#ApresJ20 ASSOCIATION COVID LONG FRANCE

PRESS RELEASE

French study on long Covid flawed in its methodology and detrimental to the care of patients

Paris, November 29, 2021 —

Summary:

The study published in *JAMA Internal Medicine* **shows mathematical, methodological and scientific bias, and there are errors which contradict the study's own conclusions**.

We also take strong exception to the biased interpretations that followed publication of this study, which have detrimental and even dangerous implications for those suffering from long Covid.

In the last few days, some of the study's authors have appeared in the media, responding to blatant errors which we have pointed out. Their response **raises questions about the principles of scientific validation of data.**

Our association, #ApresJ20 Covid Long France, calls for medical care integrating scientific evidence with the lived experience of patients.

Noteworthy:

- **The study does not take into account the international scientific corpus**. **It does not take into account the weaknesses of serological tests**; the absence or decline of detectable antibodies particular to long Covid; or the consensus established by hundreds of publications on the demonstrable causes of persistent symptoms, whether neurological, vascular or immune, of Covid-19.

- **Some of the data is not consistent from one part of the study to another, and there are calculation errors**. For example, the number of cases cited per symptom in the population that reported Covid-19 infection ("*Belief+*") is not uniform throughout the paper (see *Table 2* and *eTable7*), and many percentages in Table 2 do not match the data presented.

- **The population extracted to analyze the data between groups is very small for this type of observational study** (one thousand individuals, 4% of the cohort), and is insignificant on some key points (a group of only 51 people to evoke anosmia).

- **The study contains methodological errors that invalidate its own conclusions.** With a cohort this small, the authors do not find a statistically strong correlation with some symptoms and from this they deduce that the correlation does not exist. Absence of evidence is taken for evidence of absence. Moreover, the analysis does not take into account false positive tests. In the population that the authors accept as having had confirmed Covid-19, only 40% were actually infected.

- **The data drawn from the cohort actually seems to lead to the opposite conclusion from that formulated in the study**. The figures indicate that a large proportion of people who report having been ill with Covid-19 have indeed been ill. **Patient experience is therefore much more reliable than serological tests**. Finally, a rigorous analysis of the data also corroborates **a strong statistical link between Covid-19 infection and the presence of 16 prolonged symptoms**.

- **The study calls patients' perceptions into doubt but would have us believe that the authors' views on the situation are weighty**. The authors switch indiscriminately from the notion of "self-reported infection" to "belief", as if there was no difference between the two. While the interpretations of the study appear as *hypotheses*, those of the patients are relayed as *beliefs*, a term with negative connotation. "Belief" tends to discredit and trivialize patients' lived experience.

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On 8 November, *JAMA Internal Medicine* published a French study (Lemogne et al., Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic).
This study argues that the presence of persistent symptoms may not be related to having been infected with Covid-19 (*"the symptoms may not emanate from SARS-CoV-2 infection per se"*).

Since its creation, the **#ApresJ20 Covid Long France** association has relied on **evidence-based medicine**. In line with this principle, we hope that long Covid care will be guided by robust scientific studies. Unproven therapies should not be promoted, and the urgent need of sufferers for essential, well-adapted multidisciplinary care should not be discredited.

Soon after publication, the French study was strongly criticized internationally by long Covid associations and support groups, by researchers most focused on this disease, and by experts in statistical methodology. Yale University Associate Professor of Medicine Francis Perry Wilson published his analysis in Medscape.com (one of the most reputable online medical news journals): ***A flawed study calls the whole syndrome into question***.

Other harsh criticisms followed: that of expert Brian Hughes, or those of professors David Strain, Kevin McConway or Jeremy Rossman.

Compiling and summarizing these criticisms, it appears that the study is **discredited by major mathematical errors,** and **raises questions about the principles of scientific integrity**. Eroding their case even more, the data appears on the contrary to corroborate a strong statistical link between a Covid-19 infection and the presence of 16 prolonged symptoms, an analysis that we present here:

1. Indifference to international literature

The published study does not take into account and/or contradicts a whole body of well-reasoned work on pathophysiological elements, work which helps us begin to understand the mechanisms of long Covid (downplaying "*some state-of-the-art literature review about possible mechanisms of long COVID*"). The study does not acknowledge other thinking but advances without tangible evidence a nocebo effect as the cause of symptoms ("*I think nocebo effect could explain a part of the symptoms in some patients*"), and suggests that it is not possible to diagnose prolonged symptoms of Covid-19 by biological and medical examination.

Also, the study suggests a possible link, unsupported by their data, between symptoms and depression or other psychiatric illness (*"This disease could be, as well, depression, as you said. It could be a non-psychiatric disease. But it could be also a psychiatric disease. After all, fatigue, difficulties in concentrating, pain symptoms are symptoms of depression"*).

We observe that the message directed towards the public at large is quite different: "*our results in no way say that the disorders reported by the patients are imaginary or psychosomatic*" (franceinfo).

However, hundreds of international scientific publications have provided pathophysiological evidence for long Covid that corroborates patients' experience:

- Cerebral hypometabolism, unprecedented in size and location, which cannot be explained by anxiety, depression, somatoform disorder or post-traumatic stress disorder, observed by brain PET-SCAN
- Hypermetabolism in certain organs on whole-body PET-SCAN
- Abnormal density of dendritic cells and nerve fibers on corneal confocal microscopy
- Aortic hypermetabolism correlated with chest pain by whole-body PET-SCAN
- Abnormal levels of autoantibodies, by blood sampling, suggesting chronic autoimmune disorder
- Absence of, or rapid evanescence of antibodies or a fall in antibodies that is more pronounced the longer the symptoms last
- More frequent mast cell activation symptoms, by biopsy
- Immune dysfunction (low CD8+ T-cell levels), by blood sampling
- Impaired peripheral vasodilator function, by duplex ultrasound
- Abnormal amount of microclots, by fluorescent microscopy
- and many other multi-organ sequelae: heart, pancreas, central nervous system, lungs, kidneys, skin, reproductive organs, which can be found in this bibliography.
- The presence of severe disorders such as pericarditis, microemboli, degradation of the blood-brain barrier in the brain parenchyma via a protein creating microvascular damage, myocarditis, myositis, neuropathies, cognitive and sensory disorders, consonant with other

biomarkers and MRI imaging, single photon emission computed tomography (SPECT V/Q), inflammatory syndrome, increase in CPK.

In addition, many reports suggest an infectious origin for long Covid, as well as a full-fledged multi-organ attack. There is evidence of viral persistence, particularly in the olfactory bulbs, even in seronegative patients.

All this, attested to by teams of researchers in a hundred countries over the course of a year or more, suggest that, like SARS, **SARS-CoV-2 is likely to result in, among other things, long-term neurological after-effects**, which have already been classified as "**neurocovid**" in the literature. This is also the case following mild forms in non-hospitalized individuals, through pathophysiological mechanisms that are beginning to be clarified.

2. Small proportion of individuals linked to Covid-19 compared to the entire cohort

The study is based on a cohort of 26 823 individuals, which is considered robust by certain reviewers, even though only 1091 of the serological tests were positive.

Less than 6% of the cohort has had a positive serological test for Covid-19 or has self-reported infection. This limits the scope of statistical conclusions that can be drawn from the data (Diagram 1).

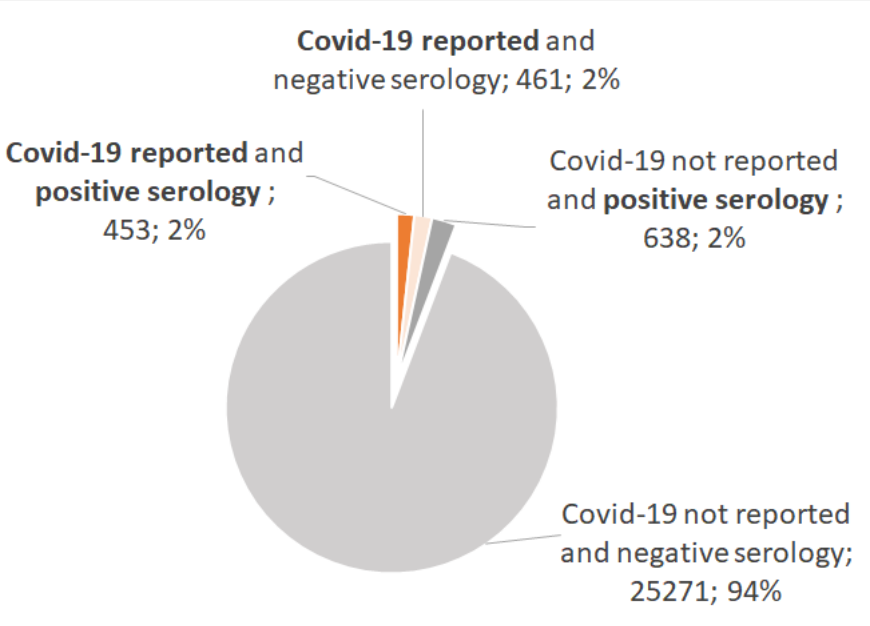

Diagram 1 – Breakdown of the cohort under investigation

Moreover carrying out analyses on people that do not report any infection is questionable. Indeed we know that prolonged symptoms appear essentially after a symptomatic viral episode, and very few after an asymptomatic infection. This bias tends to dilute the effect of symptomatic Covid-19 within the Serology+ population, reducing the ability to demonstrate statistical association with prolonged symptoms.

3. Data anomalies and methodological issues

There are discrepancies in the data from one table to the next. For example, the number of individuals reporting an episode of Covid-19 (*"positive belief"*) is 914 in Table 2 of the article, while it's 1001 in *eTable5* of Supplement 1; when broken down by symptom, the number of cases in the self-reporting population (*"positive belief"*) is different throughout the paper (see *Table 2* and *eTable7*); the percentages representing the proportion of each symptom (*Table 2*) do not match the data presented.

The authors base their conclusions on the assumption that positive serologies correspond to proven contaminations with SARS-CoV-2, and the fact that they don't find statistical correlation with the 18 prolonged symptoms under consideration, except anosmia (loss of smell) which is specific to Covid-19.

This conclusion, cornerstone of the study, poses a methodological problem for the following reason:

Weak statistical significance does not mean that a connection does not exist. The data may be insufficient to make a case. Here, absence of proof is mistaken for proof of absence.
Moreover, by analyzing the whole population with positive serological tests – including those who don't think they have had Covid-19 and thus are probably asymptomatic - those with prolonged symptoms are diluted in the population, making these symptoms less statistically significant. Unsurprisingly, anosmia stands out in spite of this dilution, because this highly-specific symptom is almost nonexistent in the general population.

4. Failure to take false positives into account

The study indicates that the serological tests that were used have a specificity of 97.5%, which carries a mathematical implication of 2.5% false positives, or 640 individuals out of 1091 with positive serological tests. The "false positive" serological tests were not taken into account (as indicated by methodology expert Prof Francis P. Wilson). This means that almost 60% of the population with positive serological tests, which the study accepts as having had Covid-19, never had the disease (Diagram 2).

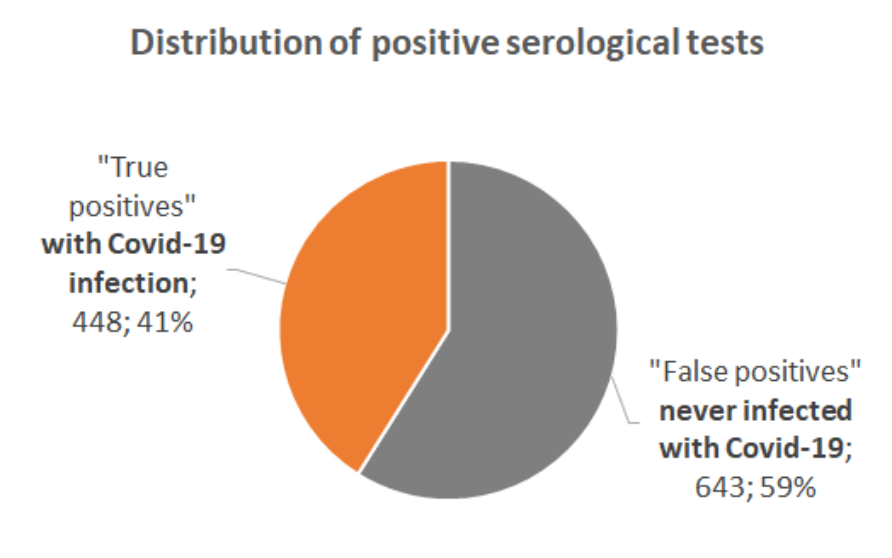

Diagram 2 – Distribution of true and false positives within the positive serological tests

5. Central to the analysis is a population which is wrongly defined

As seen previously, the population with a positive serology test result is not representative of those who have had Covid-19. Yet the analysis is based on this, thus invalidating the study.

The authors reply that their conclusions are nevertheless valid because they have found a statistical link between positive serology and anosmia (loss of smell), a symptom specific to Covid-19. The statistical significance of this is limited because it is based on a small group of only 51 people (*Table 2*) and with an odds ratio of 2.7 (*Table 3*) (Table A, below).

		No. (%) of participants			
		Serology−[a]		Serology+[a]	
Symptom	Total No.	Belief− (n = 25 271)	Belief+ (n = 461)	Belief− (n = 638)	Belief+ (n = 453)
Anosmia	146	75 (0.3)	20 (4.4)	7 (1.1)	44 (9.9)

Table A - (*extract from Table 2 of the article*): Number of cases and proportion (%) of anosmia

However, the statistical correlation with anosmia is considerably stronger in the population which claims to have had Covid-19, including those with negative serology, since there the odds ratio is over 16 (*Table 3*).

Following the authors' own reasoning, anosmia being specific to Covid-19, self-reported Covid-19 is much more closely correlated with actually having had a previous infection than is a serological test. This result is consistent with the data, as we are going to demonstrate.

6. Seropositivity following infection is overestimated

The analysis goes too far when it asserts that individuals claiming to have had Covid-19, but with negative serology test results, essentially never had the disease, although we of course recognize that some "Belief +" patients may not have been infected.

The serological tests, however, include false negatives, estimated at 139 cases by the authors. Moreover, numerous studies have shown that 25% of those who have recovered from Covid-19 never produce detectable antibodies. Assuming that the cohort is comprised of the 453 individuals with Covid-19 confirmed by a positive serology test result, as well as 139 false negatives, we can calculate that 25% of patients who don't test positive via serological test represent 197 individuals with negative serological test results despite having had a confirmed Covid-19 infection. These must be added to the false negatives, yielding aggregate figures close to the 461 with negative serology test results among those who believe they have had Covid-19 (Diagram 3).

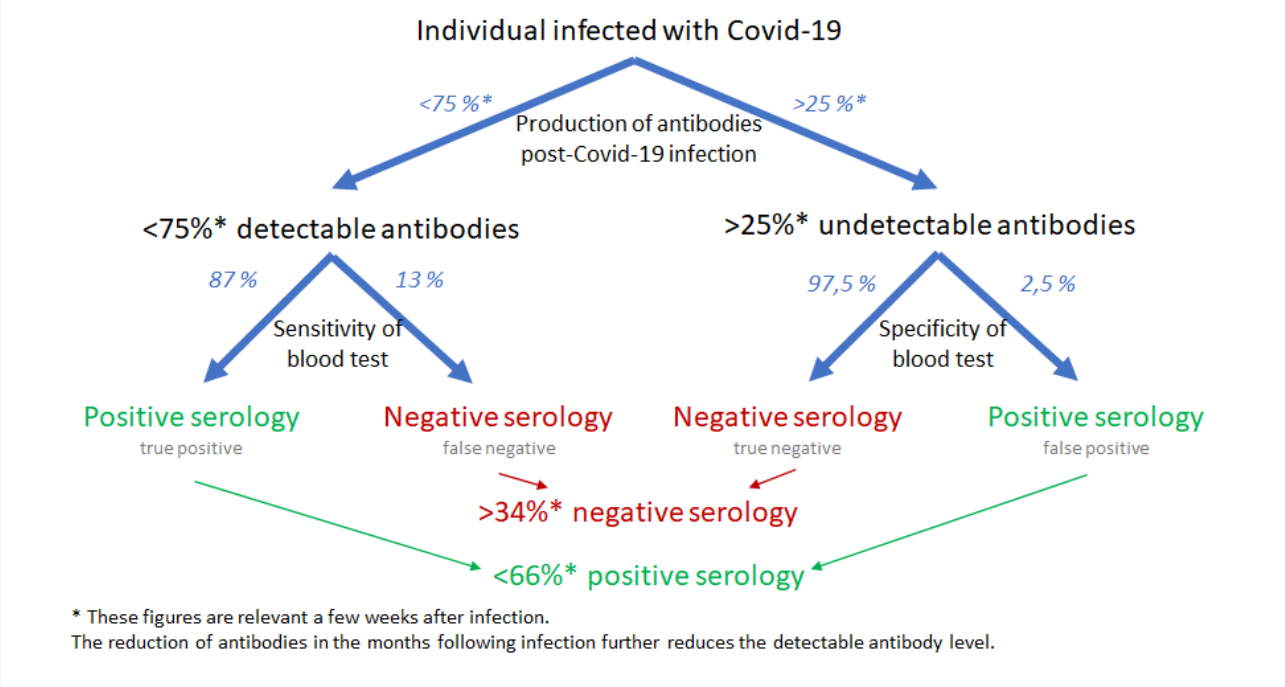

Diagram 3 – Determination of the serological status of a person infected with Covid-19

7. Issues connected with self-reporting

There are two issues:

- There is a large (but anticipated) proportion of those who are infected with Covid-19 but nonetheless have a negative serology test result.
- The very strong statistical correlation with anosmia (loss of smell specific to Covid-19) among those who claim to have had Covid-19, even with negative serological tests, substantiates the idea that a large proportion of this population really did have Covid-19 (Diagram 4).r

  We also see in the appendices (*eTable5*) that 65.5% of the individuals who say they have had Covid-19 have confirmation in the form of a PCR test, serological test, medical imaging or medical opinion.

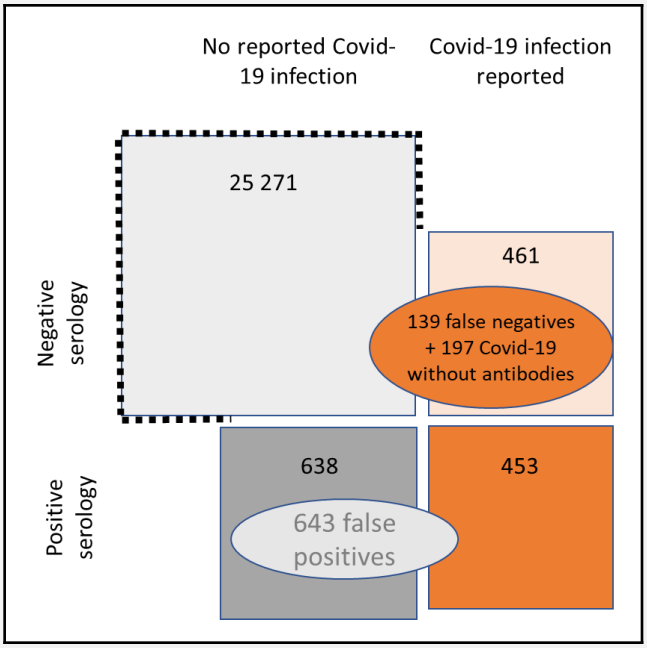

Diagram 4 – Distribution of populations by serological status and self-reported Covid-19 infections, taking into account false positives / false negatives and absence of detectable antibodies

8. Conclusions that appear to be reversed: self-reported experience is actually a more reliable indicator of Covid-19 infection than serology

We can deduce from the collected data that patients' self-reported experience is a much more reliable indicator of an episode of Covid-19 than are serological tests. This aligns with the opinion of the HAS (French Medical Authority for Health) and the World Health Organization (WHO).

9. Evidence that supports a link between self-reported infection and prolonged symptoms

Therefore, given that the population which self-reported infection *("positive belief")* is highly representative of a population that has been exposed to Covid-19, we can revisit the observed outcomes for this group.

There is a recognized correlation with 16 of the 18 prolonged symptoms ("*positive belief*" – *Table 3*) for the population with the greatest exposure to Covid-19. This result supports a connection between Covid-19 infection and the onset of persistent symptoms. This substantiated conclusion – contrary to that of the publication – is consistent with numerous other studies on the subject.

The analyses in the final part of the study reinforce this finding. First of all, the authors state that their results are not impacted when patients' state of health prior to the pandemic is taken into consideration, nor by their symptoms of depression (*eTable6*). This supports the idea that the symptoms are triggered following infection of the patients in question by a new disease.
Next, in *eTable7*, the authors concern themselves with individuals with confirmed Covid-19, be it by serological test, or other (PCR test, medical opinion…), among the population self-reporting infection. It is interesting to see that, for most of the symptoms, the odds ratio is greater than 1. Even if the sample is inadequate for statistical significance, it nevertheless indicates that in the study population reporting

having had Covid-19, the proportion of prolonged symptoms is overall higher among those for whom the infection is medically confirmed.

We have concerns as to how the article's conclusions, which do not correspond to a well-founded analysis of the data, could have appeared in a scientific journal of record.

Taking exception to the arguments defended by the authors in the media:

Some of the authors have defended the relevance of their study in the media, stating: "The probability that a person with a positive serological test was infected is only *59%. But this probability is 0.5% in the case of a negative serological test. In other words, in comparing individuals with positive serological tests to individuals with negative serological tests, our study deals with people with 100 times the probability of having been infected.*" (*Le Monde*).

The terms used here are improper, the figures are inexact and this point in no way supports the study's conclusions.

Indeed:

- "*The probability that an individual with a positive serological test result was infected*" as quoted above is in fact the probability that he or she has detectable antibodies given that his or her serology test result is positive.

  The authors estimated this when they calculated the rate of true positivity among those with positive serological test results *(but with a calculation error - false positives and true positives have been reversed; the calculated probability is the complement of what is outlined).*

P detectable antibodies/serology +=1091 "positive serology"- 643 "false positives"1091 "positive serology"=448 "true positives"1091 "positive serology"=41% not 59%.

Consequently, less than half of the positive serological tests correspond to people who were actually infected, which is one of the elements discrediting the study.

- "*The probability that an individual with a negative serology test result was infected*" is in fact the probability that an individual has detectable antibodies given that his or her serology test result is negative. The calculation here is based on false negatives,

P detectable antibodies/serology -= 139 "false negatives"25 732 "negative serology"=0.5%

This calculation does not take into account the 25% of those infected who never develop detectable levels of antibodies.

But this weak result indicates above all the lopsidedness between the positive and negative serology results (96% with negative serology test results in the cohort - see diagram 1).

Furthermore, the multiplicative ratio of 100 between the two probabilities presented here in no way resolves the methodological issues that have been raised.

Obviously, this factor is relevant when one compares the seropositive and seronegative populations, as in model 2 (*Table 3*). Here one sees, moreover, a statistically significant link between positive serological tests and 10 prolonged symptoms (*other symptoms also appear to be correlated, but the limited number of positive serology test results, 1091, involves too much uncertainty for statistical validation)*.

In model 3 - the only one drawn upon for the article's conclusions - this ratio is no longer respected. Indeed, the statistical mutual adjustment that is used compares positive and negative serological tests within the subgroup claiming to have had Covid-19 ("*positive belief*"). As we have demonstrated above, despite negative serological tests a very high proportion of this population has had Covid-19, a far cry from the 0.5% asserted by the authors.

It is necessary to look at the study with a critical eye. In the last few days, the study has been widely reported in the media. The interpretations that have been drawn from it have often been egregious, even more so than in the study itself, fueling contempt for people who are denied benefits for chronic illness on the grounds that their symptoms are not necessarily related to Covid-19.

There have been serious canards. For example, it has been falsely stated in the media on several occasions that in 26 out of 27 cases, people who believe they have long Covid were in fact never infected.

Uninformed media coverage of the study further jeopardizes patients by spreading untrue and stigmatizing misinformation**.**
Long Covid may stem from a combination of causes: direct or indirect damage by the virus; including inflammation, induced autoimmune disorder; etc. Attributing it to "belief" is detrimental. The use of the category of "belief" trivializes patients' lived experience and risks aggravating their already difficult health and social situation. Patients are already confronted with an obstacle course in obtaining appropriate medical care; they encounter denial of their symptoms, financial difficulties, derision, callousness and mishandling. Regrettably, the highly questionable interpretations of the results of this study are presented as "hypotheses," while the patients' interpretations, which are supported by numerous scientific studies, are relegated to the level of "beliefs." Revealingly, the authors switch from the notion of "self-reported infection" to that of "belief", as if they were the same thing, whereas the first formulation ("self-reported infection") is much more neutral. Using this formulation throughout would have been more accurate and less biased. **Characterization as "belief" also has a negative effect on the caregivers' work; they need to understand** the mechanisms of this disease and help their patients. They are sounding the alert, and we should listen.

Past experience with HIV, cancer and other chronic illnesses has shown that patient expertise must be taken into account. **It is urgent, in the case of the emerging disease of long Covid, that we all work together and combine medical and experiential knowledge to make progress towards a more precise scientific description of this disease**. The work that went into this press release is clear evidence that we, the associations, must be included as part of this collaborative effort.

It is by integrating all actors, including patients and associations, in a responsible, concerted and democratic approach to healthcare, that we will draw useful lessons from this controversy, which has become a crisis in part because of fallout from media coverage. In view of the resurgence of the pandemic, in view of public health concerns, questioning the reality of long Covid is all the more problematic.

Thus,

We want **science-based medicine**, based on evidence and not on flimsy interpretations.

We want **inclusive healthcare**, which makes the experience and expertise of patients in partnership with professionals central.

We want **ethical and fair healthcare**, accurate and trustworthy, with good communication.

We are sending analysis, questions and criticisms of the study to Mr. C. Lemogne, the corresponding author of the study.

We will take great interest in the answers from the authors, in the transparency of their communication, and in their refutation or validation of the data we present.
If called for, we hope they will provide corrections or clarifications to *JAMA Internal Medicine*, so that the scientific and medical community is presented with evidence that meets **the criteria for relevant, unimpeachable research**.

We are at the disposition of the media to discuss the flawed and inaccurate mathematical reasoning in this study.

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