BALANCE PROTOCOL INSTITUTE | POSITION PAPER

# NAD and GLP-1 Therapy

What the Evidence Supports, What It Does Not, and the Cost Nobody Measures

*Your doctor prescribed the medication. Nobody prescribed the rest.*

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### Position in brief

NAD biology is real and the age-related decline is real. The commercial promise built on top of that biology has outrun the human evidence.

Across randomized trials, NAD precursors reliably raise a blood marker. They have not reliably changed clinical outcomes.

Raising a level is not a benefit. Nutrient response depends on where a person started: correction helps the deficient, does little for the sufficient, and imposes clearance load on the replete. Large randomized trials have shown this repeatedly, and in at least one the same supplement harmed one baseline stratum while sparing another.

**No NAD precursor trial has ever stratified participants by baseline NAD status, because that status is not routinely measured. A category that has never established who is deficient is selling repletion to everyone.**

**Clearing surplus nicotinamide consumes methyl groups and generates an inhibitory byproduct. GLP-1 therapy independently raises methylation demand while reducing dietary methyl donor intake. Stacking the two without measuring methylation capacity is the specific hazard this paper addresses.**

Balance Protocol Institute sells no NAD, no NMN, no nicotinamide riboside, no supplements of any kind, and earns nothing from any product named in this document.

The decision belongs to you and your prescriber. The case for measuring before and during is difficult to argue against.

## 1. Why This Paper Exists

The person on GLP-1 therapy has become one of the most heavily marketed-to patients in metabolic medicine. Within weeks of the first injection, the offers arrive: NAD added to the compounded vial, an intravenous NAD drip billed as cellular restoration, a longevity stack promising to protect the mitochondria the diet is supposedly starving. The pitch is nearly always the same shape. Your medication is doing something to your cells. This molecule will fix it.

The prescriber prescribed a medication. The prescriber did not prescribe the drip, the stack, or the compounded adjuvant. That is not a failure of the prescriber. It is a structural gap in how metabolic care is delivered: the medication is supervised, and everything downstream of it is sold. This paper addresses one molecule in that gap, and it addresses it the same way we would address any other, by asking what the human evidence actually shows and what the intervention costs the system it enters.

Nothing here is a recommendation to start or stop any medication, and nothing here modifies prescribing. This is an evidence appraisal and a measurement argument.

## 2. Where We Stand, Stated Before Any Evidence Claim

In a category where the party describing the deficiency almost always sells the repletion, disclosure has to come before analysis. Otherwise the reader is asked to weigh an argument without knowing who benefits from the conclusion.

- Balance Protocol Institute does not sell NAD, NMN, nicotinamide riboside, niacin, or any supplement.
- We hold no affiliate relationships, no dispensary, and no pharmacy referral revenue.
- We are not a prescriber and we do not dispense. Independent physicians handle all prescribing.
- We earn nothing whether you take NAD precursors or never touch them.

What we do is measure and interpret. That is the entire commercial relationship, and it is why the analysis below can afford to be inconvenient in either direction.

## 3. The Kernel That Is True

Every durable piece of health marketing is built on a true kernel. Dismissing the kernel is the fastest way to lose a reader who has already felt the pull of the claim, and in this case dismissing it would also be wrong.

Nicotinamide adenine dinucleotide is the central redox cofactor of intermediary metabolism. It carries electrons through glycolysis, beta-oxidation, and the tricarboxylic acid cycle into oxidative phosphorylation. Beyond that redox role, NAD is a consumed substrate, not merely a recycled cofactor: the sirtuin deacylases, the PARP family of DNA repair enzymes, the ectoenzyme CD38, and SARM1 all cleave NAD stoichiometrically. Cellular NAD is therefore a budget, not a constant, and it is spent by exactly the processes that increase with age, inflammation, and DNA damage.

Tissue NAD declines with age across multiple preclinical models, and NAD-consuming enzyme activity rises in parallel. The interest in this biology is entirely reasonable. Anyone who dismisses NAD wholesale as pseudoscience is overcorrecting and is wrong.

Hold that concession firmly, because everything that follows is about what was built on top of it.

## 4. The Distortion Chain

Trace the argument as it is actually delivered to a patient, one link at a time.

| Link | The claim | Status |
|---|---|---|
| 1 | NAD declines with age and metabolic stress | Supported in preclinical models; human tissue data are thinner than the marketing implies |
| 2 | Low NAD correlates with metabolic dysfunction | Associative, and confounded by the diseases that consume NAD |
| 3 | Repleting NAD improves the phenotype in rodents | Broadly supported in rodents |
| 4 | Oral precursors raise blood NAD in humans | Well supported and reproducible |
| 5 | Therefore you will be healthier, younger, more energetic | Not in evidence |

The chain does not break at link 1, 2, 3, or 4. It breaks between link 4 and link 5, which is the only link the patient is actually buying.

Section 5 examines why link 4 cannot carry link 5 even in principle, because a level that rose tells you nothing about whether the person needed it to rise.

There is a second break that receives almost no attention. Whole blood NAD is not tissue NAD. In a placebo-controlled crossover trial in men aged seventy to eighty, nicotinamide riboside at one gram daily raised the skeletal muscle NAD metabolome, and muscle mitochondrial bioenergetics did not change. The marker moved. The machine did not. That single result is the cleanest available refutation of the assumption that raising a measured NAD species is equivalent to raising mitochondrial capacity.

If you have never tested your NAD levels or functional biomarkers related to it BEFORE taking NAD (or any other added nutrient), you have absolutely no idea if you were deficient, sufficient or in surplus in the first place.

## 5. The Repletion Fallacy: Why Raising a Level Is Not a Benefit

### 5.1 Grant the premise completely

Concede, without reservation, that oral NMN and nicotinamide riboside raise blood NAD. It is the most reproducible finding in the entire literature and there is no reason to contest it. The question that decides everything is the one that is never asked at the point of sale: **raised from what, and toward what?**

A level is not an outcome. The sentence it raises NAD is a statement about a number. It carries no information about whether this person was short of NAD, whether the tissue that needed it received any, or whether the increase was useful once it arrived. Those are three separate questions with three separate burdens of proof, and the mechanism story answers none of them.

### 5.2 The dose response curve is not a straight line

Underneath nearly every supplement pitch sits an unstated assumption: that the relationship between an input and a benefit is monotonic. If some is good, more is better, and considerably more

is considerably better. For essential nutrients and cofactors this is almost never true. The observed relationship is a curve with three regions, and only the first one behaves the way the marketing describes.

| Repletion state | What additional intake actually does |
|---|---|
| Deficient | Correction produces real and sometimes dramatic benefit. This is the region where every mechanism story originates, and it is the region almost no supplement buyer has been shown to occupy |
| Sufficient | The curve flattens. Additional intake produces additional excretion and additional clearance work, and very little else |
| Surplus | The curve bends downward. **The input now imposes load on the systems that transport, use, clear, and dispose of it, and it can suppress the very process it was sold to support** |

Nutritional biochemistry has understood this for decades. The retail supplement category is built on the pretense that the first region extends indefinitely to the right.

## 5.3 The precedent is large, randomized, and consistent

This is not a theoretical objection. It is the repeated, expensive finding of some of the largest nutrient trials ever conducted, in which a plausible mechanism, a real molecule, and a well-designed trial produced no benefit or produced harm, because the people being supplemented were not short of the thing being supplied. *(re-read that again and make sure you understand)*

| Nutrient | Trial | What happened |
|---|---|---|
| **Beta-carotene** | ATBC (1994) and CARET (1996) | Lung cancer incidence rose in supplemented smokers. The mechanism was plausible, the direction of effect reversed |
| **Vitamin E** | SELECT (2011) | A 17 percent increase in prostate cancer incidence among relatively healthy men who had no evidence of deficiency |
| **Selenium** | SELECT (2014 analysis) | Selenium supplementation increased high-grade prostate cancer risk specifically among men already in the highest baseline selenium tertile. Vitamin E increased risk specifically among men with low baseline selenium |
| **Folic acid** | AFPPS (2007) | One milligram daily did not reduce adenoma recurrence and was associated with higher risks of advanced lesions, of three or more adenomas, and of noncolorectal cancers |
| **Vitamin C and E** | Ristow (2009) | Antioxidant supplementation abolished the insulin-sensitizing effect of four weeks of exercise training. The supplement suppressed the system it was sold to support |
| **Nicotinic acid** | HPS2-THRIVE (2014) | Lipid surrogates moved favorably, no vascular benefit appeared, and adverse events increased, including disturbance of diabetes control |

Two caveats, because a paper that names Certainty Inflation as a pattern cannot practice it. The folic acid trial did not find statistically significant effect modification by baseline plasma folate in its primary report; the sufficiency reading rests on secondary analyses and on the fact that the population was already folate fortified. The exercise finding is contested, and other groups have not reproduced the blunting effect. Neither caveat disturbs the general claim, which is that the direction of a nutrient's effect depends on the recipient's starting position, and that this has now been demonstrated repeatedly in randomized trials enrolling tens of thousands of people.

SELECT deserves particular attention, because it is the cleanest instance available anywhere in nutritional medicine. The same supplement, at the same dose, inside the same trial, was associated with harm in one baseline stratum and not in another, and the two nutrients tested harmed opposite strata. Nothing about the molecules changed. What changed was who was swallowing them. That is the whole argument, and it took 35,533 men to establish it.

## 5.4 Why surplus is never free, and why NAD in particular is certainly not

**Surplus nicotinamide is not stored against future need.** There is no NAD reservoir that the body fills and later draws down at leisure. **Surplus is disposed of, and disposal is enzymatic work performed at a price.**

- The price is a methyl group, taken from S-adenosylmethionine by NNMT, and a molecule of S-adenosylhomocysteine generated at the same instant. The clearance reaction is itself the load, and it falls on the pathway examined in Section 8.
- NAD is consumed by CD38, by the PARP family, and by the sirtuins, all of which are regulated enzymes rather than passive sinks. Handing more substrate to a regulated enzyme does not reliably increase useful output. It increases turnover, and turnover is not the same thing as function.
- NAD is simultaneously a substrate and a signal. The ratio of NAD to NADH is a readout the cell uses to sense its own energetic state. **Flooding a signaling molecule is not equivalent to fueling it, and it can blunt the signal it was meant to strengthen.**

The exercise antioxidant trial is the most instructive parallel available. Reactive oxygen species generated during training are not merely damage to be neutralized; they are the signal that instructs the muscle to adapt. Supplementing antioxidants suppressed the signal, and the adaptation did not occur. The supplement worked exactly as advertised at the level of the molecule, and it defeated the outcome the buyer wanted. This is what it looks like to put biochemical pressure on the very system that uses the molecule.

So for the person who is already sufficient, the shape of the NAD trade is this: no reproducible clinical gain, a measurable methyl expenditure, an unknown long-term consequence, and a real price paid to remove what was never needed. ***(This is the vast majority of GLP-1 users)***

## 5.5 Mechanism Transfer, named

Here is the move, stated as it is actually performed on the patient.

1. The seller describes what the molecule does in biology. Every individual statement is true. NAD does carry electrons. Sirtuins do depend on it. NAD does decline with age.

2. The listener is invited to infer that these properties will be conferred upon them by the acts of purchasing and consuming.
3. The bridge that would license that inference, namely evidence that this particular person is short of NAD and that repleting them produces the described benefit, is never built. It is not even mentioned, because mentioning it would require a measurement, and the measurement might return a number that ends the sale.

The molecule's resume is not your diagnosis. An accurate description of what a nutrient does inside a functioning cell is not evidence that you are short of it, and it is certainly not evidence that adding more will make the cell do that thing harder.

This is the fallacy the entire NAD retail category rests upon, and it explains something that would otherwise be puzzling: how a category can absorb a decade of null trials without losing a single customer. The trials tested whether the molecule makes people better. The pitch never actually claimed that it did. The pitch recited biochemistry, accurately, and left the listener to finish the sentence. A claim that was never made cannot be falsified.

## 5.6 What the NAD trials themselves hint, and what they cannot settle

There is a suggestive pattern in the data already reviewed. The single positive NMN trial enrolled postmenopausal women with prediabetes, a population with a plausible reason to be metabolically constrained. The pooled null results are drawn substantially from relatively healthy adults. A repletion-dependent response would look precisely like that.

State the limits with precision. Nicotinamide riboside was also null in obese, insulin-resistant men, who are not a healthy population, which does not fit the pattern cleanly, although NR and NMN differ in cellular uptake and metabolism and may not be interchangeable. More importantly, and this is the finding that should end the conversation for any careful reader: no NAD precursor trial has stratified participants by baseline NAD status, because baseline NAD status is not routinely measured. The trial that would directly test the repletion hypothesis has never been run.

That is not a defense of the supplement. It is an indictment of how it is sold. A category that has never established who is actually deficient is selling repletion to everyone.

## 5.7 The missing exit

Ask someone taking NAD precursors when they intend to stop, and what result would tell them to. In nearly every case there is no answer, and the absence is structural rather than careless. No entry criterion was ever established, so no exit criterion can exist. There was no baseline, so there can be no endpoint. The intake is open-ended by construction, which is convenient for exactly one party to the transaction.

**An input with no stopping rule is not a protocol and it is not a therapy. It is a subscription. And an open-ended, methyl-consuming subscription, taken by a patient in sustained caloric deficit whose methyl donor intake has fallen along with their food intake, is the precise configuration this paper exists to flag.**

**The three questions the mechanism story never answers**

Do I actually have too little of this molecule, and how would either of us know?

If I take it, what does my body spend to dispose of what it did not need?

What result would tell me to stop?

## 6. What the Human Trials Actually Show

The table below states each claim at the grade the human evidence supports, not at the grade the label implies.

| Claim | Human evidence | Grade |
|---|---|---|
| **Oral NMN or NR raises blood NAD** | Meta-analysis of 12 randomized trials (513 participants) found a significant elevation in blood NAD | Well supported |
| **NMN improves glucose and lipid metabolism** | Two independent meta-analyses (8 and 12 trials) found no significant effect on fasting glucose, fasting insulin, HbA1c, HOMA-IR, or lipid fractions | Not supported |
| **NMN improves muscle insulin sensitivity** | One randomized trial, 25 postmenopausal women with prediabetes, 250 mg daily for 10 weeks, clamp-measured muscle insulin sensitivity improved. Not replicated | Preliminary, single trial |
| **NR improves insulin sensitivity** | 12 weeks at 2,000 mg daily in obese insulin-resistant men produced no improvement in insulin sensitivity or whole-body glucose metabolism | Not supported |
| **NR improves muscle mitochondrial function** | Muscle NAD metabolome rose; mitochondrial bioenergetics unchanged | Not supported |
| **Intravenous NAD raises intracellular NAD** | Never demonstrated in humans. The only human pharmacokinetic study found infused NAD was rapidly and completely cleared from plasma | Not demonstrated |
| **Any NAD strategy extends human healthspan or lifespan** | No trial has tested this endpoint | No evidence |
| **Safety beyond roughly 12 weeks of use** | Human data do not exist at any dose | Unknown |

Two features of that evidence base deserve emphasis, because they are what a careful reader would check first.

Risk of bias is not incidental. In the twelve-trial meta-analysis, formal RoB2 assessment raised concerns in seven trials and rated five at high risk of bias. The authors state plainly that the benefits

of NMN supplementation may be exaggerated in the field. That is the assessment of the investigators who pooled the data, not the assessment of a skeptic writing from outside it.

The one positive human signal is real and should be reported as such. The 2021 trial in postmenopausal women with prediabetes used a hyperinsulinemic-euglycemic clamp, which is the reference method, not a convenience surrogate, and it found improved skeletal muscle insulin sensitivity. It enrolled twenty-five participants, ran ten weeks, and has not been replicated. Treat it as a hypothesis worth testing in a properly powered trial, not as a reason to start injecting.

> **The pattern that matters**
>
> NAD precursors have a reproducible effect on the thing that is easy to measure and no reproducible effect on the things patients actually care about. That is the signature of a surrogate marker being sold as an outcome.

## 7. Four Delivery Routes, Audited Separately

Patients on GLP-1 therapy are offered NAD by four different routes. The marketing treats them as interchangeable. Pharmacologically they are not, and the safety questions differ at each.

| Route | What human evidence supports | Principal concern |
|---|---|---|
| **Oral NMN or NR** | Raises blood NAD; no reproducible clinical outcome benefit | Methyl consumption during clearance; product quality; unknown long-term safety |
| **Nicotinic acid and nicotinamide** | Cheap, raises NAD; nicotinic acid is the only B3 vitamer with large cardiovascular outcome trials, and both were null | Glycemic disturbance at pharmacologic dose; flushing; hepatotoxicity at high dose |
| **Intravenous NAD** | No demonstrated intracellular delivery; no outcome trials | Extracellular degradation; measurable methyl loss; proinflammatory potential of extracellular NAD; cost |
| **NAD co-formulated into compounded GLP-1** | None. No trial has evaluated this combination | Dose frequently undisclosed; the two agents cannot be stopped independently; no safety evaluation exists |

### 7.1 Oral precursors: NMN and nicotinamide riboside

These are the best-studied route and therefore the route where the negative results are most credible. They raise blood NAD dependably. In pooled analysis they do not move fasting glucose, insulin, HbA1c, insulin resistance indices, or any lipid fraction. A single clamp study in a narrowly defined population found a muscle insulin sensitivity benefit that no one has yet reproduced. Adverse events in trials up to twelve weeks have been unremarkable. Beyond twelve weeks, no one knows, because no one has looked.

## 7.2 The cheap vitamers, and the outcome trials nobody quotes

Nicotinic acid and nicotinamide are inexpensive, widely available, and may raise NAD. Nicotinic acid is also the only member of the B3 family that has been tested in large cardiovascular outcome trials, and this is where the field should be paying attention.

AIM-HIGH randomized patients on intensive statin therapy to extended-release niacin and found no incremental clinical benefit. HPS2-THRIVE randomized 25,673 high-risk patients to extended-release niacin with laropiprant for roughly four years, found no significant reduction in major vascular events, and found an excess of serious adverse events, including disturbances in diabetes control and a higher rate of new-onset diabetes.

State the limitation of this evidence honestly, because it is frequently overstated in both directions. Nicotinic acid's lipid effects are mediated substantially through GPR109A signaling and DGAT2 inhibition rather than through NAD repletion, so the failure of niacin outcome trials does not directly refute NMN or NR efficacy. Those are different molecules acting through partly different mechanisms.

What HPS2-THRIVE does establish is narrower and still important. A B3 vitamer, given at pharmacologic dose to a large population over years, moved lipid surrogates in the desired direction, failed to produce the promised clinical benefit, and specifically worsened glycemic control. The population on GLP-1 therapy is a metabolic population. A precedent in which a B3 vitamer disturbs diabetes control at scale is not a footnote for this audience.

## 7.3 Intravenous NAD: the mechanism does not survive contact with the pharmacokinetics

The drip clinic argument is intuitive. Put NAD directly into the bloodstream and bypass the digestive tract, and the cell gets NAD. Intuition is doing all the work here, because the only human pharmacokinetic study of directly infused NAD found something else.

In healthy male participants receiving a six-hour infusion at 3 micromol per minute, no rise in plasma NAD or in its metabolites, including nicotinamide, methylnicotinamide, ADP-ribose, or NMN, was detected for the first two hours. The infused NAD was rapidly and completely removed from plasma. The metabolite profile the investigators observed was consistent with NAD glycohydrolase and NAD pyrophosphatase activity, meaning the molecule was being cleaved apart in the extracellular space rather than taken up intact.

This is the expected result on first principles. NAD is a large, negatively charged dinucleotide. It does not cross the plasma membrane. Ectoenzymes including CD38 and CD73 hydrolyze extracellular NAD to mononucleotides and then to nucleosides and free bases, and it is those smaller species that enter the cell through specific transporters. The person paying for a two-hour NAD infusion is, at considerable expense and with a needle in the arm, receiving nicotinamide.

There is a second finding in that study that almost no one discusses, and it is the hinge of this entire paper. Urinary excretion of methylnicotinamide rose during the infusion. Methylnicotinamide does not appear out of nowhere. Every molecule of it excreted cost the body one methyl group. The methyl sink is not a theoretical concern that clinicians have inferred. It has been observed in human urine during NAD administration.

One further consideration: extracellular NAD functions as a damage-associated molecular signal, released by injured cells to alert the immune system, with proinflammatory potential at high concentration. Deliberately establishing high extracellular NAD concentrations for hours is not an obviously inert act, and it has not been studied for outcomes.

### 7.4 NAD compounded into the GLP-1 vial

This is the route we take the hardest line on, and the reasoning is not primarily about NAD.

- **No randomized trial has evaluated a GLP-1 receptor agonist co-formulated with NAD precursors, for efficacy or for safety.** The combination exists because it is convenient to manufacture and easy to sell, not because a clinical rationale was established.
- The dose is frequently undisclosed. You cannot evaluate what you cannot measure, and a compounding pharmacy unwilling to state the exact milligram content of every adjuvant is telling you something about the operation.
- **Co-formulation removes the patient's ability to stop one agent without stopping the other.** If symptoms emerge, the medication and the adjuvant cannot be separated, and the medication almost always takes the blame.
- The methylation load of the adjuvant is added to the methylation load of the therapy, in a patient whose methyl donor intake has fallen because they are eating less. See Section 8.

This route has no defensible version. There is no baseline read that makes an undisclosed dose acceptable.

## 8. The Methyl Sink: The Problem Specific to This Patient

Everything to this point applies to anyone considering NAD. This section is why the GLP-1 patient is a different case, and it is the argument you will not find in the marketing.

### 8.1 The biochemistry, stated exactly

Surplus nicotinamide is cleared in large part by nicotinamide N-methyltransferase. The reaction is straightforward: nicotinamide plus S-adenosylmethionine yields 1-methylnicotinamide plus S-adenosylhomocysteine.

Two things are spent, not one. The obvious cost is the methyl group taken from SAM. The less obvious and arguably more consequential cost is the S-adenosylhomocysteine that is produced. SAH is a product inhibitor of most SAM-dependent methyltransferases, and the ratio of SAM to SAH is the cell's functional methylation index. Loading the NNMT reaction therefore does not merely draw down the methyl supply; it simultaneously generates the metabolite that inhibits the enzymes competing for that supply. SAH is subsequently hydrolyzed to homocysteine and adenosine, which is why sustained methyl demand can surface as a rising homocysteine before the patient reports anything at all.

### 8.2 What else is claiming the same methyl pool

The SAM pool is not a dedicated nicotinamide clearance fund. It is a shared account with large standing obligations:

- Creatine synthesis via guanidinoacetate methyltransferase, quantitatively the largest single consumer of methyl groups in the body.
- Phosphatidylcholine synthesis via PEMT, which consumes three methyl groups per molecule.

- Catecholamine clearance via catechol-O-methyltransferase, which governs dopamine and norepinephrine turnover.
- DNA and histone methylation, the substrate of gene regulation.
- Phase II hepatic conjugation, and melatonin synthesis via acetylserotonin O-methyltransferase.

## 8.3 Now layer GLP-1 therapy on top

Three things happen concurrently in a patient in sustained caloric deficit on GLP-1 therapy, and they compound.

**Demand rises.** Mobilization of stored lipophilic compounds from adipose tissue during fat loss raises hepatic conjugation load, and several conjugation routes draw on the one-carbon economy. Neurotransmitter turnover shifts. Tissue remodeling raises DNA methylation demand.

**Supply falls.** This is the point most consistently missed. The patient is eating substantially less, and methyl donors and one-carbon cofactors arrive in food: folate, B12, B6, riboflavin, betaine, choline, and methionine. Reduced intake reduces the supply of the exact cofactors the pathway depends on, at the moment demand is rising.

**A methyl-consuming load is then added.** The NAD precursor, oral or injected or compounded into the vial, enters a system with rising demand and falling supply, and enters it without anyone having measured the balance.

> **The trap, stated plainly**
>
> If the methyl budget is overdrawn, the predicted phenotype is fatigue, cognitive dulling, flattened or labile mood, and a rising homocysteine.
>
> These are precisely the symptoms that patients and prescribers attribute to the GLP-1 medication itself.
>
> The adjuvant escapes suspicion because nobody measured the pathway it was drawing from. The medication takes the blame for a cost the supplement imposed.

## 8.4 Why this is individual, not universal

Methylation capacity is not uniform across patients, which is exactly why it must be read rather than assumed. Common variation in MTHFR affects generation of 5-methyltetrahydrofolate. Variants in MTR and MTRR affect homocysteine remethylation. COMT genotype shifts catecholamine methylation demand. PEMT variation shifts phosphatidylcholine synthesis burden.

None of this is deterministic, and genotype without functional biochemistry is close to useless. But none of it is on the supplement label either, and a patient with constrained methylation capacity is the last person who should absorb a large unmonitored methyl-consuming load. The only way to know which patient you are dealing with is to look.

## 8.5 The honest grade of this argument

This paper criticizes certainty inflation, so it will not commit it here.

- Established: NNMT clears nicotinamide by consuming SAM and generating SAH. This is textbook enzymology, not conjecture.

- Demonstrated in humans: methylnicotinamide excretion rises during NAD administration, which means methyl groups are being spent.
- Plausible and mechanistically grounded: chronic high-dose NAD precursor loading, in a patient with reduced methyl donor intake and rising methylation demand, can meaningfully draw down methylation capacity.
- Not demonstrated: that clinically meaningful methyl depletion occurs at commonly used precursor doses in humans. No controlled trial has measured SAM to SAH ratios, homocysteine trajectories, or symptom outcomes in GLP-1 patients taking NAD precursors. Nobody has run that study.

So the claim being made here is precise. This is not a proven harm. It is a mechanistically grounded, partially observed cost, running through a pathway that is already under load in this specific population, that nobody is measuring and that the seller has no incentive to raise. The correct response to that situation is not prohibition. It is measurement.

# 9. The Unsettled Safety Questions

## 9.1 Proliferation: the evidence points both ways

NAD is a permissive substrate for PARP-mediated DNA repair and for sirtuin signaling. Both pathways are routinely co-opted by malignant cells. That is a legitimate mechanistic basis for asking the question, and the preclinical literature answers it inconsistently.

A 2022 study using a bioluminescent nicotinamide riboside uptake probe reported a marked increase in brain metastases in a triple-negative breast cancer mouse model given NR. A 2023 study reported the opposite direction in hepatocellular carcinoma, where NR supplementation suppressed metastasis, reduced allograft tumor size, and extended survival in mice.

The correct reading is not that NAD precursors cause cancer, and it is not that they are safe in cancer. It is that the effect appears to be context dependent, varying by tumor type and model, and that no randomized human data exist in either direction. Anyone who tells you NAD precursors are proven safe in malignancy is exceeding the evidence. So is anyone who tells you they are proven dangerous. In active malignancy or a history of malignancy, this decision belongs with the treating oncologist, not with a drip bar.

## 9.2 Renal signal, flagged and not asserted

A 2024 preprint reported that metabolite accumulation from oral NMN drove aging-specific kidney inflammation in mice. It is a preprint. It is preclinical. It has not been replicated in humans. It is listed here because a position paper that only cites the preclinical work supporting its own thesis is doing the thing it claims to oppose. Treat it as a question worth watching, not a finding.

## 9.3 Product quality

Independent testing of NMN products has repeatedly found label-claim failures. This is a category where the same milligram figure on two bottles does not mean the same milligram entered the patient. Where a product is worth taking at all, third-party certificate of analysis is the minimum, and it does not resolve the questions raised above; it merely establishes that the substance is present.

## 10. Regulatory Reality, Because Patients Hear Two Wrong Things

Patients arrive believing either that NMN is banned or that it is approved. Both are wrong, and the record moved recently enough that even attentive clinicians have it out of date.

| When | What happened | What it means |
|---|---|---|
| **November 2022** | FDA excluded NMN from the dietary supplement definition under the drug preclusion clause, following an investigational new drug authorization for a crystalline NMN drug candidate | A market eligibility ruling, not a safety finding |
| **September 29, 2025** | FDA reversed, concluding NMN is not excluded because it had been marketed as a supplement in the United States before drug authorization | A statutory interpretation decision. Not a finding of efficacy. Not a finding of safety |
| **December 2025** | FDA issued letters reinstating prior new dietary ingredient acknowledgements | NMN remains a new dietary ingredient requiring premarket notification |

The operative facts for a patient: no NAD, NMN, or nicotinamide riboside product is approved by FDA to treat, prevent, or mitigate any disease. Intravenous NAD is not an approved drug for any indication. A regulatory decision that a substance may lawfully be sold as a supplement says nothing whatsoever about whether it works.

## 11. Naming the Patterns

The NAD pitch is not unusual. It runs on the same six moves every well-constructed health claim runs on, and naming them is more durable protection than memorizing any single rebuttal.

| Pattern | How it appears in the NAD pitch |
|---|---|
| Complexity Collapse | The entire cellular energy economy is reduced to a single lever. Add the molecule, the system improves |
| Certainty Inflation | A surrogate marker that rose becomes restored cellular energy, reversed aging, and protected mitochondria |
| Biomarker Bypass | No baseline is taken, nothing is re-measured, and no result could ever prove the intervention did nothing |
| Solution Funnel | The party who names the deficiency sells the repletion, and often compounds it into the medication so it cannot be declined |
| Authority Costume | A white coat at the infusion bar, a prestigious institutional name invoked, a rodent study cited as though it were a human trial |
| Contrarian Authority | Conventional medicine will not tell you about this, which reframes the absence of evidence as suppression |

| Pattern | How it appears in the NAD pitch |
|---|---|
| Repletion Fallacy | The benefit is presented as independent of how much you already have. The dose response curve is drawn as a straight line that never bends |
| Mechanism Transfer | What the molecule does inside a cell is described accurately, and the listener is left to infer, unaided, that it will do that for them |
| No Stopping Rule | No entry criterion was set, so no exit criterion can exist. No result could ever indicate that it is time to stop |

## 12. The Path That Actually Answers the Question

Balance Protocol is a systems biology framework: context first, objective biomarkers before inputs, order of operations respected, and interpretation individualized to the person in front of you rather than to the population mean. Applied to NAD, that framework produces four steps rather than a purchase.

| Step | The question it answers | Applied to NAD on GLP-1 therapy |
|---|---|---|
| **Qualify** | Is there a plausible reason to think this system is constrained in this person? | Symptom pattern, history, exposure, intake, medication and adjuvant inventory, including anything compounded into the vial |
| **Quantify** | How constrained, and where exactly? | Functional read of energy pathway flux: organic acid markers reflecting the citric acid cycle, beta-oxidation, and B-vitamin cofactor adequacy |
| **Measure** | What is the methyl budget before anything is spent from it? | One-time methylation genomics, plus functional methylation biochemistry including homocysteine, with folate and B12 status characterized |
| **Monitor** | Did the intervention do anything, and at what cost? | Repeat the functional read on a defined schedule. An input with no follow-up read is a purchase, not a protocol |

### 12.1 Five domains that NAD strategies press on, all of them readable

This is what converts the argument from commentary into something actionable. The molecules in this conversation press on five functional domains, and each one can be read.

| Functional domain | Why NAD strategies touch it | What a functional read surfaces |
|---|---|---|
| **Mitochondrial** | NAD is the redox currency of the citric acid cycle and fatty acid oxidation | Organic acid markers of cycle flux, beta-oxidation, and B-vitamin cofactor adequacy: the engine read |

| Functional domain | Why NAD strategies touch it | What a functional read surfaces |
|---|---|---|
| **Oxidative stress** | Greater flux generates reactive oxygen species, and defenses must keep pace | Oxidative load markers and the trace element status the antioxidant enzymes depend on |
| **Methylation** | NNMT clearance of surplus nicotinamide consumes SAM and generates SAH | Methylation genomics once, plus functional methylation markers, so the budget is visible before it is spent |
| **Membrane and fatty acid status** | Inner membrane composition, cardiolipin included, shapes electron transport | Red blood cell fatty acid composition: the membrane the machinery is embedded in |
| **Toxic exposure** | Toxic elements inhibit the very enzymes the energy system relies on | Toxic element screen, so demand is not driven onto a burdened system unknowingly |

The GPS assessment reads these domains through the NutraCoreX functional panel, a functional and nutritional assessment of more than 150 biomarkers including a one-time methylation genomics read. It is a functional panel used for education and interpretation. It is not a diagnostic device and it is not FDA approved. What it does is make the methyl budget, the mitochondrial read, and the cofactor status visible before a methyl-consuming input is added to a system already under load.

## 13. Decision Framework

### Default position

Do not add NAD, NMN, nicotinamide riboside, or intravenous NAD alongside GLP-1 therapy without a baseline read of methylation capacity and energy pathway status.

The rationale for pairing these two things is commercial, not clinical. The human outcome evidence does not support the promise, and the methylation trade is unfavorable in a patient whose methyl donor intake has fallen with their food intake.

### Conditional acceptance

A documented indication rather than a marketing rationale.

Methylation capacity characterized, genomically and functionally, and homocysteine within a healthy reference range.

One-carbon cofactor status characterized and repleted first: folate, B12, B6, riboflavin, choline and betaine intake accounted for.

Dose disclosed in milligrams, product third-party verified, taken separately from the medication so either can be stopped independently.

Prescriber informed and in agreement, and a re-measurement scheduled before the first dose is taken.

This is not the typical patient. It is a small minority of them.

**Never acceptable**

NAD precursors compounded into a GLP-1 formulation, particularly where the adjuvant dose is not disclosed in writing.

Active malignancy, or a history of malignancy, without explicit sign-off from the treating oncologist.

Any program that cannot tell you the dose, will not take a baseline, and has no plan to re-measure.

Any recommendation from a party whose revenue depends on your yes and who has not disclosed that fact.

## 14. Closing Position

NAD is not a scam per se. The biology is real, the decline is real, the enzymology is elegant, and the molecule deserves serious scientific attention. It is receiving that attention, and the trials are coming back mostly null.

What does not deserve serious attention is the assumption that a molecule's biography is a patient's prescription. The properties of NAD are not transferred to you by purchase. If you are replete, more is not better, and the surplus is not stored; it is dismantled, at a cost charged to the methylation pathway that a person on GLP-1 therapy can least afford to overdraw.

What does not deserve serious attention is the leap from a surrogate marker that moved to an outcome that was promised, sold to a patient already carrying a methylation load nobody measured, by a party whose revenue depends on the answer being yes, through a route with no human pharmacokinetic support, at a dose that is sometimes not disclosed, with no plan to check whether it worked.

The stack assumes the tank is full and the oil is clean. It never checks. It just adds boost.

**Measure first. Stack second, if at all.**

**Where to take this next**

The NutraCoreX assessment reads the five domains described in Section 12, including a one-time methylation genomics read and functional methylation biochemistry, so the methyl budget is visible before anything is spent from it.

Beyond the Scale, the 818-page clinical reference underlying this paper, treats compounded GLP-1 adjuvants in depth, including NAD precursors, cyanocobalamin, and pyridoxine, with the biochemistry and the decision criteria in full.

Balance Protocol Institute sells no supplements, holds no affiliate relationships, and earns nothing from any product named in this document. That is the point.

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## Disclosure and scope

This document is educational and is not medical advice. It does not diagnose, treat, or prescribe, and it is not a substitute for the relationship between a patient and the prescriber who manages their GLP-1 therapy. No content here constitutes guidance on initiating, adjusting, or discontinuing any prescription medication.

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The NutraCoreX panel is a functional and nutritional assessment used for education and interpretation. It is not a diagnostic device and it is not FDA approved.