BeyondMold

EVIDENCE REVIEW

THE SCIENTIFIC FOUNDATION OF TWO FRAMEWORKS

CIRS & the Cell Danger Response

An Evidence Review — Comparative Assessment of Evidence Quality, Journal Prestige, and Academic Acceptance

The two frameworks are not competing — CIRS is a special case of the CDR — but the evidence tiers are not equivalent, and understanding this distinction is essential for clinicians and patients making treatment decisions.

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The Scientific Foundation of Two Frameworks

A comparative assessment of the CIRS and Cell Danger Response literatures — evidence-tier quality, journal prestige, research-group independence, and mainstream acceptance — using standard evidence-hierarchy frameworks.

ABSTRACT

Abstract

Chronic Inflammatory Response Syndrome (CIRS), as developed by Ritchie Shoemaker, MD, and the Cell Danger Response (CDR) framework, as developed by Robert K. Naviaux, MD, PhD, represent two bodies of research that differ substantially in their evidence base, publishing venues, study design quality, and acceptance within the broader medical and scientific community. This review examines each body of evidence using standard evidence hierarchy frameworks, evaluates the journals in which this research has been published, and assesses the degree to which each framework has achieved independent scientific validation.

Our assessment finds that CIRS research, while clinically valuable and internally consistent, is largely concentrated in lower-tier or specialty journals, heavily authored by a small self-referential research group, and has not yet achieved independent replication in high-impact mainstream journals. The CDR framework, by contrast, is grounded in research published in the Proceedings of the National Academy of Sciences (PNAS), a top-10 global scientific journal, is the work of a professor at the University of California San Diego, and draws on converging evidence from mitochondrial biology, metabolomics, and immunology research groups worldwide. The two frameworks are not competing — CIRS is a special case of the CDR — but the evidence tiers are not equivalent, and understanding this distinction is essential for clinicians and patients making treatment decisions.

SECTION 1

Introduction: Why Evidence Hierarchy Matters

Medicine has developed a hierarchical system for evaluating the strength of scientific evidence. This system — commonly represented as a pyramid from expert opinion at the base to systematic reviews and meta-analyses at the apex — reflects both the internal validity of individual study designs and the capacity for findings to generalize to broader populations. The hierarchy is not a ranking of intelligence or effort; it is a recognition that some study designs are more vulnerable to bias, confounding, and error than others.

In evaluating the scientific foundations of any clinical framework, it is also important to consider:

- Journal tier and impact factor, which reflect the rigor of peer review, the selectivity of the editorial process, and the citation-based influence of published work
- Independence of research groups, since findings confirmed only by the original authors carry substantially less weight than those replicated by independent teams
- Acceptance by mainstream academic institutions, regulatory bodies, and professional societies
- Citation patterns and uptake within the broader scientific community

This review applies these criteria to the CIRS research body and the CDR framework, not to diminish either, but to provide an accurate map of where each sits on the scientific landscape — and to explain why that map matters for treatment decisions.

SECTION 2

Evidence Hierarchy Framework

The most widely used evidence hierarchy in clinical medicine is adapted from the Oxford Centre for Evidence-Based Medicine (OCEBM) and the GRADE framework. For this review, we apply a simplified five-level hierarchy:

Level	Design	Description
I	Systematic review / meta-analysis	Pooled analysis of multiple high-quality RCTs or cohort studies. Highest generalizability. Lowest risk of bias.
II	Randomized controlled trial (RCT)	Prospective, randomized allocation to treatment and control. Double-blind where possible. Gold standard for treatment efficacy.
III	Prospective cohort / controlled trial	Longitudinal observation of defined patient groups with pre-specified outcomes. Can establish association but not causation.
IV	Case series / retrospective analysis	Uncontrolled observations of patients receiving a treatment. Generates hypotheses. Cannot establish efficacy.
V	Expert opinion / consensus / mechanistic	Clinical experience, biological plausibility, theoretical framework. Necessary but lowest evidential weight.

SECTION 3

Assessment of the CIRS Evidence Base

Study Design Profile

The peer-reviewed CIRS literature consists primarily of Level IV and Level V evidence: uncontrolled case series, retrospective analyses, and mechanistic/theoretical publications. The Dooley et al. 2024 systematic review in Annals of Medicine & Surgery — the most comprehensive recent synthesis — identified 13 peer-reviewed articles comprising 14 studies on CIRS treatment. Of these:

- Two were randomized controlled trials (Level II), representing the strongest evidence in the CIRS literature
- The remainder were case series, observational cohorts, and retrospective analyses (Level IV)

- One double-blind, placebo-controlled trial showed treatment outperformed placebo with p=0.012 — a statistically significant finding and the most rigorous single piece of CIRS treatment evidence
- McMahon's 2017 cohort of 1,061 consecutive patients represents the largest published CIRS cohort and achieves Level III-IV status as a large uncontrolled prospective series

The broader CIRS evidence base also includes epidemiological support: Dooley and McMahon's 2020 review found that 112 of 114 epidemiological studies (98.2%) identified adverse health effects from indoor mold and dampness exposure, with statistically significant odds ratios (≥2.0) in 79 studies. This is robust Level III epidemiological evidence for the association between water-damaged buildings and multisystem illness. It is important to note, however, that epidemiological association is distinct from mechanistic causation and does not in itself validate the CIRS diagnostic framework or treatment protocol.

The transcriptomic research by Shoemaker, Ryan, and colleagues — including RNA-Seq analyses showing differential gene expression in CIRS patients and its normalization with treatment — represents genuinely sophisticated molecular biology. This work, published primarily in Medical Research Archives, achieves Level III status as observational molecular research with pre/post comparison designs.

Research Group Independence

One of the most substantive criticisms of the CIRS evidence base — acknowledged even by proponents — is its degree of self-referentiality. The majority of key CIRS publications are authored or co-authored by a small, interconnected group centered on Shoemaker, Ryan, McMahon, and a limited circle of certified practitioners. The Dooley 2024 systematic review notes this pattern, and immunologist Dr. Andrea Love, writing in the Skeptical Inquirer, identified this as a significant limitation, while acknowledging the validity of some underlying observations.

Independent replication — the publication of similar findings by research groups with no affiliation to the Shoemaker research network — is limited in the CIRS-specific literature. This is not unusual for emerging fields, but it does constrain the evidential weight that can be attributed to the overall body of work. By contrast, the epidemiological evidence supporting indoor mold as a health hazard is extensively replicated across independent global research groups.

Journal Tier Assessment

Journal prestige, while imperfect as a measure of individual article quality, reflects the rigor of peer review, the editorial standards applied, and the influence of a publication on subsequent research. The primary journals in which CIRS research has been published include:

Journal	Impact	Tier	Notes
Annals of Medicine & Surgery (Wolters Kluwer / LWW) Medical Research Archives (European Society of Medicine) Internal Medicine Review	Factor IF 1.6 No IF (DORA) Low/ not indexed	Mid-tier Emerging Specialty	Legitimate peer-reviewed LWW journal, PubMed indexed. IF 1.6 places it in the lower-middle tier of general medical journals. Primary venue for Dooley 2024 systematic review. Fully open-access, peer-reviewed, PubMed- indexed. Has explicitly opted out of Impact Factor measurement per DORA declaration. Primary venue for Shoemaker transcriptomic and protocol publications since 2016. Small specialty journal; lower independent peer review visibility; primary early venue for several foundational CIRS papers.
PLOS ONE / Scientific Reports (some related work)	IF 3.7 / 4.6	Mid-tier	Some mold-illness adjacent epidemiological work appears in these broad open-access venues; acceptable but not high-impact.

Journal	Impact	Tier	Notes
Health (SCIRP)	Factor Low	Lower-tier	Open-access publisher Scientific Research Publishing; lower peer review standards; venue for early VIP papers.

On the Medical Research Archives Medical Research Archives has explicitly opted out of the Impact Factor system per the San Francisco Declaration on Research Assessment (DORA). The journal is legitimate and PubMed- indexed, and DORA's principles about IF's limitations are widely accepted. However, the practical consequence for a research field is that its primary publication venue lacks the independent citation- based credibility metric that mainstream medicine uses to assess scientific influence. CIRS clinicians and advocates should understand this distinction when representing the evidence base to skeptical colleagues or payers.

Mainstream Medical Acceptance

CIRS is not recognized as a diagnostic category by the CDC, NIH, WHO, or any major US professional medical society (American College of Physicians, American Academy of Allergy Asthma and Immunology, etc.). This is relevant context for the evidence discussion — not as a definitive judgment of validity, since many legitimate conditions take decades to achieve official recognition — but as an accurate description of where the field stands.

The Government Accountability Office (GAO) has published case documentation supporting the association between water-damaged buildings and multisystem illness, which represents meaningful non- clinical validation of the environmental exposure component. The relationship between indoor mold exposure and adverse health outcomes is accepted by mainstream environmental medicine. What remains unrecognized by mainstream bodies is the CIRS diagnostic framework specifically: the HLA-DR susceptibility model, the specific biomarker panel, and the step-wise Shoemaker Protocol.

It is worth noting that mainstream non-recognition does not imply scientific invalidity. CIRS has documented real phenomena that mainstream medicine had been ignoring. The question addressed in this review is not

whether CIRS is real — it demonstrably is — but how its evidence base compares to the standards of evidence that academic and regulatory medicine apply.

SECTION 4

Assessment of the CDR Evidence Base

Study Design Profile

The CDR framework is grounded in a different kind of evidence from CIRS: less clinically applied but more fundamentally mechanistic, published in higher-tier venues, and supported by a broader and more independent scientific community. The key publications include:

Study / Finding	Evidence	Journal Tier	Study Design	Significance
	Level			
Naviaux 2014: Metabolic features of the CDR Naviaux et al. 2016: Metabolic features of ME/CFS Naviaux 2018: Healing cycle model Naviaux 2019: Incomplete healing and aging Naviaux et al. 2017: Suramin in autism (SAT1) Shoemaker et al. 2024: PD fingerprint in CIRS	III/V II–III IV–V IV–V II III	Top-tier (IF 3.9) Elite (IF 9.1) Top-tier (IF 3.9) Top-tier (IF 3.9) High-tier Mid-tier (MRA)	Review/Mechanistic in Mitochondrion Prospective metabolomics study in PNAS Mechanistic model in Mitochondrion Perspective in Mitochondrion Phase I/II RCT in Annals of Clin Transl Neurology Case-control transcriptomic study	Foundational framework paper defining CDR1/2/3. Mechanistic synthesis of mitochondrial biology, evolutionary biology, and immune signaling. Highly cited; provides biological architecture for CDR. Targeted broad-spectrum metabolomics in ME/CFS patients vs. controls. Published in PNAS — second most cited journal globally. Independent team. Demonstrates CDR metabolic signature in chronic illness cohort. Introduces CDR2/CDR3 staging and the concept of chronic disease as CDR arrest. Provides clinical framework for the healing cycle. Connects CDR arrest to aging mechanisms; foundational for the epigenetic/CDR3 phenotype model. First FDA-approved clinical trial testing CDR-modulating antipurinergic therapy (suramin) in autism. Level II evidence demonstrating CDR-targeted intervention produces measurable clinical change. Identifies Triple Positive transcriptomic fingerprint for pre-prodromal Parkinson's in CIRS patients. CDR- predicted finding. Published

Study / Finding	Evidence	Journal Tier	Study Design	Significance
	Level			
Dooley et al. 2024: CIRS evidence review Dooley & McMahon 2020: Mold literature review	I (review) I (review)	Mid-tier (IF 1.6) Mid-tier	Systematic review in Ann Med Surg Systematic review	in Medical Research Archives. 13 articles, 14 studies. Identifies 2 RCTs. Documents strongest evidence for Shoemaker Protocol efficacy. Published in Annals of Medicine & Surgery. 112/114 studies (98.2%) show adverse health effects from mold exposure. Strong epidemiological evidence base for exposure-illness association.

Journal Tier and Institutional Prestige

The contrast in publication venue between the core CDR framework papers and the core CIRS protocol papers is one of the most significant differences in the evidence profile of the two bodies of work:

Journal	Impact	Tier	Notes
PNAS (Proceedings of the National Academy of Sciences) Mitochondrion (Elsevier) Annals of Clinical and Translational Neurology	Factor IF 9.1 IF 3.9 IF 5.3	Elite (Q1 top 15) High-tier (Q1) High-tier (Q1)	Second most cited scientific journal globally. Top 10 in multidisciplinary sciences. Acceptance rate ~15%. Editorial Board members are National Academy of Sciences members. Venue for Naviaux 2016 ME/CFS metabolomics. The field's primary specialist journal, indexed in all major databases. Founding associate editor: Naviaux. Q1 SJR ranking. Primary venue for CDR framework papers (2014, 2018, 2019, 2020). Wiley / American Neurological Association affiliated. Primary venue for Naviaux suramin RCT (2017).
Nature Reviews Neurology (CDR-adjacent ISRmt work)	IF 53.7	Elite	ISRmt/GDF15/mitochondrial danger signaling increasingly cited in Nature Reviews family journals — evidence of mainstream neuroscience uptake.

Institutional Prestige and Community Acceptance

Robert Naviaux holds a triple appointment (Medicine, Pediatrics, Pathology) at the University of California San Diego School of Medicine, one of the top research universities in the United States. He is the co- founder and former president of the Mitochondrial Medicine Society, a founding associate editor of the journal Mitochondrion, and the recipient of a 2023 United Mitochondrial Disease Foundation research award. His CDR work has been cited in reviews published across major journals in neuroscience, immunology, aging biology, and metabolomics.

The ISRmt (Integrated Stress Response of the mitochondria) concept — central to the CDR2 phase and the Phenotype B and C clinical models — has been independently developed and validated by multiple research groups, including those working on GDF15 and FGF21 as mitokines. These findings are published across high-impact journals including Cell Metabolism, Nature Metabolism, and the Journal of Clinical Investigation, with no connection to the CIRS research community. The convergence of CDR- predicted findings across independent research groups in different disease areas constitutes a form of indirect replication that substantially strengthens the CDR's evidential standing.

The purinergic signaling mechanisms central to the CDR — the role of extracellular ATP as a danger signal, P2X7 receptor biology, and CD39/CD73-mediated adenosine resolution — are established mainstream biology with hundreds of independent publications across inflammation, neuroscience, and immunology. The CDR framework draws on and synthesizes this literature rather than producing it in isolation.

SECTION 5

Comparative Evidence Assessment

The following table provides a direct comparison of the two evidence bodies across key evaluation dimensions:

Dimension	CIRS Research Body	CDR Framework
Highest evidence level achieved	Level II: Two RCTs (one double-blind, placebo-controlled, p=0.012) in biotoxin illness treatment	Level II: FDA-approved Phase I/II RCT of suramin (antipurinergic CDR modulator) in autism; Level III metabolomics cohort study in PNAS
Primary publication venues	Medical Research Archives (no IF, PubMed indexed); Annals of Medicine & Surgery (IF 1.6); Internal Medicine Review (low/specialty tier)	PNAS (IF 9.1, global top 15); Mitochondrion (IF 3.9, Q1); Annals of Clinical and Translational Neurology (IF 5.3, Q1)
Research group independence	Primarily self-referential: most key publications authored by Shoemaker, Ryan, McMahon, and certified practitioners	Broadly distributed: CDR mechanism papers by independent groups across mitochondrial biology, immunology, aging, and neuroscience
Mainstream medical recognition	Not recognized by CDC, NIH, WHO, or major professional societies as a diagnostic category; environmental mold-illness association accepted	CDR-adjacent mechanisms (ISRmt/GDF15, purinergic signaling, SPM resolution biology) are mainstream biology with independent global research communities
Institutional affiliation	Primarily private practice and small clinical groups	UCSD School of Medicine; Mitochondrial and Metabolic Disease Center; National Academy of Sciences affiliations
Citation breadth	Primarily self-citation and citation within CIRS practitioner community	PNAS 2016 paper cited across ME/CFS, long COVID, autism, aging, and environmental health literature by independent researchers

Dimension	CIRS Research Body	CDR Framework
Biological plausibility	High: epidemiological evidence robust (98.2% of 114 studies); transcriptomic findings internally consistent; HLA-DR susceptibility mechanistically coherent	Highest: CDR mechanisms are evolutionarily conserved biology present across all eukaryotic life; independently validated across multiple disease areas and research groups
Treatment evidence	Two RCTs plus extensive case series; protocol shows reproducible outcomes in practitioner community but lacks independent RCT replication	Suramin RCT (CDR modulator) shows proof of concept; broader CDR3 resolution biology (SPMs, exosomes) supported by large independent research bodies

Summary Assessment

CIRS research has achieved Level II evidence for the existence of biotoxin-driven multi-system illness and for the efficacy of the Shoemaker Protocol in a limited RCT context. Its journal venue profile is mid-to-low tier, its research group is substantially self-referential, and it lacks mainstream medical recognition as a diagnostic category. The CDR framework has achieved Level II RCT evidence for CDR-mechanism-targeted intervention and Level III evidence for the CDR metabolic signature in chronic illness, published in elite venues (PNAS, Mitochondrion, Q1 journals), with the underlying mechanisms independently validated by a global research community. These are not competing bodies of evidence — CIRS is a clinical application within the CDR framework — but their evidential standing is not equivalent.

SECTION 6

What the Evidence Hierarchy Does and Does Not Mean

A critical and fair reading of this analysis requires acknowledging several important qualifications:

Lower Evidence Tier Does Not Mean Clinically Invalid

Many important medical interventions have been used effectively for decades without achieving Level I or II evidence — surgical procedures, many psychiatric medications, and nutritional interventions among them. The CIRS protocol has produced meaningful clinical improvement for thousands of patients who had previously been dismissed by mainstream medicine. That clinical reality deserves respect and credit.

The evidence hierarchy is a tool for understanding generalizability and bias risk — not a ranking of clinical value. A Level IV case series showing consistent outcomes in hundreds of patients is clinically meaningful, even if it falls below the gold standard of a blinded RCT. What it cannot do is definitively establish that the observed outcomes are attributable to the specific mechanism proposed rather than to other elements of a complex multi-step protocol.

Mainstream Non-Recognition Is Not Disproof

Many conditions now recognized by mainstream medicine — chronic Lyme disease, fibromyalgia, long COVID — spent years or decades in the liminal space between patient reality and institutional recognition. The CIRS community has good reason to be skeptical of institutional gatekeeping. The fact that the CDC does not recognize CIRS as a diagnostic category does not mean it isn't real. It means the evidence has not yet cleared the bar that mainstream medicine sets for official recognition — a bar that is sometimes too high and sometimes appropriately high, depending on context.

Journal Tier Is a Proxy, Not a Verdict

Publishing in Medical Research Archives rather than PNAS does not mean a paper is wrong. MRA is peer-reviewed, indexed in PubMed, and has published legitimate research. The journal tier difference reflects the rigor of the peer review process, the competitive selectivity of the editorial process, and the citation-based influence of the venue — all real differences, but none of them constitutes proof that the research is invalid. What journal tier does tell you is this: when a body of research is concentrated in lower-tier venues with a self-referential author group, it should be held to higher scrutiny rather than lower, because fewer independent experts have evaluated it. This is not a judgment — it is the appropriate epistemic response to the structure of the evidence.

The CDR's Strength Is Mechanistic, Not Just Clinical

The CDR framework's evidential advantage over CIRS is not primarily that it has more or better clinical trials. It is that the mechanisms it invokes are mainstream biology validated across independent research groups in multiple disease areas. When the same cellular mechanism — ISRmt/GDF15 elevation — is independently identified by research groups studying aging, cancer cachexia, ME/CFS, long COVID, and mitochondrial disease, the evidential weight of that mechanism becomes very high regardless of whether any single clinical trial has tested it in CIRS patients specifically.

This convergence of independent findings is a form of scientific validation that does not appear in evidence hierarchies explicitly, but is widely recognized as one of the strongest forms of evidence for biological mechanism. It is what makes the CDR more than a theory and what makes its application to CIRS and chronic mold illness scientifically credible at a level that the CIRS literature cannot yet achieve on its own.

SECTION 7

Implications for Clinical Practice

This evidence review has direct implications for how clinicians, patients, and institutional stakeholders should approach CIRS and CDR-informed treatment:

1. CIRS is real and clinically important. The epidemiological evidence for water-damaged building-related illness is robust (98.2% of 114 independent studies). The transcriptomic findings are genuine and

reproducible. The HLA-DR susceptibility model is mechanistically coherent. These are not artifacts of poor science.

2. The Shoemaker Protocol is the only published treatment with documented clinical efficacy for CIRS (Dooley et al. 2024). Its evidence base, while limited by tier and research group independence, is real. Two RCTs and a large-scale case series represent a credible evidence foundation for clinical application.
3. The CIRS protocol is not wrong — it is incomplete. Its mechanisms are real but partial. Its protocol addresses CDR1 reduction and attempts CDR3 initiation via VIP, but lacks explicit mechanisms for CDR2 mitochondrial restoration, ISRmt resolution, immune reconstitution, and personalized CDR3 signaling. These gaps are not theoretical — they explain the documented plateau-and-relapse patterns in complex CIRS patients.
4. The CDR framework provides the mechanistic architecture that explains why CIRS works when it works and fails when it fails. Its publication in PNAS, Mitochondrion, and top-tier journals by a UCSD professor with institutional credibility gives it a scientific standing that the CIRS literature has not yet achieved. Clinicians who integrate the CDR framework with the CIRS protocol are building on stronger mechanistic ground, not weaker.
5. Both bodies of evidence would benefit from more independent replication, larger controlled trials, and publication in higher-tier mainstream venues. This is the genuine limitation of both fields and the honest call to future research.

For Patients and Clinicians: The Bottom Line The evidence that mold illness is real is strong. The evidence that the Shoemaker Protocol helps is real but limited in rigor. The CDR framework provides the deeper mechanistic explanation for both. Neither field has achieved the level of evidence that would satisfy a systematic reviewer at NEJM or Lancet — but the CDR's publication venues, institutional affiliations, and independent corroboration place it on substantially stronger scientific ground than the CIRS protocol literature taken alone. A clinical approach that integrates both — using CIRS diagnostics within a CDR mechanistic framework — is the most evidence-coherent option currently available.

SECTION 8

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