



# Arguments in Favor of Requiring the Absence of Brain Circulation to Determine Death by Neurologic Criteria

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The Uniform Determination of Death Act (UDDA) defined death by neurologic criteria (i.e. brain death) as “irreversible cessation of all functions of the entire brain, including the brain stem ... in accordance with accepted medical standards” [1] The American Academy of Neurology and other organizations have outlined these “accepted medical standards” [2, 3].

Recent scholarly, legal, and public discourse has highlighted controversy around the fact that these accepted medical standards are not sufficient to identify *irreversibility* or interrogate *all functions of the entire brain*, as stipulated in the UDDA. Aware of the mismatch between statutory definitions of death and accepted practices for determination of death, at least two solutions to address this mismatch have been proposed: amend the law, or change accepted practice [4, 5].

In this chapter, I discuss three arguments in favor of changing accepted medical standards, in order to require the absence of brain circulation to determine death by neurologic criteria. While it is possible that patients can have irreversible loss of brain function without loss of brain circulation, technical factors can make it challenging for physicians to determine irreversibility or loss of all functions of the entire brain. Mistakenly determining death is an unacceptable practice. One way to prevent false positives is to change accepted medical standards by mandating confirmation of the absence of brain circulation. This change in practice would align the determination of death by neurologic criteria with the definition of death codified in the UDDA, by demonstrating both *irreversibility* and cessation of *all functions of the entire brain*.

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## 1 What Are the Accepted Medical Standards for Determining Death by Neurologic Criteria?

In 2010, the American Academy of Neurology published updated guidelines for the determination of death by neurologic criteria in adults. These guidelines have been adopted by a number of other professional organizations and are widely considered to be the “accepted medical standard,” as stipulated in the UDDA [6]. Guidelines have also been published for use in newborns, infants, and children [3]. It is worth noting, however, that these “accepted standards” are based on expert opinion and expert consensus, rather than empiric studies or evidence [2].

An international panel of experts recently affirmed these guidelines [7]. These experts list prerequisites for death by neurologic criteria, which include identification of “an established neurologic diagnosis that can lead to the complete and irreversible loss of all brain function” and confirmation that confounding conditions and mimickers are absent. They reaffirm that death by neurologic criteria can be determined when a bedside clinical exam demonstrates coma, brainstem areflexia, and inability to breathe spontaneously. They reinforce that ancillary tests should only be considered when the “clinical exam cannot be completed” [7], and emphasizing the clinical bedside exam for responsiveness, brainstem reflexes, and apnea is the gold standard.

### 1.1 Do the Accepted Medical Standards for Determination of Death by Neurologic Criteria Assess all Functions of the Entire Brain?

The current accepted medical standards (“standard brain death exam”) for determining death by neurologic criteria, when done correctly, are accurate for identifying irreversible loss of brain function in the vast majority of cases—particularly cases in which high intracranial pressure leads to complete loss of brain circulation. However, the standard brain death exam assesses neither all functions of the brain nor irreversibility. This mismatch between accepted practices and legal definitions opens the possibility of false positives, in which a person can be determined to be dead by neurologic criteria according to accepted standards *without* losing all functions of the entire brain, and *without* irreversible loss of such functions. Rare cases of “false positive” brain death determination have been reported: despite the correct and complete use of accepted medical standards to determine death by neurologic criteria, the patient subsequently demonstrates brain functions [8–12]. Jahi McMath, for example, was maintained on organ support for years after a determination of death by neurologic criteria, and she subsequently underwent puberty and menarche [9, 11–13]. She may have also displayed autonomic reactivity and intermittent purposeful motor movements [9, 11, 12, 14].

The details of these exceptional cases have been debated, but the inability of the accepted standards to assess *all functions of the entire brain* is not debatable. The standard brain death exam assesses arousal, motoric brainstem reflexes, motoric

limb responses, and respiratory drive. There are a number of other brain functions not contained on this list. For example, “super locked-in patients” who have completely destroyed brainstems and loss of efferent activity, might still have preserved afferent visual and olfactory pathways (which bypass the brainstem on the way to the thalamus and cortex, respectively) [4]. Also, while it is generally assumed that damage to the reticular activating system of the brainstem destroys consciousness, there is no way to empirically verify this [15, 16]. Certain neurohormonal and autonomic functions, controlled by the hypothalamus or higher cortical areas rostral to the brainstem, could also be preserved despite the absence of brainstem function on a bedside exam.

Proponents of the brainstem exam as accepted practice have responded that individuals can be dead despite preservation of discrete brain functions, such as neurohormonal and autonomic functions, because the “brain-as-a-whole” is no longer functioning [17–19]. Over the last few decades the meaning of the phrase “all functions of the entire brain” has been debated, but a general consensus has coalesced around the idea that the phrase should be interpreted as the functioning of the *brain-as-a-whole*, or the core function of the brain, and not the persistence of every single brain function [4, 18]. However, there remains at least two problems with this argument. First, the UDDA clearly states “all functions of the entire brain.” The “brain-as-a-whole” is a reasonable interpretation of intent, but it does not follow the letter of the law. Second, it has not been possible to precisely define what functions constitute the “brain-as-a-whole.” Which are the “core” functions or “critical” functions [4, 20, 21]? Is it self-preservation [22]? Somatic integration [21, 22]? Why are neurohormonal and autonomic functions excluded as important (i.e. core, critical) brain functions [9, 12]? Until the core functions that define the brain-as-a-whole are empirically verified or achieve universal consensus, debate will continue regarding the question of whether a person with a brain that is severely damaged, but not completely destroyed, is dead.

There remains uncertainty regarding how best to resolve the opposition in the meaning of death by neurologic criteria: does it require irreversible cessation of “all functions of the entire brain” (i.e. whole brain function) or merely the function of the brain-as-a-whole? Defenders of the accepted medical standards highlight the fact that no patients determined to be dead by neurologic criteria, applied properly, have ever regained meaningful neurologic function [6, 7]. However, this statement defends the prognostic accuracy of the accepted standards, and is not a comment on whether the standard exam accurately reflects the binary, biologic state of death. The philosophical conception of death, as conceived by the vast majority of the public, is more in line with the law than accepted medical practice. In other words, most people would agree that death clearly requires both irreversibility and loss of all functions, and neither alone is sufficient. For example, someone who suffers a massive stroke has irreversible loss of *some* brain functions, and someone with a massive sedative or paralytic overdose could have an exam that mimics brain death prior to recovery. However, neither individual is dead, which begs the question: how can we ensure that the accepted medical standards for determining death by neurologic criteria are 100% specific in identifying both the irreversibility and loss of all brain functions that define death?

## 1.2 Do the Accepted Medical Standards for Determination of Death by Neurologic Criteria Assess Irreversibility?

Irreversibility goes beyond prognosis and reflects the future, or what *will* occur. In contrast to *permanent loss of functions*, which means that “ceased functions will not recover because they will not restart spontaneously and no medical attempts will be made to restart them” [23], irreversibility refers to a biologic state of certainty: once functions have ceased, they “cannot restart spontaneously and cannot be restored by any available technology” [23].

Current practices for the determination of death by neurologic criteria require coma, brainstem areflexia, and loss of respiratory drive. However, it is not technically possible to distinguish irreversible neuronal death from quiescent, nonfunctional tissue, which can mimic irreversible destruction in every way. Inevitably, before brain cells die from hypoxic injury, they transition through a state of stunned hypoperfusion [4, 9]. The “ischemic penumbra” is well-recognized in stroke care, but is not sufficiently considered by proponents of the accepted standards for the determination of death by neurologic criteria [4, 9, 24, 25]. Individuals can suffer a global hypoxic injury to the brain, due to increased intracerebral pressure or another mechanism, but the degree of hypoxia and hypoperfusion may be insufficient to cause widespread neuronal death. In these cases, the individual would be pronounced dead by neurologic criteria according to accepted medical standards, but could later regain some functions if the quiescent brain tissue is supported sufficiently through the time of convalescence.

The accepted standards account for some of these scenarios by recommending that an “irreversible and proximate cause of coma” be established, and that “a certain period of time has passed since the onset of the brain insult to exclude the possibility of recovery (in practice, usually several hours)” [2]. However, the amount of time past which brain recovery is impossible is not currently known, and depends on many factors such as overall health of the patient, age, collateral circulation, degree of global ischemia, state of medical technology and available supportive capabilities, and other patient-level factors—many of which are not yet known. In addition, the requirement of an irreversible cause of coma does not clarify how to assess irreversibility.

In practice, there is no standardized wait time across countries and institutions to ensure lack of recovery, and there is no empirically derived waiting period that can ensure irreversibility. In spite of this, proponents of the accepted standards point out that the current criteria have excellent value for predicting lack of neurologic recovery [6, 7]. In other words, the current criteria are prognostically accurate. However, this line of defense is flawed for at least two reasons.

First, once a death determination is made, organ support is withdrawn; there have not been high quality natural history studies to determine the accuracy of the accepted standards. The relatively few cases with long-term observation periods actually suggest relatively poor prognostic accuracy [8, 9, 26]. Second, death (by circulatory-respiratory or neurologic criteria) requires that life *cannot* be restored (irreversibility), not just that it *will not* be restored (permanence). In other words, a

determination of death precludes recovery by definition, so the diagnostic criteria must be formulated in such a way that recovery is impossible—not just improbable.

Currently there is no way to assess some of the core, critical functions that one may include in the functions of the brain-as-a-whole. The accepted practices for determination of death by neurologic criteria only assess responsiveness, brainstem reflexes, and respiratory drive. If those are absent, it is assumed that all functions of the entire brain are lost. However, as was discussed above, this does not assess all functions of the entire brain, and there is currently no definition of the functions that constitute the brain-as-a-whole. Furthermore, there are currently no validated tests to assess brain-as-a-whole functions when the brainstem has been damaged and motor activity is lost. Better tests are required to ensure irreversible cessation of all functions of the entire brain, as required by law. So how can death by neurologic criteria be better determined?

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## **2 Argument 1: Only the Absence of Brain Circulation Can Ensure Loss of All Functions of the Entire Brain**

One solution to better align accepted practice with law is to require the absence of brain circulation. Absence of brain circulation is incompatible with life, since all functions of the entire brain inevitably cease without perfusion. Experts in the determination of death by neurologic criteria assume that loss of responsiveness, brainstem reflexes, and respiratory drive reflect loss of brain circulation, but, as discussed above, this assumption can be misguided in cases of global hypoperfusion (i.e. a global ischemic penumbra) and hypofunctional (but not dead) brain, and in cases of direct brainstem injury. An ancillary test demonstrating the absence of brain circulation may better guarantee loss of all functions of the entire brain, if it could ensure the death of all neurons.

There remains a number of concerns with requiring the absence of brain circulation to determine death by neurologic criteria, however. First, tests of brain circulation are not universally available. Newer, more widely available tests such as CT and MR angiography are not as well validated as radionucleotide scanning [27]. Requiring perfusion imaging would preclude determination of death by neurologic criteria in most areas of the world that might not have access to newer technologies.

Second, these tests are not perfect. It is possible that neurons can survive below the threshold for detection of circulation [9, 11]. In other words, currently available tests might still be plagued by insufficient specificity for brain death, if they fail to distinguish a global state of hypoperfusion from true sustained and absent brain circulation. Another concern is that although the death of all neurons would inevitably result from sustained absence of intracerebral circulation, a test such as radionucleotide imaging can confirm absent or low flow only at one moment in time. In other words, perfusion imaging cannot confirm *sustained* absence of flow unless it is repeated several times. Even in cases such as global anoxia causing secondarily increased intracranial pressure with ensuing brain herniation, intracranial pressure

would correct according to the Monroe-Kellie doctrine as brain contents herniate out of the intracranial space. Therefore, a test of brain circulation would need to be timed correctly to confirm absent circulation, before subsequent changes in tissue compliance and parenchymal movements (i.e. herniation) reduce intracranial pressure and restore perfusion. Until the thresholds and dynamics of neuronal death resulting from absent perfusion are better understood, a single test showing absent intracranial circulation will be plagued by the same issues that plague the clinical brain death examination, and may not guarantee irreversible loss of all function of the entire brain. At the least, further tests of validation are necessary before the currently available ancillary tests of brain circulation can be universally recommended to improve the determination of death by neurologic criteria.

Finally, it must be noted that requiring the absence of brain circulation could have unfortunate detrimental downstream effects. Patients who are dead by currently accepted medical standards, with no chance of meaningful neurologic recovery, could be considered alive on the basis of some minimal amount of preserved brain circulation, prolonging the uncertainty and suffering of grieving family members. There is also no way to know if these patients, who cannot communicate without efferent motor activity, might be suffering needlessly. Organ donor recipients might also suffer if the dead donor standard, which requires that organ donors be dead before their organs are retrieved, is not simultaneously reconsidered [4, 28–30].

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### **3 Argument 2: Only the Absence of Brain Circulation Can Ensure Irreversible Loss of All Functions of the Entire Brain**

Irreversibility is required by the UDDA. At the current time, only the absence of brain circulation can ensure irreversibility. A clinical bedside exam for brain death can confirm the loss of brain function at a given point in time (assuming the accepted standards sufficiently examine all functions of the entire brain). Care must be taken to ensure the absence of toxic-metabolic causes. Serial exams may be required to rule-out ongoing hypoperfusion or “shock” brain, which can mimic loss of all functions of the entire brain [4, 9, 27]. Even with serial exams, irreversibility could only be assured with sufficient wait periods, and the amount of time necessary to ensure that the absence of brain function reflects dead brain, not shocked brain, remains unknown [31]. Without this knowledge, the only way to ensure irreversible loss of function is to ensure that the neural networks are irreversibly interrupted or dead. In addition, as discussed below, judging reversibility depends on available technologies. As a result, absence of brain circulation, especially if sustained past a threshold amount of time, is the only way to ensure that neurons are dead, and that all brain functions are irreversibly lost. Relying on a clinical examination to assess irreversibility, done at a single point of time, without requiring the absence of brain circulation, creates an opportunity for false-positive declaration of death by neurologic criteria.

For example, Shewmon and others have described cases of “chronic brain death,” in which systemic collapse did not occur for long periods well after correct determination of death by neurologic criteria [8, 11, 14]. The largest neuropathology studies have concluded similarly, finding large swaths of intact (i.e. nondissolved) brain even long after the determination of death by neurologic criteria [26]. Functional brain tissue does not necessarily mean preservation of functions of the brain-as-a-whole, since it is difficult to determine precisely how much brain, and which parts, demarcate life from death. But, confirming the absence of brain circulation, especially over an extended time, is probably the safest way to guarantee widespread death of neurons, thereby ensuring the irreversibility of death by neurologic criteria and avoiding an erroneous determination of death.

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#### **4 Argument 3: Requiring the Absence of Cerebral Circulation Better Aligns Death by Neurologic Criteria with Death by Circulatory-Respiratory Criteria**

Currently there is widespread disagreement and confusion about death by neurologic criteria, both in the public and amongst physicians [32, 33]. Part of this confusion stems from the disconnect between the meaning of death, which is a binary biologic state, and the medical practice of death determination, which is nuanced and prone to error.

There is broad consensus among scientists, the public, policymakers, and religious scholars that death is an irreversible state; those who are dead cannot be brought back. This is easy to recognize in retrospect, but difficult to determine in real time. One obvious corollary to this is that there are not two kinds of death, but rather two ways to determine death: circulatory-respiratory and neurologic. Historically, these two methods of death determination have generally been held to different standards. Death by circulatory-respiratory criteria is currently identified by the permanent absence of circulation and respiration, not the irreversible absence [23, 34]. Without resuscitation (either auto-resuscitation or external resuscitation), there is no distinction: permanent cessation transitions to irreversible cessation. In the case of death by circulatory-respiratory criteria, it is not necessary to confirm irreversibility since it is a physiologic fact that the body cannot survive without circulation. For example, when a patient with a “do not resuscitate order” suffers an in-hospital asystolic arrest, an examining physician can pronounce death almost immediately after confirming the absence of heartbeat, respirations, pupillary response, and motor responsiveness. At this point, irreversibility has not been confirmed; circulation could possibly be restored with resuscitation or perhaps extracorporeal membrane oxygenation (ECMO). This technologic innovation, can facilitate circulatory-respiratory function and allows for an individual to be “conscious without a heartbeat or even a heart” [35]. More recently, scientists have restored some pig brain neuronal functions 4 h after decapitation [36]. While restored cellular activity may not meet the threshold of meaningful brain function, one can foresee a time in the future when more advanced technology is applied to



humans, further blurring the boundaries of when lost brain function becomes irreversible. Regardless, at some point the threshold of irreversibility is crossed, and an individual is unmistakably dead. This irreversible, binary state of death is independent of whether the determination is done using circulatory-respiratory or neurologic criteria.

One way to align the two methods for determining death is to add a requirement that the determination of death by neurologic criteria require the absence of brain circulation. This would mirror the determination of death by circulatory-respiratory criteria in two ways. First, circulatory-respiratory arrest leads to absence of brain circulation, so the determination of death by circulatory-respiratory criteria already requires the absence of brain circulation. Second, requiring the absence of brain circulation to determine death by neurologic criteria removes the need to confirm irreversibility, since the absence of circulation ensures irreversibility.

Many countries (such as Switzerland) already consider brain death to be the sole criterion for death in organ donation [31]. This concept is increasingly adopted around the world: “the onset of cardiorespiratory arrest is merely a prospective predictor that irreversible loss of brain functions is inevitable unless the circulation and cerebral perfusion are restored” [37]. There is no need to confirm irreversible cessation of all functions of the entire brain after the determination of death by circulatory-respiratory criteria, since brain death inevitably follows loss of circulatory-respiratory function, with accompanying loss of brain circulation [31]. Requiring the absence of brain circulation to determine death by neurologic criteria would mirror the absence of systemic circulation (which includes brain circulation) required during the determination of death by circulatory-respiratory criteria. This alignment may help abate the confusion that results from two distinct methods to determine death, which are held to different standards of permanence and irreversibility, helping to garner support and consensus for the concept and practice of death by neurologic criteria.

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## 5 Conclusions

The UDDA currently requires “irreversible cessation of all functions of the entire brain, including the brain stem ... in accordance with accepted medical standards,” but the accepted medical standards cannot adequately assess either irreversibility or all functions of the entire brain.

In this chapter, we discussed three arguments for revising the accepted medical standards to require the confirmation of the absence of brain circulation. Required absence of brain circulation would align accepted medical standards with the law and with consensus conceptualization of the binary biologic state of death, by ensuring both irreversibility and loss of all functions of the entire brain. There could be detrimental downstream effect consequences for organ donor recipients and grieving families, however.

A number of other solutions exist, such as amending the UDDA to focus on permanent cessation of brain function, and better aligning the criteria for death



determination no matter what the cause [35, 38]. A full discussion of these alternatives is beyond the scope of this chapter, but covered in more detail elsewhere in this book.

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