asymptomatic men from the Lipid Research Clinics Mortality Follow-Up,³⁶ in which each 2–standard deviation decrement in CRF was associated with a 2- to 5-fold higher rate of CVD or all-cause death. More recent studies, including one from the Lipid Research Clinics, have substantiated these findings in women with no evidence of CVD at the time of evaluation.^{8,31} Gulati et al⁸ suggested that the strength of CRF in predicting risk of mortality was even greater among women than men, reporting a 17% reduction in risk for every 1-MET increase in fitness. In the Lipid Research Clinics trial, ≈ 3000 asymptomatic women underwent exercise testing and were followed up for up to 20 years.³¹ A 20% reduction in mortality attributable to cardiovascular causes was observed for every 1-MET increase in exercise capacity. This study also pointed out the relative weakness of ischemic electrocardiography responses in predicting CVD and all-cause mortality among women, similar to what had been reported among men.^{9,37}

Over the past decade, this issue has also been addressed in numerous clinical populations, most often in patients referred for exercise testing for clinical reasons.^{4,9,30,32} In a study performed among US veterans, 6213 men underwent maximal exercise testing for clinical reasons and were followed up for a mean of 6.2 years.⁹ The subjects were classified into 5 categories by gradients of CRF. Among both normal subjects and those with CVD, the least fit individuals had >4 times the risk of all-cause mortality compared with those with the highest level of CRF. Importantly, an individual's CRF level was a stronger predictor of mortality than the more traditional risk factors, including smoking, hypertension, high cholesterol, and type 2 diabetes mellitus. These observations were more recently confirmed in a cohort of $>15\,000$ veterans stratified by race.³² Other populations of clinically referred subjects,

including those from the Cleveland Clinic,³⁰ Mayo Clinic,^{28,29} and Toronto Rehabilitation Institute,^{38,39} have documented the importance of CRF as a predictor of mortality, demonstrating survival benefits in the range of 15% to 35% per MET achieved. The strength of the association between CRF and both CVD and all-cause mortality was recently underscored in an eloquent meta-analysis by Kodama et al.⁴ Data were extracted from 33 studies and nearly 103 000 participants. Compared with subjects in the high CRF tertile, those with low fitness had a 70% higher risk for all-cause mortality and a 56% higher risk for CVD mortality. Across all studies, 13% and 15% reductions in CVD and all-cause mortality, respectively, were observed per MET achieved.

An important and consistent finding in these studies is the fact that the greatest health outcome benefits are observed between the least fit and the next least fit group; lesser improvements in health outcomes occur between individuals who are in the moderate- to high-fit groups. Stated differently, the health benefits of CRF are most evident in the low end of the CRF spectrum. Most often these studies have categorized subjects by quintiles, but this nonlinear gradient has been observed in studies that expressed the data in a wide range of categories. This finding has been influential for national and international guidelines on PA and health, in that relatively small improvements in CRF have a major impact on health outcomes, particularly among low-fit individuals. Because PA plays a significant contributory role in enhancing CRF, modest amounts of PA that might lead to improved CRF among the most unfit individuals potentially have the greatest impact on public health. The widely recognized recommendation that all adults should perform a minimum of 150 minutes of moderate intensity PA per week or 75 minutes of vigorous intensity PA per week^{40,41} stems in part from the view that this relatively small amount of PA may improve CRF modestly and therefore strongly impact morbidity and mortality.

CRF has also been demonstrated to be an important marker of functional limitations and frailty. This is an important issue because functional capabilities and frailty are related to an individual's quality of life during the extended longevity that may result from higher CRF, and they have major implications for disability, increased dependency, and hemorrhaging healthcare costs. Functional limitations are defined by the inability to perform normal daily tasks.⁴² Difficulty walking, climbing stairs, and performing household tasks are all hallmarks of functional decline.^{43,44} Frailty is usually quantified by the degree of impairment in functional reserve across multiple organ systems and is often associated with fatigue, reduced muscle strength, and high susceptibility to disease.⁴⁵ Elderly individuals who are relatively fit or physically active have a significantly lower risk of functional loss during follow-up periods ranging from 5 to 30 years,⁴⁶⁻⁴⁸ and among more active individuals, disability is delayed and compressed into fewer years at end of life.⁴⁸ Frailty status, determined by a composite criterion that includes walking speed, grip strength, low PA level, weight loss, and fatigue, is inversely related to CRF and other physiological responses to exercise.⁴⁹ Although direct measures of CRF from exercise testing in this context are comparatively sparse, surrogate measures of PF have been

demonstrated to be important markers of functional limitations, disability, and frailty in the elderly. Higher PF scores predict lower mortality and lower rates of frailty and reliance on healthcare services at all age levels.^{50,51} Numerous studies have demonstrated frailty to be an independent risk factor for all-cause mortality, adverse postoperative events, hospitalization, and other outcomes.⁵⁰⁻⁵⁶ Performance on a 6-minute walk test is strongly and inversely related to frailty.⁵⁷ The 6-minute walk test and similar walking tests are associated with multiple domains of physical function and outcomes in the elderly and patients with CVD.⁵⁷⁻⁶⁰ These results strongly suggest that in addition to improved survival, higher CRF is related to better health and physical function in elderly individuals. In addition to enhanced CRF, improving functional status and attenuating frailty are important objectives for the application of exercise therapy.

The value of CRF in estimating risk has reinvigorated the clinical value of exercise testing, which has been used less frequently in recent years in favor of more technological diagnostic imaging procedures. In addition to being a strong predictor of mortality in both asymptomatic and clinically referred populations, CRF level has been shown to be useful in predicting outcomes in the perioperative evaluation of patients undergoing bypass surgery,⁶¹ abdominal aortic aneurysm repair,^{62,63} bariatric surgery,⁶⁴ and other surgical interventions.^{65,66} Higher CRF predicts lower mortality and lower rates of frailty and reliance on healthcare services at all age levels.⁵⁰ There is direct and growing evidence that an improvement in CRF over time has a considerable effect on lowering mortality.^{18,24,32} These studies have promoted calls for the assessment of CRF more routinely for a broad range of conditions.^{6,67-69} Low CRF is a poorly appreciated but exceedingly important risk factor that is modifiable without reliance on further diagnostic or costly therapeutic interventions. Simple adherence to some basic and widely available evidence-based tenets on PA will improve CRF in most individuals.^{40,41} To optimize the value and usefulness of CRF, there is a need to have standards to clearly define levels of CRF that are associated with poor health outcomes for the entire US population.

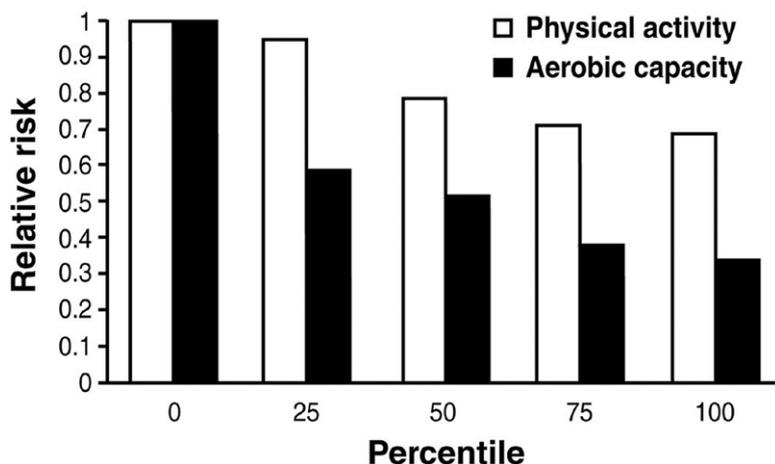
PF Versus PA Assessment

Although levels of both PA and CRF are inversely associated with risk of CVD, there are many important differences between these measures both in terms of assessment and in terms of association with CVD and prognosis. PA is a behavior that when performed with regularity and requisite quality results in improvement or maintenance of PF. This has been well documented in numerous cross-sectional studies that have reported a direct association between the amount of regular PA and level of CRF, as well as the many exercise training trials that have definitively shown that increasing the amount (volume) of weekly PA or the quality (intensity) of PA improves CRF.^{70,71} However, there are many other factors that contribute to CRF level other than PA. For example, men have higher levels of CRF than women, CRF decreases with age, and non-Hispanic whites have been reported to have higher CRF levels than non-Hispanic blacks.^{72,73} CRF also has a strong genetic contribution, which is important in terms of baseline CRF

level and the magnitude of the training response to a given level of PA.⁷⁴⁻⁷⁶

The concept that CRF represents more than PA habits alone has been supported by a series of outstanding reports of studies that used rats bred for either low or high running capacity (ie, low or high CRF). Koch, Britton, and colleagues reported low-fit rats to have higher blood pressures, visceral adiposity, fasting glucose, insulin, triglycerides, and free fatty acids levels. In contrast, rats with high CRF had considerably higher levels of maximal oxygen consumption ($\dot{V}O_{2max}$), skeletal muscle oxidative enzyme capacity, and proteins such as peroxisome proliferator-activated receptor- γ coactivator 1- α (PGC-1 α), known to be integral to mitochondrial content and function.⁷⁴⁻⁷⁶ The authors suggested that these “observations support the notion that impaired regulation of oxidative pathways in mitochondria may be the common factor linking reduced total-body CRF to CV and metabolic risk.” Collectively, animal and human data suggest that CRF is a reflection of overall physiological health and function, especially the cardiovascular system. As a result, it should come as no surprise that CRF is a powerful predictor of premature morbidity and mortality, because poor CRF may represent the early physiological manifestation of these conditions. Thus, although CRF is related to PA, it clearly has a strong physiological basis.

PA assessment is commonly performed by relatively simple and inexpensive self-report instruments, which unfortunately are prone to considerable measurement error.⁷⁷ In addition, there are multiple PA variables (energy expenditure, different intensity levels, etc), with each representing a different behavior, which leaves the clinical importance of each measure subject to debate. Conversely, quantification of CRF has substantially lower measurement error and is highly reproducible. In addition, CRF can be measured directly and accurately as level of $\dot{V}O_2$ (typically expressed in mL O₂·kg⁻¹·min⁻¹) achieved, which has direct clinical utility as noted above. The most important difference between CRF and PA is seen in the magnitude of CVD benefit across exposure categories. When CRF and PA are compared directly, the prognostic outlook across levels of the former are steeper than those observed across levels of the latter (Figure). Thus, CRF provides a more clinically meaningful prognostic measure than PA.



Proposed Plan to Develop a National CRF Registry

Goals of the Registry

There is a compelling need for a better understanding of normative CRF levels in the US population. To address this issue, this policy article proposes the development of a national CRF registry that would have 5 major goals:

1. The registry will determine normative adult CRF levels, via direct $\dot{V}O_2$ measurement, in groups subdivided by age, sex, and body composition in a large and representative sample of the US population. CRF levels are known to decline with aging, and this is mediated in part by a decreasing peak heart rate associated with the aging process.⁷⁸ CRF levels are also lower in women than in men, and this is mediated in part by lower hemoglobin concentrations, smaller heart sizes, and lower stroke volume. CRF levels are also generally higher in individuals with greater lean body mass and with a greater proportion of slow-twitch muscle fibers. As the population becomes increasingly older and because the prevalence of overweight/obese has increased, understanding CRF norms in age, sex, and body composition subgroups will become increasingly important. With greater understanding of norms by age, sex, and body composition, we can begin separating anticipated subgroup-related differences in CRF levels from those related to disease.
2. The registry will help determine normative CRF levels based on other demographics such as race and socioeconomic status. Minorities and individuals of low socioeconomic status have been inadequately represented in previous investigations assessing CRF levels. It remains unclear whether there are race/ethnicity-related differences in normative CRF levels.^{72,73} Also, disparities in the prevalence of CVD exist across race and socioeconomic strata, and these disparities may be mediated by disparities in CRF levels. As a result, greater understanding of normative CRF levels may have important implications for reducing disparities in cardiovascular health and disease across race and socioeconomic strata.
3. The registry will help define norms for CRF levels across strata of PA levels. Although PA is intimately linked to CRF, and both are important and related parameters in

Figure. The risks of coronary heart disease and cardiovascular disease decrease linearly in association with increasing percentiles of physical activity. In contrast, there is a precipitous decrease in risk when the lowest is compared with the next-lowest category of aerobic capacity. Beyond this demarcation, the reductions in risk parallel those observed with increasing physical activity but are essentially twice as great for aerobic capacity (cardiorespiratory fitness). Adapted from Williams⁷⁷ with permission of the publisher. Copyright © 2001, the American College of Sports Medicine.

cardiovascular health and disease, as noted above, they do not completely share the same pathways to health and disease and have independent contributions to health outcomes. Indeed, there is considerable variability in an individual's response to standardized and equivalent exercise training programs.⁷⁹ Thus, the same amount of PA can lead to different levels of CRF, which is potentially mediated by differences in genetics and varied environmental modulators. In addition, although CRF is an index of PA in apparently healthy individuals, it may also be affected by subclinical disease. With greater understanding of normative CRF values by PA strata, the associations between these measures of PF will become better understood, leading to improved strategies for exercise prescription on a population level.

4. The registry will help determine normative values of many other non-CRF physiological parameters obtained from cardiopulmonary exercise testing (CPX). Physiological parameters such as exercise blood pressure and heart rate recovery have been shown to provide added prognostic information to CRF levels.⁶⁹ It is possible that other measures routinely assessed during exercise tests could likewise provide additional prognostic information.⁸⁰ In addition, normative standards for estimations of CRF via predicted METs can also be performed and compared with directly measured $\dot{V}O_2$ data, via ventilatory expired gas, at peak/maximal exercise. Previously published regression formulas can be revised to provide more accurate estimations of CRF. Many of these existing regression formulas for prediction of CRF were derived from specific treadmill or cycle ergometer protocols. There is a need for regression formulas that account for the diversity of testing protocols used in practice. Although the protocol is of importance in determining CRF levels, it is of less importance when metabolic testing is available for direct measurement of CRF.⁸⁰ Understanding the normative values for these physiological parameters will have important implications in the interpretation of non-CRF exercise testing parameters.
5. This registry will help serve as a tracking device for CRF levels in the US population, complementing present PA surveillance systems, which lack robustness. NHANES uses estimations of CRF as opposed to direct measurements of CRF. As more public health campaigns are introduced to promote PA and CRF, surveillance programs such as these will provide a metric of their effectiveness. Moreover, surveillance programs will identify worrisome trends in the general population and high-risk subgroups that may prompt action by policy makers on this important factor in cardiovascular health and disease.

Phase I: Establishment of the CRF Registry

Phase I of the development of the CRF registry should be able to be accomplished in 1 year. This will begin with the establishment of an advisory board (AB). The members of the AB will conduct both the development and ongoing operation of the CRF registry. The AB would be composed of ≈ 10 experts from the fields of CVD, pulmonology, public health, and exercise physiology from academic institutions/medical centers that routinely measure CRF for clinical and/or research applications. At least 1 AB member will also have previous

experience with secondary database management. The AB would meet annually at an annual scientific conference, such as the AHA Scientific Sessions, and at least quarterly by conference call to provide necessary support to these initial objectives. The roles of the AB would initially be the following:

1. To establish a CRF registry office.
2. To define inclusion and exclusion criteria for the registry.
3. To determine the specific variables to be included in the registry, with regard to both the descriptive characteristics of the individuals and the CPX variables to be included (including both peak and submaximal exercise measures). If data are available, participating centers will also be encouraged to enter adverse event data (ie, hospitalizations and deaths). An initial list of proposed variables that will be collected is presented in the Table. Please note that this proposed list may expand or retract after the AB is established and phase I of this project is implemented.
4. To develop and oversee data use agreements for participating centers.
5. To develop criteria for validation of centers that will be contributing to the registry and the procedures necessary to ensure strict quality control over data submission and inclusion.
6. To develop procedures for data input, storage, and backup.
7. To recruit 5 to 10 well-established centers, experienced in CPX, in which databases already exist, to provide an appropriate geographic representation of the United States that would include a reasonably diverse set of individuals (eg, with respect to age, sex, CRF levels, ethnicity, and health history). Each of the centers will be responsible for completing data use agreements with the CRF registry, obtaining local institutional review board approval for registry participation, deidentifying data before registry upload, and ensuring compliance with Health Insurance Portability and Accountability Act (HIPAA). Documentation of institutional review board approval and HIPAA compliance will be sent to the AB.
8. To provide preliminary assessment of data (ie, means, ranges, and variability), scan for database entry errors (both manually and by use of smart-check software applications), and initiate/edit publications generated from the CRF registry.

The data necessary for this CRF registry already exist, and, as such, we anticipate each of the phase I centers will be able to contribute $>10\,000$ test files. However, the necessary coordination and management of a pooled national database are currently lacking.

Phase II: Expansion of the CRF Registry

Phase II will focus on expansion, primarily developing and implementing processes for other centers to contribute data to the CRF registry and establishing a CPX core laboratory. For the database to grow and capture an even greater representative sample of the US population, other centers across the country will be solicited via an advertised call for data in journals of the AHA. It is the opinion of this writing group that a 2-phased approach, as opposed to an open call for all

Table. Initial Proposed List of Baseline, CPX, and Outcome Variables That Will Be Collected for the Registry

Category	Variable	Significance
Baseline characteristics	Age	Allows for key exercise variables to be analyzed in the context of unique subgroup characteristics; further refining the ability to describe and analyze fitness characteristics of the US population
	Sex	
	Height and weight – BMI	
	CVD risk factors	
	Comorbidities/diagnoses	
	Resting heart rate and blood pressure	
	Geographic location	
	Race/ethnicity	
CPX variables	Physical activity profile	Primary CPX variable used to characterize aerobic capacity trends in the US population
	Peak $\dot{V}O_2$	
	$\dot{V}O_2$ at VT	
	Peak RER	
	$\dot{V}E/\dot{V}CO_2$ slope	
	Rest and exercise $P_{Et}CO_2$	
	Heart rate and blood pressure response during exercise and recovery	
	Exercise test protocol, test time, and peak workload obtained	
	$\dot{V}E$, RR, V_T	
	RPE	
Outcomes data	ECG response to exercise	Allows for determination of the frequency and type of ECG abnormalities during CPX
	Adverse events during CPX	Allows for characterization of the safety of CPX and identification of variables/ characteristics that indicate increased risk
	Hospitalization and mortality	Allows for ability to further examine the prognostic characteristics of CPX variables

CPX indicates cardiopulmonary exercise test; BMI, body mass index; CVD, cardiovascular disease; $\dot{V}O_2$, oxygen consumption; VT, ventilatory threshold; RER, respiratory exchange ratio; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production; $P_{Et}CO_2$, partial pressure of end-tidal carbon dioxide production; MET, metabolic equivalent; RR, respiratory rate; \dot{V}_T , tidal volume; RPE, rating of perceived exertion; and ECG, electrocardiogram.

interested facilities to participate during phase I, is essential to initially establish a rigorous, high-quality data collection process. Such an approach will ultimately serve to improve the reliability, validity, and clinical applicability of the data collected.

The criteria for data inclusion and procedures for submission used in phase I will be revised as necessary to facilitate expansion of the database. We envision procedures/requirements for additional centers to provide data to the CRF registry may include the following: (1) Facilities that are interesting in sharing their data would be asked to initially submit background information and answer a series of standardized questions about their data collection procedures and complete a data reliability assessment with the CPX core laboratory. (2) The CRF registry AB would review the application packet and would determine whether the data are acceptable for inclusion in the registry. (3) Once a facility is approved to upload their data to the CRF registry, a core guidance document will be provided. This document will enable the new registry sites to directly upload data in a manner consistent

with the established protocol. Through this process, data entry errors can be avoided. Within this guidance document, there will be an established glossary of terms and a data dictionary. To aggregate data from different laboratories or clinics to facilitate analysis, data must be captured and collected in a standardized manner. Additionally, a coding system will be developed to document acceptable variation in data collection (eg, protocol, metabolic measurement system). Thus, the use of common data elements will facilitate the standardization of data collection and allow for harmonization, sharing, and exchange of information within registry contributors. The CRF registry office will establish a minimal set of common data elements that will be required from any participating facility. Additionally, a system of checks, to be completed by the new registry site, must be established to ensure data validation (ie, normal ranges). Approved registry sites will have also have access to phone and internet support if questions arise or guidance is needed as the data are being prepared for submission. (4) Once an approved registry site has prepared its deidentified data for submission and documentation of institutional

review board approval and HIPAA compliance has been sent to the AB, a process will be in place to have the data uploaded through a secure server with an emailed password. (5) After successful submission, the data will be inspected by the CPX core laboratory before being added to the main CRF registry.

Data ultimately included in the CRF registry will be stored electronically in a secure database managed by the CRF registry office as directed by the CRF registry AB. The overall data will be accessible by all registry contributors in the form of tables and downloadable spreadsheets. No patient identifiers will be stored within the CRF registry data.

The writing group considers it likely that the CRF registry data will eventually be publically accessible to approved researchers. Ultimately, the goal of any such data registry is to facilitate communication, assist in ongoing research, and provide data to clinical researchers on a larger scale than any individual researcher or research team can establish alone. Any research group wishing to use collective data will have to submit a formal written request to the CRF registry AB for review. A standardized written application process for data analysis will be established by the CRF registry AB.

Potential Immediate Utility of the CRF Registry

The writing group anticipates that once established, the CRF registry would provide immediate value on a number of fronts. As mentioned previously, a registry that captures CRF patterns on a national level is not currently available in the United States. Therefore, once the CRF registry is established, reporting CRF means according to age, sex, body composition, geographic location, and race/ethnicity, among other variables, will be the first priority and viewed as an objective that can be accomplished rapidly. The AHA publishes CVD and stroke statistical updates on a yearly basis, incorporating data on PA patterns from NHANES.¹ Once established, CRF registry data could likewise be incorporated into the annual AHA statistical update, providing the clinical and research communities, as well as policy makers and the general public, with important information about CRF and related clinical measures in the US population. This would include a more thorough ability to study population changes in CRF over longer time periods than is currently possible.⁸¹ Given that strong data already exist to demonstrate that CRF is a more potent measure of health and prognosis than PA patterns,⁷⁷ the inclusion of the former measure in the AHA CVD and stroke statistical update would be considered a highly valuable and immediate benefit of this CRF registry. As specific examples, normative CRF data generated from the registry can immediately be used by the following groups: (1) Worksites for their health promotion initiatives; (2) clinical sites currently performing CPX, to accurately interpret patients' CRF; and (3) groups responsible for public health policy initiatives to raise population awareness regarding the importance of improving CRF.

Currently, normative CRF data are either reported as a percentile range (eg, 10th to 90th percentile)¹⁶ or are based on a specific percent-predicted value using one of several available prediction equations.^{82,83} Currently available prediction equations were developed for the most part with the use of relatively small data sets and have a limited number of predictor variables. Thus, an additional and immediate potential utility of the proposed CRF registry is to explore the development

of new CRF regression equations derived from a large and diverse cohort, which would allow for the assessment of a significantly greater number of potential predictor variables. The rapid development and dissemination of this type of regression equation would obviously have immediate applicability in the clinical, research, and public health arenas.

Use of the Proposed CRF Registry for Future Research and Policy Initiatives

We anticipate that the proposed CRF registry, once established, will immediately create the ability to address clinically relevant research questions and provide much needed information on CRF patterns to the public health arena. Moreover, once the proposed adult CRF registry is established, the expectation of this writing group is that it will serve as a catalyst for new research endeavors and public policy initiatives. Several proposed directions for future endeavors are described below.

Arena et al⁶⁹ present compelling evidence supporting the concept of CRF as a vital sign in clinical practice. Although not commonly performed, there is a growing body of evidence that aerobic exercise testing needs to be extended as a primary prevention assessment.^{8,9,31,84,85} Kodama et al⁴ suggest that future research needs to further develop a CVD prediction algorithm that includes CRF parameters, and they suggest that physicians could incorporate CRF assessments in the risk factor profiles of their patients in clinical settings. Such assessment would not necessarily need to be conducted by physicians. Previous research has demonstrated appropriately trained nonphysician health professionals, with physician proximity, can conduct the CRF assessment in a safe and effective manner.^{86,87} Research to gauge the value of CRF assessment in the primary care setting is needed to determine whether population-level fitness screening has a measurable impact that influences policy makers. Additionally, future research will need to address the cost-benefit ratio of this type of screening. The proposed CRF registry can be a valuable resource in this area of research by providing a comprehensive resource of CRF values representative of the entire US population.

The hope of this writing group is that the adult CRF registry we are proposing herein will also serve as a template for the development of a pediatric CRF registry in the future. Although the National Association for Sport and Physical Education recommends that schools should require daily physical education for students in kindergarten through 12th grade, only 33.3% of students attend physical education classes in schools.⁸⁸ Moreover, the proportion of students who met activity recommendations of ≥ 60 minutes of PA on ≥ 5 days of the week was 37% nationally and declined from 9th to 12th grade, and at each grade level, the proportion was higher in boys than in girls.⁸⁸ These declines in PA are likely paralleled by reductions in CRF in the pediatric US population. Furthermore, directly measured CRF likely provides more accurate health information than self-reported PA in children.

Another potential endeavor for the proposed CRF registry is expansion of national surveillance of CRF in all Americans. The Department of Health and Human Services is viewed as a key partner in this effort. The mission of the Department of Health and Human Services is to protect the health of

and provide essential health services to all Americans. The Department of Health and Human Services is already responsible for funding and conducting numerous surveillance efforts and is thus in a position to bring together stakeholders from both the public and private sectors. Therefore, the Department of Health and Human Services, and specifically the Centers for Disease Control and Prevention, is viewed as a key partner for the expansion of the national surveillance of CRF in all Americans. It will be essential to select fitness surveillance indicators and develop data sets for surveillance sources that can be made broadly accessible to a variety of users, such as public health agencies, health systems, researchers, and policy makers. There is a great potential for the use of electronic health records as a source of surveillance information. The proposed CRF registry may help to facilitate new Department of Health and Human Services initiatives centered on CRF.

Improved population health is the ultimate goal of surveillance; thus, risk factors, including CRF, need to be tracked with an increased emphasis on data from individuals of diverse races and ethnicities. Physical inactivity is disproportionately prevalent in non-Hispanic blacks, Hispanics/Latinos, American Indians, and Pacific Islanders compared with non-Hispanic whites.¹ The inability of current models, which lack CRF data, to explain ethnic and racial disparities in CVD underscores the need for heightened efforts to examine the novel biobehavioral and environmental factors that contribute to adverse outcomes in these subgroups. Additional research is essential to determine effective methods for reaching underserved populations and optimize fitness interventions for individuals of diverse races, ages, ethnicities, and socioeconomic statuses. Concerted efforts at the national and local policy levels are needed, including development of the necessary linkages among diverse sources of data and of methods to use data in a dynamic manner to effect public health policy decisions. A national CRF registry that sufficiently captures diverse races and ethnicities would help further analyze CRF disparities and assist in shaping future healthcare initiatives directed at improving CRF in the most unfit populations.

Finally, it is clear that the importance of CRF to health and longevity is not unique to the US population. The proposed national CRF registry for the United States may be used as a foundation to ultimately create an international CRF registry in the near future. An international collaboration of this nature could have significant implications for how health is quantified and addressed on a global scale.

Conclusions

The incidence and prevalence of CVD, as well as its associated direct and indirect healthcare costs, justify the significant ongoing efforts directed toward preventing, identifying, and treating this condition. Guidelines and recommendations for traditional CVD risk factors are widely available, as are clinically relevant threshold values for hypertension, cholesterol and its subfractions, overweight/obesity, and impaired fasting glucose.^{16,89} Although the body of evidence that demonstrates that increasing the level of CRF significantly reduces the risk of CVD and dramatically improves prognosis is overwhelming, national surveillance data, guidelines, and recommendations similar to those available for the aforementioned traditional CVD risk factors do not currently exist for this important health metric. Although CRF is often interpreted via normative values reported by the Cooper Institute on a selected, relatively small ($\approx 45\,000$ men and $\approx 15\,000$ women) homogeneous "membership," there are numerous limitations in extrapolating these estimated CRF data, based on the attained treadmill speed, grade, and duration, to a regionally, racially, ethnically, and socioeconomically diverse US population of varied body habitus. The development of a national CRF registry that uses directly measured Vo_2 during exercise testing in well-established centers throughout the United States is essential to the establishment of valid normative values for the population, which can be used in the research, clinical, and policy arenas to advance our understanding of the clearly important role that PF and CRF play in assessing health status.

Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person’s gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

*Modest.
†Significant.

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References

- Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association [published correction appears in *Circulation*. 2012;125:e1002]. *Circulation*. 2012;125:e2–e220.
- Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; on behalf of the American Heart Association Advocacy Coordinating Committee, Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease, Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944.
- Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association’s strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613.
- Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301:2024–2035.
- Artero EG, Lee DC, Lavie CJ, España-Romero V, Sui X, Church TS, Blair SN. Effects of muscular strength on cardiovascular risk factors and prognosis. *J Cardiopulm Rehabil Prev*. 2012;32:351–358.
- Franklin BA, McCullough PA. Cardiorespiratory fitness: an independent and additive marker of risk stratification and health outcomes. *Mayo Clin Proc*. 2009;84:776–779.
- Lavie CJ, Swift DL, Johannsen NM, Arena R, Church TS. Physical fitness: an often forgotten cardiovascular risk factor. *J Glycomics Lipidomics*. doi:10.4172/2153-0637.1000e104. <http://www.omicsonline.org/2153-0637/2153-0637-2-e104.php?aid=6746>. Accessed December 4, 2012.
- Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, Al-Hani AJ, Black HR. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003;108:1554–1559.
- Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
- Sui X, Laditka JN, Church TS, Hardin JW, Chase N, Davis K, Blair SN. Prospective study of cardiorespiratory fitness and depressive symptoms in women and men. *J Psychiatr Res*. 2009;43:546–552.

11. Milani RV, Lavie CJ. Impact of cardiac rehabilitation on depression and its associated mortality. *Am J Med.* 2007;120:799–806.
12. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011;86:876–884.
13. Liu R, Sui X, Laditka JN, Church TS, Colabianchi N, Hussey J, Blair SN. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. *Med Sci Sports Exerc.* 2012;44:253–259.
14. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA.* 2005;293:2479–2486.
15. Peel JB, Sui X, Matthews CE, Adams SA, Hébert JR, Hardin JW, Church TS, Blair SN. Cardiorespiratory fitness and digestive cancer mortality: findings from the Aerobics Center Longitudinal Study. *Cancer Epidemiol Biomarkers Prev.* 2009;18:1111–1117.
16. American College of Sports Medicine. Health-related physical fitness testing and interpretation. In: Thompson WR, Gordon NF, Pescatello LS, eds. *ACSM's Guidelines for Exercise Testing and Prescription.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:60–104.
17. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA.* 1989;262:2395–2401.
18. Blair SN, Kohl HW 3rd, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. *JAMA.* 1995;273:1093–1098.
19. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA.* 1996;276:205–210.
20. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care.* 2004;27:83–88.
21. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med.* 2005;165:2114–2120.
22. Church TS, Kampert JB, Gibbons LW, Barlow CE, Blair SN. Usefulness of cardiorespiratory fitness as a predictor of all-cause and cardiovascular disease mortality in men with systemic hypertension. *Am J Cardiol.* 2001;88:651–656.
23. Sui X, LaMonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, Blair SN. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA.* 2007;298:2507–2516.
24. Lee DC, Sui X, Church TS, Lavie CJ, Jackson AS, Blair SN. Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia. *J Am Coll Cardiol.* 2012;59:665–672.
25. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW 3rd, Blair SN. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation.* 2011;124:2483–2490.
26. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation.* 2010;122:1637–1648.
27. Archer E, Blair SN. Physical activity and the prevention of cardiovascular disease: from evolution to epidemiology. *Prog Cardiovasc Dis.* 2011;53:387–396.
28. Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. *Circulation.* 1998;98:2836–2841.
29. Goraya TY, Jacobsen SJ, Pellikka PA, Miller TD, Khan A, Weston SA, Gersh BJ, Roger VL. Prognostic value of treadmill exercise testing in elderly persons. *Ann Intern Med.* 2000;132:862–870.
30. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. *J Am Coll Cardiol.* 1997;30:641–648.
31. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the Lipid Research Clinics Prevalence Study. *JAMA.* 2003;290:1600–1607.
32. Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, Karasik P, Greenberg M, Papademetriou V, Singh S. Exercise capacity and mortality in black and white men. *Circulation.* 2008;117:614–622.
33. Myers J. The health benefits and economics of physical activity. *Curr Sports Med Rep.* 2008;7:314–316.
34. Mark DB, Lauer MS. Exercise capacity: the prognostic variable that doesn't get enough respect. *Circulation.* 2003;108:1534–1536.
35. Myers J. Beyond ST-segment displacement: newer diagnostic and prognostic markers from the exercise test. *Am J Med Sports* 2003;5:332–336.
36. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med.* 1988;319:1379–1384.
37. Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. *JAMA.* 2004;292:1462–1468.
38. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shephard RJ. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol.* 2003;42:2139–2143.
39. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shephard RJ. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation.* 2002;106:666–671.
40. US Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. 2008. ODPHP publication No. U0036. <http://www.health.gov/paguidelines/pdf/paguide.pdf>. Accessed December 4, 2012.
41. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A; American College of Sports Medicine; American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116:1081–1093.
42. Huang Y, Macera CA, Blair SN, Brill PA, Kohl HW 3rd, Kronenfeld JJ. Physical fitness, physical activity, and functional limitation in adults aged 40 and older. *Med Sci Sports Exerc.* 1998;30:1430–1435.
43. Fried LP, Bandeen-Roche K, Chaves PH, Johnson BA. Preclinical mobility disability predicts incident mobility disability in older women. *J Gerontol A Biol Sci Med Sci.* 2000;55:M43–M52.
44. Unger JB, McAvay G, Bruce ML, Berkman L, Seeman T. Variation in the impact of social network characteristics on physical functioning in elderly persons: MacArthur Studies of Successful Aging. *J Gerontol B Psychol Sci Soc Sci.* 1999;54:S245–S251.
45. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, González-Colago Harmand M, Bergman H, Carcaillon L, Nicholson C, Scuteri A, Sinclair A, Pelaez M, Van der Cammen T, Beland F, Bickenbach J, Delamarche P, Ferrucci L, Fried LP, Gutiérrez-Robledo LM, Rockwood K, Rodríguez Artalejo F, Serviddio G, Vega E: on behalf of the FOD-CC group (Appendix 1). Searching for an operational definition of frailty: a Delphi method based consensus statement. the Frailty Operative Definition-Consensus Conference Project. *J Gerontol A Biol Sci Med Sci.* Published online before print April 16, 2012, doi: 10.1093/gerona/gls119. <http://biomedgerontology.oxfordjournals.org/content/early/2012/04/15/gerona.gls119.long>. Accessed December 4, 2012.
46. Blair SN, Wei M. Sedentary habits, health, and function in older women and men. *Am J Health Promot.* 2000;15:1–8.
47. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci.* 1998;53:S9–16.
48. Vita AJ, Terry RB, Hubert HB, Fries JF. Aging, health risks, and cumulative disability. *N Engl J Med.* 1998;338:1035–1041.
49. Weiss CO, Hoenig HH, Varadhan R, Simonsick EM, Fried LP. Relationships of cardiac, pulmonary, and muscle reserves and frailty to exercise capacity in older women. *J Gerontol A Biol Sci Med Sci.* 2010;65:287–294.
50. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ.* 2011;183:E487–E494.
51. Rockwood K, Howlett SE, MacKnight C, Beattie BL, Bergman H, Hébert R, Hogan DB, Wolfson C, McDowell I. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian Study of Health and Aging. *J Gerontol A Biol Sci Med Sci.* 2004;59:1310–1317.
52. Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M. Frailty is associated with postoperative complications in older adults with medical problems. *Arch Gerontol Geriatr.* 2009;48:78–83.
53. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J, Fried LP. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg.* 2010;210:901–908.
54. Dupre ME, Gu D, Warner DF, Yi Z. Frailty and type of death among older adults in China: prospective cohort study. *BMJ.* 2009;338:b1175.

55. García-González JJ, García-Peña C, Franco-Marina F, Gutiérrez-Robledo LM. A frailty index to predict the mortality risk in a population of senior Mexican adults. *BMC Geriatr*. 2009;9:47.
56. Hastings SN, Purser JL, Johnson KS, Sloane RJ, Whitson HE. Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. *J Am Geriatr Soc*. 2008;56:1651–1657.
57. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail*. 2010;16:208–213.
58. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*. 2000;55:M221–M231.
59. Onder G, Penninx BW, Ferrucci L, Fried LP, Guralnik JM, Pahor M. Measures of physical performance and risk for progressive and catastrophic disability: results from the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci*. 2005;60:74–79.
60. Markides KS, Black SA, Ostir GV, Angel RJ, Guralnik JM, Lichtenstein M. Lower body function and mortality in Mexican American elderly people. *J Gerontol A Biol Sci Med Sci*. 2001;56:M243–M247.
61. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Ferguson JC, Fisher LD, Tristani F. The value of preoperative exercise testing in predicting long-term survival in patients undergoing aortocoronary bypass surgery. *Circulation*. 1984;70(pt 2):I226–I231.
62. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg*. 2007;94:966–969.
63. Brown LC, Thompson SG, Greenhalgh RM, Powell JT; UK Small Aneurysm Trial Participants. Fit patients with small abdominal aortic aneurysms (AAAs) do not benefit from early intervention. *J Vasc Surg*. 2008;48:1375–1381.
64. McCullough PA, Gallagher MJ, Dejong AT, Sandberg KR, Trivax JE, Alexander D, Kasturi G, Jafri SM, Krause KR, Chengelis DL, Moy J, Franklin BA. Cardiorespiratory fitness and short-term complications after bariatric surgery. *Chest*. 2006;130:517–525.
65. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. *Anaesthesia*. 2009;64:883–893.
66. Lee JT, Chaloner EJ, Hollingsworth SJ. The role of cardiopulmonary fitness and its genetic influences on surgical outcomes. *Br J Surg*. 2006;93:147–157.
67. Froelicher VF. Screening with the exercise test: time for a guideline change? *Eur Heart J*. 2005;26:1353–1354.
68. Kraus WE, Douglas PS. Where does fitness fit in? *N Engl J Med*. 2005;353:517–519.
69. Arena R, Myers J, Guazzi M. The future of aerobic exercise testing in clinical practice: is it the ultimate vital sign? *Future Cardiol*. 2010;6:325–342.
70. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334–1359.
71. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA*. 2007;297:2081–2091.
72. Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*. 2005;112:674–682.
73. Lavie CJ, Kuruwanka T, Milani RV, Prasad A, Ventura HO. Exercise capacity in adult African-Americans referred for exercise stress testing: is fitness affected by race? *Chest*. 2004;126:1962–1968.
74. Howlett RA, Gonzalez NC, Wagner HE, Fu Z, Britton SL, Koch LG, Wagner PD. Selected contribution: skeletal muscle capillarization and enzyme activity in rats selectively bred for running endurance. *J Appl Physiol*. 2003;94:1682–1688.
75. Thyfault JP, Rector RS, Uptergrove GM, Borengasser SJ, Morris EM, Wei Y, Laye MJ, Burant CF, Qi NR, Ridenhour SE, Koch LG, Britton SL, Ibdah JA. Rats selectively bred for low aerobic capacity have reduced hepatic mitochondrial oxidative capacity and susceptibility to hepatic steatosis and injury. *J Physiol (Lond)*. 2009;587(pt 8):1805–1816.
76. Bye A, Høydal MA, Catalucci D, Langaas M, Kemi OJ, Beisvag V, Koch LG, Britton SL, Ellingsen Ø, Wisløff U. Gene expression profiling of skeletal muscle in exercise-trained and sedentary rats with inborn high and low $\dot{V}O_{2max}$. *Physiol Genomics*. 2008;35:213–221.
77. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33:754–761.
78. Whaley MH, Kaminsky LA, Dwyer GB, Getchell LH, Norton JA. Predictors of over- and underachievement of age-predicted maximal heart rate. *Med Sci Sports Exerc*. 1992;24:1173–1179.
79. Skinner JS, Wilmore KM, Rasnoff JB, Jaskólski A, Jaskólska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med Sci Sports Exerc*. 2000;32:157–161.
80. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225.
81. Willis BL, Morrow JR Jr, Jackson AW, Defina LF, Cooper KH. Secular change in cardiorespiratory fitness of men: Cooper Center Longitudinal Study. *Med Sci Sports Exerc*. 2011;43:2134–2139.
82. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Normal values. In: Weinberg R, ed. *Principles of Exercise Testing and Interpretation*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:160–182.
83. Kim ES, Ishwaran H, Blackstone E, Lauer MS. External prognostic validations and comparisons of age- and gender-adjusted exercise capacity predictions. *J Am Coll Cardiol*. 2007;50:1867–1875.
84. Lauer M, Froelicher ES, Williams M, Kligfield P. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation*. 2005;112:771–776.
85. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. *Circulation*. 2004;110:1920–1925.
86. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation*. 2007;116:329–343.
87. Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, Balady GJ; on behalf of the American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention of the Council on Clinical Cardiology, the Council on Nutrition, Physical Activity, and Metabolism, and the Council on Cardiovascular Nursing. Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association. *Circulation*. 2009;119:3144–3161.
88. Eaton DK, Kann L, Kinchen S, Shanklin S, Ross J, Hawkins J, Harris WA, Lowry R, McManus T, Chyen D, Lim C, Whittle L, Brener ND, Wechsler H; Centers for Disease Control and Prevention (CDC). Youth risk behavior surveillance: United States, 2009. *MMWR Surveill Summ*. 2010;59:1–142.
89. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis JF Jr, Smith SC Jr, Stone NJ, Taubert KA. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation*. 2002;106:388–391.

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