failure, early mortality and discharge to long term care.[7-9]

The widespread application of CFS at the front door for assessment of patients with COVID-19 led to concerns from patients and an outcry from disability advocacy groups.[10,11] These concerns primarily centred around the risk that clinicians may be influenced by the value that society places on disabled individuals' lives. A misapplication of the CFS in patients with stable disability may lead to snap judgments based on high social care or support needs an individual may have.

NICE amended the guideline on 25th March 2020 to include the statement: "The CFS should not be used in younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disability or autism. An individualised assessment is recommended in all cases where the CFS is not appropriate."

We believe there may still be a dilemma for doctors, and risk of harm to patients. Does this brief caveat give new users of the CFS enough information to judge when its use is not appropriate? It is amply clear that the CFS is inappropriate for people with learning disabilities and autism. However, clinicians may be falsely reassured that outside of these stated examples, the CFS can be applied with confidence, even in those as young as 65 years.

Interpretation of the NICE amendment is hampered by the lack of a consistent concept of disability. Cerebral palsy is a health condition. Those who score highly on the CFS are almost certain to have disability. The CFS descriptors draw heavily on activities of daily living, and activity limitation is a key aspect of what constitutes disability, according to the International Classification of Functioning, Disability and Health (ICF) model.[12] Indeed there has been found to be a very high degree of overlap between frailty and disability (when defined as dependency in at least one basic ADL).[13]

Perhaps the emphasis should be with the word stable. However, the CFS captures only a single point in time, suggested to be two weeks prior to the acute presentation. The presence or absence of an underlying trend to increased dependency consistent with frailty will not be apparent. In short, despite the appearance of this disclaimer, invalid use of the CFS may continue. If this happens it would not only be discriminatory, it would be ineffective and would result in making the wrong decisions about best use of limited healthcare resources.

The CFS is not a direct measure of frailty, which is a physiological state. It is a series of roughly ordinal descriptions based mostly in the 'activity' domain. Its use is intuitive for clinicians as the descriptions are neatly described and are of recognisable phenotypes. Although the CFS functions well in older people as a surrogate for the likelihood of frailty, the score and the frailty are two different things. The assumption being made when a CFS score is used to predict a health outcome is that the interaction is mediated by frailty. When applied to younger people, or those for whom measuring activity would be confounded, the assumption is not valid. Many health conditions cause limitations in activity, such as arthritis, COPD or anxiety, not necessarily via frailty. This is especially true in younger people and when the disease process is largely confined to a single body system. In someone with a previous traumatic brain injury, the link between needing assistance with finances, and chance of surviving an ICU admission may not be present at all, or may be present via another causal mechanism.

This highlights the risk of over-medicalising our decision making. Learning from the social model of disability, and recognising the significance of social determinants of health, we should accept that 'physiological vulnerability' is not the only plausible causal link between activity limitation and health outcomes. This is important because if younger disabled people experience worse outcomes from hospitalisation, this may be for reasons other than physiological frailty. These reasons need to be exposed and challenged, not made into a self-fulfilling prophecy.

We also risk losing the trust of disabled people and those with long term conditions, especially in the climate of an unprecedented pandemic. A policy for blanket administration of the CFS on admission may lead to an anchoring bias in subsequent decision making, even by clinicians aware of its limitations. This must be consciously resisted. Some people with activity limitations associated with a longstanding stable health condition may indeed be less likely to benefit from ICU admission. Ideally, this requires an individualised assessment by a clinician experienced in that particular patient group, in partnership with the individual. Availability of ideally experienced clinicians may be difficult to achieve during this pandemic. The use of a patient passport can ensure relevant information is available to all hospital clinicians to aid decision making. Effective advanced care planning reduces the need for decisions to be made in an emergency and enables the values and priorities of the individual to be incorporated fully into decision making.

As a way forward we suggest that to apply the CFS appropriately requires an understanding of its underlying premise. Geriatricians are already familiar with this, but this new guidance may see staff groups who are not well versed in frailty concepts using the CFS under pressure. The team behind the CFS have recently published a helpful one page 'top tips' guide which should be available in all clinical areas where the CFS is being used.[14] The NHS Clinical Frailty Network provides training in the use of the CFS.[15] Where Trusts have incorporated CFS into their local guidelines or documentation, the caveats to its use must be clearly indicated.

In conclusion, we suggest that in addition to the recent amendments to NICE guidance on use of the CFS in making treatment escalation decisions, where there is doubt as to the applicability of the frailty concept, the CFS should not be used. There is no substitute for an individualised assessment by an experienced clinician.

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Mass cytometry provides unprecedented insight into the role of B cells during the pathogenesis of multiple sclerosis

Key take-home messages

- B cells can play a detrimental and protective role in the pathogenesis of multiple sclerosis
- Mass cytometry provides insight into the multitude of B cell subsets
- Interrogating B cell subsets will provide further insight into the pathogenesis of multiple sclerosis

Abstract
In recent years, it has become clear that B cells play a prominent role in the pathogenesis of multiple sclerosis (MS). This is most evident when considering the effectiveness of anti-CD20 monoclonal therapeutics including rituximab and ocrelizumab. In fact many successful therapeutics alter the level of switched memory B cells. It is however unlikely all switched memory B cells are detrimental in the context of MS. The ability to distinguish between various B cell subsets is hence important if we are to more specifically target detrimental from potentially beneficial B cells. Mass cytometry provides the ability to interrogate a larger number of markers in a single experiment, allowing unprecedented insight into B cell subsets and how they contribute to MS disease progression. This review highlights the importance of investigating B cells in the context of MS, and how mass cytometry provides the ability to interrogate a large number of subsets for an in-depth characterisation.

B cells can play a detrimental and protective role in the pathogenesis of multiple sclerosis

In recent years, it has become clear that B cells play a prominent role in the pathogenesis of multiple sclerosis (MS). This is most evident when considering the effectiveness of anti-CD20 monoclonal therapeutics including rituximab[1] and ocrelizumab.[2] The majority of successful disease-modifying therapeutics (DMTs) including monoclonal antibodies, are incapable of crossing the blood-brain barrier, cladribine[3,4] and fingolimod[5] being exceptions. The mechanism of action of successful therapeutics such as cladribine,[6] anti-CD19 (inebilizumab), anti-CD52 (alemtuzumab), S1P agonist (fingolimod), anti-VLA-4 (natalizumab) and dimethyl fumarate,[7] appears to involve modulating the level of circulating B cells within peripheral blood. More specifically, these studies have found $CD27^+$ memory B cells to be particularly affected, with efficacy correlating with large numbers of memory B cells being removed from circulation. It has therefore been proposed that memory B cells play a key role in MS pathogenesis.[8] As part of the adaptive immune response, memory B cells provide defence against previously encountered pathogens. In people with MS, the majority of B cells found within white matter lesions are $CD27^+$ memory B cells.[9] Although the exact role of memory B cells in the context of MS is yet to be fully understood, recent work by Jelcic et al.[10] found memory B cells were capable of activating brain-homing T cells that may contribute to disease pathogenesis. However, it is unlikely all circulating memory B cells contribute to disease pathogenesis, meaning that more work is needed to differentiate pathogenic from non-pathogenic subsets of memory B cells.

There is growing evidence not all B cells are detrimental in the context of MS, with some playing a protective role. These so called "regulatory B cells" or B_{Regs} are capable of suppressing an immune response and many studies have investigated B_{Regs} in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Mice deficient in IL-10-producing B cells are incapable of recovering from EAE.[11] While depleting B cells with anti-CD20 prior to EAE induction worsens disease, removal of B cells *after* signs of clinical disease reduces disease severity.[12] Thus, B cells are important for preventing the development of CNS-autoimmunity and limiting disease severity, but once disease has developed, different B cells subsets are pathogenic. Novel DMTs such as exposure of the skin to ultraviolet (UV) radiation which can protect mice from EAE[13] and delay the onset of MS[14], work in part by activating EAE-protecting B cells.[15]

In contrast to regulatory T cells, which are routinely defined by their high expression of CD25 and FoxP3 and low levels of CD127[16] there is no defined phenotype that enables the reliable identification of B_{Regs}. This has led to the hypothesis that any B cell has the potential to become regulatory, and that it depends on the environment in which it finds itself as to whether the B cell exerts immune regulation.[17] In fact, many subsets of B cells