BeyondMold

CLINICAL MONOGRAPH

DIAGNOSTIC FRAMEWORK · BIOMARKER ANALYSIS

Reclassifying the CIRS Panel Through the Cell Danger Response

Expanded Edition — the panel as a gated, conditional staging instrument, not a flat count

The classic biotoxin markers are not one inflammation panel. Read through Naviaux's healing-cycle model they stratify across three phases of recovery and four clinical phenotypes — and because the phases run in sequence, the markers are not statistically independent: an abnormal alarm-phase reading contaminates the repair-phase readings downstream of it. The panel must be read as a gated, conditional instrument rather than a flat count.

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Diagnostic Framework · Biomarker Analysis

The CIRS laboratory panel, read through the cell danger response, resolves into three sequential phases and four phenotypes. Because the phases run in sequence the markers are conditionally dependent — this edition develops the gated reading protocol that follows.

ABSTRACT

Abstract

The laboratory panel developed for chronic inflammatory response syndrome (CIRS) is conventionally read as a single measure of biotoxin-driven inflammation. This framing obscures what the markers actually report. When each analyte is mapped to its mechanism rather than its diagnostic tradition, the panel resolves into three sequential states of Naviaux's cell danger response (CDR): the innate-immune alarm phase (CDR1), the proliferative repair phase (CDR2), and the differentiation-and-reintegration phase (CDR3).

The first edition of this monograph established that reclassification and mapped the resulting phase structure onto the four phenotypes of the CDR/ISRmt framework — **Stuck Alarm, Drained Battery, Worn-Out Defender,** and **Closed Gate.** This edition addresses the consequence that the phase structure forces but the additive reading conceals: *because the phases occur in sequence, the markers are conditionally dependent.* A marker's meaning is set not by its own value but by the state of the markers upstream of it.

The dependence is **directional**. An active alarm phase degrades the reliability of every repair- and reintegration-phase readout downstream of it, while the reverse contamination is negligible — downstream remodeling markers do not corrupt the alarm reading. Three mechanisms drive this coupling: a shared integrated-stress-response (ISR) transcriptional hub, cellular-population mosaicism within any sample, and metabolic substrate lock. TGF-β1 is the canonical casualty: the same molecule signals active repair or stuck fibrosis depending entirely on the alarm markers surrounding it, and it is partly *generated* by them — MMP-9 proteolytically activates latent TGF-β1.

The practical output is a reading protocol: establish a danger tier from the unambiguous alarm markers first, then interpret the repair and reintegration markers *conditionally on that tier*. This converts the panel from a checklist that counts abnormalities into a staging instrument that reads them in the order the biology produces them — and it clarifies precisely where the Shoemaker construct and the CDR construct diverge as instruments.

Read mechanistically, the biotoxin panel was a cell-danger-response staging instrument all along. Read sequentially, it is also a conditional one — the markers cannot be scored in parallel because the biology does not produce them in parallel.

SECTION 1

A checklist without a cycle

The CIRS case definition asks the clinician to count abnormalities across roughly eight serum markers — TGF-β1, VIP, MSH, MMP-9, C4a, VEGF, ACTH/cortisol, and ADH/osmolality — and to treat their collective derangement as evidence of a single inflammatory state. The construct has clinical utility, but it flattens a crucial distinction: these analytes do not all report the same biology, and they do not move on the same clock.

Some are anaphylatoxins and proteases of the acute innate response. Others are growth factors whose job begins only after the danger is contained. Still others are anti-inflammatory neuropeptides whose release signals that the body is ready to stand down. Counting them together as "inflammation" treats an alarm bell, a construction crew, and an all-clear siren as if they were the same instrument. The information lost is precisely the information a clinician most needs: *where in the arc of recovery is this patient stuck?*

Naviaux's model of the cell danger response supplies the missing scaffold. It reframes chronic illness not as the persistence of a remote trigger but as a healing cycle that has failed to advance through its stages. Laid over that scaffold, the CIRS panel stops being a checklist and becomes a map.

SECTION 2

Three phases, three metabolisms

Naviaux characterizes recovery from any chemical, physical, or biological injury as a sequence of three metabolically distinct phases, gated by quality-control checkpoints and powered by different mitochondrial states.

CDR1 · Containment & Innate Immunity

The alarm phase is devoted to damage control, intruder detection, and clean-up. It runs on glycolysis with pro-inflammatory (M1) mitochondria and high extracellular ATP as the danger signal. Oxygen is diverted from energy production toward oxidative shielding — reactive oxygen species and oxylipin signaling for defense. Gap junctions are lost; the cell goes "offline" from its neighbors to fight.

CDR2 · Proliferation & Biomass Replacement

Once danger is contained, lost cells must be replaced. CDR2 supports stem-cell recruitment and cell division. Its metabolic signature is aerobic glycolysis — the Warburg pattern — and it depends on angiogenesis to vascularize newly proliferating tissue. Growth factors are the effectors of this phase, not the alarm.

CDR3 · Differentiation & Reintegration

CDR3 begins when proliferation stops and recently divided cells differentiate into organ-specific roles. Extracellular ATP falls; anti-inflammatory (M2) mitochondria and oxidative phosphorylation return. Its defining event is the re-establishment of physical, autonomic, and neuroendocrine communication between cells — the gate reopening. Anti-inflammatory neuropeptides are the signals that permit it.

Crucially, the phases are not synchronized across the body: different organs may sit in different phases simultaneously, and a patient's presentation reflects the dominant unresolved phase. **This asynchrony is not a footnote — it is the origin of the conditional-dependence problem developed in Part II.** A blood draw averages over cells at every phase at once.

SECTION 3

Each marker to its mechanism

Marker	What it actually indexes	CDR phase	Phenotype
C4a / C3a	Complement anaphylatoxins; innate-immune alarm signal	CDR1	A · Stuck Alarm
MMP-9	Neutrophil/innate activation and ECM access; bridges toward angiogenesis *and activates latent TGF-β1*	CDR1 → CDR2	A · Stuck Alarm
vWF	Endothelial injury and activation; vascular danger	CDR1	A / B
NLR	Innate skew with relative lymphopenia; alarm-tier gate *and* proxy for suppressed resolution capacity	CDR1	A · Stuck Alarm
VEGF	HIF-1α/hypoxia-driven angiogenesis; vascular biomass repair (bidirectional)	CDR2	B (low = hypoperfusion)
TGF-β1	ECM deposition, fibrosis, Treg/immunosuppression, EMT (Janus)	CDR2 → CDR3	C · Worn-Out Defender
ACTH / cortisol	HPA/allostatic-axis capacity to fund the cycle (now via DUTCH)	reserve	B · Drained Battery
Leptin	Metabolic gating upstream of α-MSH	reserve	B → D
α-MSH	Anti-inflammatory neuropeptide; neuroendocrine reintegration	CDR3	D · Closed Gate
VIP	Parasympathetic/vagal tone; autonomic–neuroendocrine reconnection	CDR3	D · Closed Gate

Marker	What it actually indexes	CDR phase	Phenotype
ADH / osmolality	Downstream hypothalamic–pituitary reintegration readout	CDR3	D · Closed Gate
ACLA / AGA	Loss of immune tolerance; failed CDR3 maturation	CDR3	C / D
MARCoNS / HLA-DR	Perpetuating exposome input / host terrain — not a phase state	terrain	terrain modifier

Phase assignments are inferred from each analyte's mechanism; Naviaux frames phases at the level of mitochondrial states and signaling classes rather than naming individual markers. Two additions to this edition — NLR as a formal alarm-tier gate, and MMP-9's dual role as a TGF-β1 activator — are the pivots on which Part II turns.

SECTION 4

Why sequence makes the markers conditionally dependent

The additive reading assumes the markers are independent — that TGF-β1 means the same thing whether or not C4a is elevated, so their abnormalities can simply be summed. The healing-cycle scaffold makes that assumption untenable. If the phases occur in a fixed order, then a marker reporting a *late* phase is being measured in a body whose *early* phase may still be active, and the early activity bleeds into the late reading.

The critical feature is that this contamination is **not symmetric**. Upstream danger degrades the reliability of downstream recovery markers far more than the reverse. An abnormal CDR1 reading makes a CDR3 readout untrustworthy; an abnormal CDR3 reading does essentially nothing to the CDR1 readout. Alarm markers are therefore the *conditioning variables*, and repair/reintegration markers are the *conditioned variables*. Three distinct mechanisms produce the coupling, and they are worth separating because they call for different mitigations.

MECHANISM 1 · SHARED ISR TRANSCRIPTIONAL HUB

GDF15 and FGF21 — the ISRmt hub markers — and much of the CDR3 "recovery" signaling sit downstream of the same node: eIF2α phosphorylation driving ATF4. ATF4 (with CHOP) transcribes both mitokines and coordinates the broader stress program. If CDR1 is active, the ISR is engaged, and that engagement shows through in anything read as CDR3 remodeling. A recovery marker reading abnormal may simply be the alarm phase's own ATF4 program surfacing in a different assay — classic common-cause confounding. Two markers sharing a transcriptional hub cannot be independent.

MECHANISM 2 · POPULATION MOSAICISM

Naviaux's phases are cell-level and sequential, but a blood or tissue sample is an *average* over cells sitting at CDR1, CDR2, CDR3, and M0 simultaneously. Any CDR3 marker value is really (fraction of cells that reached CDR3) × (per-cell signal). A grossly abnormal CDR1 tells you the mixing fraction is shifted toward the alarm end — so the CDR3 value is a biased estimate of true CDR3 biology, not because the assay failed but because the denominator moved under it.

MECHANISM 3 · SUBSTRATE LOCK

This is the one that reaches the A-vs-B routing fork directly. If CDR1 has forced the glycolytic, oxidized defensive shift, then lactate and the lactate:pyruvate ratio are elevated for reasons intrinsic to CDR1, and spare respiratory capacity (Seahorse SRC) is being measured in a cell still metabolically committed to defense. SRC read under active alarm does not carry the same meaning as SRC read after resolution — the floor is contaminated. An unresolved Phenotype A will therefore masquerade as, or mask, a Phenotype B engine reading. The energetics fork is exactly where cross-talk bites hardest.

Note that the treatment framework already *presupposes* non-independence: "resolve before fortify" and "engine before safety" are gating rules that only make sense if the sequence is real. The gap this edition closes is that the *interpretation* logic must be made conditional in the same way the *protocol* already is. Where the protocol reads markers in series, the panel reading has still been treating them in parallel.

Don't score a recovery marker as valid until the alarm tier is quiescent. Under active danger signaling, a repair reading is indeterminate — not normal, not abnormal, but uninterpretable until the gate clears.

SECTION 5

TGF-β1: the same number, opposite clinical vectors

TGF-β1 is the sharpest possible illustration because its ambiguity is not measurement noise — it is biology. TGF-β1 is genuinely Janus-faced: it drives Th17 skewing, fibrosis, EMT, and immune dysregulation *and* it is the central effector of resolution, Treg induction, and tissue remodeling. Same molecule, opposite meaning, and the sign is set entirely by the state of the markers around it. The legacy panel treats it as a flat "elevated = inflamed" count-toward-case-definition marker — the exact reading that collapses under sequencing.

The mechanism is upstream, not merely correlated

The alarm markers are not just statistically associated with TGF-β1 — they are *mechanistically upstream* of its activation. TGF-β1 is secreted latent, sequestered in the matrix by its latency-associated peptide, and does nothing until an activator liberates it. **MMP-9 is one of those activators:** it proteolytically cleaves latent TGF-β and releases the active cytokine (Yu & Stamenkovic, 2000). The other physiologic activators — integrins, thrombospondin-1, reactive oxygen species, low pH, plasmin — are, notably, all CDR1 conditions (Annes, Munger & Rifkin, 2003).

So high TGF-β1 in the presence of high MMP-9 is partly just MMP-9's downstream footprint. You are not necessarily seeing an independent repair program; you may be seeing the danger machinery generating active TGF-β1 as a byproduct. That is a *mechanistic* reason the CDR1 reading contaminates the CDR2/3 reading, not merely a statistical one.

NLR closes the trap from the other side

High NLR signals innate skew with relative lymphopenia. But TGF-β1's *resolution* arm runs through lymphocytes — specifically through Treg induction. Under active alarm, therefore, TGF-β1 can be elevated while its repair function cannot execute, because the cellular substrate for resolution is suppressed. Elevated ligand, absent effect. That is the whole difference between "repair underway" and "stuck activation," and the TGF-β1 number alone cannot distinguish them. NLR supplies the missing conditioning variable.

The reading resolves once it is gated, not summed

Read conditionally against the alarm tier, the same TGF-β1 elevation splits into two opposite clinical vectors:

One preanalytic caveat compounds all of the above: platelet activation during sample handling releases TGF-β1 and inflates the measured value independent of any of this biology. TGF-β1 should never be read as a standalone number for that reason alone — the conditional logic is a second, deeper reason.

SECTION 6

Which markers reverse sign, and which are stable gates

The conditional-dependence problem does not hit every marker with equal force. Sorting the panel by *how badly the ambiguity bites* is what tells the clinician which markers to trust as gates and which to never read unconditioned.

Marker	Ambiguity class	Reading rule
TGF-β1	**Sign-reversing.** Means opposite things across CDR1/2/3. Maximally conditional.	Never read unconditioned. Gate against MMP-9 / C4a / NLR (see §5).
VEGF	**Sign-reversing.** Low = failed angiogenesis / hypoperfusion; high = active repair drive. Bidirectional.	Interpret direction only after the alarm tier is read. Low-under-hot ≠ low-under-clear.
MMP-9	**Gate-grade.** CDR1-locked; close to unambiguous danger. Its repair role is a bridge, not a reversal.	Use as a *conditioning variable*, not a conditioned one. Anchor the alarm tier here.
C4a / C3a	**Gate-grade.** Anaphylatoxins; stable alarm signal with little downstream contamination.	Second anchor of the alarm tier. Reliable when hot.
NLR	**Gate-grade, dual-duty.** Reports alarm skew *and* proxies suppressed resolution capacity.	Third anchor. Its lymphopenia arm is what makes TGF-β1 legible (§5).
VIP · α-MSH	**Temporally ambiguous.** Directionally stable, but low can mean *never-mounted* vs. *spent-down.*	Not a contamination problem — a history problem. This is the Phenotype D "safety signals spent" question, read against reserve markers.
Mycotoxin burden · ERMI / HERTSMI-2	**Stable anchor.** Upstream of the entire CDR cascade — an input, not a response within it.	The fixed point when every response marker is cross-contaminating. Trust these when the panel is internally incoherent.

The operational takeaway

Define a **CDR1 danger tier** from the three gate-grade alarm markers (MMP-9, C4a, NLR). Make the sign-reversing markers (TGF-β1, VEGF) a gated interpretation against that tier rather than a threshold flag. Read the temporally ambiguous neuropeptides (VIP, α-MSH) against reserve, not against the alarm tier. And when the response markers contradict each other, fall back to the exposure anchors, which cannot be contaminated by the cycle because they precede it.

SECTION 7

Shoemaker and CDR: two grammars for the same analytes

The divergence between the Shoemaker construct and the CDR construct is not a disagreement about which markers matter, nor about the biology of any single analyte. It is a difference in *grammar* — in the logical operation used to combine the markers into a judgment. And that grammatical difference is what determines whether the conditional-dependence problem can even be represented.

The CIRS case definition is, at its core, an **OR-gate over a count**: tally the analytes above threshold, and a sufficient count establishes the case. A parallel additive score of this kind *structurally cannot* encode the statement "TGF-β1 means the opposite thing depending on MMP-9." There is no slot in a count for a conditional. The markers were selected for correlation with illness, not for stage-specificity — so TGF-β1, VEGF, and C4a each carry stage ambiguity that a flat count necessarily erases.

The CDR construct is a **sequential, gated grammar**: it stages the patient within the healing cycle by reading the alarm tier first and conditioning everything downstream on it. This grammar can represent the conditional because it is built from conditionals. It is the same move the treatment protocol already makes with "resolve before fortify," pushed from the intervention layer down into the interpretation layer.

Dimension	Shoemaker / CIRS	CDR / ISRmt
Logical operation	Additive count (OR-gate over thresholds)	Sequential gate (conditional on alarm tier)
Question asked	Is this patient *a case?*	*Where* has recovery stalled?
Marker independence	Assumed — abnormalities are summed	Rejected — upstream conditions downstream
TGF-β1	Counts as inflammation, one flag among many	Sign-reversing; scored only against the gate
Output	Binary label + treatment sequence	Phenotype + phase-matched intervention point
Can represent conditionals?	No — a count has no slot for context	Yes — built from conditionals
Failure mode	Miscounts contaminated markers as independent signal	Requires a defensible alarm-tier definition to gate on

Read this way, the retire-and-reassign decisions of the CDR framework are not relabeling. TGF-β1 and VEGF were removed from the CDR1 alarm reading because they were never CDR1 markers, and they regain diagnostic value precisely as stuck-repair (TGF-β1, Phenotype C) and failed-vascularization (low VEGF, Phenotype B) signals. The legacy panel measured them; it simply misfiled them under inflammation — and, more subtly, read them in a grammar that could not have used them correctly even if they had been filed right.

The CIRS markers are not unreliable in isolation. They are being read with the wrong grammar — summed when they should be gated.

SECTION 8

The reading protocol, and where the evidence stops

The reading protocol in four steps

HONEST EVIDENCE GRADING

The *direction* of contamination is well-grounded on first principles and on established activation biology. MMP-9's proteolytic activation of latent TGF-β1 (Yu & Stamenkovic, 2000), the multiplicity of latent-TGF-β activators that coincide with CDR1 conditions (Annes et al., 2003), and the ATF4-driven induction of GDF15/FGF21 under the ISR are all documented mechanisms. The claim that upstream alarm degrades downstream repair readings follows from them.

What is not yet measured: nobody has published a covariance structure for these markers across CDR stages in a mold-CDR cohort. The *direction* of conditional dependence is defensible; the *quantitative* parameters — how much a given degree of CDR1 abnormality degrades a specific CDR3 marker — are reasoned, not fitted. The gate thresholds in this monograph are therefore conservative interpretive defaults, not empirically derived cutoffs. Stated plainly so the framework does not overclaim: this is a mechanistic reading protocol awaiting a covariance dataset, and gating is the conservative call precisely because that dataset does not yet exist.

A diagnostic construct, distinct from a case definition

The shift is conceptual as much as clinical. A case definition counts abnormalities to assign a label; a CDR diagnostic construct stages a patient within a healing cycle to direct phase-matched intervention. The same analytes, read through a conditional grammar, become a different instrument — one that asks not whether a patient is "a case" but where, mechanistically, their recovery has stalled, and which readings can be trusted to tell you.

The panel did not need new markers. It needed a model that could tell the clinician what the existing markers were already reporting — and a grammar that could read them in the order the biology writes them.

REFERENCES

References

This monograph presents a mechanistic framework for clinical interpretation and is intended for professional and educational use. It is not a substitute for individualized clinical judgment. Phase assignments for individual analytes represent inferences from published mechanism rather than direct phase designations in the cited primary literature. The conditional-dependence structure described in Part II is grounded in established activation biology (refs 4–7); the quantitative gate parameters are conservative interpretive defaults awaiting a marker-covariance dataset in mold-CDR cohorts. Citations marked `verified` *were confirmed against primary sources during preparation of this edition.*

Colophon

This monograph is set in **Source Serif 4** for text and headings and **IBM Plex Mono** for labels, tabular keys, and citation apparatus, in the Beyond Mold house palette of forest green, gold, and cream.

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