After COVID-19 Infection

To the Editor

We read with great interest the recently published article by Phelan et al.1 The clinical implications of asymptomatic to mild coronavirus disease 2019 (COVID-19) remain undetermined. We agree that physicians need to address the broad clinical manifestations of this disease until enough evidence is gathered to create definitive recommendations for return-to-play guidelines for athletes. COVID-19 should be considered in the differential diagnosis of patients with upper respiratory tract infection,2 especially with unusual symptoms, like anosmia and ageusia. Although athletes have a lower risk of severe disease, even those with asymptomatic to mild disease may present with subclinical, exercise-induced complications.3

Phelan et al1 provide relevant recommendations regarding the cardiovascular assessment in competitive athletes and highly active people after COVID-19 infection, which are in agreement with recommendations from Dorés and Cardim.4 Furthermore, Phelan et al1 recommend a 2-week asymptomatic resting period following positive findings on antigen testing before returning to play; however, retesting is not mentioned. We consider athletes should be retested until a negative result is obtained before returning to play to account for reinfection or reactivation. Furthermore, it has been shown that patients can remain positive even if asymptomatic for several weeks.5 Serological testing should also be considered in athletes with negative antigen findings who presented late with mild to moderate symptoms beyond the first 2 weeks of onset.

We propose a symptom-based algorithm for return-to-play eligibility that goes beyond cardiovascular assessment. All athletes recovered from COVID-19 should perform a preparticipation screening, including a comprehensive clinical examination and testing for active severe acute respiratory syndrome coronavirus 2 infection. In addition, complications from the disease must be excluded prior to returning to play. Pulmonary and cardiac fibrosis are potentially the most relevant for athletes, which may lead to reduced lung capacity or cardiac dysfunction, malignant arrhythmias, and sudden death. Those who test positive or have a history of suspected or confirmed COVID-19 (including mild or complicated disease) or presenting with suggestive signs or symptoms should undergo additional investigations according to presentation and disease severity. These may include blood tests, electrocardiography, echocardiography, 24-hour and/or 48-hour Holter monitoring, exercise testing, or lung function tests.4 Particularly with the latter 2 tests, it is important to ensure safety and minimize the risk of transmission via aerosols.4

We suggest future guidelines regarding returning to play for athletes with COVID-19 should mainly emphasize clinical presentation and severity rather than temporal progression of the disease. Antigen or serological retesting should also be included. We agree that throughout this process, physicians should remain attentive to new symptom development or decreased performance, even if the athlete had negative test results before.

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Return-to-Play Guidelines for Athletes After COVID-19 Infection

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Letters

Risk-standardized mortality following percutaneous coronary intervention: A systematic review and meta-analysis. Coll Cardiol 2008;1016/j.jcin.2016.12.019 JAMA Cardiol

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COMMENT & RESPONSE

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To the Editor We read with interest the Viewpoint “A Game Plan for the Resumption of Sport and Exercise After COVID-19 Infection,” where Phelan et al provide an expert opinion-based algorithm for resuming physical activity after recovering from coronavirus disease 2019 (COVID-19). They carefully state that the recommendations are not evidence based, suggesting the criteria will evolve as data emerge. However, several areas of laboratory testing listed in this article could be problematic.

One relates to high-sensitivity cardiac troponin (hs-cTn) assays. The 99th percentile is an appropriate cutoff for diagnosis of acute myocardial infarction. In nonacute situations, more modest increases within the hs-cTn normal range have been of prognostic significance. Thus, adopting the 99th percentile as a gatekeeper for return-to-sport activity after COVID-19 could lead to a false sense of security in some patients or unnecessary concern in others. We suggest that before embracing such an approach that reference intervals are established for the specific population. Athletes may have more left ventricular hypertrophy and/or dilation, which could change the interval. Similarly, professional athletes may have higher systemic hs-cTn levels compared with sedentary adults given they exercise so heavily and therefore could be penalized because of their athletic prowess. Even with implementation of a more appropriate reference interval, hs-cTn is best interpreted relative to baseline. This requires use of hs-cTn assays, not yet widely available, but most hospitals and medical centers in the US are still using less sensitive or conventional cTn assays. These will not suffice.

Second, there are known differences in the hs-cTn concentrations between sexes that are unaccounted for in this algorithm. Third, the lack of standardization between hs-cTn assays may cause inconsistencies in interpretation because their critical values are not harmonized.

Additionally, Phelan et al refer to testing for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen. The vast majority of SARS-CoV-2 detection is accomplished by amplifying viral RNA. Detection of RNA, not antigen, is the preferred approach. Although detection of serum antibodies to SARS-CoV-2 infers a prior infection, there is no guarantee of immunity. Therefore, we agree on a limited role for serology in the return-to-play clearance.

We concur that data and trials are critical to guideline development, and their current absence is a limitation. One approach to consider may be to obtain baseline hs-cTn concentrations on all athletes so comparisons can be made. If the baseline samples are obtained in a consistent and careful manner, the manufacturer’s sample assay is consistently used for hs-cTn quantification, confounding variables will be reduced and may allow a better paradigm to develop.

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In Reply We appreciate comments on our recent Viewpoint1 and the opportunity to respond to these important questions. Santos-Ferreira and colleagues recommend that coronavirus disease 2019 (COVID-19) return-to-play guidelines should emphasize symptoms and retesting. In terms of the controversy of retesting, recent data report recovered and noninfectious patients may shed detectable severe acute respiratory syndrome coronavirus 2 RNA for up to 3 months. Further, persons with mild to moderate COVID-19 infection do not ap-
pear to be infectious after 10 days following symptom onset; persons with more severe illness are likely not infectious after 20 days following symptom onset.2

We agree that burden of symptoms should dictate the degree of cardiac testing, which was included as part of our risk stratification algorithm.1 However, more expedient testing (including lung function tests) prior to the conclusion of quarantine introduces public health risks and should be ordered with caution. Current guidelines from the US Centers for Disease Control and Prevention, with which we concur, support these recommendations and advise a quarantine period for asymptomatic individuals with COVID-19 and those with mild symptoms.2 Importantly, symptoms may worsen during the second week of active infection, and a quarantine period of at least 10 days after symptom onset is still recommended by the Centers for Disease Control and Prevention.2 Santos-Ferreira and colleagues remind us that the pulmonary complications of COVID-19 manifest as pulmonary fibrosis, particularly in those with persistent exercise intolerance. Our approach would be to first prioritize public health measures. In combination with cardiac risk stratification, it would then be reasonable to consider lung function tests at the appropriate end of the quarantine period.

Greene and colleagues provide insightful comments regarding high-sensitivity cardiac troponin (hs-cTn) testing. They correctly point out that established reference ranges for athletes are lacking and that there should be consideration of the effect of prolonged strenuous exercise on release of hs-cTn. However, exercise-induced hs-cTn release typically returns to baseline within 24 to 48 hours, which differs from the kinetics of pathologic myocardial injury.3,5 We recommend a rest period of 48 hours prior to testing to avoid this potential confounder. We also appreciate concerns about hs-cTn as a gatekeeper for returning to play. However, the combination of electrocardiography, echocardiography, and hs-cTn should be sufficient to avoid false negatives. Risk of false positives also remains low as, in our experience, outside of the immediate postexercise period, it is rare for athletes to present with hs-cTn levels higher than the 99th percentile. We agree that sex-specific reference ranges for hs-cTn are important but might be assay dependent. We concur that serial hs-cTn should be interpreted using the same assay for clinically meaningful comparisons. While we strongly advocate for research to establish normal hs-cTn ranges in athletic populations and for interpretation of serial measures of hs-cTn, it is our opinion that these undertakings should not delay use of our algorithm and do not lessen the utility of hs-cTn in the current algorithm.

Finally, it is accurate that the most common screening test for COVID-19 is now polymerase chain reaction amplification of RNA vs antigen testing. This preference has evolved, and we would defer the selection of which test to local resource considerations.

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PCSK9 Inhibition—A Tale of 2 Potential Treatment Opportunities

To the Editor. To our knowledge, no known medical therapy has been shown to reduce the need for aortic valve replacement in calcific aortic stenosis (AS), a disorder with an initiation phase that resembles atherosclerosis followed by a progressive phase where calcification predominates. Despite initial enthusiasm, statin use was not beneficial in slowing progression.1 We now read with great enthusiasm the results from Bergmark et al2 on their secondary analysis of 63 patients treated with evolocumab from the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial with new or worsening AS or need for aortic valve replacement (termed AS events). AS events were associated with higher lipoprotein(a) (Lp[a]) levels and not with corrected low-density lipoprotein cholesterol concentration and provide the mechanistic basis for evolocumab’s effect in AS.

The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in vascular biology and its effect on cholesterol metabolism are gaining importance, and it is already known that inhibition appears to moderate modulation of inflammation and slow the progression of coronary artery calcification.3 Recent data have also shown a correlation of Lp(a) levels with serum levels of matrix Gla protein, a known inhibitor of bone morphogenetic protein 2, and also with aortic valve calcification.4

Despite the possible pathophysiological underpinnings, caution is required in interpreting the provided data. First, it is unknown if aortic valve replacement was performed for progressive, symptomatic severe AS or for events related to mild to moderate AS, such as endocarditis or concomitant surgical revascularization of coronary disease. Second, the cause of AS (bicuspid vs tricuspid, calcific vs rheumatic, native vs prosthetic) is unknown. Third, the median duration of follow-up of this study is short compared with the