

PERSPECTIVE ARTICLE

The cardio–neuro–psycho–oncological axis in modern cellular and bispecific antibody therapies: A perspective on brain–heart interactions, autonomic vulnerability, and patient-centered monitoring

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Abstract

Chimeric antigen receptor T-cell therapy and T-cell-engaging bispecific antibodies have transformed hematologic oncology, but their toxicities frequently cross organ-based boundaries. Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), cardiovascular stress, autonomic dysregulation, sleep disruption, fatigue, and psychological distress may overlap in time and amplify one another. This perspective proposes a cardio–neuro–psycho–oncological framework for immune effector therapy. The model integrates inflammatory and endothelial activation, neurological and cognitive vulnerability, cardiovascular and autonomic regulation, and patient-reported burden. Rather than replacing established CRS and ICANS grading, it supports baseline risk stratification, longitudinal multimodal monitoring, actionable escalation pathways, and survivorship-oriented follow-up. It further distinguishes essential, recommended, and exploratory monitoring components and emphasizes therapy-specific monitoring needs, privacy-preserving implementation, workload-sensitive workflows, and prospective validation. Prospective studies should evaluate whether combined brain–heart–autonomic and patient-reported monitoring improves toxicity prediction, functional recovery, and quality of life as immune effector therapies move into broader patient populations.

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1. Introduction

Cellular and T-cell-redirecting immunotherapies have created a new therapeutic era in hematologic oncology. This transformation occurs against the background of a substantial global burden of hematologic malignancies. A recent global burden analysis indicates that leukemias, lymphomas, and multiple myeloma continue to contribute meaningfully to worldwide cancer incidence, mortality, and disability-adjusted life years, with marked differences by age, sex, geography, and sociodemographic development.¹

This epidemiological context is clinically relevant because immune effector therapies are increasingly moving from highly selected trial populations into broader real-world cohorts that include older patients, patients with cardiovascular or neurological comorbidity, and patients with cumulative prior treatment exposure. Chimeric antigen receptor (CAR) T-cell products and bispecific antibodies can produce clinically meaningful responses in patients with otherwise refractory disease, but their benefit is accompanied by immune-mediated toxicity patterns that are not confined to a single organ system. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) have therefore become central to treatment planning, patient education, and acute management pathways. The American Society for Transplantation and Cellular Therapy consensus criteria provided a common language for CRS and ICANS grading, and European best-practice recommendations have supported standardized delivery of CAR T-cell therapy across specialized centers.^{2,3}

Despite this progress, the clinical phenotype of immune effector therapy is broader than that captured by formal toxicity grades alone. Fever, hypotension, tachycardia, hypoxia, confusion, tremor, sleep disruption, fatigue, dizziness, palpitations, anxiety, and subjective cognitive slowing may occur in overlapping temporal windows. Mechanistic reviews increasingly emphasize that CRS and ICANS involve systemic inflammation, endothelial activation, cytokine signaling, perturbation of the blood-brain barrier, and neurovascular vulnerability.^{4,5} At the same time, cardiovascular studies show that myocardial injury and cardiovascular events can occur after CAR T-cell therapy, often in association with CRS severity and inflammatory burden.^{6,7}

This perspective proposes a cardio-neuro-psycho-oncological framework for immune effector therapy. The term does not describe a new diagnosis or a substitute for existing toxicity grading. Rather, it is a clinical integration model in which inflammatory toxicity, brain function, cardiovascular reserve, autonomic regulation, and psychosocial vulnerability should be interpreted as interacting dimensions of a single patient's trajectory. Such a model is especially relevant as CAR T-cell therapies and bispecific antibodies are used in older, comorbid, and increasingly outpatient-treated populations.

2. Why is an integrative brain-heart framework needed

The current standard of care rightly prioritizes the timely recognition and treatment of CRS and ICANS.

However, an organ-by-organ approach can leave important interactions underrecognized. CRS-related fever and inflammatory activation may increase metabolic demand, drive tachycardia, impair vascular tone, and contribute to hypotension or hypoxia. Mechanistically, systemic inflammation may affect autonomic regulation through several converging pathways. Pro-inflammatory mediators such as IL-6, IL-1 β , TNF- α , interferon- γ , and GM-CSF can promote endothelial activation, vascular permeability, nitric oxide-mediated vasodilation, and blood-brain barrier perturbation. These changes may influence central autonomic networks involving the insula, anterior cingulate cortex, hypothalamus, brainstem nuclei, and vagal afferent signaling. At the peripheral level, fever, capillary leak, hypoxia, anemia, pain, corticosteroid exposure, and intravascular volume shifts may increase sympathetic drive while reducing parasympathetic modulation. The baroreflex may be particularly vulnerable because inflammatory vasodilation and capillary leak challenge blood pressure homeostasis, while cytokine-mediated neurovascular effects may impair compensatory heart rate and vascular responses. Autonomic dysfunction should therefore be understood not as a separate toxicity category, but as a physiological interface through which inflammatory, neurological, cardiovascular, and psychological stressors may amplify one another. Such inflammatory and autonomic perturbations may unmask limited cardiovascular reserve and simultaneously reduce cerebral perfusion or cognitive resilience. Conversely, neurological symptoms such as confusion, aphasia, tremor, sleep-wake disruption, or agitation may complicate the assessment of dyspnea, chest discomfort, dizziness, and subjective palpitations.

Cardio-oncology literature supports this concern. In adults receiving CAR T-cell therapy, cardiovascular events and cardiac injury have been described as clinically relevant complications, with a graded relationship among CRS, troponin elevation, and subsequent cardiovascular events.⁶ Biomarker studies further suggest that serious cardiovascular events after CAR T-cell therapy are associated with higher inflammatory and myocardial injury markers.⁷ Contemporary cardio-oncology guidance and reviews therefore emphasize risk-adapted assessment, early recognition of hemodynamic deterioration, and interdisciplinary care for patients receiving potentially cardiotoxic cancer therapies.^{8–10}

A brain-heart framework also aligns with neurocardiology concepts. Orthostatic intolerance, autonomic dysfunction, syncope, cognitive impairment, and cardiovascular-cerebrovascular interactions sit at the border of neurology and cardiology. In immune effector

therapy, this border is crossed frequently. A patient with fever, tachycardia, sleep loss, dizziness, mild word-finding difficulty, anxiety, and rising inflammatory markers may not yet fulfill criteria for severe ICANS or a major adverse cardiac event, but the trajectory may still represent clinically meaningful vulnerability. The framework proposed here is intended to make such multidimensional trajectories visible earlier and more consistently. Emerging technologies for objective brain-state monitoring may further extend this research field. Recent electroencephalography (EEG) and brain-computer interface studies have introduced convolutional attention architectures for motor imagery EEG decoding, large EEG foundation models designed to learn generic representations from heterogeneous EEG datasets, and pretrained transformer models for universal EEG feature extraction.^{11–13} These approaches illustrate the growing ability of machine learning systems to extract temporal, spectral, and spatial information from complex brain signals. However, they should not be interpreted as validated ICANS screening tools. Within the present framework, EEG-derived or machine learning-assisted brain-state features should therefore be considered exploratory research components rather than established clinical monitoring requirements.^{14,15}

3. Autonomic vulnerability as the missing clinical link

Autonomic regulation may be one of the most clinically useful bridges between immune activation, brain symptoms, and cardiovascular stress. Patients with cancer can develop cardiovascular autonomic dysfunction through disease-related inflammation, treatment exposure, deconditioning, pain, anemia, cachexia, neuropathy, diabetes, or amyloidosis.¹⁶ Heart rate variability (HRV) has also been explored as a non-invasive marker of autonomic dysfunction and symptom burden in advanced cancer, although it remains sensitive to confounding and measurement conditions.¹⁷

In immune effector therapy, autonomic vulnerability may matter at three levels. First, baseline autonomic impairment may reduce physiological flexibility when patients are exposed to CRS-related fever, vasodilation, capillary leak, and hypoxia. Second, longitudinal changes in resting heart rate, orthostatic blood pressure, palpitations, dizziness, and sleep-wake regulation may provide clinically meaningful trend information when interpreted alongside laboratory and neurological findings. Third, autonomic dysregulation may help explain why some patients experience prolonged fatigue, subjective cognitive dysfunction, anxiety-like arousal, or reduced exercise tolerance after the acute toxicity phase has resolved.

The objective is not to overstate the diagnostic value of autonomic markers. HRV should not be used as a stand-alone predictor of ICANS, cardiotoxicity, or psychological distress. If HRV is included in prospective studies, reporting should distinguish time-domain and frequency-domain parameters. Candidate time-domain measures include standard deviation of normal-to-normal R-R intervals, which reflects overall variability, and root mean square of successive differences, which reflects short-term vagally mediated variability. Candidate frequency-domain measures include high-frequency (HF) power, commonly interpreted as a marker of parasympathetic modulation, and low-frequency (LF) power or the LF/HF ratio, which may reflect mixed sympathetic-parasympathetic influences and should be interpreted cautiously.¹⁸ In immune effector therapy, the most clinically meaningful signal is unlikely to be a single HRV value. Rather, a rapid within-patient decline in vagally mediated variability, persistent resting tachycardia, reduced nocturnal heart rate recovery, loss of circadian variability, or new orthostatic symptoms may become relevant when occurring together with fever, hypotension, rising inflammatory markers, cognitive change, sleep disruption, or patient-reported deterioration. HRV should therefore be positioned as an exploratory component of multimodal monitoring, requiring prospective validation before it can guide escalation decisions.

4. The psychosocial dimension of immune toxicity

Psycho-oncological vulnerability is often treated as separate from acute toxicity management. This separation is practical in busy clinical settings, but incomplete. Patients undergoing CAR T-cell therapy or bispecific antibody treatment may face fear of rapid deterioration, prolonged hospitalization, isolation, uncertainty during manufacturing or step-up dosing, prior traumatic medical experiences, and concern about neurological symptoms. These factors can influence sleep, autonomic arousal, symptom perception, adherence to monitoring, and the ability to perform cognitive tasks.

Recognizing this dimension does not mean attributing immune toxicity to psychological causes. Fever, hypotension, hypoxia, seizures, delirium-like symptoms, myocardial injury, and ICANS require biomedical vigilance and evidence-based management. Rather, the patient experiences toxicity as an integrated bodily and psychological event. Anxiety may amplify palpitations or dyspnea; sleep loss may reduce cognitive reserve; cognitive slowing may increase distress; and distress may complicate the interpretation of subjective neurological symptoms.

Patient-reported outcome (PRO) monitoring offers one way to make this dimension clinically visible. Randomized studies in oncology have shown that electronic symptom monitoring can improve patient-centered outcomes and, in some settings, survival-related endpoints.^{19,20} These studies were not designed specifically for immune effector therapy, but they provide a strong rationale for structured symptom capture. In this field, relevant patient-reported domains include sleep, fatigue, dizziness, palpitations, anxiety, headache, tremor, word-finding difficulty, concentration, and subjective cognitive fog. For clinical research, these domains should be captured with validated instruments whenever possible. A pragmatic core set could combine the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) for global health status, functioning, fatigue, pain, sleep disturbance, appetite loss, and emotional burden with selected Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items tailored to immune effector therapy.^{21–23} Relevant PRO-CTCAE items may include feverishness, chills, dizziness, shortness of breath, palpitations, confusion, memory problems, concentration difficulties, headache, tremor, insomnia, anxiety, depressed mood, fatigue, pain, diarrhea, nausea, appetite loss, and oral intake difficulties. Short distress screening, for example, with the Distress Thermometer or Patient Health Questionnaire-4, may be added when psychological burden is a central endpoint. The purpose of PRO monitoring is not to replace clinician grading, but to capture early subjective deterioration, symptom clustering, functional impact, and recovery trajectories that may be missed by episodic hospital-based assessment.

5. Bispecific antibodies extend the monitoring challenge

Bispecific antibodies are particularly important for this framework because they move T-cell-redirecting therapy toward more continuous, repeated, and potentially outpatient-oriented care models. Teclistamab and talquetamab have demonstrated clinically meaningful activity in heavily pretreated relapsed or refractory multiple myeloma, with CRS commonly observed, usually low grade, particularly around step-up dosing.^{24,25} Reviews of CAR T-cell and bispecific antibody toxicity in multiple myeloma emphasize overlapping immune-mediated adverse events, including CRS, neurotoxicity, infection risk, cytopenias, and treatment-specific symptom burdens.²⁶ The detailed analysis of CRS with teclistamab in MajesTEC-1 further illustrates the need for structured monitoring during early dosing and escalation periods.²⁷

Compared with CAR T-cell therapy, bispecific antibody treatment requires a different monitoring approach. CAR T-cell therapy is typically administered as a one-time cellular product after lymphodepleting chemotherapy and is followed by a relatively short window of early toxicity. CRS commonly occurs within the first days after infusion, whereas ICANS often follows or overlaps with CRS during the first one to two weeks, although timing varies by product, disease entity, tumor burden, baseline vulnerability, and management strategy. Bispecific antibodies, by contrast, are off-the-shelf agents administered repeatedly, frequently with step-up dosing to mitigate early CRS. Their CRS risk is often concentrated around step-up dosing and first full doses, while infections, cytopenias, fatigue, autonomic complaints, sleep disturbance, dysgeusia, mucosal toxicity, and functional burden may accumulate during ongoing therapy. Neurotoxicity with bispecific antibodies is generally less frequent than with several CAR T-cell products, but it remains clinically relevant and should be assessed systematically. These kinetic differences support therapy-adapted monitoring: intensive short-interval monitoring during the early post-infusion period for CAR T-cell therapy, and dose- and cycle-sensitive monitoring during step-up dosing, outpatient transitions, and long-term treatment for bispecific antibodies. [Table 1](#) summarizes these therapy-adapted monitoring implications.

6. A proposed cardio-neuro-psycho-oncological framework

The proposed framework organizes monitoring into four interacting domains: inflammatory/endothelial activation, neurological and cognitive vulnerability, cardiovascular/autonomic regulation, and psychosocial or patient-reported burden. The aim is not to create a new grading scale, but to complement established CRS and ICANS criteria with a systems-level view of patient vulnerability and recovery.

The proposed axis should therefore be understood as an integrative layer positioned between existing frameworks. Cardio-oncology frameworks provide structured approaches to baseline cardiovascular risk assessment, electrocardiogram (ECG) interpretation, cardiac biomarker assessment, echocardiography, and the management of cancer therapy-related cardiovascular toxicity. Neurotoxicity and immune effector cell frameworks provide established approaches to ICANS recognition, immune effector cell-associated encephalopathy (ICE) scoring, seizure assessment, neuroimaging or EEG in selected cases, corticosteroid treatment, and escalation. Supportive care and psycho-oncology frameworks emphasize symptom burden, distress, fatigue, sleep, quality

Table 1. Therapy-adapted monitoring implications for CAR T-cell therapy and bispecific antibodies

Therapy type	Treatment pattern	Typical risk window	Main monitoring focus
Chimeric antigen receptor (CAR) T-cell therapy	One-time cellular infusion after lymphodepletion	Early concentrated toxicity window, typically first days to approximately two weeks after infusion	Cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome grading, immune effector cell encephalopathy score, neurological examination, electrocardiogram/telemetry when indicated, inflammatory markers, rapid escalation pathways
Bispecific antibodies	Repeated off-the-shelf T-cell-engaging therapy with step-up dosing and ongoing cycles	CRS risk around step-up and first full doses; cumulative risks during continued therapy	Dose-step-linked monitoring, outpatient safety checks, patient-reported outcome monitoring, infection surveillance, reassessment of functional recovery and cumulative burden

of life, caregiver involvement, and survivorship. The novel contribution of the present model is not the invention of these individual domains, but their explicit integration into a single longitudinal monitoring logic for immune effector therapies, with autonomic vulnerability and patient-reported burden serving as connecting interfaces between inflammation, brain function, cardiovascular stress, and lived experience.

Future extensions of this framework may also draw on machine learning and nanoscale methods. Machine learning approaches may support risk prediction by integrating baseline vulnerability, treatment history, laboratory kinetics, ECG-derived features, EEG-derived features, PRO trajectories, and wearable data. Nanoscale and biophysical techniques may help characterize endothelial, immune cell, or neurovascular processes that contribute to the biology of toxicity, although their role in clinical monitoring is currently indirect.²⁸ These approaches should therefore be regarded as research enablers rather than established components of routine immune effector therapy care. Any predictive model would require transparent reporting, external validation, bias assessment, and clinical interpretability before implementation.²⁹

Figure 1 summarizes this concept. The inflammatory/endothelial domain captures the systemic immune response that drives fever, hypotension, hypoxia, capillary leak, changes in inflammatory biomarkers, and clinical CRS grade. The neurological/cognitive domain captures orientation, attention, language, handwriting, tremor, headache, seizures, level of consciousness, sleep-wake disruption, and subjective cognitive change. The cardiovascular/autonomic domain includes resting heart rate, blood pressure, orthostatic symptoms, rhythm

disturbances, ECG abnormalities, troponin, natriuretic peptides, echocardiographic findings where indicated, and potentially HRV trends. The psychosocial/patient-reported domain captures distress, fear, sleep, fatigue, perceived cognitive function, dizziness, palpitations, coping resources, and social support. Table 2 summarizes essential, recommended, and exploratory monitoring components across these domains.

The clinical value of the framework lies in cross-domain interpretation. For example, a mild increase in resting heart rate may be non-specific, but it becomes more relevant when accompanied by fever, poor sleep, subjective cognitive slowing, rising inflammatory markers, and new dizziness. Similarly, anxiety should not be used to dismiss neurological complaints, but it can be understood as part of an arousal state that may interact with sleep loss, autonomic activation, and symptom perception.

7. Operationalizing the framework in clinical care

A practical monitoring model should remain simple enough for real-world use. For implementation, the framework should distinguish essential, recommended, and exploratory components. Essential components are those already embedded in safe immune effector therapy practice: baseline clinical risk assessment, medication review, vital signs, CRS and ICANS grading, ICE score or equivalent cognitive screening, ECG, standard laboratory monitoring, and clear escalation pathways. Recommended components include baseline cardiovascular risk stratification, selected cardiac biomarkers, structured PRO monitoring, distress screening, and survivorship-oriented follow-up for patients with persistent fatigue, sleep disruption, palpitations, cognitive symptoms, or

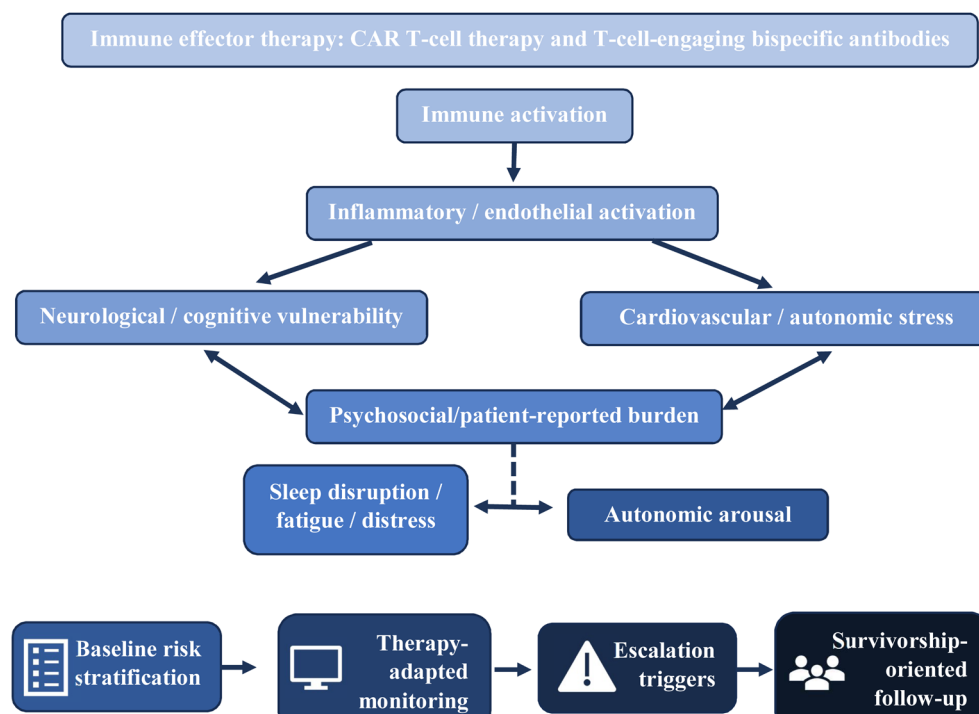


Figure 1. Directional cardio-neuro-psycho-oncological framework for immune effector therapy. The model illustrates hypothesized pathways by which chimeric antigen receptor (CAR) T-cell therapy and T-cell-engaging bispecific antibodies may trigger inflammatory and endothelial activation, contributing to neurological and cognitive vulnerability, cardiovascular and autonomic stress, and patient-reported symptom burden. Bidirectional arrows indicate feedback loops between autonomic regulation, sleep disruption, fatigue, distress, symptom perception, and cognitive resilience. The framework is intended to complement established grading for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome and to support baseline risk stratification, therapy-adapted monitoring, actionable escalation pathways, and survivorship-oriented follow-up.

functional decline. Exploratory components include HRV, wearable sensors, EEG-derived digital biomarkers, extended cytokine panels, and machine learning-based risk prediction. This distinction is important for centers with limited resources because the framework should improve prioritization rather than create an unrealistic monitoring burden. At baseline, clinicians could document prior neurological disease, cognitive concerns, seizure risk, cerebrovascular history, cardiovascular risk, previous cardiotoxic therapies, autonomic symptoms, sleep problems, frailty, psychological distress, and social support. Baseline assessment should also capture cumulative toxicity from prior lines of therapy. A practical research approach is to document prior exposure across four organ-reserve domains: cardiovascular reserve, neurological reserve, immune/hematologic reserve, and psychosocial-functional reserve. Cardiovascular reserve should include prior anthracycline or proteasome-inhibitor exposure, thoracic radiation, pre-existing heart failure, arrhythmia,

coronary disease, hypertension, abnormal ECG, elevated troponin, or elevated natriuretic peptides. Neurological reserve should include prior stroke, seizure, neuropathy, central nervous system involvement, baseline cognitive impairment, previous ICANS, sedating medication burden, and sleep disruption. Immune/hematologic reserve should include prior transplant, prolonged cytopenias, recurrent infections, hypogammaglobulinemia, renal impairment, and frailty. Psychosocial-functional reserve should include baseline distress, fatigue, low social support, caregiver burden, travel burden, and limited digital access. For future studies, these domains could be graded as absent, mild, moderate, or severe cumulative vulnerability and tested prospectively as predictors of CRS, ICANS, cardiovascular events, delayed functional recovery, and quality-of-life decline.

During high-risk treatment windows, the emphasis should be on trend-based interpretation of vital signs, CRS grade, oxygen requirement, neurological examination,

Table 2. Essential, recommended, and exploratory monitoring components within the cardio–neuro–psycho–oncological framework

Domain	Essential components	Recommended components	Exploratory components	Clinical use
Inflammatory/ endothelial	Vital signs; temperature; oxygen requirement; cytokine release syndrome (CRS) grade; complete blood count; renal and hepatic function; C-reactive protein; ferritin	IL-6, where locally available or used in institutional protocols; coagulation markers in clinically severe CRS; documentation of capillary leak or fluid requirement	Extended cytokine panels; endothelial activation markers; machine learning-based inflammatory risk scores	Identification of systemic immune activation, CRS severity, vascular instability, and inflammatory escalation
Neurological/ cognitive	Baseline neurological history; medication review; immune effector cell encephalopathy score or equivalent cognitive screening; neurological examination; assessment of orientation, attention, language, handwriting, tremor, headache, seizure, and level of consciousness	Delirium screening in older or medically vulnerable patients; neurology consultation for atypical or progressive symptoms	Brief digital cognitive tasks; electroencephalogram-derived features; wearable or app-based cognitive monitoring; machine learning-assisted brain-state analysis	Early recognition, grading, and differential diagnosis of immune effector cell-associated neurotoxicity syndrome and related neurological syndromes
Cardiovascular/ autonomic	Resting heart rate; blood pressure; oxygen saturation; 12-lead electrocardiogram (ECG) with QTc interval; rhythm assessment; orthostatic symptoms; review of prior cardiotoxic therapy	High-sensitivity troponin T or I; N-terminal pro-B-type natriuretic peptide or B-type natriuretic peptide in selected patients; echocardiography in patients with cardiovascular history, abnormal biomarkers, abnormal ECG, hemodynamic instability, or high-risk profile	Heart rate variability parameters such as standard deviation of NN intervals, root mean square of successive differences, high-frequency (HF) power, low-frequency (LF) power, LF/HF ratio, wearable-derived resting heart rate, nocturnal heart rate recovery, step count, activity variability, and sleep regularity	Detection of myocardial stress, arrhythmia risk, hemodynamic instability, corrected QT interval (QTc) prolongation, reduced cardiovascular reserve, and autonomic vulnerability
Psychosocial/ patient-reported	Brief symptom inquiry; distress screening when feasible; documentation of sleep, fatigue, dizziness, palpitations, anxiety, subjective cognition, and caregiver concern	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; selected Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events items; Patient Health Questionnaire-4 or Distress Thermometer; structured survivorship follow-up for persistent fatigue, sleep disturbance, cognitive symptoms, or functional decline	Electronic patient-reported outcome trajectories; passive sleep/activity monitoring; digital phenotyping; predictive symptom-cluster algorithms	Detection of patient-experienced toxicity, functional recovery problems, distress, adherence barriers, and survivorship needs

ICE or equivalent cognitive screening, ECG findings where indicated, troponin or natriuretic peptide testing in selected patients, orthostatic symptoms, and brief patient-reported symptom capture.

After acute toxicity, follow-up should not stop at the

resolution of fever or normalization of formal ICANS grade. Some patients may experience persistent fatigue, concentration problems, sleep disruption, palpitations, reduced exercise tolerance, anxiety, or functional decline. These symptoms may be particularly important for survivorship and return to daily life, even when they do

not meet criteria for a severe adverse event. A structured follow-up pathway could therefore connect hematology, neurology, cardio-oncology, psycho-oncology, rehabilitation, and primary care.

The framework also supports team communication. Nurses may notice sleep disruption, subtle cognitive changes, dizziness, or fear before physicians document them. Psycho-oncology teams may identify distress that interferes with symptom interpretation or self-monitoring. Cardio-oncology teams may contextualize tachycardia, troponin elevation, arrhythmia, and hemodynamic instability. Neurology teams may help distinguish ICANS, seizure risk, delirium, medication effects, metabolic encephalopathy, and pre-existing neurological disease. A shared framework can reduce fragmentation without creating unnecessary complexity.

Operationally, this could be implemented through a cross-disciplinary huddle among clinicians involved in immune effector cell therapy. Such a huddle may include hematology/oncology, nursing, neurology, cardio-oncology or cardiology, psycho-oncology, rehabilitation, and pharmacy when indicated. It does not need to be a daily meeting for every patient. A resource-sensitive model would use automated triage: routine monitoring for low-risk patients, short virtual huddles for intermediate-risk patients or new warning signals, and full multidisciplinary consultation for high-risk patients or patients meeting predefined escalation triggers. Electronic medical record integration is central. Vital signs, ICE score, selected laboratory markers, ECG/corrected QT interval (QTc) findings, cardiac biomarkers, PRO alerts, and wearable-derived signals, if used, should feed into a concise dashboard that highlights actionable changes rather than displaying unfiltered data streams.

7.1. Actionable escalation triggers for prospective evaluation

The following triggers are proposed as pragmatic escalation signals for prospective evaluation rather than as validated universal thresholds. Multidisciplinary review should be considered when any of the following occur: new decline in ICE score from baseline or ICE score < 10; new confusion, aphasia, handwriting deterioration, seizure, severe headache, or reduced level of consciousness; persistent resting heart rate > 120 beats/min; new sustained tachyarrhythmia; syncope; new chest pain; QTc $\geq$ 500 ms; hypotension requiring intravenous fluids or vasopressor assessment; new oxygen requirement or rapidly increasing dyspnea; high-sensitivity troponin T or I above the local upper reference limit with dynamic change; new or worsening N-terminal pro-B-type natriuretic peptide

(NT-proBNP) or B-type natriuretic peptide (BNP) elevation with symptoms; rapidly rising inflammatory markers together with clinical deterioration; patient-reported acute worsening in cognition, dyspnea, palpitations, dizziness, fatigue, sleep, or distress; or caregiver-reported change in behavior, speech, orientation, or functional independence. For wearable-based monitoring, escalation should not be based on a single unverified value, but on persistent within-patient deviation, such as sustained resting tachycardia, loss of nocturnal heart rate recovery, marked sleep disruption, or an abrupt decline in activity combined with clinical symptoms.

8. Digital monitoring: promise, boundaries, and implementation principles

Digital monitoring may help implement the framework because immune toxicity evolves dynamically. Short electronic assessments can capture symptoms, cognition, sleep, and functional changes between clinical encounters. Wearables may add passive information on heart rate, activity, and sleep, although such data require careful interpretation. The value of digital monitoring lies not in maximal data collection, but in clinically meaningful signal compression.

Digital monitoring must also be designed around privacy, governance, and data minimization. Home-based wearable monitoring may generate continuous streams of heart rate, activity, sleep, symptom information, and metadata from which location or behavioral patterns may be inferred, which can be highly sensitive. In settings regulated by the European Union General Data Protection Regulation, implementation requires a defined legal basis, purpose limitation, data minimization, transparent patient information, secure storage, access control, retention limits, and clear rules for secondary research use. In settings regulated by the Health Insurance Portability and Accountability Act, protected health information generated by remote monitoring must be handled in accordance with appropriate technical, administrative, and contractual safeguards. Across jurisdictions, patients should be informed which data are collected, who reviews them, which findings trigger clinical action, and which data are not monitored in real time. A clinically safe system should avoid creating an implicit promise of continuous surveillance unless staffing and escalation pathways can actually support it.

Five implementation principles are central. First, monitoring should be low burden, ideally requiring only a few minutes. Second, interpretation should be longitudinal and individualized, because within-person change may be more informative than population thresholds. Third, alerts

should be linked to clear escalation pathways. Fourth, patient-reported and sensor-derived signals should be interpreted with clinical context rather than treated as diagnostic proof. Fifth, digital pathways should be co-designed with patients, nurses, physicians, and psycho-oncology teams to avoid workflow overload and alert fatigue.

This issue is not merely technical but organizational. Multimodal monitoring can increase workload if data streams are not filtered, prioritized, and linked to clear responsibilities. Dashboards, PRO alerts, wearable outputs, and biomarker trends may otherwise contribute to alert fatigue and provider burnout. Implementation should therefore use tiered monitoring intensity, nursing-led first-line triage, predefined escalation thresholds, electronic medical record-integrated alerts, and concise interdisciplinary huddles restricted to patients with high-risk baseline profiles or new warning signals. The goal is not to monitor everything continuously, but to identify a minimal actionable dataset that improves safety and patient-centered outcomes.

Equity and bias must also be considered. Age, sex, gender, race, ethnicity, socioeconomic status, language, digital literacy, disability, caregiver availability, and geographic distance from the treating center may influence baseline vulnerability, symptom reporting, access to monitoring, and escalation. Older patients and heavily pretreated patients may have lower organ reserve and higher frailty, whereas younger patients may experience distinct work, fertility, family, and role-related distress. Digital monitoring should not disadvantage patients with limited technical literacy, language barriers, visual or cognitive impairments, low trust in digital surveillance, or restricted access to devices. A robust model should therefore allow caregiver support, paper-based alternatives, telephone-based symptom checks, and clinician-entered observations. If machine learning tools are developed, future studies should report subgroup performance, patterns of missing data, false-alert and false-negative rates, and patient acceptability across demographic and socioeconomic groups. The aim is not to replace clinical care with technology, but to extend the reach of careful, equitable, patient-centered observation.

9. Research agenda

The proposed framework is hypothesis-generating and should be tested prospectively. The single most critical next study is a multicenter observational cohort study comparing standard CRS/ICANS monitoring with an integrated cardio-neuro-psycho-oncological monitoring protocol in patients receiving CAR T-cell therapy and

bispecific antibodies. Patients should be enrolled before therapy and followed across the acute toxicity window and early survivorship phase. Baseline assessment should capture organ reserve, cumulative prior-treatment toxicity, neurological history, cardiovascular risk, frailty, distress, sleep, social support, and treatment type. Longitudinal monitoring should combine vital signs, CRS grade, ICE score, neurological examination, ECG/QTc, high-sensitivity troponin T or I, NT-proBNP or BNP in selected patients, C-reactive protein and ferritin, selected PRO-CTCAE items, EORTC QLQ-C30, and optional exploratory wearable or HRV variables. The primary objective should be to determine whether combined baseline vulnerability and early multimodal change predict clinically relevant toxicity, delayed functional recovery, unplanned hospitalization, or quality-of-life decline better than established clinical monitoring alone.

Future studies should also evaluate interventions. Prehabilitation, psycho-oncological support, sleep stabilization, exercise-based conditioning, autonomic biofeedback, and cardio-oncology co-management may be especially relevant for vulnerable patients, but their role in immune effector therapy remains insufficiently defined. Because bispecific antibodies are increasingly administered over longer periods, research should distinguish acute high-grade toxicity from lower-grade cumulative symptom burden and functional decline.

Methodologically, future work should combine standardized toxicity grading with PROs, neurocognitive testing, cardiovascular biomarkers, ECG or rhythm data, and selected autonomic metrics. The cardiovascular meta-analysis literature highlights the need for standardized definitions and longer follow-up when estimating risk after CAR T-cell therapy.³⁰ Similar standardization will be required if brain-heart-autonomic monitoring is to move from a plausible concept to a clinically validated pathway.

10. Limitations

This perspective does not present new empirical data and does not claim that the cardio-neuro-psycho-oncological axis is an established predictive model. The framework synthesizes existing evidence from CRS/ICANS biology, cardio-oncology, autonomic dysfunction, bispecific antibody toxicity, and PRO monitoring. Direct prospective evidence linking all domains in immune effector therapy cohorts remains limited. HRV and other autonomic markers are confounded by fever, medication, hydration, movement, sleep, and device quality. Patient-reported symptoms are clinically important but non-specific. Similarly, wearable-derived variables may detect physiological change but remain limited by device accuracy, missing data, patient

adherence, algorithm transparency, false-positive alerts, false reassurance, and digital inequity. The framework also raises privacy and governance challenges because remote monitoring may generate sensitive longitudinal data outside the hospital. Finally, implementation may increase workload if monitoring is introduced without triage logic, staffing, and clear responsibility for responding to alerts. Therefore, the proposed model should guide research and structured clinical thinking rather than replace validated toxicity criteria.

A further limitation is that immune effector therapy programs differ substantially in infrastructure. Highly specialized CAR T-cell units, outpatient bispecific antibody clinics, community oncology networks, and health systems with limited digital capacity may require different implementation strategies. The framework should therefore be adapted to local resources and evaluated for feasibility, safety, workload, patient acceptance, and equity before broad clinical adoption.

Future validation studies should also assess whether model performance differs by age, sex, gender, race, ethnicity, socioeconomic status, language, comorbidity, disability, and digital access. This is particularly important if machine learning or wearable-derived features are incorporated into risk prediction.

11. Conclusion

Modern immune effector therapies challenge traditional organ-based models of toxicity. CRS, ICANS, cardiovascular events, autonomic dysregulation, distress, sleep disturbance, fatigue, and cognitive symptoms may interact through inflammatory, neurovascular, cardiovascular, autonomic, and psychosocial pathways. A cardio-neuro-psycho-oncological perspective can complement established toxicity grading by integrating patient vulnerability, dynamic monitoring, and survivorship-oriented care. A clinically useful version of this axis will require a minimal actionable core set, therapy-specific monitoring timelines, prospective validation of escalation triggers, and careful attention to privacy, equity, and clinical workload. Its immediate value is therefore not to replace established toxicity grading, but to organize currently fragmented cardiovascular, neurological, autonomic, and patient-reported information into a coherent research and implementation agenda. As CAR T-cell therapy and bispecific antibodies expand into broader clinical settings, such integrative approaches may become increasingly important for safe, precise, and humane cancer treatment.

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Conflict of interest

The author declares no competing interests related to this manuscript.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Availability of data

Not applicable.

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