

Pediatric brain death certification: a narrative review

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Abstract: In the five decades since its inception, brain death has become an accepted medical and legal concept throughout most of the world. There was initial reluctance to apply brain death criteria to children as they are believed more likely to regain neurologic function following injury. In spite of early trepidation, criteria for pediatric brain death certification were first proposed in 1987 by a multidisciplinary committee comprised of experts in the medical and legal communities. Protocols have since been developed to standardize brain death determination, but there remains substantial variability in practice throughout the world. In addition, brain death remains a topic of considerable ethical, philosophical, and legal controversy, and is often misrepresented in the media. In the present article, we discuss the history of brain death and the guidelines for its determination. We provide an overview of past and present challenges to its concept and diagnosis from biophilosophical, ethical and legal perspectives, and highlight differences between adult and pediatric brain death determination. We conclude by anticipating future directions for brain death as related to the emergence of new technologies. It is our position that providers should endorse the criteria for brain death diagnosis in children as proposed by the Society of Critical Care Medicine (SCCM), American Academy of Pediatrics (AAP), and Child Neurology Society (CNS), in order to prevent controversy and subjectivity surrounding what constitutes life versus death.

Keywords: Pediatric brain death; brain death diagnosis; brain death legislation; brain death guidelines; brain death ethics

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Introduction

The boundary between life and death has been imbued with religious, philosophical and cultural meaning for most of human history. In the 1950s, advances in medical technology allowed for the preservation of physiologic functions after severe neurologic injury, prompting physicians to re-explore the definition of death. It has now been over 50 years since an ad hoc committee convened at Harvard University to respond to this quandary by introducing the concept of brain death (1). Since their report's publication in 1968, brain death has become generally accepted as a medical and legal concept, with criteria for its diagnosis periodically revised (2-4). Nonetheless, inconsistencies remain in brain death determination protocols worldwide (5,6), and legal and ethical controversies have emerged and continue to persist (7-9).

This review will examine pediatric brain death determination from its inception to the present day, including guidelines in diagnosis, past and present controversy, and future directions, and how pediatric and adult guidelines differ. Our views are in alignment with the current published guidelines for pediatric brain death determination and other brain death guidance statements written by our professional societies. We advocate that it is important that providers familiarize themselves with these documents to prevent perpetuation of controversy and confusion surrounding brain death in children. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi. org/10.21037/tp-20-350).

Historical perspectives, definitions, and current guidelines

The origins of brain death

For millennia, death was determined by the irreversible cessation of circulatory and respiratory functions. As medicine advanced in the mid-20th century, this paradigm shifted. In 1947, the first successful defibrillation of a human heart was performed (10). In the 1950s, spurred in part by the resurgence of polio, the use of mechanical ventilation became widespread throughout the world (11,12). As its successful utilization increased, physicians could provide physiologic support to neurologically devastated patients who would have otherwise died from respiratory failure. Physicians began to observe the absence of primitive reflexes and respiratory effort in some severely brain-injured patients, despite a functioning circulatory system. They called these patients "hopelessly unconscious" or "beyond coma," and in many cases, the ventilator was withdrawn, resulting in the circulatory death of the patient (13).

In 1963, Robert Schwab suggested that standardized clinical and electroencephalographic (EEG) criteria could provide sufficient evidence of "*death of the nervous system*" (14). These criteria included: (I) fixed and dilated pupils, no elicitable reflexes, and no spontaneous movements; (II) apnea; and (III) an isoelectric EEG. He posited that those who met these criteria could be considered dead "in spite of cardiac action," which defied previous writings by physicians who were hesitant to "pretend to know the boundary between life and death" in this regard (15).

Definitions and criteria

The events from 1947 to 1966 led to the formation of the Harvard Ad Hoc Committee in January of 1968 that created the modern definition of brain death in use today. "A Definition of Irreversible Coma" was published by the Harvard Ad Hoc Committee in *JAMA* in August of 1968 (16). The report raised the question of whether irreversible coma should be considered death from utilitarian and ethical perspectives. The publication was challenged by some in the medical and bioethics communities, but throughout the 1970s, state legislatures throughout the country began to legally recognize this new standard for determining death (17).

In 1981, the United States President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report that formed the basis of the Uniform Determination of Death Act (UDDA) (18). The UDDA proposed that death could be declared by (I) "irreversible cessation of circulatory and respiratory functions" or (II) "irreversible cessation of all functions of the entire brain, including the brainstem." The UDDA delegated the "acceptable medical standards" by which to diagnose brain death up to the medical community. The UDDA equated brain death with circulatory death, and served as a model federal statute that states could codify into law to hopefully lead to a standard definition of death nationwide, such that a person would not be considered dead in one state yet alive in another (18).

Medical criteria for the diagnosis of brain death in children were developed in 1987 by a multidisciplinary panel of medical and legal experts, and updated in 2011 by a joint committee from the AAP, SCCM and CNS (4). The guidelines recommend that to diagnose brain death in children, a mechanism of irreversible brain injury must be identified with confounders and mimicking conditions excluded, such as electrolyte derangements, drug intoxication, and hypothermia. To be declared brain dead, children must have two exams and apnea tests be performed by different physicians, with an observation period between the exams. Per these guidelines, death is declared after "confirmation and completion of the second clinical examination and apnea test" (19). The guidelines also discuss how ancillary studies can be used to aid in the diagnosis of brain death when needed. Age-specific recommendations address the challenge of diagnosing brain death in the pediatric patient, as physiology and disease processes manifest differently depending on age (19). For term neonates up to 30 days of age, the observation period between examinations should be 24 hours, but only 12 hours is required for infants and children from 30 days to 18 years of age. Ancillary studies in neonates may 2740

have limited sensitivity, and thus providers should rely on repeated examinations to make the diagnosis when possible. The guidelines state that it is not appropriate to diagnose brain death in preterm infants, as brainstem reflexes may be incompletely developed in this patient population.

Philosophy, ethics, and brain death

The Ad Hoc Committee at Harvard

When the Ad Hoc Committee at Harvard convened in 1968 to address whether "hopelessly unconscious" patients should be considered dead, they expressed a concern that "the burden is great on patients who suffer loss of intellect, on their families, and on those in need of hospital beds" (1). Their statement reflected a growing unease among physicians about imposing life-sustaining therapies on patients with irreversible brain injury (7). Does keeping such patients alive violate their right to accept or decline medical treatment? Does it compromise the equitable distribution of resources across society? What factors define life and personhood as opposed to a collection of tissues and organs? Controversy surrounding brain death has centered largely around these ethical and philosophical questions and has resurfaced in the wake of several highly-publicized cases in which a belief was expressed that brain death is not equivalent to biological death (8,9).

Biophilosophical perspectives

The introduction of a new definition of death by the UDDA provoked ethical and philosophical discussion regarding life, death, and personhood (7). Some scholars expressed concern that adopting two definitions of deathby circulatory or by neurologic criteria-represented too great a change from the way death had been perceived for centuries (20). But the use of criteria and technology to diagnose death long preceded brain death and has evolved over time. The oldest known somatic criteria for death are decomposition and rigor mortis. Before the advent of tools such as the stethoscope, fear of premature burials led to the construction of waiting mortuaries and coffins with builtin alarms, as well as other techniques intended to detect the presence of life, such as placing leeches near the anus or applying pincers to the nipples (21). Recognizing this, other scholars maintained that the concept of death had not changed with the UDDA; rather, new technology mandated re-examination of the standards by which it is defined (22).

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Brain death relies on a belief in integrative unity-that the brain transforms a disparate collection of organs and tissues into the whole organism (23,24). Following this logic, death of the brain would confer death upon the being. Legal and medical policies in the United States implicitly invoke integrative unity in defining brain death in biological terms-irreversible cessation of the entire brain, including brainstem (or, so-called whole brain death) (25,26). Western cultures in general are more accepting of this notion, in which body and mind are separate entities with personal identity residing in the brain (27). Some cultures and religions, however, view the body and mind as integrated, with one's identity residing in the heart (28). Nonetheless, the majority of countries in both the developed and developing world now recognize legal provisions for brain death (5).

Some scholars have challenged the notion that the integrating function of the brain can be used to equate brain death with death of the organism. They cite that many elements of bodily integration are carried out by other organs (25,29,30). Others hold that the capacity for consciousness is the defining feature of personhood, proposing that permanent loss of this capability should define death (7,31). This "higher brain" standard becomes problematic when considering patients who are permanently unconscious, such as those born with anencephaly; the notion that individuals who breathe spontaneously are in fact dead would likely be unacceptable to the public at large (32). Philosophical debate aside, there is a societal need to delineate the boundary between life and death. A clear, objective definition permits us to determine who is entitled to constitutional rights, when wills should be enacted, and to prevent utilization of resources by imposing treatment on the deceased (9,29).

The dead donor rule

The same ICU technology that led to the definition of brain death raised questions about which patients could be organ donors. Joseph Murray reported the first successful kidney transplantation from one twin to another in 1954, followed by the first liver and lung transplantations in the decade that followed (17). It soon became clear that the demand for organs outweighed their supply, and a fundamental question emerged: when is it ethically and legally acceptable to procure organs?

In 1966, Guy Alexandre created criteria similar to

Schwab's that would allow death to be declared in severely brain-injured patients and provide a pathway to procure organs for transplantation from donors whose hearts were still beating (33). Discussion and controversy led to an ethical norm known as the dead donor rule. This deontological mandate requires patients to be deceased prior to procurement of their organs. In other words, organ procurement must not harm the donor by causing his or her death (34-36). Defenders of the dead donor rule have called it "a centerpiece of the social order's commitment to respect for persons and the human life" and in-line with the Hippocratic mandate that doctors must not kill (35). From this view, if brain death is not equated with death, then donation from heart-beating donors is an ethical impossibility (7).

Organ donation after brain death became increasingly common during the latter half of the 20th century and remains the most common means of donation today (34). In an international survey, health care providers expressed greater confidence in the determination of brain death over circulatory death in the context of organ procurement (37). Brain death determination should be standardized and objective, denoting a sharp boundary between life and death that upholds the dead donor rule and precludes significant ethical quandaries related to identifying suitable organ donors. Because the development of transplantation was temporally linked with recognition of the "hopelessly unconscious" patient, discussions of brain death and organ donation have been historically intertwined, although this is a simplistic reduction.

Controversies in brain death determination

Today, it is generally accepted in medicine and medical ethics that brain dead patients are diagnosed based on a set of clinical rather than philosophical criteria (7). The procedures by which this diagnosis is made in adults were first standardized by the American Academy of Neurology in the 1990s and revised in 2010, and in children in 1987 with revisions in 2011. A consensus statement by the World Brain Death Project in August of 2020 contains recommendations for the minimum criteria that must be met to diagnose brain death in both adult and pediatric patients (2,19,38). Current controversies center on whether brain death can be equated with biological death, as well as whether its means of determination accurately measures irreversible loss of function of the entire brain (7,28,39-42).

Whole brain versus brainstem death

Whole brain death, or irreversible cessation of all clinical functions of the brain, remains the philosophical basis for the legal definition of brain death in the United States. Guidelines for adult and pediatric determination of brain death endorse this view explicitly and provide a minimum set of criteria by which to make the diagnosis (3,19). In contrast, the framework for the diagnosis of brain death in the United Kingdom is known as brainstem death (43,44). In this formulation, the diagnosis of brain death requires cessation of functions of the brainstem only rather than the whole brain. Christopher Pallis, who popularized this view in 1983, argued that higher-brain functions cannot occur without input from the ascending reticular activating system of the brainstem. Therefore, permanent loss of consciousness, circulatory control and respiratory function all ensue with death of the whole brainstem (44,45). By this view, cessation of function of the brainstem (rather than the entire brain) is sufficient to confer death of the individual. Critics of the brainstem death formulation argue that while isolated brainstem injury may cause coma, apnea and loss of brainstem reflexes, it does not preclude preservation of supratentorial structures, and therefore the possibility of maintained clinical brain functions cannot be excluded (46).

Some scholars express concern that assessing consciousness, brainstem reflexes, and apnea does not accurately measure all functions of the entire brain, as required by the legal definition of brain death in the U.S. (43,47). They believe that the accepted criteria for diagnosing brain death do not establish that all biological functioning driven by the brain has irreversibility ceased, as some functions can remain intact for years following a brain death diagnosis (48). For example, some patients declared brain dead can still regulate free water balance via neurohormonal secretion by the hypothalamus, menstruate, and even support gestation of a fetus to term (42,49,50). To circumvent this challenge, some propose relaxing the whole brain criterion to include only those functions essential to the brain as a whole, though acknowledge that defining such essential functions may be difficult (43,51). Other scholars do not believe that preserved neuroendocrine function excludes brain death diagnosis by the whole brain definition. They maintain that the whole brain concept of brain death requires the cessation of clinical *functions* of the brain, which must be distinguished from the isolated function of individual cells or groups of neurons; the latter may persist after clinical

functions of the brain have ceased (43). By this view, intact neuroendocrine functions do not preclude a patient a diagnosis of irreversible injury of the brainstem and cerebral hemispheres. The American Academy of Neurology endorses this view (52).

Consent and the apnea test

Another controversy related to brain death diagnosis is whether informed consent should be required. The apnea test in particular has been scrutinized in this context. During this portion of the brain death examination, the patient is pre-oxygenated and then disconnected from the ventilator. If the child fails to breathe spontaneously after the arterial carbon dioxide (PaCO₂) concentration rises above 60 and 20 mmHg above the pre-test baseline, which provides a maximal stimulus to the brainstem's respiratory centers, the apnea test is consistent with brain death (53).

Critics point out that the apnea test violates the ethical pillar of non-maleficence due to its potential to harm the subject. A rise in $PaCO_2$ and the resulting acidosis can cause hemodynamic instability, cardiac dysrhythmias, and even cerebral herniation due to a theoretical rise in intracranial pressure (54). Several studies seem to corroborate these risks (55,56), while others suggest that apnea testing is safe provided that appropriate prerequisites are met (57-59). Nevertheless, some have questioned whether it should be defined as a medical procedure with sufficient risk to warrant informed consent (60-62). Guidelines for pediatric determination of brain death provide clear recommendations for conducting this test, including prerequisites that must be met to reduce the risk of cardiopulmonary instability (19).

It is currently not standard practice of neurologists and intensivists to obtain informed consent prior to apnea testing in both pediatric and adult patients (40,63). A recent survey demonstrated that 70% of pediatric providers do not believe consent should be required (64). Judicial rulings in recent cases on whether consent should be required are split, with Montana and Kansas mandating consent for the apnea test while courts in Virginia and Kentucky deemed that it was not required (62,65). Those opposed to a mandate of consent invoke the ethical pillar of justice, noting that potential delays in diagnosing brain death prevent the allocation of scarce medical resources (63). More generally, opponents believe that a declaration of death should not represent a choice: "a person is alive or dead, and delay of this determination affects the patient, family, society and hospital personnel" (63).

Ancillary testing

While brain death is a clinical diagnosis, it is not always feasible to complete or interpret all portions of the examination and apnea test. Patients may have severe cardiopulmonary dysfunction that precludes tolerance of the apnea test, injuries that affect feasibility of the exam (such as ocular trauma, facial fractures, or cervical spine injury), or other conditions that are unable to be corrected (such as electrolyte abnormalities) that can confound the clinical evaluation. When this occurs, ancillary testing can help support a diagnosis of brain death. Pediatric guidelines permit use ancillary testing when there is uncertainty about elimination of medications that can confound the exam. However, it is recommended that in such cases, providers also serially measure drug levels and allow five elimination half-lives to pass prior to conducting the exam (3).

Ancillary testing has been incorporated into brain death guidelines since its inception, and recommendations differ for adults and children. The first technical aid used for this purpose was the EEG. In the 1960s, it was proposed that an isoelectric EEG be used as a criterion for cessation of neurologic function in adults (14). This changed over time; EEG is now not recommended for routine use as an ancillary test in adults due to its inadequate sensitivity and specificity (38), but is a permissible study in children if performed and interpreted according to published guidelines (3,66). Ancillary tests available for use in adult patients have expanded to include transcranial Doppler angiography (TCD), CT angiography (CTA), magnetic resonance angiography (MRA), somatosensory evoked potentials (SEP), radionuclide angiography, and radionucleotide perfusion scintigraphy (the latter studies often referred to jointly as radionucleotide cerebral blood flow) (38). In children, the use of ancillary tests is limited by a paucity of data (67). Several studies have investigated use of advanced technologies such as intracerebral blood oxygenation monitoring and doppler ultrasonography of the retinal vessels (68,69), but sample sizes are small. Of the studies permissible for use in adults, only radionucleotide cerebral blood flow is recommended for pediatric patients in the United States, as the others have not yet been validated in children (19,67).

The use of ancillary tests in assisting in the diagnosis brain death has challenges in both adults and pediatric patients (70). Many ancillary studies require skilled personnel for study performance and interpretation, which are not always available. Moreover, false positives

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and negatives arise, and cases have been described in both adults and children in which ancillary studies have yielded discordant results from clinical testing (51,71,72). Commonly cited examples include retained cerebral perfusion and/or EEG activity in spite of absent brain function on clinical testing. There are additional challenges in infants, as the presence of an open fontanelle may affect measurement of resistive indices by transcranial doppler ultrasonography and therefore complicate assessment of cerebral blood flow (73). Additionally, cerebral blood flow may exist below the detectable limit for some of the technologies. The reason for discordant results in unclear, but some posit that there may be preserved blood flow or residual neuronal activity that does not generate brain function that is identifiable on a clinical examination (51). In light of these challenges, some advocate for a more careful analysis of cases in which such a discrepancy is noted between ancillary testing and the clinical exam. One proposed solution is to modify the whole brain criterion of death to include only irreversible cessation of relevant brain functions (51). However, this may yield substantial philosophical and ethical debate about what constitutes a relevant brain function. In the meantime, because it is not always possible to perform or accurately interpret all parts of the clinical evaluation, ancillary testing remains recommended in certain circumstances (38).

Brain death refusal: legal challenges and the role of the media

Public perception and the media

After the UDDA, there were occasional legal challenges to brain death in state legislatures and courts. In 2013, there was widespread media attention focused on the case of Jahi McMath (74-76). She was a 13-year-old girl from Oakland, California who was declared brain dead after suffering a cardiac arrest from hemorrhagic shock following a tonsillectomy. Her family sought a court order to have her death declaration overturned (65). Her case gained international notoriety in the medical and legal communities. Her body was transferred on a ventilator to New Jersey, and it wasn't until 2018, four and a half years after she was declared dead in the state of California, that she suffered a "somatic" death when her heart stopped.

Brain death is a rather uncommon event (77). In many cases, television, film, and news media are the only ways in which the public has exposure to the concept. Lewis *et al.* found that film and television frequently provide

medically inaccurate portrayals of brain death, as well as unprofessional and misleading discussions around organ donation (78). Daoust *et al.* found that news outlets are equally guilty of providing medically inaccurate and confusing information about brain death. Examples include lack of a clear definition for brain death as well as the assertion that brain death is not death until circulation ceases (79). Additionally, news media coverage of brain death controversies, including that of Jahi McMath, is frequently sympathetic to the plight of the families in their pursuit of accommodations and continued ventilatory support (76).

Inaccurate portravals in film and television as well as confusing depictions from news media and the Internet can affect the public's acceptance of brain death and trust in ability of the medical profession to accurately declare death. One recent study by Jones et al. evaluated public perception of brain death by analyzing the most commonly accessed online resources. The authors found a significant amount of misinformation as well as negative emotions toward brain death and the medical community (80). Another study found that only 3% of newspaper articles that mentioned brain death in the United States and Canada provided an accurate definition of brain death, and many insinuated in specific cases that death occurred twice: once by neurologic criteria, and again at the time of organ procurement (79). These misunderstandings about brain death also impact the process of organ donation. Eighty percent of respondents in one survey would authorize organ donation from a "dead" relative; however, this decreased to 63% when the words "brain dead" were used (81). Additionally, brain death was associated with negative connotations when mentioned in conjunction with organ donation on the Internet (80).

Overall, there is significant misinformation among the public regarding brain death, which has been facilitated by the lay media. If left uncurbed, public misperception may grow over time, as the spread of misinformation has been facilitated by newer technologies such as social media and smart phones. The ethical and social implications of this misinformation are profound; it may propagate mistrust in the medical system, divert fair allocation of resources away from the living, and burden the psyches of families and providers alike. There must be a concerted effort from the medical and bioethics communities to provide more public education about brain death, including advocacy for accurate portrayals in television, film, and the news. This approach is supported by the American Academy of Neurology (52).

Variability in the law

A difficult reality of brain death legislation is that state laws are not uniform. Some states require that consent be obtained to perform the brain death exam; others state that medical professionals have the authority to perform the exam over the objection of a family (52). Some states allow religious exemptions from brain death. New Jersey prohibits brain death declaration if it violates "personal religious beliefs". New York, Illinois and California contain similar stipulations mandating that "reasonable accommodations" be provided to families who object to brain death determination. This lack of uniformity nationwide has contributed to confusion and further mistrust on the part of those who have deep concerns about brain death. And while the UDDA outlines the legal understanding of brain death, it does not address the diagnostic process, deferring that to the medical community. Legal challenges have thus far been unsuccessful at changing laws in most states, but many more cases await litigation (65).

Accommodations

Varied perceptions about brain death due to personal, religious and/or cultural beliefs have led surrogates of some patients declared dead to request continuation of organ or somatic support such as ventilators. One study found that over half of surveyed physicians had encountered accommodation requests from families of children declared brain dead (64). To provide additional guidance in these matters, the American Academy of Neurology released a consensus statement in 2019. They advocate that, while it is important to have sympathy for families making accommodation requests, there is no legal obligation to provide continued medical treatment to deceased patients other than in New Jersey. In fact, they maintain that acquiescing to such requests generates harmful ethical and social consequences, such as deprivation of the decedent's dignity, provision of false hope with resultant mistrust, and contribution to inconsistent standards of death (52). Overall, it is helpful to be familiar with one's institutional and state policies regarding accommodation requests as well as particular religious and cultural factors that may influence surrogates' perceptions of brain death. Involving institutional leadership early as well as legal and ethical consultation may be necessary when disagreement about the diagnosis persists between families and providers.

Brain death and evolving technologies

The authors of the UDDA anticipated that the means of diagnosing brain death would change over time as new technology became available, stipulating that "...a determination of death is made with acceptable medical standards" (18). Accordingly, advances in medical technology have led to revised recommendations in its diagnosis. This may be most evident in the use of ancillary testing, which has undergone substantial change over time. As new tests become available, and new data emerges regarding the sensitivity and specificity of existing tools, recommendations regarding ancillary testing will continue to be revised.

Technologies worthy of mention include functional magnetic resonance imaging (fMRI) and pupillometers, though both have been studied more in adults than in children. The former may emerge as an ancillary test in diagnosing brain death, and the latter may improve the sensitivity of clinical testing, although in each case, more data are needed before they can be recommended for adults or children. fMRI was developed in the 1990s and can be a surrogate measure of neuronal metabolism and function (82). For over two decades, it has been used to assess for the presence of consciousness in brain injured adult patients (83,84). Early studies in the mid-2000s suggested that patients in a minimally conscious state may have some degree of intact cortical neuronal systems in spite of inability to speak or follow commands (85). More recently, fMRI has been used to attempt to detect covert consciousness in comatose adults after severe brain injury (86), but to our knowledge no data exist for children. Use of this technology could be applied to patients being evaluated for brain death in the future. Automated pupillometry allows for rapid and non-invasive measurement of the pupillary light reflex. Studies have demonstrated that it outperforms manual examination for adults in the critical care setting (87,88). Data regarding the efficacy of pupillometry in children is limited (89). Because absence of the pupillary light reflex is a requisite for brain death, pupillometers may help to prevent false positive diagnoses if more data arises to support its reliability.

There are some newer technologies used in the critical care setting which may necessitate modifications to certain aspects of the brain death evaluation process. One example is extracorporeal membrane oxygenation (ECMO), which has necessitated changes to the traditional apnea

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test (90,91). Protocols for performing the apnea test in patients on ECMO have been suggested in both children and adults, which typically involve reducing the sweep flow to decrease clearance of carbon dioxide in addition to removing intermittent mandatory ventilation (90-93). The most recent guidelines for diagnosing brain death in patients supported with ECMO were published in 2020 by the World Brain Death Project (38). The future will likely see additional guidelines emerge, as well as new challenges in diagnosis brought on by novel technologies.

Conclusions

Since it was introduced in the mid-20th century, the concept of brain death has engendered clinical, ethical, philosophical, and legal challenges. Controversies have centered on the idea itself as well as its means of diagnosis. As time has progressed, some emerging technologies have contributed to our ability to determine brain death, while others have made its diagnosis more complex. A more recent challenge to the concept of brain death is the lay media, which has brought notoriety to specific cases in which its diagnosis was challenged.

Controversy about brain death will likely increase as more cases come to the public's attention, and as novel technologies lead to amendments in procedures for assessing brain death criteria. It is thus imperative that providers educate themselves and their peers regarding the most up-to-date science and guidelines regarding brain death determination. Additionally, providers who perform brain death evaluations must be familiar with the published criteria for brain death determination in children, as well as state laws and institutional protocols. Maintaining a uniform definition of death as proposed in the UDDA and delineated in guidelines from professional societies will help maintain an objective and consistent means of determining of death.

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References

- A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 1968;205:337-40.
- Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995;45:1012-14.
- Greer DM, Shemie SD, Lewis A, et al. Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. JAMA 2020;324:1078.
- 4. Nakagawa TA, Ashwal S, Mathur M, et al. Clinical report—Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics 2011;128:e720-40.

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- Wahlster S, Wijdicks EFM, Patel PV, et al. Brain death declaration: Practices and perceptions worldwide. Neurology 2015;84:1870-9.
- Greer DM, Wang HH, Robinson JD, et al. Variability of Brain Death Policies in the United States. JAMA Neurol 2016;73:213.
- 7. Nair-Collins M. Clinical and ethical perspectives on brain death. Medicoleg Bioeth 2015;5:69-80.
- 8. Luce JM. The Uncommon Case of Jahi McMath. Chest 2015;147:1144-51.
- Gostin LO. Legal and Ethical Responsibilities Following Brain Death: The McMath and Muñoz Cases. JAMA 2014;311:903.
- Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. J Am Med Assoc 1947;135:985.
- Slutsky AS. History of Mechanical Ventilation. From Vesalius to Ventilator-induced Lung Injury. Am J Respir Crit Care Med 2015;191:1106-15.
- Puri N, Puri V, Dellinger RP. History of Technology in the Intensive Care Unit. Critical Care Clinics 2009;25:185-200.
- Belkin GS. Brain death and the historical understanding of bioethics. Journal of the History of Medicine and Allied Sciences 2003;58:325-61.
- Schwab R, Potts F, Bonazzi A. EEG as an aid to determining death in the presence of cardiac activity (ethical, legal and medical aspects). Electroencephalogr Clin Neurophyiol 1963;15:145-66.
- 15. Mollaret P, Goulon M. The depassed coma (preliminary memoir). Rev Neurol (Paris) 1959;101:3-15.
- A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 1968;205:337-40.
- 17. De Georgia MA. History of brain death as death: 1968 to the present. Journal of Critical Care 2014;29:673-8.
- 18. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Defining Death: A Report on the Medical, Legal and Ethical Issues in the Determination of Death. Available online: http://www.thaddeuspope.com/images/President_ Comm_on_Def_Death_1981.pdf
- Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: An update of the 1987 Task Force recommendations*. Crit Care Med 2011;39:2139-55.
- 20. Fox RC. Ethical and existential developments in contemporaneous American medicine: their implications

for culture and society. Milbank Mem Fund Q 1974;52:445-83.

- Gardiner D, Shemie S, Manara A, et al. International perspective on the diagnosis of death. Br J Anaesth 2012;108 Suppl 1:i14-28.
- 22. Bernat JL, Culver CM, Gert B. Defining death in theory and practice. Hastings Cent Rep 1982;12:5-8.
- 23. Bernat JL. Whither Brain Death? Am J Bioeth 2014;14:3-8.
- Shewmon AD. The Brain and Somatic Integration: Insights Into the Standard Biological Rationale for Equating Brain Death With Death. J Med Philos 2001;26:457-478.
- 25. Nair-Collins M, Miller FG. Do the 'brain dead' merely appear to be alive? J Med Ethics 2017;43:747-53.
- 26. Guidelines for the Determination of Death: Report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 1981;246:2184-6.
- 27. Bowman KW. Culture, Brain Death, and Transplantation. Prog Transplant 2003;13:211.
- Potter K. Controversy in the Determination of Death: Cultural Perspectives. J Pediatr Intensive Care 2017;6:245-7.
- 29. Magnus DC, Wilfond BS, Caplan AL. Accepting Brain Death. N Engl J Med 2014;370:891-4.
- Shewmon DA. Brain Death: A Conclusion in Search of a Justification. Hastings Cent Rep 2018;48 Suppl 4:S22-5.
- Green MB, Wikler D. Brain death and personal identity. Philos Public Aff 1980;9:105-33.
- Truog RD. Brain Death Too Flawed to Endure, Too Ingrained to Abandon. J Law Med Ethics 2007;35:273-81.
- 33. Murray JE. Organ Transplantation: The Practical Possibilities. In: Wolstenholme G, O'Connor M, eds. Ethics in Medical Progress: With Special Reference to Transplantation. Boston: Little, Brown, 1966.
- Bernat JL. Life or Death for the Dead-Donor Rule? N Engl J Med 2013;369:1289-91.
- Robertson JA. The dead donor rule. Hastings Cent Rep 1999;29:6-14.
- Truog RD, Miller FG, Halpern SD. The Dead-Donor Rule and the Future of Organ Donation. N Engl J Med 2013;369:1287-9.
- 37. Rodríguez-Arias D, Tortosa JC, Burant CJ, et al. One or two types of death? Attitudes of health professionals towards brain death and donation after circulatory death in three countries. Med Health Care Philos 2013;16:457-67.

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Translational Pediatrics, Vol 10, No 10 October 2021

- Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. JAMA 2020;324:1078-97.
- Truog RD, Berlinger N, Zacharias RL, et al. Brain Death at Fifty: Exploring Consensus, Controversy, and Contexts. Hastings Cent Rep 2018;48:S2-5.
- 40. Lewis A, Greer D. Current controversies in brain death determination. Nat Rev Neurol 2017;13:505-9.
- Lewis A, Cahn-Fuller K, Caplan A. Shouldn't Dead Be Dead?: The Search for a Uniform Definition of Death. J Law Med Ethics 2017;45:112-8.
- 42. Joffe A. Confusion about brain death. Nat Rev Neurosci 2006;7:590.
- Bernat JL. Refinements in the Organism as a Whole Rationale for Brain Death. Linacre Q 2019;86:347-58.
- 44. Pallis C. Brainstem death: the evolution of a concept. Semin Thorac Cardiovasc Surg 1990;2:135-52.
- 45. Pallis C. ABC of brain stem death. From brain death to brain stem death. Br Med J (Clin Res Ed) 1982;285:1487-90.
- Kirschen MP, Lewis A, Rubin M, et al. New perspectives on brain death. J Neurol Neurosurg Psychiatry. J Neurol Neurosurg Psychiatry 2021;92:255-62.
- 47. Nair-Collins M, Northrup J, Olcese J. Hypothalamic-Pituitary Function in Brain Death: A Review. J Intensive Care Med 2016;31:41-50.
- Truog RD, Krishnamurthy K, Tasker RC. Brain Death— Moving Beyond Consistency in the Diagnostic Criteria. JAMA 2020;324:1045.
- 49. Shewmon DA. Truly Reconciling the Case of Jahi McMath. Neurocrit Care 2018;29:165-70.
- 50. Spike J. Brain death, pregnancy, and posthumous motherhood. J Clin Ethics 1999;10:57-65.
- Dalle Ave AL, Bernat JL. Inconsistencies Between the Criterion and Tests for Brain Death. J Intensive Care Med 2020;35:772-80.
- 52. Russell JA, Epstein LG, Greer DM, et al. Brain death, the determination of brain death, and member guidance for brain death accommodation requests: AAN position statement. Neurology 2019;92:304.
- Machado C, Perez J, Scherle C, et al. Brain death diagnosis and apnea test safety. Ann Indian Acad Neurol 2009;12:197.
- Joffe AR, Anton NR, Duff JP. The apnea test: rationale, confounders, and criticism. J Child Neurol 2010;25:1435-43.
- 55. Jeret JS, Benjamin JL. Risk of hypotension during apnea testing. Arch Neurol 1994;51:595-9.
- 56. Goudreau JL, Wijdicks EF, Emery SF. Complications

during apnea testing in the determination of brain death: predisposing factors. Neurology 2000;55:1045-8.

- Datar S, Fugate J, Rabinstein A, et al. Completing the apnea test: decline in complications. Neurocrit Care 2014;21:392-6.
- Wijdicks EFM, Rabinstein AA, Manno EM, et al. Pronouncing brain death: Contemporary practice and safety of the apnea test. Neurology 2008;71:1240-4.
- 59. Puccetti DF, Morrison W, Francoeur C, et al. Apnea Testing Using Continuous Positive Airway Pressure When Determining Death by Neurologic Criteria in Children: Retrospective Analysis of Potential Adverse Events. Pediatr Crit Care Med 2020;21:e1152-6.
- 60. Yanke G, Y Rady M, Verheijde J, et al. Apnea Testing is Medical Treatment Requiring Informed Consent. Am J Bioeth 2020;20:22-4.
- Truog RD, Tasker RC. COUNTERPOINT: Should Informed Consent Be Required for Apnea Testing in Patients With Suspected Brain Death? Yes. Chest 2017;152:702-4.
- 62. Berkowitz I, Garrett JR. Legal and Ethical Considerations for Requiring Consent for Apnea Testing in Brain Death Determinatio. Am J Bioeth 2020;20:4-16.
- Lewis A, Greer D. POINT: Should Informed Consent Be Required for Apnea Testing in Patients With Suspected Brain Death? No. Chest 2017;152:700-2.
- Lewis A, Adams N, Chopra A, et al. Organ Support After Death by Neurologic Criteria in Pediatric Patients. Crit Care Med 2017;45:e916-24.
- Pope T. Brain Death and the Law: Hard Cases and Legal Challenges. The Hastings Cent Rep 2018;48 Suppl 4:S46-8.
- 66. Stecker MM, Sabau D, Sullivan LR, et al. American Clinical Neurophysiology Society Guideline 6: Minimum Technical Standards for EEG Recording in Suspected Cerebral Death. Neurodiagn J 2016;56:276-84.
- Henderson N, McDonald M. Ancillary Studies in Evaluating Pediatric Brain Death. J Pediatr Intensive Care 2017;6:234-9.
- Figaji AA, Kent SJ. Brain tissue oxygenation in children diagnosed with brain death. Neurocrit Care 2010;12:56-61.
- Riggs BJ, Cohen JS, Shivakumar B, et al. Doppler Ultrasonography of the Central Retinal Vessels in Children With Brain Death. Pediatr Crit Care Med 2017;18:258-64.
- Robbins NM, Bernat JL. Practice Current: When do you order ancillary tests to determine brain death? Neurol Clin Pract 2018;8:266-74.
- 71. Welschehold S, Boor S, Reuland K, et al. Technical aids

Fainberg et al. Pediatric brain death certification

in the diagnosis of brain death: a comparison of SEP, AEP, EEG, TCD and CT angiography. Dtsch Arztebl Int 2012;109:624-30.

- Shewmon DA. False-Positive Diagnosis of Brain Death Following the Pediatric Guidelines: Case Report and Discussion. J Child Neurol 2017;32:1104-17.
- 73. Zamora C, Tekes A, Alqahtani E, et al. Variability of resistive indices in the anterior cerebral artery during fontanel compression in preterm and term neonates measured by transcranial duplex sonography. J Perinatol 2014;34:306-10.
- 74. Viswanathan R. There's a surprisingly rich debate about how to define death. Published online August 6, 2018. Available online: https://www.vox. com/2018/8/6/17635098/jahi-mcmath-2018-brain-deathdefinition
- 75. Schmidt S. Jahi McMath, the Calif. girl in life-support controversy, is now dead. The Washington Post. June 29, 2018. Available online: https://www.washingtonpost.com/ news/morning-mix/wp/2018/06/29/jahi-mcmath-thecalif-girl-declared-brain-dead-4-years-ago-is-taken-offlife-support/
- 76. Aviv R. What does it mean to die? The New Yorker. Published online 2018. Available online: https://www. newyorker.com/magazine/2018/02/05/what-does-itmean-to-die
- 77. Kirschen MP, Francoeur C, Murphy M, et al. Epidemiology of Brain Death in Pediatric Intensive Care Units in the United States. JAMA Pediatr 2019;173:469.
- Lewis A, Weaver J, Caplan A. Portrayal of Brain Death in Film and Television. Am J Transplant 2017;17:761-9.
- Daoust A, Racine E. Depictions of "brain death" in the media: Medical and ethical implications. J Med Ethics 2014;40:253-9.
- Jones AH, Dizon ZB, October TW. Investigation of Public Perception of Brain Death Using the Internet. Chest 2018;154:286-92.
- Tessmer CS, Da Silva AR, Barcellos FC, et al. Do people accept brain death as death? A study in Brazil. Prog Transplant 2007;17:63-7.

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- 82. Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am 2011;22:133-9, vii.
- Fernández-Espejo D, Norton L, Owen AM. The clinical utility of fMRI for identifying covert awareness in the vegetative state: a comparison of sensitivity between 3T and 1.5T. PLoS One 2014;9:e95082.
- Moritz CH, Rowley HA, Haughton VM, et al. Functional MR imaging assessment of a non-responsive brain injured patient. Magn Reson Imaging 2001;19:1129-32.
- Schiff ND, Rodriguez-Moreno D, Kamal A, et al. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 2005;64:514-23.
- Edlow BL, Fins JJ. Assessment of Covert Consciousness in the Intensive Care Unit: Clinical and Ethical Considerations. J Head Trauma Rehabil 2018;33:424-34.
- Lussier BL, Olson DM, Aiyagari V. Automated Pupillometry in Neurocritical Care: Research and Practice. Curr Neurol Neurosci Rep 2019;19:71.
- Meeker M, Du R, Bacchetti P, et al. Pupil examination: validity and clinical utility of an automated pupillometer. J Neurosci Nurs 2005;37:34-40.
- Olgun G, Newey CR, Ardelt A. Pupillometry in brain death: differences in pupillary diameter between paediatric and adult subjects. Neurol Res 2015;37:945-50.
- 90. Beam WB, Scott PD, Wijdicks EFM. The Physiology of the Apnea Test for Brain Death Determination in ECMO: Arguments for Blending Carbon Dioxide. Neurocrit Care 2019;31:567-72.
- 91. Saucha W, Sołek-Pastuszka J, Bohatyrewicz R, et al. Apnea test in the determination of brain death in patients treated with extracorporeal membrane oxygenation (ECMO). Anaesthesiol Intensive Ther 2015;47:368-71.
- 92. Jarrah RJ, Ajizian SJ, Agarwal S, et al. Developing a Standard Method for Apnea Testing in the Determination of Brain Death for Patients on Venoarterial Extracorporeal Membrane Oxygenation: A Pediatric Case Series. Pediatr Crit Care Med 2014;15:e38-43.
- 93. Smilevitch P, Lonjaret L, Fourcade O, et al. Apnea test for brain death determination in a patient on extracorporeal membrane oxygenation. Neurocrit Care 2013;19:215-7.