

Brain Death—Moving Beyond Consistency in the Diagnostic Criteria

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In this issue of JAMA, contributors to the World Brain Death Project present an international consensus report on criteria for the diagnosis of brain death, or determination of death by neurologic criteria (BD/DNC).¹ The report addresses inconsistencies in clinical guidelines across different countries and focuses attention on the need for better education and certification of clinicians who are authorized to make this clinical diagnosis.

Highlights of the summary report, along with the 13 in-depth reports provided in the accompanying supplemental material, include recommendations for the minimum clinical standards for determination of BD/DNC in adults and



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children, with helpful checklists and flowcharts. When the clinical examination cannot be completed, the Special Communication provides guidance for the use of

ancillary diagnostic techniques. The report offers recommendations for testing patients who have received therapeutic hypothermia and for those supported with extracorporeal membrane oxygenation (ECMO). In addition, the report considers the importance of religious, cultural, and legal factors in making the diagnosis. The materials also include more than 70 questions to guide further research. The depth and scope of this project are reflected in the detailed and extensive content of the reports.

This Editorial aims to frame these recommendations within a larger context, by focusing on 2 key issues: the definition of death and the conceptual basis for defining death by neurologic criteria.

First, while consensus on the diagnostic standards is important, clinicians (and patients) must remember that the determination of death is not merely a scientific question to be answered by medical experts. Conceptions about what it means to be a living human being, and what it means for that life to end, rest on profound questions involving personal and foundational views in philosophy, religion, and culture. For example, the assumption that death can be defined in neurologic terms privileges a largely Western cartesian view above the more holistic views typical of Eastern cultures and religions.² Development of these consensus criteria should not be misinterpreted to imply that the concept of BD/DNC is universally accepted, and future research should include consideration of cross-cultural differences around these fundamental existential questions.

Second, even accepting the view that death can be defined in terms of neurologic functioning, no consensus exists on whether BD/DNC represents the death of the

whole brain, or just the brainstem. In the US (and most other countries), whole-brain death is the legal standard, requiring determination of the irreversible cessation of all functions of the entire brain, including the brainstem.³ This view is founded on the premise that a functioning brain is required for the continued functioning of the organism as a whole.⁴ Once brain functioning ceases, the body is no longer “integrated”—and literally disintegrates—such as after cardiac arrest. As one US expert suggested, “[physicians] now invariably equate brain death with death and do not distinguish it biologically from cardiac arrest.”⁵

In contrast, the standard in the UK and other countries and regions (such as India and Hong Kong) focuses exclusively on the loss of brainstem functions.^{6,7} These include functioning of the reticular activating system (which is necessary for maintaining consciousness) and the respiratory centers (which are necessary for spontaneous respiration). Under the brainstem standard, BD/DNC is therefore conceptualized as a state of “irreversible apneic unconsciousness.” The UK standard does not claim that BD/DNC is equivalent to biological death, acknowledging that biological activity may persist, but rather asserts that brainstem death is death because it “entails the irreversible loss of those essential characteristics which are necessary to the existence of a living human person.”⁸

Over past decades, evidence has shown that the whole-brain concept has empirical flaws. First, experts now recognize that the diagnostic criteria for whole-brain death do not, in fact, diagnose the loss of all brain functions. Some patients correctly diagnosed by current criteria retain some brain functions, such as hypothalamic functions that regulate vital biological processes like temperature control and fluid homeostasis.⁹ Second, the 2008 US President’s Commission concluded that patients correctly diagnosed with BD/DNC can maintain integrated biological functioning for months and even years.^{10,11} In other words, whole-brain death fails on 2 counts: it is neither the complete loss of all brain function, nor is it synonymous with biological death.

In contrast, the UK concept of brainstem death, conceptualized by Pallis in the 1980s,¹² avoids both of these problems. Rather than requiring the loss of all brain function, it focuses on the irreversible loss of only 2 critical brain functions: consciousness and spontaneous respiration.

The distinction between whole-brain and brainstem death⁶ is critically important, for 2 reasons. First, the US position characterizes BD/DNC as a scientific “fact” (biological death), implying that those who disagree with this concept are either uninformed or irrational. In contrast, the UK approach adopts a values-based position regarding the essential characteristics

of a living human being. The UK has therefore given the force of law to a particular set of values that it presumes to be widely shared within that society, even while accepting that some citizens may hold personal views not aligned with them.

The second reason that clarity about the meaning of BD/DNC is critical is because progress in improving and refining the criteria will be impossible without it. Under the US approach, the criterion standard for assessing the validity of the tests is whether they correlate with the loss of integrated functioning of the organism as whole, ie, biological death. But this reveals a fundamental problem: none of the tests fulfill the criterion for the US standard. In contrast, the UK standard provides clear diagnostic “targets” by which current and new tests can be assessed, ie, whether the patient is in a state of “irreversible apneic unconsciousness.”

Is the patient unconscious? Clinical assessment of the loss of consciousness requires that “there is no evidence of arousal or awareness to maximal external stimulation.”¹¹ For many decades, this was the same standard used for diagnosing unconsciousness in the persistent vegetative state. Advanced neuroimaging such as functional magnetic resonance imaging (fMRI) has shown this criterion to be incorrect in a substantial number of cases.¹³ This is not to imply that every case of BD/DNC needs to have confirmatory fMRI evidence, but rather that the guidelines from the World Brain Death Project for establishing unconsciousness need additional empirical support, particularly for patients who have isolated brainstem pathology.

Has the patient lost the capacity for spontaneous respiration? Guidelines for the management of patients with increased intracranial pressure call for tight control of the PCO₂ (partial pressure of carbon dioxide) to the low normal range (35-40 mm Hg). Yet the procedures for performing the apnea test require allowing the patient’s PCO₂ to increase to 60 mm Hg or more, potentially causing the condition that the test is intended to diagnose. In addition to safety concerns, empirical questions remain about the threshold levels of PCO₂ necessary for a valid test, particularly in children, and how these may vary at different levels of oxygenation.¹⁴

Given these risks and uncertainties, future research should explore alternatives to the apnea test based on demonstrating irreversible destruction of the brainstem. While existing neurophysiologic and neuroimaging technologies are not sufficiently sensitive or specific, future research may

be successful in further refining these technologies or developing new tools to eliminate the need to perform the controversial apnea test.

Are the conditions of unconsciousness and apnea irreversible? Irreversibility can never be a certainty; it is always a refutable hypothesis contingent upon the absence of evidence to the contrary. This is further complicated because the diagnosis of BD/DNC is essentially a self-fulfilling prophecy, since biological death usually follows the diagnosis within a short period (by either organ donation or ventilator withdrawal), making it impossible to know if these patients might have shown some evidence of recovery had somatic support been continued.

Furthermore, empirical evidence of irreversibility would be difficult to establish. Large numbers of patients would have to be studied for prolonged periods to establish a false-positive rate that would be low enough to be deemed acceptable for the diagnosis of death. The fact that such studies are probably not feasible does not mean that irreversibility can never be assumed, only that the assumption will likely need to be based on theoretical considerations of the degree of neurologic injury, rather than on empirical studies.¹⁵

The World Brain Death Project guidelines represent an important contribution and serve as a foundational report for all clinicians involved in determining brain death. Scientific experts and representatives of numerous societies contributed to this process and were able to provide recommendations for the minimum clinical standards for determination of BD/DNC in adults and children, with clear guidance for various clinical circumstances. Bringing these recommendations to the entire international community will require a 2-pronged approach. First, evidence to support the existing tests needs to be bolstered, and this may require greater use of advanced neurodiagnostic techniques. A key question will be whether the whole-brain biological standard for defining BC/DNC will remain tenable, or whether this concept should be replaced by the values-based brainstem standard. Second, since much of the world does not have access to advanced technologies, the World Brain Death Project will need to focus on development and validation of tests that rely on the clinical examination and widely available diagnostic tools. This will be essential if the capacity for accurately diagnosing BD/DNC is to become accessible to all clinicians around the world.

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