Review Article

The Relevance of Irreversible Loss of Brain Function as a Reliable Sign of Death

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*on behalf of the working group "The relevance of irreversible loss of brain function as a reliable sign of death" of the Scientific Advisory Board within the German Medical Association; for a detailed list of collaborators see *Box 3* at the end of this article

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Summary

Background: There is an ongoing need for clear explanation of the diagnostic entity called "irreversible loss of brain function" (ILBF), as the absolute reliability of this diagnosis and its significance continue to be widely misunderstood. The determination of death as an objective medical-scientific matter is often not clearly distinguished from various other aspects of death, such as its metaphysical and cultural aspects and the ways in which the living deal with the dead.

Method: This review is based on articles retrieved by a selective literature search in the PubMed database and on guidelines and standardized diagnostic protocols from Germany and abroad.

Results: ILBF can be caused by brain ischemia or anoxia or by any other type of brain disease or injury leading to an elevation of the intracranial pressure above the blood pressure and thereby to an arrest of the cerebral circulation. All situations in which brain function is merely reduced but not abolished, or only temporarily but not permanently abolished, can be clearly differentiated from ILBF through the use of standard diagnostic procedures as recommended in the relevant guidelines. Biological features that are common to all human beings underlie the medical criteria for the determination of death. The most important elements of the determination of death are irreversibility of the loss of brain function, loss of integration of bodily functions into a single living being, and loss of ability for any self-reflection or any independent interaction with the environment.

Conclusion: ILBF is a reliable sign that a human being is dead. There has never been even one known case of incorrect determination of ILBF after proper application of the standardized diagnostic procedures that are set down in the guideline according to §16 of the German Transplantation Law.

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The diagnosis of irreversible loss of brain function (ILBF) means that the patient's brain has irretrievably ceased to function despite the ongoing maintenance of cardiovascular function by the methods of intensive care medicine *(Box 1)*. In §3 of the German Transplantation Law (*Transplantationsgesetz,* TPG), ILBF is described as "the final, irreversible loss of all function of the cerebrum, cerebellum, and brainstem."

The significance of ILBF as a reliable sign of death has been definitively established in Germany (as in other countries) in position statements of multiple involved organizations, including the German Medical Association (*Bundesärztekammer*) *(Box 2)*, medical-scientific specialty societies, and religious communities (2–8).

The basic elements of the determination of ILBF have not changed, and the position statements concerning them are still applicable. The present article, however, differs from previous writings on the subject in its terminology. ILBF and the colloquial term "brain death" denote the same entity. In this article, we will consistently use the term ILBF (except in quotations), as it is the correct term from the point of view of medical science.

There is an ongoing need for clear explanation of ILBF, as the absolute reliability of this diagnosis and its significance continue to be widely misunderstood. The determination of death as an objective medical-scientific matter is often not clearly distinguished from various other aspects of death, such as its metaphysical and cultural aspects and the ways in which the living deal with the dead. The Executive Committee of the German Medical Association has therefore given its Scientific Advisory Board (*Wissenschaftlicher Beirat*) the task of presenting again, in writing, the medical-scientific significance of ILBF as a

BOX 1

The etiology, pathogenesis, and relevance of irreversible loss of brain function (ILBF)

The etiology and pathogenesis of ILBF

ILBF can be caused by any type of brain disease or injury that raises the pressure within the bony cranial vault above the arterial blood pressure and thereby leads to cessation of the cerebral circulation. For example, ischemia and/or hypoxia due to a transient cardiac arrest can cause ILBF.

The relevance of ILBF in intensive care medicine

The determination of ILBF is an indispensable diagnostic instrument in intensive care medicine, independently of the matter of tissue or organ donation. The question whether ILBF is present arises when the brain functions that are regularly checked in intensive care are absent, while gas exchange and circulatory function continue to be sustained by means of artificial ventilation or extracorporeal oxygenation. In this situation, it must be decided whether

- intensive-care measures are to be terminated, or else
- tissue and/or organ transplantation are to be initiated, in accordance with the wishes of the deceased.

BOX 2

The legal framework in Germany

§ 16 of the German Transplantation Law (*Transplantationsgesetz,* TPG) entrusts the German Medical Association with the task of establishing written guidelines, in accordance with the current state of medical scientific knowledge, for the rules for the determination of death according to § 3 Abs. 1 S. 1 Nr. 2 TPG, and for the procedural rules for the determination of the final, irreversible loss of all function of the cerebrum, cerebellum, and brainstem (ILBF) according to § 3 Abs. 2 Nr. 2 TPG.

This guideline, according to § 16 Abs. 1 S. 1 Nr. 1 TPG, was last revised by the German Medical Association in 2015, as recommended by the Scientific Advisory Board and with the approval of the Federal Ministry of Health (1). The special legally conferred role of the German Medical Association extends beyond the creation of guidelines and includes a role as guarantor.

reliable sign of death, and, in particular, of addressing various concerns relating to this subject.

Method

This review is based on a selective search in PubMed for relevant publications up to 4 October 2017 (without any limit going back in time), including guidelines and standardized diagnostic protocols from Germany and abroad.

The reliability of the diagnosis of irreversible loss of brain function

Standardized diagnostic protocols

In Germany, the details of the process for diagnosing and documenting ILBF, as well as the qualifications required of the persons carrying out this process, have existed in standardized form since 1982, when they were issued by the German Medical Association on the recommendation of its Scientific Advisory Board. The corresponding guideline, issued under a legal mandate, reports on the state of relevant medical scientific knowledge. The principles underlying the German guideline are represented in the *Figure.*

Decades of experience in the diagnosis of ILBF now enable us to state that the diagnosis of ILBF in conformity with the guideline is absolutely reliable. There has never been even one known case of incorrect determination of ILBF after proper application of the standardized diagnostic procedures that are set down in the guideline and in the German Transplantation Law.

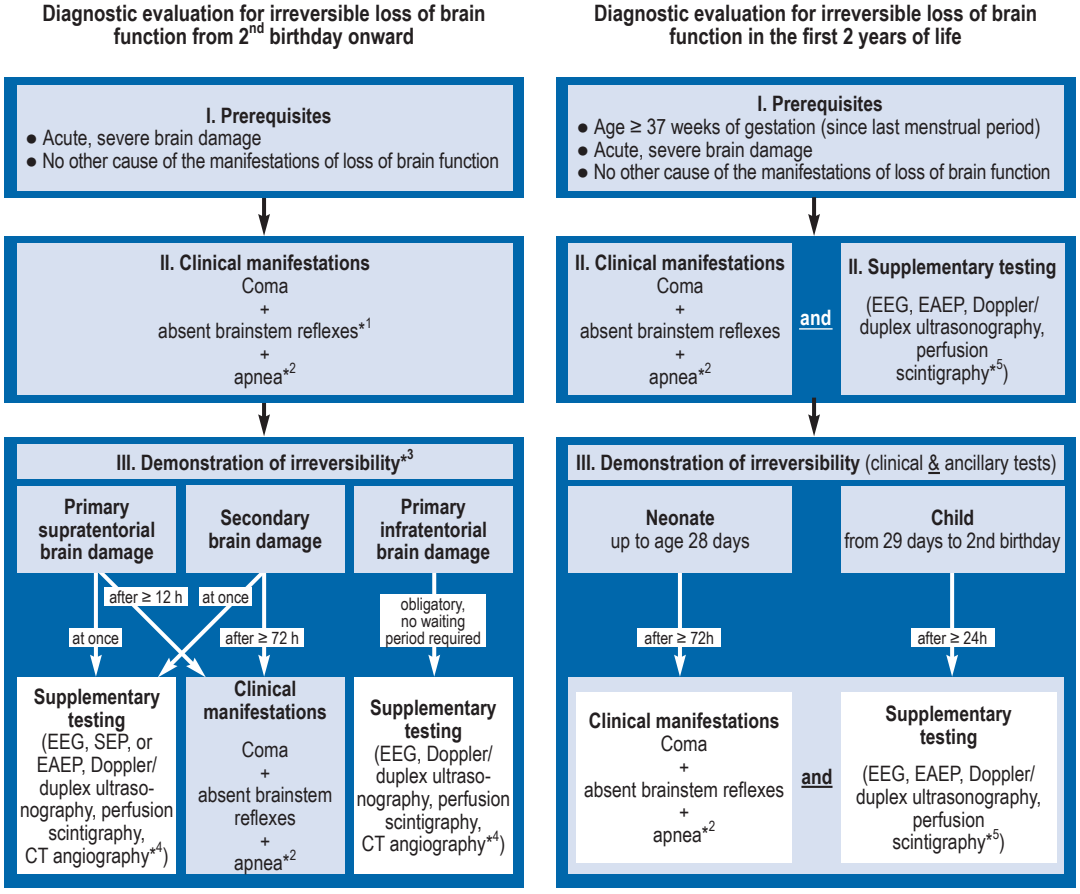
Addressing concerns about the reliability of the diagnosis of ILBF

In addressing any doubts about the determination of ILBF, a distinction must be drawn between questions concerning concrete individual cases on the one hand, and general methodological concerns on the other. All questions and concerns deserve serious consideration.

The checking of individual cases of the diagnosis of ILBF is the responsibility of the Oversight Committee (*Überwachungskommission*) that is maintained jointly, as required in §11 TPG, by the Association of Health Insurance Carriers *(Spitzenverband Bund der Krankenkassen),* the German Hospital Association (*Deutsche Krankenhausgesellschaft*), and the German Medical Association. The following remarks address general methodological concerns:

- ILBF can be differentially diagnosed with absolute reliability against states of severely impaired but not totally abolished brain function, such as the following:
  - Wakeful coma (coma vigile, also known as the apallic syndrome, persistent vegetative state [PVS], and the syndrome of unresponsive wakefulness [SUW])
  - Loss of cerebral cortical function ("neocortical death")
  - Locked-in syndrome (a state of absence of any voluntary movement except vertical gaze movements, with intact consciousness, intact sensory perception, and intact respiration)
  - Anencephaly (a congenital malformation in which the brain is not entirely absent, despite the misleading name of the condition; rather, some part of the brainstem is present, in a variable state of development).
- ILBF can be differentially diagnosed with absolute reliability against any potentially *reversible* loss of brain function. The potential causes of transient, not final or irretrievable absence of the totality of brain function are known, in particular, to the physicians who are qualified to diagnose ILBF. These causes include certain inflammatory diseases of the nervous system, metabolic disorders, and intoxications, as well as (by far the most common cause) the effects

FIGURE



Three-step algorithm for the determination of irreversible loss of brain function (1)

*1 If not all of the required clinical deficits are testable, supplementary ancillary testing is mandatory

*2 If an apnea test cannot be performed, or if the initial p_aCO_2 is above 45 mmHg, the loss of brainstem function must be additionally documented by the demonstration of cerebral circulatory arrest

*3 For the procedure to be followed in case of combined brain damage, see Section 3 of the guideline

*4 See Comment 9 in the guideline (CT angiography is validated for use only in patients aged 18 years or older)

*5 See comments 6 and 9 in the guideline (perfusion scintigraphy is required after the 2nd clinical examination after the stated waiting period)

CT, computed tomography; EAEP, early auditory evoked potentials; EEG, electroencephalography; SEP, somatosensory evoked potentials

of pain-relieving and tranquilizing drugs (analgosedation).

All situations in which brain function is merely reduced but not abolished, or only temporarily but not permanently abolished, are clearly differentiable from ILBF through the use of standard diagnostic procedures as recommended in the relevant guidelines.

Remarks on specific methodological concerns

There is an apparent need to explain why:

1. No special criteria for the demonstration of the loss of cerebellar function have been established anywhere in the world;
2. In cases of primary infratentorial brain damage (i.e., damage to the brainstem and/or cerebellum), the demonstration of ILBF in Germany—but not in other countries—requires the use of suitable supplementary diagnostic techniques with special apparatus (9–14);
3. A finding that pituitary function is preserved to some extent does not rule out the diagnosis of ILBF (15);
4. There is as yet no worldwide, uniform standard for the diagnosis of ILBF (16–21), and in Germany, for example, the relevant guidelines continue to be revised (1).

As to concerns 1 and 2: Clinical manifestations of loss of brain function that have been ascertained in accordance with the guidelines indicate loss of function of the brainstem and therefore also of the pathways connecting the cerebellum and cerebrum to other parts of the central nervous system. The loss of cerebellar connections leaves the cerebellum

completely isolated and unable to perform its functions, i.e., the coordination and modulation of movement and the stabilization of balance. This situation is analogous to blindness or deafness due to loss of function of the optic nerve or the cochlear nerve, respectively.

Moreover, the loss of brainstem function leaves the cerebrum completely isolated. In cases of primary loss of brainstem function, EEG recordings may continue to demonstrate electrical activity in some cerebral areas, including visual evoked potentials (9). The difference between the procedures specified in Germany and those specified in other countries lies only in the manner in which such neurophysiological findings are used and does not affect the reliability of the determination of the clinical manifestations of loss of brain function. The German guideline requires, in particular, in the interest of internal consistency and public acceptance, that the loss of cerebral function should always be documented by a suitable supplementary examination, even in cases where ILBF is due to a primary infratentorial lesion.

As to concern 3: There has been repeated discussion to the effect that persistent secretion of antidiuretic hormone (ADH) by the posterior lobe of the pituitary gland, recognizable by the absence of diabetes insipidus (loss of free water via the kidneys, which is prevented by the effect of ADH), may indicate persistent function of the hypothalamus—a part of the brain—even in cases when ILBF has been diagnosed through the proper application of the existing guidelines (15). Such findings have been known for decades and can be explained pathophysiologically, firstly, by the fact that the pituitary gland has its own blood supply and therefore does not always cease to function at once when the cerebral circulation stops, and, secondly, by the fact that it can also be stimulated by certain products of extracerebral metabolism. These nonspecific hormonal findings have not led to a change in the required diagnostic procedures for ILBF anywhere in the world.

As to concern 4: At present, the World Health Organization (WHO) and other organizations are working on the harmonization of the diagnostic procedures that are required for the determination of ILBF in different countries of the world. Differences between the requirements in other countries, and changes over time in the requirements in Germany because of continued revision of the guidelines, neither affect the diagnostic reliability of the determination of ILBF nor do they reflect any difference in its scientific understanding. The revision of the guidelines in Germany is due mainly to the following factors: the development of new examining techniques employing ancillary apparatus; the response to questions about how the detailed procedural specifications are to be understood; necessary changes mandated by the Transplantation Law; and linguistic clarifications.

The consequences of a diagnosis of ILBF for the patient

A person with ILBF has suffered the irretrievable loss of the following:

- Bodily functioning:
  - Any possibility of establishing contact with other persons or with living things and inanimate objects in the environment; all spontaneity as an independent living being
  - The totality of innate or acquired, instinctual or externally induced, goal-oriented and purposefully directed activity with sequential movements, and thereby all possibility of adjusting behavior at any time in accordance with the current internal state, adapting behavior to altered external and internal conditions, or selecting among external stimuli and internal drives
  - Any possibility of being awake or asleep or of alternating between these two states
  - All spontaneous breathing and any modification of breathing in response to bodily needs; regulation of body temperature, blood pressure, and (after exhaustion of whatever amount of hormone still remains) sodium homeostasis; autonomic integration
  - Independent bodily development
  - The integration of individual bodily activities into a single living unit.
- Specifically human and personal aspects: the necessary and irreplaceable physical basis for all functions that are not themselves physical but can only exist in the presence of brain activity:
  - Consciousness, including any ability to
    - direct one's attention
    - feel, perceive
    - think, consider, conclude, evaluate, decide, plan
    - reflect on oneself
    - interact with others.

Intensive care medicine can only compensate for particular absent brain functions at the respective end organs.

The significance of ILBF as a reliable sign of death

The conceptualization of death incorporates basic facts about human biology as well the anthropological view of the human being as an inseparable unity. It must be borne in mind that a comprehensive definition of death is not the same thing as a valid criterion for the determination of death. Accordingly, the following discussion solely concerns the medical-scientific rationale for the significance of ILBF as a full reliable criterion for death, i.e., for the biological end of the life of a human being. The diverse cultural, religious-metaphysical, and other aspects of death are separate matters that will not be considered.

Biological features that are common to all human beings underlie the medical criteria for the determination of death. In the medical-scientific sense, there

can be only one death for each individual, which can be determined in accordance with the current state of medical-scientific knowledge. The most important elements of the determination of death are the irreversibility of the loss of brain function, loss of the integration of bodily functions into a single living being, and loss of the ability for any self-reflection or any independent interaction with the environment.

All human beings are characterized as living beings in the same way, i.e., by the indivisible unity of body and mind that constitutes the individual. The "mind" encompasses everything that distinguishes human beings from other living creatures as well as everything that makes each human being personally unique; nonetheless, the mind is only found in coexistence with the body. The brain is the necessary, irreplaceable physical basis for this indivisible somatic and mental unit. Consequently, the loss of this physical basis, i.e., ILBF that has been reliably determined in accordance with the knowledge base of medical science, is a reliable sign that the life of the individual has come to an end. Death has occurred despite the continuation of artificial respiration and despite the continued functioning of the heart, which is sustained by the measures of intensive care and which, in turn, sustains the functioning of other extracerebral organ systems (22, 23). A living human being is more than just the sum of his or her body parts; the death of a human being is, therefore, a distinct concept from the death of individual body parts (24). This distinction underlies the Sydney Declaration on human death issued in 1968 by the World Medical Assembly (25–27). The widely known and externally recognizable signs of death—livor mortis and rigor mortis at first, then signs of putrefaction and decomposition—are lacking in ILBF because of the continued blood perfusion of the skin and musculature for as long as the circulation is sustained by intensive care medicine. This also explains why the earliest literature on ILBF after its initial scientific description mainly concerned basic questions of intensive care; it was only in the late 1960s that medical panels turned their attention mainly to the issue of the determination of death by neurological criteria (28–33). At present, the significance of ILBF as a reliable sign of death is accepted by all of the responsible medical specialty societies and physicians' organizations around the world. Official position statements of religious communities have also made an important and valuable contribution to the acceptance of ILBF as a reliable sign of death. In many countries, acceptance and legal certainty have also been furthered by pertinent legislation.

The greatest difficulties that still beset the acceptance of ILBF as a reliable sign of death are likely due to the fact that persons with ILBF do not look dead and can even, at times, display movements due to activity of the spinal cord (spinal automatisms). Information about these phenomena of ILBF and the reasons for them is needed in order to avoid misunderstanding. None of the following objections is a valid argument against the significance of ILBF as a reliable sign of death:

1. The fact that important bodily functions are still present, e.g., digestion, the acceptance (resorption and assimilation) of nutrients by the body, urination and defecation, maintenance of body temperature, increase of blood pressure in response to external stimuli, and maintenance of pregnancy until the fetus has developed sufficiently to be born.
2. The notion that the brain supports the individual's ability to live through its regulatory action and improves the quality of life and the potential for further survival, but is not itself constitutive of the life of the individual. According to this notion, the integral unity of a human being is an inherent and non-localizable property of this complex organism (34).
3. The fact that, even without a brain, the body can still respond to certain stimuli and signals from the environment.
4. The supposition that ILBF has been declared a reliable sign of death merely in order to enable the removal of organs and tissues for transplantation.

These objections will be countered in sequence.

In response to objection 1: After ILBF, the various organs that are interconnected by the circulation, the autonomic nervous system, and the spinal cord do not continue to function on their own, but rather only because, and as long as, the perfusion of these organs with oxygenated blood is sustained by methods of intensive care medicine. The spontaneity and independence of the affected person have been irretrievably lost.

The intrauterine development and maturation of a fetus are regulated by the placenta. After ILBF of the

Key messages

- Biological features that are common to all human beings underlie the medical criteria for the determination of death.
- The irreversible loss of brain function (ILBF) involves the loss of all regulatory circuits in which the brain participates and of the physical basis of consciousness and personality. The spontaneity of function of other organs besides the brain, and their integration into the individual as a unitary living being, are now impossible.
- ILBF is a reliable sign of human death.
- The diagnosis of ILBF, as determined by the procedure required in the guidelines, is reliable.
- There has not been any known case of incorrect determination of ILBF after proper application of the required standardized diagnostic procedures.

BOX 3

Further collaborators

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mother, her artificially sustained circulation continues to supply nutrients to the fetus. Animal experiments have shown that intrauterine maturation up to viability is possible even in an isolated uterus (35, 36). Pregnancy in a mother with ILBF is associated not only with biological issues, but with ethical ones as well; this, however, does not alter the significance of ILBF as a reliable sign of death (37, 38).

In response to objection 2: ILBF implies the loss of all regulatory circuits connected to the brain. This abolishes the spontaneity of all other organ functions as well as their integration into a unitary human individual as a living being.

In response to objection 3: After ILBF, the individual has no more than a passive relation to the environment. The ability of the environment to influence the individual is limited to effects on the skin and muscles. Thus, there can be stereotypic skin changes, blood pressure phenomena, or movement patterns depending on the particular stimulus and depending on whatever physiological connections are still present in the cutaneous nerves, autonomic nervous system, or spinal cord (e.g., spinal automatisms). The perception of, and reaction to, acoustic, visual, olfactory, and gustatory stimuli is irreversibly lost.

In response to objection 4: This objection is not correct in either a historical (29–33) or a factual sense. For instance, the German Surgical Society (39) declared ILBF to be a sign of death, independently of any potential organ retrieval, months before the publication by the Harvard Committee in 1968 (28). The significance of ILBF as a sign of death is scientifically based. It was described at a time when intensive care medicine and transplantation medicine were developing in parallel. The determination of ILBF is valid independently of its context.

Individual modes of dealing with ILBF as a reliable sign of death

German law (§5 Abs. 2 TPG) provides that family members of persons with ILBF should be given the opportunity to see all relevant medical documents (e.g., protocols of the determination of ILBF), and that they may review these documents with a person whom they trust. From the medical point of view, this legal provision is to be welcomed without reservation. Experience has also shown that it is beneficial to offer family members the opportunity to be present during the examinations and to ask questions about them.

Physicians, nurses, and hospital chaplains are obliged to deal with the issue of ILBF meticulously and with full consideration, and to maintain the distinction between factual matters on the one hand, and questions of sense and meaning on the other. In order to preserve an atmosphere of trust, family members of persons with ILBF should be enabled to talk with physicians and to receive the counseling they need. The individual acceptance of ILBF is not merely a question of knowledge of the underlying medical-scientific realities; it is also a question of trust in medical science and its clinical application.

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Conflict of interest statement
The authors state that they have no conflict of interest.

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CLINICAL SNAPSHOT

A Guinea Pig as a Source of Infection

A 9-year-old girl presented to us with pruritic, coin-sized, marginated, erythematosquamous plaques in the perioral and mental regions and a similar efflorescence on the medial surface of the right thigh. The lesions were characterized by mid-lamellar, whitish-yellow desquamation and rare, small pustules at the periphery. A mycological preparation of native desquamated skin from an affected area was found to contain septated hyphae when viewed under the microscope. PCR and fungal culture confirmed a dermatophytosis with Trichophyton benhamiae (formerly called Trichophyton species of Arthroderma benhamiae). Local treatment of the affected areas with ciclopirox olamine twice per day was initiated. The infection was traced to a guinea pig that the patient had been keeping as a pet for just a few weeks; the first skin changes arose three weeks after the acquisition of the animal. Although it had no fur alterations, it nonetheless had to be given antimycotic treatment by a veterinarian. Marked infections and tinea capitis require systemic treatment with terbinafine (or, alternatively, fluconazole or itraconazole). Our patient was asymptomatic after six weeks of treatment.

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