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## Response to Commentaries: Frequent Preservation of Neurologic Function in Brain Death and Brainstem Death Entails False-Positive Misdiagnosis and Cerebral Perfusion

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We thank the authors of commentaries for their thoughtful discussion of our target article. Here we briefly summarize the points made in the target article (Nair-Collins and Joffe 2023). Then we emphasize how the commentary authors overall agreed with us that false positive diagnoses of brain death (BD) are common. Finally, we discuss where we believe that commentary authors made some errors, common in the literature, when discussing the concept of BD.

Our target article discussed that osmoregulation is an essential brain function that involves the delivery of “a stimulus to provoke central processing and an efferent response” (Greer et al. 2020, Suppl 5, p. 20). Osmoregulation is achieved by release of vasopressin from magnocellular neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus, with additive glutamatergic input from circumventricular basal forebrain areas. About half of patients diagnosed with BD according to accepted medical standards have this homeostatic brain function maintained. This means that the diagnosis of BD was a false positive, incompatible with the Uniform Determination of Death Act (UDDA) that requires “irreversible cessation of all functions of the entire brain,” and that there was preservation of some brain perfusion despite ancillary cerebral blood flow testing that incorrectly diagnosed brain circulatory arrest.

Based on the commentaries, we consider our target article successful in having shown that false positive diagnoses of BD are common. Most commentary authors straightforwardly agreed that the continued brain function of osmoregulation means that the current American Academy of Neurology (and other) guidelines for the diagnosis of BD result in pervasive false positive diagnoses according to the law (e.g., as stated in the UDDA) (Batra and Latham 2023, 269;

Bernat 2023, 271; Weber 2023, 271). This was implied by other commentary authors who argued that the diagnosis of BD only meets the standard for a higher-brain-death criterion, which is not consistent with the UDDA (Batra and Latham 2023, 269; Hanson 2023, 278; Martin, Forlini, and Tumilty 2023, 280; Milian and Franco 2023, 275; Weber 2023). This was also implied by Bernat (2023) with the “brain-as-a-whole” argument that depends on the “*sui generis*” emergent-function of the brain (“conscious functions … qualitatively different from nonbrain functions because they are non-reducible”) (Huang and Bernat 2019, 217). Molina-Pérez (2023) went further, pointing out that the “two criteria of the UDDA are inconsistent in their use of the notion of function”—because circulatory function refers to both spontaneous and artificially supported functions, while brain function refers to only spontaneous functions (i.e., excluding artificial support of “breathing, thermoregulation, and blood pressure regulation”)—suggesting there are even more false positive BD diagnoses than we considered. Here we do not discuss debates regarding higher-brain-death (for discussion, see Joffe, Khaira, and de Caen 2021).

Of note, the recent three-year deliberations by the Uniform Law Commission to consider revision of the UDDA were “stayed,” meaning, for the time being the wording of the UDDA remains unchanged, and current practice in the diagnosis of BD remains incompatible with the legal definition of death in the United States. Moreover, arguing that the law should change to accord with medical standards (Bernat 2023) is both moot—revising the UDDA was debated and it remains unchanged—and incorrect—“accepted medical standards” were meant to be those used to diagnose the condition explicitly stated as the legal criterion of death (that is, “irreversible cessation of all

functions of the entire brain") (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research 1981, 78). Indeed, the law regulates medical practice (not the other way around), including regulation of the scope of medical practice, the scope and obligation of informed consent, all aspects of clinical research, end-of-life practices, and of course, the diagnosis of death.

The literature on BD can be confusing (Joffe, Khaira, and de Caen 2021). We suggest that some commentary authors fell prey to common fallacious arguments, those that we would argue are important to clarify and explain here. First, the appeal to authority, without engaging in critical scrutiny of arguments questioning the authority consensus. For example, Martin, Forlini, and Tumilty (2023, 281) stated that diagnosis of BD "is well established and confidently implemented around the world," Milian and Franco (2023, 275) argued that there "is broad consensus," and Bernat (2023, 271) wrote that there is "widespread international agreement among physicians." This despite Bernat (2023, 273) pointing out that "most clinicians had only a vague understanding of brain death." The appeal to authority is the exact fallacy that we aimed to address with critical scrutiny.

Second, straw-man arguments that similarly, while important, do not engage with the underlying question of whether BD meets the legal definition of death. For example, Batra and Latham (2023, 269) discussed the risk of "depriving potential organ recipients of lifesaving interventions," and Martin, Forlini, and Tumilty (2023, 280) mentioned the risk of "preclud[ing] the successful recovery of organs for transplantation." But the concept of death has no bearing on organ donation, and considering this an implication is usually said to introduce conflict of interest. No concept of death hinders or facilitates organ donation, rather, the dead-donor-rule does that, intended to constrain medical practice in vital organ donation. The question we do not debate here, as Weber (2023) identified, is whether to abandon the dead-donor-rule. Martin, Forlini, and Tumilty (2023, 280) argued that the problem would be "families [that] insist on continuing at all costs." This suggestion is not supported by evidence (Nair-Collins 2023) and does not directly address the question at hand. Martin, Forlini, and Tumilty (2023, 279) were also concerned that we were setting "the epistemic bar" for diagnosing BD "unreasonably high." But how any physiological state is diagnosed does not depend on how difficult the diagnosis might be. Moreover, loss

of brain osmoregulation function is not difficult to diagnose, requiring only bedside measurement of urine output, plasma sodium (required anyways to rule out confounding conditions), and consideration of confounding conditions (as for any finding in BD).

We also suggest that some of the authors fell prey to often repeated, yet mistaken, assertions regarding the diagnosis of BD. We would argue that these mistaken assertions, common in the literature, are crucial to clarify and explain here. Batra and Latham (2023, 270) suggested that the President's Commission's "intended meaning [of 'irreversible'] was permanent" based on personal communication to James Bernat by Alexander Capron, the executive director of the President's Commission. They considered this interpretation important because "no one should be prevented from donating an organ because their circulatory or brain function could conceivably be restored against their will" (Batra and Latham 2023, 270). However, it is important to point out that Capron explicitly denied this interpretation in 1999:

The Pittsburgh protocol [i.e., DCD] seems less a challenge to the UDDA than simply a contradiction of it... irreversibility must mean more than simply "we choose not to reverse, although we might have succeeded" ... replacing "irreversible cessation of circulatory and respiratory functions" with "we choose not to reverse" flies in the face of the UDDA's underlying premise (Capron 1999, 132).

Milian and Franco (2023, 275, 276) suggested that "the extremely rare case reports suggesting the recovery of partial neurological functions are typically attributed to misdiagnoses arising from noncompliance with established guidelines" and that "the spirit of the law refers to the cognitive functions of the brain." But that these case reports are rare is not unexpected, because the diagnosis of BD is a self-fulfilling prophecy, leading to withdrawal of life-support (sometimes with organ donation). We pointed out, and again emphasize, that there are multiple case reports of "recovery of partial neurological functions" (including spontaneous breathing or other brainstem functions) in patients diagnosed in full compliance "with established guidelines" (referenced in our target article and discussed further in Joffe, Khaira, and de Caen 2021). In addition, it is important to clarify that the "spirit of the law" was explicitly to exclude patients in vegetative state, who have no cognitive function, yet are considered alive (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research 1981; and reaffirmed by the President's Council on Bioethics 2008).

Molina-Pérez (2023) made a novel and interesting argument that hypothalamic function in BD is “not the normal case” such that the “term ‘function’ for preserved hypothalamic activity assumes that the organism is alive” (i.e., the concept of function only applies in “the normal case”). This was supported by the analogy of the functioning explanted heart that falsely implies “declaring the donor’s death based on the irreversible loss of heart function constitutes a false positive.” We respectfully disagree with this assessment. First, we would argue that all positions in debating BD are not to presuppose death, but rather consider brain and other organism function(s) to define whether death has occurred; indeed, it is impossible to explain any disease condition in medicine (i.e., “not the normal case”) in absence of the concept of function. Second, heart function is not a criterion of death at all—rather, the criterion is irreversible loss of *circulation* in the organism.

In summary, our thesis stands—false positive diagnoses of whole-brain-death according to accepted medical standards are common, and the commentary authors agree. This state of affairs we consider to be a risk to the trustworthiness of medicine.

## CONFLICTS OF INTEREST

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