

NAD+ restoration

Pathway, compartment, exposure, active drain and
demonstrated response

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ABSTRACT AND SCOPE

Restoration is not delivery alone.

This is a mechanistic clinical monograph, not a marketing paper and not a conventional efficacy guideline. It addresses four questions:

The monograph covers intravenous NAD⁺, oral NMN, oral NR and conditional methyl-donor support. It does not treat all vitamin B3 derivatives as interchangeable. Nicotinic acid, nicotinamide, NR, NMN, NADH and NAD⁺ enter the network through different enzymes, generate different metabolites and have different tolerability and evidence profiles.

The manuscript deliberately separates three questions that are often collapsed:

An affirmative answer at one level does not decide the next.

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SECTION 01

Purpose and scope

This is a mechanistic clinical monograph, not a marketing paper and not a conventional efficacy guideline. It addresses four questions:

- What is biologically established about NAD⁺ synthesis, transport, compartmentation and consumption?
- What does each route of administration actually expose the organism to?
- Which human outcomes have been demonstrated, which remain signals, and which are unsupported extrapolations?
- How should a clinician determine whether an NAD-directed strategy is coherent for a particular patient and whether it is working?

The monograph covers intravenous NAD⁺, oral NMN, oral NR and conditional methyl-donor support. It does not treat all vitamin B3 derivatives as interchangeable. Nicotinic acid, nicotinamide, NR, NMN, NADH and NAD⁺ enter the network through different enzymes, generate different metabolites and have different tolerability and evidence profiles.

The manuscript deliberately separates three questions that are often collapsed:

- Can the molecule or precursor alter the NAD metabolome?
- Does that alteration engage the intended tissue and mechanism?
- Does the engagement produce a meaningful, durable clinical effect?

An affirmative answer at one level does not decide the next.

SECTION 02

Evidence construction and epistemic method

2.1 Evidence sources

The evidence base was constructed from:

- targeted PubMed/MEDLINE searches through 12 August 2026;
- primary biochemical and transport studies;
- randomized and controlled human trials of NR and NMN;
- human pharmacokinetic, metabolomic and tolerability studies of intravenous NAD-related compounds;
- systematic reviews used to map the human trial landscape and identify discordant results;
- the Clinic Terrain internal scientific corpus concerning mitochondria, redox biology, methylation, metabolic terrain, oncology and IV practice.

The principal search concept blocks were:

- NAD metabolism AND compartmentation AND salvage AND NAMPT AND NMNAT;
- SLC25A51 AND mitochondrial NAD transport;
- CD38 AND NAD decline AND aging AND senescence;
- intravenous NAD AND human AND metabolome OR tolerability;
- nicotinamide riboside AND randomized controlled trial AND human;
- nicotinamide mononucleotide AND randomized controlled trial AND human;
- NNMT AND methylation AND SAM AND SAH AND homocysteine;
- betaine OR trimethylglycine AND homocysteine AND lipids;
- NAD precursor AND cancer AND tumor metabolism OR chemotherapy resistance.

This is not presented as a PRISMA systematic review. It is a structured mechanistic monograph. Search reproducibility, evidence cutoff, study type and counter-evidence are nevertheless made explicit so that future updates can be audited.

2.1.1 Eligibility and extraction rules

Primary human trials were prioritized for clinical claims. Primary biochemical, isotope-tracing, genetic and transport studies were prioritized for mechanistic claims. Systematic reviews were used to locate trials, test whether a narrative conclusion survived aggregation and identify discordance; they were not substituted for primary studies when a pivotal trial was available. Animal and cell studies were retained only when they established mechanism, distribution or a safety boundary that could not ethically or practically be defined first in humans.

For each human study, extraction focused on population, randomized sample, comparator, intervention, duration, prespecified primary outcome, quantitative result, adverse events, attrition, funding and declared conflicts. Secondary and exploratory results are labelled as such. A statistically significant within-group change is not treated as proof of a treatment effect when the relevant between-group comparison is null. A biomarker change is not relabelled as clinical efficacy.

2.1.2 Bias controls

Five recurring distortions were actively countersearched: baseline imbalance in small trials; multiplicity without correction; sponsor or inventor conflicts; practice and expectancy effects; and selective emphasis on responders or secondary endpoints. Null trials were intentionally retained. This is essential in a field where target engagement is common, sample sizes are small and outcome hierarchies can be blurred.

2.1.3 Evidence domains

The monograph integrates evidence by domain rather than allowing one institution to monopolize truth: chemical identity and stoichiometry; cellular mechanism; human pharmacokinetics and tissue engagement; controlled clinical outcomes; safety and counterevidence; preparation quality; and reproducible longitudinal response. Regulatory status is reported when operationally relevant but is not assigned scientific weight.

2.2 Hierarchy of inference

Clinic Terrain does not equate a regulatory decision with scientific truth. Market authorization, product classification and administrative status are relevant to lawful operations and disclosure, but receive no weight in deciding whether a biochemical mechanism exists.

The scientific inference hierarchy is instead:

- Chemical and biochemical identity: the molecule, reaction, enzyme and stoichiometry are established.
- Cellular mechanism: the pathway operates in a defined biological system.
- Distribution and target engagement: the administered intervention reaches or alters the relevant compartment or a defensible proxy.
- Functional biological response: metabolism, signaling or physiology changes in the predicted direction.
- Patient-relevant outcome: symptoms, performance, disease measures or quality of life improve meaningfully.
- Durability and reproducibility: the effect persists, recurs on rechallenge or generalizes beyond a narrow cohort.

The lower levels are not dismissed merely because a large outcome trial is absent. The higher levels are not assumed merely because the lower levels are compelling.

2.2.1 Independent clinical-validation axis

Causal depth and clinical validation answer different questions and are therefore reported independently. Causal depth describes identity, mechanism, distribution and biological response. Clinical validation describes the strength of patient-relevant human outcome evidence for the specified intervention, route, population and endpoint. Neither axis substitutes for the other.

RECORD 01

CLINICAL CLASS

A

HUMAN-OUTCOME EVIDENCE

Replicated, adequately powered controlled human outcomes

PERMITTED CONCLUSION

Population-, intervention-, route- and indication-specific effect estimate

PRINCIPAL LIMITATION

Does not predict every individual response or establish every mechanism

RECORD 02

CLINICAL CLASS

B

HUMAN-OUTCOME EVIDENCE

Controlled human study or convergent trials with material limitations

PERMITTED CONCLUSION

Human outcome signal or robust target engagement

PRINCIPAL LIMITATION

Power, duration, endpoint, comparator or replication may be limited

RECORD 03

CLINICAL CLASS

C

HUMAN-OUTCOME EVIDENCE

Uncontrolled human observation or small physiology study

PERMITTED CONCLUSION

Feasibility, heterogeneity, safety signal or hypothesis

PRINCIPAL LIMITATION

Cannot isolate treatment effect reliably

RECORD 04

CLINICAL CLASS

D

HUMAN-OUTCOME EVIDENCE

No direct therapeutic outcome; human endogenous association or adjacent exposure only

PERMITTED CONCLUSION

Human contextual relevance

PRINCIPAL LIMITATION

Exogenous treatment effect remains untested

RECORD 05

CLINICAL CLASS

E

HUMAN-OUTCOME EVIDENCE

No adequate human exposure or outcome evidence for the exact intervention and route

PERMITTED CONCLUSION

Research proposition only

PRINCIPAL LIMITATION

Identity-, route- or model-adjacent evidence cannot fill the gap

A strong biochemical mechanism can coexist with Class D or E clinical validation. Conversely, a controlled clinical result cannot repair a failure of molecular identity, exposure or route correspondence. This two-axis system is the same epistemic architecture used in the Clinic Terrain peptide monograph; it is applied here to NAD-directed interventions at claim level.

2.3 Confidence language

- Established: repeatedly demonstrated with direct measurement and no major contradiction.
- Supported: coherent evidence from more than one domain, with residual uncertainty.
- Signal: a finding worth testing that is not yet stable enough for a broad conclusion.
- Conditional: likely dependent on phenotype, route, dose, tissue or baseline state.
- Unresolved: evidence is sparse, contradictory or measured with inadequate proxies.
- Refuted as a universal claim: evidence directly contradicts a broad formulation, even if narrower contexts remain plausible.

SECTION 03**NAD⁺ as a redox cofactor and consumed substrate**

NAD⁺ and NADH form a redox couple central to glycolysis, pyruvate oxidation, the tricarboxylic acid cycle, beta-oxidation and oxidative phosphorylation. NAD⁺ accepts a hydride to become NADH; NADH transfers reducing equivalents toward mitochondrial electron transport or other redox reactions. The total amount of NAD is therefore only one dimension. The NAD⁺/NADH ratio, flux through the pool and compartment-specific redox state can matter as much as total concentration.

NAD⁺ is also irreversibly consumed. Poly(ADP-ribose) polymerases use NAD⁺ in DNA-damage signaling and repair. Sirtuins cleave NAD⁺ during deacetylation. CD38 and related ectoenzymes metabolize extracellular or membrane-accessible NAD-related substrates. SARM1 can trigger catastrophic NAD depletion in injured axons. These reactions connect NAD availability to genomic maintenance, epigenetic regulation, calcium signaling, immune function and neuronal integrity.

This dual role creates a central clinical ambiguity. A reduced NAD pool may reflect inadequate synthesis, excessive consumption, redistribution between compartments, altered redox flux or a combination. Increasing precursor supply may correct a supply-limited state but may not resolve an active drain driven by inflammation, DNA damage, immune activation, sleep disruption, alcohol exposure, metabolic overload or another continuing stressor.

Conclusion: NAD⁺ is not simply “cellular fuel.” It is a dynamically synthesized, transported, reduced, oxidized and consumed network metabolite. The phrase may be understandable for patient communication, but it is scientifically insufficient for clinical reasoning.

SECTION 04

Biosynthetic routes and salvage architecture

Human cells maintain NAD through several interconnected routes.

4.1 De novo synthesis

Tryptophan can enter the kynurenine pathway and ultimately generate quinolinic acid, which is converted through QPRT-dependent steps toward NAD⁺. This route is metabolically expensive and strongly shaped by liver function, immune signaling, micronutrient availability and competing kynurenine-pathway fates. Increased kynurenine flux therefore does not guarantee increased NAD synthesis.

4.2 Preiss-Handler pathway

Nicotinic acid is converted through NAPRT to nicotinic acid mononucleotide and then toward NAD⁺. This route differs pharmacologically from amidated precursor pathways and should not be treated as equivalent to NR or NMN.

4.3 Amidated salvage pathway

Nicotinamide generated by NAD-consuming reactions can be recycled by NAMPT to NMN, then adenylated by NMNAT enzymes to NAD⁺. This pathway is quantitatively important in many mammalian tissues. It explains why the effectiveness of NAD restoration can depend not only on precursor intake but also on NAMPT activity, ATP availability, tissue-specific enzyme expression and the rate at which nicotinamide is diverted toward methylation and excretion.

4.4 NR and NMN entry

NR is phosphorylated by nicotinamide riboside kinases toward NMN. NMN can be dephosphorylated extracellularly to NR before cellular entry in some contexts, while direct transport mechanisms may operate in specific tissues. The relative contribution of intact NMN transport, extracellular conversion and microbiome-mediated transformation remains context-dependent. In mammalian cellular models, NRK1 is rate-limiting for the use of exogenous NR and NMN, and isotope tracing supports extracellular NMN conversion to NR before uptake in those systems [50]. Oral administration therefore cannot be reduced to a single universal absorption pathway.

The precursor field is not closed around NR and NMN. Trigonelline has been identified as an NAD precursor through isotope tracing and mechanistic models, accompanied by human observational associations with muscle status [57]. This makes it a research candidate, not evidence of clinical

equivalence or a current substitute for intervention trials.

Clinical implication: precursor choice is a pathway decision. It should consider the likely bottleneck rather than assume that the molecule closest to NAD in a pathway diagram is necessarily the best-delivered precursor to every tissue.

SECTION 05

Cellular compartmentation changes the meaning of “raising NAD”

NAD pools in cytosol, nucleus and mitochondria are functionally linked but not interchangeable. Nuclear and cytosolic pools can communicate through diffusible intermediates and local synthesis. The inner mitochondrial membrane imposes a distinct transport problem.

The identification of SLC25A51 as a mammalian mitochondrial NAD transporter established that intact NAD⁺ can enter mitochondria through a regulated carrier [1,30]. Genetic loss of SLC25A51 depletes mitochondrial NAD, impairs respiratory-chain function and alters ATP production. Conversely, changing SLC25A51 activity can redistribute NAD toward cytosolic and nuclear pools and modify PARP1-dependent DNA repair [2].

These findings invalidate a common inference: a measured increase in plasma or whole-blood NAD does not establish that mitochondrial NAD increased in the tissue responsible for the patient's symptoms. Blood is a useful accessible compartment, but it is not a universal surrogate for brain, skeletal muscle, liver, immune cells or mitochondrial matrix.

The same distinction applies to the NAD⁺/NADH ratio. Total NAD may rise while compartment-specific redox conditions remain constrained by substrate overload, hypoxia, impaired electron transport or insufficient reoxidation of NADH.

Established: mammalian NAD biology is compartmentalized and SLC25A51 is a major mitochondrial NAD transporter.

Unresolved clinically: the degree to which a particular intravenous or oral intervention changes mitochondrial NAD in a symptomatic human tissue, and whether that change is the causal mediator of clinical benefit.

SECTION 06

Metrology and biomarker interpretation

6.1 The analyte is inseparable from its matrix

“NAD level” is incomplete unless the report identifies the chemical species, biological matrix, cellular fraction, collection method, stabilization interval, extraction procedure and analytical platform. Whole blood is dominated by cellular material, particularly erythrocytes; plasma, serum, PBMCs, skeletal muscle and brain spectroscopy interrogate different biological spaces. Total NAD, NAD⁺, NADH, NAD⁺/NADH ratio, NADP(H), NMN, NR, NAAD and methylated disposal products answer different questions.

NAD metabolites are analytically demanding. Oxidation-reduction can continue after sampling, cellular lysis can redistribute analytes and delays in quenching can create ex-vivo biology. Validated isotope-dilution LC-MS methods improve specificity and recovery, but even technically excellent measurement does not solve tissue mismatch [58,59]. A precise whole-blood value remains a whole-blood value.

6.2 Exposure, state and outcome biomarkers

Three uses must be distinguished:

- Exposure biomarker: demonstrates that an intervention altered an accessible NAD metabolome. Whole-blood NAD and NAAD commonly function at this level after oral NR [49].
- State biomarker: estimates a relevant biological condition before treatment. Whole-blood NAD has not been validated as a universal marker of tissue NAD constraint or human biological aging [43].
- Outcome biomarker: predicts or mediates a patient-relevant benefit. A rise in circulating NAD has not been validated as a universal surrogate for energy, cognition, physical performance or disease modification.

Conflating these categories is the central interpretive error in commercial NAD medicine.

6.3 Whole-blood NAD and aging

The most rigorous recent counterevidence comes from Trętowicz and colleagues, who used a validated UHPLC-high-resolution MS method across seven independent human cohorts. Whole-blood NAD remained remarkably stable with age and across lifestyle interventions, while rising after NR supplementation as expected [43]. This result simultaneously supports whole-blood NAD as an exposure marker and challenges its use as an aging-state marker.

Earlier human studies are not simply “wrong”; they measured different cohorts, matrices or tissues. A study of 1,518 participants reported sex-specific whole-blood associations with age, with a clearer decline in men [44]. Human pelvic skin samples showed an age-associated tissue decline linked with oxidative stress and PARP activity [45]. Phosphorus-MRS studies indicate age-related differences or physiologic associations in cerebral NAD, but the measurements are small, method-specific and not interchangeable with blood [46]. The scientifically correct synthesis is tissue heterogeneity, not a universal decline curve.

6.4 Compartment-resolved measurement

Genetically encoded biosensors demonstrate that free NAD can be measured separately in nucleus, cytosol and mitochondria and that these pools respond differently [47]. Isotope tracing and perturbation of SLC25A51 further show that mitochondrial NAD can buffer or redistribute the wider cellular system [1,2,30,48]. These tools are not routine clinical tests, but they define the inference boundary: systemic measurement cannot by itself identify the symptomatic intracellular compartment.

6.5 Minimum reporting standard

Every Clinic Terrain NAD measurement intended for scientific interpretation should record: fasting or fed state; time of day; recent exercise and alcohol; collection tube; time to quench or freezing; storage temperature and freeze-thaw history; matrix and fraction; assay method; internal standards; units; laboratory reference procedure; and relation to last exposure. Serial values should use the same matrix and method whenever possible.

Metrological conclusion: a blood NAD rise can confirm biochemical exposure. It cannot independently diagnose NAD deficiency, localize the deficit, prove mitochondrial delivery or certify clinical benefit.

SECTION 07

Aging and the problem of the active drain

Age-associated NAD change is not uniform across every tissue or person, and popular fixed-percentage age charts are not scientifically defensible. The 2026 seven-cohort study found no meaningful age relationship in whole blood [43], while other human studies reported tissue-, sex- or method-dependent associations [44-46]. It is therefore inappropriate to diagnose an age-defined NAD deficit or tell a patient that NAD necessarily falls to a specified percentage at a given age. Aging remains a mechanistic risk context, not a laboratory diagnosis derived from date of birth.

Mechanistically, however, several drivers are well supported. CD38 expression and NADase activity increase in multiple aging models. Senescent-cell secretory factors can induce CD38 in macrophages and other non-senescent cells. In mouse tissue, accumulation of CD38-positive inflammatory cells contributes to age-related NAD decline [3-5]. DNA damage can increase PARP demand. Chronic immune activation may simultaneously increase consumption and redirect tryptophan metabolism. Reduced NAMPT activity, altered circadian regulation, metabolic overload and mitochondrial dysfunction can further constrain recovery. NAMPT expression and cellular NAD oscillate under circadian control in experimental systems, providing a mechanistic reason to treat sleep timing and circadian disruption as potential modifiers rather than lifestyle footnotes [52]. SARM1 adds a distinct neuronal drain: injury-induced elevation of the NMN/NAD ratio activates its intrinsic NADase and can drive feed-forward axonal metabolic collapse [51]. This mechanism is established in experimental neurons and axon-injury models; it is not a generic explanation for brain fog.

This produces an important therapeutic principle: replacement without drain control may yield transient biochemical correction without durable restoration. If inflammatory activity, sleep debt, alcohol exposure, persistent infection, glycemic overload, medication effects or untreated

endocrine dysfunction continue to increase demand, repeated NAD exposure may produce diminishing returns.

The initial clinical question should therefore not be “How much NAD?” but “Why is this patient likely to be NAD-constrained, in which tissue, and through which mechanism?”

SECTION 08

Intravenous NAD+: what the route does and does not establish

8.1 Acute extracellular exposure

Intravenous administration bypasses gastrointestinal absorption and creates direct vascular exposure. This statement is pharmacologically true. It does not justify the phrase “100% cellular bioavailability.” The infused molecule remains exposed to plasma distribution, endothelial interfaces, extracellular metabolism, renal handling and ectoenzymes before any claim about intracellular delivery can be made.

In the principal human metabolomic pilot, eight participants received 750 mg NAD+ over six hours at approximately 3 $\mu\text{mol}/\text{min}$ [6]. During at least the first two hours, infused NAD+ was rapidly and completely removed from plasma at that infusion rate. The metabolite pattern was consistent with extracellular degradation, including increases in nicotinamide, ADP-ribose-related products and methylated nicotinamide excretion. This study demonstrates metabolism of the infused substrate. It does not establish how much intact NAD entered a particular tissue or organelle.

8.2 Tolerability is rate-dependent information

A 2026 retrospective study compared four consecutive days of 500 mg IV NAD+ with IV NR in a commercial setting [7]. IV NAD+ was associated with more moderate-to-severe gastrointestinal symptoms, chest pressure and increased heart rate during infusion, producing a longer mean infusion time than IV NR. Symptoms resolved after infusion. The study is useful as real-world tolerability evidence but is limited by retrospective design, small samples, selection effects and exploratory endpoints.

Rate intolerance should not be dismissed as a nuisance. It is pharmacodynamic information. Symptoms that emerge with faster administration and recede when the rate is reduced indicate that peak extracellular exposure or rapid metabolite generation matters. The practical response is individualized rate control and reassessment, not a universal timetable.

8.3 What has not been demonstrated

No robust controlled outcomes trial establishes IV NAD+ itself as a universal therapy for fatigue, brain fog, healthy aging, addiction recovery or “cellular regeneration.” The 2026 systematic review of NAD-related interventions identified consistent biochemical engagement with oral precursors but no eligible outcome trials of IV or intramuscular NAD+ itself for anti-aging or wellness indications [8].

This absence does not prove that individual patients cannot benefit. It means the clinician cannot use published population-level outcome evidence as the sole justification. A clinical use must instead be framed as a mechanistically coherent, monitored therapeutic trial with pre-defined

targets and falsifiers.

8.4 Defensible role of IV NAD⁺

IV NAD⁺ is best conceptualized as an acute exposure component within a broader restoration program. Its defensible advantages are controlled administration, direct vascular exposure, immediate rate adjustment and the possibility of close observation. Its unresolved elements are tissue delivery, optimal dose, optimal frequency, durable functional effect and responder phenotype.

The route is therefore neither magic nor meaningless. It is a distinct pharmacologic exposure whose value depends on patient selection, preparation quality, rate, companion architecture and measured response.

SECTION 09

Oral NR and NMN as continuity companions

The kinetics and evidence profile of oral precursors differ materially from IV NAD⁺. Oral NR and NMN are not merely weaker versions of an infusion; they are sustained pathway inputs.

9.1 Biochemical target engagement

The first human pharmacokinetic study demonstrated dose-dependent changes in the blood NAD metabolome after single oral NR doses of 100, 300 and 1,000 mg and identified NAAD as a sensitive marker of effective repletion [49]. Multiple randomized human trials subsequently showed that oral NR raises whole-blood NAD-related metabolites in a dose-responsive manner [9-12]. In healthy middle-aged and older adults, daily NR increased circulating NAD metabolites and was generally well tolerated over weeks. In aged men, 1,000 mg/day for 21 days altered the skeletal-muscle NAD metabolome and transcriptomic inflammatory signatures without improving mitochondrial bioenergetics [12]. In overweight or insulin-resistant participants, other trials found metabolomic engagement but no improvement in insulin sensitivity or skeletal-muscle mitochondrial respiration [13,14].

NMN trials similarly demonstrate circulating target engagement. In prediabetic postmenopausal women, 250 mg/day for ten weeks improved insulin-stimulated muscle glucose disposal and signaling in a small randomized trial [15]. A methodological critique noted a substantial baseline liver-fat imbalance between groups, reducing confidence in broad causal interpretation [16]. Other studies found signals in walking speed, sleep measures, body weight, blood pressure or arterial stiffness, but primary endpoints were sometimes null and cohorts were small [17-19]. Meta-analyses through 2024 found consistent increases in NAD-related biomarkers but no reliable improvement in fasting glucose, insulin, HbA1c or lipid outcomes across mainly short, small trials [20,21]. A 54-participant hypertension pilot using NR 1,000 mg/day for six weeks did not improve its primary daytime systolic-blood-pressure endpoint versus control; pulse-wave velocity and nocturnal pressure findings remained trend-level or post hoc [56].

Short-term safety data extend across several contexts but do not settle long-term efficacy. A randomized phase I study tested NR at 3,000 mg/day for four weeks in twenty people with Parkinson's disease [40]. A small dose-escalation study of NR combined with pterostilbene in acute kidney injury documented biochemical engagement and short-term tolerability, but was not

designed to establish therapeutic efficacy [41]. These studies widen the observed exposure range; they do not justify routine high dosing.

9.2 Brain exposure

The NADPARK phase I trial reported that 1,000 mg/day NR for 30 days was well tolerated and produced a variable increase in cerebral NAD measured by phosphorus magnetic resonance spectroscopy, with changes in cerebral metabolism and inflammatory markers [22]. A separate acute spectroscopy study found an increase in cerebral NAD four hours after 900 mg NR in ten healthy volunteers [23]. A 2026 phase I pharmacokinetic study of NR or NMN at 1,200 mg/day in twelve participants reported slower blood accumulation, a plateau after approximately two weeks and measurable cerebral increases after four weeks [24]. These studies are important because they move beyond blood-only measurement, but they remain small and do not establish durable cognitive benefit.

9.3 Functional heterogeneity is not failure of the pathway

Explicitly null studies sharpen rather than weaken the model. In 14 physically compromised older adults, a 32-day mixture of tryptophan, nicotinic acid and nicotinamide increased muscle methyl-nicotinamide but did not increase muscle NAD, mitochondrial respiration or exercise efficiency [53]. In 32 adults aged 55-80, 1,000 mg NR plus 200 mg pterostilbene daily increased whole-blood NAD-related metabolites yet did not improve muscle stem-cell recruitment, strength recovery or histological regeneration after experimental injury [54]. In a 20-person MCI pilot, NR increased blood NAD 2.6-fold but did not change cognition [55]. These trials demonstrate why exposure, tissue state and outcome must be reported separately.

The recurring human pattern is coherent:

- biochemical target engagement is common;
- tissue engagement is demonstrated in some settings;
- functional benefit is variable;
- broad anti-aging outcomes are unproven.

This is not logically contradictory. It implies that NAD constraint is not the only determinant of function and may not be the dominant bottleneck in every patient. A patient whose fatigue is driven by iron deficiency, thyroid dysfunction, sleep apnea, uncontrolled inflammation, caloric insufficiency, medication effects or major depression should not be expected to normalize through NAD augmentation alone.

9.4 Continuity architecture

Oral NR or NMN can serve as a continuity companion when the clinical objective is sustained pathway input between acute interventions. The choice should be based on tolerability, product identity, dose actually studied, adherence, measured response and plausible pathway bottleneck. It should not be based solely on proximity to NAD in a diagram or marketing claims about absorption.

SECTION 10

One-carbon metabolism, nicotinamide disposal and conditional TMG

10.1 The biochemical connection

NAD-consuming reactions release nicotinamide. Nicotinamide can be salvaged through NAMPT or methylated by nicotinamide N-methyltransferase (NNMT). NNMT transfers a methyl group from S-adenosylmethionine (SAM) to nicotinamide, generating N1-methylnicotinamide and S-adenosylhomocysteine (SAH). The reaction therefore connects NAD turnover with the methionine cycle and cellular methyl-donor economy [25].

TMG, or betaine, can donate a methyl group through betaine-homocysteine methyltransferase, predominantly in liver and kidney, converting homocysteine toward methionine. This is a real biochemical route. It does not prove that every person receiving NAD, NR or NMN becomes methyl-depleted or requires TMG.

10.2 Human evidence argues against automatic supplementation

In a double-blind placebo-controlled analysis of 29 people with Parkinson's disease, high-dose short-term NR did not produce a deleterious change in DNA methylation homeostasis, including in participants with common MTHFR variants [26]. Longer-term NR studies have also not consistently shown disruption of one-carbon metabolism [10,11]. These findings refute the universal statement that NAD precursor use necessarily “drains methyl groups.”

At the same time, intravenous NAD metabolomics demonstrate increased methylated nicotinamide excretion [6], and the NNMT reaction is biochemically established. A conditional burden is therefore plausible when turnover is high, methyl supply is marginal, homocysteine is elevated or liver handling is altered.

10.3 TMG has benefits and trade-offs

Randomized evidence shows that betaine can lower homocysteine. A meta-analysis found a pooled reduction of approximately 1.23 $\mu\text{mol/L}$ with at least 4 g/day for six weeks or longer [27]. Another synthesis found lower-dose effects but also an increase in total and LDL cholesterol at higher exposure [28]. In controlled studies, 6 g/day increased LDL cholesterol by approximately 0.36 mmol/L and triglycerides by approximately 0.14 mmol/L after six weeks [29].

TMG is therefore not a harmless ritual companion. It is a targeted intervention with a biochemical purpose and measurable trade-offs.

10.4 Clinic Terrain position

TMG is considered when one or more of the following are present:

- elevated or rising homocysteine;
- high cumulative precursor exposure with increased methylated nicotinamide disposal;
- low dietary choline/betaine or inadequate protein and methionine context;
- folate, vitamin B12 or vitamin B6 insufficiency requiring correction;

- liver-related or genetic context that changes one-carbon handling;
- a reproducible clinical pattern suggesting loss of benefit during continued NAD-directed exposure, after more direct explanations have been assessed.

TMG is reconsidered when lipids worsen, there is no biochemical need, the companion stack obscures causality, or correction of a more proximal deficiency is sufficient.

Conclusion: TMG is a conditional methyl-support companion, not an automatic component of every NAD program.

SECTION 11

The NAD-5D clinical reasoning model

Clinic Terrain proposes a five-domain model to prevent administration-centered reasoning.

11.1 Deficit

What supports an NAD-constrained state? The evidence may include age and inflammatory burden, but should extend to phenotype, diet, alcohol exposure, medications, sleep, metabolic condition, organ function and-where feasible-direct or proxy metabolomic measurements. Symptoms alone are nonspecific.

11.2 Delivery

What substrate is being delivered, by which route, at what rate, dose and duration? IV NAD⁺, oral NR and oral NMN are distinct exposures. Product identity and actual delivered dose belong in this domain.

11.3 Distribution

Which tissue and compartment must be reached for the clinical hypothesis to be true? What direct measure or defensible proxy will indicate engagement? Whole-blood NAD is not automatically a brain or mitochondrial measurement.

11.4 Drain

Which processes may be consuming or diverting the pool? Relevant domains include CD38-associated inflammation, PARP activation and DNA damage, oxidative stress, infection, metabolic overload, poor sleep, alcohol, exercise/recovery imbalance, nicotinamide disposal through NNMT and other competing metabolic demands.

11.5 Demonstrated response

Was there a reproducible response at the biochemical, physiological and patient-relevant levels? Did it persist? Was there a dose or rate relationship? Did the effect disappear on withdrawal and recur on rechallenge? Did an objective marker move in the predicted direction? What result would falsify the working hypothesis?

The model is deliberately multiplicative in spirit. Strong delivery cannot compensate automatically for a wrong deficit hypothesis, irrelevant distribution, uncontrolled drain or absent response.

SECTION 12

Clinical phenotypes and testable hypotheses

12.1 Fatigue and low energy

Fatigue is not a diagnosis of NAD deficiency. A defensible NAD-directed hypothesis requires evidence that common and consequential causes have been assessed: anemia and iron status, thyroid function, sleep quantity and quality, infection or inflammation, glycemic dysregulation, nutritional adequacy, medication effects, cardiopulmonary limitation, mood disorder and overtraining.

An NAD-related component becomes more plausible when fatigue is associated with metabolic stress, poor recovery, post-infectious change, age-related decline, or a reproducible response to prior NAD-directed exposure. Even then, the response should be tested against functional measures rather than impression alone.

12.2 Brain fog and cognitive complaints

NR studies establish that cerebral NAD can be altered in humans [22-24]. They do not prove that nonspecific brain fog is generally caused by cerebral NAD insufficiency. Sleep disruption, anxiety, depression, thyroid dysfunction, iron or B12 deficiency, post-viral inflammation, glucose variability, medication effects and neurodegenerative disease remain competing explanations.

Useful longitudinal measures may include a standardized symptom scale, processing-speed or attention task, sleep metrics, work-function measures and timing relative to intervention. A transient feeling of clarity is clinically relevant but not equivalent to disease modification.

12.3 Metabolic dysfunction

Selected NMN trials show insulin-sensitivity signals, while pooled analyses are largely null for routine glucose and lipid measures [15,20,21]. A 2026 blood-pressure meta-analysis found a modest pooled reduction in diastolic pressure and an age-restricted systolic signal, but the evidence remained preliminary [42]. The correct conclusion is conditionality, not universal efficacy or universal failure. Baseline metabolic phenotype, tissue NAD constraint, duration and companion lifestyle changes likely modify response.

12.4 Recovery and physical performance

Human trials show changes in skeletal-muscle NAD metabolites and acetylcarnitine handling, but mitochondrial respiration, insulin sensitivity and performance outcomes are often unchanged [12-14]. A performance claim therefore requires direct measurement of the performance domain rather than extrapolation from a biomarker.

12.5 Healthy aging

NAD metabolism intersects with several hallmarks of aging, including mitochondrial dysfunction, genomic instability, altered nutrient sensing, cellular senescence and inflammation. This network relevance makes NAD a serious target of geroscience. It does not establish that raising blood NAD slows human aging, extends lifespan or reverses a biological-age clock. The appropriate objective is preservation or restoration of defined function, not an unmeasured promise of rejuvenation.

SECTION 13

Oncology: neither blanket prohibition nor casual reassurance

NAD is required by normal and malignant cells. Tumors can depend on NAMPT-mediated salvage, mitochondrial NAD transport, PARP activity and NAD-supported stress resistance. SLC25A51 is upregulated in multiple cancers and can sustain mitochondrial metabolism and tumor growth in experimental systems [31]. NAMPT dependence is a therapeutic vulnerability in several tumor models [32,33]. A 2022 animal study reported increased prevalence and brain metastasis in a triple-negative breast-cancer model with NR supplementation [34]. A 2026 pancreatic-cancer study found that vitamin B3 derivatives could support chemotherapy resistance in experimental models [35].

The relationship is not unidirectional. Other models report prevention of DNA damage or improved treatment response with NAD precursors [36,37]. This apparent contradiction is biologically plausible: restoring NAD may protect normal tissue in one context, correct a carcinogenic deficiency in another, or support the metabolic resilience of an established tumor in a third.

The Clinic Terrain conclusion is therefore context-specific:

- active or recently treated cancer requires oncology-aware review;
- tumor type, treatment mechanism and timing matter;
- NAD-directed interventions should not be represented as inherently pro-cancer or inherently anti-cancer;
- concurrent use with cytotoxic, PARP-directed or metabolically targeted therapy requires explicit mechanistic consideration;
- uncertainty should lead to individualized risk analysis, not slogan-level fear.

This position is more scientifically defensible than either automatic exclusion or blanket reassurance.

SECTION 14

Compounded preparation as part of the scientific intervention

A clinical conclusion is uninterpretable if the administered material is not adequately characterized. Preparation quality is therefore not administrative decoration; it is part of causal inference.

For a patient-specific compounded NAD-related preparation, the minimum scientific record should include:

- supplier and chain of custody;
- batch and lot identity;

- certificate of analysis linked to the lot;
- identity testing and quantitative assay;
- impurity profile and relevant residuals;
- sterility and endotoxin controls for parenteral material;
- storage conditions, light protection and temperature history;
- reconstitution record, diluent, final concentration and beyond-use logic;
- visual inspection and release by an authorized pharmacy professional;
- exact administered dose, rate, timing and any interruption;
- adverse-event and response record linked longitudinally to the same batch.

The certificate of analysis should not be treated as a decorative PDF. Its analyte identity, method, acceptance limits, laboratory, date and batch linkage must be readable and auditable. A generic certificate or a document not linked to the administered lot cannot establish product identity.

When Clinic Terrain sources and compounds a preparation, this traceability permits the clinical record to connect observed tolerability or effect to a defined material. That is scientifically superior to reasoning from an unnamed “NAD drip.”

SECTION 15

Measurement and longitudinal falsification

Sections 15 and 16 translate the mechanistic framework into prospective observation: predefined hypotheses, measurable outcomes, temporal attribution, counterfactual assessment and explicit stopping rules. They are included because reproducible observation is part of the scientific method, not as an administrative or commercial workflow.

15.1 Baseline model

The baseline should be hypothesis-driven rather than an indiscriminate panel. Depending on phenotype, relevant domains may include:

- complete blood count, iron indices and B12/folate context;
- renal and hepatic function;
- fasting glucose, insulin, HbA1c and lipid profile;
- thyroid function;
- inflammatory markers interpreted in context;
- homocysteine when methyl-donor support is contemplated;
- sleep, activity and recovery data;

- standardized symptom and functional measures;
- NAD metabolome or related research measurements when available and analytically credible.

15.2 Acute infusion record

The record should capture formulation, lot, concentration, dose, start and stop time, rate changes, vital signs, symptoms, interventions and recovery. “Tolerated well” is inadequate if clinically relevant rate changes occurred.

15.3 Response hierarchy

- Exposure confirmed: the intended material and dose were delivered.
- Biochemical engagement: the relevant metabolite or proxy changed.
- Functional engagement: physiology or performance changed.
- Patient benefit: the target symptom or capability improved meaningfully.
- Durability: improvement persisted beyond an acute nonspecific effect.

15.4 Falsifiers

The working hypothesis should be revised when:

- repeated adequately delivered exposures produce no target response;
- only a transient subjective effect occurs without functional or durable change;
- biomarkers move without the predicted physiological effect;
- adverse effects outweigh the target benefit;
- a competing diagnosis better explains the phenotype;
- escalating complexity is required to preserve a weak initial story;
- the patient improves when another identified bottleneck is corrected, independent of NAD-directed exposure.

Failure to respond is information. It should narrow the model rather than trigger automatic dose escalation.

SECTION 16

Prospective clinical intelligence protocol

16.1 Purpose

Clinic Terrain's clinical intelligence system should convert routine care into analysis-ready longitudinal evidence without representing observation as randomization. The purpose is to determine which baseline configurations, routes and dose-rate patterns are associated with reproducible benefit, non-response or intolerance, and to expose the hypotheses that fail.

16.2 Minimum prospective dataset

Each patient episode should contain five linked layers:

- Baseline terrain: indication, duration and severity; competing diagnoses; sleep, nutrition, alcohol, activity and recent infection; medication and supplement exposure; hepatic, renal, hematologic, thyroid, glycemic and methylation-relevant context.
- Intervention identity: source, lot, CoA linkage, assay, preparation record, diluent, concentration, dose, route, rate, timing, co-interventions and any rate interruption.
- Immediate pharmacology: vital signs, symptom onset and resolution, rate relationship, rescue measures and time to discharge.
- Target outcomes: one primary patient-relevant outcome selected before exposure; secondary functional and biochemical outcomes; measurement instrument and clinically meaningful threshold.
- Longitudinal state: follow-up at predefined intervals, durability, adherence to oral continuity, adverse events, changes in drain variables, withdrawal and rechallenge where clinically appropriate.

16.3 Consultation depth

A transactional episode records exposure and safety. A light consultation adds a bounded indication, common competing causes and a target outcome. A deep consultation builds the full mechanistic hypothesis, compartment and drain model, laboratory context, longitudinal plan and stopping rules. The software should label consultation depth explicitly so that analytic confidence is not inflated by sparse records.

16.4 Predefined response classes

- Biochemical responder only: target metabolite changes without the predefined functional or patient-relevant outcome.
- Acute clinical responder: target outcome improves within the exposure window but durability is not established.
- Durable responder: improvement exceeds the predefined threshold and persists at follow-up.
- Rate-limited responder: potential benefit is accompanied by reproducible rate-dependent intolerance requiring a modified exposure strategy.

- Non-responder: adequate exposure without meaningful target response.
- Indeterminate: missing data, major co-intervention, adherence failure or uncontrolled competing event prevents attribution.

These categories must be assigned by deterministic rules defined before aggregate analysis. “Responder” should never mean that any favorable observation was found after inspection.

16.5 Causal discipline

Routine longitudinal data are vulnerable to regression to the mean, expectancy, concurrent treatment, spontaneous recovery and selective follow-up. Clinic Terrain can strengthen inference with repeated baseline measurements, fixed follow-up windows, pre-specified outcome thresholds, within-person interrupted time series, withdrawal/rechallenge when safe, batch linkage, complete non-responder capture and explicit recording of missingness. The system should preserve negative observations with the same fidelity as positive ones.

16.6 Research outputs

The first defensible publication should be a prospective observational cohort or methods paper, not a retrospective success-rate claim. It should publish the data dictionary, deterministic response definitions, missing-data rules, adverse-event taxonomy and statistical plan before reporting outcomes. Subsequent phenotype-specific analyses can then test hypotheses generated by NAD-5D without converting clinical practice into promotional evidence.

SECTION 17

Human evidence atlas

RECORD 01

INTERVENTION
IV NAD+ [6]

POPULATION AND DESIGN
8 adults; open metabolomic pilot

EXPOSURE
750 mg over 6 h

DIRECTLY SUPPORTED RESULT
Rapid plasma removal; downstream NAD metabolites and urinary MeNAM

IMPORTANT LIMITATION
No control; no tissue delivery or clinical efficacy outcome

RECORD 02

INTERVENTION

IV NAD+ vs IV NR [7]

POPULATION AND DESIGN

Retrospective commercial cohort

EXPOSURE

500 mg daily ×4

DIRECTLY SUPPORTED RESULT

IV NAD+ had more rate-limiting symptoms and longer infusion time

IMPORTANT LIMITATION

Retrospective; small; exploratory biomarkers

RECORD 03

INTERVENTION

NR [11]

POPULATION AND DESIGN

Healthy middle-aged/older adults; randomized crossover

EXPOSURE

1,000 mg/day ×6 weeks

DIRECTLY SUPPORTED RESULT

Whole-blood NAD metabolome increased; generally tolerated

IMPORTANT LIMITATION

Small; exploratory clinical outcomes

RECORD 04

INTERVENTION

NR [12]

POPULATION AND DESIGN

12 older men; randomized crossover

EXPOSURE

1,000 mg/day ×21 days

DIRECTLY SUPPORTED RESULT

Skeletal-muscle metabolome and transcriptome changed

IMPORTANT LIMITATION

No improved mitochondrial bioenergetics

RECORD 05

INTERVENTION

NR [13]

POPULATION AND DESIGN

Obese insulin-resistant men; randomized

EXPOSURE

2,000 mg/day ×12 weeks

DIRECTLY SUPPORTED RESULT

No meaningful skeletal-muscle NAD or mitochondrial benefit

IMPORTANT LIMITATION

Specific male metabolic phenotype

RECORD 06

INTERVENTION

NR [14]

POPULATION AND DESIGN

13 overweight/obese adults; crossover

EXPOSURE

1,000 mg/day ×6 weeks

DIRECTLY SUPPORTED RESULT

Muscle metabolites and acetylcarnitine changed

IMPORTANT LIMITATION

No insulin-sensitivity or mitochondrial-function improvement

RECORD 07

INTERVENTION

NMN [15]

POPULATION AND DESIGN

25 prediabetic postmenopausal women; randomized

EXPOSURE

250 mg/day ×10 weeks

DIRECTLY SUPPORTED RESULT

Improved muscle insulin sensitivity and signaling

IMPORTANT LIMITATION

Small; important baseline liver-fat imbalance

RECORD 08

INTERVENTION

NMN [18]

POPULATION AND DESIGN

60 older adults; randomized

EXPOSURE

250 mg/day ×12 weeks

DIRECTLY SUPPORTED RESULT

Higher blood NAD; secondary walking and sleep signals

IMPORTANT LIMITATION

Primary stepping endpoint not different; sponsor employees

RECORD 09

INTERVENTION

NMN [19]

POPULATION AND DESIGN

36 healthy middle-aged adults; randomized

EXPOSURE

250 mg/day ×12 weeks

DIRECTLY SUPPORTED RESULT

NAD-metabolite engagement; arterial-stiffness trend

IMPORTANT LIMITATION

No significant between-group PWV difference

RECORD 10

INTERVENTION

NR [22]

POPULATION AND DESIGN

30 newly diagnosed PD patients; phase I randomized

EXPOSURE

1,000 mg/day ×30 days

DIRECTLY SUPPORTED RESULT

Variable cerebral NAD increase and multi-omic engagement

IMPORTANT LIMITATION

Phase I; not powered for clinical efficacy

RECORD 11

INTERVENTION

NR [23]

POPULATION AND DESIGN

10 healthy adults; acute spectroscopy

EXPOSURE

900 mg once

DIRECTLY SUPPORTED RESULT

Cerebral NAD increased at 4 h

IMPORTANT LIMITATION

Very small; acute; no clinical endpoint

RECORD 12

INTERVENTION

NR/NMN [24]

POPULATION AND DESIGN

12 healthy/PD participants; phase I PK

EXPOSURE

1,200 mg/day ×4 weeks

DIRECTLY SUPPORTED RESULT

Blood plateau ~2 weeks; cerebral NAD increase ~4 weeks

IMPORTANT LIMITATION

Very small; exploratory

RECORD 13

INTERVENTION

NR [38]

POPULATION AND DESIGN

58 long-COVID participants; randomized

EXPOSURE

2,000 mg/day up to 20 weeks

DIRECTLY SUPPORTED RESULT

NAD increased 2.6-3.1-fold

IMPORTANT LIMITATION

No significant cognitive benefit; high dropout

RECORD 14

INTERVENTION

NR [39]

POPULATION AND DESIGN

40 COPD patients; randomized

EXPOSURE

6 weeks

DIRECTLY SUPPORTED RESULT

Sputum IL-8 reduced versus placebo

IMPORTANT LIMITATION

Disease-specific; functional implications require follow-up

RECORD 15

INTERVENTION

Niacin-equivalent mixture [53]

POPULATION AND DESIGN

14 older adults with impaired physical function; randomized crossover

EXPOSURE

207.5 mg niacin equivalents/day ×32 days

DIRECTLY SUPPORTED RESULT

Muscle MeNAM increased

IMPORTANT LIMITATION

Muscle NAD, respiration and exercise efficiency were null

RECORD 16

INTERVENTION

NR + pterostilbene [54]

POPULATION AND DESIGN

32 adults aged 55-80; randomized

EXPOSURE

NR 1,000 mg + PT 200 mg/day; before and 30 days after induced injury

DIRECTLY SUPPORTED RESULT

Whole-blood NAD-related metabolites increased

IMPORTANT LIMITATION

No effect on muscle stem cells, strength recovery or histologic regeneration

RECORD 17

INTERVENTION

NR in MCI [55]

POPULATION AND DESIGN

20 older adults; randomized pilot

EXPOSURE

Escalation to 1,000 mg/day ×10 weeks

DIRECTLY SUPPORTED RESULT

Blood NAD increased 2.6-fold; no excess adverse events

IMPORTANT LIMITATION

Cognition unchanged; CBF finding did not survive multiplicity boundary

RECORD 18

INTERVENTION

High-dose NR in PD [40]

POPULATION AND DESIGN

20 participants; randomized phase I

EXPOSURE

3,000 mg/day ×4 weeks

DIRECTLY SUPPORTED RESULT

Up to 5-fold blood NAD increase; no moderate/severe AE

IMPORTANT LIMITATION

Symptom signal confounded by levodopa timing; inventors declared patents

RECORD 19

INTERVENTION

Whole-blood NAD metrology [43]

POPULATION AND DESIGN

Seven independent human cohorts

EXPOSURE

Observational and lifestyle-intervention datasets

DIRECTLY SUPPORTED RESULT

Whole-blood NAD stable with age/lifestyle; changed after NR

IMPORTANT LIMITATION

Supports exposure use, challenges aging-biomarker use

SECTION 18

Claim-evidence-counterevidence matrix

RECORD 01

CORE ASSERTION

NAD is central to redox metabolism and is consumed by PARPs, sirtuins and CD38

SUPPORTING EVIDENCE

Established biochemistry; cellular studies

COUNTEREVIDENCE OR BOUNDARY

Total pool alone does not describe flux or compartment

CONFIDENCE

Established

RECORD 02

CORE ASSERTION

Mammalian mitochondrial NAD import is regulated by SLC25A51

SUPPORTING EVIDENCE

Genetic and transport studies [1,2]

COUNTEREVIDENCE OR BOUNDARY

Human intervention studies rarely measure this directly

CONFIDENCE

Established mechanism; unresolved clinical translation

RECORD 03

CORE ASSERTION

Inflammation and senescence can drive CD38-associated NAD loss

SUPPORTING EVIDENCE

Tissue and animal studies [3-5]

COUNTEREVIDENCE OR BOUNDARY

Human magnitude and individual variability remain uncertain

CONFIDENCE

Supported mechanism

RECORD 04

CORE ASSERTION

IV NAD+ creates direct vascular exposure

SUPPORTING EVIDENCE

Route definition; human infusion study [6]

COUNTEREVIDENCE OR BOUNDARY

Does not establish intact intracellular or mitochondrial delivery

CONFIDENCE

Established exposure; unresolved distribution

RECORD 05

CORE ASSERTION

IV NAD+ is “100% bioavailable” to cells

SUPPORTING EVIDENCE

None adequate

COUNTEREVIDENCE OR BOUNDARY

Rapid extracellular metabolism and plasma disappearance [6]

CONFIDENCE

Refuted as a cellular claim

RECORD 06

CORE ASSERTION

Oral NR/NMN raise circulating NAD-related metabolites

SUPPORTING EVIDENCE

Multiple RCTs and reviews [8-12,15,17-21]

COUNTEREVIDENCE OR BOUNDARY

Functional outcomes are heterogeneous

CONFIDENCE

Established target engagement

RECORD 07

CORE ASSERTION

Raising blood NAD necessarily improves energy, cognition or aging

SUPPORTING EVIDENCE

No adequate universal evidence

COUNTEREVIDENCE OR BOUNDARY

Multiple null functional trials and meta-analyses [13,14,20,21,38,53-55]

CONFIDENCE

Refuted as a universal claim

RECORD 08

CORE ASSERTION

Whole-blood NAD is a biomarker of biological aging

SUPPORTING EVIDENCE

Earlier heterogeneous human associations [44-46]

COUNTEREVIDENCE OR BOUNDARY

Seven-cohort validated analysis found stability with age [43]

CONFIDENCE

Not validated; refuted as a universal claim

RECORD 09

CORE ASSERTION

NR/NMN can act as continuity companions

SUPPORTING EVIDENCE

Sustained oral kinetics and tissue engagement [11,12,22-24]

COUNTEREVIDENCE OR BOUNDARY

Optimal agent and responder phenotype unresolved

CONFIDENCE

Supported, conditional

RECORD 10

CORE ASSERTION

NAD-directed exposure necessarily depletes methyl donors

SUPPORTING EVIDENCE

NNMT mechanism makes burden plausible [25]

COUNTEREVIDENCE OR BOUNDARY

Human NR study found no methylation disruption [26]

CONFIDENCE

Refuted as universal; conditional risk remains

RECORD 11

CORE ASSERTION

TMG should accompany every NAD intervention

SUPPORTING EVIDENCE

No adequate evidence

COUNTEREVIDENCE OR BOUNDARY

Lipid trade-offs and absence of universal methyl disturbance [26-29]

CONFIDENCE

Refuted as universal

RECORD 12

CORE ASSERTION

Active cancer requires mechanistic caution

SUPPORTING EVIDENCE

Tumor NAD dependencies and context-dependent experimental results [31-37]

COUNTEREVIDENCE OR BOUNDARY

Some models show protective or treatment-enhancing effects

CONFIDENCE

Supported, highly context-dependent

SECTION 19

Discussion

The strongest conclusion from current human research is not that NAD restoration “works” or “does not work.” It is that biochemical engagement is easier to produce than durable functional change. That pattern should improve clinical reasoning rather than disappoint it.

The pathway is biologically real. The measurement problem is equally real. A 2026 multi-cohort analysis overturns the casual use of whole-blood NAD as an age clock while preserving its usefulness as an exposure marker [43]. This distinction is a major advance: it allows the field to retain biochemical rigor without manufacturing a deficiency diagnosis from an accessible sample.

Oral precursors frequently alter the NAD metabolome. Cerebral and skeletal-muscle engagement has been measured. Intravenous NAD⁺ is rapidly metabolized and produces a distinct tolerability profile. None of these facts justifies treating nonspecific symptoms as proof of NAD deficiency or using a standard dose as a universal solution.

The most productive clinical use of NAD-directed interventions is as a bounded experiment inside a richer model of the patient. This requires identifying the suspected bottleneck, selecting a route consistent with that bottleneck, controlling product quality, measuring a target response and being willing to abandon the hypothesis if the predicted response does not occur.

The NAD-5D model formalizes this discipline. Deficit prevents symptom-to-product matching. Delivery distinguishes molecules and routes. Distribution prevents blood measurements from masquerading as tissue proof. Drain forces attention to the continuing biology that may consume the restored pool. Demonstrated response makes the program longitudinal and falsifiable.

This framework also clarifies the place of companions. Oral NR or NMN can provide continuity after an acute exposure because their kinetics are slower and sustained. TMG can support remethylation when the methylation context warrants it. Neither companion should be automatic. Automatic stacks make it difficult to identify what produced benefit, what caused harm and what is unnecessary.

The approach differs from a purely regulatory or trial-hierarchical model without rejecting controlled human data. A randomized trial remains powerful for estimating causal effects in the population studied. It is not the only admissible source of knowledge about chemistry, transport,

tissue distribution or an individual longitudinal response. Likewise, elegant biochemical reasoning is valuable but cannot claim a patient outcome it has not measured.

The intended standard is therefore stricter than either extreme: neither “not approved, therefore meaningless” nor “mechanistically plausible, therefore clinically proven.”

SECTION 20

Conclusions

NAD⁺ restoration is a credible mechanistic field with demonstrated human biochemical target engagement and incomplete clinical translation. Its scientific value lies in the network: synthesis, transport, compartmentation, consumption, redox state, route, tissue and patient terrain.

Intravenous NAD⁺ provides acute vascular exposure but is rapidly metabolized, can be rate-limited by tolerability and lacks robust controlled outcome evidence for broad wellness claims. Oral NR and NMN are rational continuity tools because sustained administration can increase circulating and, in selected studies, tissue or cerebral NAD-related measures. Their functional effects are heterogeneous and should not be generalized beyond the populations and endpoints studied. TMG is mechanistically coherent when methyl-donor support is indicated, but automatic use is contradicted by human methylation data and by its own lipid trade-offs.

The Clinic Terrain position is not that every patient should receive NAD-directed therapy. It is that the intervention can be used intelligently when the suspected deficit, delivery route, tissue distribution, active drain and measured response form a coherent and falsifiable whole.

Clinical bottom line

A universal recommendation of NAD⁺ precursors or intravenous NAD⁺ for general fatigue, cognitive complaints or wellness is scientifically incoherent because NAD constraint is not a universal diagnosis and biochemical engagement is not a universal clinical response.

Individualized use becomes coherent when it is framed as a structured therapeutic trial with a defined mechanistic hypothesis, explicit target outcomes, objective or reproducible response measures, quality-controlled material and stopping rules established before escalation. Absence of response is a result, not an invitation to preserve the hypothesis indefinitely.

This position is neither an apology nor a regulatory retreat. It is a direct consequence of pathway biology: the clinical value of NAD restoration depends on deficit, delivery, distribution, drain and demonstrated response.

SECTION 21

Authorship, declarations and verification

Author and contributions: Valentine Wibowo, Clinical Researcher, Clinic Terrain Clinical Intelligence Unit, conceptualized the monograph, conducted the evidence synthesis, interpreted the findings and drafted the manuscript. She approved the final version and accepts responsibility for the integrity of the work.

Medical review: dr. I Wayan Cahyadi Surya Distira Putra, MPH reviewed the manuscript for medical coherence, clinical interpretation and safety framing, and approved the final version. This internal medical review is not represented as independent external peer review.

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Patient data and ethics: No patient-level data, identifiable patient information or newly conducted human-subject research are reported in this monograph. Research-ethics approval and protocol registration were therefore not applicable to this work.

Reference-verification statement: All 59 PubMed identifiers, article titles and core bibliographic records were checked against the corresponding PubMed records. Material quantitative claims were checked against indexed abstracts and, where required for interpretation, accessible full text. Abstract-level verification is not represented as full-text verification. The verification confirmed bibliographic correspondence and the reporting of the cited sources; it does not constitute independent replication of the underlying studies.

Attestations: The author declaration and medical-review approval have been signed.

Update policy: The evidence search and claim matrix will be rerun at least annually and after any material human trial, safety signal or change in the intervention framework.

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