

# Should RT-PCR be considered a gold standard in the diagnosis of COVID-19?

To the Editor,

To face the new coronavirus disease 2019 (COVID-19) pandemic, the need for early and accurate diagnosis of the disease among suspected cases quickly became obvious for effective management, and for better control of the spread of the disease in the population. Since the beginning of this disease epidemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), reverse transcriptase-polymerase chain reaction (RT-PCR) has routinely been used to confirm the diagnosis. However, several authors have pointed out the poor performance of this technique, particularly in terms of sensitivity.<sup>1,2</sup> Indeed, according to some authors, sensitivity could be as low as 38%<sup>3</sup> (ie, not better than chance). This made it necessary to find a more sensitive test, given the contagiousness of SARS-CoV-2. We, therefore, read with great interest the article published in your journal by Cassaniti et al.<sup>4</sup> This article deals with the diagnosis of COVID-19 by serology (immunoglobulin m/immunoglobulin G) as a complementary approach to RT-PCR to improve its sensitivity. According to Cassaniti et al<sup>4</sup> and Xiang et al,<sup>5</sup> serology is faster to implement, less expensive, easier to use, and more accessible to staff with no specific laboratory training.<sup>5</sup> The article describes the metrological performances of serology, and compare it with RT-PCR as the gold standard. Using a test as the gold standard when its metrological properties are clearly perfectible raises questions from a methodological point of view. Indeed, when an existing test is considered as a reference, this suggests that the test in question is always correct and that all misclassifications (false negatives and false positives) are due to the new test. However, the new test (in this case, serology) might be better than the old test (in this case, RT-PCR), but it would be impossible to demonstrate this. Consequently, the new test will never be able to achieve a sensitivity of 100%, since it is considered responsible for all misclassifications. The same mistake has also been made by other authors regarding the use of chest computed tomography scans as a diagnostic method.<sup>6,7</sup> In this situation, the best strategy would be to measure the degree of agreement (using the Kappa coefficient measures<sup>8</sup>) between the two tests, that is, neither of the two tests is considered to be the reference and, therefore, any discrepancies could be linked to either of the tests. Thus, the serology performances presented by Xiang et al<sup>5</sup> are certainly better than those presented in their paper.

The difficulty of using a gold standard is an old debate,<sup>9,10</sup> but still relevant nonetheless. In the absence of an accurate reference

test, alternative strategies could be to perform the test repeatedly over time, to use the patient's clinical course, or the combination of several tests as the gold standard.


The purpose of writing this contribution is not to discuss the best diagnostic strategy for COVID-19, nor is it to question the results of the authors who used RT-PCR as a reference. On the contrary, it purports that their results might actually be even better than those presented.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

Moustapha Dramé MD, PhD<sup>1</sup>   
 Maturin Tabue Teguo MD, PhD<sup>2</sup>  
 Emeline Proye MD<sup>3</sup>  
 Fanny Hequet MD<sup>3</sup>  
 Maxime Hentzien MD, PhD<sup>4</sup>  
 Lukshe Kanagaratnam MD, PhD<sup>5</sup>  
 Lidvine Godaert MD, PhD<sup>3</sup>

<sup>1</sup>Department of Clinical Research and Innovation, University Hospital of Martinique, Fort-de-France, Martinique, France

<sup>2</sup>Department of Geriatrics, University Hospital of Guadeloupe, Pointe-à-Pitre, Guadeloupe

<sup>3</sup>Department of Geriatrics, General Hospital of Valenciennes, Valenciennes, France

<sup>4</sup>Department of Infectious Diseases, University Hospital of Reims, Reims, France

<sup>5</sup>Department of Clinical Research and Public Health, University Hospital of Reims, Reims, France

## Correspondence

Moustapha Dramé, Department of Clinical Research and Innovation, University Hospital of Martinique–Pierre Zobda-Quitman Hospital, CS 90632, Fort-de-France, MTQ 97261, France.

Email: [moustapha.drame@chu-martinique.fr](mailto:moustapha.drame@chu-martinique.fr)

## ORCID

Moustapha Dramé  <http://orcid.org/0000-0002-6662-8832>

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