HHS Public Access

Author manuscript

Nat Rev Neurol. Author manuscript; available in PMC 2022 July 27.

Published in final edited form as:

Nat Rev Neurol. 2022 July ; 18(7): 419–427. doi:10.1038/s41582-022-00644-7.

Neuroprognostication: a conceptual framework

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Abstract

Neuroprognostication, or the prediction of recovery from disorders of consciousness caused by severe brain injury, is as critical as it is complex. With profound implications for mortality and quality of life, neuroprognostication draws upon an intricate set of biomedical, probabilistic, psychosocial and ethical factors. However, the clinical approach to neuroprognostication is often unsystematic, and consequently, variable among clinicians and prone to error. Here, we offer a stepwise conceptual framework for reasoning through neuroprognostic determinations — including an evaluation of neurological function, estimation of a recovery trajectory, definition of goals of care and consideration of patient values — culminating in a clinically actionable formula for weighing the risks and benefits of life-sustaining treatment. Although the complexity of neuroprognostication might never be fully reducible to arithmetic, this systematic approach provides structure and guidance to supplement clinical judgement and direct future investigation.

After severe brain injury has caused a disorder of consciousness, the prediction of neurological recovery — termed neuroprognostication — poses profound challenges[1,2]. The aim of neuroprognostication is to answer several questions. First, what level of

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Competing interests

The authors declare no competing interests.

Peer review information

Nature Reviews Neurology thanks James Bernat, Johanna Horn, Niklas Nielsen and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

consciousness and functionality (both physical and cognitive) is the patient likely to regain? Second, what is the likely time frame for recovery? Third, considering the patient's values, what quality of life would such a recovery be likely to yield? Last, what level of confidence is associated with each prediction?

In most clinical contexts, prognostication pertains to progressive medical conditions, in which an individual initially presents as reasonably healthy, and the task of the clinician is to predict the severity of future disease. Neuroprognostication, by contrast, operates in reverse. The causes of severe brain injury — such as trauma, hypoxia, ischaemia and haemorrhage — typically occur acutely, and the role of neuroprognostication is to determine the likelihood of improvement. The sudden, unpredictable and severe nature of such injury presents unique challenges, as critical clinical decisions must often be made rapidly, and patients typically cannot express their wishes or participate in those decisions.

Despite these challenges, effective neuroprognostication is crucial. A poor neurological prognosis often becomes the impetus for withdrawing life-sustaining treatment (LST), which leads to death[3–11]. The risks of error, therefore, are substantial: an erroneously poor prognosis might cause the death of someone who would have otherwise recovered to a satisfactory functional status, and an erroneously optimistic prognosis might cause someone to remain in a state they would consider unacceptable, perhaps even worse than death[12]. Given the importance of neuroprognostication, a growing field of research has investigated biomarkers for the prediction of outcomes[13].

Although these biomarkers might improve prognostic accuracy, other important factors must be considered. Neuroprognostication relies not only on biomedical data, but also on probabilistic, psychosocial and ethical factors. However, the integration of these factors has not been explicitly outlined, which makes it difficult to act on increasingly complex prognostic data, exacerbates the risk that vital considerations are omitted, and is likely to contribute to the variability observed in prognostic determinations[3–5]. Here, we offer a systematic, stepwise conceptual framework for neuroprognostication and decisions about LST. This framework aims to supplement, but not supplant, clinical judgement. Its precise, numerical approach might not always be achievable in clinical practice, and it cannot exhaustively capture the nuances of individualized patient care. However, by distilling neuroprognostication into its fundamental components and mathematically expressing the relationships between those components, this framework provides structure and guidance for clinical reasoning and goals for future investigation.

Step 1: current function

To predict a patient's prospects for neurological recovery, the first step is to determine their current level of neurological function (schematized in FIG. 1 as the degree to which the neurological function curve falls after brain injury), which is sometimes framed as their current level of consciousness. Levels of consciousness include coma (neither awake nor aware), the unresponsive wakefulness syndrome (awake but not aware; also known as the vegetative state) and the minimally conscious state (awake and intermittently aware)[14–19]. These states, studied most extensively in the subacute or chronic periods after brain injury,

have prognostic implications — the higher a patient's level of consciousness following brain injury, the higher the likelihood of their recovery in the future[20–22]. Moreover, a patient's level of consciousness has ethical implications, as it dictates the extent to which they can understand their surroundings, communicate with others and participate in medical decision-making[23].

However, framing a patient's neurological function purely in terms of consciousness has limitations[24–26]. First, identifying unconsciousness is problematic. The unresponsive wakefulness syndrome, which is thought to imply a lack of conscious awareness, is defined by the absence of behaviours that indicate consciousness, such as answering questions or following commands[14–19]. However, although the presence of such behaviours assures us that a patient is conscious, the absence of these behaviours does not necessarily indicate that a patient is unconscious (for example, blindness, aphasia or inattention might manifest similarly). That is, the absence of evidence is not necessarily evidence of absence. As such, categorizing patients in terms of their consciousness (or lack thereof) might imply more certainty about a patient's consciousness than we actually have, which could mislead surrogates. Second, the reflexive behaviours that characterize patients who are unconscious and the purposeful behaviours that characterize patients who are conscious can be difficult, if not impossible, to distinguish[24]. Third, although these categories have become more granular with time, they remain imprecise relative to the continuous spectrum of consciousness. Last, the existing categories do not readily account for evolving technologies for assessing brain activity — such as EEG or functional MRI (fMRI) — which provide alternative means of gauging neurological function. Indeed, a subset of behaviourally unresponsive patients can willfully modulate their brain activity in response to commands or questions, as measured by task-based EEG or fMRI[27,28]. This phenomenon, termed 'covert consciousness' or 'cognitive motor dissociation'[29], highlights the imperfect sensitivity of behavioural assessments and the importance of incorporating technological evaluations of neurological function[2,30,31].

Thus, as opposed to categorizing patients solely in terms of consciousness, characterizing patients along dimensions of neurological function, as evaluated by different methods, might be informative[13,32,33] (TABLE 1). Each method — including behavioural assessment with the neurological examination, or brain activity assessment with technologies such as EEG or fMRI — could reveal different levels of neurological function: spontaneous activity, responsive activity or communicative activity. Spontaneous activity occurs in the absence of any observable inputs; for behaviour, this includes spontaneous eye opening or movements[14,17–19], and for brain activity, this includes spontaneous, resting state oscillations[34–37]. Responsive activity occurs in reaction to a sensory stimulus; for behaviour, this includes movement in response to a noxious stimulus, or reaching for an object[14,17–19], and for brain activity, this includes activity evoked by a sensory stimulus[38–40]. Of note, responsive activity includes both reflexive and purposeful reactions to stimuli, the latter implying a higher level of neurological function than the former. Although for some responsive activities the distinction between reflexive and purposeful reactions is clear — for example, responses that are involuntary even in a fully conscious individual are unambiguously reflexive — for some activities the distinction remains challenging[24]. Communicative activity is demonstrated by a coherent response to a stimulus conveying

encoded information[24–26]; for behaviour, this includes answering questions or following commands[14,17–19], and for brain activity, this includes the willful modulation of activity in response to commands[41–44].

This novel classification scheme, which focuses on empirical assessments of neurological function (as opposed to the subjective determinations of consciousness necessitated by the existing classification schemes), has several advantages. First, these levels of neurological function have prognostic significance[20,21,35,38,44]. Second, this approach offers more precision when describing patients and conducting research. Third, it applies to all methods of assessing brain activity. Fourth, the classification is intellectually honest; although we can still tell surrogates that patients with communicative activity are conscious[24–26], this scheme does not feign certainty about the level of consciousness in patients with only spontaneous and/or responsive activity.

Step 2: trajectory of recovery

After characterizing a patient's current level of neurological function, the next step is to determine the likely trajectory of neurological recovery. The data elements used to predict neurological recovery can be divided into three categories (BOX 1)[2,30]: biomarkers that evaluate the brain's structural integrity, biomarkers that evaluate the brain's functional capacity, and contextual factors that influence the patient's potential for recovery. The prognostic significance of each data element might depend upon the patient's individual circumstances (for example, some prognostic biomarkers are only relevant to specific aetiologies of brain injury), and many prognostic biomarkers, such as the behavioural examination[45] and serum biomarkers[46,47], are most predictive when repeated over time.

Once prognostic data are collected, the aim is to synthesize them into an anticipated recovery trajectory. When the prognostic data are concordant, that is, when all data elements predict a similar recovery trajectory, this synthesis might be straightforward. However, when the prognostic data are discordant, that is, when different data elements predict differing recovery trajectories, this synthesis can be challenging. Proposed algorithms for synthesizing prognostic data can provide guidance[48–50], but only apply to specific circumstances and do not account for evolving research. Clinicians must therefore tailor this synthesis to the patient's circumstances, the prognostic data available, and the current state of the literature, by evaluating each data element according to two principles. First, the quality of the data should be evaluated — for example, is the biomarker free of artefact or confounds, of sufficient resolution and appropriately timed from the brain injury? Second, the strength of the supporting literature should be considered — for example, have high quality studies demonstrated that the biomarker is strongly predictive of meaningful outcomes in a relevant patient population? When predicting a recovery trajectory, data elements of high quality and with strong literature support should be weighted more heavily than data elements of low quality and with weak literature support.

The anticipated recovery trajectory suggested by the prognostic data is schematized by the 'probability cloud' depicted in FIG. 1, which represents the range of possible outcomes, where some are more likely (indicated by darker regions) and others less likely (indicated

by lighter regions). Prognostic data that are strong (that is, of high quality and predictive value) and concordant will yield greater predictive certainty (a narrower range of possible outcomes), whereas prognostic data that are weak or discordant will yield less predictive certainty (a broader range of possible outcomes). The upper bound of the probability cloud represents the best-case scenario for recovery, and the lower bound represents the worst-case scenario.

Of note, recovery after brain injury is not linear as depicted by this schematization, but rather plateaus with time[51–53]. Nevertheless this simplified model of recovery allows us to consider the range and time frames of possible outcomes.

Step 3: goals of care

To guide clinical decisions, the anticipated recovery trajectory must be contextualized by the patient's goals of care; that is, what the patient hopes to achieve with medical intervention. For the purpose of neuroprognostication, where the 'care' in question is often LST, the goal of care can be defined as the minimum level of neurological function that would make life worth living for the patient. The aim of any life-prolonging intervention is to support the patient in attaining or exceeding this level of neurological function. If that level of neurological function cannot be attained with LST — that is, if life-prolonging interventions do not produce a life worth living for the patient — then LST might cease to be useful, and might be withdrawn in favour of care that is focused on the patient's comfort. Of note, clinicians sometimes use 'goals of care' to refer to whether care should be focused towards prolonging life or maintaining comfort; that is, whether LST should be continued or withdrawn. However, although decisions about LST reflect whether a patient's goals can be met with LST, they themselves do not typically constitute the patient's goals.

Goals of care also include a second component: a deadline for achieving the minimum level of neurological function that would make life worth living. Many patients are not willing to wait indefinitely in a rehabilitation or long-term care facility to attain their goals, and thus the deadline estimates how long the patient would probably be willing to wait to obtain this minimum level of neurological function.

Determining that minimum level of neurological function, and a deadline for achieving such function, is challenging for anyone, and even more so for a patient who cannot communicate. However, our approach can be directed by several principles, as discussed below[54]. The patient, in the present and future, is the one who must bear the consequences of medical intervention, and therefore their interests should guide our decisions. Because the patient is unable to express those interests, we must estimate them through proxies (FIG. 2).

The best approximation of a patient's interests is the patient's past interests. Therefore, when defining goals of care, we prioritize advance directives, which offer concrete instructions for specific circumstances. However, advance directives can have limitations. For example, they are only available for ~10% of patients with disorders of consciousness[55], they might not pertain to the specific circumstance, they might be outdated, and they might lack foresight into what the patient will want in the present and future. Such imperfect foresight,

particularly for younger patients, might reflect an ableist bias — that is, an often incorrect preconception that being able-bodied is necessary for happiness[56]. Therefore, advance directives might suggest that a high level of neurological function is necessary for a life worth living, when patients might actually find lower levels of function acceptable[57–59].

The second available proxy is the patient's family, a health-care proxy or other surrogate decision-makers. The surrogate might offer a more nuanced and current understanding of the patient's values than an advance directive. However, the use of a surrogate decision-maker also has limitations. Similar to advance directives, the decisions of surrogates might be susceptible to an ableist bias, and even with the best intentions, their interests might not align with those of the patient. A desire to keep a loved one alive might incentivize a surrogate to set a lower bar for desired neurological function, or a later deadline for achieving that function. Conversely, the burden of becoming a care giver[60–62] might incentivize them to set a higher bar or a shorter deadline.

A third available proxy is population data, or studies that describe the quality of life after brain injury. Brain injury is often foreign to those formulating advance directives, and to surrogates, leaving both vulnerable to the ableist bias that overestimates the detriments of disability[56]. Studies have shown that many patients in fact enjoy a high quality of life despite disability after brain injury[57,58], termed the disability paradox[59]. Providing surrogates with these data might counteract the ableist bias and refine the goals of care to more accurately reflect the patient's interests. However, the available data might not extrapolate to the patient's specific circumstances. Further research on quality of life after brain injury will help supplement these goals of care determinations.

Ultimately, these three sources of information are synthesized to define the patient's goals of care: the past patient's wishes given precedence when available, the surrogates' perspectives to provide nuance, and population data to help inform (but not supplant) the surrogates' perspectives. The goals of care can be depicted schematically, relative to the recovery trajectory estimated earlier (FIG. 3): the height of the goals of care threshold is defined by the minimum level of neurological function that would make life worth living, and the duration of the goals of care threshold is defined by the maximum amount of time the patient would be willing to wait to attain that level of function.

Step 4: good and bad outcomes

With the goals of care defined, the range of possible outcomes can be partitioned into those considered good, and those considered bad (FIG. 3). Good outcomes are those in which the patient recovers to meet the goals of care; that is, they recover the minimum level of neurological function to make life worth living, and before the specified deadline. Bad outcomes are those in which the patient either does not recover to the minimum level of neurological function to make life worth living, or does so after the deadline.

With these partitions, we can estimate the probability of good and bad outcomes. The probability of a good outcome (P_{GO}) equals the range of good outcomes divided by the

range of all possible outcomes (FIG. 4a). Likewise, the probability of a bad outcome (P_{BO}) equals the range of bad outcomes divided by the range of all possible outcomes (FIG. 4b).

Step 5: 'value modifiers'

Although determining the probabilities of good and bad outcomes is necessary for effective neuroprognostication and decision-making, it is not sufficient. We would not, for example, universally withdraw LST from patients with a 40% probability of a good outcome and a 60% probability of a bad outcome. Rather, we must account for how patients weight the importance of good and bad outcomes. To do so, we must add two variables to our framework: a 'good outcome value modifier' (VM_{GO}) and a 'bad outcome value modifier' (VM_{BO}). The VM captures the degree to which a patient values obtaining a good outcome, and the VM_{BO} captures the degree to which a patient values avoiding a bad outcome. The same sources of information used to define the goals of care can be used to estimate these modifiers.

The VM_{GO} and VM_{BO} can be expressed numerically (FIG. 4c,d), with each falling between 0 (representing apathy towards a good or bad outcome) and 1 (representing the maximum importance of obtaining a good outcome or avoiding a bad outcome). As the VM_{GO} and VM_{BO} are based on subjective interpretations of the patient's values, to pinpoint each number might be difficult. However, the absolute numbers are less important than their relative values. If one outcome would be most crucial, consider the relative importance of the alternative. Therefore, if a good outcome is extremely important to pursue (VM_{GO} = 1), the objective is to determine how important, comparatively, a bad outcome is to avoid, for example, just as important (VM_{BO} = 1), half as important (VM_{BO} = 0.5), a tenth as important (VM_{BO} = 0.1) and so on.

Step 6: decision-making

Often the most important clinical decision after brain injury is whether LST should be continued or withdrawn. Having defined the probability and importance of good and bad outcomes, we can approach this challenging risk–benefit analysis systematically (FIG. 4e).

Multiplying P_{GO} by VM_{GO} produces a 'good outcome term', which represents the probability of a good outcome, modified by how good that outcome would be. Multiplying P_{BO} by VM_{BO} produces a 'bad outcome term', which represents the probability of a bad outcome, modified by how bad that outcome would be. Subtracting the bad outcome term from the good outcome term produces a 'predicted life quality' (PLQ) value, ranging from 1 to −1. If the probability and/or importance of a good outcome outweigh the probability and/or importance of a bad outcome, the good outcome term will be greater than the bad outcome term, and PLQ will be positive. If the probability and/or importance of a bad outcome outweigh the probability and/or importance of a good outcome, the bad outcome term will be greater than the good outcome term, and PLQ will be negative.

For PLQ to guide decisions about LST, we must consider the consequences of LST, and what different PLQ values indicate. The benefit of LST is that, by keeping patients alive, they maintain a chance of attaining a good outcome (assuming that chance exists). The risk

of LST is that patients, although alive, might not recover to a state they would consider acceptable. If PLQ is close to 1, the good outcome term strongly outweighs the bad outcome term, and thus the benefit of LST strongly outweighs the risk; in these cases we should consider continuing LST. If PLQ is close to −1, the bad outcome term strongly outweighs the good outcome term, and thus the risk of LST strongly outweighs the benefit; in these cases we should consider withdrawing LST.

However, PLQ values closer to 0 carry more risk than those closer to 1 or −1. If PLQ is only slightly positive, the good outcome term only slightly outweighs the bad outcome term, and thus the benefit of LST only slightly outweighs the risk. If LST is continued, there is a reasonable chance that the goals of care will not be met. The consequence of this outcome is that the patient remains in a prolonged state that they might consider unacceptable. Although challenging, in such cases surrogates might withdraw LST at a later point[63]. Alternatively, if PLQ is only slightly negative, the bad outcome term only slightly outweighs the good outcome term, and thus the risk of LST only slightly outweighs the benefit. If LST is withdrawn and the patient subsequently dies, there is a reasonable chance that if LST had been continued, the patient would have recovered to meet their goals of care and resume a life worth living. This would be a dire outcome that cannot be corrected. The consequences of both forms of error are profound. However, the continuation of LST is typically reversible (LST can usually be withdrawn later if goals of care are not met), whereas the withdrawal of LST is typically not. As such, it is especially crucial to avoid erroneously withdrawing LST, and thus the PLQ should guide management accordingly (FIG. 4e).

If the PLQ is positive (0 to 1), we should consider continuing LST. If the PLQ is highly negative (−0.7 to −1), we should consider withdrawing LST. If the PLQ is only slightly negative (0 to −0.3), we should consider continuing LST until the patient's recovery trajectory becomes clearer. If the PLQ is moderately negative (−0.3 to −0.7), the decision is more difficult, and the clinician and surrogate must use their judgement on a case-by-case basis to determine whether it is more ethical to continue LST until the prognosis becomes clearer (accepting a moderate risk of a bad outcome) or withdraw LST (accepting that the possible opportunity for a good outcome may be lost).

Of note, the PLQ assists in another challenging aspect of neuroprognostication: its timing. The advantage of waiting to prognosticate is that the patient's early recovery might inform their subsequent trajectory, which will narrow the range of possible outcomes and thus improve the accuracy and precision of their anticipated recovery. However, waiting to prognosticate also carries risk; for a patient whose LST will ultimately be withdrawn, waiting might prolong a state that the patient might consider unacceptable, lead to potentially avoidable medical interventions, and increase health-care costs. Guidelines suggest waiting at least 72 h[64], and potentially as long as 28 days[2], after brain injury before prognosticating and withdrawing LST. However, the risks and benefits of waiting to prognosticate vary drastically between patients, and will evolve if research improves the accuracy, and therefore reduces the risk, of early prognostication. Although the framework presented here can be applied immediately after brain injury, the PLQ offers patient-specific guidance on when the withdrawal of LST might be appropriate — if PLQ is positive or

slightly to moderately negative, decisions to withdrawal LST might be deferred, whereas a highly negative PLQ might justify the earlier withdrawal of LST.

If LST is continued, no matter the PLQ, the framework can and should be reassessed in an iterative fashion. With time, as the patient's recovery trajectory becomes clearer, the probabilities of good and bad outcomes will evolve. Moreover, as patients and surrogates experience the realities of rehabilitation and what different outcomes entail, the value modifiers — how important it is to achieve a good outcome and avoid a bad one — might also evolve. As these variables change, so too will the PLQ, and if the PLQ ever becomes sufficiently negative, the withdrawal of LST should be reconsidered. See BOX 2 for hypothetical examples of this framework's application.

Step 7: communication

Surrogates might find it difficult to quantify such emotional considerations and interpret probabilities while grieving[65,66]. Thus, this framework is intended for clinicians as a 'back-end' means of reasoning through neuroprognostic decisions, as opposed to a 'front-end' means of presenting information to surrogates. Nevertheless, for this framework to be properly tailored to each patient, accurate and compassionate communication with surrogates and shared decision-making is essential[67]. Effective communication can be challenging: clinicians must collect and convey sensitive information while adapting discussions to the individual circumstances, respecting the surrogates' needs, and remaining careful not to bias discussions with their own personal values. In TABLE 2, we suggest approaches for communicating with surrogates about neuroprognostication and LST.

Although this framework assumes a completely rational approach to neuroprognostication, it is important to note that the decisions of grieving surrogates might not always be strictly rational. For example, despite a recovery trajectory incompatible with a patient's goals of care, and thus a highly negative PLQ, a family might not feel emotionally prepared to immediately withdraw LST[68]. Giving surrogates time to process the tragedy is important, and frequently necessary for maintaining a therapeutic alliance (as long as the patient's interests are ultimately prioritized). Similarly, for cultural or religious reasons, some surrogates might feel that the withdrawal of LST is not an option, regardless of prognosis[69]. Thus, although this framework is intended to guide neuroprognostication decisions, it should never supersede overall clinical judgment in these complex and emotional scenarios.

Limitations and challenges

We understand that the framework we present here has limitations and might elicit objections. One might, for example, object to this framework's complexity; however, neuroprognostication is indeed unavoidably complex. Each consideration within this framework is indispensable to a complete neuroprognostic evaluation, particularly when the consequences include the withdrawal of LST, and thus death. Although this framework cannot alleviate the inherent complexity of neuroprognostication, it aims to break down and organize that complexity to elucidate the risk–benefit analysis that we already strive to perform.

Conversely, others might object that this framework oversimplifies neuroprognostication, neglecting the intangible nuances of clinical judgement. Indeed, this framework cannot replace clinical judgement, which best accounts for the subtleties of individualized patient care. For example, as mentioned, emotionally charged decisions about LST might not always be strictly rational, and thus compassionate clinical care might mandate deviation from this framework. Therefore, the aim of this framework is to supplement without supplanting clinical judgement, offering a roadmap for approaching complex neuroprognostication decisions systematically.

Another potential objection is that the framework demands a level of precision and certainty that is typically unachievable in clinical practice. To pinpoint the exact values for some elements (for example, outcome probabilities, goals of care or value modifiers), and therefore to fully reduce neuroprognostication to arithmetic is indeed often challenging, perhaps impossible. However, the numerical approach of the framework is not intended to imply that neuroprognostication can or must be precise (as the current state of the field typically prohibits such precision), but instead to illustrate relationships between concepts. This framework of conceptual relationships can then be applied to the imperfect estimates that are typical of clinical practice to provide several useful functions, even when precise calculations are not feasible. First, the framework provides a systematic approach to uncertainty. Although prognostic data are indeed difficult to translate into a certain recovery trajectory, this difficulty is only compounded without a framework for interpreting and implementing those data — it is precisely when the data are murkiest that the need for a systematic approach is greatest. Second, the framework encourages a clear and explicit thought process. Although incomplete information and ambiguity are common in clinical practice[70], explicitly estimating each framework element forces us to consider and synthesize all pertinent data available. Moreover, explicit reasoning improves communication; formulating an assessment of these elements, then discussing them with others, allows us to refine those assessments. Third, the framework helps us to identify shortcomings in neuroprognostication, and provides an ideal to strive towards. The elements that are most difficult to define are those we should seek to better understand, both clinically and scientifically. As we learn more, we will continuously approach the level of accuracy and precision modelled by this framework.

Conclusions

Neuroprognostication represents one of the most important clinical services within neurology, yet presents one of its greatest challenges. Although the stakes are tremendously high — in terms of both mortality and quality of life — the approach to neuroprognostication tends to be unsystematic, and consequently, variable and prone to error. The framework proposed here and summarized in BOX 3 offers a stepwise method for reasoning through challenging prognostic determinations. For experienced clinicians, this framework might outline what has already been implicitly understood. For those newer to neuroprognostication, this framework might provide structure and guidance in an endeavour that might otherwise appear daunting, and hopefully, might stimulate interest in this complex, interdisciplinary and impactful field.

Acknowledgements

The authors have received funding from the NIH National Institute of Neurological Disorders and Stroke (R25NS06574309, R21NS109627), the NIH Director's Office (DP2HD101400), James S. McDonnell Foundation, the Tiny Blue Dot Foundation, and the National Institute on Disability, Independent Living and Rehabilitation Research (90DPTB0011).

Glossary

Advance directives	Legal documents that individuals prepare to specify their preferences about medical care, to be used if they are unable to make those decisions themselves in the future.
Surrogates	Individuals who have been designated to make decisions on a patient's behalf, if the patient is unable to make those decisions themselves.

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Box 1 |

Examples of neuroprognostic factors

Factors that influence a patient's estimated trajectory of neurological recovery include structural biomarkers (those that evaluate the brain's structural integrity), functional biomarkers (those that evaluate the brain's functional integrity) and contextual factors that impact the patient's recovery potential. A non-exhaustive list of such factors is included below. Some factors have been validated only in specific aetiologies of brain injury.

Structural biomarkers

- CT
- Structural MRI
- Tractography
- Serum biomarkers

Functional biomarkers

- Neurological examination
- EEG
- Somatosensory evoked potentials
- Event-related potentials
- Functional MRI
- Transcranial magnetic stimulation–EEG
- PET
- Single-photon emission computed tomography

Contextual factors

- Age
- Cause of brain injury
- Premorbid level of function
- Medical and neurological co-morbidities
- Social supports

Box 2 |

Neuroprognostication framework applied to hypothetical cases

Case A

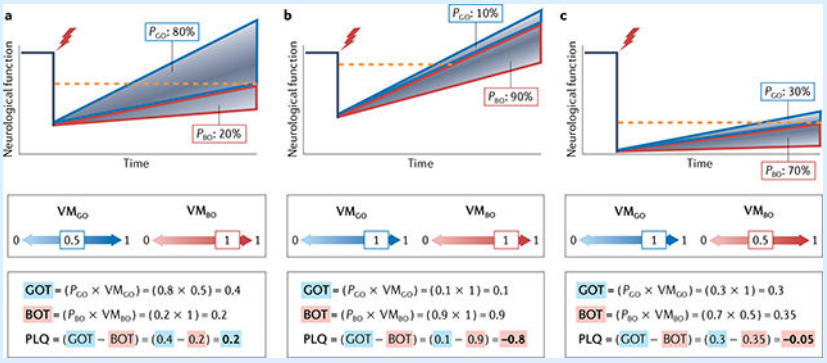
A 70-year-old patient with a moderate but uncertain recovery potential, who has previously expressed to his family a willingness to live with moderate disability, a willingness to endure a prolonged recovery, a strong preference to avoid burdening his family with severe disability (VM_{BO} = ~1), and a comparatively moderate enthusiasm about returning to his previous quality of life (VM_{GO} = ~0.5). The probability of recovery and his tolerance for moderate disability allow us to confidently continue life-sustaining treatment (LST) for now.

Case B

An 80-year-old patient with a strong recovery potential, who has previously expressed to her family a low tolerance for disability and rehabilitation, and a strong desire both to return to her existing quality of life and to avoid disability (VM_{GO} = ~1; VM_{BO} = ~1). Despite a strong recovery potential, her low tolerance for disability and rehabilitation render the risks of continuing LST unacceptably high, and therefore the withdrawal of LST should be considered.

Case C

A 40-year-old patient with a poor recovery potential, who has previously demonstrated to his family a willingness to tolerate substantial disability and prolonged rehabilitation, a strong desire to continue living (VM_{GO} = ~1), and the potential to cope with more severe disability (VM_{BO} = ~0.5). A poor recovery trajectory makes a bad outcome probable. However, the patient's high tolerance for disability and potential to cope with a bad outcome increase the risk of withdrawing LST. Therefore, despite a negative PLQ, LST should be continued until there is more clarity about the trajectory of his recovery.



BOT, bad outcome term; GOT, good outcome term; P_{BO}, probability of bad outcome; P_{GO}, probability of good outcome; PLQ, predicted life quality; VM_{BO}, bad outcome value modifier; VM_{GO}, good outcome value modifier.

Box 3 |

Neuroprognostication framework steps

- Step 1: Determine the patient's current level of neurological function using the neurological examination and other tools when available (for example, EEG and functional MRI).
- Step 2: Use information about the patient's brain structure, brain function and context to estimate a likely recovery trajectory.
- Step 3: Use advance directives, surrogates and population data to determine the patient's goals of care — both the minimum level of neurological function to make life worth living, and the deadline to attain that level of function.
- Step 4: On the basis of the estimated recovery trajectory and goals of care, determine the probabilities of a good outcome (P_{GO}) and a bad outcome (P_{BO}).
- Step 5: Use advance directives, surrogates and population data to determine how good a good outcome would be (good outcome value modifier, VM_{GO}) and how bad a bad outcome would be (bad outcome value modifier, VM_{BO}).
- Step 6: Multiply P_{GO} by VM_{GO} to obtain the good outcome term, and multiply P_{BO} by VM_{BO} to obtain the bad outcome term. Subtract the bad outcome term from the good outcome term to obtain the predicted life quality (PLQ) term. If PLQ is positive or slightly negative, consider continuing life-sustaining treatment (LST). If PLQ is highly negative, consider withdrawing LST. If PLQ is moderately negative, consider the risks and benefits of continuing or withdrawing LST on a case-by-case basis.
- Step 7: Use the preceding considerations to frame and guide discussions with surrogates, while acknowledging and respecting the emotional complexity of these decisions.

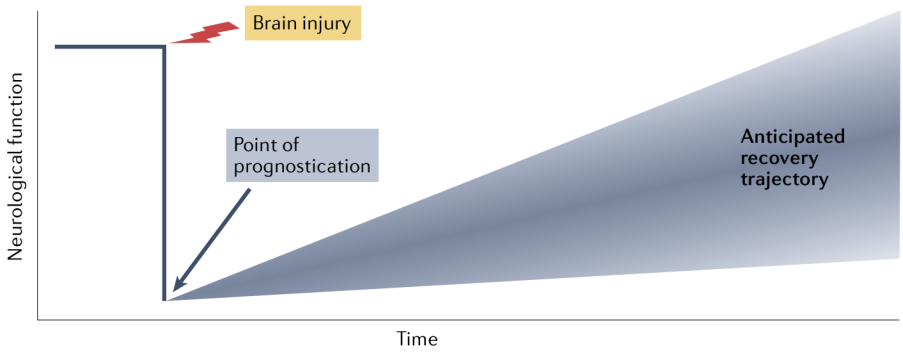


Fig. 1 |. Schematization of neuroprognostication: steps 1 and 2.

When prognosticating after acute brain injury, step 1 is to identify the patient's current level of neurological function, which corresponds schematically to the depth of the curve's downward deflection and the starting point for recovery. Step 2 is to synthesize the prognostic data to identify the patient's likely recovery trajectory. Because trajectories cannot be anticipated precisely, the estimation of recovery resembles a 'probability cloud' of possible outcomes, where darker regions within the cloud represent outcomes of higher probability, and lighter regions represent outcomes of lower probability.

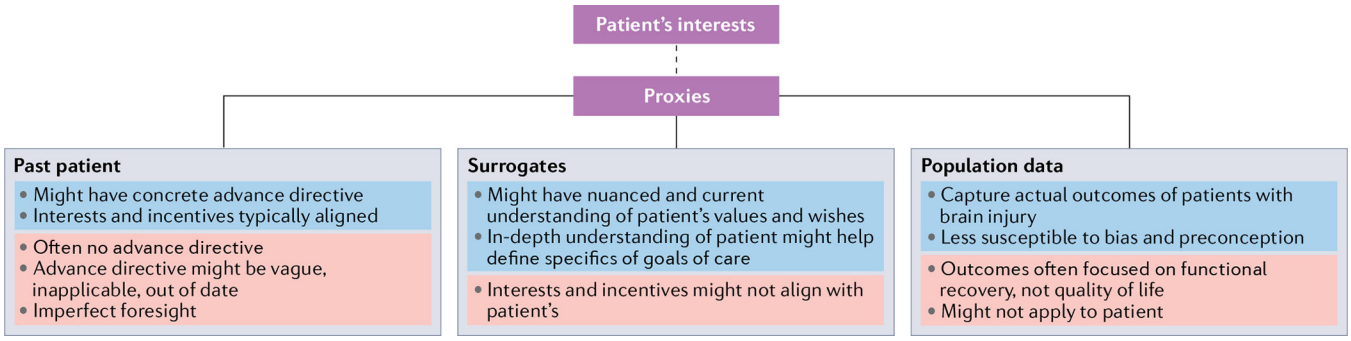


Fig. 2 |. Sources of information about a patient's goals of care.

Decisions about the objectives of medical intervention (that is, a patient's goals of care) should prioritize the patient's interests, but in the case of severe brain injury, the patient's current interests are typically unknown. Thus, clinicians must rely on proxies to approximate those interests: the interests that the patient had expressed in the past (for example, advance directives), the patient's family or surrogates, and population data on the quality of life of other patients with similar brain injury. The advantages of each proxy are highlighted in blue, and the disadvantages in red.

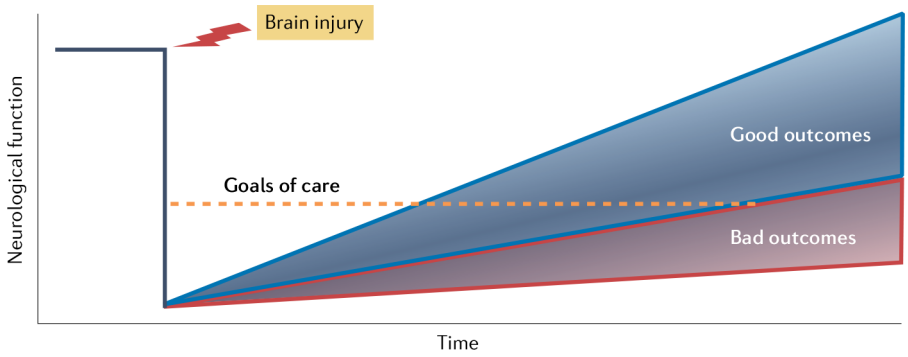


Fig. 3 |. Schematization of neuroprognostication: steps 3 and 4.

Step 3 of neuroprognostication is to identify the patient's goals of care, both in terms of the minimum level of neurological function that would make life worth living for the patient (represented as the position of the orange line on the *y* axis) and the deadline to attain that level of function (represented by the duration of the orange line on the *x* axis). Step 4 is to partition the range of possible outcomes into good outcomes (that is, those in which the patient reaches the goals of care by the deadline (outlined in blue)) and bad outcomes (that is, those in which the patient does not reach the goals of care, or does so after the deadline (outlined in red)).

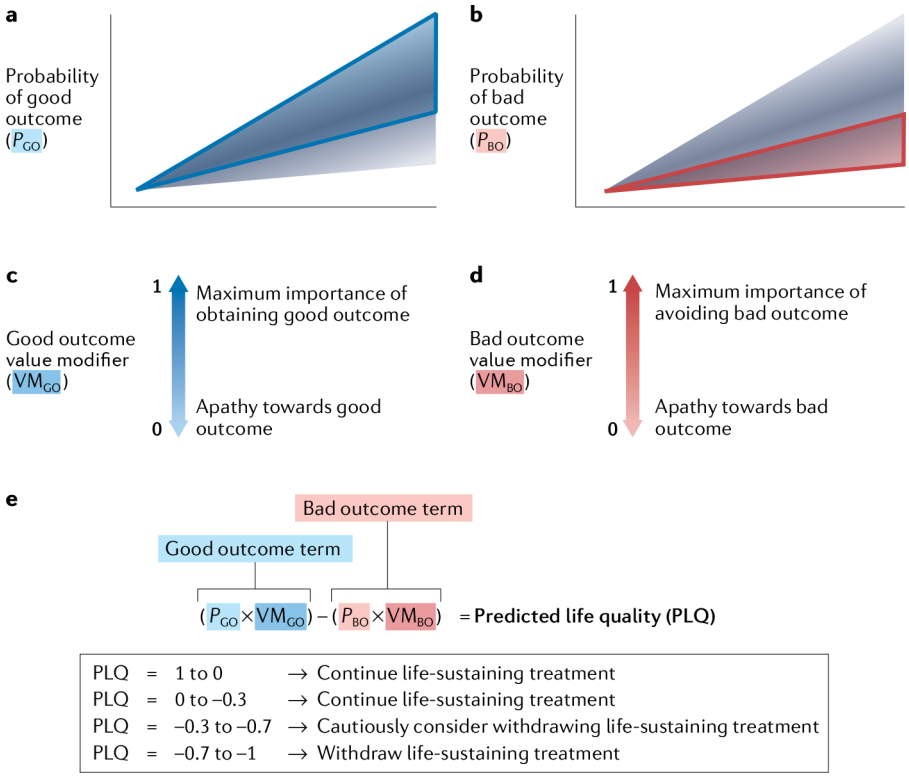


Fig. 4 |. Schematization of neuroprognostication: steps 5 and 6.

The probability of a good outcome (P_{GO}) (part **a**) is defined by the range of good outcomes (the weighted area, or amount of black, outlined in blue) divided by the range of all outcomes. The probability of a bad outcome (P_{BO}) (part **b**) is defined by the range of bad outcomes (the weighted area, or amount of black, outlined in red) divided by the range of all outcomes. Step 5 of neuroprognostication is to identify value modifiers, both for good outcomes (part **c**) and bad outcomes (part **d**). Step 6 (part **e**) is to synthesize the considerations above to guide whether life-sustaining treatment should be continued or withdrawn.

Table 1 |

Characterization of neurological function

Level of neurological function	Behaviour	Brain activity
Communicative	Answers questions coherently Follows commands	Modulates activity to answer questions Modulates activity to command
Responsive	Reaches for objects Visually tracks target Movement prompted by noxious stimulus	Complex activity evoked by stimulus Simple activity evoked by stimulus
Spontaneous	Spontaneous movements Spontaneous eye opening	Network connectivity Spontaneous oscillations

Table 2 |

Approaches to communicating with surrogates

Information to be communicated		**Possible approach to surrogate**		
Goals of care	Minimum level of neurological function	“Tell me about [the patient] and what they were like before this happened. What kinds of things were important to them? How much disability might they be willing to live with?”		
	Accounting for ableist bias (if applicable)	“Research suggests that many people report a good quality of life, despite disability. Do you think [the patient] might be one of those people?”		
	Deadline	“The road to recovery can be long and challenging. How would [the patient] have felt about this? How long do you think [the patient] would have been willing to wait for the possibility of a good outcome?”		
Value modifiers	Good outcome value modifier (VM_{GO})	“In these situations, the outcome is always uncertain. How strongly would [the patient] have felt about having the chance to recover, so that they might reach the [goals of care]?”		
	Bad outcome value modifier (VM_{BO})	“There is always a chance that [the patient] won’t recover to the point we'd hope. If that was to happen, how do you think [the patient] would feel about it?”		
Prognosis	Predicted life quality (PLQ) is positive	“It sounds like [goals of care] are important for [the patient] …”	“And while we can never be certain about the outcome, I think it is worth continuing life-sustaining treatment to give [the patient] a chance of reaching those goals.”	“... How does this sound to you?”
	PLQ is slightly negative		“And at this point I do not know whether those goals are realistic. I think we should continue life-sustaining treatment for now so that we can learn more about [the patient’s] chances of recovery.”	
	PLQ is highly negative		“And based on the information we have, I worry that that there is a significant risk that [the patient] will not reach those goals. Therefore, perhaps we should consider whether to withdraw life-sustaining treatment and focus instead on [the patient’s] comfort.”	