

Drs. Rich and Peterson report receiving a grant (R01 AG060499) from the National Institute on Aging (NIA) for the MACRO trial; Dr. Rich, receiving a grant (AG 078153) from the NIA for the REHAB-HFpEF trial; and Dr. Peterson, receiving grants (R33 HL155858 and R01 HL165238-01A1) from the National Heart, Lung, and Blood Institute, a grant (R01 AG071717-01A1) from the NIA, a grant (23SCISA1145192) from the American Heart Association, and funding from the Children's Discovery Institute and the Clinical and Translational Research Funding Program at Washington University in St. Louis. No other potential conflict of interest relevant to this letter was reported.

1. Świątkiewicz I, Di Somma S, De Fazio L, Mazzilli V, Taub PR. Effectiveness of intensive cardiac rehabilitation in high-risk patients with cardiovascular disease in real-world practice. *Nutrients* 2021;13:3883.
2. Husaini M, Deych E, Waken RJ, et al. Intensive versus traditional cardiac rehabilitation: mortality and cardiovascular outcomes in a 2016-2020 retrospective Medicare cohort. *Circ Cardiovasc Qual Outcomes* 2023;16(12):e010131.
3. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med* 2021;385:203-16.
4. Forman DE, Racette SB, Toto PE, et al. Modified Application of Cardiac Rehabilitation in Older Adults (MACRO) trial: protocol changes in a pragmatic multi-site randomized controlled trial in response to the COVID-19 pandemic. *Contemp Clin Trials* 2022;112:106633.

DOI: 10.1056/NEJMc2403909

THE AUTHOR REPLIES: The comments by Kambič and colleagues are important regarding personalized exercise training for each patient who participates in cardiac rehabilitation, in the shorter term and longer term. Certification programs for cardiac rehabilitation aim to help standardize the quality of methods used, but further studies are needed to assess the effect of these programs on improving the quality of exercise training methods provided to patients. Innovative and beneficial advances in exercise training approaches¹ and strategies for other components of cardiac rehabilitation² will be critically important as cardiac rehabilitation continues to evolve and improve.

The comments by Rich and colleagues highlight an alternative delivery model of cardiac re-

habilitation — ICR. It includes components similar to those in traditional cardiac rehabilitation, with twice as many sessions (i.e., 72 sessions vs. 36 sessions) and at substantially higher cost.³ Particular focus is placed on plant-based diets and stress-management strategies. ICR is provided by just under 2% of all cardiac rehabilitation programs in the United States, with less than 1% of all enrolled patients participating in such programs.⁴ Randomized studies of head-to-head comparisons between ICR and traditional cardiac rehabilitation are needed. Until such studies are conducted and show a favorable cost–benefit effect on patient participation and outcomes, it appears that the role of ICR in expanding the reach of cardiac rehabilitation may be limited. Meanwhile, a number of head-to-head randomized studies comparing home-based with traditional center-based cardiac rehabilitation have shown promising results on patient outcomes and participation,⁵ with additional studies in progress.

Randal J. Thomas, M.D.

Mayo Clinic
Rochester, MN
thomas.randal@mayo.edu

Since publication of the article, the author reports no further potential conflict of interest.

1. Wewege MA, Ahn D, Yu J, Liou K, Keech A. High-intensity interval training for patients with cardiovascular disease—is it safe? A systematic review. *J Am Heart Assoc* 2018;7(21):e009305.
2. Golbus JR, Lopez-Jimenez F, Barac A, et al. Digital technologies in cardiac rehabilitation: a science advisory from the American Heart Association. *Circulation* 2023;148:95-107.
3. Lee AJ, Shepard DS. Costs of cardiac rehabilitation and enhanced lifestyle modification programs. *J Cardiopulm Rehabil Prev* 2009;29:348-57.
4. Husaini M, Deych E, Racette SB, Rich MW, Joynt Maddox KE, Peterson LR. Intensive cardiac rehabilitation is markedly underutilized by medicare beneficiaries: results from a 2012-2016 national sample. *J Cardiopulm Rehabil Prev* 2022;42:156-62.
5. McDonagh ST, Dalal H, Moore S, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev* 2023;10:CD007130.

DOI: 10.1056/NEJMc2403909

False Positive Covid-19 Rapid Antigen Tests

TO THE EDITOR: The letter by Herbert et al. (Feb. 22 issue)¹ explores persistent false positive results on SARS-CoV-2 rapid antigen tests but overlooks various factors, such as interfering substances and testing conditions.² Structural similarities between

pathogens such as dengue virus and SARS-CoV-2 imply potential cross-reactivity.³

The potential for IgM cross-reactivity with rheumatoid factor–positive serum samples was observed in blood tests used to detect IgM SARS-

CoV-2 by means of gold immunochromatographic and enzyme-linked immunosorbent assays.⁴ SARS-CoV-2 rapid antigen tests differ from antibody tests, with the former identifying SARS-CoV-2 viral proteins and the latter detecting human IgM SARS-CoV-2 antibodies. Thus, the possible link between false positive rapid antigen tests, which use nasal swabs, not blood samples, and antibody cross-reactivity with rheumatoid factor deserves reconsideration.

The absence of discussion about patients with negative results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing for SARS-CoV-2 but positive results on SARS-CoV-2 rapid antigen tests raises questions about persistent viral infection. For instance, despite negative results on RT-PCR testing of nasopharyngeal swabs or bronchoalveolar-lavage samples, autopsies revealed continued shedding of SARS-CoV-2 in lung tissue up to 300 days after the remission of infection.⁵ Overall, the letter provides insights into persistent false positive results on rapid antigen testing but neglects factors of relevance for the accurate interpretation of SARS-CoV-2 test results.

Chengliang Yang, M.D.

Estefanía Espín, M.Sc.

Scott J. Tebbutt, Ph.D.

University of British Columbia
Vancouver, BC, Canada
scott.tebbutt@hli.ubc.ca

No potential conflict of interest relevant to this letter was reported.

1. Herbert C, McManus DD, Soni A. Persistent false positive Covid-19 rapid antigen tests. *N Engl J Med* 2024;390:764-5.
2. Patriquin G, Davidson RJ, Hachette TF, et al. Generation of false-positive SARS-CoV-2 antigen results with testing conditions outside manufacturer recommendations: a scientific approach to pandemic misinformation. *Microbiol Spectr* 2021; 9(2):e0068321.
3. Lustig Y, Keler S, Kolodny R, et al. Potential antigenic cross-reactivity between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and dengue viruses. *Clin Infect Dis* 2021; 73(7):e2444-e2449.
4. Vinyé Bausà M, Bausà Peris R, Corominas H. Cross-reactions between rheumatoid factor and IgM SARS-CoV-2. *Med Clin (Engl Ed)* 2020;155:417-8.
5. Bussani R, Zentilin L, Correa R, et al. Persistent SARS-CoV-2 infection in patients seemingly recovered from COVID-19. *J Pathol* 2023;259:254-63.

DOI: 10.1056/NEJMc2403409

THE AUTHORS REPLY: In our letter, we describe persistent false positive SARS-CoV-2 rapid antigen tests and suggest rheumatoid factor as a potential mechanism. Our postulation was based on previous reports of cross-reactivity and the ob-

servation that IgM and IgA rheumatoid factors are detected in saliva and nasal secretions.¹ It is important to underscore that our findings were observational and that we did not investigate causal relationship. Yang and colleagues raise important considerations about persistent viral shedding in lung tissue. However, all the participants in our study were asymptomatic and reported that they had not tested positive for SARS-CoV-2 in the previous 3 months. By contrast, viral shedding is commonly observed in persons with prolonged olfactory dysfunction after infection.²

Finally, we received more than 30 accounts from patients and providers in response to our letter sharing similar experiences of persons with autoimmune conditions who had persistent positive results on specific SARS-CoV-2 rapid antigen tests without positive PCR tests. We believe that such anecdotal evidence, combined with our findings and previous reports,³ warrants further investigation of the potential associations between autoimmunity and persistent false positive results on SARS-CoV-2 rapid antigen tests.

Carly Herbert, B.A.

David D. McManus, M.D.

Apurv Soni, M.D., Ph.D.

University of Massachusetts Chan Medical School
Worcester, MA
apurv.soni@umassmed.edu

Since publication of the letter, the authors report no further potential conflict of interest.

1. Elkon KB, Gharavi AE, Patel BM, Hughes GR, Frankel A. IgA and IgM rheumatoid factors in serum, saliva and other secretions: relationship to immunoglobulin ratios in systemic sicca syndrome and rheumatoid arthritis. *Clin Exp Immunol* 1983;52: 75-84.
2. Costa Dos Santos J, Ximenes Rabelo M, Mattana Sebben L, et al. Persistence of SARS-CoV-2 antigens in the nasal mucosa of eight patients with inflammatory rhinopathy for over 80 days following mild COVID-19 diagnosis. *Viruses* 2023;15:899.
3. Vinyé Bausà M, Bausà Peris R, Corominas H. Cross-reactions between rheumatoid factor and IgM SARS-CoV-2. *Med Clin (Engl Ed)* 2020;155:417-8.

DOI: 10.1056/NEJMc2403409

Correspondence Copyright © 2024 Massachusetts Medical Society.

THE JOURNAL'S WEB ADDRESSES

To submit a letter to the Editor or to obtain information about the status of a submitted manuscript:
authors.NEJM.org

For general information on the Journal's editorial policies:
nejm.org/about-nejm/editorial-policies

The Journal's website: NEJM.org