Practice Current

When do you order ancillary tests to determine brain death?

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Abstract

Brain death has been accepted as a legal definition of death in most countries, but practices for determining brain death vary widely. One source of variation is in the use of ancillary tests to assist in the diagnosis of brain death. Through case-based discussions with 3 experts from 3 continents, this article discusses selected aspects of brain death, with a focus on the use of ancillary tests. In particular, we explore the following questions: Are ancillary tests necessary, or is the clinical examination sufficient? What ancillary tests are preferred, and under which circumstances? Are ancillary tests required when the primary mechanism of injury is brainstem injury? Should the family's wishes play a role in the need for ancillary tests? The same case-based questions were posed to the rest of our readership in an online survey, the preliminary results of which are also presented.

Brain death is the common term for the determination of human death by showing the irreversible cessation of clinical brain functions. Brain death has been accepted as a legal definition of death in the United States and many other countries. However, methods for determining brain death vary among countries, across institutions within the same country, and among physicians within the same institution.¹⁻⁴

Brain death is fundamentally a clinical determination. Professional and institutional guidelines rely on performing a bedside neurologic examination to determine brain death. A systematic neurologic examination must show apnea, cranial nerve areflexia, and unresponsiveness to the environment. Primary brain pathology (as opposed to systemic metabolic or toxic disturbances) must account for the clinical findings, and the findings must be irreversible.⁵

A current source of variability in physicians' brain death determinations is their use of so-called ancillary tests. Ancillary tests are not routinely required for brain death determination, but may be indicated to support the clinical determination of brain death, or to supplement the clinical examination when extenuating circumstances preclude a complete brain death examination. Ancillary tests include tests of neuronal electrical function, such as EEG and somatosensory and brainstem auditory evoked potentials (EPs), and neuroimaging tests of brain perfusion, such as transcranial Doppler ultrasonography (TCD), 4-vessel contrast angiography, CT and magnetic resonance (MR) angiography and perfusion, and cerebral scintigraphy (radionuclide brain scan).^{6,7}

In this commentary, we discuss selected aspects of brain death, with a focus on the use of ancillary tests in the diagnosis of brain death. Three international experts then discuss clinical

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vignettes highlighting controversies in the use of ancillary tests for the determination of death by brain criteria.

A brief history of brain death

The concept of brain death originated with the advent of mechanical ventilation. Before this time, circulation and respiration would soon cease after profound brain injury. In the 1950s, French neurologists observed that patients with catastrophic brain injuries who were maintained on ventilators showed an unprecedented depth of coma, cranial nerve areflexia, and apnea—a state they termed coma dépassé, meaning a state beyond coma.⁸ A landmark 1968 article by a Harvard Medical School committee proposed the first set of tests demonstrating that the irreversible cessation of all brain functions is a criterion of human death.^{9,10} Since then, many countries have reached consensus that a person whose brain's clinical functions have permanently ceased is medically and legally dead, regardless of whether the respiratory and circulatory systems are supported artificially.¹¹ This consensus within the medical community has not precluded legal challenges, and societal distrust and uncertainty surround some aspects of brain death.¹²

Brain death determination

In the United States, the Uniform Determination of Death Act legally defines death as follows: “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards.”¹¹ All US states have adopted this Act or a variation of it. While professional societies have codified “accepted medical standards” (particularly the American Academy of Neurology [AAN]), considerable variation in the practice of brain death determination persists in the United States and elsewhere, in both adult and pediatric patients.^{1,3,13}

The AAN published a practice parameter for determining brain death in adults,¹⁴ and the diagnosis of brain death has recently been reviewed for both adults and children.^{5,13,15,16} Briefly, the current practice standard for assessing brain death involves confirmation of coma (i.e., utter unresponsiveness to the environment, including painful stimulation), absence of brainstem reflexes (i.e., pupillary, corneal, vestibulo-ocular and oculocephalic, cough, and gag), and apnea. An irreversible lesion must account for the neurologic findings and substantial reversible factors must be excluded. Nevertheless, some ambiguities remain.

A 2002 survey of international brain death practices found an accepted practice of brain death determination in 80 countries surveyed. Seventy countries had practice guidelines and 55 countries had legal standards. Although there was

widespread agreement on the general concept of brain death, methods for determining brain death varied widely.^{2,4} A more recent detailed survey of international brain death practices in 91 countries found that the presence of institutional brain death protocols correlated highly with the presence of an organized organ transplantation network.³ Several organizations, including The World Federation of Neurology Ethics Committee and the WHO, have worked to standardize brain death determination throughout the world. Another international effort led by the Neurocritical Care Society is now underway.

The use of ancillary testing in the determination of brain death

Several reviews have addressed the use of ancillary tests in the determination of brain death in adults and children.^{6,7,13,17-19} An adequate confirmatory test requires 100% positive predictive value, because a false-positive will uniformly result in a fatal outcome after withdrawal of supportive care.

Many ancillary tests, such as EEG, EPs, and TCD, require considerable technical expertise and are prone to artifact. Cerebral angiography and radionuclide brain scans are highly specific when no intracranial blood flow is found, and they are generally considered the preferred method for confirming brain death when an ancillary test is required. However, they are not uniformly available. Also, while the absence of brain perfusion precludes function, the opposite is not true. False negatives are seen in which a patient meets the clinical criteria for brain death but retains a degree of brain perfusion.^{7,20} This situation may not be uncommon, as demonstrated in a recent autopsy series in which many patients fulfilling clinical brain death criteria had only mild necrosis at autopsy.²¹ CT and MR angiography and perfusion are non-invasive and more widely available than nuclear scans. However, they have not yet been adequately tested as ancillary tests for brain death.¹⁶ Initial studies with CT angiography have found both false-positives and false-negative errors.¹⁹ These errors may be due to technical factors, but may also highlight the discrepancy between tests of perfusion and the gold standard clinical brain death examination, which assesses brainstem function. If one were to accept lack of brain perfusion as the sole gold standard, the clinical examination confirming brainstem death would likely produce false-positives. In part due to logistical considerations and published data validating them, the AAN considers EEG, nuclear scans, and cerebral angiography to be the preferred ancillary tests.¹⁶ The American Academy of Pediatrics guidelines also recommend these 3 methods when ancillary tests are required.¹⁵

Due to potential problems with all currently available ancillary tests, most professional societies do not require ancillary tests to declare brain death, and the determination of death by neurologic criteria remains fundamentally a clinical diagnosis.

Controversies in brain death diagnosis: Brainstem death or whole brain death and ancillary tests of cortical function

The large majority of brain death cases feature transtentorial herniation caused by raised intracranial pressure leading to destruction of the brainstem. But given the prominence of brainstem function testing for brain death determination, some cases of complete primary brainstem injury (e.g., massive brainstem hemorrhage) may become problematic because they may meet the clinical criteria for brain death yet retain preserved intracranial blood flow. It remains unknown whether such a patient truly has “irreversible cessation of whole brain function.” Such a patient might retain a degree of cerebral hemispheric function that we cannot measure, because the clinical examination relies on observable motor responses.

This concern is somewhat analogous to the finding that some patients who are clinically determined to be in a vegetative state can demonstrate awareness and cognition when assessed by functional neuroimaging techniques.²²⁻²⁴ This observation lends plausibility to the concern that a patient with primary brainstem damage could meet clinical criteria for brain death but retain some level of cognition not detectable by the bedside brain death examination. A patient with brainstem destruction and some preserved cortical function would have an equally dismal prognosis as one with destruction of the entire brain, but such a patient would not strictly meet the definition of “irreversible cessation of whole brain function.” The United Kingdom and other nations that rely on the criterion of brainstem death finesse the question of the presence of any residual cortical function.

Expert opinion

Three experts were asked to comment on the following cases and the use of ancillary testing to help diagnose brain death in these circumstances. These are also the basis for the online survey (appendix e-1, links.lww.com/WNL/A536).

Case 1

A 58-year-old man was admitted with coma and apnea (cessation of respiration) from a traumatic brain injury. Examination 2 days after admission disclosed no evidence of cerebral hemispheric or brainstem function. An apnea test could not be performed because of hypoxemia from neurogenic pulmonary edema.

Case 2

A 10-year-old girl became comatose and apneic (cessation of respiration) after the delayed treatment of bacterial meningitis. Two days later, she was diagnosed as brain dead after a clinical examination including a proper apnea test. Her parents are skeptical of the finality of the diagnosis.

Since the goal of the brain death examination (including ancillary testing) is to predict death and irreversibility with 100% specificity, tests that are prone to artifact are unacceptable. (D. Greer)

Case 3

A 62-year-old woman had a large hypertensive hemorrhage of the pons and medulla extending into the midbrain. On day 2, she had apnea (cessation of respiration), coma, and complete cessation of all brainstem function.

David Greer, MD (United States)

The clinical brain death examination is always preferred since it is widely validated. Ancillary tests should never be used to supplement a complete and thorough clinical brain death examination. However, when the clinical brain death examination is not possible, or cannot be trusted, ancillary tests are absolutely required. If the apnea test cannot be trusted due to neurogenic pulmonary edema, as in case 1, an ancillary test is absolutely necessary.

Ancillary tests can be divided into 2 categories: tests of perfusion and electrical tests. The gold standard ancillary test is conventional angiography. It has the longest track record and best supporting evidence. However, it can be difficult to obtain this test at times since it requires some technical expertise, and it cannot be performed at the bedside in most cases. As a result, many people also use either TCD or SPECT to study cerebral perfusion. These tests are highly reliable and are acceptable ancillary tests.

In contrast, I do not trust EEG and do not think it is a reliable enough test to be used in most cases, even though it is in the guidelines. First, EEG tells you basically nothing about the brainstem, so EEG should always be used along with EPs that interrogate the brainstem. In addition, artifact is a large problem in the intensive care unit (ICU), which makes the interpretation of both EEG and EPs problematic in this setting. Since the goal of the brain death examination (including ancillary testing) is to predict death and irreversibility with 100% specificity, tests that are prone to artifact are unacceptable. For these reasons, I am working on taking EEG out of the guidelines for the determination of death by neurologic criteria.

Case 2 highlights a pediatric brain death case, which at age 10 is physiologically fairly similar to an adult. In this case I would not recommend any additional ancillary testing and do not

believe that family wishes should play a role. Medical decision-making is based on biomedical science, and once physicians allow family wishes to dictate medical care, we proceed down a slippery slope. The child in this case meets the clinical criteria for brain death, and an ancillary test could only confuse the issue, so I would not recommend it.

Brainstem death is a controversial issue, and there is no formal position in the United States regarding this topic. I conducted a poll of the Neurocritical Care Society a few years ago, and the members were split down the middle: half of the members believed that a patient such as this was brain dead, and half believed the patient had brainstem death but not brain death. I used to be a firm believer that brainstem death was equivalent to death, since according to the guidelines that spell out the clinical diagnosis of brain death, a patient with clinical brainstem death is dead. However, several years ago I had a patient with a brainstem insult such as this who initially met brain death criteria, but after we contacted the organ bank, the patient then developed some extensor posturing and some other clinical signs of improvement. The core issue in these cases is whether you can state that the condition is 100% irreversible. Often patients develop obstructive hydrocephalus and secondary cerebral death from a brainstem insult, in which case the situation is clear. However, sometimes some of the examination findings after a brainstem infarct could be due to edema, which improves. In these instances, even if the clinical examination shows brain death, I wait several days to ensure that the edema has resolved and that the clinically evident brain death is irreversible.

The current guidelines do not capture this initial uncertainty in cases with primary brainstem damage, and the guidelines need to be amended to highlight that this is an area that requires further inquiry. Philosophically, a question remains about whether a patient who is clinically brain dead may have some spared subclinical cortical function that could be detected with more sophisticated testing, such as fMRI. However, it is not feasible to do research-based fMRI and PET on every patient with suspected brain death, nor is it appropriate or necessary. As a community, physicians have drawn a line in the sand, and since the clinical brain death examination has been so widely validated over many years, I remain a firm believer in its use according to the current published guidelines. I hope that more work will be done in the future to improve tests of clinical and subclinical function.

Arnold Hoppe, MD (Chile)

The clinical diagnosis of brain death is the gold standard. However, if every single criterion for brain death cannot be evaluated, an ancillary test is mandatory and necessary for the diagnosis. The choice of which ancillary test to use should be guided by pathophysiology, local legal provisions, and logistical considerations. In Chile, brain death diagnosis has been codified in law, which mainly adheres to the AAN guidelines. We have 4 legally acceptable ancillary tests: TCD, cerebral angiography, radionuclide angiography, and EEG.

TCD and EEG are widely available and can be done at the bedside, which can be an important logistical consideration in a busy ICU.

Regarding pathophysiology, the vast majority of cases of brain death are due to a catastrophic space-occupying brain lesion. Since the cranial vault of adults is rigid, the classical Monroe-Kellie doctrine is applicable. Increased mass effect demands reduction in volume of CSF and venous blood volume. Eventually, as this dramatic increase in intracranial pressure exceeds mean arterial pressure, brain perfusion will cease. This phenomenon is an intracranial circulatory arrest. In these cases, the ancillary test of choice will be one based on flow, or perfusion. In Chile, I prefer TCD ultrasound due to its recognized legal status and ease of use. Angiography (intra-arterial, radionuclide, CT or MRI angiography) or cerebral perfusion scans by CT or MRI are acceptable alternatives. A minority of brain death cases are not mediated by this pathophysiology, such as some cases of hypoxic-ischemic brain injury after cardiac arrest, severe hypoglycemia, and exceptional cases of carbon monoxide poisoning. In these cases, extensive neuronal injury may result in brain death, but intracranial blood flow may be preserved. For these cases, I prefer an electrophysiologic ancillary test such as EEG or evoked potentials rather than a test of perfusion. Extreme caution must be taken in these cases, and I almost always recommend an observation period (generally 12–24 hours) with repeat testing to ensure the absence of reversibility when the pathophysiology of brain death is not intracranial circulatory arrest.

Case 2 highlights the discrepancy between public understanding of brain death and the acceptance among the medical and legal professions. A considerable minority of families (around 10%–25% in my practice) would have trouble conceptualizing the diagnosis of brain death. They do not challenge the declaration, but do not understand its meaning. In a case like this I would also choose to do TCD ultrasound in order to assist in my ability to communicate with the family. I find that a reluctance to accept the diagnosis of brain death stems from 3 factors: ambivalence, fear, and distrust. Ambivalence comes from the fact that patients with brain death do not appear dead, as lay people conceive the term. The patient is not a cadaver—not pale, not stiff, and not cold. Related to this is the widespread cross-cultural fear of being buried alive. Most cultures have developed ways to deal with this fear, such as a vigil during which time people can become accustomed to the dead body. In order to overcome these barriers and help the family accept the abstract concept of brain death, I would order a TCD in this case. The family could easily understand that the brain no longer is getting blood. By translating brain death into these terms, I build trust to assist with communication.

Case 3 highlights the importance of rare cases of brain death that are not a pathophysiologic result of intracranial circulatory arrest. The most important aspect of the brain death

diagnosis is irreversibility. The diagnosis of brain death is the final diagnosis. Misdiagnosis is unacceptable, and only 100% specificity is permissible. Our clinical criteria for brain death have been consistently validated over the last few decades; there have been 0 instances of false-positive diagnoses, though it is important to remember that most cases are due to intracranial circulatory arrest. In those cases, the loss of brainstem reflexes reflects destruction of brain, and liquefactive necrosis is invariably irreversible. This is not necessarily the case in a posterior fossa lesion, in which the loss of brainstem reflexes could reflect distortion of brain tissue rather than destruction. In this case, I do not believe the patient is necessarily brain dead on the basis of the clinical brain death examination. I would mandate a waiting period of 12–24 hours to see if there is any recovery of the reflexes. Ancillary tests would not be helpful in this case, since they will not help to answer the question of irreversibility. Indeed, in this case there may be some preserved blood flow or EEG activity initially. However, after a waiting period, there is almost always global circulatory arrest. Based on the pathophysiology of this last case, I would perform serial TCDs. In cases like this, the cerebral blood flow generally disappears within a few hours, stressing the need for a follow-up period to confirm the absolute irreversibility that is required when making a brain death determination. The clinical brain death examination is not 100% reliable in cases of nonclassic pathophysiology, so extreme caution and judgment needs to be applied in these exceptional cases to ensure 100% specificity. Probably our brain death criteria should be narrowed to cases in which the pathophysiology is intracranial circulatory arrest. Like in all other aspects of medicine, judgment needs to be used when applying guidelines and criteria.

Steven Laureys, MD, PhD (Belgium)

In Belgium, ancillary tests are not formally required to make the diagnosis of brain death. It is a clinical diagnosis made under appropriate circumstances by skilled physicians. However, many circumstances will require ancillary tests in order to make the diagnosis. Since this is such an important diagnosis—the final diagnosis—objective testing is often used for confirmation. This is analogous to many other situations in medicine: often a clinical history and physical is sufficient, but occasionally additional tests are required for confirmation. However, unlike many areas of medicine, which deal in probabilities, 100% certainty is required to diagnose brain death. A mistake is catastrophic for the patient, and it also undermines family and public trust in the very concept of brain death, which is a difficult concept to begin with when faced with a corpse whose heart beats, who feels warm, and whose chest continues to rise and fall.

I am not aware of a single reported case in which a proper brain death examination misdiagnosed brain death or of any properly examined brain dead patient subsequently recovering consciousness. Accordingly, if the clinical criteria are met and properly evaluated, no additional ancillary requests are needed. However, misdiagnoses exist when

physicians do not perform the proper clinical assessment, and this must be avoided at all costs. I therefore routinely recommend a confirmatory perfusion test.

If the clinical examination cannot be performed, such as in case 1, ancillary tests are required. Selection of the ancillary test used is generally pragmatic, and there is no codified standard test in Belgium. Examining physicians can use their medical judgment, as long as they are independent from the organ transplant team.²⁵ At our center, we systematically choose TCD, since it is inexpensive, portable, and practical, and since we are experienced in its use. In general, tests of perfusion are preferred over tests of electrical function. Tests such as EEG can have false-positives and false-negatives, but the absence of cerebral blood flow is definitive. If TCDs cannot be performed due to technical factors or shows ambiguous findings, we would next choose CT angiography. MR angiography is less widely available. Some hospitals use radionuclide angiography if available.

Since brain death is a clinical diagnosis, family consent and acceptance are not required. However, I would still recommend ancillary tests in case 2. Often in medicine we perform tests to comfort patients. In this case, ancillary tests will aid in explaining to the family the concept of brain death. People are often visually oriented. It is easy to see an isoelectric EEG or an image demonstrating the absence of blood flow. Depending on the situation, I might perform several tests if it helps the family understand the situation.

Occasionally discordant ancillary testing can complicate the situation. In these cases, I would repeat the testing some time later to confirm whole brain death.

In Belgium, like most European countries, we adhere to the whole brain concept of brain death, rather than the concept of brainstem death. Case 3 highlights this discrepancy, since I would not consider this patient to be brain dead without proof of whole brain death, such as absent blood flow.

There could be a mismatch in rare cases; it is theoretically possible that a patient could have a complete super locked-in syndrome and be clinically brain dead, yet still have cortical perfusion and conceivably even some degree of minimal function. In this case, I would advocate for patience and a repeat examination at a later time to ensure the correct diagnosis of whole brain death. I am a strong proponent of evidence-based medicine. I am not aware that such a hypothetical situation has ever occurred, though I admit I am also not aware of anyone outside of our group who has done fMRI on a patient with clinical brain death.²⁶ It is technically difficult to perform these studies, though not impossible.

It is important to be pragmatic and to standardize our diagnoses. Physicians need to be 100% accurate to retain the public trust, so my main message is to maintain a high

standard of clinical training so all physicians in the position to diagnose brain death are well-trained regarding potential pitfalls. There is often a problem with large medical teams, when certain team members communicate divergent messages that can erode a family's trust. It is essential to be patient; to share our uncertainties when they occur; to take the time to communicate a clear, accurate, and transparent message; and to permit enough time for a family to accept the medical reality. In addition, any discussion of organ donation must be kept completely separate—particularly in the context of any disputes.

Preliminary survey results (April 16, 2018): Section editor: Luca Bartolini, MD

We collected a total of 117 complete questionnaires since April 6, 2018, primarily from general neurologists (80%) treating adults (77%) in a hospital setting (74%). Most responders were attending physicians (77%) practicing in the United States (58%).

For the first case regarding cessation of cortical and brainstem function after TBI with inability to perform an apnea test due to pulmonary edema, there is consensus among survey takers to request ancillary testing to confirm brain death ($n = 101$ [86%]). Half of the respondents chose to perform at least an EEG ($n = 50$); 21% also recommended a radionuclide angiography and 18% a TCD.

Our survey takers were then presented with a challenging pediatric case of a 10-year-old girl who became comatose and apneic due to delayed treatment of bacterial meningitis.

While the majority of responders were satisfied with the clinical examination and apnea test to diagnose brain death, 49 (42%) requested ancillary tests, especially EEG ($n = 32$). When asked if they would change their mind in case parents were skeptical of the diagnosis and order some tests, half of survey takers held steady and said no (figure 1). For those who had already decided to order ancillary tests initially, if the parents were still skeptical of the diagnosis, 40% would proceed to order more tests. This case highlights the complex nuances of brain death in children and the delicate interaction that often occurs between the family and the physician, which may sometimes result in altering the decision-making. In fact, 60 survey takers (51%) admitted that family requests have influenced their decision in at least 10% of cases they have managed and it is possible that this percentage would be higher if more pediatric neurologists had taken the survey.

For the third case regarding apnea, coma, and cessation of brainstem function in case of extensive brainstem hypertensive hemorrhage, 40% of survey takers would order ancillary tests, at least to include an EEG ($n = 32$). After the ICU staff saw a limb movement, an EEG was obtained and showed low-amplitude irregular delta activity and TCD ultrasound found pulsations of intracranial arteries. Presented with this information, 55% of responders stated that the patient could not be considered brain dead anymore. Opinions were split almost in half on whether brainstem death is sufficient to declare brain death (figure 2).

This article represents the first step towards a global discussion regarding the highly emotionally and ethically charged issue of

Figure 1 Interactive map shows if survey takers would order ancillary tests if parents were skeptical of the diagnosis

Figure 2 Interactive map shows opinions on whether brainstem death is sufficient to declare brain death

brain death. While we offer opinions from 3 continents, there is a multitude of difference in how people of different religious and cultural backgrounds view death. We encourage readers to share their comments in response to this article and engage in a productive discussion on this topic. We hope that the survey and responses to this commentary will also incorporate opinions from non-Christian-majority countries, to complement the points of view that are being presented.

David Greer, MD, received a BA in English literature from Williams College, an MD from the University of Florida, a Master of Arts in English literature from the University of Florida, and a Master of Arts *privatim* from Yale University. He completed his internship and residency in neurology at Massachusetts General Hospital (MGH), followed by fellowship training in vascular neurology and neurocritical care, also at MGH. Previously, he was an Associate Professor of Neurology at Harvard Medical School before being recruited to Yale University School of Medicine in 2010, where he most recently served as Professor of Neurology and Clinical Vice Chairman before joining our department as Professor and Chairman of Neurology. Among his many honors and awards, Dr. Greer has been named one of the Best Doctors in America since 2007; he has received the Yale Neurology Residency Program's Teacher of the Year Award, 2 Presidential Citations each from the Society of Critical Care Medicine and the

Neurocritical Care Society, the Partners Neurology “Superman” Resident Teaching Award from the MGH Department of Neurology, and 3 Stanley M. Wyman Teaching Awards from the MGH Department of Medicine. Dr. Greer is the editor-in-chief of both *Neurocritical Care Live* and *Seminars in Neurology*. He serves as a reviewer for several journals, including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Brain*, *Neurology*[®], and *Stroke*. He is a fellow of the Society of Critical Care Medicine, American Academy of Neurology, American Heart Association, American Neurological Association, and Neurocritical Care Society. He has authored more than 150 peer-reviewed manuscripts, reviews, chapters, guidelines, and books. His research interests include predicting recovery from coma after cardiac arrest, brain death, and multiple stroke-related topics, including acute stroke treatment, temperature modulation, and stroke prevention. He is a leader in the Neurocritical Care Society, the Society of Critical Care Medicine, and the American Stroke Association.

Arnold Hoppe, MD, is Professor and Senior Lecturer at the Facultad de Medicina Clínica Alemana, Universidad del Desarrollo in Santiago de Chile. He specializes in cerebrovascular diseases and the care of patients in the whole range of emergency, acute, and rehabilitation settings, with pioneer work in the organization of thrombolysis and telemedicine. The main topics of his publications are in

acute treatment of stroke, stroke epidemiology, and brain death. Dr. Hoppe received an MD from Universidad de Chile Medical School and the Honor Award for the best graduate 1984 by the Chilean Medical Association. He was granted the Fundación Gildemeister scholarship for the residency in clinical neurology at the Pontificia Universidad Católica de Chile. He became staff member of Clínica Alemana de Santiago in 1989 and worked as neurologic consultant at the emergency, ICU, and stroke unit. He was head of the Neurology Service from 1993 to 2011 and Director of the Neurology and Mental Health Institute from 2012 to 2015. He is a recipient of several teaching awards and the Excellence in Teaching Award 2015 from the Universidad del Desarrollo. Dr. Hoppe served as Vice-President and Treasurer of the Chilean Society of Neurology, Psychiatry and Neurosurgery, as Chair of the Finance Committee Chile for the World Congress of Neurology 2015, and at the Membership Committee of the World Federation of Neurology. Dr. Hoppe has a long-standing interest in brain death with contributions in the legal field and clinical research, and a leading role in educational efforts of the topic. Dr. Hoppe is a representative of the World Federation of Neurology at the World Brain Death Project.

Steven Laureys, MD, PhD, graduated as a Medical Doctor from the Vrije Universiteit Brussel, Belgium, in 1993. While specializing in neurology, he entered a research career and obtained an MSc in Pharmaceutical Medicine working on pain and stroke using in vivo microdialysis and diffusion MRI in the rat (1997). Drawn by functional neuroimaging, he moved to the Cyclotron Research Center at the University of Liège, Belgium, where he obtained a PhD studying residual brain function in the vegetative state in 2000. He is board-certified in neurology (1998) and in end-of-life and palliative medicine (2004). He is a recipient of the William James Prize from the Association for the Scientific Study of Consciousness and the Cognitive Neuroscience Society Young Investigator Award and has published several books. He leads the Coma Science Group at the Cyclotron Research Centre of the University of Liège, Belgium. He is clinical professor of neurology at the Liège University Hospital and Research Director at the National Fund for Scientific Research. Prof. Laureys is chair of the World Federation of Neurology's Coma and Disorders of Consciousness Research Group and of the European Neurological Society's Subcommittee on Coma and Disorders of Consciousness. Since 2009, he has been an invited professor at the Royal Academy of Belgium. In 2010, he was invited to give a research lecture at Nobel Forum. His research focuses on clinical expertise and bedside behavioral evaluation of altered states of consciousness with state-of-the-art multimodal imaging combining the information from PET, fMRI, structural MRI,

EEG, event-related potential, and transcranial magnetic stimulation data.

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Author contributions

N. Robbins and J. Bernat: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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