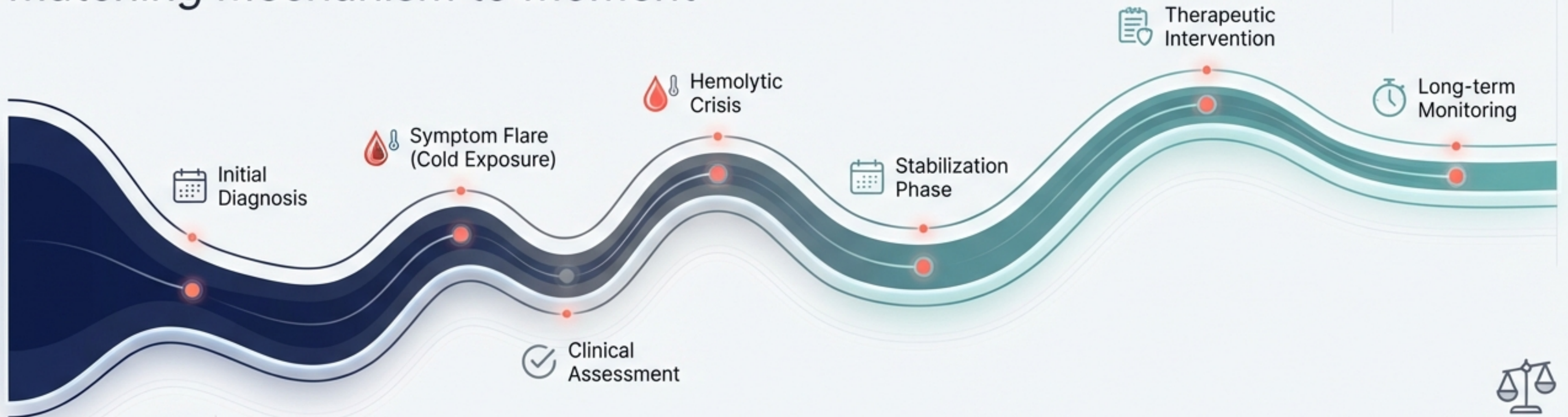


The Dynamic Management of Cold Agglutinin Disease

Matching Mechanism to Moment

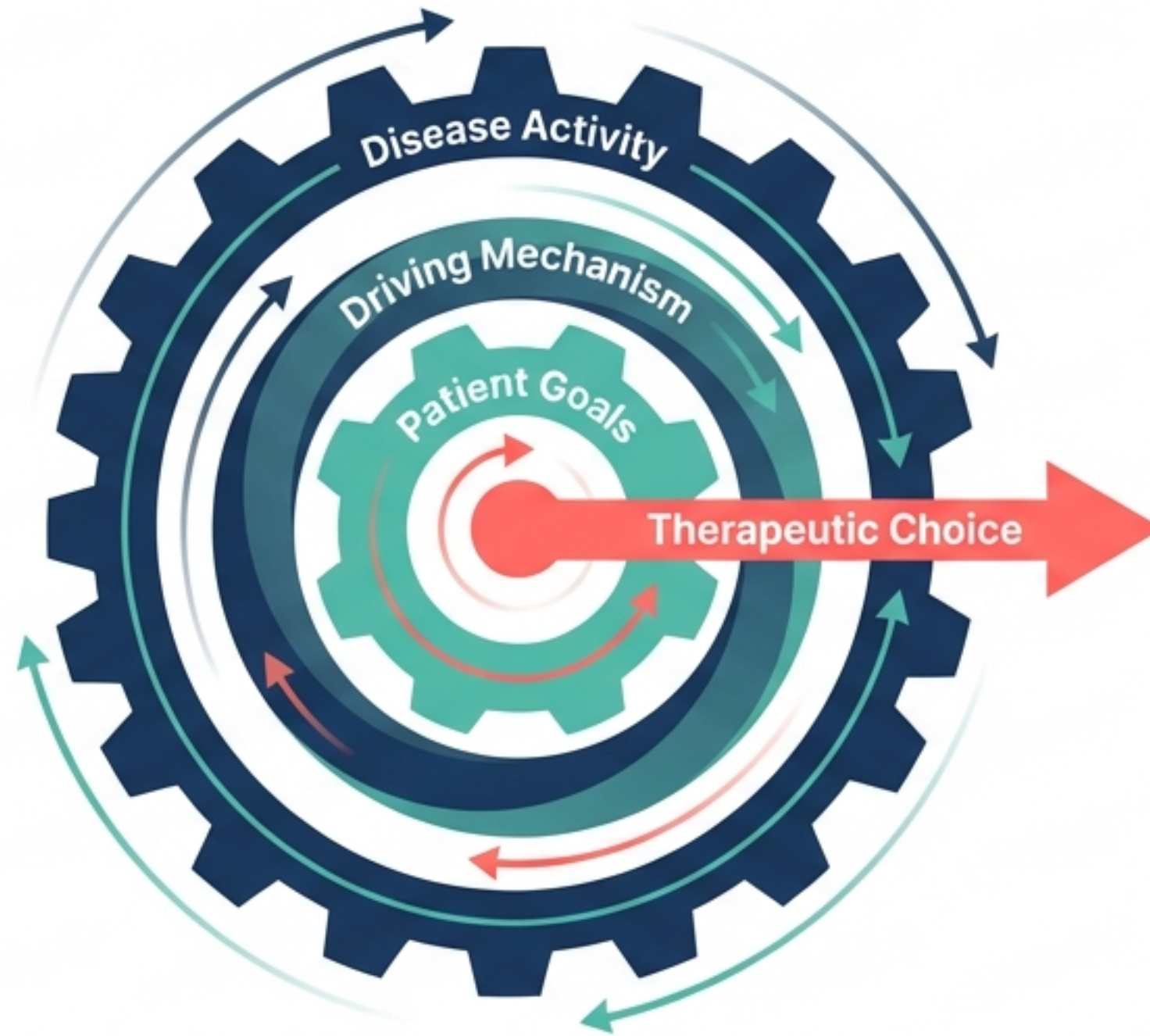


CAD is not managed with a single decision point. It unfolds over time, across changing disease activity, evolving priorities, and shifting risk–benefit balances.

Management requires alignment, not a fixed ladder





The Static Treatment Algorithm



Orbital Alignment

- There is **no fixed** treatment ladder in CAD.
- The 'right' therapy is **time-dependent**, not diagnosis-dependent.
- **A strategy appropriate at one point may become inappropriate later.**

Select the clinical question before selecting the drug

| | Clinical Question | Strategic Tool |
|--------------------------------|-----------------------------------|--|
| Active Hemolysis / Symptomatic | How do we achieve rapid control? | Complement Inhibition  |
| Stable / Tolerable | Can we modify the disease course? | Clone-Directed Therapy  |

Low Impact / Mild Anemia

Observation & Supportive Care



This framing avoids false competition between therapies. It emphasizes purpose.

In mild disease, treatment risk often exceeds disease burden

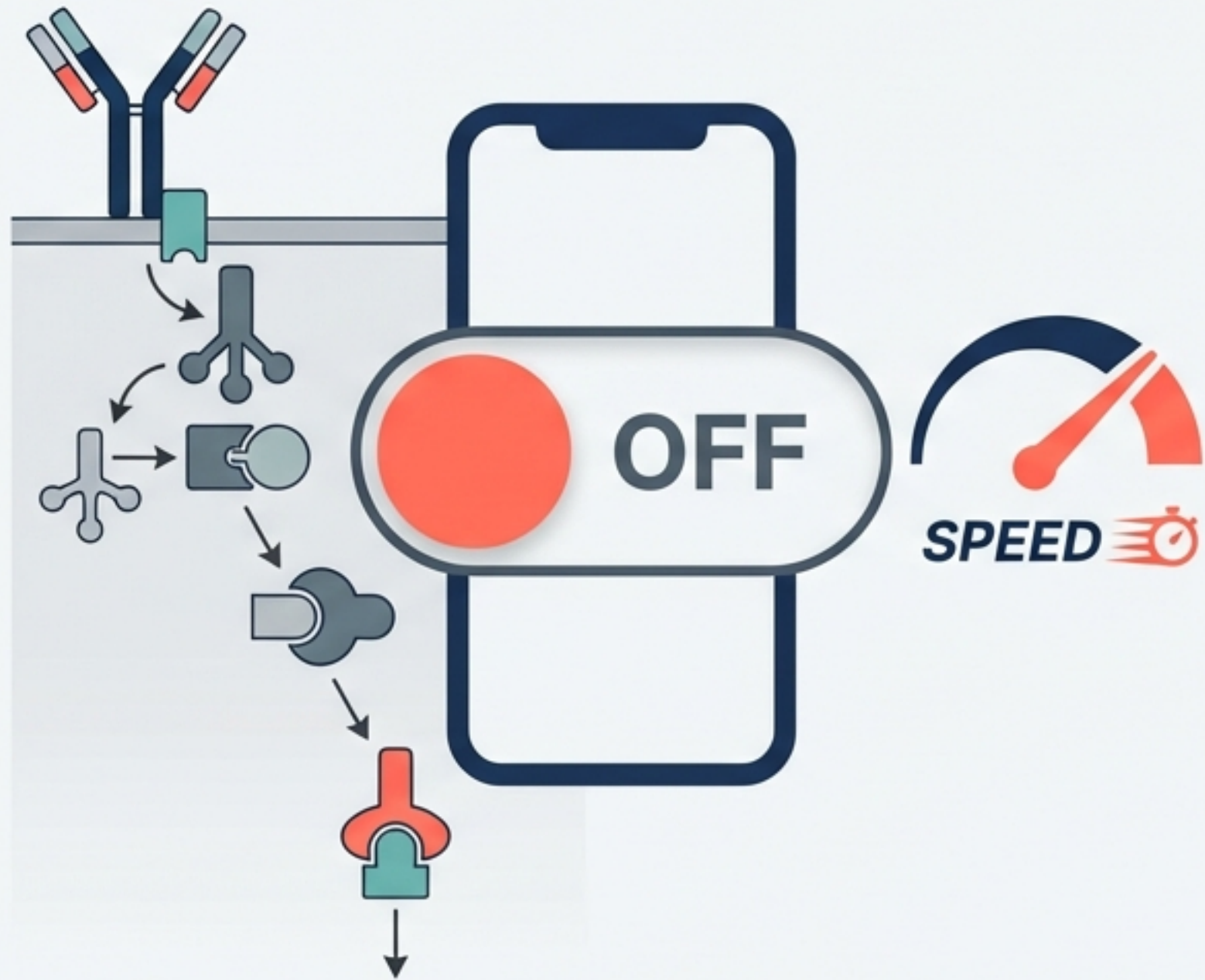


- ✓ Cold avoidance
- ✓ Treatment of precipitating infections
- ✓ Active monitoring (not passive neglect)

Key Insight

Supportive strategies remain sufficient when hemolysis is stable and symptoms are minimal. In these patients, the underlying clone may remain biologically stable for years.

Complement-directed therapy is a switch for rapid control



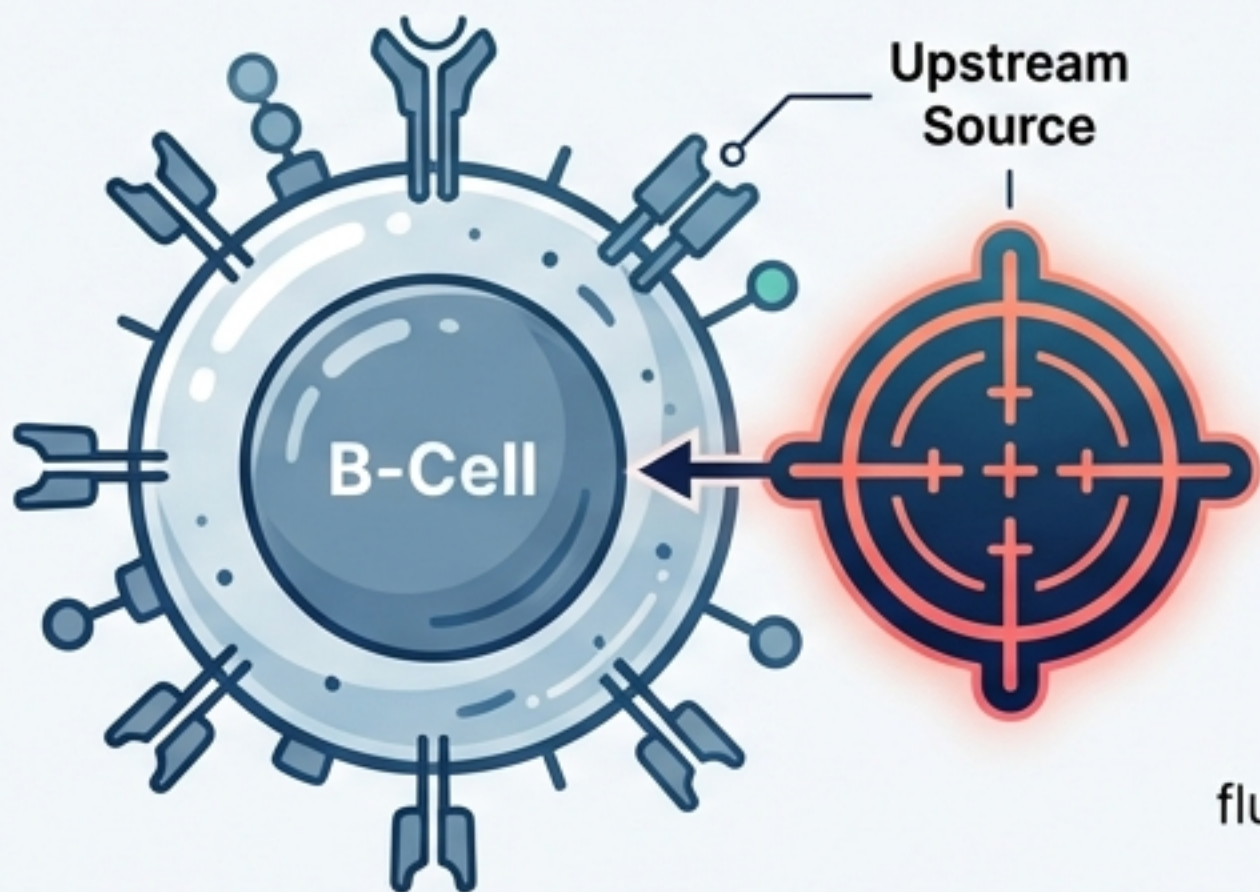
Mechanism & Role

- **Target:** Complement activation (central effector of hemolysis)
- **Role:** First-line for active hemolysis, bridging, or exacerbations

Profile

- **Strength:** Speed and predictability
- **Limitation:** Regulates activity without eliminating the upstream driver. Control usually persists only while therapy continues.

Clone-directed therapy targets the upstream driver



The decision is rarely about efficacy alone; it is about how much durability the clinical situation justifies purchasing at the price of immunologic risk.

Mechanism mismatch leads to treatment failure

Corticosteroids



Ineffective for IgM-mediated hemolysis.

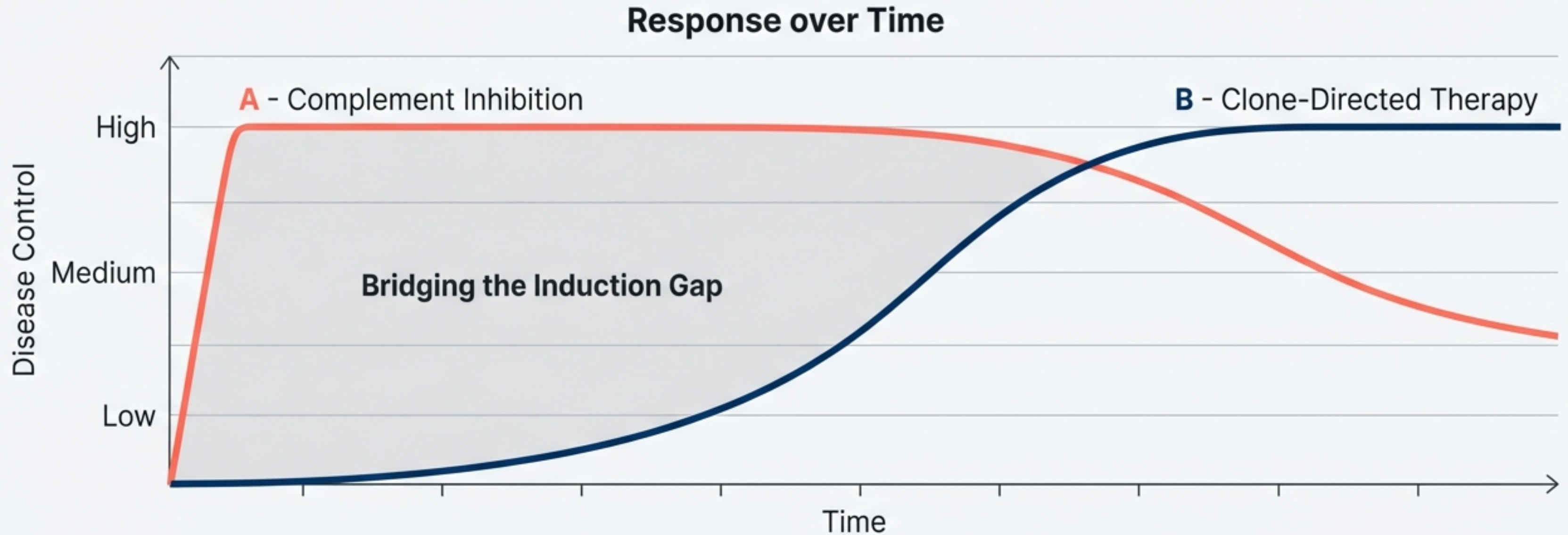
Splenectomy



Ineffective. CAD is not primarily a splenic clearance process.

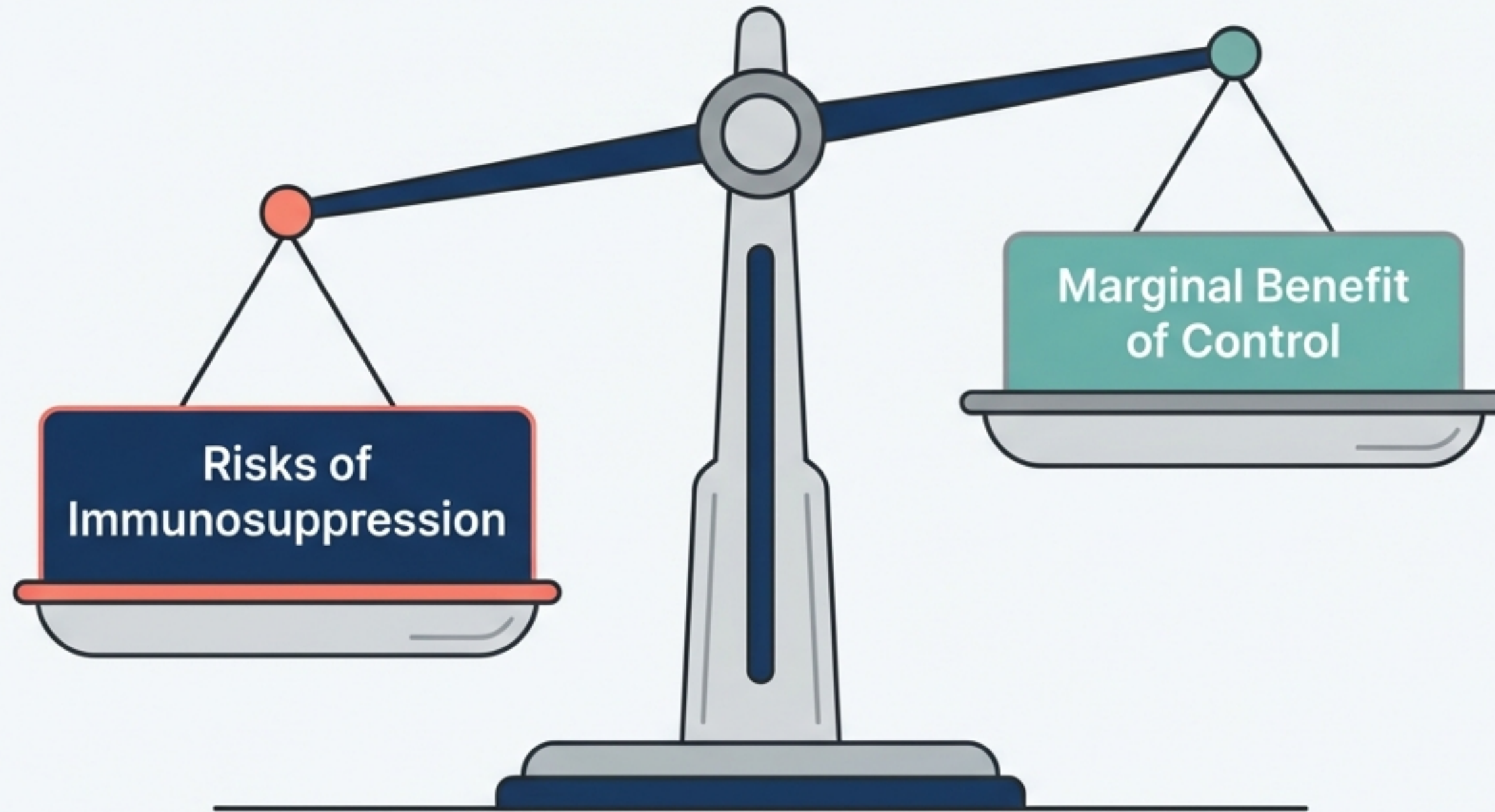
These therapies fail not by accident but by mechanism.

Combination therapy is goal-driven, not additive by default



Use **complement inhibition** for **immediate control** while **clone-directed therapy reduces antibody production**. Concurrent drugs do not always mean “combination strategy”—sometimes they represent sequential logic executed safely.

More therapy is not better therapy

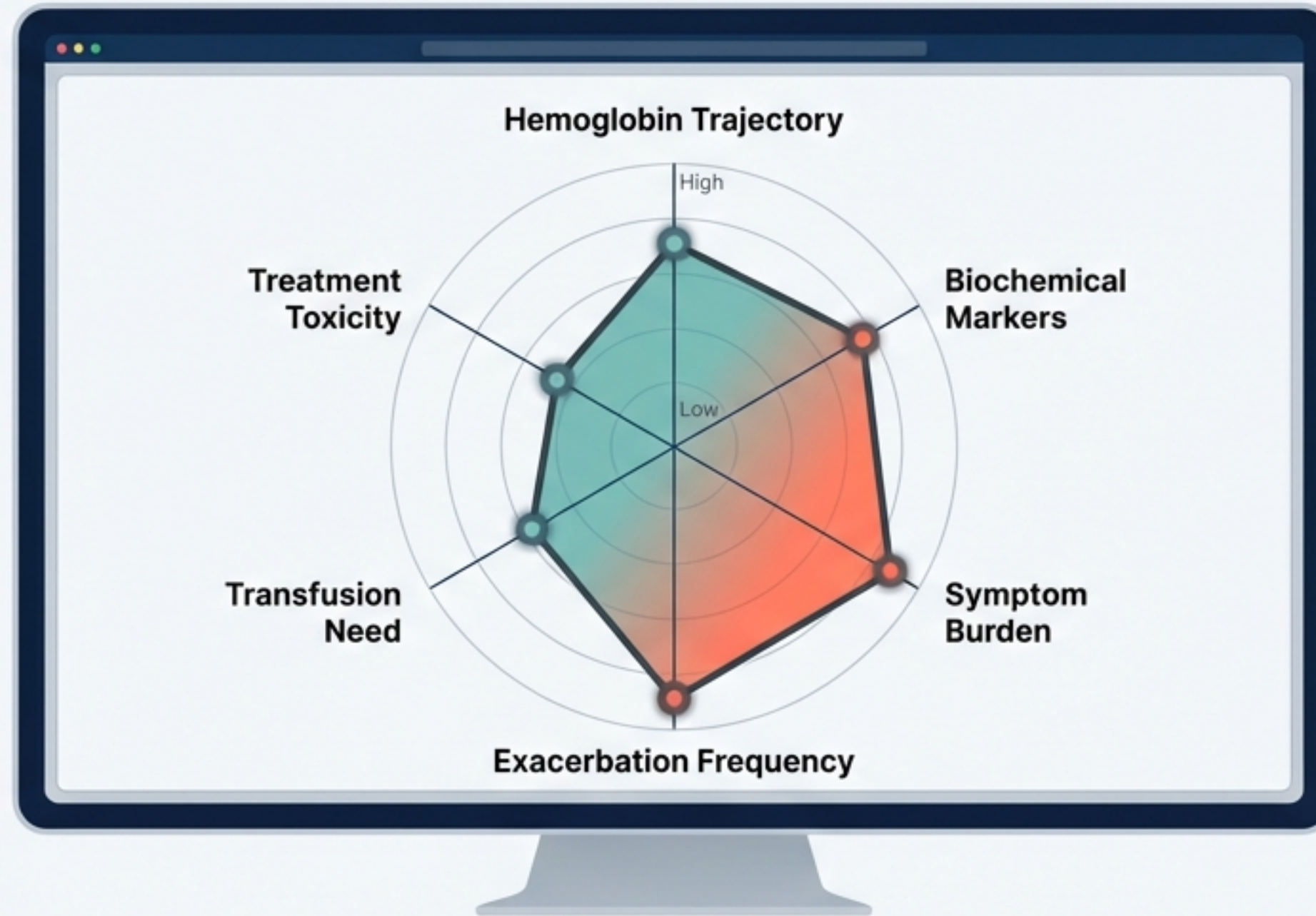


When to Stop Escalating

- Avoid layering therapy when disease impact is mild.
- Avoid escalation when patient preference favors minimal intervention.






“Avoiding unnecessary escalation is as important as escalation itself.”

Reassessment is a therapeutic intervention



Reassessment determines whether to continue, **escalate**, **de-escalate**, or **switch**. It is not passive monitoring.

Identify triggers to avoid therapeutic inertia

-  Persistent symptomatic anemia
-  Breakthrough hemolysis
-  Increasing transfusion dependence
-  Unacceptable adverse effects
-  Progression of underlying clone

Inertia is the default failure mode because changing course requires uncertainty tolerance and cognitive effort.

Asymmetry determines the de-escalation path

Complement Inhibitors

Control only while continued.

Clone-Directed

Potential for Treatment-Free Intervals.

De-escalation Criteria:

- Disease activity diminishes
- Toxicity rises
- Patient priorities shift

There is no single correct sequence in Cold Agglutinin Disease

Anticipation

Manage by **anticipation** rather than reaction.

Alignment

Align therapy with **life context**.

Mastery

Reassessment is not uncertainty, it is **mastery**.

Expert care lies in matching mechanism to moment.