WHITE PAPER 01 · EXIA INTERPRETATION LIBRARY · VERSION 1.0

Beyond the Reference Range

The Exia Five-Pass Interpretation Framework for reading blood data more carefully.

What if every result looks “normal” — but the story is changing?

A laboratory flag answers a useful question: how a value compares with a defined reporting interval. It does not automatically answer how related markers fit together, whether the person’s own trajectory changed, why measurements disagree, or what the data still cannot establish.

TEST A	ILLUSTRATIVE
HbA1c	**5.2%**
Triglycerides	**0.8 mmol/L**
ALT	**16 U/L**

No out-of-range flag shown*

TEST B	ILLUSTRATIVE
HbA1c	**5.4%**
Triglycerides	**1.0 mmol/L**
ALT	**22 U/L**

No out-of-range flag shown*

TEST C	ILLUSTRATIVE
HbA1c	**5.6%**
Triglycerides	**1.5 mmol/L**
ALT	**29 U/L**

No out-of-range flag shown*

*Fictional display for teaching only. Reference intervals vary by analyte, laboratory, method and population. “No flag” is not a clinical conclusion.

60-SECOND ANSWER

Reference status is one layer of interpretation — not the whole interpretation.

SHORT ANSWER

A laboratory result should not be interpreted only by whether it sits inside or outside a population reference interval. Reference intervals are important statistical tools, but they are not interchangeable with clinical decision limits and do not by themselves capture relationships among markers, individual context, serial change, discordant information or the limits of what the available data can establish. The Exia Five-Pass Interpretation Framework asks five questions — Relationships, Context, Trajectory, Discordance and Boundary — before action is considered.

WHY

Laboratory medicine already distinguishes measurement, reference intervals, decision limits and serial variation. Repeated results are affected by analytical and within-person variation, and related tests can measure different biological dimensions or time windows. [1–7]

WHAT CHANGES THE INTERPRETATION

Meaning can change when related markers are added, collection or physiological context is known, prior values reveal a trajectory, related measurements disagree, or laboratory method/provenance changes. The purpose of testing also matters.

WHAT WE CANNOT CONCLUDE

The framework cannot diagnose a condition, identify a causal mechanism, decide treatment or prove that a before/after change was caused by an intervention. A changed value is not automatically a clinically meaningful change.

EVIDENCE FOUNDATION

The framework is informed by established concepts in reference-interval methodology, clinical decision limits, biological variation and disease-specific examples of discordance. [1–15]

VALIDATION STATUS

The five-pass organization is an Exia Bio communication and product-design framework. It has not been validated as an independent clinical decision rule, diagnostic instrument or outcome-prediction model.

1 · WHY THIS MATTERS

A report can be accurate and still encourage an incomplete reading habit.

Blood reports are designed to measure and report reliably. Their row-by-row format is necessary. The problem begins when the interface is mistaken for the interpretation.

A typical report encourages a familiar sequence: analyte, value, unit, reference interval, flag. That is efficient for reporting. But the biological question a person cares about often spans several rows and several dates. A value can be inside its reporting interval while changing relative to the person's own prior measurements. Two connected tests can disagree because they sample different time windows or dimensions. Additional context can make a simple explanation less — not more — defensible.

A flag on a report is an interface state attached to a laboratory result. It is not the complete biological interpretation of that result.

This white paper proposes a disciplined way to preserve those distinctions without replacing clinical evaluation. The aim is not to extract a hidden diagnosis from every dataset. The aim is to ask better-controlled questions before turning measurements into conclusions.

2 · PRECISE VOCABULARY

Measurement, reference interval, decision limit and serial change answer different questions.

This section intentionally becomes more precise. The opening explained *why* the report can be misread; here we define the vocabulary that keeps different layers of interpretation from collapsing into one another.

CONCEPT	WHAT IT DOES	WHAT IT DOES NOT DO
Measurement	Quantifies a measurand using a defined specimen, method and reporting unit.	Does not by itself state why the value occurred or what action is appropriate.
Reference interval	Provides a population-based comparison interval established or verified for a measurement system. [1]	Is not automatically a diagnostic threshold, risk threshold or treatment target. [2]
Clinical decision limit	Supports a defined clinical decision, often based on disease or outcome evidence rather than population distribution.	Should not be assumed to be interchangeable with the laboratory reference interval. [2]
Serial change	Compares current and prior measurements and can add within-person information.	Is not automatically meaningful unless timing, method, analytical variation and within-person biological variation are considered. [3–6]

Design implication for Sentinel. Reference status, decision context and trajectory should remain separate information layers. Collapsing them into one score may make an interface simpler while obscuring why a result deserves attention.

3 · THE FRAMEWORK

Five passes before action.

The Five-Pass Framework is not a scoring formula. It is a sequence of interpretive questions designed to prevent common reasoning shortcuts.

1	2	3	4	5
Relationships	**Context**	**Trajectory**	**Discordance**	**Boundary**
What belongs together?	What changes confidence?	What does history add?	What resists the first story?	What are we not entitled to conclude?

The goal is not to manufacture a conclusion for every dataset. A valid output can be: "Here is what the data support, here are the competing explanations, and here is what prevents a narrower conclusion."

PASS 1

Relationships: one marker is rarely the whole question.

A laboratory value can be measured accurately and still be insufficient for the question being asked. The useful next step is not automatically "order more tests." It is to identify which related measurements materially alter the interpretation.

That relationship depends on the biological and clinical question. HbA1c and fasting glucose are related to glycaemia but do not represent identical windows or sources of uncertainty; substantial discordance is a recognized reason for follow-up rather than forced reconciliation. [7,8] In lipid assessment, LDL-C and apoB are connected but can provide different information about atherogenic lipoprotein burden, and discordance has been studied in relation to cardiovascular risk. [10–13]

Interpretation principle. Related does not mean redundant. Adding another marker is useful only when it can resolve or characterize a relevant uncertainty.

▼ **Go deeper: when another marker adds real information**

The aim of a relationship pass is not to build the largest possible panel. A second measurement earns its place when it changes the interpretation problem in a defined way: it may represent a different biological dimension, a different time window, a different compartment, or a relevant confounder. If the additional marker merely restates the same information with no credible effect on the next question, complexity increases without a corresponding gain in interpretation. This is why the framework treats "more data" and "more information" as different concepts.

For a reader, the practical discipline is to ask what would change if the related marker moved in the opposite direction. If the answer is “nothing,” the marker may not be central to that question. If the answer is “I would reconsider the explanation, confidence, or need for follow-up,” the relationship is analytically meaningful. This is also why disagreement between connected measurements can be valuable rather than something to smooth away.

PASS 2

Context: more information can increase — or decrease — confidence.

Context is not a collection of excuses added after a preferred conclusion. It changes the evidentiary meaning of a measurement. Relevant context can include collection conditions, acute illness, inflammation, pregnancy, medication or supplementation, a recent intervention, specimen handling, laboratory/method changes and biological factors that affect a particular analyte.

Ferritin is a simple example of why context can weaken an apparently straightforward interpretation. WHO guidance notes that inflammation can raise ferritin and should be considered when interpreting iron status. [9] In this situation, more information can appropriately make the interface *less* decisive.

Design implication for Sentinel. A sophisticated interface should sometimes become less decisive when relevant confounding information appears. Confidence is not a reward for having more fields filled in.

▼ **Go deeper: context is part of the evidence, not a footnote**

Context matters most when it changes the plausibility of competing explanations or the reliability of the measurement. A recent illness can alter the meaning of an inflammatory marker; a laboratory or assay change can complicate a serial comparison; a medication change can create a new time boundary around which later measurements need to be interpreted. None of those facts automatically supplies the “correct” explanation. Their value is that they change how strongly a conclusion can be defended.

This creates an important design requirement for health software: contextual information should not simply be appended as narrative text after the result. Where it materially affects interpretation, it should be linked to the measurement and date it modifies. The appropriate result of adding context can be a narrower explanation, a broader set of competing explanations, or a deliberate reduction in confidence.

PASS 3

Trajectory: the person’s own history adds another dimension.

A single result is a snapshot. Serial measurements add direction, persistence and within-person context. They also create a new risk: a line chart can make ordinary analytical or biological variation look like a meaningful trend.

Biological-variation research and the EFLM Biological Variation Database provide analyte-specific estimates used in laboratory medicine, including reference change concepts. These estimates are not one universal consumer threshold: they vary by measurand, analytical performance, population, sampling design and use case. [3–6]

> **Interpretation principle.** Trajectory asks whether the current value changes the story. It does not presume that every movement is a trend.

▼ **Go deeper: why we do not put one universal "meaningful change" percentage on the page**

Reference change calculations depend on analyte-specific within-person biological variation and analytical variation, among other assumptions. A single percentage applied across HbA1c, triglycerides, ferritin, ALT and creatinine would imply a precision the evidence does not support. Exia therefore treats the measurement history, assay/provenance and question being asked as part of the interpretation problem rather than manufacturing one cross-marker threshold.

PASS 4

Discordance: disagreement can be information.

When two pieces of information do not fit the same explanation, the temptation is to average them, choose the familiar one or label one as error. A more disciplined response is to identify *what kind of disagreement* is present, because different kinds of discordance lead to different next questions.

DISCORDANCE TYPE	EXAMPLE	WHAT THE DISAGREEMENT CHANGES
Different time windows / constructs	HbA1c vs repeated glucose measurements	The measures may represent glycaemia differently; marked discordance can justify follow-up rather than blending. [7,8]
Different biological dimensions	LDL-C vs apoB	Connected markers can provide different information about the lipoprotein system. [10–13]
Confounding context	Ferritin with inflammatory context	Additional information may reduce confidence in a simple iron-store interpretation. [9]
Historical inconsistency	One abrupt result after a long stable series	Verification, provenance or repeat measurement may become the first analytical priority.

Discordance therefore has no single meaning. It can deepen interpretation, weaken it, or temporarily stop synthesis until measurement or context is verified.

▼ **Go deeper: four discordance types imply four different responses**

Discordance caused by different time windows asks whether the measurements are sampling the same biological period. Discordance between different biological dimensions asks whether two connected measures are revealing different aspects of the same system. Confounding asks whether a third piece of information changes the apparent meaning of one or both measurements. Historical inconsistency asks whether the newest value is sufficiently unusual relative to the person's prior series that provenance, method, collection conditions or repeat measurement should be checked before a new story is built around it.

Those are not interchangeable problems. One may justify deeper synthesis; another may justify less confidence; another may make verification the first priority. Treating all disagreement as "noise" discards information, while treating every disagreement as pathology overstates it. The useful task is to classify the disagreement before deciding what kind of reasoning should follow.

PASS 5

Boundary: disciplined interpretation needs an explicit stopping point.

The boundary pass is the part most likely to disappear when software is optimized for decisiveness. Yet it is often the most important. Available data may support a relationship, a directional change, a risk association or a reason to follow up without supporting diagnosis, causal attribution or a specific intervention.

THE DATA MAY SUPPORT	THE SAME DATA MAY STILL NOT ESTABLISH
A pattern worth following	The diagnosis responsible for the pattern
A biomarker changed after an intervention	That the intervention caused the change
A plausible mechanism	A patient-important outcome
A reference-range flag	The cause or appropriate treatment
A longitudinal shift	That disease is present

Deeper analysis should not mean "more confident answers." Sometimes the deeper result is a better-defined uncertainty.

▼ **Go deeper: why a boundary is a positive analytical output**

A boundary is not a disclaimer pasted onto an otherwise confident answer. It is the point at which the available evidence stops supporting a narrower claim. Making that point explicit protects against several common upgrades in reasoning: an association becoming a cause, a pattern becoming a diagnosis, a plausible mechanism becoming an outcome claim, or a before/after change becoming proof that an intervention worked.

The boundary pass is also operational. It can specify what missing information would actually reduce uncertainty. Sometimes that is another laboratory measurement; sometimes it is repeat testing,

clinical history, symptoms, medication timing, examination or imaging. And sometimes the available information is already sufficient for the question being asked. The framework therefore does not equate disciplined interpretation with endless testing.

4 · WORKED SYNTHETIC CASE

Use the framework: same report, five different questions.

The following case is fictional. It demonstrates information structure, not diagnosis. The interface intentionally withholds a clinical verdict.

Illustrative longitudinal panel

Three tests · fictional values · no patient data

MEET THE CASE FIRST

See the longitudinal pattern before applying the Five Passes.

The worked case is easier to follow when the measurements are visible first. Three analytes have complete Test A–C series below. Two additional measurements are used later as A-to-C comparators. The case is fictional and no diagnosis is implied.

Observation first.
Direction can be displayed before significance, cause or action is inferred.

HBA1C

5.2 → 5.4 → 5.6%

TRIGLYCERIDES

0.8 → 1.0 → 1.5 mmol/L

ALT

16 → 22 → 29 U/L

How to read the mini-charts: each analyte uses its own visual scale. Compare direction within a row; do not compare slope magnitude between analytes.

FASTING GLUCOSE — **4.8 → 5.2 mmol/L**
Test A → Test C

HDL-C — **1.6 → 1.3 mmol/L**
Test A → Test C

Now apply the framework.
The values stay the same. Each pass changes the question the reader is allowed to ask of them.

Pass 1 — Relationships: widen the question without widening it indefinitely.

QUESTION	WHAT THIS CHANGES	STILL WITHHELD
What belongs together?	The question broadens from a headline marker to related glycaemic, lipid and liver-chemistry information.	Diagnosis and cause remain open.

HBA1C **5.6%**	FASTING GLUCOSE **5.2**
TRIGLYCERIDES **1.5**	HDL-C **1.3**
ALT **29**	

Units: fasting glucose and triglycerides mmol/L; ALT U/L. Values are illustrative.

If the reader sees only HbA1c and fasting glucose, the glycaemic picture appears relatively stable across the three tests. Adding the lipid and liver-chemistry rows does not diagnose a metabolic disorder — but it changes the *question*. The broader panel now contains a coordinated-looking directional shift worth examining rather than five isolated rows.

What Relationships reveals: the headline marker is not the whole information problem.

Pass 2 — Context: the same pattern can deserve different confidence.

QUESTION	WHAT THIS CHANGES	STILL WITHHELD
What changes confidence?	Collection, exposure and physiological context can strengthen one explanation or make the pattern less comparable.	Context can change plausibility without proving causality.

The laboratory values are unchanged below. Change the surrounding context and notice that the appropriate interpretation becomes more or less specific — without changing a single number.

HBA1C
5.6%

FASTING GLUCOSE
5.2

TRIGLYCERIDES
1.5

HDL-C
1.3

ALT
29

CONTEXT STATE: NO ADDITIONAL CONTEXT

No additional context supplied.

- Several plausible explanations remain open.
- The pattern can be described, but causal confidence should remain low.
- Collection conditions, recent illness, medication or supplement changes, alcohol exposure, body-composition change and intervention timing may matter.

Interpretation effect: describe the pattern and trajectory, but keep competing explanations visible instead of privileging a single cause.

CONTEXT STATE: ILLUSTRATIVE CONTEXT A

Illustrative Context A — a more internally consistent metabolic story.

- Recent reduction in habitual activity.
- Recent increase in body weight.
- No known acute illness or recent medication change reported around the tests.

Interpretation effect: this context can make a metabolic/exposure-related explanation more plausible than in the no-context state, but it still does not diagnose a condition or establish causality. The useful next question becomes whether the pattern persists and whether other relevant clinical information supports or weakens that explanation.

CONTEXT STATE: ILLUSTRATIVE CONTEXT B

Illustrative Context B — comparability and competing explanations become more important.

- A medication or supplement change occurred near one test.
- Collection conditions and fasting history were not consistent across all tests.
- A recent acute exposure or strenuous activity may have differed around one measurement.

Interpretation effect: a simple single-cause story becomes less defensible. Timing, provenance and repeat measurement under more comparable conditions may deserve priority before the pattern is narrowed to one explanation.

What Context reveals: additional information can narrow an explanation, but it can also expose confounding, reduce comparability and make a simple explanation less defensible.

Pass 3 — Trajectory: the current result is not the whole timeline.

QUESTION	WHAT THIS CHANGES	STILL WITHHELD
What does history add?	Repeated values make direction and persistence visible relative to the person's prior measurements.	Direction alone does not establish clinical significance or disease.

HBA1C
5.2 → 5.4 → 5.6%

TRIGLYCERIDES
0.8 → 1.0 → 1.5

ALT
16 → 22 → 29

The longitudinal overview above already makes direction visible. Pass 3 asks what that history changes about interpretation. HbA1c, triglycerides and ALT all move upward in this fictional series, but their biological meaning, expected variation and measurement characteristics are not interchangeable.

What Trajectory reveals: history changes what deserves attention. **What it does not reveal:** whether any specific movement exceeds analyte- and method-specific expected variation, is clinically meaningful, or proves disease.

Pass 4 — Discordance: ask what does not fit the first explanation.

QUESTION	WHAT THIS CHANGES	STILL WITHHELD
What resists the first story?	The markers do not all move in the same way, so one simple explanation should not be forced across the panel.	Discordance redirects the question; it does not identify the cause.

HBA1C
5.2 → 5.6

FASTING GLUCOSE
4.8 → 5.2

TRIGLYCERIDES
0.8 → 1.5

HDL-C
1.6 → 1.3

ALT
16 → 29

The glycaemic markers change modestly while several other measurements move more visibly in this fictional display. That mismatch does not identify a cause. It does tell us that "HbA1c is still unflagged, therefore nothing changed" is an incomplete summary.

What Discordance reveals: disagreement can redirect the analytical question. Sometimes it increases information; sometimes it reduces confidence or triggers verification.

Pass 5 — Boundary: write down what the data are still not entitled to establish.

QUESTION	WHAT THIS CHANGES	STILL WITHHELD
What are we not entitled to conclude?	The analysis ends with an explicit stopping point and a more precise follow-up question.	Diagnosis, mechanism and treatment are not established by this panel.

Supported at this level

- Several measurements changed across repeated tests.
- The broader pattern deserves contextual review.
- Provenance, timing and expected variation matter.
- Follow-up questions can be stated more precisely.

Not established by this panel

- A diagnosis of insulin resistance, metabolic syndrome or fatty-liver disease.
- The cause of the observed changes.
- That a specific treatment is indicated.
- That the trend is clinically meaningful without appropriate context and measurement considerations.

What Boundary reveals: a structured analysis can be useful without producing a diagnosis. The stopping point is part of the reasoning.

Why the case is deliberately incomplete. A white paper about disciplined interpretation should not secretly demonstrate its framework by smuggling in a diagnosis. The case is designed so that each pass changes the question while the final causal/clinical explanation remains legitimately open.

AFTER EACH PASS	HOW THE WORKING SUMMARY CHANGES
Start	“Most headline values are not flagged.”
Relationships	“The relevant question spans glycaemic, lipid and liver-chemistry measurements rather than one row.”
Context	“The same pattern deserves different confidence depending on collection, illness, intervention and exposure context.”
Trajectory	“Several values moved across repeated tests; direction is visible, but significance is not assumed.”

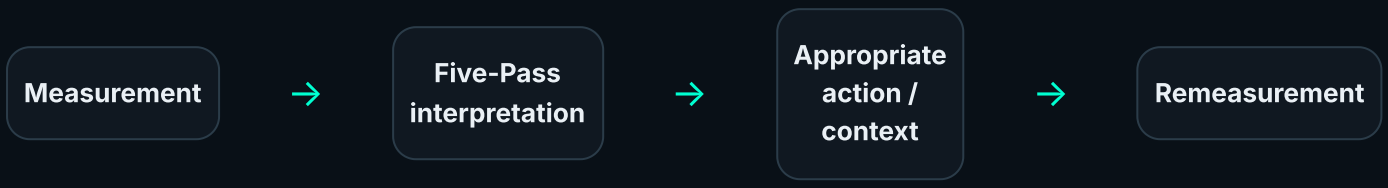
AFTER EACH PASS	HOW THE WORKING SUMMARY CHANGES
Discordance	“The measures do not all change in the same way, so the first explanation should not be forced across the panel.”
Boundary	“The data support a more precise follow-up question, but not a diagnosis, cause or treatment conclusion.”

The summaries above are deliberately phrased as information states, not clinical conclusions. The value of the framework is that each pass changes what can be said — and sometimes what should no longer be said.

5 · AFTER INTERPRETATION

Action and remeasurement are a loop — not proof that the original story was correct.

After Relationships, Context, Trajectory, Discordance and Boundary comes a different category of question: *what next step actually follows from what the data support?* Depending on the situation, that may mean clinical follow-up, repeat measurement, collecting missing information, continuing an already-directed intervention, lifestyle or nutrition work, or no immediate action.



The key discipline is that remeasurement asks a **new question**. Suppose, in a synthetic follow-up, triglycerides are lower and ALT is lower after a period in which several things changed — diet, activity, medication adherence and time. The new measurements can tell us that those values were lower at the later time point. They do not automatically prove which change caused the difference or that every relevant health outcome improved.

What the repeat measurement can establish

- The later measured values.
- The direction and magnitude of change.
- Whether a prior pattern persisted, reversed or became more discordant.
- Whether the next interpretation question changed.

What before/after alone does not prove

- Which intervention caused the change.
- That the original causal explanation was correct.
- That a biomarker change equals a patient-important benefit.
- That no confounding or regression-to-the-mean effects were present.

Remeasurement should update the model, not merely validate the story we already wanted to believe.

▼ **Go deeper: remeasurement can confirm a measurement change without confirming the story**

Consider two different follow-up situations. In the first, one repeat measurement returns close to the previous long-term pattern after an isolated unexpected result. The useful conclusion may be that verification changed the confidence placed on the outlier. In the second, several measurements continue moving in a similar direction over appropriately comparable tests. The useful conclusion may be that persistence is now better supported and that the next question should become more specific. Neither situation, by itself, identifies the biological cause.

This distinction matters when interventions are involved. If several behaviors, medications, supplements or other exposures change between tests, a later biomarker shift is real as a

measurement but causally ambiguous. A rigorous system should preserve the intervention timeline and the observed response while avoiding language that silently converts temporal sequence into proof.

6 · PRODUCT INTERPRETATION

How Sentinel is intended to preserve the framework.

Public-level design principles

Sentinel is intended to structure incoming laboratory information so units, dates, provenance and related markers can be compared consistently; keep relevant relationships and longitudinal context visible; represent missing information, discordance and confidence where they affect interpretation; use governed scientific logic and evidence provenance rather than relying on fluent generative language to create conclusions; and provide a bounded handoff when the next useful question requires information or clinical evaluation outside the available data.

Disclosure boundary: this public framework does not disclose Sentinel's proprietary rule implementation, thresholds, weighting, governed logic packages or internal validation architecture. It describes reasoning principles the product is intended to preserve.

7 · VALIDATION STATUS AND LIMITATIONS

The framework is a structured interpretation model, not a validated clinical decision rule.

> **Current status.** The Exia Five-Pass Interpretation Framework is a communication and product-design framework informed by established concepts in laboratory medicine and evidence interpretation. It has not been validated as an independent clinical decision rule, diagnostic instrument or outcome-prediction model.

Not every pass is equally relevant to every laboratory question. The framework does not specify universal thresholds for "meaningful change." It does not imply that more biomarkers are always better. It does not replace clinical evaluation when symptoms, examination, imaging, repeat testing or other information are required.

Future Sentinel validation should test whether governed implementation improves defined outcomes such as interpretive consistency, calibration, error rates, appropriate uncertainty handling and safe handoff compared with prespecified alternatives. Those validation claims should be made only after the relevant study design and results exist.

8 · REUSABLE READER CHECKLIST

Seven questions to carry into your next blood report.

Relationships
What else belongs to this question?

Context
What might change how strongly I should read this result?

Trajectory
Is this result different from the person's own prior pattern?

Discordance
What information does not fit my first explanation?

Boundary
What am I still not entitled to conclude?

Action
What next step actually follows from the supported interpretation?

Remeasurement
If I measure again, what question will the new result answer?

NEXT · SEE THE PRODUCT LAYER

See how Sentinel turns a blood report into structured educational biomarker intelligence.

The current Exia Bio site includes a Sentinel output preview, product routes and the non-diagnostic service boundary. The dedicated interactive conversion experience can replace this destination later without changing the white paper.

Opens the current official Exia Bio Sentinel overview and output preview.

Evidence foundation

The Five-Pass organization is Exia's synthesis. The scientific concepts it is designed to preserve — reference-interval methodology, decision limits, biological variation, assay/context effects and interpretable discordance — come from established laboratory-medicine and disease-specific evidence. The references below are selected to support propositions actually used in this paper rather than to maximize citation count.

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particle concentration, type, and content. *JAMA Cardiol.* 2022. PMID 34773460. Source

14 Mora S, et al. Discordance of LDL cholesterol with alternative LDL-related measures and future coronary events. 2014. PMID 24345402. Source

15 American Diabetes Association Professional Practice Committee. Glycemic Goals, Hypoglycemia, and Hyperglycemic Crises: Standards of Care in Diabetes—2026. Discussion includes reasons A1C can be discordant with glucose-monitoring measures. Source guideline

Scientific review status: Exia Bio internal scientific and claims review completed 14 Aug 2026. External clinical/laboratory review has not been performed or represented. Version 1.0. This page is educational and is not medical advice.