

REVIEW ARTICLES

## International perspective on the diagnosis of death

D. Gardiner<sup>1\*</sup>, S. Shemie<sup>2</sup>, A. Manara<sup>3</sup> and H. Opdam<sup>4</sup>

<sup>1</sup> Adult Intensive Care, Nottingham University Hospitals NHS Trust, Derby Road, Nottingham NG7 2UH, UK

<sup>2</sup> Division of Critical Care, Montreal Children's Hospital, McGill University Health Centre, 2300 Tupper Street, Montreal, QC, Canada H3H 1P3

<sup>3</sup> Anaesthesia and Intensive Care Medicine, Frenchay Hospital, North Bristol NHS Trust, Bristol BS16 1LE, UK

<sup>4</sup> Department of Intensive Care, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia

\* Corresponding author. E-mail: dalegardiner@doctors.net.uk

### Editor's key points

- Death can be diagnosed using three different sets of criteria: circulatory, somatic, and neurological.
- These criteria are now robust, specific, and based on scientific principles.
- A diagnosis of death requires irreversible loss of the capacity for consciousness and capacity to breathe.
- Additional minimum observation periods are required to diagnose death using different criteria.

**Summary.** There is growing medical consensus in a unifying concept of human death. All human death involves the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe. Death then is a result of the irreversible loss of these functions in the brain. This paper outlines three sets of criteria to diagnose human death. Each set of criteria clearly establishes the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe. The most appropriate set of criteria to use is determined by the circumstances in which the medical practitioner is called upon to diagnose death. The three criteria sets are somatic (features visible on external inspection of the corpse), circulatory (after cardiorespiratory arrest), and neurological (in patients in coma on mechanical ventilation); and represent a diagnostic standard in which the medical profession and the public can have complete confidence. This review unites authors from Australia, Canada, and the UK and examines the medical criteria that we should use in 2012 to diagnose human death.

**Keywords:** brain death; cardiopulmonary arrest; death; diagnosis; resuscitation orders

The diagnosis of death is, in most countries, the legal responsibility of a medical practitioner. It marks a point in time after which consequences occur including no medical or legal requirement to provide resuscitation or life-sustaining technologies, loss of personhood, and most individual rights, the opportunity for organ donation and autopsy proceedings, execution of the decedent's legal will, estate and property transfer, payment of life insurance, final disposition of the body by burial or cremation and, of course, religious or social ceremonies to mark the end of a life.<sup>1</sup> Dying, however, is a process, which effects different functions and cells of the body at different rates of decay. Doctors must decide at what moment along this process there is permanence and death can be appropriately declared.

A definition of death, just like a definition of life, continues to elude philosophers. Death can be considered in terms of medical, legal, ethical, philosophical, societal, cultural, and religious rationales. The medical definition of death is primarily a scientific issue based on the best available evidence. There is growing consensus that there is a unifying medical concept of death; all human death is anatomically located to the brain.<sup>2–9</sup> That is, human death involves the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe.<sup>8 10 11</sup> These two essential capacities are found in the brain, particularly the brainstem, and represent the most basic manner in which the human

organism can sense and interact with its environment. Death is a result of the irreversible loss of these functions in the brain; either from an intra-cranial cause such as trauma or haemorrhage, or from an extra-cranial cause such as cardio-respiratory arrest, where impaired cerebral perfusion will culminate in cerebral and brainstem damage.

In this paper, we outline three sets of criteria to diagnose human death. Each set of criteria clearly establishes irreversible loss of the capacity to breathe combined with the irreversible loss of the capacity for consciousness. The most appropriate set of criteria to use is determined by the circumstances in which a medical practitioner is called upon to diagnose death. These three criteria sets are somatic (features visible on external inspection of the corpse such as rigor mortis or decapitation), circulatory, or neurological; and represent a diagnostic standard in which the medical profession and the public can have complete confidence.

For more than 40 yr, medical practitioners have been diagnosing death using neurological criteria. For nearly 200 yr, we have been using the stethoscope, as a technological aid for circulatory criteria, to diagnose the same death. Our understanding and the criteria we use may have evolved, but our duty remains the same, to make a timely diagnosis of death whilst avoiding any diagnostic errors; an obligation medical professionals cannot and should not abdicate. This review unites authors from Australia, Canada, and the UK

and examines the medical criteria that we should use in 2012 to diagnose human death.

## A history of diagnosing death

*'Have me decently buried, but do not let my body be put into a vault in less than two days after I am dead.'*  
Alleged dying request of George Washington, 1799.

Humans have long used criteria and technology to assist in the diagnosis of death. Somatic criteria, such as the presence of decomposition and rigor mortis, are the oldest in human history. The link between breath and life is equally as ancient and found in both Genesis (2:7) and the Qur'an (32:9). Shakespeare writes of King Lear requesting a looking-glass, 'If that her breath will mist or stain the stone, why then she lives.' (King Lear Act V Scene III). Feathers and candles were often utilized for a similar purpose.

Other influential proponents of criteria for human death were the twelfth-century rabbi and physician scholar Moses Maimonides, who was the first to argue that a decapitated person was immediately dead, despite the presence of residual movement in the body<sup>12 13</sup> and William Harvey, who in the seventeenth century first described the circulation of blood and the function of the heart as a pump and which, under this concept, death was when the heart and circulation stopped.<sup>14</sup>

Fears of premature burial appear to have culminated in the eighteenth century, when George Washington made his dying request and Jean-Jacques Winslow in 1740 famously stated that putrefaction is the only sure sign of death. This fear led to the construction of waiting mortuaries and security coffins with alarm mechanisms and permanent air supply.<sup>15</sup> Diagnostic criteria for death were unclear and Egbert Guernsey, writing in the 1853 Homeopathic Domestic Practice, warned against diagnosing death on the basis of cold or pulse or the use of a feather to detect respiration and advocated rigor mortis or its termination as the only safe criteria.<sup>16</sup>

A few years before in 1846 Paris, Dr Eugene Bouchut won the Academy of Sciences prize for '*the best work on the signs of death and the means of preventing premature burials*'. He advocated the use of the stethoscope, invented in 1819 by René Laennec, as a technological aid to diagnose death.<sup>15 17 18</sup> Several of Bouchut's chief critics were fellow contestants for the prize. They advanced alternate ideas for diagnosing death such as, introducing leeches near the anus, applying specially designed pincers to the nipples, or piercing the heart with a long needle with a flag at the end, which would wave if the heart were still beating. Bouchut believed that if a heartbeat was absent for >2 min, a person could be considered dead. In the face of opposition, he extended the period to 5 min.<sup>18</sup>

Case reports from physicians such as Harvey Cushing, writing around the beginning of the twentieth century, had observed that patients with cerebral pathology would die from respiratory arrest and *subsequent* circulatory collapse.<sup>6</sup> In the decades that followed, it was proposed that the loss of electrical activity in the brain and cerebral circulatory arrest

might signify human death. With the advent of mechanical ventilation, halting the inevitable circulatory collapse that follows cessation of spontaneous respiration, for the first time in human history, the need to diagnose death using neurological criteria was realized.

In 1959, two landmark accounts were published. First, Pierre Wertheimer's group characterized criteria for the 'death of the nervous system' and a few months later Mol-laret and Goulon coined the term *coma dépassé* for an irreversible state of coma and apnoea.<sup>17 19 20</sup> These criteria became widely used as an indicator of medical futility and a point at which ventilation could be stopped.

In 1963, the Belgian surgeon Guy Alexandre, using neurological criteria, carried out the first transplantation from a heart-beating donor and in 1967 Christiaan Barnard performed the first heart transplantation (incidentally, a case of donation after circulatory determined death in a patient who satisfied criteria for coma dépassé).<sup>6 20</sup> The publication the following year by the *Ad Hoc* Committee of the Harvard Medical School represented the culmination of over a decade of research and debate into neurological criteria for diagnosing death.<sup>21</sup> Simultaneously, the World Medical Assembly announced the Declaration of Sydney, which differentiated the meaning of death at the cellular and tissue levels from the death of the person and emphasized that the determination of death remained the responsibility of the medical practitioner.<sup>22</sup> Clinical, legal, and national codification followed<sup>23-26</sup> but vocal opponents to neurological criteria for diagnosing death persist.

In the last decade, the rapid expansion of organ donation from individuals diagnosed deceased using circulatory criteria, known now as donation after circulatory death (DCD), has led to new debate about the definition and determination of death. A unifying medical concept of death, which combines all the previous historical criteria, is emerging.

## A unifying medical concept of death

In 2008, the US President's Council on Bioethics explored all the justifications that can be used to define brain death as human death.<sup>10</sup> The President's Council concluded by a majority decision that the best justification for brain death equating to human death is that there is a 'fundamental vital *work* of a living organism – the work of self-preservation, achieved through the organism's need-driven commerce with the surrounding world' [page 60]. For a human being, this commerce is manifested by the drive to breathe, demonstrating the most basic way a human being can act upon the world, combined with consciousness, or the ability to be open to the world. The irreversible loss of these two functions equates to human death. This conclusion is reflected in a growing consensus that all criteria used to diagnose human death rely upon the demonstration of the irreversible loss of the capacity to breathe, combined with the irreversible loss of the capacity for consciousness.<sup>4 8 27</sup>

Consciousness was defined by William James in 1890 and entails a state of being awake and aware of self and

environment.<sup>28</sup> This is manifested by two physiological components: arousal (wakefulness) and awareness. A patient in a persistent vegetative state may lack awareness but demonstrates arousal and cannot be considered deceased. Some argue that the irreversible loss of awareness alone represents the loss of the person and signals human death.<sup>29 30</sup> The position outlined in this paper, consistent with many other authors and medical bodies, is that any demonstration of arousal or awareness is incompatible with a concept of human death.<sup>6 8 10 11 31</sup>

The capacity for consciousness and breathing are both functions of the brain and unlike any other organ, the brain is both essential and irreplaceable.

In this respect, all human death is death of the brain; although this should not be taken to imply that neurological criteria is the only criteria appropriate to diagnose death. Rather, death is diagnosed using the most appropriate criteria for the circumstances in which a medical practitioner may be called upon to diagnose it. Three sets of criteria are apparent (Fig. 1) and all can be used to demonstrate the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe. In the community and where death may have occurred hours to days before, somatic criteria will reliably indicate the loss of these two essential capacities. When death is more recent and especially within a hospital setting, death is usually diagnosed by the use of circulatory criteria after cardiorespiratory arrest. It is only within the critical care environment, where mechanical ventilation is used, that the diagnosis of death using neurological criteria is applied.

### Diagnosis and confirmation of death using somatic criteria

Somatic criteria for human death are those that can be applied by simple external inspection of the corpse without a requirement to examine for signs of life or evidence of internal organ function. The criteria are historically ancient

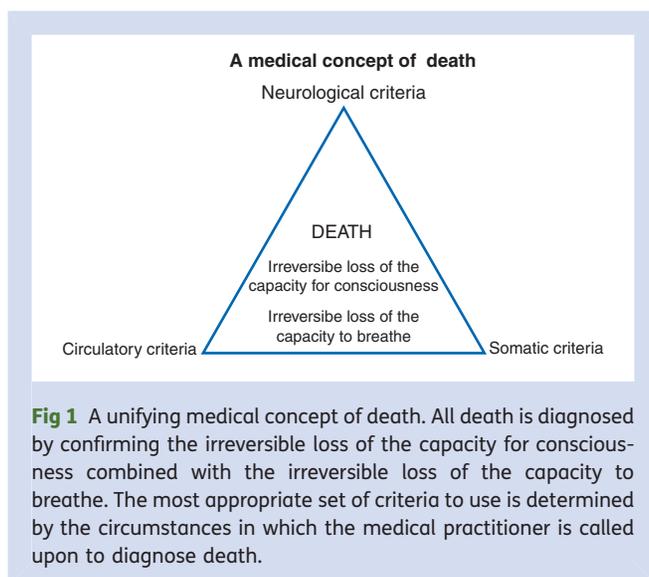
and include such signs as rigor mortis, decapitation, and decomposition. Somatic criteria unequivocally indicate irreversible loss of consciousness and irreversible apnoea. Today, ambulance officers and paramedics recognize these criteria, known sometimes as Recognition of Life Extinct (ROLE), where death is so clearly obvious that attempts at resuscitation should not be made (Table 1).<sup>32</sup>

Whilst useful in diagnosing death that has occurred sometime beforehand, somatic criteria are not practical when death is more recent, considering the importance of a timely diagnosis with its legal and societal implications.

### Diagnosis and confirmation of death using circulatory criteria

The simultaneous onset of circulatory arrest, unconsciousness, and apnoea (cardiorespiratory arrest) has long been used as a basis for diagnosing death, both in the hospital and in the community. Within 15 s of absent cerebral circulation consciousness is lost, the EEG becomes iso-electric and apnoea rapidly ensues, if not already present.<sup>33–36</sup> Circulatory criteria to diagnose death predict the permanent and irreversible loss of the capacity for consciousness and the capacity to breathe. The criteria are based on the knowledge that the brain suffers anoxic structural damage when the cerebral circulation is halted.

What is perhaps surprising is that until the publication of the Academy of Medical Royal Colleges' Code of Practice in 2008, there was no guidance for doctors in the UK on how to confirm death after cardiorespiratory arrest.<sup>37</sup> Before the widespread introduction of DCD, there was less need for proscriptive criteria, as in practice there was no necessity to confirm death in such a time-critical manner. Neither was it routine practice to test for corneal reflexes or motor responses to supraorbital pressure. In the new more explicit code, the diagnosis of death in patients after cardiorespiratory arrest (circulatory criteria) or for a patient in coma (neurological criteria) are very similar (Table 2), reflecting the concept that all criteria for diagnosing death must



**Table 1** Recognition of life extinct: conditions unequivocally associated with death<sup>32</sup>

1. Massive cranial and cerebral destruction
  2. Hemisporrectomy
  3. Massive truncal injury incompatible with life including decapitation
  4. Decomposition/putrefaction (where tissue damage indicates that the patient has been dead for some hours)
  5. Incineration (the presence of full thickness burns with charring of >95% of the body surface)
  6. Hypostasis (the pooling of blood in congested vessels in the dependent part of the body in the position in which it lies after death)
  7. Rigor mortis (the stiffness occurring after death from the post mortem breakdown of enzymes in the muscle fibres)
- In the newborn, fetal maceration

demonstrate the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe.

Essential components for diagnosing death using circulatory criteria include an agreement that further resuscitation will not be attempted, a minimum observation period, and a prohibition against activities that might restore the cerebral circulation (Table 3). Table 4 outlines variation in the implementation of circulatory criteria for the purposes of DCD in Australia, Canada, the UK, and the USA.<sup>8 10 31 38-40</sup> There remains considerable international variation and variation within individual countries.<sup>41</sup>

The observation period begins at the time of loss of the circulation, in association with coma and apnoea; the minimum acceptable duration of observation depends on the criterion used for diagnosing death (Table 5).<sup>42</sup> It is important to note that palpation of the pulse may be insufficient to ensure circulatory arrest as low output circulatory states can persist even when the pulse is impalpable to the clinician. Where the technology is readily available,

monitoring to confirm circulatory arrest is recommended, such as intra-arterial pressure monitoring, electro, or echocardiography. Any return of the circulation or any respiratory activity during this period necessitates a further observation period after subsequent circulatory arrest.

On the basis of Devita's work suggesting that 65 s is the shortest acceptable observation time for the determination of death after cardiorespiratory arrest, surgeons in Denver chose 75 s as their period of observation in paediatric heart DCD.<sup>43</sup> For many clinicians and philosophers, and indeed for the authors of this review, an observation period of such a short duration is considered unacceptable.<sup>44 45</sup> Devita recommended 2 min as a safe observation time and many institutions in Australia and in the USA have adopted this as a minimum standard for DCD.<sup>31 42</sup> Canada and the UK have adopted a more conservative 5 min standard,<sup>8 39</sup> while in Italy 20 min is required.<sup>46</sup>

The Lazarus phenomenon of auto-resuscitation, as described in the literature, appears to occur only in the context of failed or inadvertently continued CPR (e.g. continuing mechanical ventilation in a patient declared 'dead') and not after the planned withdrawal of life-sustaining treatment.<sup>47</sup> A recent systematic review could identify only eight cases of return of spontaneous circulation with ECG monitoring and exact times recorded, all followed failed CPR; in one case return of spontaneous circulation occurred at 3 min, in six cases at 5 min and in one case (from 1996) at 7 min.<sup>48</sup>

Since death after failed CPR is often diagnosed after extremely short observation periods, codes of practice that insist on a defined observation period and a specific set of clinical observations are likely to increase the certainty and confidence in the diagnosis of death and reduce the rare cases of wrong diagnosis.<sup>49</sup> The practice of switching monitors off as soon as resuscitation is abandoned is no longer acceptable.

### Areas of contention

The requirement of a short warm ischaemic time for successful transplantation after DCD has brought circulatory

**Table 2** Similarity within the UK Code of Practice (2008) for the diagnosis of death after cardiorespiratory arrest and in a patient in a coma<sup>8</sup>

Diagnosing and confirming death after cardiorespiratory arrest ( <u>circulatory</u> criteria)	Diagnosis and confirmation of death in a patient in a coma ( <u>neurological</u> criteria)
<i>Demonstration of loss of the capacity for consciousness</i>	
Absence of the <u>pupillary</u> response to light	Absence of the pupillary response to light
Absence of the <u>corneal</u> reflex	Absence of the corneal reflex
Absence of <u>any motor</u> response to <u>supra-orbital</u> pressure	Absence of <u>any motor</u> response to supra-orbital pressure
<i>Demonstration of loss of the capacity to breathe</i>	
<u>Five</u> minutes observation of maintained cardiorespiratory arrest	<u>Five</u> minutes <u>apnoea</u> test to demonstrate no spontaneous respiratory effort

**Table 3** Essential components for the diagnosis of death using circulatory criteria after cardiorespiratory arrest<sup>8 9 27</sup>

Component	Explanation
1. A clear intention not to attempt cardiopulmonary resuscitation (CPR) in order to restore circulatory, and therefore cerebral, function	An exclusion of indications to commence or continue CPR. This may be because there has been a decision not to perform CPR, or a decision after unsuccessful CPR that further attempts are futile. Importantly, contributory causes to any cardiorespiratory arrest (e.g. hypothermia ≤34°C, endocrine, metabolic, or biochemical abnormality) should be considered and treated, if appropriate, before diagnosing death
2. An observation period to confirm continuous apnoea, absent circulation, and unconsciousness; after which the likelihood of spontaneous resumption of cardiac function will have passed	After this observation period the circulation will not spontaneously return and the inevitable anoxic ischaemic injury to the brain, that follows the loss of the cerebral circulation, will continue unabated. There is international variation in the length of observation period required to establish safe practice
3. The prohibition at any time of any intervention that might restore cerebral blood flow by any means	Were cerebral circulation to be <u>reestablished</u> , the <u>diagnosis of death</u> using <u>circulatory</u> criteria would be <u>invalidated</u>

**Table 4** Variation in the implementation of circulatory criteria to diagnose death in Australia, Canada, the UK, and the USA

	Australia <sup>31 38</sup>	Canada <sup>39</sup>	The UK <sup>8</sup>	The USA <sup>10 40</sup>
Guidance to be used in	DCD	DCD	Any death after cardiorespiratory arrest.	DCD
Any specific concept	Cessation of circulation is the basis for the declaration of death	The fact of death shall be determined in accordance with 'accepted medical practice'	The individual should be observed to establish that irreversible cardiorespiratory arrest has occurred	Irreversible should be understood as, cessation of circulatory and respiratory functions under conditions in which those functions cannot return on their own and <i>will not</i> be restored by medical interventions
Medical personal who can confirm death	Intensivist recommended, or other nominated doctor who is not a member of the organ retrieval or transplantation teams	Two physicians required. The physician present during the 5-min period of continuous observation and who makes one of the determinations of death must be a staff physician with the requisite skill and training	No specific recommendation	No specific recommendation
Observation period	2–5 min (not <2 min and not more than 5 min)	5 min	5 min	2–5 min (Institute of Medicine recommends 5 min)
Examination	Death should be determined on the basis of immobility, apnoea, absent skin perfusion and the absence of circulation. The absence of circulation is determined by clinical means and preferably supplemented with intra-arterial pressure monitoring	Beginning with the onset of circulatory arrest, there must be a 5-min period during which the absence of palpable pulses, blood pressure, and respiration are continuously observed by at least one physician. Death is determined by two physicians by documenting the absence of palpable pulses, blood pressure and respiration on completion of this 5-min period	Demonstration of apnoea and unconsciousness in the absence of the circulation by clinical examination. Supplemented in some hospital settings with ECG, pulsatile flow on an arterial line or contractile activity on echocardiography. Additionally, after 5 min of continued cardiorespiratory arrest the absence of the pupillary responses to light, the corneal reflexes, and any motor response to supra-orbital pressure should be confirmed	Institute of Medicine recommends ECG and arterial pressure monitoring
Warnings	After death, the retrieval team may intubate to prevent aspiration and ensuing pulmonary damage. Insufflation with 100% oxygen is permissible. Procedures that may inadvertently restore cerebral circulation, myocardial perfusion or oxygenation, such as cardiac compressions and mechanical ventilation, are to be avoided until after the commencement of organ retrieval surgery	Interventions that may re-institute cerebral perfusion and oxygenation after the fact of death should not be performed	It is obviously inappropriate to initiate any intervention that has the potential to restore cerebral perfusion after death has been confirmed	Attempting to revive such a patient would be ruled out ethically

**Table 5** Observation times, which might theoretically be used to diagnose death in humans using circulatory criteria after cardiorespiratory arrest. [Adapted from DeVita using his table and text (used with permission).]<sup>42</sup>

Theoretical observation time	Point of diagnosis	Explanation
0	Patient not dead	Time of cessation of circulation, respiration, and responsiveness
15 s	Brain activity ceases, spontaneous recovery possible	Flat electroencephalogram
<u>65 s</u>	Shortest acceptable observation time for determination of death	<u>Longest</u> duration of <u>observed absence</u> of cardiopulmonary function followed by <u>spontaneous</u> recovery of circulation
11 min	Shortest acceptable observation time for determination of death if criterion is impossibility of restoring whole brain function	Successful resuscitation and restoration of normal cerebral function in laboratory animals
60 min	Shortest acceptable observation time for determination of death if criterion is impossibility of restoring some brain activity	Last point at which the brain may be stimulated and respond
Hours	Shortest acceptable observation time for determination of death if criterion is impossibility of restoring cardiac activity	Heart may still resume function in laboratory or <u>transplant</u> setting

criteria for the diagnosis of death into sharp focus.<sup>10 44 50–52</sup>

If death is the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe, then what is the required observation period using circulatory criteria that will ensure irreversibility? If an observation period of 2–5 min is used to confirm continuous cardiorespiratory arrest, then neither the heart nor the brain can be considered completely and irreversibly structurally damaged. At this point, CPR can restore function.<sup>50 53–55</sup> This has led to the claim that DCD violates the dead donor rule (persons must be dead before their organs are taken), since irreversibility cannot be established within the time frames required for successful donation.<sup>56–58</sup>

The counter argument is that death diagnosed using circulatory criteria rests on the intention not to attempt CPR and not a literal definition of ‘irreversible’, that is a circulation that cannot be restored using any currently available technology. To insist on the latter standard would ignore how death is diagnosed every day in every hospital worldwide. Unless one is prepared to undertake open cardiac massage and direct cardiac defibrillation before diagnosing anyone in hospital as dead, we cannot know that the heart has irreversibly ceased. DeVita’s work suggests that if a literal definition of irreversible is used, where function cannot be restored by any known technology, then for the brain this would be 1 h of cerebral circulatory arrest, whilst for the heart it would be many hours. This would lead to a death watch in which there would be no place for a stethoscope and modern medicine would be turned back 150 yr, to a time when only the satisfaction of somatic criteria, such as rigor mortis, was widely accepted, yet still not publically trusted.

A North American collaboration of authors<sup>9</sup> suggested that a better term for the cessation of function, which allows death to be diagnosed by circulatory criteria, is ‘permanent’. Permanent is a contingent and equivocal condition that admits possibility (the restoration of the circulation) and

relies on intent, a clear intention not to attempt CPR and the prohibition at any time of any action that might restore cerebral blood flow.

### Diagnosis and confirmation of death using neurological criteria

The neurological determination of death utilizes clinical criteria for confirming death in profound coma when cardiorespiratory activity is being maintained by continued mechanical ventilation. Essential components for diagnosing death using neurological criteria are outlined in Table 6. There is international acceptance and legal support for neurological criteria to determine death in this circumstance and there has been little substantial change to the criteria in nearly 40 yr.<sup>8 10 21 23 24 26 31 59–63</sup> although there is some variation in implementation in different countries (Table 7).

When the essential components are carried out with appropriate diligence and by appropriately trained clinicians, neurological criteria has a certainty equal to that of the other two criteria outlined in this paper.<sup>63–69</sup>

### Areas of contention

#### Recovery after a diagnosis of ‘brain death’

Three recent case reports of transient return of some neurological function after a diagnosis of death using neurological criteria (Table 8)<sup>70–72</sup> have led some clinicians to question the reliability of clinical testing. A recent (2010) systematic review in adults could find no published reports of recovery of neurological function.<sup>63</sup> These three new cases must be seen in the following contexts: 40 yr of diagnosing death using neurological criteria, 10 000 confirmed diagnoses in the UK alone over the last decade, and patients (particularly in countries like Japan) being maintained on mechanical ventilation for prolonged periods after satisfying neurological criteria for death and yet not regaining brain function. This history tells us that the diagnostic standard for death

**Table 6** Essential components for the diagnosis of death using neurological criteria

Component	Explanation
(1) An established aetiology capable of causing structural damage to the brain which has led to the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe	There should be no doubt that the patient's condition is due to irreversible brain damage of known aetiology With some diagnoses a more prolonged period of continued clinical observation and investigation is required to be confident of the irreversible nature of the prognosis, e.g. anoxic brain injury, isolated brainstem lesions (in the UK)
(2) An exclusion of reversible conditions capable of mimicking or confounding the diagnosis of death using neurological criteria	Pharmaceutical agents (both cerebral depressant and neuromuscular), and temperature, cardiovascular, endocrine and metabolic disturbances, which might be contributing to the unconsciousness and apnoea, must be excluded
(3) A clinical examination of the patient, which demonstrates profound coma, apnoea and absent brainstem reflexes	The patient must have a persisting Glasgow Coma Score of 3 demonstrating the functional loss of the reticular activating system and any other centres of consciousness A formal apnoea test demonstrating the lack of the capacity to breathe, and thereby the functional loss of the respiratory centres located in and associated with the medulla oblongata. The apnoea test is preferably carried out after the examination of brain stem reflexes The cranial nerves (with the exception of I, II and the spinal component of XI) originate in the brainstem and the demonstration of their functional loss confirms the widespread damage to the brainstem and by association, the reticular activating system and medulla oblongata. All of the following brainstem derived cranial nerve reflexes are examinable and must be demonstrated to be absent: <ul style="list-style-type: none"> <li>• Pupils should be fixed in diameter and unresponsive to light (Cranial Nerves II, III)</li> <li>• Nystagmus or any eye movement should not occur when each ear is instilled with ice cold water. Each ear drum should be clearly visualized before the test (Vestibulo-ocular reflex—Cranial Nerves III, IV, VI, VIII)</li> <li>• There should be no corneal reflex (Cranial Nerves V, VII)</li> <li>• There should be no facial or limb movement when supraorbital pressure is applied (Cranial Nerves V, VII)</li> <li>• There should be no gag reflex following stimulation to the posterior pharynx or cough reflex following suction catheter passed into the trachea (Cranial Nerves IX, X)</li> </ul>

confirmed using neurological criteria is safe. Certain well-publicized reports of supposed survival after a diagnosis of 'brain death' have reflected either a misunderstanding of the concept<sup>73–75</sup> or a failure to follow criteria such as those outlined in this paper.<sup>76</sup>

These three case reports emphasize the absolute importance of the preconditions required for a diagnosis of death using neurological criteria. These include establishing an aetiology capable of causing structural damage to the brain sufficient to result in the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe; and an exclusion of reversible conditions capable of mimicking or confounding the diagnosis of death using neurological criteria.

It is well known that a longer period of observation is required to establish irreversibility in the face of anoxic ischaemic brain injury and especially now that therapeutic

hypothermia is being applied more commonly, though the appropriate length for this extended observation remains unclear.<sup>8 63</sup> If there is any doubt over the irreversibility of the brain injury, the clinician should observe the patient for an extended period or use a cerebral blood flow investigation, to clearly establish irreversibility.

### The role of confirmatory investigation

Confirmatory investigations are not routinely required in most jurisdictions for the diagnosis of death using neurological criteria,<sup>8 10 11 31 77</sup> though in some countries they are required by law.<sup>78</sup> They may be useful however where it is not possible to fully satisfy the 'Essential Components for the Diagnosis of Death using Neurological Criteria' (Table 5). For example, where a primary metabolic or pharmacological derangement cannot be ruled out, or in cases of high cervical

**Table 7** Variation in the implementation of neurological criteria to diagnose death in Australia, Canada, the UK, and the USA

	Australia <sup>31</sup>	Canada <sup>11</sup>	The UK <sup>8</sup>	The USA <sup>10 63</sup>
Concept	Brain death requires that there is unresponsive coma, the absence of brainstem reflexes, and the absence of respiratory centre function, in the clinical setting in which these findings are irreversible  Brain death is determined by: clinical testing if preconditions are met; or imaging that demonstrates the absence of intracranial blood flow. However, no clinical or imaging tests can establish that every brain cell has died.	Brain death is defined as the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions including the capacity to breathe	When the brainstem has been damaged in such a way, and to such a degree, that its integrative functions (which include the neural control of cardiac and pulmonary function and consciousness) are irreversibly destroyed, death of the individual has occurred	If there are no signs of consciousness <i>and</i> if spontaneous breathing is absent <i>and</i> if the best clinical judgement is that these neurophysiological facts cannot be reversed, a once-living patient has now died
Aetiology	Evidence of sufficient intracranial pathology to cause whole brain death. Brain death cannot be determined when the condition causing coma and loss of all brainstem function has affected only the brainstem, and there is still blood flow to the supratentorial part of the brain.	Established aetiology capable of causing neurological death  There must be definite clinical or neuro-imaging evidence of an acute central nervous system event consistent with the irreversible loss of neurological function	There should be no doubt that the patient's condition is due to irreversible brain damage of known aetiology	Establish irreversible and proximate cause of coma  The cause of coma can usually be established by history, examination, neuroimaging, and laboratory tests
Minimum observation period before clinical testing	4 h  In cases of acute anoxic-ischaemic brain injury, clinical testing for brain death should be delayed for 24 h subsequent to the cardiorespiratory arrest.	Any time after exclusion of confounders. In cases of acute anoxic-ischemic brain injury, clinical evaluation should be delayed for 24 h subsequent to the cardiorespiratory arrest or an ancillary test could be performed	Left to the clinician to be satisfied that the patient's condition is due to irreversible brain damage of known aetiology	Left to the clinician to be satisfied that an appropriate period of time has passed since the onset of the brain insult to exclude the possibility of recovery

Continued

Table 7 Continued

	Australia <sup>31</sup>	Canada <sup>11</sup>	The UK <sup>8</sup>	The USA <sup>10 63</sup>
Medical personnel who can confirm death	Two medical practitioners. Qualification and experience varies between each state in Australia	Recommended minimum level of physician qualification is full and current licensure for independent medical practice in the relevant Canadian jurisdiction and possessing skill and knowledge in the management of patients with severe brain injury and in the neurological determination of death	Two medical practitioners who have been registered for >5 yr and are competent in the conduct and interpretation of brainstem testing. At least one of the doctors must be a consultant	Legally, all physicians are allowed to determine brain death in most US states. It seems reasonable to require that all physicians making a determination of brain death be intimately familiar with brain death criteria and have demonstrated competence in this complex examination
Repetition of tests	Each medical practitioner must separately carry out a clinical examination, in order that the doctors and the tests are seen to be truly independent  The tests may be done consecutively but not simultaneously	Two clinical tests at no fixed interval, one apnoea test if performed concurrently with both physicians present. If performed at different times, a full clinical examination including the apnoea test must be performed, without any fixed examination interval, regardless of the primary aetiology	Testing should be performed completely and successfully on two occasions with both doctors present	Perform one neurologic examination (sufficient to pronounce brain death in most US states)  Some US state statutes require two examinations
Apnoea test	Apnoea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial $P_{aCO_2} > 60$ mm Hg (8 kPa) and an arterial $pH < 7.30$ . The period of observation to achieve an adequate threshold of stimulus of the respiratory centre is variable	Thresholds at completion of the apnoea test: $P_{aCO_2} \geq 60$ mm Hg (8 kPa) and $\geq 20$ mm Hg (2.7 kPa) above the pre-apnoea test level and $pH \leq 7.28$ as determined by arterial blood gases	$P_{aCO_2} > 6.0$ kPa (45 mm Hg) and $pH < 7.4$ before disconnection from mechanical ventilation followed by 5 min of observed apnoea, confirming the $P_{aCO_2}$ has increased by more than 0.5 kPa (4 mm Hg)	No respiratory movements for 8–10 min and arterial $P_{aCO_2}$ is $\geq 60$ mm Hg (8 kPa) or there is a 20 mm Hg (2.7 kPa) increase in arterial $P_{aCO_2}$ over a baseline normal arterial $P_{CO_2}$
Role of confirmatory investigation	If clinical testing cannot be relied upon because preconditions are not met, absence of intracranial blood flow is diagnostic	An ancillary test should be performed when it is impossible to complete the minimum clinical criteria	In instances where a comprehensive neurological examination is not possible, where a primary metabolic or pharmacological derangement cannot be ruled out or in cases of high cervical cord injury	When uncertainty exists about the reliability of parts of the neurologic examination or when the apnoea test cannot be performed. In some protocols, ancillary tests are used to shorten the duration of the observation period
Recommended confirmatory investigation	Demonstration of absence of intracranial blood flow. Four-vessel angiography and radionuclide imaging are the preferred imaging techniques for assessing intracranial blood flow	Demonstration of the global absence of intracerebral blood flow. EEG is no longer recommended	Nil specifically recommended	EEG, nuclear scan, or cerebral angiogram, are considered the preferred tests

**Table 8** Key facts in the three recent case reports of return of neurological function after a diagnosis of death using neurological criteria

	Case 1 <sup>70</sup>	Case 2 <sup>70</sup>	Case 3 <sup>71 72</sup>
Country of origin	Canada	Canada	USA
Aetiology of neurological injury	Unilateral space occupying lesion caused by temporal lobe abscess with surrounding vasogenic oedema ( <i>Escherichia coli</i> isolated in blood)	Traumatic brain injury after a fall with associated pulseless electrical activity requiring advanced cardiac life support for 5 min	Pulseless electrical activity, preceded by respiratory arrest, requiring advanced cardiac life support for 20 min
Time from onset of profound coma, absent brainstem reflexes and apnoea, until clinical examination for death using neurological criteria	7 h	6 h	Unclear, maximum of 16 h since last documented presence of brain stem reflexes (72 h from aetiology)
Potential confounders to the diagnosis of death using neurological criteria	Chronic otitis media and acute mastoiditis that may have interfered with vestibulo-ocular testing	Anoxic brain injury	Propofol and fentanyl (14 mg in total) infusions, in the setting of renal and hepatic dysfunction and therapeutic hypothermia, were ceased 22 h before testing. Normothermia ( $\geq 37^{\circ}\text{C}$ ) restored 16 h before testing
Seniority and specialty of clinicians performing the testing	Intensivist and neurosurgeon	2 intensivists	2 neurologists
Number of clinical examinations	2	2	2
Number of apnoea tests	1	1	1
Apnoea test duration	10 min	8 min	10 min
Other investigations	MRI performed 2 h after diagnosis of brain death, which demonstrated preserved intracranial arterial flow	Cerebral radionuclide angiogram after the diagnosis of brain death, demonstrated intracranial arterial flow	EEG before testing revealed no discernible cerebral electrical activity but frequent myoclonic activity obscured the tracing
Reversal of the diagnosis of death using neurological criteria	Return of respiration 28 h after the onset of coma. No return of brainstem reflexes	Return of respiration 11 h after the onset of coma. No return of brainstem reflexes	Return of respiration and brainstem reflexes 26 h after the first clinical examination consistent with brain death. Repeat EEG still demonstrated no discernible cerebral electrical activity
Patient outcome	Repeat MRI demonstrated absence of intracranial venous outflow. After 5 days the spontaneous respirations decreased and cardiovascular collapse ensued	Withdrawal of life sustaining treatment after family discussion	Loss of brainstem function on repeat clinical examination 73 h after the first clinical examination consistent with brain death and confirmed with bi-lateral median somatosensory-evoked potentials, MRI and technetium-based dynamic nuclear medicine cerebral blood flow study

**Table 9** Confirmatory investigations commonly in use internationally to aid the diagnosis of death using neurological criteria<sup>6 8 20 31 79 81-83</sup>

Confirmatory Test	Description	Advantages	Disadvantages
<i>Loss of bioelectrical activity</i>			
Electroencephalography (EEG)	16–18 channel instrument with recordings over at least 30 min	Long history of ancillary use in diagnosing brain death Portable	Artifacts from intensive care environment common Limited use in setting of sedation Cortical activity rather than deep cerebral activity
Evoked potentials	Visual, auditory, somatosensory, and multi-modal	Portable Less resistant to sedation compared with EEG	Restricted availability Complex interpretation. Testing of isolated neural tracts
<i>Cessation of cerebral circulation</i>			
Four-vessel intra-arterial catheter angiography	Direct injection of contrast medium into both carotid arteries and both vertebral arteries	Direct visualization of cerebral blood flow Current gold standard	Invasive Not portable Risk <1%
Contrast computed tomography angiography (CTA)	CT indicators are: absent enhancement bilaterally of the middle cerebral artery cortical branches (beyond the Sylvian branches), P2 segment of the posterior cerebral arteries, pericallosal arteries and internal cerebral veins; in the presence of contrast enhancement of external carotid arteries	Readily available Rapid acquisition Growing literature base Can be combined with perfusion studies	Not portable
MR angiography (MRA)	Magnetic resonance imaging with contrast enhanced angiography	Can be combined with perfusion studies	Not portable Restricted availability Requires dedicated MR-safe anaesthetic equipment Slow
Single photon emission computed tomography (SPECT)	Imaging of brain tissue perfusion using a tracer isotope [e.g. <sup>99m</sup> Tc-hexamethylpropyleneamine oxime (HMPAO)]	Images brain perfusion	Restricted availability
Positron emission tomography (PET)	Imaging of brain with biologically active positron-emitting nuclides (e.g. fluorine-18 fluorodeoxyglucose)	Quantitative Can assess brain metabolism	Restricted availability Not portable
Transcranial Doppler	Doppler measurement of middle cerebral artery velocity and direction through the temporal bone	Portable Non-invasive Rapid	Operator dependent Many consider unreliable

cord injury preventing the formal assessment of the irreversible loss of the capacity to breathe secondary to functional and structural damage to the brainstem, or if extensive facial injuries prevent a full neurological examination of the brainstem reflexes. In such cases, confirmatory investigation may reduce uncertainty, facilitate a more timely diagnosis of death, or assist in the diagnosis of complex cases as discussed above.

Any investigation should always be considered as additional to a full clinical assessment of the patient, conducted to the best of the clinician's ability in the given circumstances. The clinician must take into account the potential for error and misinterpretation with all the known confirmatory investigations, especially by investigators with limited experience in their use and because the investigations are often being utilized in difficult clinical circumstances.<sup>62 79 80</sup> A comparison of confirmatory investigations in common use internationally is given in Table 9.<sup>6 8 20 31 79 81–83</sup>

The use of confirmatory tests to demonstrate the loss of bioelectrical activity in the brain, particularly the EEG, is often problematic. It is in the very conditions where confirmatory investigation may be useful, such as where a primary metabolic or pharmacological derangement cannot be ruled out, where the EEG is least helpful.<sup>79</sup> The common techniques used to demonstrate complete cessation of cerebral circulation include four vessel cerebral angiography (the gold standard), CT angiography, MR angiography, radionuclide imaging, and transcranial doppler. The latter suffers from significant operator dependence. If these investigations demonstrate residual cerebral circulation, a longer clinical observation period or a repetition of the test will be required to establish the diagnosis.

### Brainstem vs whole brain formulations of 'brain death'

The irreversible loss of consciousness combined with the irreversible loss of the capacity to breathe can all be accounted for by structural damage to the brainstem. As has been shown above, demonstration of structural and functional damage to the brainstem is essential to the neurological criteria for confirming death and essential to every country's current guidelines and practice.

The UK, Indian, and Canadian practices are similar in accepting a determination based on brainstem function.<sup>8 11 84</sup> In many other parts of the world, the diagnosis of death using neurological criteria is based on a whole brain concept, which suggests a loss of all functions of the brain.<sup>10 31</sup> This difference in international practice is less than it first appears. Diagnosing death using neurological criteria in isolated brainstem injuries is extremely rare because such conditions are rare and present considerable uncertainty with regards to irreversibility (an essential component of neurological criteria). In other countries, despite having a whole brain concept of death, a clinical examination (virtually identical around the world) is usually all that is required for the diagnosis, provided the usual preconditions are satisfied and the aetiology of the structural damage to the brain is not isolated to the brainstem.

### The preservation of spinal, autonomic, and integrative bodily function

The preservation of spinal and autonomic (cardiovascular) function and reflexes after the diagnosis of death using neurological criteria has led to concern by some clinicians that this residual function represents evidence for continued or potential consciousness.<sup>85 86</sup> There is overwhelming evidence that continued spinal cord activity, including complex withdrawal movements, is possible and indeed expected after a diagnosis of death using neurological criteria.<sup>63 68 87 88</sup> Likewise, there is increasing knowledge regarding the complex integration of the autonomic nervous system at the spinal cord level, including cardiovascular responsiveness to peripheral stimulation.<sup>89–93</sup> The continued secretion of pituitary hormones observed in some cases of confirmed 'brain death' is not a surprise, since anatomically the posterior pituitary and, to a lesser degree the anterior pituitary (indirect partial supply via short portal vessels), is supplied by the inferior hypophysial artery, which is extra-dural in origin.<sup>10 20 94–97</sup>

EEG monitoring during organ retrieval has failed to demonstrate any cerebral activity during organ retrieval<sup>98</sup> and any 'anaesthesia' during organ retrieval is for the maintenance of physiologic stability, neuromuscular block, and possibly ischaemic preconditioning of the retrieved organs, not for the benefit of the deceased patient.<sup>99</sup>

### Philosophical and religious criticism

Critics of neurological criteria for the diagnosis of human death fall into three broad groups:

- (i) those who wish to see the abandonment of the dead donor rule (persons must be dead before their organs are taken), for the apparent purpose of expanding the potential donor pool to include those in minimal conscious states or at the end of life,<sup>100–104</sup>
- (ii) those who hold to the philosophical belief that loss of personhood equates to human death, sometimes referred to as a higher brain concept of brain death, which would allow donation from patients in vegetative states or with anencephaly;<sup>30 105</sup> and
- (iii) those who believe that locating human death to functions in the brain is reductionist and does not accord the body sufficient dignity.<sup>12 106–108</sup> Many religious writers fall into this latter category.

We believe the neurological criteria, as outlined above, represent international practice in which the medical profession and the public can have complete confidence. 'In comparison the diagnosis of vegetative states fails to satisfy both a timely diagnosis and a specific one, and no robust criteria exist for the irreversible loss of personhood'.

### Conclusions

Criteria are best understood as pragmatic deductions of the truth, a truth that we can never fully know in medicine because our knowledge and understanding is always

increasing. This should not make us feel wary about using criteria to make diagnoses even in such important areas as death. Criteria are the foundation of all diagnoses, from myocardial infarction to microbiology. One should however be always mindful of a diagnostic criterion's sensitivity and specificity. The criteria we use to diagnose human death, which demonstrate the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe, have an unequalled specificity in modern medicine. This is just as well, as this is the standard expected by society.

Using either somatic, circulatory, or neurological criteria to diagnose death as outlined above, the medical practitioner can be sure that, in 2012, he or she is maintaining an exemplary standard by using criteria that are international, ethically substantial, and supported by sound scientific and physiological rationale.

## Declaration of interests

D.G. and A.M. are regional clinical leads for organ donation in the UK. S.S. is Loeb Chair in Organ and Tissue Donation, University of Ottawa and Executive Medical Director, Donation, Canadian Blood Services. H.O. is the State Medical Director for DonateLife, Victoria, Australia.

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