BeyondMold

POSITION PAPER

PRECISION MEDICINE · CDR / ISRMT FRAMEWORK

Precision Versus the Average

How a one-size protocol and an omics-guided, terrain-matched model of the Cell Danger Response diverge — read through the single lens of Number Needed to Treat.

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01 — THE REGRESSION

A framework that began precise, and a product that flattened it

CIRS, as originally conceived, was an attempt at biomarker-guided medicine. It carried HLA risk typing, a panel of inflammatory and neuroregulatory markers, and a sequenced protocol meant to be read off what each patient's labs showed. Whatever its limits, the intent was stratification: measure, then follow the sequence the measurements imply.

Its commercial descendant — call it the condensed three-medication protocol — has, in the act of scaling, regressed toward the very thing functional medicine was founded to escape: a standard medical model. One diagnosis (biotoxin illness), one assumed mechanism, one protocol, delivered to every patient as though the underlying biology were identical in all of them. It is allopathic averaging wearing an integrative label.

The problem is not that the protocol is wrong. It is that it is uniform — and the disease is not.

02 — CIRS AS A SPECIAL CASE

A pioneering map of one country, in an age that has charted the continent

Twenty years ago, CIRS was a real advance. When mainstream medicine still waved away water-damaged-building patients as anxious or deconditioned, Shoemaker's framework took them seriously: it named an environmental cause, proposed measurable biomarkers, articulated an innate-immune and neuroregulatory mechanism, and offered a sequenced, falsifiable protocol. For its moment, that was progressive science — and the patients it helped were real.

But what CIRS described was a special, limited case. It captured one trigger class — biotoxins from water-damaged buildings — and one slice of the downstream biology, then reified that slice as a discrete syndrome with its own name. The deeper phenomenon it had glimpsed was never specific to mold at all.

The science has since moved ahead. The same patients are now recognized as instances of a universal, evolutionarily conserved program — the Cell Danger Response (Naviaux, 2014–2019) — governed at the mitochondrion by the integrated stress response, the OMA1–DELE1–HRI axis and eIF2α/ATF4 signaling characterized around 2020, and now readable through transcriptomics and the ISRmt-native mitokines GDF15 and FGF21.

The CDR is trigger-agnostic: biotoxins, chronic infection, dietary and metabolic load, and psychological–autonomic stress all converge on the same checkpoint and produce overlapping phenotypes.

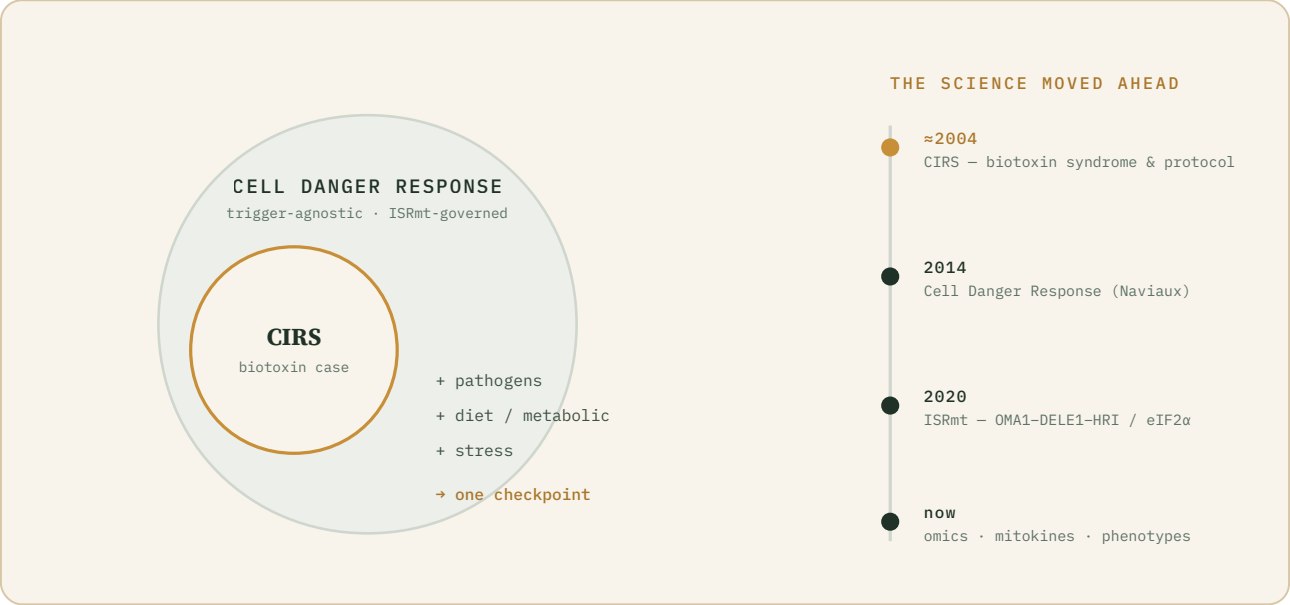

FIGURE 1. CIRS is one trigger-case nested inside the general program. The CDR is what the same checkpoint produces across many triggers; CIRS is what it looks like when the trigger is a water-damaged building and the readout is the marker set CIRS chose to measure.

The map contained one country. The new science drew the continent — and located that country within it.

This is no insult to the original work; it is how science is supposed to behave. Every framework is eventually subsumed by a more general one, and being right for 2004 is not the same as being right today. The CDR model does not discard CIRS — it explains why CIRS worked when it worked, why it fails for the patients it never fit, and why a framework built around a single trigger cannot, on its own, deliver complete healing across a multi-trigger disease.

Mistaking the special case for the general law is the root error from which the rest follows: the high NNT, the partial responses, and the relapses anatomized below.

03 — THE INSTRUMENT

What Number Needed to Treat actually measures

Number Needed to Treat is the count of patients who must receive a therapy for one additional patient to benefit beyond what the comparator would have produced. Formally, NNT = 1 / ARR, the reciprocal of the

absolute risk reduction. An NNT of 1 is the ideal — every treated patient benefits. The larger the number, the more people are treated for each one helped.

The number's quiet flaw is that it is a population average, and an average hides its distribution. An NNT of eight is equally compatible with "a weak effect in everyone" and with "a near-cure in one patient and nothing in the other seven." The arithmetic cannot distinguish the two.

An NNT of eight can mean a near-cure in one patient and nothing in seven. The arithmetic cannot tell them apart — but the clinic can, because the seven keep coming back.

04 — WHY ONE PROTOCOL EARNS A HIGH NNT

The terrain is not uniform, so the average fits almost no one

Chronic, CDR-driven multisystem illness is not a single terrain. The same stalled Cell Danger Response presents as at least four distinct phenotypes — the stuck alarm, the drained battery, the worn-out defender, and the closed gate — each with a different dominant biology, a different rate-limiting lesion, and a different final push needed to complete recovery. They are not four diseases; they are four points at which the same recovery can stall.

A single fixed sequence is, by construction, matched to the average patient — in practice, to whichever phenotype the protocol's implicit mechanism happens to fit. The patients whose terrain matches that assumption respond. The rest get partial response, a plateau, or relapse, and are then relabeled "complex" or "refractory." The model's NNT is high not because its interventions are useless, but because most patients are being handed an intervention aimed at someone else's biology.

05 — THE MECHANISM OF IMPROVEMENT

Precision lowers NNT toward one

The single move that lowers NNT is enrichment: identify, before treating, the subgroup whose biology a given treatment actually fits, and give each subgroup the therapy its terrain calls for. This is the entire logic of stratified medicine. The textbook case is oncology — an unselected agent may post a discouraging NNT across all comers, yet within the biomarker-defined responder group the same agent approaches a one-to-one benefit.

The precision CDR model does this with omics and phenotyping: transcriptomic signatures, the ISRmt-native mitokines (GDF15, FGF21), the paired reading of residual alarm against emerging reserve, and assignment to one of the four phenotypes locate the individual on the CDR arc and route them to the matched arm. Within a correctly identified stratum the responder fraction rises, the absolute risk reduction rises with it, and NNT falls toward one. The asymptote — every treated patient helped — is the direction of travel, not a destination anyone should claim to have already reached.

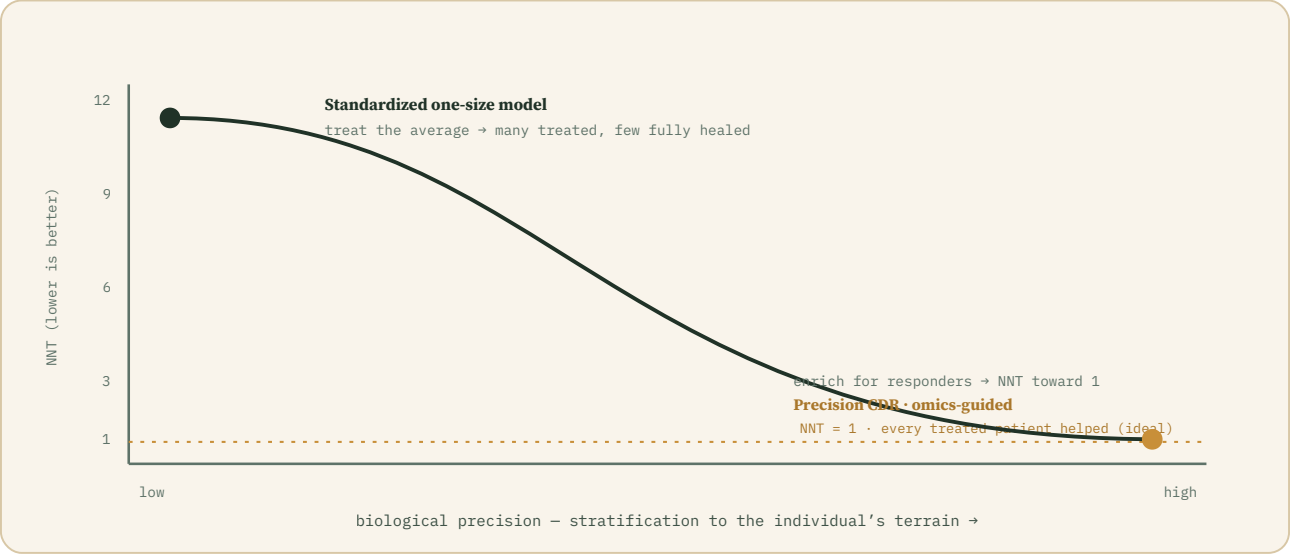

FIGURE 2. As stratification matches treatment to terrain, the responder fraction rises and NNT descends toward its floor of one. The descent is conditional on the stratifiers being biologically valid — an invalid marker buys complexity and cost without moving NNT.

> **The honesty clause.** This advantage is conditional, not automatic. It holds only insofar as the stratifiers are biologically valid and genuinely predictive of response. That is precisely why the markers must be CDR-native and mechanism-linked rather than borrowed and correlational — and why, in this model, a non-response is read as information that re-stratifies the patient, not as a treatment failure to be waited out.

06 — THE WRONG FINISH LINE

Two things averaging cannot deliver: complete healing and robustness

Even where the standardized model helps, it aims at the wrong finish line. Its endpoint is symptom and inflammation reduction — resolution, partially achieved. But resolution is only half of recovery. A patient whose

inflammation falls while their reserve is never rebuilt sits at a fragile partial remission: the alarm is quieter, but the system is still one bad exposure from re-entry.

The standardized protocol has no fortification phase. It does not confirm the completion of CDR3 — the genuine all-clear — and it does not build the mitochondrial, redox, and autonomic reserve that makes a recovery durable. It can quiet the alarm; it cannot raise the baseline. The precision model treats complete healing (the resolved CDR3 state) and robustness (mitohormetic fortification above the prior baseline) as explicit, separate endpoints — which is the reason its successes hold rather than relapse.

07 — THE FAIR CASE FOR THE OTHER SIDE

What standardization gets right — and why it still loses here

Standardization has real virtues, and they should be stated plainly. A fixed protocol scales; it is teachable and reproducible; it is cheaper per patient; it spares clinicians decision fatigue and reduces idiosyncratic error. For a homogeneous disease with one mechanism, the average is the right answer, and added precision is wasted motion and wasted money.

The argument here is therefore narrow and strictly biological. CDR-driven multisystem illness is heterogeneous in mechanism — so the population average is the wrong answer for most individuals, and the cost of getting it wrong (years of partial response, plateau, and relapse) dwarfs the up-front cost of learning the terrain. Where the biology is uniform, standardize. Where it is not, standardizing is simply choosing a high NNT on purpose.

Dimension	Standardized 3-medication protocol	Precision CDR / ISRmt model
Model of biology	One shared mechanism, assumed identical in all patients	Heterogeneous terrain; four phenotypes read from the individual
Assessment	Syndrome label + fixed marker checklist	Omics + phenotyping + paired alarm/reserve staging
Treatment assignment	The same sequence for everyone	Matched to stage, phenotype, and dominant pathway
Implicit NNT logic	Treat the average → many treated, few fully helped (high NNT)	Enrich for responders → NNT toward 1, stratum by stratum
Primary endpoint	Symptom & inflammation reduction (partial resolution)	Complete healing (CDR3) + fortified robustness
Durability	Fragile, relapse-prone — no reserve is built	Reserve raised above prior baseline
Failure mode	Non-responders relabeled “complex / refractory”	Non-response re-stratifies the terrain

CONCLUSION

Two models, one number

The standardized model accepts a high NNT as the price of scale and files the non-responders under "complex." The precision model spends effort up front to learn the terrain, drives NNT toward one a stratum at a time, and refuses to call a patient healed until the alarm is off and the reserve is built.

Precision, in this framing, is not an embellishment layered on top of a protocol. It is the mechanism by which NNT falls, by which healing becomes complete instead of partial, and by which recovery becomes durable instead of provisional. To standardize a heterogeneous disease is to choose a high NNT — and to call the resulting relapses someone else's complexity.

Educational and conceptual; not a substitute for individualized clinical judgment. "Condensed three-medication protocol" denotes a representative standardized commercial model, not a specific named entity.

NNT figures in the diagram are illustrative of the precision–outcome relationship, not measured values; the responder-enrichment benefit is conditional on validated, mechanism-linked stratifiers. The four-phenotype CDR / ISRmt framework and its biomarker assignments are presented as this program's organizing hypotheses.