RESEARCH PAPER | REVISION 4 | PREPRINT

Nicotinamide Riboside, Nicotinamide Mononucleotide, and NAD+

A Comparative Evidence Map of NAD Target Engagement and Route Pharmacology

Critical comparative evidence map and target-engagement hypothesis paper

Not a treatment protocol. Not a clinical recommendation. Not evidence of longevity benefit.

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Evidence cutoff: 7 August 2026

Status: Preprint; not peer reviewed

A bounded comparison of molecular fate, target engagement, tissue delivery, and clinical translation.

Evidence boundary

This paper is a research synthesis, not a treatment protocol. It does not recommend, prescribe, optimize, or validate the use of nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), direct nicotinamide adenine dinucleotide (NAD+), or any branded formulation. It supplies no individualized dose, titration, route, compounding, sourcing, or administration instruction. Intravenous (IV) and subcutaneous (SC) administration are medical procedures with route-specific risks and are not treated as interchangeable with oral supplementation.

The phrase "which is better" is not scientifically complete unless route, formulation, dose, molar exposure, time, biological compartment, endpoint, population, and decision criterion are declared. This paper therefore does not create a universal winner. Its only numeric cross-agent comparison is administered-dose-normalized whole-blood NAD+ target engagement, not pharmacokinetic bioavailability, absorbed-dose efficiency, tissue-delivery efficiency, clinical efficacy, or cost-effectiveness. It separates measured evidence from calculation, mechanistic inference, and speculation.

Two human head-to-head datasets comparing oral NR with oral NMN were published in 2026. The premise that no head-to-head human research exists is therefore outdated as of the evidence cutoff. Those datasets do not fully settle superiority: a 65-person randomized parallel trial found comparable whole-blood NAD+ elevation after 14 days, while a six-person randomized crossover PK study found a larger blood NAD response to NR over eight days but no detectable difference in cerebral NAD. No route-matched, dose-normalized three-way trial of NR, NMN, and direct NAD+ with tissue PK and validated clinical outcomes was identified.

Direct oral NAD+ evidence is formulation-specific and immature. One 2026 industry-funded preprint reported a short-term intracellular whole-blood NAD signal after a proprietary oral formulation, without increased plasma NAD; it was not peer reviewed by the cutoff. A conference abstract reported no cognitive advantage over placebo after oral NAD+. Direct IV NAD+ has one small human plasma-and-urine fate study, one disease-specific randomized trial, and a tiny retrospective tolerability comparison. The fate study showed rapid removal from plasma at its tested infusion rate, but did not measure intact tissue or intracellular delivery. No published human SC NAD+ PK, intracellular-delivery, efficacy, or safety result was identified. One direct NR-versus-NAD+ injectable trial was listed as recruiting without results, although its status record was stale and its registered outcomes do not measure NAD PK, intracellular delivery, absorption, or efficacy [48]. These findings cannot be transferred to general wellness, longevity, or oral-route comparisons.

No randomized trial has demonstrated that NR, NMN, or direct NAD+ extends human lifespan, prevents aging, or produces a general healthspan advantage. Increasing a blood NAD measure is target engagement, not proof of clinical benefit.

Abstract

NR, NMN, and NAD+ are often presented as competing ways to replenish nicotinamide adenine dinucleotide. That framing compresses several different pharmacologic questions into one. NR is a nucleoside, NMN is a phosphorylated nucleotide, and NAD+ is a larger dinucleotide. Their administered forms encounter different stability, transport, extracellular metabolism, gut microbial transformation, first-pass handling, cellular entry, subcellular transport, and clearance constraints. A comparison that ignores route and compartment can reward an invasive route for bypassing the gut or reward a blood biomarker that does not establish tissue delivery.

This paper constructs a route-resolved evidence map through 7 August 2026. Priority was given to primary human trials, human PK/PD studies, primary isotope-tracing and transporter studies required to interpret molecular fate, trial registries, and official regulatory records. A 2026 PRISMA-guided systematic review was

used as a coverage cross-check, not as a substitute for primary evidence [50]. Evidence was adjudicated at claim level using explicit labels: established background, direct human observation, derived calculation, mechanistic inference, unresolved conflict, unknown, and contradicted claim.

The best direct comparative evidence concerns oral NR and NMN. In a randomized, open-label, placebo-controlled trial in 65 analyzed healthy adults, 1,000 mg/day NR (3.4 mmol/day) and 1,000 mg/day NMN (3.0 mmol/day) for 14 days increased baseline whole-blood NAD+ by placebo-adjusted 49.4 umol/L and 43.1 umol/L, respectively. The authors concluded the effects were comparable. A simple derived normalization gives 14.5 and 14.4 umol/L per administered mmol/day, a difference of about 1 percent. In a separate randomized open-label crossover PK study in six healthy adults, 1,200 mg/day of each precursor for eight days raised blood NAD more with NR than NMN; the reported difference remained significant after molecular-weight adjustment. Brain NAD did not differ between precursors during that short stage. The larger trial supports practical equivalence at its tested regimen; the smaller within-person trial supports a provisional NR advantage in blood response under its regimen. Differences in design, regimen, baseline, product, sampling, and analysis prevent a definitive synthesis.

Human oral NR has the most mature evidence base for dose-responsive whole-blood NAD elevation, repeated dosing, high-dose short-term safety, and cerebral target engagement. Human oral NMN also raises blood NAD and has several short randomized trials, including a rigorous study that improved clamp-measured muscle insulin sensitivity in a specific population. Direct oral NAD+ remains preliminary and formulation-dependent. IV NAD+ is rapidly removed from plasma at the only directly studied human infusion rate, produces metabolites compatible with extracellular enzymatic cleavage, and is partly recovered through urinary NAD+ and methyl-nicotinamide. It can be difficult to tolerate at faster commercial infusion rates and has not been shown to provide general intact-cell delivery or clinical superiority. SC NAD+ has no published human PK or efficacy basis from which target engagement can be calculated.

The defensible ranking is conditional. For oral whole-blood NAD target engagement at approximately gram-scale tested regimens, NR and NMN are effectively tied, with a provisional NR edge that requires replication. For evidence maturity and human cerebral target engagement, NR ranks first. For direct evidence of a metabolic clinical effect in postmenopausal women with prediabetes, NMN has a positive trial, but that does not generalize to other populations or outcomes. Direct oral NAD+ ranks behind both precursors because its evidence is too formulation-specific and unreplicated. IV NAD+ is not ranked against oral agents because the route, burden, safety, and estimand differ. SC NAD+ is unrankable because the necessary human data are absent. No compound is proven superior for longevity or broad clinical benefit.

Keywords: NAD+; nicotinamide riboside; NR; nicotinamide mononucleotide; NMN; intravenous NAD+; subcutaneous NAD+; pharmacokinetics; pharmacodynamics; metabolomics; target engagement; oral bioavailability; cellular delivery; cerebral NAD; microbiome; evidence map; sterile compounding

Plain-language summary

The current evidence supports five plain conclusions:

- NR and NMN both raise whole-blood NAD after repeated oral use in humans.
- The largest direct comparison found them essentially equal at the tested doses. A much smaller crossover study found a larger blood response to NR.
- NR has more mature human evidence and stronger direct evidence of brain target engagement. That is an evidence advantage, not proof of better health outcomes.

- Direct NAD+ is not automatically more efficient because it is the final molecule. IV administration bypasses the gut, not extracellular enzymes or the cell membrane. SC administration adds an absorption depot and still does not establish intact cellular entry.
- The strongest critical conclusion is not that injected NAD+ is biologically inert. It is that efficient intact plasma-to-cell delivery has not been demonstrated in humans; any effect may instead arise from extracellular signaling or cleavage into smaller salvageable precursors.
- None of the three has been shown to slow human aging, extend life, or provide a universal clinical benefit.

If a single research candidate must be selected for the next definitive oral comparison, NR is presently the most defensible reference standard because its human PK, safety, tissue, and trial literature is the most developed. If the question is only "which raises whole-blood NAD better after two weeks at about 1 gram per day," the correct answer is NR and NMN are functionally tied within the best larger trial. Direct NAD+ cannot be ranked fairly until its route and formulation are specified.

1. Research question and rationale

The relevant research question is:

> *For a verified material administered by a defined route at a known molar exposure, how much NAD-related target engagement occurs in a prespecified human compartment over a prespecified time, what meaningful physiological or clinical effect follows, and what safety, uncertainty, cost, and procedural burden are required to obtain it?*

This formulation prevents six recurrent errors.

1. It prevents equal milligrams from being treated as equal molecule counts.
2. It prevents blood NAD from being treated as whole-body or mitochondrial NAD.
3. It prevents acute metabolite appearance from being treated as durable benefit.
4. It prevents a mechanistic shortcut from being treated as intact-molecule absorption.
5. It prevents an IV route from winning an oral comparison by definition.
6. It prevents a surrogate biomarker from becoming an anti-aging claim.

The smallest defensible primary comparison is oral NR versus oral NMN in adults, evaluated for repeated-dose whole-blood NAD target engagement. Direct oral NAD+ is a secondary comparator because the evidence and formulations are not yet commensurate. IV and SC NAD+ are separate route-specific evidence objects; absence of gastrointestinal exposure does not make them equivalent to intracellular NAD+ delivery.

2. Methods

2.1 Review design

This is a curated, adversarial mechanistic evidence map. It is not a registered systematic review and does not claim exhaustive retrieval or pooled clinical efficacy. Searches were updated through 7 August 2026 in PubMed, PubMed Central, ClinicalTrials.gov, primary journal records, and official regulator records. A contemporaneous PRISMA-guided systematic review covering 113 eligible human and rodent intervention studies through October 2025 was used to test retrieval completeness; its conclusion that no eligible IV or IM NAD+ outcomes trial supported anti-aging or wellness use was consistent with this map [50].

The minimum reproducible update queries were:

- `(nicotinamide riboside OR NR) AND (NAD OR pharmacokinetic* OR trial OR randomized OR brain OR muscle)`
- `(nicotinamide mononucleotide OR NMN) AND (NAD OR pharmacokinetic* OR trial OR randomized OR brain OR muscle)`
- `(NAD+ OR nicotinamide adenine dinucleotide) AND (oral OR intravenous OR infusion OR subcutaneous OR intramuscular) AND (human OR trial OR pharmacokinetic* OR safety)`
- `(NAD+ OR NR OR NMN) AND (CD38 OR CD73 OR CD203a OR ENPP1 OR connexin 43 OR SLC25A51 OR SLC12A8 OR microbiome OR isotope)`

ClinicalTrials.gov was searched by the intervention strings `NAD`, `nicotinamide adenine dinucleotide`, `nicotinamide riboside`, and `nicotinamide mononucleotide`, with study records checked for posted results, status-verification date, outcome definitions, interventions, and sponsor. FDA records were searched for the same compound names with `compounding`, `sterile`, `warning letter`, `dietary supplement`, `new dietary ingredient`, and `GRAS`. Searches were deduplicated by DOI, PMID, registry identifier, title, population, and intervention.

Priority was assigned in this order:

1. Direct randomized human comparisons.
2. Randomized human single-material trials with validated target-engagement or clinical endpoints.
3. Human PK/PD and tissue studies.
4. Primary isotope-tracing, transport, and enzyme studies necessary to interpret fate.
5. Trial registrations and official regulatory records.
6. Preprints and conference abstracts, clearly labeled and not allowed to overturn peer-reviewed evidence without replication.

Animal and cell studies were used only for mechanistic plausibility and pathway discrimination. They were not scored as proof of human efficacy.

2.2 Evidence labels

Label	Meaning
Established background	Reproducible biochemical fact not specific to a marketed intervention
Direct human observation	Measured in a human trial or PK/PD study
Derived	Independently calculated from reported human data; not an author-reported endpoint
Mechanistic inference	Plausible explanation supported by pathway or tracing evidence but not directly established for the stated human endpoint
Unresolved conflict	Credible primary studies point in different directions or differ materially in design
Unknown	The necessary experiment has not been reported or was not identified
Contradicted	A stated general claim is inconsistent with direct evidence

2.2A DRPS-1.0 result-direction and attribution contract

Revision 4 applies the Defiance Research Publication Standard (DRPS-1.0). Each evidence object is recorded separately for source-reported result, signal direction, certainty, directness, and attribution scope. Favorable, unfavorable, null, mixed, neutral, and unresolved findings are preserved even when the evidence is indirect, mechanistic, confounded, industry-linked, or at high risk of bias. Those limitations qualify certainty and causal attribution; they do not erase or reverse the result.

Complete-regimen, component-specific, exact-intervention, mechanistic, adjacent-intervention, and contextual evidence are not pooled. Absence statements are bounded to the named search surfaces and 7 August 2026 cutoff. In particular, lack of a completed subcutaneous NAD+ outcome study is not a measured null result, rapid plasma disappearance after intravenous dosing is neither proof of intact cellular delivery nor proof of biological inactivity, and a favorable indication-specific IV result is retained without generalizing it to wellness or longevity.

2.3 Comparator definition

The oral comparison uses the chemically administered material, not the marketing label. NR chloride and beta-NMN have different molecular weights, counterion states, stability profiles, and analytical specifications. Direct NAD+ products may be free acid, salts, mixtures, or proprietary formulations. A label stating "NAD+" does not establish identity, intact content, purity, stability, sterility, or bioavailability.

The analysis uses administered moles where studies provide them. Equal mass is not equal molar exposure:

Equation 1. Administered amount

```
n_admin = mass / molecular_weight
```

For illustration, 1,000 mg NR chloride at molecular weight 290.70 g/mol is approximately 3.44 mmol. One thousand milligrams beta-NMN at 334.22 g/mol is approximately 2.99 mmol. One thousand milligrams NAD+ free acid at approximately 663.43 g/mol would be approximately 1.51 mmol, before accounting for salt state, hydration, purity, or formulation.

2.4 Target-engagement estimands

The primary calculation is administered-dose-normalized target engagement. It is not labeled pharmacologic efficiency because the administered denominator does not measure absorption, parent-drug exposure, tissue delivery, or biologically active exposure.

Equation 2. Administered-dose-normalized blood target engagement

```
E_blood(t) = placebo_adjusted_change_in_blood_NAD(t) / administered_mmol_per_day
```

Equation 3. Administered-dose-normalized tissue target engagement

```
E_tissue(t) = placebo_adjusted_change_in_target_tissue_NAD(t) / administered_mmol_per_day
```

Equation 4. Exposure-normalized clinical effect

```
E_clinical(t) = clinically_meaningful_effect(t) / cumulative_exposure
```

Equation 4 is not estimable across the three materials with current evidence because populations, endpoints, routes, durations, and assays are not harmonized.

The decision vector is:

```
V = {blood target engagement, target-tissue engagement, durability, clinical effect, safety,
                evidence maturity, route burden, material certainty, cost}
```

Any scalar score requires declared weights. Because different users may value brain exposure, glucose disposal, convenience, regulatory certainty, or cost differently, this paper reports a Pareto-style conditional ranking and refuses to conceal preferences inside a universal number.

2.5 Primary endpoint and time horizon

The primary estimand is repeated-dose oral whole-blood NAD target engagement at 8 to 14 days. Whole blood is selected because it is the only compartment with direct NR-versus-NMN human comparisons. It is not treated as a validated surrogate for clinical benefit or for NAD in liver, muscle, brain, or mitochondria.

Secondary estimands are cerebral NAD, skeletal-muscle NAD metabolome, clinical endpoints in defined populations, short-term safety, and evidence maturity. Acute single-dose observations are separated from steady-state or near-steady-state findings.

2.6 Bias and interpretation domains

Each pivotal study was considered for randomization, blinding, comparator, sample size, duration, matrix and assay, prespecification, multiplicity, missing data, product error, funding, conflicts, and generalizability. Industry involvement was treated as a risk-of-bias domain, not as automatic invalidation. Conversely, peer review was not treated as proof that an endpoint was clinically meaningful.

2.7 Study-level bias adjudication

Evidence object	Principal strengths	Material limitations	Funding or conflict signal	Overall concern
Christen 2026 NR-vs-NMN parallel trial [1]	Randomized; placebo-controlled; prespecified whole-blood NAD+ endpoint; largest direct comparison	Open label; not a formal NR-vs-NMN equivalence or noninferiority design; two wrong-product errors	Extensive sponsor-employee authorship	Moderate
Berven 2026 crossover PK study [2]	Randomized within-person crossover; serial blood and brain measures	Six-person comparative stage; open label; no formal power calculation; related but nonidentical blood endpoint	NAD-related patent interests reported	High for comparative superiority
Grant 2019 IV fate study [21]	Direct plasma and urine time course during IV NAD+	NAD n=8, saline n=3; open label; no isotope tracer, tissue, red-cell, or complete mass balance	Clinic and commercial-context relationships	High for cellular-delivery inference

Evidence object	Principal strengths	Material limitations	Funding or conflict signal	Overall concern
Reyna 2026 commercial tolerability study [22]	Directly reports symptoms and infusion duration	Retrospective; NAD n=6; NR n=8; patient-controlled rates; no placebo	Designed and conducted in a commercial setting	High
Yu 2026 ischemic-cardiomyopathy trial [34]	Randomized; placebo-controlled; n=180; clinical disease population	Single center; short course; LVEF surrogate; blinding and primary-endpoint reporting incompletely described; LOCF; same sonographer	Study drug and support supplied by industry	Moderate to high
LNAD+ oral preprint [32]	Double-blind placebo-controlled design; parent and metabolite measurements	Retrospective registration; short duration; proprietary assay and formulation; no multiplicity-surviving clinical endpoint	Industry funded with extensive conflicts	High

The ratings are domain-level judgments for the claims used here, not validated RoB 2 scores. Industry involvement is not automatic invalidation, but it increases the need for prespecification, independent replication, transparent analysis, and product verification.

2.8 Search limitations

The literature is changing rapidly. A missed, corrected, retracted, or newly published study could alter a material-specific conclusion. Publication bias is plausible. Trials use different formulations, matrices, storage methods, assays, baseline NAD values, doses, schedules, foods, and populations. These differences can produce apparently inconsistent effects without requiring fraud or biological impossibility.

3. Material identity, stoichiometry, and evidence asymmetry

Material	Pharmacologic class	Approximate molecular weight used for comparison	Immediate biochemical requirement	Central uncertainty
NR chloride	Pyridinium nucleoside salt	290.70 g/mol	Phosphorylation by NRK to NMN, then NMNAT to NAD+; may also be cleaved or microbially transformed	Fraction reaching each tissue as intact NR versus transformed species
beta-NMN	Phosphorylated pyridinium nucleotide	334.22 g/mol	NMNAT conversion to NAD+ after entry or extracellular conversion to NR/other species	Extent and relevance of intact transport versus extracellular dephosphorylation and microbiome pathways
NAD+ free acid	Dinucleotide	about 663.43 g/mol	Intact transport where available or extracellular cleavage and resynthesis	Oral stability, absorption, extracellular catabolism, formulation dependence, and cellular access

NR has the largest and longest human development program of the three. It has repeated-dose dose-ranging studies, high-dose short-term safety, disease-specific randomized trials, blood metabolomics, skeletal-muscle biopsies, cerebrospinal-fluid observations, and brain magnetic-resonance spectroscopy. The results demonstrate target engagement more consistently than broad clinical benefit.

NMN has a smaller but substantial human trial base. Several studies report increased blood NAD or NAD-related metabolites and good short-term tolerability. Some trials report improvements in insulin sensitivity, exercise thresholds, sleep, walking time, or muscle function, but endpoints and populations vary and many findings are secondary or exploratory.

Direct NAD+ has the weakest commensurate evidence. IV studies establish that administered NAD-related material is rapidly removed or metabolized and can alter excretion profiles. A single-center heart-failure trial reported an LVEF difference after a short IV course, while most clinical secondary endpoints were not statistically significant. Oral evidence includes a negative cognition conference abstract and a positive proprietary-formulation preprint. Neither establishes general superiority.

4. NAD pharmacology and compartmentation

4.1 NAD is both redox cofactor and consumed substrate

NAD cycles between oxidized NAD+ and reduced NADH in redox reactions. NAD+ is also consumed by enzymes including poly(ADP-ribose) polymerases, sirtuins, and CD38-family enzymes. Consumption produces nicotinamide and other products, requiring continuous resynthesis. A higher measured pool can reflect increased synthesis, reduced consumption, altered cell composition, changed redox state, or analytical handling; it does not identify the causal mechanism by itself.

4.2 Biosynthetic routes converge but are not equivalent

The amidated salvage pathway converts nicotinamide through NAMPT to NMN and then through NMNAT enzymes to NAD+. NR can be phosphorylated by nicotinamide riboside kinases to NMN. The Preiss-Handler pathway uses nicotinic acid and converges through nicotinic acid mononucleotide and nicotinic acid adenine dinucleotide. Tryptophan contributes through de novo synthesis.

Stable-isotope and microbiome studies in mice show that oral NR and NMN can contribute substantially through microbial deamidation to nicotinic acid and the Preiss-Handler pathway [27-30]. The 2026 human head-to-head trial found a compatible metabolomic footprint and ex vivo human microbiota conversion [1]. That does not prove that every molecule follows the same route or that direct uptake never occurs. It does show that the simplistic diagrams "NR to NMN to NAD" and "NMN directly to NAD" are incomplete descriptions of oral human exposure.

4.3 Cell and organelle boundaries matter

Extracellular NMN can be dephosphorylated to NR and then taken up in mammalian model systems; NRK1 was required for efficient use of both exogenous NR and NMN in a primary mechanistic study [25]. A separate study proposed SLC12A8 as an intestinal NMN transporter [26], but the quantitative contribution and generality of intact NMN transport remain debated. The appropriate conclusion is not that intact NMN transport is impossible; it is that its dominance in adult human oral pharmacology is unproven.

Mitochondria are a further compartment. Independent 2020 studies identified SLC25A51/MCART1 as a mammalian mitochondrial NAD transporter [23,24]. This discovery shows that intact NAD can cross the inner mitochondrial membrane through a dedicated carrier. It does not show that orally or intravenously administered NAD reaches the cytosol or mitochondrial intermembrane space intact in sufficient concentration. Plasma entry, cell entry, and mitochondrial entry are distinct gates.

4.4 Blood is a mixed compartment

Whole-blood NAD is heavily influenced by erythrocytes and other blood-cell composition. Plasma NAD, intracellular whole-blood NAD, peripheral blood mononuclear-cell NAD, and tissue NAD are not interchangeable. The 2026 NAD-brain study explicitly noted that cell composition could influence whole-blood concentrations [2]. Cross-trial comparisons that mix matrices or assays can be misleading even when every reported measurement is analytically correct.

4.5 No validated universal NAD-deficiency threshold

No clinically validated universal reference range or deficiency cutoff was identified for whole-blood, plasma, PBMC, muscle, liver, or brain NAD. Age-associated differences are tissue-, matrix-, population-, and assay-dependent; a group-average age association does not diagnose an individual deficiency. Claims of "repletion" should therefore identify the matrix, redox species, assay, reference population, preprocessing, normalization, and baseline phenotype rather than presuming that every older adult is NAD deficient.

Assay handling is part of the exposure model. Whole-blood results can change with erythrocyte abundance, hematocrit, cell separation, extraction, storage, freeze-thaw history, and whether the assay reports NAD+, NADH, or total NAD. A percentage increase from a low baseline is not interchangeable with an absolute concentration change, and neither is a validated clinical benefit threshold.

5. Route-resolved pharmacokinetic chain

5.1 Oral NR

The full chain is: verified NR salt and formulation -> gastrointestinal dissolution and stability -> intestinal or microbial transformation -> absorption of intact NR and/or metabolites -> portal and hepatic handling -> systemic appearance of NR-related metabolites -> cellular transport -> NRK phosphorylation to NMN -> NMNAT conversion to NAD+ -> compartment-specific transport and turnover -> methylated and oxidized excretion products.

Human studies show dose-responsive changes in the blood NAD metabolome after NR, including NAD+, nicotinic acid adenine dinucleotide, methyl-nicotinamide, and pyridone products [3-7]. Rapid metabolite changes can occur before whole-blood NAD reaches a plateau. In the 2026 NAD-brain study, blood NAD rose slowly and approached a new steady state around two weeks, while several metabolites responded faster [2].

5.2 Oral NMN

The full chain is: verified beta-NMN and formulation -> gastrointestinal stability -> possible intact transport and/or dephosphorylation to NR -> microbial deamidation and other transformation -> portal and hepatic handling -> systemic metabolite appearance -> cell entry of NMN or derived species -> NMNAT conversion to NAD+ -> compartment-specific distribution and turnover -> excretion products.

Human studies show that repeated NMN can increase whole-blood NAD or NAD-related measures [1,12-20,31]. However, direct appearance of a compound or higher blood NAD does not disclose which molecular route dominated. The 2026 head-to-head trial found no acute whole-blood NAD rise from NR or NMN despite chronic increases, and proposed slow gut-dependent conversion as an important route [1].

5.3 Direct oral NAD+

The full chain is: verified NAD+ salt or formulation -> chemical stability in the product and stomach -> luminal enzymatic cleavage and microbial metabolism -> absorption of intact NAD+ and/or nucleotides, nucleosides, bases, and phosphate-containing fragments -> first-pass handling -> cellular and organelle entry or resynthesis -> turnover and excretion.

There is no basis for assuming that direct oral NAD+ remains intact from capsule to target-cell cytosol. A proprietary formulation may alter dissolution or supramolecular behavior, but such a formulation is a separate evidence object and cannot establish a class effect for all oral NAD+ products.

5.4 Intravenous NAD+

The route-resolved chain is: verified sterile NAD+ drug substance -> venous administration -> immediate extracellular dilution in blood -> competition among ectoenzymatic cleavage, protein or surface association, tissue distribution, and possible intact uptake -> appearance of smaller products such as NMN, AMP/adenosine, ADP-ribose, nicotinamide, and methylated metabolites -> cellular uptake of intact NAD+ in any permissive cell system and/or uptake of smaller precursors -> intracellular salvage to NAD+ -> organelle transport, including SLC25A51-mediated mitochondrial import after NAD+ reaches the appropriate intracellular compartment -> renal filtration, tubular handling, further catabolism, and urinary excretion.

The only direct human plasma-and-urine fate study randomized 11 healthy men to 750 mg NAD+ (n=8) or saline (n=3) over six hours, approximately 3 umol/min [21]. Plasma NAD+, nicotinamide, methyl-nicotinamide, ADP-ribose, and NMN did not significantly rise during the first two hours despite continuous infusion. By six hours, plasma NAD+, nicotinamide, methyl-nicotinamide, and ADP-ribose had increased; urinary NAD+ and methyl-nicotinamide also increased and then fell after infusion. The investigators interpreted the early phase as rapid, near-complete plasma removal and the metabolite pattern as compatible with NAD+ glycohydrolase and pyrophosphatase activity.

That study establishes rapid loss from the measured plasma pool at one slow infusion rate. It does not establish the fraction cleaved extracellularly, reversibly distributed, bound, taken up intact, or excreted; it did not measure red-cell, tissue, cytosolic, or mitochondrial NAD. "Not present in plasma" therefore cannot be converted into either "delivered intact to cells" or "biologically inactive." The defensible conclusion is narrower: quantitatively important intact delivery into human target-cell cytosol has not been demonstrated.

Human-cell experiments strengthen the cleavage pathway but do not supply human in-vivo fractions. HEK293 cultures cleaved extracellular NAD+ to NMN, and using extracellular NAD+ to maintain intracellular NAD required conversion to smaller permeant precursors under the tested conditions [45]. Enzyme attribution must be specific: CD38 is an NAD glycohydrolase; CD203a/ENPP1 can process NAD-derived nucleotides toward AMP; and CD73 acts principally downstream by converting AMP to adenosine in the described CD38/CD203a/CD73 chain [52]. Recombinant human CD73 did not process NAD+ and only poorly processed NMN in another human-cell study, so direct NAD cleavage should not be assigned to CD73 as a general rule [51].

Conversely, connexin-43-mediated transmembrane NAD+ flux has been demonstrated in selected intact cell systems [46,47]. Exogenous NAD also increased hypothalamic NAD in mice and entered a hypothalamic cell model through a connexin-43-dependent, CD73-independent mechanism [53]. Extracellular NAD produced a calcium signal in freshly isolated human monocytes [54]. In a susceptible mouse model, IV NAD triggered ART2/P2X7-dependent depletion of peripheral T cells, demonstrating route-dependent extracellular signaling while providing no evidence of analogous human efficacy [55]. These findings show that extracellular or injected

NAD can be biologically active without establishing efficient intact delivery into human target-cell cytosol. They are why the categorical claims that NAD+ "cannot enter a cell" or "cannot become biologically active" are too strong; no human isotope-resolved study has shown that intact flux is a major, scalable whole-body delivery route after infusion.

Commercial IV practice often uses different total doses and faster patient-controlled rates. In a 2026 retrospective commercial cohort, all six recipients of 500 mg NAD+ on four consecutive days reported moderate-to-severe cramping, gastrointestinal symptoms, increased heart rate, throat or chest discomfort during infusion; symptoms stopped when infusion ended [22]. Mean infusion time was 97 minutes for NAD+ versus 37 minutes for IV NR. The study was small, nonrandomized, commercially conducted, and not an efficacy trial. It demonstrates route burden and poor tolerability under that setting, not universal toxicity or therapeutic ineffectiveness.

5.5 Subcutaneous NAD+

The proposed SC chain is: verified sterile NAD+ drug substance -> deposition in interstitial fluid -> local dilution and pH/osmolality exposure -> local ectoenzyme cleavage and possible inflammatory or purinergic signaling -> capillary and lymphatic absorption of intact NAD+ and/or products -> systemic extracellular distribution -> the same cellular-boundary, salvage, compartmental, and renal-clearance steps described for IV administration.

SC injection does not solve the intact-delivery problem. It adds a prevascular depot where residence time, local enzymes, tissue perfusion, dose volume, formulation, and injection-site reaction can affect exposure. No published human study identified through the cutoff quantified SC NAD+ bioavailability, intact parent in plasma, tissue uptake, intracellular NAD labeling, dose proportionality, elimination half-life, or clinical efficacy. Therefore no SC target-engagement estimate can be calculated and no evidence-based claim can be made that SC is more sustained, more cellular, safer, or more effective than IV or oral delivery.

NCT06919328 is listed as a recruiting randomized, parallel, quadruple-masked study estimated to enroll 70 participants and compare labeled 100 mg/2 mL NR, NAD+, and placebo by IM, SC, and IV-push routes [48]. The record was last verified in April 2025 even though its estimated completion date was June 2025, so the recruiting status was stale at the evidence cutoff. Its primary outcomes are pain and subjective discomfort one minute after injection; secondary outcomes are C-reactive protein, erythrocyte sedimentation rate, and plasma viscosity. It does not register NAD PK, intact absorption, intracellular delivery, or clinical efficacy outcomes. The "NR via IV push" arm description also says "100 mg NAD+," an internal registry inconsistency that prevents uncritical interpretation. No results were posted.

A separate recruiting open-label study evaluates repeated SC and IM injectable NR, not NAD+, through day 100; whole-blood NAD+ is a secondary pharmacodynamic endpoint and safety is primary [49]. These registrations show that basic parenteral tolerability and target-engagement questions remain under investigation; they are not evidence for SC NAD+ efficacy or intact cellular delivery.

6. Agent-level evidence: nicotinamide riboside

6.1 Mechanistic proposition

NR is smaller and less phosphorylated than NMN and NAD+. It can enter NAD biosynthesis after NRK-dependent phosphorylation. Oral NR also participates in microbiome and enterohepatic pathways, so its effect cannot be reduced to direct intact cellular uptake.

6.2 Human blood PK and target engagement

The first human NR PK study reported dose-dependent effects of 100, 300, and 1,000 mg single doses on the blood NAD metabolome [3]. An eight-person open-label repeated-dose study reported approximately doubled whole-blood NAD at steady state after escalation to 1,000 mg twice daily [4]. A randomized 140-person dose-ranging trial found 22, 51, and 142 percent increases in whole-blood NAD after 100, 300, and 1,000 mg/day, respectively, within two weeks, maintained through eight weeks [7].

These studies establish oral target engagement. They do not prove that higher blood NAD produces better clinical outcomes, nor that the dose-response remains linear beyond studied conditions.

6.3 Tissue and cerebral evidence

A six-week crossover study in 13 overweight or obese adults found increases in skeletal-muscle markers of NAD synthesis and acetylcarnitine changes, but no effects on insulin sensitivity, mitochondrial function, liver or intramyocellular lipid, cardiac energy status, blood pressure, or inflammatory markers [9]. A related 12-week study in obese insulin-resistant men found no change in muscle NAD+, mitochondrial respiration, content, or morphology [10]. Tissue response is therefore not guaranteed by blood response.

In Parkinson disease, the 30-person NADPARK phase I trial found that 1,000 mg/day NR for 30 days was tolerated and increased cerebral NAD in variable responders, with related CSF and metabolic changes [11]. A 2024 acute 7-T MRS study in ten healthy volunteers reported increased cerebral NAD four hours after 900 mg NR [35]. The 2026 NAD-brain study reported a significant pooled cerebral total-NAD increase after four weeks of 1,200 mg/day NR, while acknowledging limited 3-T MRS sensitivity and inability to separate NAD+ from NADH [2,39]. These studies give NR the strongest direct human cerebral target-engagement evidence of the three materials, but none proves neuroprotection or cognitive benefit.

6.4 Clinical outcomes

NR clinical results are mixed and population-specific. Twelve weeks of 2,000 mg/day did not improve clamp-measured insulin sensitivity, glucose metabolism, energy expenditure, lipolysis, or body composition in obese insulin-resistant men [8]. A six-week crossover study similarly found no insulin-sensitivity or mitochondrial-function benefit despite tissue metabolomic changes [9]. A small older-adult crossover trial suggested exploratory blood-pressure and arterial-stiffness signals but was not a definitive efficacy trial [5]. A 20-person mild-cognitive-impairment pilot safely raised blood NAD about 2.6-fold but did not establish cognitive efficacy [13].

The evidence supports reliable biochemical target engagement more strongly than meaningful clinical benefit.

6.5 Safety

Across short randomized trials, NR has generally been tolerated. Four weeks of 3,000 mg/day in 20 people with Parkinson disease met prespecified safety outcomes, while producing marked metabolome changes [12]. Longer exposure at lower doses also appears tolerated in studied adults [5,7,8]. These data do not establish lifetime safety, safety in pregnancy, cancer, severe liver or kidney disease, or safety of unverified products. Increased methylated nicotinamide products are pharmacodynamic observations whose long-term meaning is not fully resolved.

6.6 Defensible conclusion for NR

Direct human observation: Oral NR reliably raises whole-blood NAD-related measures after repeated dosing and has direct human brain target-engagement evidence.

Not established: General anti-aging benefit, lifespan extension, universal tissue delivery, or broad clinical superiority.

Current position: Best-developed oral reference standard; provisional first rank for evidence maturity and cerebral target engagement.

7. Agent-level evidence: nicotinamide mononucleotide

7.1 Mechanistic proposition

NMN is one enzymatic step from NAD+ once it is available to NMNAT in the relevant intracellular compartment. That structural proximity does not establish oral delivery efficiency. Its phosphate increases polarity, and extracellular dephosphorylation, intact transport, microbiome conversion, enterohepatic cycling, and salvage from released nicotinamide may all contribute.

7.2 Human blood PK and target engagement

A first-in-human single-dose study in ten healthy Japanese men evaluated 100, 250, and 500 mg and found rapid changes in nicotinamide metabolites without major safety signals [14]. Repeated-dose randomized trials at 250 mg/day, 300 to 900 mg/day, 1,000 mg once or twice daily, and 1,250 mg/day have reported increased blood NAD or NAD-metabolome measures with generally favorable short-term tolerability [16-20]. Assays and matrices differ, limiting numeric cross-study comparison.

The 2026 direct comparisons are more informative than separate-arm historical comparisons and are analyzed in Section 9.

7.3 Tissue and clinical evidence

In a rigorous ten-week randomized double-blind trial of 25 postmenopausal women with prediabetes who were overweight or obese, 250 mg/day NMN increased insulin-stimulated glucose disposal by clamp and enhanced skeletal-muscle insulin signaling and remodeling markers [15]. The intervention did not significantly change body composition, fasting glucose, insulin, or several systemic outcomes. This is a credible population-specific clinical signal, not evidence of universal metabolic benefit.

Six weeks of NMN plus exercise in 48 recreational runners improved some ventilatory-threshold measures at 600 and 1,200 mg/day, while VO2max and peak power did not differ [36]. In older-adult trials, 250 mg/day has produced secondary signals involving lower-limb function, walking time, fatigue, or sleep, but primary endpoints were often negative or findings depended on timing and multiplicity [17,37]. A 36-person arterial-stiffness trial found a nonsignificant trend, not a confirmed effect [19].

The evidence is compatible with selective benefits in some contexts. It is not consistent enough to support a general healthspan claim.

7.4 Safety

NMN has generally been tolerated in short studies up to 1,250 mg/day for four weeks and other regimens for up to approximately 12 weeks [16-20]. Samples are too small and durations too short for uncommon or delayed risks. Product purity and regulatory status vary. A tolerable study product cannot validate every commercial NMN material.

7.5 Defensible conclusion for NMN

Direct human observation: Oral NMN raises blood NAD-related measures and has a positive clamp-based insulin-sensitivity trial in a defined population.

Not established: Consistent intact absorption, universal tissue delivery, general anti-aging benefit, or superiority over NR.

Current position: Strong second evidence base; approximately tied with NR for larger-trial whole-blood target engagement, with less mature human brain evidence.

8. Agent-level evidence: direct NAD+

8.1 Mechanistic proposition

Direct NAD+ removes the intracellular synthesis step only if the molecule arrives intact at the relevant intracellular compartment. That condition cannot be assumed. The same molecule can be a substrate for extracellular enzymes, an extracellular signal, a source of smaller precursors, a plasma analyte, or an intact mitochondrial transport substrate depending on location. A molecule cleaved outside the cell may still contribute to intracellular NAD after NR, nicotinamide, or another product enters a salvage pathway; that is indirect precursor delivery, not proof of intact NAD+ entry.

8.2 Oral evidence

A 2025 conference abstract described 37 Latina women randomized to oral NAD+ or placebo for 28 days. Cognitive scores improved in both groups, with no significant between-group advantage [33]. The abstract did not establish NAD target engagement and is insufficient for formulation-wide conclusions.

A 2026 double-blind randomized phase 0/1b preprint evaluated a proprietary "LathMized" oral NAD+ formulation in 60 healthy adults aged 45 to 75, with a primary analysis of 50 after five days. It reported a 53 percent placebo-adjusted increase in intracellular whole-blood NAD, no change in circulating plasma NAD, increased catabolites, similar symptom incidence, and no multiplicity-surviving secondary clinical endpoint [32]. The trial was retrospectively registered, short, industry-funded, rich in conflicts, and not peer reviewed by the cutoff. Its signal is hypothesis-generating and formulation-specific. It does not demonstrate intact absorption, target-tissue delivery, or superiority to NR or NMN.

8.3 Intravenous PK, tolerability, and outcomes

The 2019 six-hour infusion pilot is the most direct human fate study. Rapid disappearance from plasma during the first two hours, later increases in plasma metabolites, and urinary NAD+ plus methyl-nicotinamide are consistent with extensive distribution, extracellular removal, metabolism, and excretion [21]. Because mass balance was incomplete and intracellular tissue NAD was not measured, "removed from plasma" cannot be translated into "delivered intact to cells," "all immediately excreted," or "incapable of metabolic activity."

The most plausible human chain supported across direct and mechanistic evidence is: a rapidly constrained extracellular parent pool -> ectoenzyme cleavage and/or tissue distribution -> smaller salvageable products and extracellular signaling species -> intracellular resynthesis where transport and enzymes permit -> organelle-specific delivery -> further catabolism and renal elimination. The relative contribution of each branch remains unknown in humans. The missing experiment is isotope-resolved mass balance across plasma, red cells, tissue, and urine, not another unlabelled before-and-after blood NAD measurement.

A 2026 single-center randomized placebo-controlled trial enrolled 180 adults with ischemic cardiomyopathy and LVEF at or below 45 percent. IV NAD+ 10 mg/day for seven days plus guideline-directed therapy produced a larger reported one-month LVEF change than placebo (4.49 versus 2.25 percentage points; p=0.023); the post-treatment group means were 45.44 versus 42.44 percent (p=0.024) [34]. NT-proBNP, six-month major adverse cardiac and cerebrovascular events, heart-failure hospitalization, NYHA improvement, and structural measures did not reach conventional statistical significance. The trial used LOCF for missing data, the same sonographer for echocardiograms, and incompletely reported participant, clinician, allocation-concealment, and outcome-assessor blinding. Study drug and support were supplied by industry. The signal warrants independent multicenter replication with blinded core-laboratory imaging. It does not establish benefit in healthy adults, longevity, or superiority over oral precursors.

The FDA has warned compounders about use of food-grade NAD+ for sterile compounding and emphasizes ingredient suitability for sterile preparations [43]. FDA reported severe chills, shaking, vomiting, and fatigue after NAD+ injectable drugs, with some patients requiring medical treatment; the agency described the reactions as consistent with excessive endotoxin exposure [43]. These reports do not establish incidence or causality for every formulation, but they demonstrate that material quality is a clinical safety variable, not an administrative detail.

The claim that IV NAD+ is "ineffective" must therefore be resolved by endpoint:

Endpoint	Finding	Adjudication
Efficient intact delivery into human target-cell cytosol	Not measured or demonstrated	Unsupported
Avoidance of extracellular metabolism	Metabolite pattern is compatible with glycohydrolase and pyrophosphatase activity	Contradicted
Sustained intact parent in plasma at 3 umol/min	No significant rise for the first 2 hours; later accumulation occurred	Inefficient early plasma retention at the tested rate
Complete immediate urinary loss	Urinary NAD+ and methyl-nicotinamide increased, but administered-dose recovery was not established	Not proven
General wellness, anti-aging, or longevity efficacy	No validating randomized outcome trial identified	Unsupported
Every disease-specific clinical effect	One randomized heart-failure trial reported an LVEF signal	A universal null claim is contradicted; clinical value remains preliminary
Practical infusion utility	Substantial acute symptoms and longer administration in one tiny commercial comparison	Unfavorable route burden in that setting

8.4 Subcutaneous evidence

No published human SC NAD+ PK, intracellular-delivery, efficacy, or completed safety dataset was identified. NCT06919328 was listed as recruiting without posted results, but the record was stale and its registered outcomes do not measure NAD PK, absorption, intracellular delivery, or clinical efficacy [48]. Because neither intact exposure nor clinical effect has been quantified, SC NAD+ cannot be assigned a target-engagement or efficacy rank. Claims that it supplies slow, direct, or superior cellular NAD are unsupported.

The absence of evidence does not establish that every SC dose is inert. A depot could release intact NAD+, breakdown products, or both; local and systemic effects could arise without intact cellular delivery. Those alternatives are hypotheses requiring measurement. Until then, the route has procedural risk and biological uncertainty without a demonstrated advantage.

8.5 Defensible conclusion for direct NAD+

Direct human observation: IV NAD+ is rapidly removed from plasma at the studied rate and generates later plasma/urine metabolite signals; commercial IV tolerability can be poor; a small oral evidence base includes one negative cognition abstract and one positive proprietary-formulation preprint; one disease-specific IV trial reported an LVEF signal. No completed human SC NAD+ dataset was identified.

Not established: General intact oral, IV, or SC cellular bioavailability; efficient cytosolic or mitochondrial delivery; SC PK or efficacy; clinical superiority; longevity benefit; or equivalence across formulations.

Current position: Direct oral NAD+ ranks behind NR and NMN for evidence maturity. IV NAD+ remains a separate investigational route with an unfavorable evidentiary-burden profile for general wellness claims. SC NAD+ is unrankable, not proven ineffective, because the necessary human evidence has not been produced.

9. Direct head-to-head evidence

9.1 The 65-person randomized parallel trial

Christen and colleagues randomized 67 healthy adults to placebo, nicotinamide, NR, or NMN for 14 days; two people received the wrong product and were excluded from the modified intention-to-treat analysis, leaving 65 [1]. The analyzed groups were placebo n=17, nicotinamide n=17, NR n=16, and NMN n=15. Participants were 18 to 50 years old, and the study was open label with objective metabolomic endpoints.

NR 1,000 mg/day (3.4 mmol/day) increased baseline whole-blood NAD+ by a placebo-adjusted 49.4 umol/L (95% CI 39.5 to 59.3; p<0.001). NMN 1,000 mg/day (3.0 mmol/day) increased it by 43.1 umol/L (95% CI 32.7 to 53.4; p<0.001). NADH, NADP+, and NADPH were not significantly changed. NR and NMN produced similar increases in degradation metabolites and a footprint compatible with Preiss-Handler pathway involvement. Neither produced an acute four-hour whole-blood NAD rise. One probable product-related event occurred in each active precursor group: hypotension with NR and headache with NMN.

The paper was performed largely by Nestle employees and used commercial products. It was powered to compare each active arm with placebo, not necessarily to demonstrate NR-versus-NMN equivalence or noninferiority. "Comparable" is therefore a descriptive conclusion supported by overlapping estimates, not a formal equivalence margin.

9.2 Derived molar normalization

Using author-reported placebo-adjusted changes and administered mmol/day:

Material	Reported change	Administered amount	Derived E_blood	Relative value
NR	49.4 umol/L	3.4 mmol/day	14.53 umol/L per mmol/day	1.011
NMN	43.1 umol/L	3.0 mmol/day	14.37 umol/L per mmol/day	1.000

Derived conclusion: The point estimates differ by about 1.1 percent after this simple normalization. This calculation does not propagate covariance, does not establish a dose-response slope, and should not be interpreted as proof that the molecules are intrinsically identical. It shows that the larger trial supplies no meaningful numeric basis for a strong administered-dose-normalized target-engagement ranking at the tested regimen.

9.3 The six-person randomized crossover PK study

In stage 1 of the 2026 NAD-brain study, six healthy adults completed randomized crossover periods of 1,200 mg/day NR and 1,200 mg/day NMN for eight days, with washout [2]. NR increased mean blood total NAD from 27.30 to 70.51 umol/L, a mean relative increase of 161 percent. NMN increased it from 31.79 to 53.67 umol/L, a mean relative increase of 68.9 percent. The authors reported an approximately 2.3-fold larger increase with NR through day eight; the difference remained significant after adjustment for molecular weight and alignment to each treatment's maximal time point.

Neither precursor significantly changed cerebral total NAD over eight days, and no between-precursor brain difference was detected. Estimated washout half-lives for elevated blood total NAD were similar, approximately 6.76 days for NR and 5.74 days for NMN. Both were tolerated without moderate or severe events in this stage.

The crossover design controls stable person-level differences, but n=6 is extremely small, the trial was open label, products differed in capsule count and manufacturer, and the endpoint was total NAD rather than necessarily the same oxidized NAD+ estimand used in the larger trial. The large effect is credible enough to matter and too uncertain to define a universal rank.

9.4 Adjudication of the conflict

Domain	65-person trial	Six-person crossover	Adjudication
Design	Randomized parallel, placebo-controlled, open label	Randomized crossover, open label	Each has a different strength
Duration	14 days	8 days	NR/NMN kinetics may not be fully aligned at day 8
Schedule	Once daily	Twice daily	Peak/trough behavior may differ
Endpoint	Baseline whole-blood NAD+	Whole-blood total NAD	Related, not identical
Result	Comparable; molar-normalized point estimates nearly equal	NR produced larger blood rise	Genuine unresolved conflict
Brain	Not measured	No short-stage difference	No evidence of NMN or NR superiority over 8 days

The larger study receives greater weight for the primary oral whole-blood ranking because it had more participants, a placebo arm, and a prespecified whole-blood NAD+ primary endpoint. The crossover study increases the probability that regimen-dependent NR superiority exists and justifies a provisional edge, not a definitive verdict.

10. Dose, time, and matrix are part of the drug effect

10.1 Nonlinearity

A dose in milligrams is not an exposure measurement. Absorption, microbial conversion, transporter saturation, first-pass handling, enzyme capacity, cell turnover, and renal elimination can make dose-response nonlinear. A material that appears more efficient at one dose may not remain so at another.

10.2 Time to plateau

The 2026 NAD-brain data indicate that blood NAD rises over days and approaches a plateau around two weeks, then decays over days after discontinuation [2]. A four-hour or one-day comparison can miss a delayed whole-blood effect while still detecting fast metabolites. Conversely, a two-week blood plateau does not show that all tissues have plateaued.

10.3 Matrix-specific ranking

An agent can rank first in whole blood and fail to change muscle NAD. An agent can alter brain MRS without a validated clinical outcome. Plasma, erythrocytes, PBMCs, muscle, liver, CSF, and brain spectroscopy answer different questions. "NAD increased" is incomplete unless the matrix, redox species, normalization, timing, and assay are supplied.

Measurement	What it can establish	What it cannot establish by itself
Plasma intact NAD+ and metabolites	Extracellular parent and product time course	Intracellular or tissue delivery
Whole-blood NAD+	Composite blood-cell target engagement	Which cell type changed or whether tissue NAD changed
Whole-blood total NAD	NAD+ plus NADH composite, assay dependent	Redox ratio or equivalence to NAD+ alone
PBMC or erythrocyte NAD	Cell-fraction target engagement	Liver, muscle, brain, or mitochondrial exposure
Tissue biopsy NAD metabolome	Local tissue response at sampled time	Whole-organ distribution or clinical benefit
Brain phosphorus MRS total NAD	Noninvasive cerebral NAD-related signal	Cellular localization or reliable separation of NAD+ from NADH at every field strength
Urinary NAD-related products	Renal appearance of measured analytes	Complete administered-dose recovery without a labeled mass-balance design

10.4 Durability

The persistence of elevated blood NAD after cessation in the crossover study likely reflects system turnover and salvage, not prolonged persistence of intact administered NR or NMN. Estimated NAD-pool decay is not the same as parent-compound elimination half-life.

11. Tissue delivery and the brain

11.1 NR

NR has three independent forms of human cerebral evidence: a placebo-controlled Parkinson phase I trial with brain MRS and CSF measures [11], an acute 7-T MRS study in healthy volunteers [35], and the 2026 longitudinal phase I study [2]. Each has limitations, but together they establish that oral NR can alter a human cerebral NAD-related signal.

11.2 NMN

NMN was evaluated in the six-person crossover stage of the NAD-brain study. It did not produce a significant cerebral total-NAD change over eight days, and it did not differ from NR [2]. This is not proof of failure. The same study found that eight days of NR was also insufficient for a group-level brain change, while four weeks of NR produced a pooled increase. NMN needs a longer, adequately powered brain study before ranking.

11.3 Direct NAD+

No convincing human study identified through the cutoff demonstrated that oral, IV, or SC direct NAD+ raises brain NAD by validated spectroscopy or CSF metabolomics. Because SLC25A51 transports NAD into mitochondria only after NAD reaches the appropriate cellular compartment, mitochondrial transport biology cannot fill this clinical evidence gap.

11.4 Cerebral ranking

NR > NMN > direct NAD+ for evidence maturity, not necessarily for intrinsic molecular capability. The gap reflects what has been measured. NMN is uncertain, not disproven. Direct NAD+ lacks commensurate data.

12. Clinical outcomes: target engagement is not benefit

12.1 Why whole-blood NAD is insufficient

A biomarker can be pharmacologically useful without being a validated surrogate. To establish clinical benefit, a trial must show that assignment to the intervention changes a patient-relevant outcome, not merely that responders with larger biomarker changes look better. Responder analyses can be confounded and should be considered exploratory unless prespecified and randomized comparisons are preserved.

12.2 NR outcome pattern

NR repeatedly raises blood NAD but has produced null findings for insulin sensitivity, whole-body glucose metabolism, muscle mitochondrial function, and several cardiometabolic measures in well-controlled studies [8-10]. Early neurological studies demonstrate target engagement and feasibility, not disease modification [11-13]. This pattern weakens any general claim that biochemical repletion reliably becomes clinical benefit.

12.3 NMN outcome pattern

NMN has one particularly strong positive mechanistic-clinical signal: improved clamp-measured muscle insulin sensitivity in postmenopausal women with prediabetes [15]. Other trials report selective secondary outcomes in exercise, sleep, or walking, with negative or nonsignificant primary outcomes in several cases [17,19,36,37]. The correct interpretation is heterogeneity and possible context dependence, not a class-wide benefit.

12.4 Direct NAD+ outcome pattern

Oral direct NAD+ did not outperform placebo for cognition in a small conference report [33]. A proprietary-formulation preprint reported biochemical target engagement but no multiplicity-surviving secondary clinical endpoint over five days [32]. The IV heart-failure trial reported an LVEF signal but not statistically significant major clinical secondary endpoints [34]. SC NAD+ has no published human outcome dataset. These do not support general claims.

12.5 Clinical ranking

No defensible universal ranking exists. By narrow indication:

- Prediabetic postmenopausal women, muscle insulin sensitivity: NMN has direct positive randomized evidence; NR has negative trials in different obese populations, so no molecule-wide conclusion is valid.
- Human cerebral target engagement: NR has the lead.
- Heart failure with ischemic cardiomyopathy by short-course IV route: direct NAD+ has one positive LVEF trial requiring replication.
- Longevity, lifespan, or generalized healthy aging: all three are unproven.

13. Safety, tolerability, and material quality

13.1 NR

NR has the largest short-term human safety exposure, including randomized studies up to 3,000 mg/day for four weeks and lower-dose studies over longer intervals [5,7,8,12]. Adverse events are generally mild and similar to placebo in small trials. Rare, population-specific, and long-latency risks remain unresolved.

13.2 NMN

NMN studies through approximately 12 weeks and short higher-dose studies report generally favorable tolerability [16-20,38]. The total exposed population and duration remain smaller than needed to exclude uncommon adverse effects. Differences among beta-NMN purity, polymorph, storage, and degradation limit product-level generalization.

13.3 Direct oral NAD+

Short-term proprietary-formulation evidence reported similar symptoms to placebo and one mild nausea event [32]. This is inadequate for class-wide or long-term safety. Direct NAD+ products may differ substantially in salt, stability, degradation, and assay-confirmed content.

13.4 Intravenous NAD+

IV delivery adds line placement, contamination, compounding, sterility, endotoxin, particulate, osmolarity, infusion-rate, and monitoring risks. In the small retrospective commercial comparison, all six NAD+ recipients reported moderate-to-severe symptoms during infusion and required a mean 97-minute administration, although no serious adverse event was documented and symptoms resolved when infusion stopped [22]. A different slow six-hour pilot reported no adverse event in eight NAD+ recipients [21]. The contrast suggests strong regimen and rate dependence, but the samples are too small to estimate incidence or rare harm. Separately, FDA has received injectable-NAD+ adverse-event reports consistent with excessive endotoxin exposure [43]. An IV material must satisfy sterile-drug quality requirements; food-grade identity is not sufficient.

13.5 Subcutaneous NAD+

SC delivery avoids venous access but adds local pain, irritation, infection, dosing, storage, sterility, and self-administration risks. NAD+-specific incidence and severity cannot be estimated because no completed human SC dataset was identified. NCT06919328 makes immediate pain and discomfort its posted primary outcomes, confirming that basic tolerability is an open question rather than an established advantage [48]. Sterile material quality remains mandatory.

13.6 Critical quality attributes for route interpretation

Attribute	Oral relevance	IV/SC relevance	Why it can change the conclusion
Chemical identity, anomer, salt, hydration	High	High	Changes administered molecule count, stability, and comparability
Assay-confirmed intact content and degradants	High	Critical	A labeled dose may contain less intact parent or different active species
Dissolution and gastrointestinal stability	Critical	Not applicable	Determines luminal availability and transformation opportunity
pH, osmolality, buffer, concentration	Moderate	Critical	Alters local tolerance, vascular or tissue exposure, and usable rate
Sterility, endotoxin, bioburden, particulates	Not applicable to ordinary oral products	Critical	Can create serious harm unrelated to NAD pharmacology
Container-closure and in-use stability	Moderate	Critical	Adsorption, hydrolysis, oxidation, or contamination can change delivered material
Batch traceability and storage history	High	Critical	Prevents class-wide transfer from a verified trial product to an unverified product

No route comparison is interpretable if the tested material is not independently qualified. These attributes are reporting requirements, not preparation instructions.

13.7 Theoretical and unresolved risks

NAD metabolism supports normal repair and metabolic function, but it also supports the metabolism of proliferating cells. Current human trials do not establish that NR, NMN, or NAD+ causes or prevents cancer. Claims in either direction exceed evidence. Long-term effects on one-carbon metabolism, methylated metabolites, immune signaling, tumor biology, pregnancy, and severe organ disease require dedicated study.

13.8 Safety ranking

For ordinary studied oral formulations and durations, **NR has the strongest evidence maturity**, followed by **NMN**, then **direct oral NAD+**. IV and SC NAD+ are not placed on the same ladder because procedural and sterile-compounding risks make the routes categorically different. SC NAD+ has less human safety evidence than IV NAD+.

14. Regulatory and product-status boundary

FDA does not approve dietary supplements for safety and effectiveness before marketing [42]. An FDA "no questions" response to a GRAS notice is not approval of a supplement or proof of efficacy. FDA had no questions regarding a notifier's conclusion that a specified NR chloride ingredient was GRAS for specified food uses and maximum levels [40]. EFSA has separately evaluated NR chloride as a novel food for defined uses [41].

FDA records link NMN to new-dietary-ingredient notifications and legal-definition questions relevant to its US supplement status [44]. Notification submission or an FDA response is not product approval. Because the records and legal posture are dynamic and formulation-specific, status must be verified against the current FDA record at each publication update and should not be inferred from online availability.

Compounded drugs are not FDA-approved, and FDA does not verify their safety, effectiveness, or quality before marketing [56]. In a January 2026 warning letter to one registered 503B outsourcing facility, FDA stated that NAD+ was not eligible for the claimed 503B exemptions because it was not on the 503B bulks list and was not being used to compound a shortage-listed drug [57]. That finding is specific to the inspected facility and the 503B circumstances described; it should not be universalized to every patient-specific 503A prescription or every jurisdiction.

No NR, NMN, oral NAD+, IV NAD+, or SC NAD+ product should be described as FDA-approved for anti-aging or longevity. Product identity is part of the evidence: a clinical trial of a verified material does not validate a different seller, salt, formulation, or compounded injection.

15. Conditional ranking and decision matrix

15.1 Ranking rules

Ranks are assigned only where two or more materials have commensurate evidence. "Insufficient" is not converted into zero efficacy. A material with no data cannot lose biologically, but it loses as an evidence-supported decision.

Decision question	First	Second	Third	Confidence	Reason
Repeated oral whole-blood NAD target engagement	NR approximately NMN	NR approximately NMN	Direct NAD+	Moderate	Larger head-to-head is a molar-normalized tie; small crossover gives NR an edge; oral NAD+ evidence is preliminary
Human cerebral target engagement	NR	NMN	Direct NAD+	Moderate for evidence rank, low for intrinsic rank	NR has multiple human MRS/CSF studies; NMN has only short underpowered comparison; direct NAD+ lacks commensurate data
Evidence maturity	NR	NMN	Direct NAD+	High	More human trials, dose-ranging, tissue, disease, and safety data for NR

Decision question	First	Second	Third	Confidence	Reason
Short-term oral safety evidence	NR	NMN	Direct NAD+	Moderate	All appear tolerable short term; exposure base differs
Prediabetes muscle insulin sensitivity	NMN	Not rankable	Not rankable	Moderate within the studied population	Positive clamp trial for NMN; cross-population comparisons are invalid
Longevity or broad anti-aging benefit	Unproven	Unproven	Unproven	High	No human lifespan or validated healthspan superiority trial
IV disease-specific cardiac signal	Direct NAD+ IV	Not comparable	Not comparable	Low to moderate	One single-center heart-failure RCT; different route and indication
Intact cellular delivery after IV or SC NAD+	Unproven	Not comparable	Not comparable	High for evidence-gap conclusion	No isotope-resolved human tissue mass balance; plasma disappearance is non-diagnostic
SC NAD+ target engagement or efficacy	Insufficient	Insufficient	Insufficient	High for evidence-gap conclusion	No published human PK or efficacy result identified

15.2 Overall adjudication

If the task is to select the **best-supported oral reference compound for future research**, NR ranks first because it combines reliable blood target engagement, the broadest safety record, more mature tissue and brain evidence, and a larger clinical literature. This is a decision under uncertainty, not proof that NR is intrinsically superior.

If the task is to select the **strongest administered-dose-normalized oral whole-blood NAD+ target engagement after approximately two weeks**, NR and NMN are tied within the strongest larger trial. NR receives only a provisional edge because the small crossover found a larger response.

If the task is to select the **best compound for a specific clinical outcome**, there is no universal answer. NMN has a credible positive insulin-sensitivity result in one population; NR has stronger brain target-engagement evidence; direct IV NAD+ has a preliminary heart-failure signal. None generalizes to longevity.

If the task is to select **direct NAD+ because it is already the final molecule**, the premise is rejected. Comparative pharmacology depends on arrival at the target compartment, not structural proximity on a pathway diagram.

If the task is to select **IV or SC NAD+ for direct intracellular delivery**, current evidence does not support the premise. IV plasma disappearance is not a cellular-uptake measurement, and SC NAD+ has no completed human PK record. Any proposed benefit must be separated into intact-parent delivery, extracellular signaling, and salvage from breakdown products.

15.3 Why no composite score is reported

A composite score would require arbitrary weights and would hide uncertainty. For example, increasing the weight on brain evidence favors NR; increasing the weight on the prediabetes clamp result favors NMN; allowing IV route to dominate delivery favors direct NAD+ while ignoring burden; weighting product availability or price would change with time and vendor. Transparent conditional ranks are more defensible than false precision.

15.4 DRPS-1.0 evidence-balance dashboard

Direction	Strongest retained findings	Attribution and certainty boundary
Favorable	Both oral NR and NMN raise whole-blood NAD; the six-person crossover favored NR; NR has cerebral target-engagement signals; NMN improved clamp-measured insulin sensitivity in one population; a proprietary oral NAD+ formulation reported a blood signal; short-course IV NAD+ produced a preliminary heart-failure LVEF signal.	Exact tested products, routes, populations, matrices, and endpoints only; none proves universal clinical or longevity superiority.
Unfavorable	Commercial-rate IV NAD+ produced substantial symptom and time burden in a very small cohort; FDA reports identify a material-quality/endotoxin safety signal for some compounded injectable NAD+ products; a generalized CD73-direct-cleavage claim is not supported.	Route- and product-quality findings do not establish that every formulation causes harm or that NAD+ is biologically inert.
Null	Several NR trials found no muscle mitochondrial or metabolic benefit despite systemic target engagement; NR and NMN did not differ in cerebral total NAD in the small crossover; an oral NAD cognition abstract found no significant advantage.	Each null applies only to the measured population, formulation, route, endpoint, and duration.
Mixed	NMN clinical outcomes are heterogeneous; the two head-to-head studies conflict in comparative magnitude; IV NAD+ rapidly left measured plasma while later metabolites and urinary species increased.	Mixed direction is retained without converting uncertainty into efficacy or inefficacy.
Neutral	Molecular identity, administered-mole normalization, plateau timing, and evidence-maturity ranking provide interpretive context.	These are methods or context, not efficacy results.
Unresolved	Human longevity benefit, universal NAD-deficiency thresholds, efficient intact target-cell delivery after IV or SC NAD+, and SC NAD+ clinical efficacy remain unresolved through the cutoff.	No qualifying result identified is a bounded evidence gap, not proof of zero effect.

16. Failure modes and falsifiers

16.1 Failure mode: milligram ranking

Equal milligrams provide unequal molecule counts. Even molar normalization does not correct for bioavailability or nonlinear dose-response.

Falsifier required: multi-dose crossover exposure-response curves with verified products and matched administered moles.

16.2 Failure mode: pathway-step ranking

Calling NMN "one step closer" or NAD+ "already complete" ignores delivery gates.

Falsifier required: isotopically labeled human studies quantifying intact and transformed material from lumen through plasma, cells, and target tissues.

16.3 Failure mode: blood-to-body extrapolation

Whole-blood NAD may not track muscle, brain, liver, or mitochondrial NAD.

Falsifier required: simultaneous multi-compartment measurements with prespecified concordance analysis.

16.4 Failure mode: biomarker-to-benefit conversion

Raising NAD is not equivalent to improving function or preventing disease.

Falsifier required: randomized trials powered for patient-relevant outcomes, with mediation analysis prespecified rather than post hoc responder narratives.

16.5 Failure mode: product-class transfer

A proprietary oral NAD+ formulation, specific NR chloride, or microcrystalline NMN cannot validate all products carrying the same ingredient name.

Falsifier required: independent identity, potency, impurity, dissolution, stability, and bioequivalence testing.

16.6 Failure mode: route collapse

IV or SC exposure cannot be compared with oral exposure without incorporating procedural burden, safety, cost, local or vascular exposure, and different systemic kinetics. Nor can IV and SC be collapsed together: SC adds a tissue depot and absorption phase, while IV produces immediate vascular exposure.

Falsifier required: route-stratified trials with identical target endpoints and a declared route-utility framework.

16.7 Failure mode: plasma disappearance becomes cellular delivery or inactivity

Rapid loss of NAD+ from plasma can reflect enzymatic cleavage, distribution, binding, intact uptake, or excretion. Without isotope-resolved mass balance and tissue sampling, it proves neither successful intact-cell delivery nor total biological inactivity.

Falsifier required: chemically labeled NAD+ with simultaneous parent/metabolite measurements in plasma, red cells, target tissue, and urine, plus compartment-appropriate intracellular assays.

17. Definitive validation pathway

17.1 Stage 0: analytical qualification

Before human comparison, each material should be verified for identity, beta anomer where relevant, counterion, water content, purity, degradation products, microbial contamination, heavy metals, stability, dissolution, and blinded capsule equivalence. Direct IV and SC materials require pharmacopeial sterile-drug controls, endotoxin testing, particulate testing, container-closure compatibility, and validated compounding.

17.2 Stage 1: stable-isotope microtracer study

A human crossover microtracer study should administer separately labeled NR, NMN, and NAD+ by oral route. Serial portal sampling is impractical in healthy volunteers, but dense plasma, whole-blood, urine, stool, breath, and optional tissue sampling can quantify labeled parent and downstream species. A nested antibiotic experiment would be ethically and biologically confounded; microbiome contribution should instead use stool metagenomics, ex vivo transformation rates, and mechanistic modeling.

Primary questions:

- What fraction appears as intact parent in plasma?
- What fraction reaches NAD+ through amidated versus deamidated routes?
- How variable is microbial conversion?
- Which early metabolites predict later whole-blood and tissue NAD?

17.3 Stage 2: randomized double-blind molar-matched crossover PK/PD trial

The decisive oral comparison should use NR chloride, beta-NMN, direct NAD+, and placebo in a four-period crossover. Doses should be matched by administered moles and evaluated at two or more exposure levels. Each period should last at least four weeks, with washout long enough to restore each participant's NAD metabolome to baseline.

Prespecified endpoints should include:

- Whole-blood NAD+, NADH, total NAD, and redox ratio using a validated central assay.
- Plasma parent compounds and full targeted NAD metabolome.
- PBMC and erythrocyte fractions.
- Skeletal-muscle biopsy NAD metabolome in a powered subset.
- Brain NAD by a validated high-field MRS method in a powered subset.
- Safety chemistry, hematology, urinalysis, symptoms, ECG, blood pressure, and adverse events.
- Product blinding integrity and adherence by capsule count and chemical exposure markers.

The primary contrast should be NR versus NMN for dose-normalized whole-blood NAD+ area under the effect curve at steady state. Equivalence and superiority margins must be declared before unblinding.

17.4 Parenteral isotope and route study

IV and SC NAD+ require a separate ascending-exposure study, not an extra arm appended casually to the oral trial. Stable-isotope-labeled NAD+ should be used to distinguish intact parent from newly synthesized endogenous NAD+. Dense early sampling must capture the rapid IV phase; SC sampling must quantify injection-site disappearance, lymphatic/systemic appearance, and absolute bioavailability relative to IV. Plasma, whole blood, separated red cells and PBMCs, urine, and a justified tissue biopsy should be analyzed for labeled NAD+, NMN, NR, nicotinamide, ADP-ribose, adenosine-related products, methyl-nicotinamide, 2PY, and 4PY. Pain, local reactions, hemodynamics, ECG, chemistry, and adverse events should be prespecified.

Success should require more than blood NAD elevation. The study must demonstrate labeled intact NAD+ inside a target-cell compartment at a level and duration that exceed labeled salvage-derived NAD+, or explicitly conclude that the intervention operates mainly as an extracellular precursor mixture. SC claims require absolute bioavailability and local tolerability before efficacy testing.

17.5 Stage 3: tissue and population replication

The crossover result should be replicated in older adults and in one biologically justified disease population. Tissue-specific endpoints should be selected before clinical outcomes. A compound should not advance because of a favorable blood result if the target tissue fails to engage.

17.6 Stage 4: outcome trials

Clinical trials should test a single defined indication and patient-relevant primary outcome. Candidate examples include clamp-measured insulin sensitivity in prediabetes or a validated functional endpoint in a neurodegenerative population. Lifespan claims require impractically long study and cannot be substituted with an unvalidated "biological age" score.

17.7 Statistical requirements

The statistical analysis plan should be public before unblinding and specify estimands, equivalence margins, carryover testing, period effects, multiplicity, assay batches, missing data, responder definitions, mediation analysis, clinically meaningful thresholds, and stopping rules. Participant-level de-identified data and executable code should be preserved where consent permits.

18. Discussion

The central result of this evidence map is not that one molecule wins. It is that the ranking changes when the question becomes precise.

The largest direct human trial makes NR and NMN nearly indistinguishable for dose-normalized whole-blood NAD+ after 14 days. The small crossover study challenges a complete tie and suggests that NR can produce a larger blood response under a twice-daily eight-day regimen. Because the crossover result persisted after molecular-weight adjustment, it cannot be dismissed as a simple molecule-count artifact. Because it comes from six participants and a related but not identical endpoint, it cannot override the larger study. The combined evidence supports a provisional NR edge nested inside a practical tie.

Mechanistic evidence explains why simplistic ranking fails. Oral NR and NMN are not isolated arrows in a textbook pathway. They can be deamidated by microbes, cleaved, salvaged, recycled, and transported through multiple compartments. NMN may enter intact in some settings, but extracellular conversion to NR and other species is demonstrable. NR may enter cells and be phosphorylated, but much oral exposure can also reach

host NAD through microbial nicotinic-acid production. Direct NAD+ may be transported by mitochondria once it is present in the right cellular location, yet extracellular NAD+ is also rapidly metabolized. Selected connexin-expressing cells can exchange NAD+ across the plasma membrane, but that does not establish quantitatively important systemic delivery after an injection. Each statement is location-dependent.

The clinical literature reinforces the separation between target engagement and benefit. NR has abundant blood-NAD evidence and several null metabolic trials. NMN has positive and negative outcome signals depending on population and endpoint. Direct NAD+ has early route- and indication-specific observations. This pattern is expected when NAD biology is homeostatic, compartmentalized, and not necessarily rate-limiting in every person or disease.

An evidence-maturity ranking is still useful. It answers which material is the least speculative platform for the next trial. On that axis, NR leads. It has dose-ranging data, safety data, tissue biopsies, brain studies, and disease trials. NMN is a close but less mature competitor with one especially compelling metabolic result. Direct oral NAD+ is an emerging formulation question. IV NAD+ has medical and pharmacologic questions that cannot be answered by wellness-market use. SC NAD+ is earlier still: its basic human PK, intracellular fate, dose response, and clinical value are unknown.

The user-facing answer should therefore be explicit:

> *NR is currently the most defensible overall research reference because its evidence base is the most mature and its human brain target engagement is better documented. NR is not proven universally superior to NMN. At the best-supported oral whole-blood endpoint, the compounds are effectively tied, with a small-study signal favoring NR. Direct NAD+ is not yet competitive as a general oral evidence claim, and IV NAD+ must be judged separately.*

19. Limitations

This is a critical evidence map, not a systematic review or meta-analysis. The search may have missed studies, unpublished data, corrections, or jurisdiction-specific regulatory actions. No pooled estimate was attempted because interventions, formulations, doses, matrices, assays, populations, and outcomes were too heterogeneous.

The central molar normalization uses administered dose, not absorbed or target-tissue exposure. It is a useful correction for equal-mass comparisons but not a true bioavailability estimate. Confidence intervals for the derived ratio were not reconstructed from individual data, and the larger trial was not designed as a formal NR-versus-NMN equivalence study.

The 2026 crossover comparison includes only six healthy adults. Its within-person design is strong for exploratory kinetics but unstable for population ranking. The larger trial is open label and includes two product-dispensing errors. Both use blood endpoints whose clinical-surrogate status is unvalidated.

Brain MRS methods differ in field strength, spectral model, normalization, and ability to distinguish NAD+ from NADH. Cerebral findings are target-engagement signals, not direct measures of every brain region or mitochondrion.

Direct oral NAD+ evidence is especially unstable. The positive study is a preprint of a proprietary formulation, retrospectively registered, short, and industry-linked. The negative cognition report is a conference abstract with limited formulation and biomarker detail. Neither supports a class-level estimate. The IV fate literature is dominated by one 11-person plasma-and-urine pilot without tissue sampling; the tolerability comparison

contains only six NAD+ recipients. No completed human SC NAD+ study was identified, so absence of benefit data cannot be mistaken for a measured null effect.

Safety data are short and underpowered for uncommon events. Absence of a signal in small trials is not proof of long-term safety. Cost was not ranked because audited product potency, price, route burden, and jurisdiction change over time; a scientifically valid cost-effectiveness analysis requires a verified product and a validated benefit endpoint.

20. Conclusions

1. Two 2026 human studies directly compare oral NR and NMN; the earlier claim that no head-to-head research exists is no longer correct.
2. In the larger 65-person trial, repeated oral NR and NMN produced comparable whole-blood NAD+ increases. Simple molar normalization yields nearly identical point estimates.
3. In a six-person crossover PK study, NR produced a larger blood total-NAD response than NMN even after molecular-weight adjustment, while short-stage brain responses did not differ.
4. The conflict supports a practical tie with a provisional NR edge, not a definitive universal winner.
5. NR ranks first for evidence maturity and human cerebral target engagement. NMN has credible blood target engagement and a strong population-specific insulin-sensitivity result. Direct oral NAD+ remains preliminary and formulation-specific.
6. IV NAD+ bypasses the gut but not extracellular metabolism, the plasma membrane, or tissue-delivery barriers. At 750 mg over six hours, it was rapidly removed from the measured plasma pool for at least two hours, later generated plasma metabolites, and increased urinary NAD+ and methyl-nicotinamide.
7. Plasma disappearance does not prove intact cellular delivery, complete excretion, or total inactivity. Efficient intact human target-cell delivery remains unproven; indirect metabolic activity through extracellular cleavage and salvage remains plausible.
8. Commercial IV NAD+ can impose substantial acute tolerability and time burden. One indication-specific heart-failure LVEF signal prevents a categorical claim that IV NAD+ is clinically ineffective in every context.
9. SC NAD+ has no published human PK, intracellular-delivery, efficacy, or completed safety dataset identified through the cutoff. It is unrankable and unsupported for claims of direct or superior cellular delivery.
10. No material is proven superior for longevity, lifespan, or generalized healthspan.
11. A definitive answer requires a blinded, molar-matched oral crossover trial plus a separate isotope-resolved IV/SC mass-balance study with validated blood, tissue, urine, safety, and route-burden endpoints.

The most accurate current verdict is:

> ***Best-supported overall oral research reference: NR. Best-supported administered-dose-normalized oral whole-blood NAD+ target engagement: NR and NMN are effectively tied, with a provisional NR edge. Direct oral NAD+: insufficient comparative evidence. IV NAD+: rapid plasma removal and meaningful route burden, but intact cellular delivery and general efficacy are unproven. SC NAD+: no completed human PK or efficacy basis. Best compound for longevity: unknown.***

21. Claim register

ID	Claim	Class	Evidence	Status
C01	NR and NMN comparably increased baseline whole-blood NAD+ after 14 days	Direct human observation	Christen et al. 2026; PMID 41540253	Supported within tested regimen
C02	Dose-normalized point estimates in the 65-person trial were nearly identical	Derived	Christen et al. 2026 reported effects and mmol/day	Derived comparison only
C03	NR produced a larger blood total-NAD response than NMN through day 8	Direct human observation	Berven et al. 2026; PMID 41858901	Supported but requires replication
C04	NR and NMN did not differ in cerebral total NAD over 8 days	Direct human observation	Berven et al. 2026; PMID 41858901	Uncertain rather than equivalent
C05	Repeated oral precursor use may require approximately 2 weeks for blood NAD plateau	Direct human observation	Berven et al. 2026; PMID 41858901	Supported as design principle
C06	Oral NR raises the human blood NAD metabolome dose dependently	Direct human observation	Trammell 2016; Conze 2019	Supported
C07	Blood target engagement does not guarantee muscle mitochondrial benefit	Direct human observation	Dollerup 2018/2020; Remie 2020	Supported
C08	Oral NR can alter a human cerebral NAD-related signal	Direct human observation	Brakedal 2022; Nanga 2024; Berven 2026	Supported for target engagement
C09	Short-term oral NR is generally tolerated at studied doses	Direct human observation	Martens 2018; Conze 2019; Dollerup 2018; Berven 2023	Supported within studied bounds
C10	Repeated oral NMN raises blood NAD-related measures	Direct human observation	Okabe 2022; Igarashi 2022; Yi 2023; Christen 2026	Supported
C11	NMN improved clamp-measured muscle insulin sensitivity in a defined population	Direct human observation	Yoshino et al. 2021; PMID 33888596	Supported only for population and endpoint
C12	NMN clinical effects are heterogeneous and often secondary	Direct human observation	Liao 2021; Kim 2022; Katayoshi 2023; Morifuji 2024	Hypothesis-generating
C13	Short-term oral NMN is generally tolerated in studied adults	Direct human observation	Fukamizu 2022; Yi 2023; Okabe 2022	Supported within studied bounds
C14	Oral NR and NMN can contribute to NAD through microbial deamidation and nicotinic acid pathways	Mechanistic inference supported by tracing	Shats 2020; Chellappa 2022; Kim 2023; Yaku 2025; Christen 2026	Supported mechanism with human quantitation gap
C15	SLC12A8 is the dominant intact oral NMN transporter in adult humans	Mechanistic claim	Grozio et al. 2019	Unknown

ID	Claim	Class	Evidence	Status
C16	Extracellular NMN can be converted to NR and used through NRK1	Mechanistic observation	Ratajczak et al. 2016; PMID 27725675	Supported mechanism
C17	SLC25A51 transports intact NAD into mammalian mitochondria	Established mechanism	Luongo 2020; Kory 2020	Supported
C18	A proprietary oral NAD formulation increased intracellular whole-blood NAD after 5 days	Preprint human observation	Kornilov et al. 2026; doi 10.64898/2026.03.25.714130	Preliminary
C19	Oral NAD improved cognition more than placebo	Conference abstract human observation	Tavares and Tsotsoros 2025	Not supported
C20	IV NAD is rapidly removed from the measured plasma pool at the studied rate	Direct human PK observation	Grant et al. 2019; PMID 31572171	Supported only for measured plasma fate
C21	Short-course IV NAD produced an LVEF signal in ischemic cardiomyopathy	Direct human clinical observation	Yu et al. 2026; PMID 40954388	Preliminary indication-specific signal
C22	IV NAD has route-specific tolerability and sterile-compounding burdens	Human observation and official guidance	Reyna et al. 2026; FDA sterile compounding notice	Supported route boundary
C23	NR NMN or direct NAD extends human lifespan	Clinical claim	No qualifying primary human trial identified	Unknown not supported
C24	NR is the best-supported oral reference for the next definitive trial	Decision inference	Integrated evidence map	Reasoned conclusion
C25	NR and NMN are effectively tied for the best larger-trial oral blood endpoint with a provisional NR edge	Decision inference	Christen 2026 plus Berven 2026	Reasoned conclusion
C26	Rapid IV NAD plasma disappearance proves intact cellular delivery	Translational inference	Grant et al. 2019	Not supported
C27	Rapid IV NAD plasma disappearance proves complete immediate renal excretion	Mass-balance inference	Grant et al. 2019	Not supported
C28	Injected NAD cannot become metabolically or biologically active	Absolute mechanistic claim	Kulikova 2019; Bruzzone 2001; Song 2011; Roh 2018; Gerth 2004; Adriouch 2007	Contradicted as an absolute claim
C29	Efficient intact NAD delivery into human target-cell cytosol after IV or SC dosing is established	Human delivery claim	No qualifying isotope-resolved human tissue study identified	Not established

ID	Claim	Class	Evidence	Status
C30	SC NAD has demonstrated human PK intracellular delivery or efficacy	Route claim	ClinicalTrials.gov NCT06919328; literature search through 2026-08-07	Not supported
C31	SC NAD is proven ineffective	Route efficacy claim	No completed published human dataset identified	Unknown
C32	Commercial-rate IV NAD can impose substantial acute symptom and time burden	Human observation	Reyna et al. 2026; PMID 41704678	Supported within setting
C33	NCT06919328 will determine intact NAD absorption or intracellular delivery	Registry interpretation	ClinicalTrials.gov NCT06919328	Not supported
C34	Injectable NAD has no documented material-quality safety signal	Regulatory safety	FDA sterile-compounding notice 2024	Contradicted
C35	CD73 directly cleaves extracellular NAD as a general human pathway	Mechanistic claim	Wilk 2020; Horenstein 2013	Not supported as a general claim
C36	Every older adult can be classified as NAD deficient using a validated universal threshold	Clinical measurement claim	Evidence-gap assessment across human matrices and assays	Not supported
C37	Change per administered mmol per day is equivalent to pharmacologic efficiency	Methods claim	Derived-normalization analysis	Contradicted

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Revision 4 change log and supersession

Revision 4 supersedes Revision 3 for interpretation while preserving Revisions 1 through 3 unchanged. It adds the DRPS-1.0 result-direction contract, a six-direction evidence-balance dashboard, a canonical 22-field evidence register, a reproducible search log, and platform-compatible publication metadata. A bounded confirmatory update on 7 August 2026 rechecked PubMed and ClinicalTrials.gov for head-to-head NR/NMN, oral and parenteral NAD+, and injectable-route studies. The positive IV heart-failure result remains included; the injectable NR-versus-NAD+ registry remained without posted results; and no new evidence changed the conditional ranking or conclusions.

Publication note

This manuscript is structured for Defiance publication intake. It remains a preprint and has not been independently peer reviewed. A signed publication receipt, if later issued by the platform, would verify release provenance and integrity, not scientific validity, efficacy, safety, or suitability for human use.

Declarations

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Author contributions: Kamil Khoury conceived the research question, defined the evidence architecture, adjudicated the comparative claims, and approved the publication candidate. Literature retrieval, structured extraction, calculations, and document production used computational research assistance under author direction and were manually reviewed against the cited records.

Ethics: This work is a secondary synthesis of published and publicly registered evidence. It enrolled no participants, collected no identifiable private data, and required no new human-subject intervention.

Data and code availability: The publication package includes the authoring manuscript, a claim-level evidence register, a release manifest with SHA-256 hashes, and a text-extractable PDF. No participant-level dataset was created. Derived calculations are stated in the manuscript and evidence register.

Acknowledgment: The author acknowledges the investigators and participants whose primary studies made this comparison possible. Inclusion of a study does not imply endorsement of its intervention or conclusions.