CLINICAL ADVANCES • SPECIALIST REVIEW

EASD 2026
Milan

Metabolic therapies, disease modification
and the next generation of diabetes care

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Evidence reviewed through 3 October 2026

EASD

European Association for the Study of Diabetes

Science for a world without diabetes

Leading diabetes research, education and care across Europe and beyond for **over 60 years**



62nd EASD Annual Meeting

MILAN, ITALY
28 September – 2 October 2026

Milan 2026

PEOPLE · SCIENCE · INNOVATION
FOR A HEALTHIER TOMORROW

HISTORY & MILESTONES



1965 – Founded in 1965
Established by a group of European diabetes researchers to advance the study of diabetes in Europe and worldwide.



1967 – First Annual Meeting
The first EASD scientific meeting was held in 1967 in Montecatini, Italy.



Since 1967 – Annual Scientific Meetings
Held every year in major European cities, now the largest diabetes congress in Europe and one of the most influential globally.

ABOUT EASD

Mission
To promote excellence in diabetes research, education and clinical care, and to translate knowledge into better health for people with diabetes.

Vision
A world without diabetes and its devastating complications.

Members
> 5,000 healthcare professionals, researchers and allied experts from around the world.

Global reach
A truly international community, collaborating with partner organizations including ADA, IDF and national diabetes associations.

KEY ACTIVITIES

Annual scientific meeting
Cutting-edge science, late-breaking research, clinical advances and technology.

Education and training
EASD Postgraduate Education (EASD PE), EASD Virtual Meeting, webinars and fellowships.

Guidelines and position statements
Evidence-based recommendations that influence global diabetes care.

Research networks and collaborations
Basic, translational, clinical and population research.

Advocacy and awareness
Promoting better diabetes prevention, care and policy across Europe and beyond.

EASD ANNUAL MEETINGS IN RECENT YEARS

2022	Stockholm, Sweden	
2023	Hamburg, Germany	
2024	Madrid, Spain	
2025	Vienna, Austria	
2026	Milan, Italy (28 Sept – 2 Oct)	

WHY EASD MATTERS?

- Shapes the future of diabetes research and care
- Brings together a multidiscipnliary global community
- Showcases major scientific breakthroughs and innovations
- Influences guidelines, policy and real-world practice
- Ultimately aims to improve the lives of people with diabetes worldwide

EASD 2026 – MILAN

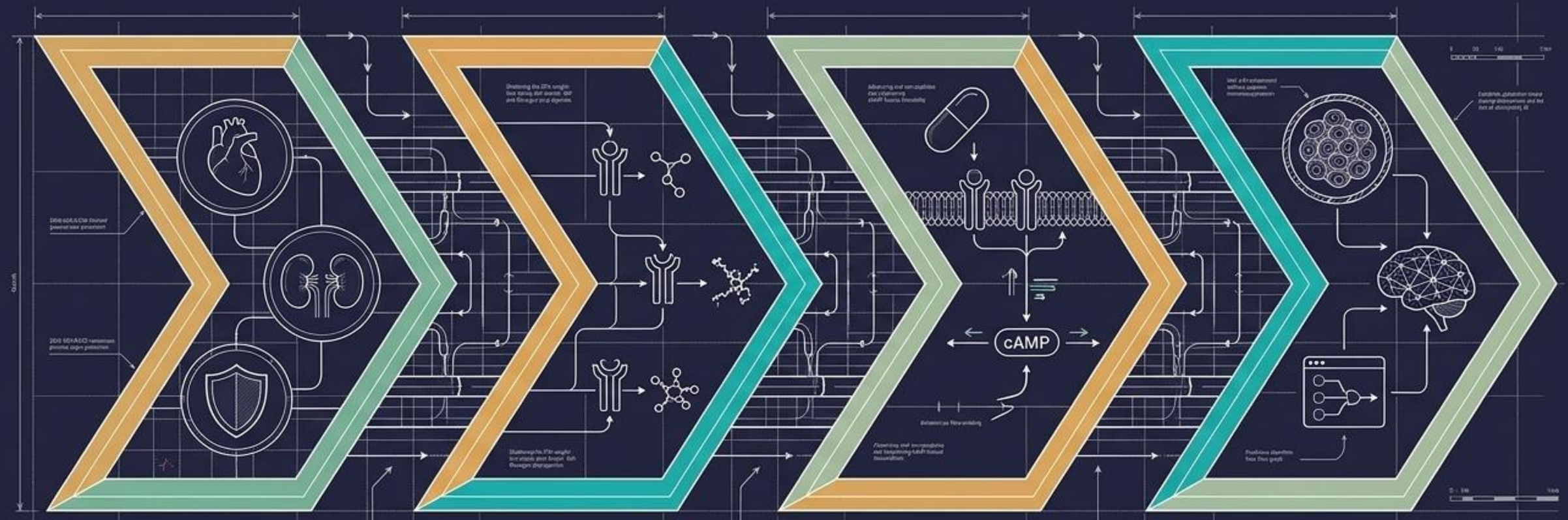
- Latest science
- Technological innovation
- Global collaboration
- Education & young investigators
- In the heart of one of Europe's most inspiring cities

Milan welcomes the world of diabetes

From scientific discovery to better lives ... together

EASD
European Association for the Study of Diabetes

Redefining the Metabolic Baseline



Phase 1: The New Foundation

2026 ADA/EASD consensus prioritizes organ protection over HbA1c alone

Phase 2: The Multi-Receptor Era

Shattering the 20% weight-loss ceiling with Amylin, GIP, and Glucagon poly-agonists

Phase 3: Accessibility & Tolerability

Advancing oral non-peptides and engineering cAMP-biased tolerability

Phase 4: Redefining T1D & Digital Care

Islet cell replacement without systemic immunosuppression and the rise of anticipatory AI

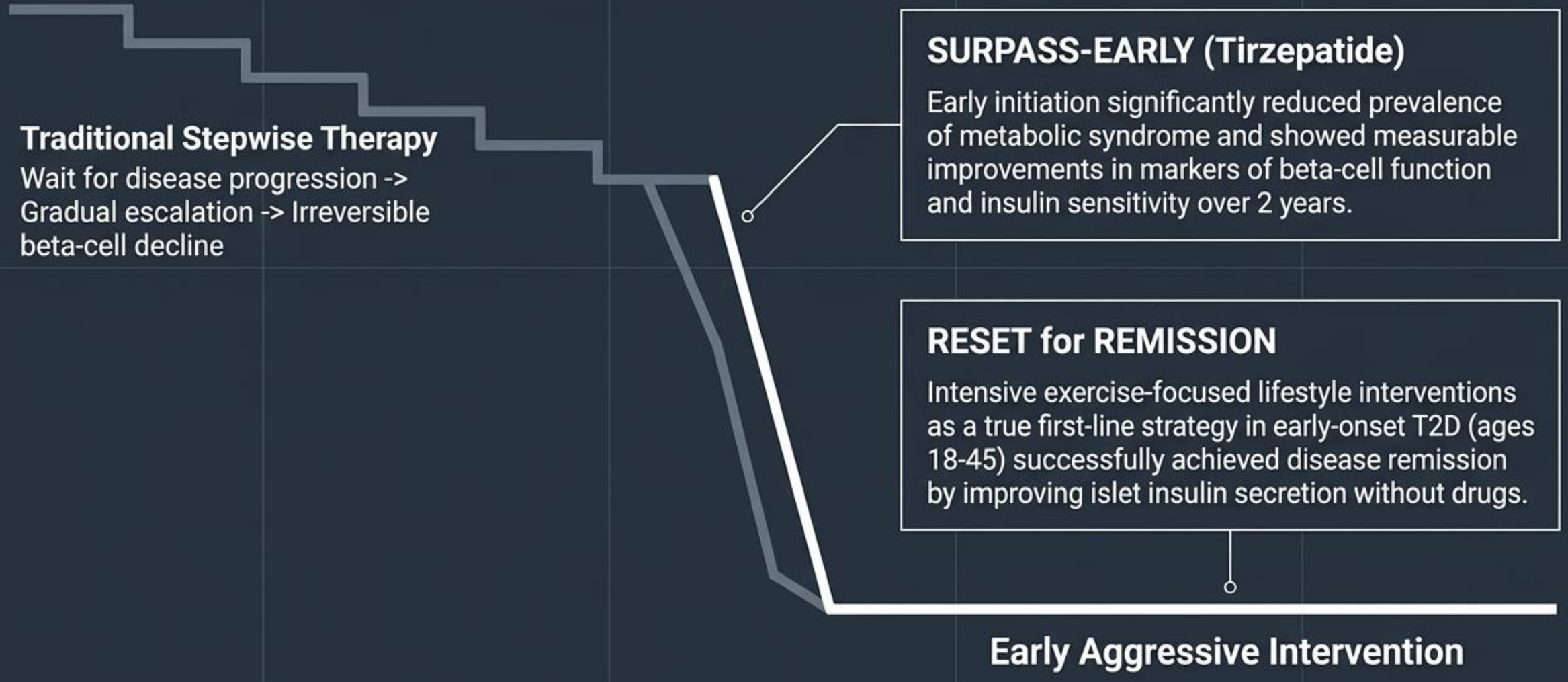
Gemini Notebook

Translating the 2026 ADA/EASD Consensus

Standard Care Pre-2026	2026 ADA/EASD Consensus
First-Line Therapy: Metformin as default. 	First-Line Therapy: GLP-1 RA or SGLT2i first-line (SMARTEST trial data showing superior CV protection). Metformin explicitly re-evaluated. 
Screening: Standard eye, kidney, heart, nerve. 	Screening: Mandatory MASLD/Liver screening integrated into routine risk management. 
Monitoring: Standard capillary testing for non-insulin T2D. 	Monitoring: Expanded Continuous Glucose Monitoring (CGM) encompassing non-insulin and basal-only T2D patients. 

Gemini Notebook

The Paradigm Shift to Early Aggressive Intervention



Gemini Notebook

RESET for REMISSION

Intensive Lifestyle Intervention in Early-Onset Type 2 Diabetes

Randomized, open-label, blinded-endpoint efficacy trial • 24 weeks

EASD 2026
Milan, Italy
15–19 September 2026



1 Study design and population

96 adults
with early-onset type 2 diabetes and obesity

Age 18–45 years
(mean 38 years)

Diabetes duration ≤ 6 years

Obesity
(mean BMI 35.2 kg/m²)

Not receiving insulin
at enrolment

3 centres
in England and Canada

Randomized 1:1
(N = 96)

Combined intensive lifestyle intervention (n = 50)



Low-energy diet + structured exercise
No glucose-lowering medication (initially withdrawn)

Usual care (n = 46)



Standard diabetes care according to local guidelines
Glucose-lowering medication as needed

2 Intervention protocol (24 weeks)

Weeks 1 – 12
Intensive phase



Low-energy diet 800–900 kcal/day
Using meal replacements and selected foods

+



Structured exercise 3 sessions per week
- 2 supervised aerobic and resistance sessions
- 1 independent exercise session

Weeks 13 – 24
Maintenance phase



Weight-maintenance diet
- Gradual food reintroduction
- Nutritional counselling

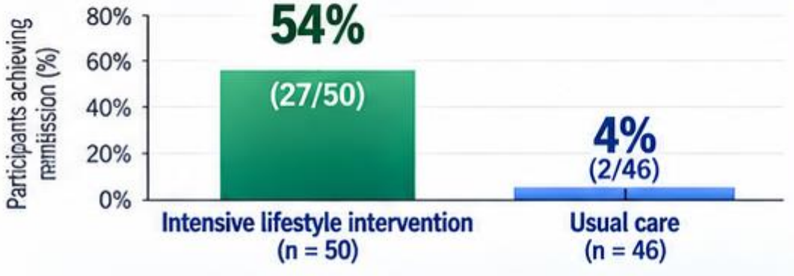


Continued exercise
- Independent exercise (unsupervised)

Glucose-lowering medication was withdrawn at intervention initiation with clinical supervision and adjustment when necessary.

3 Primary outcome: Diabetes remission at 24 weeks

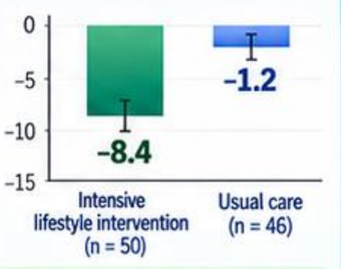
Remission: HbA1c < 6.5% without glucose-lowering medication for at least 12 weeks



Absolute difference
50
percentage points
(95% CI 33–64)

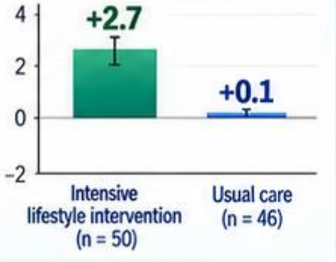
4 Secondary outcomes at 24 weeks

Body weight
Mean change from baseline (kg)



Adjusted between-group difference:
–7.5 kg

Cardiorespiratory fitness
Mean change in fitness (mL/kg/min)



Greater improvement in fitness in the intervention group

5 Key points and safety

Intensive combined lifestyle intervention achieved drug-free diabetes remission in 54% of younger adults with early-onset type 2 diabetes, versus 4% with usual care.

Significant weight loss, improved cardiorespiratory fitness, and preservation of muscle mass.

Diet and exercise were combined; independent effect of exercise alone cannot be determined.

24-week trial; long-term durability of remission is unknown.

No serious adverse events reported; minor diet-related symptoms were common.

Dasgupta K. et al. RESET for REMISSION. The Lancet Regional Health – Americas. 2026; doi:10.1016/j.lana.2026.101664.

SURPASS-EARLY | Early Tirzepatide vs Intensified Conventional Care

Phase 4 randomized open-label trial • 78 sites, 10 countries (NCT05433584)

EASD 2026
Milan, Italy
15–19 September 2026

1 Study design and population

Adults with type 2 diabetes
- Diagnosed ≤ 4 years
- Inadequately controlled on stable metformin (monotherapy)
- HbA1c 7.0 – 9.5%
- BMI 25 – 45 kg/m²
- Age ≥ 18 years

Phase 4
Multicentre
Open-label

78 sites
in 10 countries

Randomized 1:1
(N = 794)

Tirzepatide + metformin (n = 398)



2.5 mg weekly, titrated every 4 weeks to **15 mg** or maximum **tolerated dose**

Background metformin

Intensified conventional care + metformin (n = 396)



Individualized glucose-lowering drugs according to clinical guidelines (including GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, insulin, etc.; tirzepatide excluded)

Background metformin

Primary assessment
104 weeks
Treatment-regimen estimand (initial noninferiority objective, followed by superiority testing)

Planned total duration
208 weeks
(4 years)

Baseline characteristics (randomized population, N = 794)

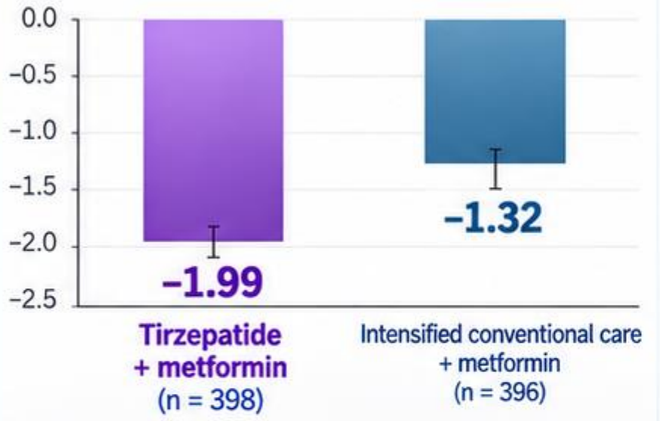
53.5 ± 9.8 years	2.6 ± 1.4 years	7.81 ± 0.8%	35.4 ± 5.8 kg/m²
Mean age	Mean diabetes duration	Mean HbA1c	Mean BMI

2 Results at 104 weeks (2 years)

Treatment-regimen estimand

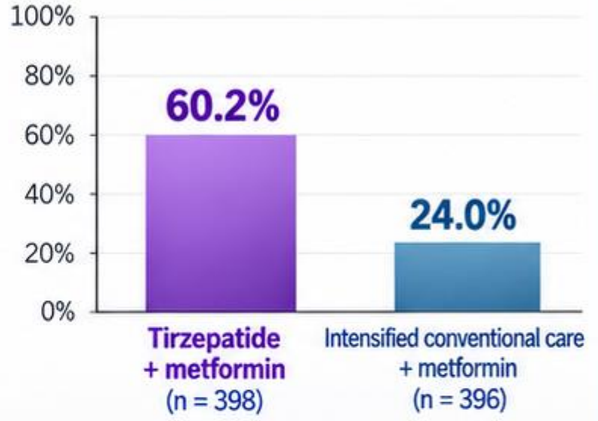
Change in HbA1c at 104 weeks

Mean change from baseline (percentage points)



Participants achieving HbA1c < 5.7%

(Normoglycemia) at 104 weeks



Between-group estimated treatment differences at 104 weeks

Tirzepatide versus intensified conventional care

Body weight
−8.0 kg
Estimated treatment difference
(95% CI not shown on slide)

Waist circumference
−6.2 cm
Estimated treatment difference
(95% CI not shown on slide)

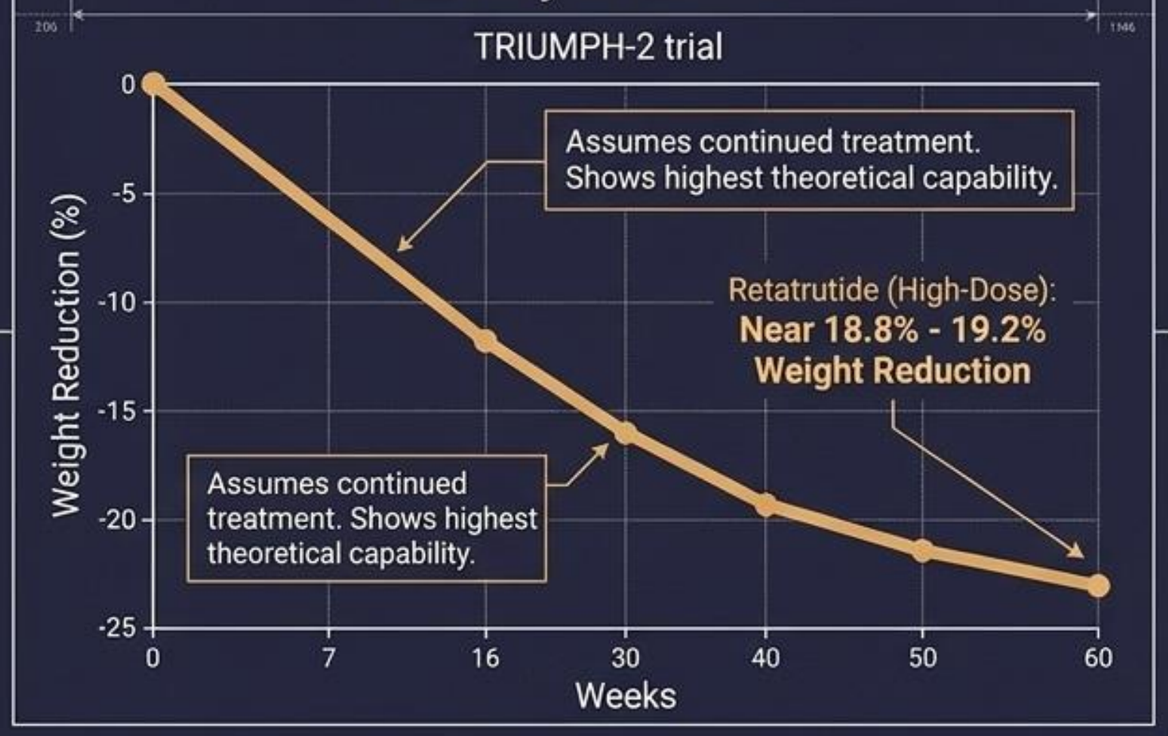
Key take-home message
Greater glycemic and weight benefits with early tirzepatide; normoglycemia on treatment is **NOT drug-free remission.**

SURPASS-EARLY (NCT05433584). Del Prato S, et al. Ann Intern Med. 2026. DOI: 10.7326/ANNALS-25-05602.

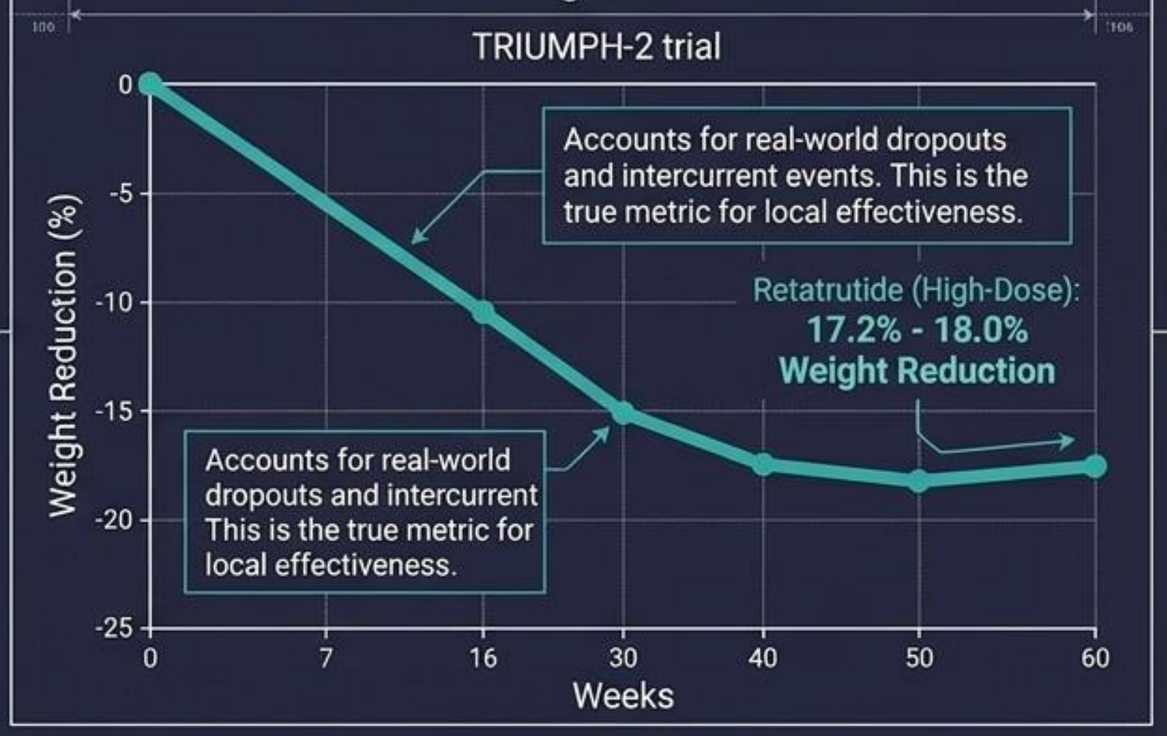
The Clinical Impact of Trial Estimands

An estimand changes the treatment question. Effect size, tolerability, and evidence maturity must travel together.

Efficacy Estimand



Treatment-Regimen Estimand



Clinical Insight: The largest weight response is not automatically the best individual choice if adverse-event discontinuation rates (e.g., severe GI events) are high.

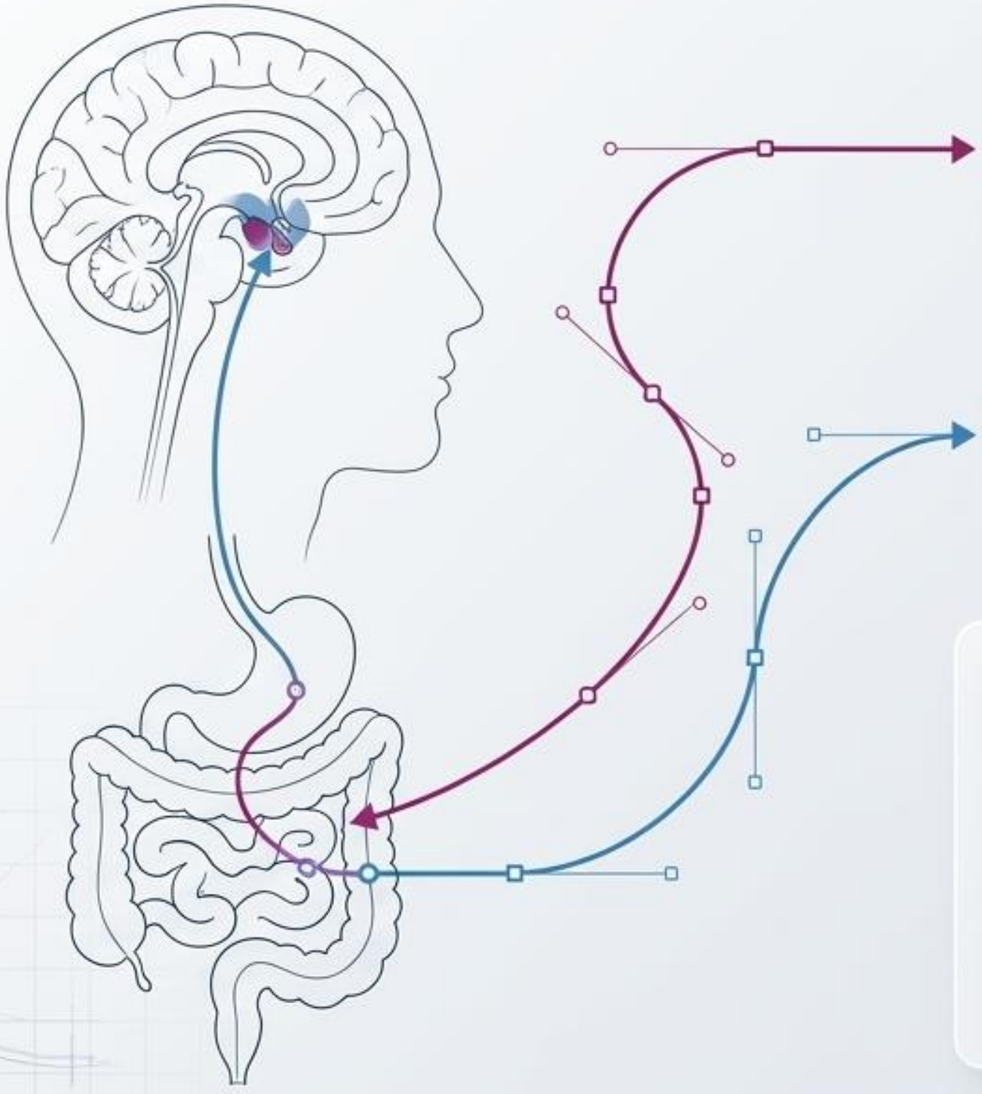
Gemini Notebook

The Incretin and Amylin Matrix

Drug	Receptor Targets	Trial	Max Weight Loss	Differentiators
Tirzepatide	GLP-1 + GIP	SURPASS	-	The baseline multi-receptor standard
Retatrutide	GLP-1 + GIP + Glucagon	TRIUMPH-2	18.8 - 19.2%	Highest obesity resolution in T2D
Survodutide	GLP-1 + Glucagon	SYNCHRONIZE	13% (T2D)	Substantial liver fat/fibrosis reversal
CagriSema	GLP-1 + Amylin	REIMAGINE	22.4%	Reduces food noise via brain sensory pathways
EloraTZP	GLP-1 + GIP + Amylin	Phase 2b	23.3%	Record efficacy, requires sequential dosing for GI tolerability

Gemini Notebook

THE FOOD NOISE ARCHITECTURE: AMYLIN'S NEURO-METABOLIC ROLE



PATHWAY 1: THE GUT (GLP-1/GIP)

Delays gastric emptying, increases insulin secretion, provides baseline satiety.

PATHWAY 2: THE AMYGDALA (AMYLIN)

Backed by **52-week fMRI data** presented at EASD. Amylin receptor agonism actively modifies brain responses to high-calorie food cues.

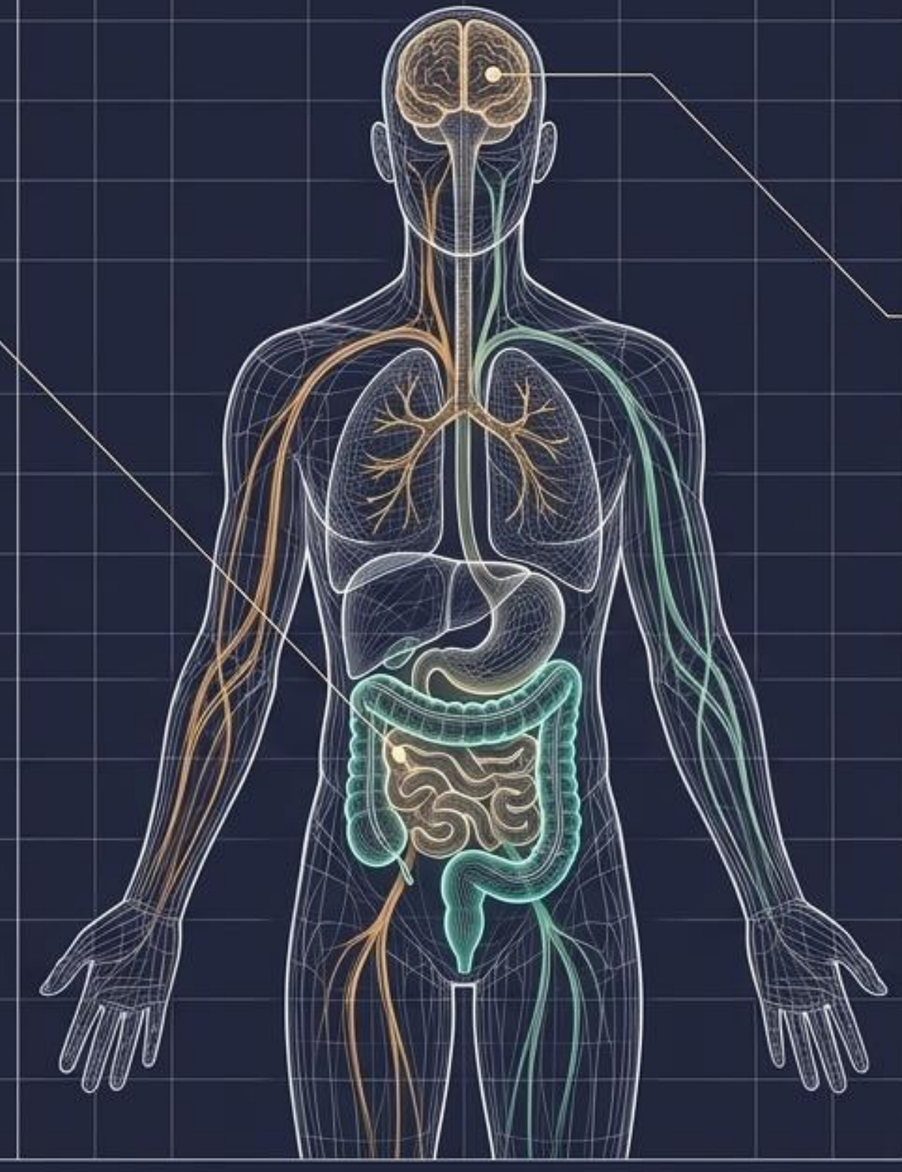
CLINICAL TRANSLATION

Combining these pathways **reduces measurable food noise, cravings, and food preoccupation, addressing the psychological drivers of obesity**, not just caloric intake.

Note: EloraTZP requires careful titration, as Phase 2 showed a **27% discontinuation rate** at the highest dose, primarily due to GI side effects.

Gemini Notebook

Shattering the 20% Efficacy Ceiling



23.3%
Weight Loss

EloraTZP

- 23.3% Weight Loss & 2.9% HbA1c reduction at 48 weeks

Clinical Note: Highest recorded weight loss in T2D/Obesity, but Phase 2b data shows 27% discontinuation rate vs 2.9% for tirzepatide alone, mandating step-wise introduction protocols.

22.4%
Weight Loss

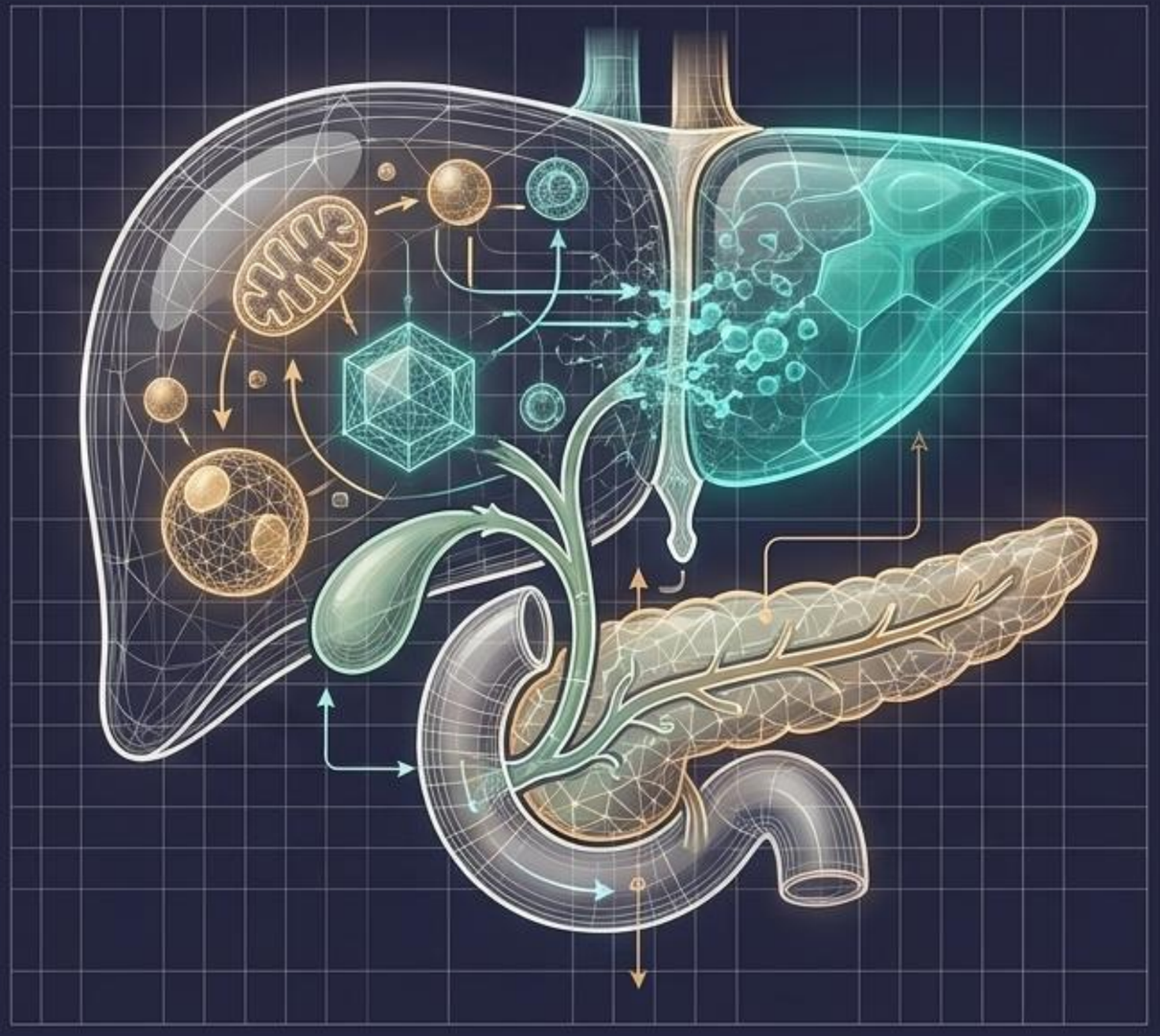
CagriSema

- 22.4% Weight Loss

Mechanism Callout: Dampening Neurological Food Noise. fMRI brain scan data from REIMAGINE proves modification of brain reward responses to high-calorie cues, specifically targeting sensory processing to reduce persistent cravings.

Gemini Notebook

Hepatic Reprogramming via Glucagon Signaling



Core Mechanism:

Glucagon directly increases hepatic energy expenditure and mitochondrial respiration, complementing GLP-1's peripheral insulin sensitivity.

Clinical Evidence (Survodutide / SYNCHRONIZE):

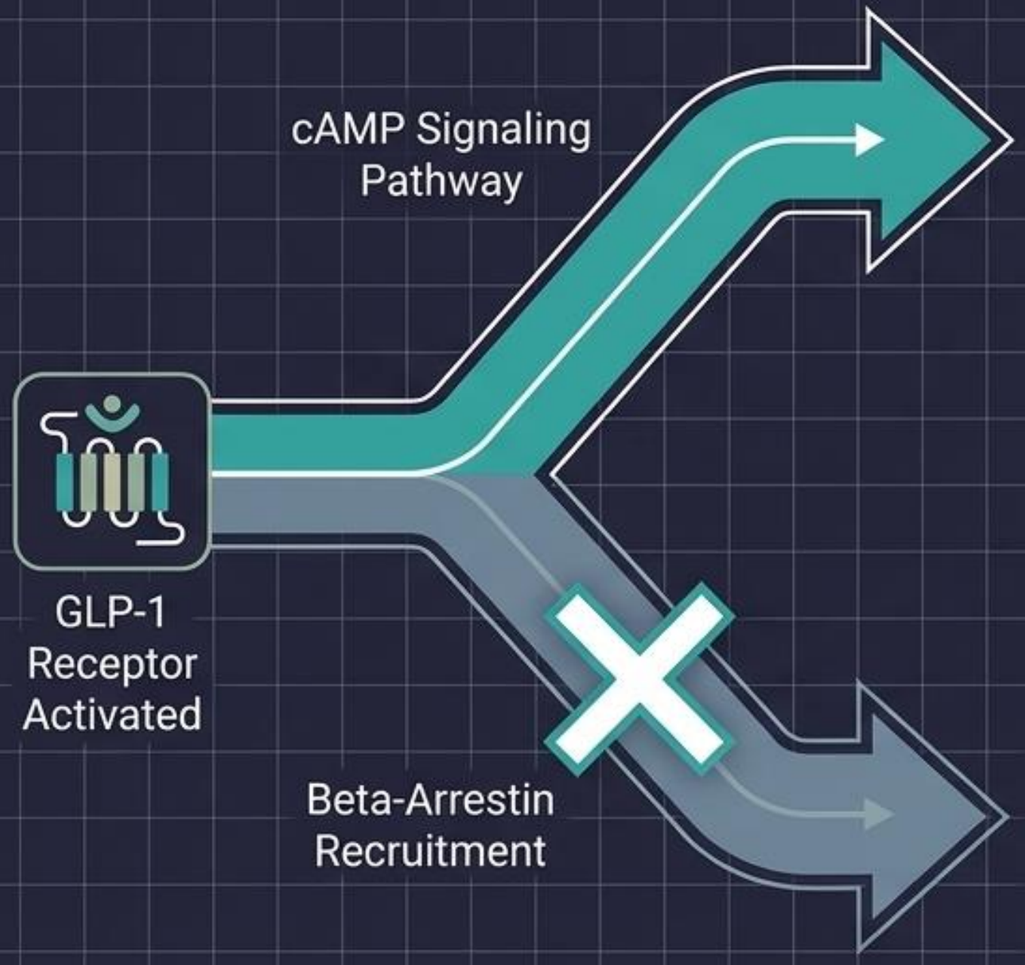
Drives up to **83%** **histological resolution** of MASH without worsening of fibrosis.

Disease Modification:

Over **50%** of trial subjects achieved a **≥1-stage improvement** in liver fibrosis, significantly altering the trajectory toward cirrhosis and portal hypertension.

Gemini Notebook

Engineering Tolerability via Biased Signaling



The Mechanism: Ecnoglutide preferentially activates the intracellular cAMP signaling pathway while minimizing beta-arrestin recruitment

Target Niche: Addressed in Phase 1b/2 adolescent obesity trials

Clinical Validation: Delivered up to 12.6% BMI reduction at 20 weeks in actively growing demographics while maintaining a highly favorable safety profile, avoiding standard GLP-1 RA traps

Gemini Notebook

Oral Delivery Meets Cardiorenal Safety

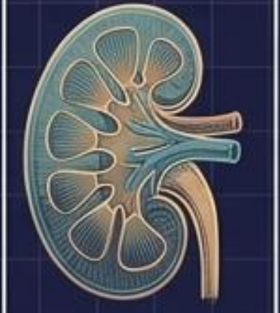
ACHIEVE-4 Trial Context:
Daily oral Orforglipron (non-peptide) vs. titrated Subcutaneous Insulin Glargine



Cardiovascular Endpoint:

MACE-4 event rate **HR 0.84**.

- Non-inferiority established against Glargine. (Crucial appraisal: Non-inferiority does not equal proven superiority, but confirms safety).



Efficacy & Renal Endpoints:

Superior HbA1c reduction (-1.7% to -2.1%) and profound weight loss vs vs insulin-induced gain.

- Blunted eGFR decline (-0.05 vs -1.08 ml/min/1.73 m^2 per year) showing sustained renal protection.

Gemini Notebook

Refining the Basal Baseline

The Weekly Debate

Ludefen weekly vs Degludec daily shows numerically greater HbA1c reductions, but frequency is a pharmacologic commitment, not just a convenience.

HbA1c change:	-1.00 ↘ vs	-0.58 ↘
ETD	-0.42 percentage points.	

The True Differentiator

Hypoglycemia. SWITCH 1/2 trials establish Degludec's 36-42% reduction in nocturnal symptomatic events.

Guideline Placement: EXPECT trial data supports Degludec safety in pregnancy.

Hypoglycemia Event Rate Reduction (Crossover Trial): Overall Symptomatic (30-11%), Nocturnal Symptomatic (42-36%).

Clinical Imperative: Choose the basal insulin, titration strategy, and monitoring together—not just injection frequency alone.

Gemini Notebook

NEW CONGRESS EVIDENCE • 28 SEP–2 OCT 2026

Degludec at EASD Milan 2026

A daily basal reference in the next wave of insulin innovation

INSULIN DEGLUDEC • TRESIBA



PHASE 3 • SUPER-2 • PRESENTATION 8

Ludefen weekly vs degludec daily

631 adults with T2D | 26 weeks | China

Change in HbA1c

−1.00 vs **−0.58**

Ludefen | Degludec

ETD −0.42 percentage points

95% CI −0.55 to −0.30 | p<0.0001

HbA1c <7% without level 2/3 hypoglycaemia: 23.7% vs 13.7%*

PHASE 2 • SHR-3167 • LBA 96

Weekly insulin vs degludec

16-week HbA1c change: −0.57 / −0.61 vs −0.33 percentage points.

Numerical differences; superiority not established here.

CLAMP STUDIES • LBA 98 & PRESENTATION 7

GZR4 and GZR33 vs degludec

GZR4: weekly PK/PD coverage. GZR33: daily profile reported as flatter in a T1D clamp study.

Pharmacology signals ≠ proven clinical benefit.

Milan’s novelty: new comparator evidence. No new Tresiba indication identified.

*Final 12 weeks. Investigational comparators; results partly from sponsor reports. SHR numbers were reported before EASD.

Sources: EASD 2026 programme; Gan & Lee, 2 & 8 Oct 2026; Hengrui, 5 Jun 2026.

ESTABLISHED EVIDENCE • NOT NEW MILAN RESULTS

Hypoglycaemia: the strongest clinical advantage

Randomised evidence is most persuasive against insulin glargine U100

INSULIN DEGLUDEC • TRESIBA



SWITCH TRIALS • RANDOMISED, DOUBLE-BLIND, CROSSOVER

Relative reduction in event rates during maintenance

Trial	Population	Overall symptomatic	Nocturnal symptomatic
SWITCH 1	**T1D • n=501**	**11%**	**36%**
SWITCH 2	**T2D • n=721**	**30%**	**42%**

HIGH-RISK T1D • HYPODEG

37% lower nocturnal level 2 rate

Also 35% lower all-day severe event rate vs U100.

HIGH-RISK T2D • DEVOTE

40% lower severe event rate

Patients with severe events: 4.9% vs 6.6%.

Comparable glycaemic control with fewer hypoglycaemic events in selected trial populations.

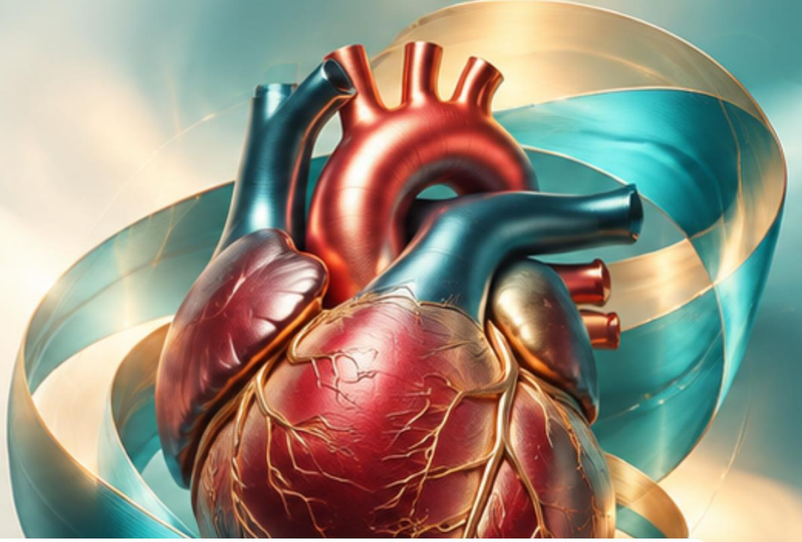
Percentages describe relative event-rate reductions, not absolute risk reductions. Definitions and observation periods differ across trials.

Sources: SWITCH 1/2, JAMA 2017; HypoDeg, Diabetes Obes Metab 2022; DEVOTE, NEJM 2017.

EVIDENCE INTERPRETATION • DEVOTE / BRIGHT / CONCLUDE

Cardiovascular safety and the limits of superiority

Read the primary endpoint before interpreting favourable secondary outcomes



INSULIN DEGLUDEC • TRESIBA

DEVOTE • 2017 • N=7,637

MACE-3: noninferiority established

8.5% vs **9.3%**

Degludec — Glargine U100

HR 0.91 | 95% CI 0.78–1.06



CV safety demonstrated. Cardiovascular protection was not established.

BRIGHT • 2018 • INSULIN-NAIVE T2D

Degludec vs glargine U300

Similar HbA1c and overall hypoglycaemia over 24 weeks. Some early titration outcomes favoured U300.

CONCLUDE • 2020 • INSULIN-TREATED T2D

Primary superiority not established

Overall symptomatic rate: RR 0.88

95% CI 0.73–1.06

Favourable secondary results became exploratory.

Lower hypoglycaemia vs U100 does not establish universal superiority over U300.

MACE-3 = cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. DEVOTE met its prespecified noninferiority criterion.

Sources: DEVOTE, NEJM 2017; BRIGHT, Diabetes Care 2018; CONCLUDE, Diabetologia 2020.

Pregnancy and guideline placement

A broader clinical role, supported by EXPECT and updated recommendations



INSULIN DEGLUDEC • TRESIBA

EXPECT • 2023 • N=225 RANDOMISED

Pregnancy with type 1 diabetes

Degludec vs detemir; both with mealtime insulin aspart.

6.2% Degludec vs **6.3%** Detemir

Last planned HbA1c before delivery: noninferiority confirmed.

EU label: may be considered in pregnancy if clinically needed.

CURRENT RECOMMENDATIONS

Where degludec appears

ADA 2026 • pregnancy

Listed among basal insulin options.

ADA/EASD 2026 • T1D

Second-generation basal analogues may be preferred with problematic hypoglycaemia.

ADA 2026 • T1D / T2D

Lower hypoglycaemia risk vs glargine U100.

NICE NG17 • adults with T1D

Consider U100 for concern about nocturnal hypoglycaemia.

Pregnancy evidence supports use when needed; it does not prove equivalence for rare obstetric harms.

Original approvals: EU Jan 2013; FDA Sep 2015. These are established approvals, not new EASD 2026 indications.

Sources: EXPECT, Lancet Diabetes Endocrinol 2023; EMA SmPC; ADA Standards 2026; ADA/EASD T1D 2026; NICE NG17.

PRACTICAL APPLICATION • ESTABLISHED USE + 2026 TECHNOLOGY

Daily use meets data-guided care

Stable basal coverage remains relevant as CGM and weekly insulins evolve

INSULIN DEGLUDEC • TRESIBA



LABEL-BASED USE

Daily basal insulin

>42 hours

Duration of action does not change the once-daily schedule.

Dose increases: usually 3–4 days apart (US label).
Adult missed dose: ≥8 hours between injections.
U100 / U200 pens: no dose conversion.

SMALL RCT • 2026

CGM-guided titration

+14.6 pp

Estimated TIR treatment difference favouring CGM-based algorithmic titration.

30 adults with T2D; 16 weeks.
Noninferiority confirmed; superiority exploratory.
No severe hypoglycaemia. Larger studies needed.

PRIOR WEEKLY TRIALS

Safety still matters

ONWARDS 6 • T1D

Icodec: 1.9× the level 2/3 hypoglycaemia event rate vs degludec.

QWINT-5 • T1D

Severe hypoglycaemia: 10% with efsitora vs 3% with degludec.

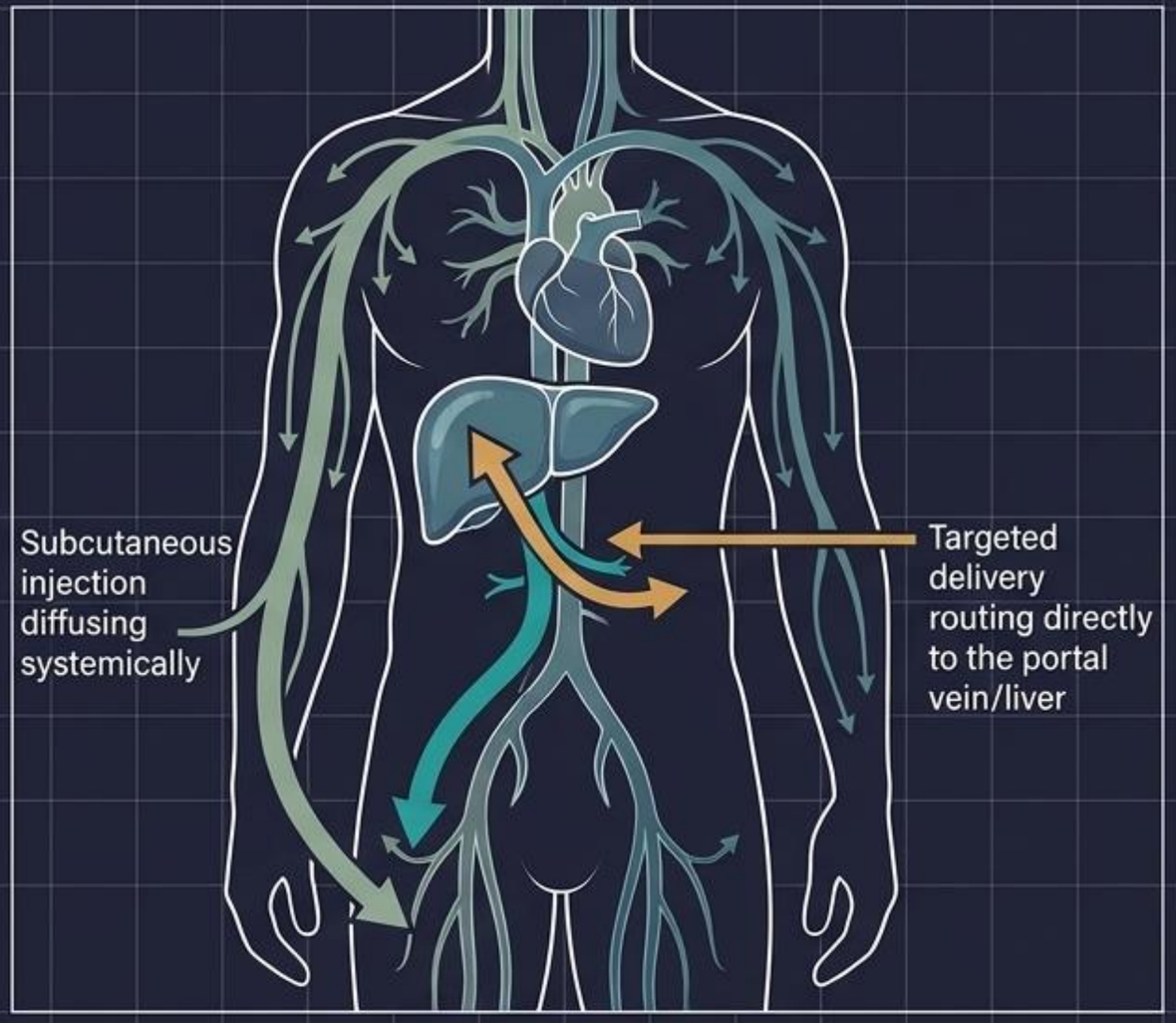
Weekly basal insulin is not recommended routinely in T1D.

Choose the basal insulin, titration strategy and monitoring together—not injection frequency alone.

CGM RCT publication is from 2026; presentation at EASD Milan was not confirmed. TIR = 70–180 mg/dL; pp = percentage points.

Sources: Tresiba US PI / EMA SmPC; El Fathi et al., DTT 2026; ONWARDS 6, Lancet 2023; QWINT-5, Lancet 2024.

Portal vs. Systemic Exposure



The Biological Rationale:

Endogenous insulin reaches the liver first; standard subcutaneous insulin enters systemic blood. HDV-lispro aims to alter hepatic exposure to match physiology.

Clinical Evidence (OPTI-2 Trial):

13-week maintenance phase showed a reduction in Level 2 hypoglycemia events (Rate ratio 0.72).

Vanguard Appraisal:

The primary hypoglycemia superiority was not met in the optimization phase. A delivery hypothesis and secondary-period signals require larger confirmatory trials before changing practice.

Gemini Notebook

Redefining Type 1 Diabetes: Bypassing Systemic Immunosuppression



Step 1: Cell Source

VX-880 (Zimislecel) - Fully differentiated, stem-cell-derived islet cells are transplanted to restore endogenous insulin production.



Step 2: Targeted Immune Blockade

Patients receive Tegoprubart (an anti-CD40L monoclonal antibody) instead of highly toxic, systemic immunosuppressants.



Step 3: Functional Cure

12 out of 12 patients in the INNODIA cohort achieved complete insulin independence with sustained islet graft survival and elimination of severe hypoglycemic events.

Gemini Notebook

Bypassing Systemic Immunosuppression



Step 1: Cell Source

VX-880 (Zimislecel) fully differentiated stem-cell-derived islets restore endogenous insulin production.



Step 2: Targeted Immune Blockade

Tegoprubart (anti-CD40L monoclonal antibody) provides co-stimulatory blockade, eliminating the need for nephrotoxic calcineurin inhibitors (tacrolimus/cyclosporine).



Step 3: Functional Cure

INNODIA cohort trial updates show 100% of participants achieved sustained insulin independence with excellent renal safety.
(FORWARD trial alone showed 83% independence).

Gemini Notebook

THE IMMUNOSUPPRESSION BYPASS: FUNCTIONAL CELLULAR CURES

Stem-Cell Derived Islet (VX-880 / Zimislecel)

Fully differentiated pancreatic islets implanted into the patient

Toxic Immunosuppressants



Tegoprubart Stealth Cloak

An anti-CD40L monoclonal antibody protects the graft without systemic toxicity

CLINICAL RESULT (INNODIA Symposium Data)

100%

12 out of 12 patients in Ricordi cohort

83%

in the FORWARD trial aggregate

reached total exogenous insulin independence, eliminating severe hypoglycemic events.

Gemini Notebook

EXECUTING THE STAGE 2 INTERVENTION PROTOCOL

PHASE 1: GATEKEEPING

- Confirm Stage 2 criteria (≥2 autoantibodies, confirmed dysglycemia via OGTT).
- Verify negative EBV/CMV PCR.

PHASE 2: PREPARATION

- Calculate Body Surface Area (BSA) for specific dosing.
- Administer premedications.

PHASE 3: EXECUTION

- Administer Tzield (teplizumab-mzwv) via a strict 14-day BSA-escalation infusion protocol.
- Monitor CBC and LFTs.



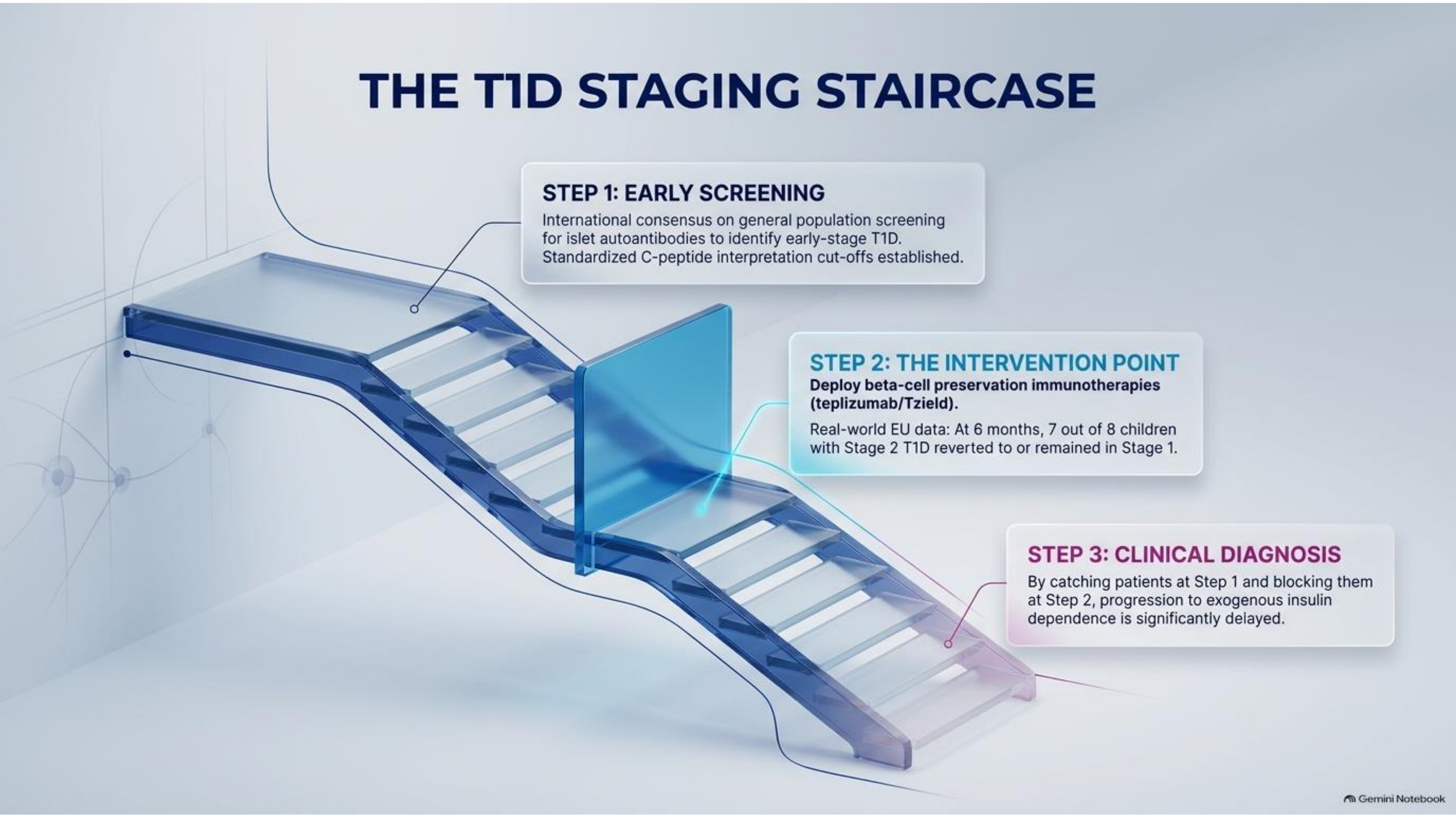
PHASE 4: SURVEILLANCE

- Mandatory monitoring for viral reactivation (EBV/CMV) due to the boxed warning.
- Confirm lymphocyte recovery.

AMBER = GATEKEEPING/SURVEILLANCE
SAGE = PREPARATION
TEAL = EXECUTION

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THE T1D STAGING STAIRCASE



STEP 1: EARLY SCREENING

International consensus on general population screening for islet autoantibodies to identify early-stage T1D. Standardized C-peptide interpretation cut-offs established.

STEP 2: THE INTERVENTION POINT

Deploy beta-cell preservation immunotherapies (teplizumab/Tzield).

Real-world EU data: At 6 months, 7 out of 8 children with Stage 2 T1D reverted to or remained in Stage 1.

STEP 3: CLINICAL DIAGNOSIS

By catching patients at Step 1 and blocking them at Step 2, progression to exogenous insulin dependence is significantly delayed.

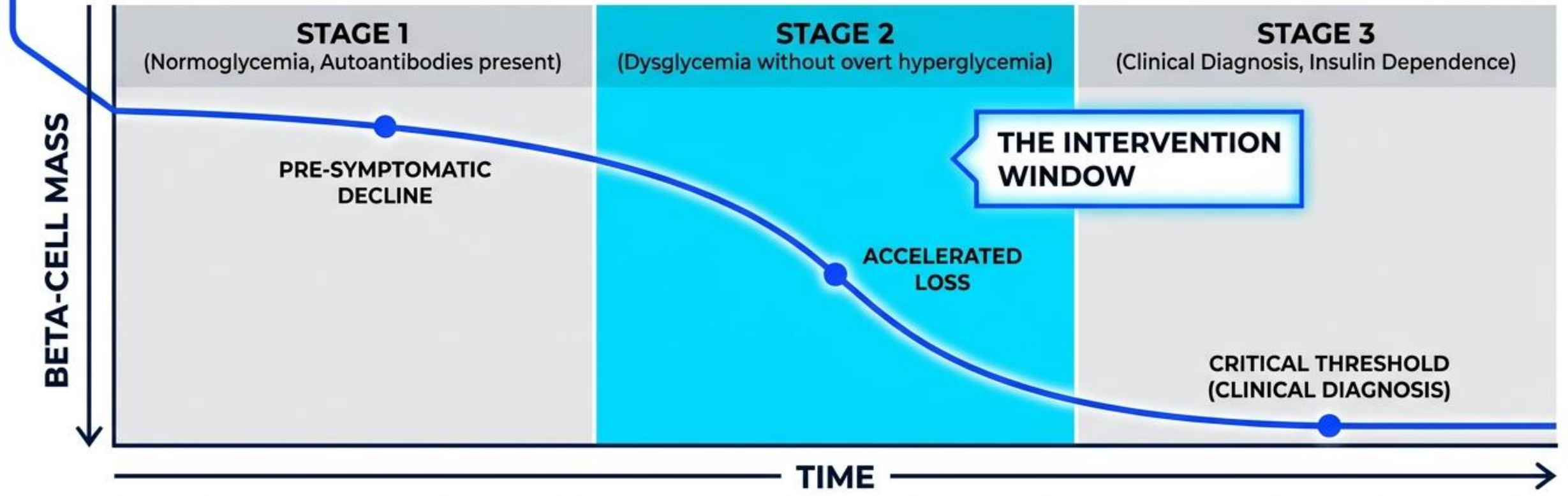
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Executing the Tzield (teplizumab-mzwv) Clinical Protocol

A chronological playbook for patient staging, 14-day infusion administration, and safety surveillance in Stage 2 Type 1 Diabetes.

Gemini Notebook

DISEASE PROGRESSION CURVE



MECHANISM OF ACTION: TEPLIZUMAB-MZWV

Teplizumab-mzwv is a **CD3-directed monoclonal antibody**. It binds to CD3 on T lymphocytes, causing partial agonistic signaling, **deactivation of beta-cell autoreactive T cells**, and an **increase in regulatory T cells**.

CLINICAL OBJECTIVE

Delay the onset of Stage 3 T1D.

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STAGE 2 PATIENT QUALIFICATION GATE

AUTOANTIBODY CONFIRMATION

Must have ≥2 positive pancreatic islet cell autoantibodies:

- ☑ GADA
- ☑ IA-2A
- ☑ IAA
- ☑ ZnT8A
- ☑ ICA

DYSGLYCEMIA PARAMETERS

Confirmed dysglycemia without overt hyperglycemia.

REQUIRED TEST:

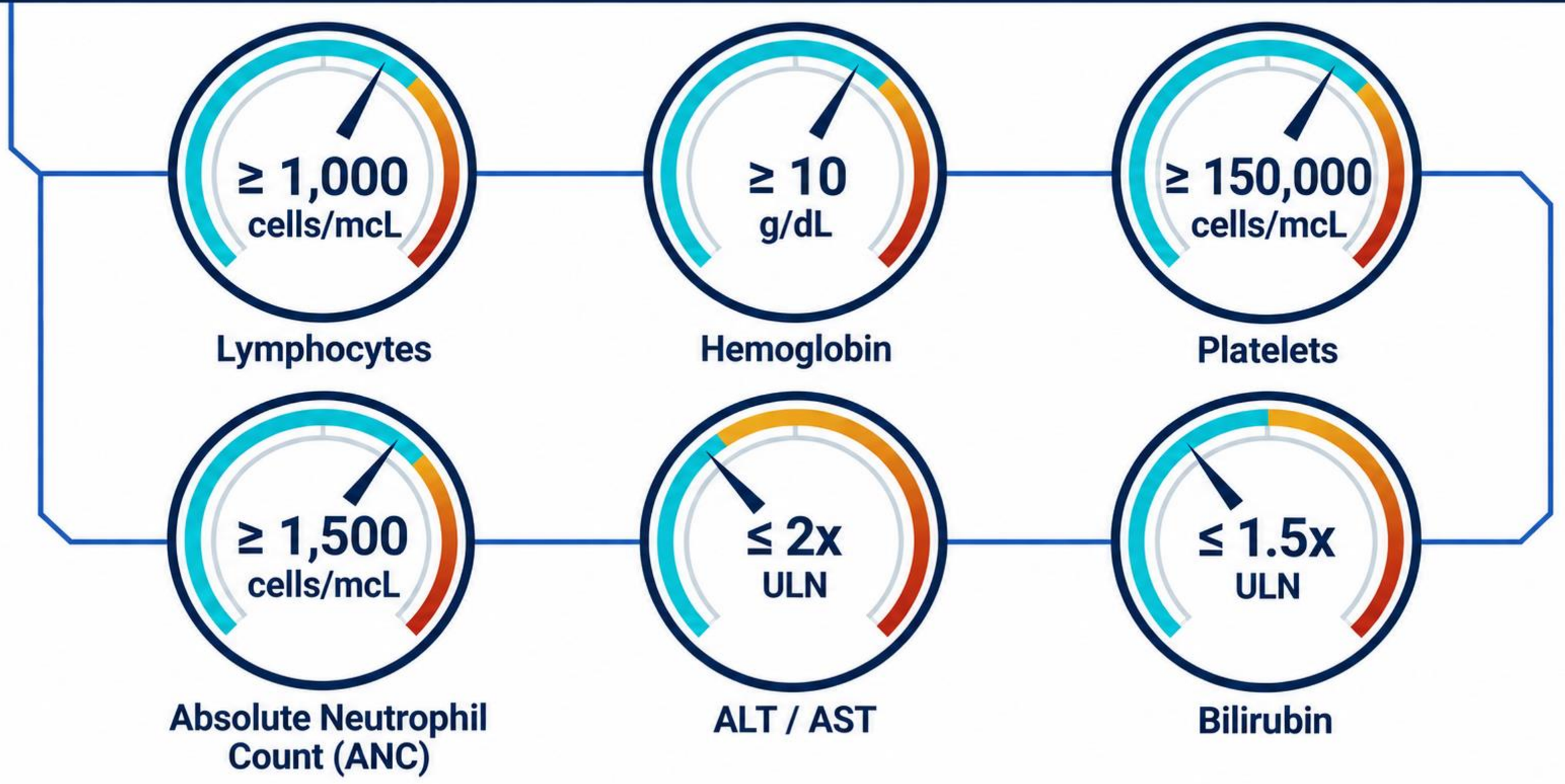
Oral Glucose Tolerance Test (OGTT)

AUTOIMMUNE ORIGIN

Clinical history must exclude Type 2 Diabetes, MODY, LADA, or secondary secondary diabetes.

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Prior to initiating TZIELD, confirm the following baseline parameters.



WARNING: Viral Reactivation

The Threat

Serious, life-threatening cases of **viral reactivation**, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

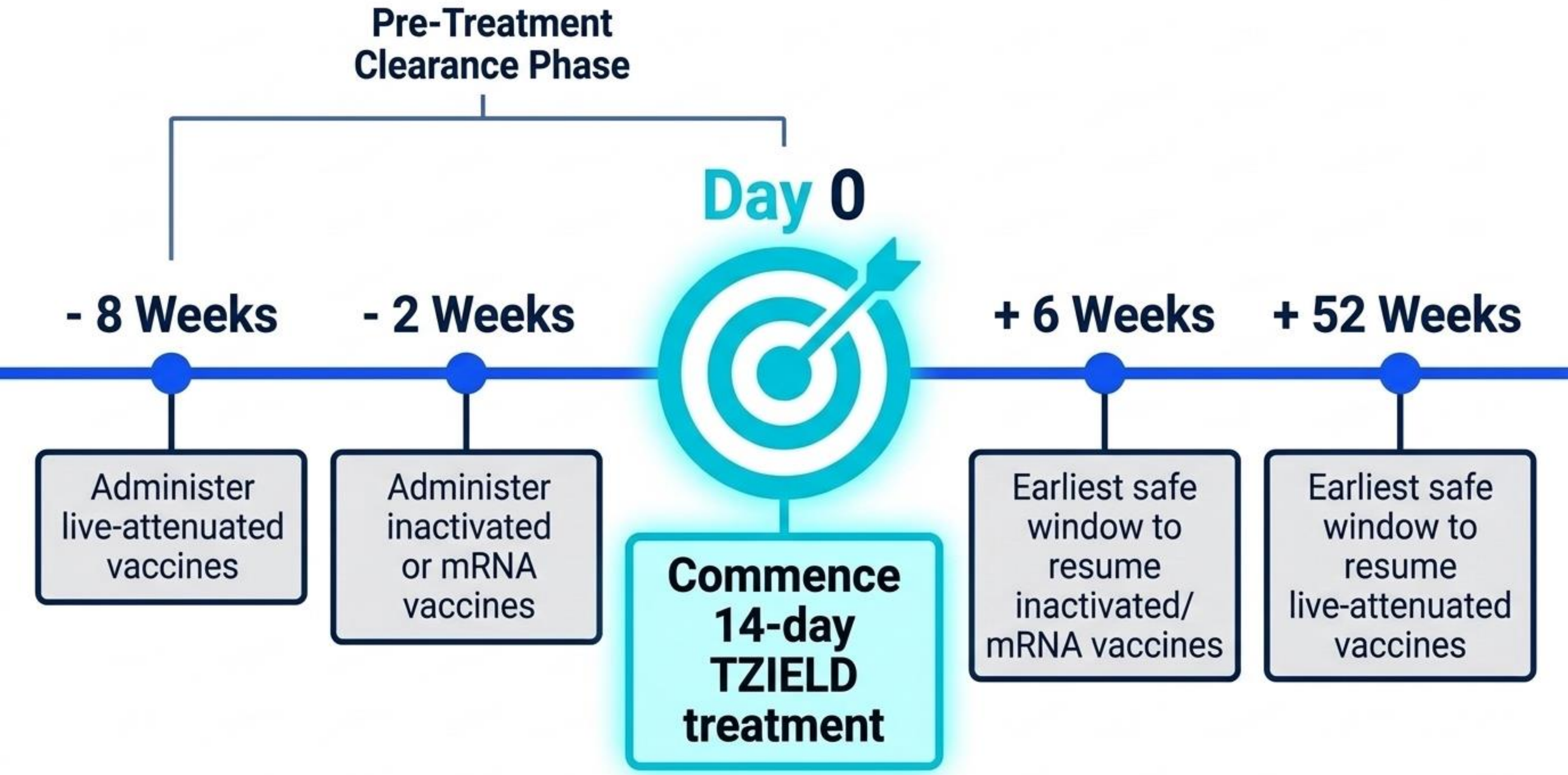
The Requirement

1: Evaluate for active EBV/CMV prior to treatment. → **2: Confirm undetectable viral load via PCR testing.** →  **3: Absolute Contraindication: Do not use in patients with clinical/lab evidence of active EBV/CMV.**

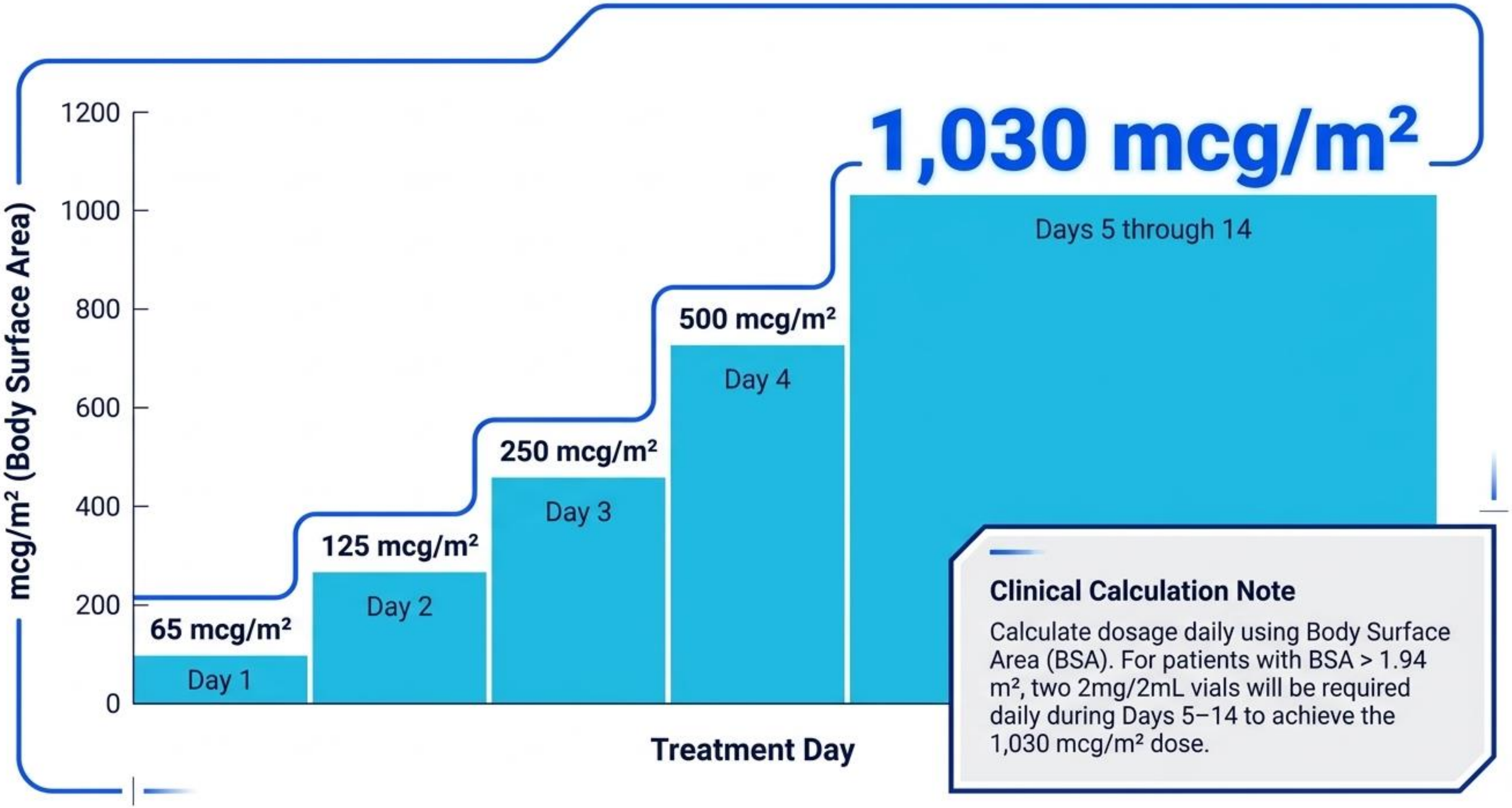
High-Risk Populations

- Immunocompromised patients
- Patients with Down syndrome
- Patients with persistent, severe lymphopenia.

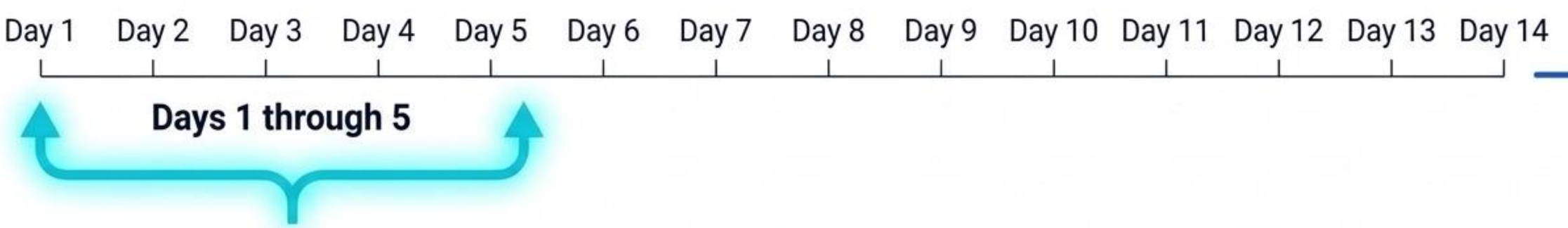
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Antipyretic / Analgesic

(Required)

NSAID or Acetaminophen

Antihistamine

(Required)

Administer to mitigate early CRS manifestations.

Antiemetic

(Highly Recommended)

Especially for pediatric patients <8 years due to vomiting/diarrhea risk.

Administer prior to each of the first 5 infusions. Treat symptoms of Cytokine Release Syndrome (CRS) with antipyretics, antihistamines, and/or antiemetics as needed.

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Stage 1

The First Dilution



- Extract **2 mL** from **TZIELD** single-dose vial.
- Add to **18 mL** of **0.9% NaCl**.
- Mix gently. **DO NOT SHAKE**.
- Yields **100 mcg/mL** solution.

Stage 2

The Calculated Draw



- Using an appropriately sized syringe, withdraw exact volume for today's BSA-calculated dose.
- Discard the unused portion.

Stage 3

The Final Infusion Bag



- Add syringe contents to **25 mL 0.9% NaCl** PVC infusion bag.
- Store at room temp (15°C–30°C).
- Complete infusion within **4 hours**.

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Minimum Infusion Duration

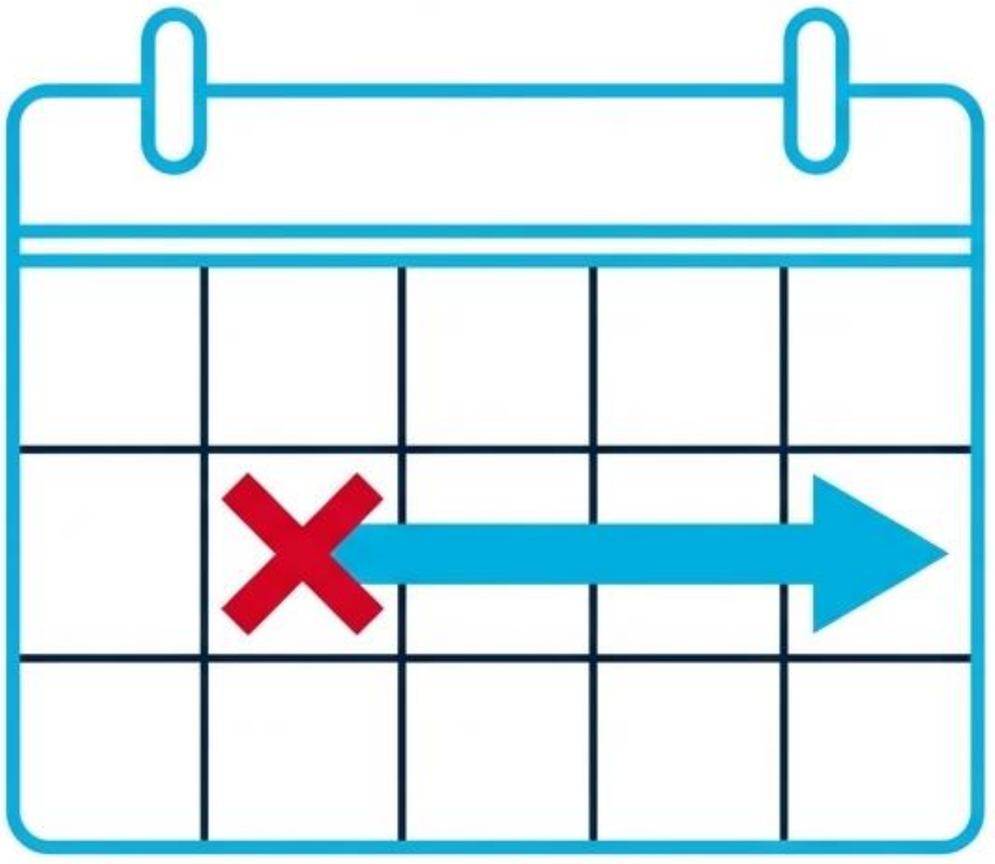
Patients ≥ 8 Years Old (and Adults) — **30 Minutes**

Pediatric Patients 1 to < 8 Years Old — **2 Hours**

Technical Infusion Rules

- ✓ Do not use light-protected infusion sets.
- ✓ In-line filters not recommended (use PES only if necessary).
- ✓ Flush IV set with ≥ priming volume of 0.9% NaCl at the same rate post-infusion.

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Missed Dose Protocol

The Rule:
If a planned TZIELD infusion is missed, resume dosing by administering all remaining doses on consecutive days.

The Goal:
Complete the full 14-dose treatment course, regardless of the delay.

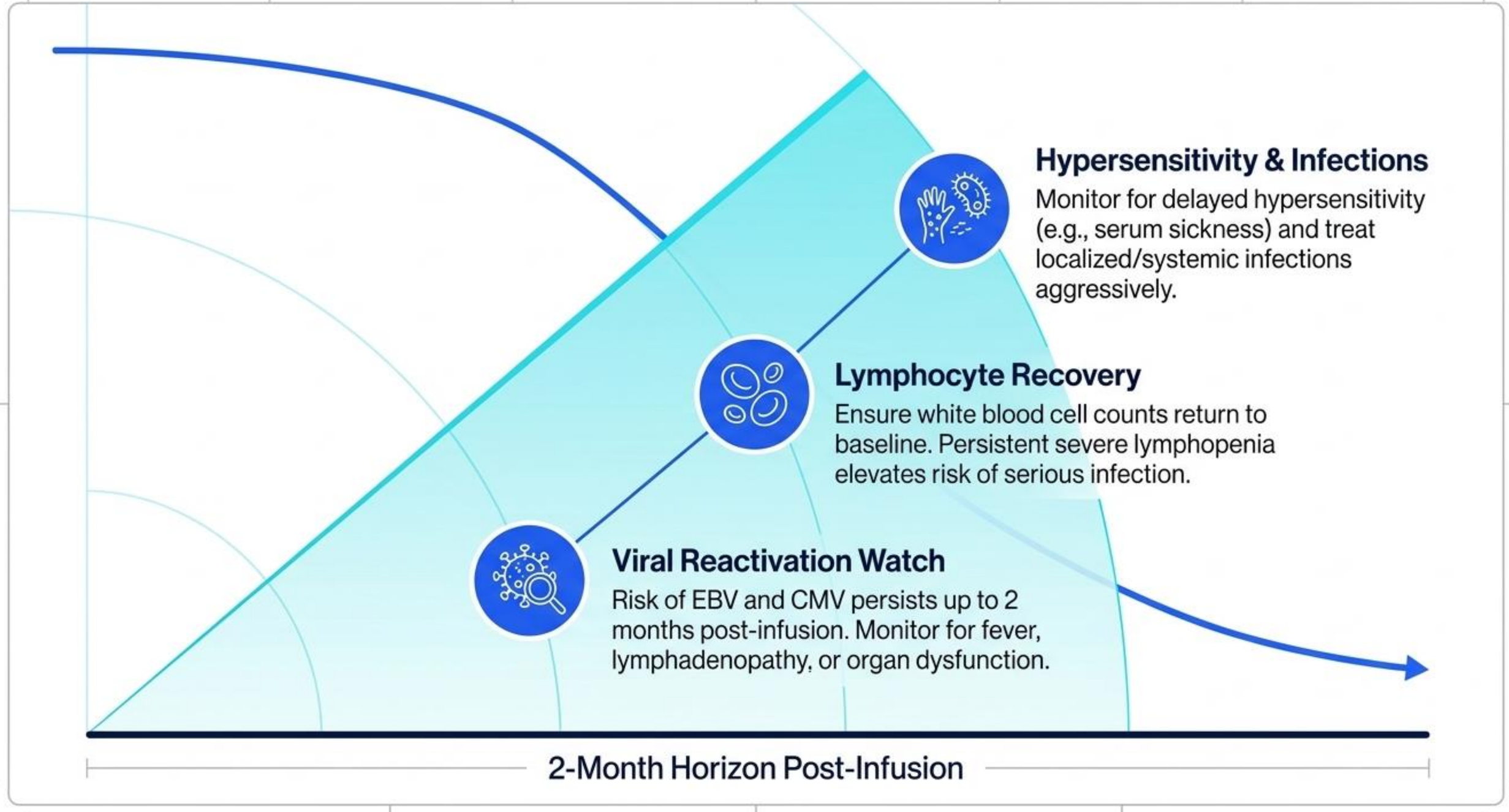
NEVER ADMINISTER TWO DOSES ON THE SAME DAY.

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ADVERSE EVENT DISCONTINUATION MATRIX

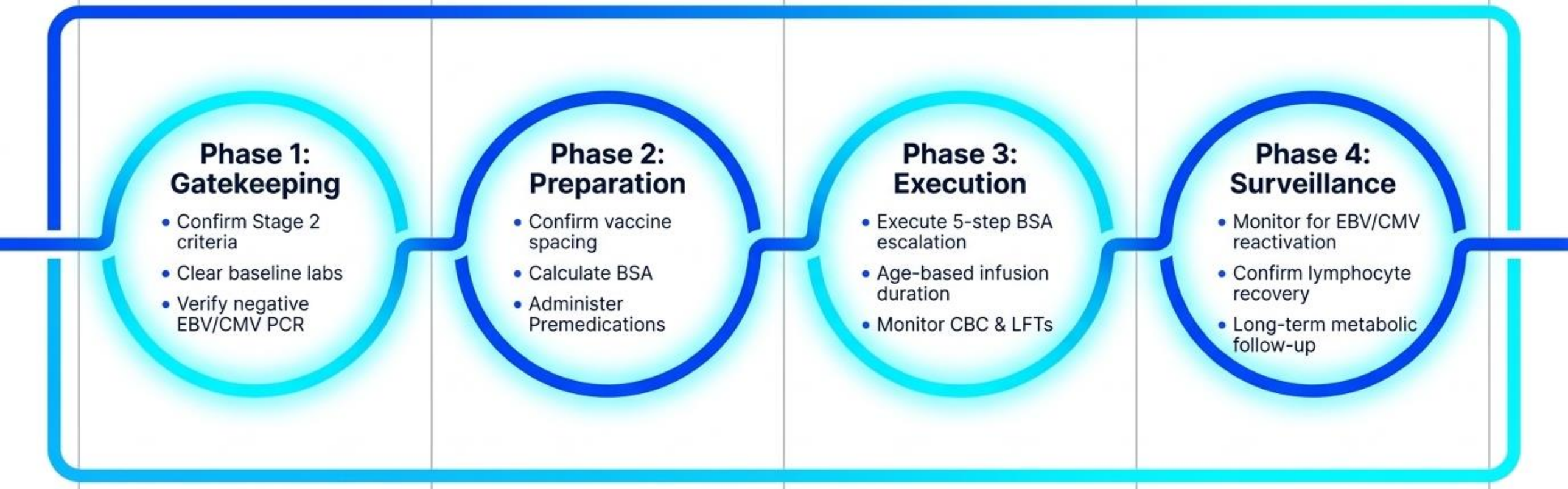
Threat & Presentation	Monitoring Cadence	Hard Stop Triggers
Lymphopenia (78% incidence) | Nadir at Day 5, recovery within 2 weeks.	**CBC every 2-3 days.**	**Permanently discontinue if <500 cells/mcL lasts 1 week or longer.**
Cytokine Release Syndrome (CRS) | Fever, nausea, headache. First 5 days.	**Liver enzymes and bilirubin daily during early treatment.**	**Pause dosing 1-2 days if severe. Permanently stop if ALT/AST > 5x ULN or Bilirubin > 3x ULN.**
Viral Reactivation (Boxed Warning) | EBV/CMV reactivation, swollen glands, severe fatigue.	**Clinical symptoms during treatment + 2 months post-infusion.**	**Discontinue immediately if suspected. Permanently discontinue if viral load PCR is confirmed positive.**

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The Tzield Clinical Pathway Master Map



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FROM OBSERVATION TO ANTICIPATION

OBSERVATION
Measuring glucose

→

ANTICIPATION
Metabolic risk forecasting & CKM

→

INTEGRATION
Closed-loop action & AI

The Paradigm Shift

Diabetes tech is moving from measuring glucose to forecasting metabolic risk and closing the loop between data and action.

Expanded CGM Use

2026 EASD position expands CGM CGM to non-insulin T2D and basal-only patients to capture high glycemic variability.

Appraising the Evidence

FreeDM2 trial emulations show massive mortality/hospitalization reductions associated with CGM use, but matching emulation does not replace randomized evidence.

CGM alone does not prevent death; the resulting clinical action does.

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EASD 2026 Technology Evidence Review

A Specialist Synthesis for IEMRC & Prof. Mansour Siavash

Public-source review completed 11 October 2026.

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The 2026 Paradigm Shift: From Observation to Anticipation

Current Status: Macro Trend



Diabetes technology is moving from measuring glucose to anticipating metabolic risk, supporting decisions, and closing the loop between data and action.

The 5 Key Signals

1. CGM relevance expands in T2D.
2. Dual sensing achieves regulatory authorization, but requires outcomes evidence.
3. AID superiority depends heavily on the comparator.
4. AI screening is clinically mature; AI autonomous treatment is not.
5. Access, training, and engagement dictate the actual clinical benefit.

Gemini Notebook

Predictive CGM

From Glucose Monitoring to Glucose Anticipation

A key innovation highlighted at EASD 2026 (Milan)

EASD 2026
Milan, Italy
15–19 September 2026

1 What is predictive CGM?

Predictive continuous glucose monitoring combines real-time glucose measurements with mathematical models, machine learning or artificial intelligence to forecast future glucose concentrations and the risk of hypo- or hyperglycemia.

Traditional CGM

Tells us **what** glucose **is doing**



- Current glucose value
- Trend arrow
- Retrospective profile

Predictive CGM

Tells us **what** glucose **may do next**



- Forecast glucose values
- Probability of low or high glucose
- Early warning
- Opportunity to intervene

2 How does it work?



1. **CGM sensor**
   Glucose readings every few minutes



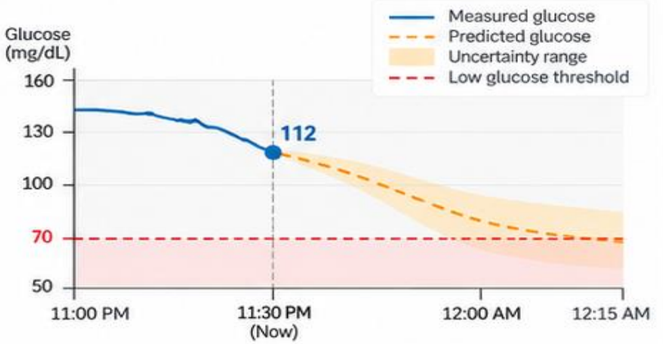
2. **Predictive algorithm**
   Recent glucose trajectory
   + personal patterns
   + optional inputs (insulin, meals, activity)



3. **Forecast and alerts**
   - Expected glucose values (15, 30 or 60 minutes ahead)
   - Risk of hypoglycemia
   - Early warning to allow preventive action

3 Example: Preventing nocturnal hypoglycemia

A predictive alert can warn the patient before glucose reaches the low threshold, creating an opportunity for individualized action.



4 Predictive CGM at EASD 2026

Dedicated sessions highlighted clinical utility, nocturnal hypoglycemia and real-world experience.

Date	Session title	Main focus
September 29	One technology, many realities: the real-world value of (predictive) CGM	Clinical utility
September 30	Did you sleep well? How predictive CGM technology transforms nocturnal hypoglycaemia management	Overnight hypoglycemia prevention
October 1	Exploring the power of predictive CGM: Insights on performance, psychology, and the perspective of people living with diabetes	Prediction accuracy, patient experience

5 Roche Accu-Chek SmartGuide Predict

A concrete example of predictive CGM presented at EASD 2026.



Three prediction functions

30 minutes — Low Glucose Predict
Warns when hypoglycemia is likely within 30 minutes.

2 hours — Glucose Predict
Displays a forecast glucose trajectory, with increasing uncertainty over time.

7 hours — Night Low Predict
Estimates the risk of hypoglycemia during the coming night.

6 Performance data (SmartGuide Predict)

A. Algorithm validation study

Measure	Result
Sensitivity for low glucose prediction (within 30 minutes)	95.2%
Specificity	98.9%
Mean warning lead time	16.2 minutes
Sensitivity for nighttime low prediction	55.3%
Specificity for nighttime low prediction	91.6%

B. Real-world observational study (2026)

Retrospective study of **249 people using** Night Low Predict.
When predictions were received vs. nights without predictions:

20% lower odds of any nocturnal hypoglycemic event

31% lower odds of Level 2 nocturnal hypoglycemia (subset of 159)

No associated increase in hyperglycemic events.
Retrospective and observational study – does not prove causality.

7 How predictive CGM fits within diabetes technology

Conventional CGM	Predictive CGM	Predictive low-glucose suspend	Advanced hybrid closed-loop / AID
Measures and displays glucose	Forecasts future glucose or hypoglycemia risk	Predicts hypoglycemia	Predicts and responds to glucose changes
Patient responds	Patient responds proactively	Pump suspends insulin	Algorithm adjusts insulin delivery

8 Potential benefits

- Early detection and prevention of hypoglycemia (especially nocturnal)
- Greater confidence and better sleep
- Particularly useful for people on multiple daily injections
- May reduce diabetes distress
- Support for individualized treatment decisions

9 Key considerations and limitations

- Predictions are estimates with uncertainty
- Accuracy decreases over longer horizons
- Missed events and false alarms can occur
- Not a direct instruction to administer insulin
- Clinical benefits beyond modern CGM still need confirmation in large, independent trials

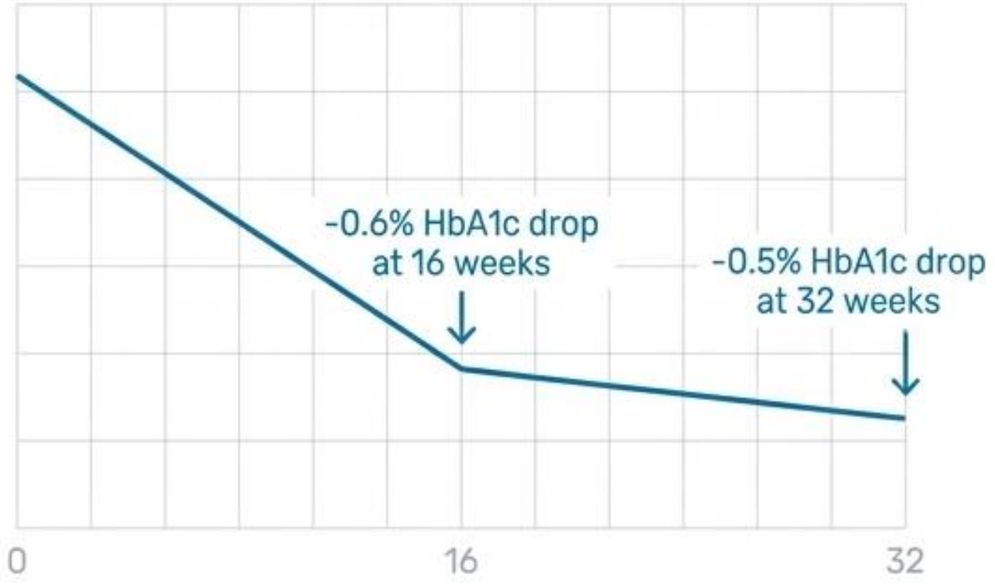
Take-home message

Predictive CGM is a genuine technological advance.
The goal is no longer simply to recognize abnormal glucose, but to anticipate clinically important excursions early enough to prevent them.

Efficacy in Modern T2D Therapy: FreeDM2 & Outcome Emulations

Published Evidence / Observational Caution

FreeDM2 Trial Data



FreeDM2 Trial Data
(N=303 on basal insulin + SGLT2/incretin)

45%

Mortality Reduction
(12 months, target-trial emulation)

47-81%

Hospitalization Reduction
(French study across varied insulin groups)

Clinical Interpretation: Associations strengthen the case for outcomes research, but matching emulation does not replace randomized evidence. Do not present observational percentages as proof that CGM alone prevents death.

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Translating Evidence to Guidelines: EASD 2026 Consultation

Status: Consultation Draft

	Draft Position	Certainty
T1D, basal-bolus insulin	Offer as an option	Low
T1D, basal insulin only	Offer as an option	Low
T1D, other treatments	Offer as an option	Low
T2D, basal-bolus insulin	Offer as an option	Low
T2D, basal insulin only	Offer as an option	Low
T2D, non-insulin agents	Offer as an option	Very low
Pregnancy (GDM/pre-existing DM)	Offer as an option	Very low
Inpatient/critical care	Offer as an option	Very low
Masked CGM, routine use	Suggest against	Low

Strategic Directive:

Define the clinical question before prescribing a sensor (basal-dose adjustment, suspected nocturnal lows, lifestyle learning).

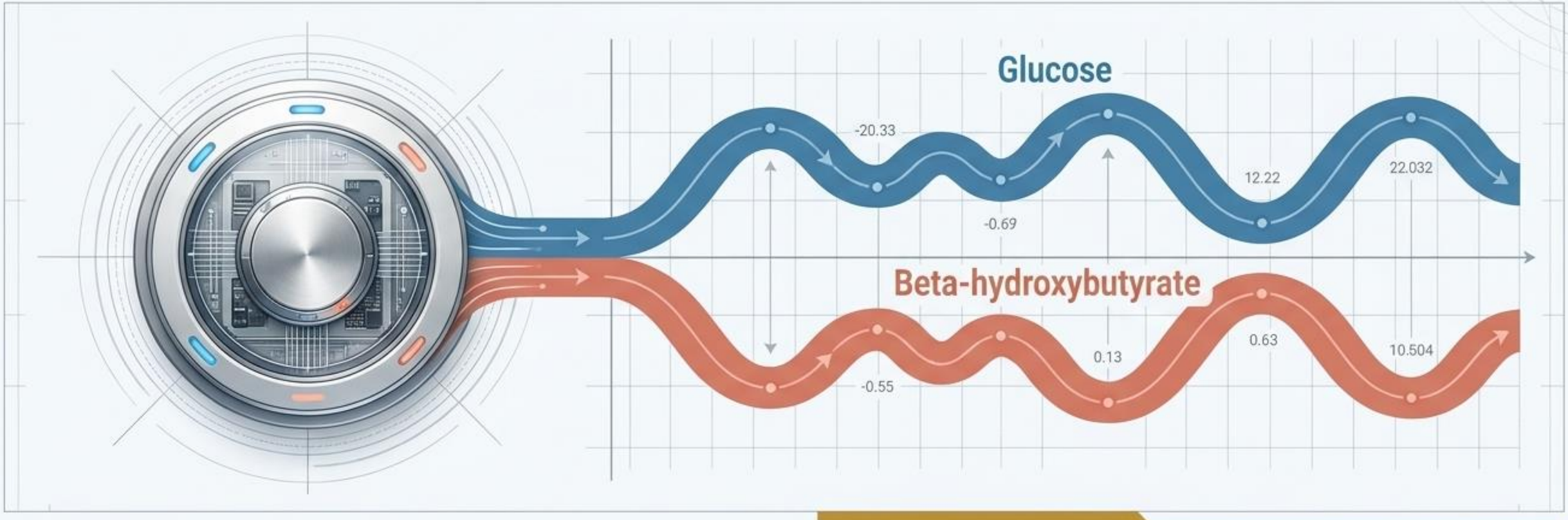
Guideline Note:

Initiative supports offering CGM across treatment groups. Final published wording requires verification.

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The Regulatory Milestone: Dual Sensing and the Libre Duo

Status: FDA De Novo Authorized



Key Facts

- FDA De Novo authorization (August 2026) for real-time dual interpretation.
- Approved for diabetes management from age 2 years.
- European CE marking announced May 2026.

Clinical Requirement

- The label mandates integrating ketone data with glucose readings, physical symptoms, eating patterns, and exercise.
- A raised ketone value does not, by itself, diagnose ketoacidosis.

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DKA Prevention: The GLP-1 & SGLT2 Era Safety Net

Status: Clinical Implementation Gap



Core Insight:

CKM provides earlier recognition of ketosis when glucose is not markedly raised.

Clinical Reality Check:

Capability does not automatically equal demonstrated DKA prevention.

Open Questions for Practice:

Does the early alert reliably lead to timely action? Who receives alerts outside clinic hours?

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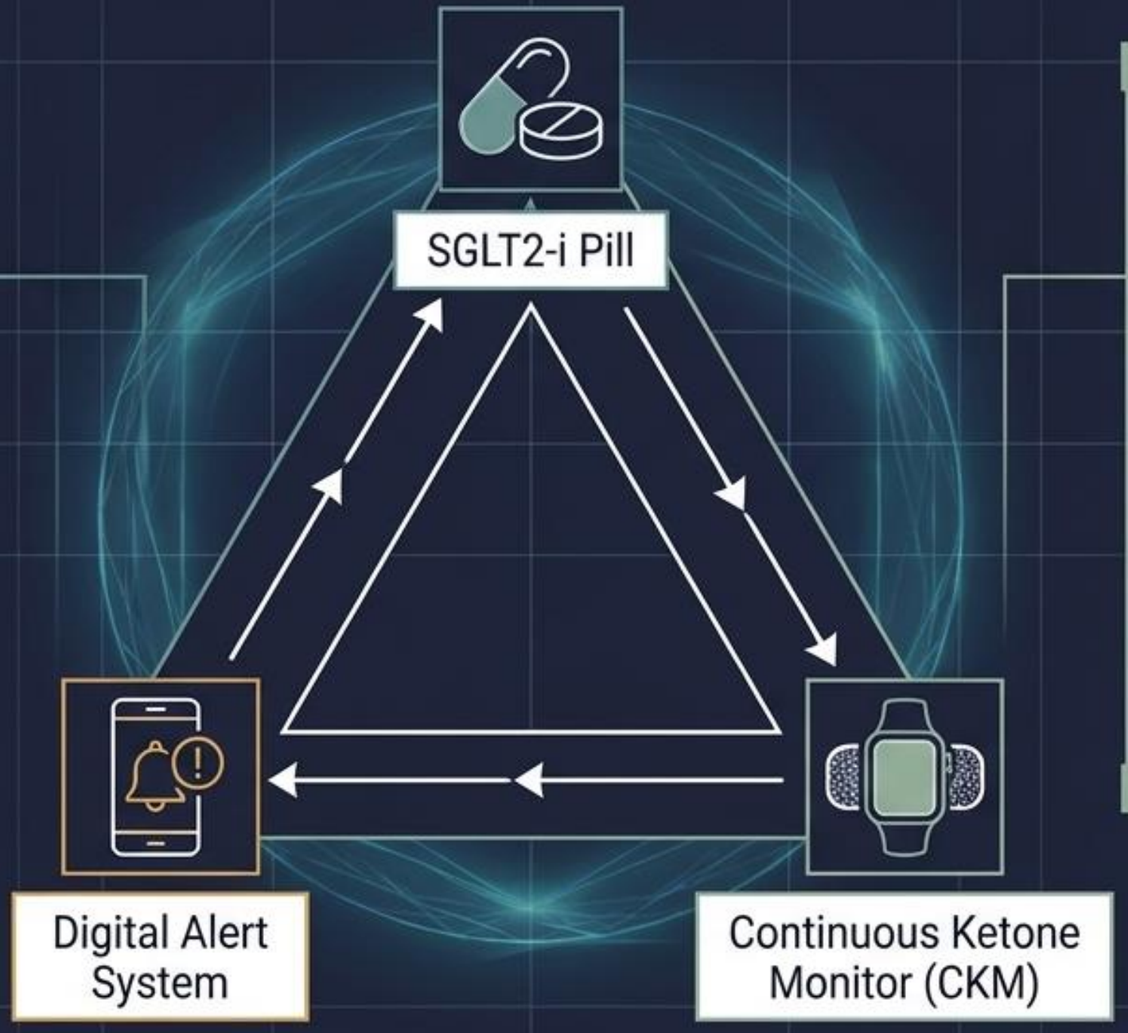
Unlocking SGLT2i in T1D via Dual Sensing

The Clinical Problem:

SGLT2 inhibitors offer immense heart/kidney protection but are withheld in T1D due to severe Diabetic Ketoacidosis (DKA) risks.

The Regulatory Milestone:

Libre Duo achieves FDA De Novo authorization for real-time dual interpretation of glucose and beta-hydroxybutyrate.



Trial Outcomes:

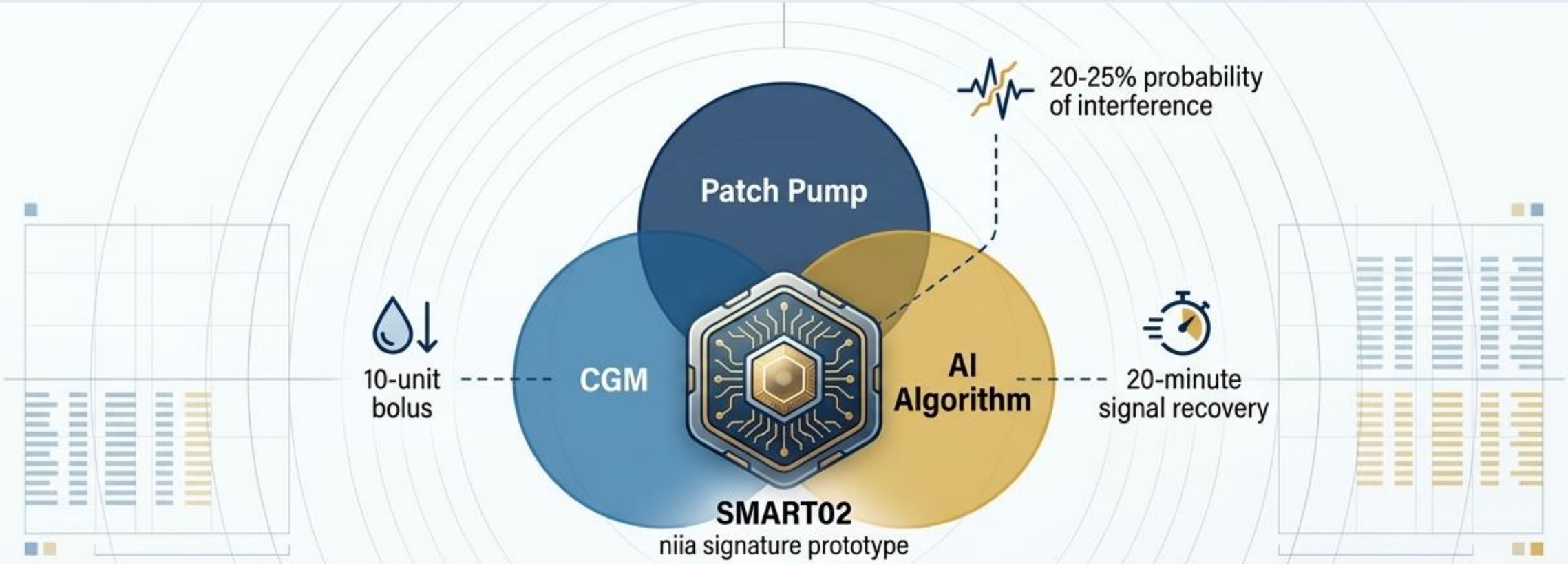
Adults with T1D using SGLT2i paired with CKM experienced zero increases in DKA episodes while achieving greater time-in-range.

A raised ketone value triggers protocolized action before clinical crisis.

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The System-Level Engineering of Single-Wearables

Status: Investigational / Prototype



Context: SIBIONICS / PharmaSens SMART02 prototype combines sensing and delivery to reduce insertion burden.

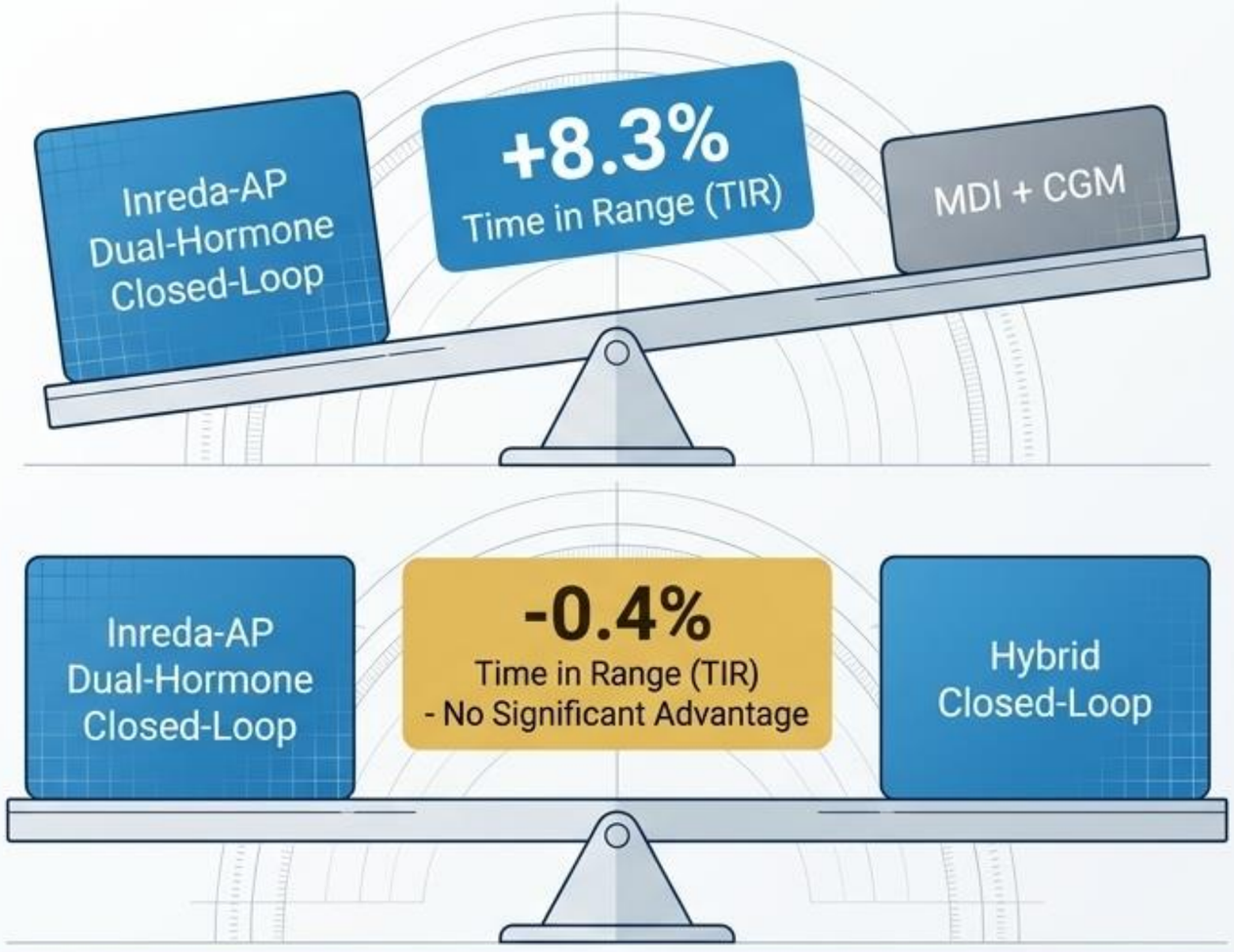
The Engineering Hurdle: Nearby insulin infusion disturbs sensor readings. Temporary interference noted during boluses ≥10 units.

Clinical Appraisal: A single wearable places sensing and delivery failures close together. True evaluation must address transient signal loss, occlusion, and adhesive failure, not just sensor accuracy.

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AID Efficacy: The Comparator Dictates the Conclusion

Status:
Published Trial Data



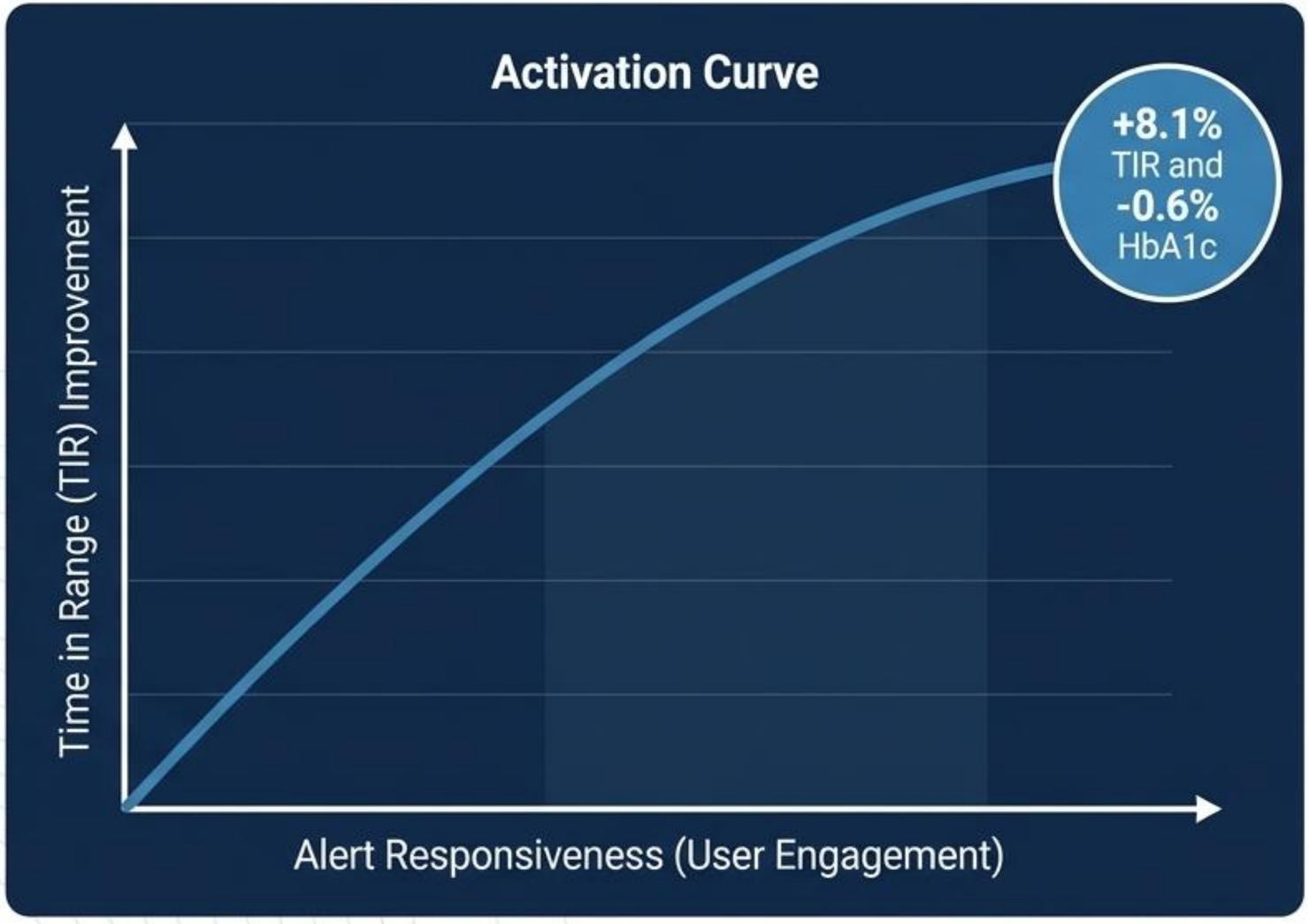
Core Insight: Greater automation is not synonymous with clinical superiority.

Trial Context: The DARE trial (N=243, 12 months) shows fully closed-loop systems dominate standard MDI but plateau when compared to modern hybrid closed-loop systems. Evaluate the comparator, event rates (9 severe hypos vs 2), and user treatment burden.

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Status: EASD Congress Result

Smart MDI: The User Engagement Multiplier



Context:

6-month MiniMed study (N=143, initial HbA1c >8%).
Combines insulin pen, CGM, and dose prompts.

The Crucial Nuance:

System is non-inferior to MDI + CGM.

However, among users, high responders achieve dramatic results.

This is an engagement comparison, not a randomized between-arm treatment effect.

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Smart MDI: Integrated Insulin Pen, CGM and Decision Support

6-Month MiniMed Study in People with Type 2 Diabetes

EASD 2026 CONGRESS MILAN, ITALY

IEMRC Isfahan Endocrine & Metabolism Research Center

Study Design and Population

Design 6-month, multi-center prospective study (MiniMed)

Population Adults with type 2 diabetes using multiple daily injections
- N = 143
- Baseline HbA1c > 8%

Intervention **Smart MDI system**
- Smart insulin pen (with dose capture)
- CGM
- Mobile app with dose calculator, alerts and feedback

Comparator Standard MDI + CGM (without smart decision support)

Primary Outcomes
- Time in Range (TIR)
- HbA1c

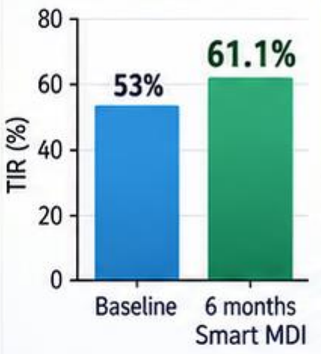
Follow-up 6 months



Smart Insulin Pen (dose capture) + CGM (real-time glucose) → Decision Support App (dose guidance, alerts and reminders)

Main Results at 6 Months

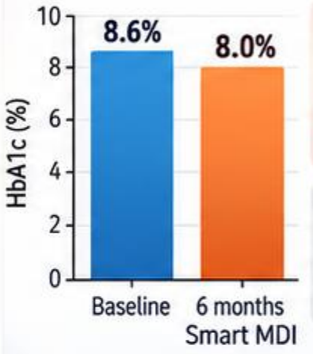
Time in Range (70–180 mg/dL)



+8.1% absolute increase in TIR

Participants achieved **8.1 percentage points more time in range** compared with baseline.

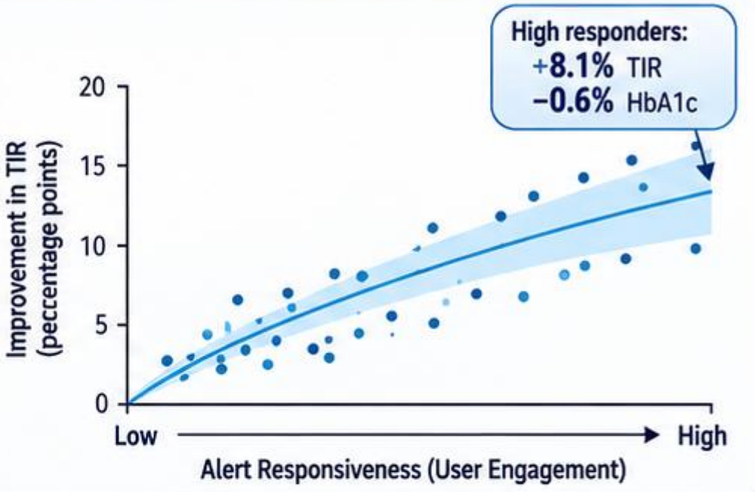
HbA1c (%)



−0.6% absolute ireduction in HbA1c

Mean HbA1c decreased by **0.6 percentage points** from baseline.

User Engagement Drives Outcomes



Proportion of High Responders



High responders (N=49/143)

High responders
Regularly acted on app alerts and dose prompts.

High responders achieved significantly greater improvements in TIR and HbA1c compared with low/moderate responders.

Key Findings

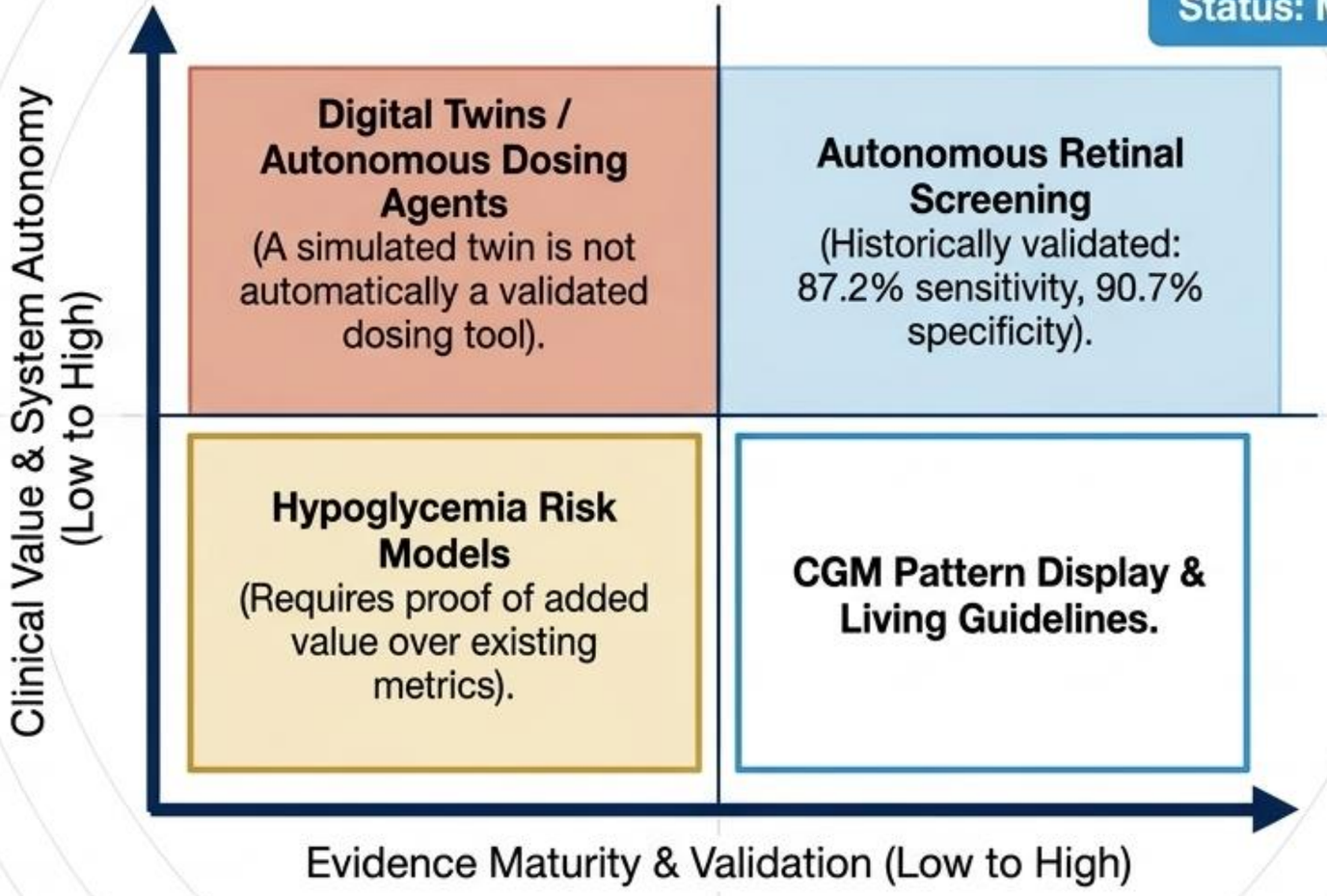
Efficacy	Smart MDI improved TIR by **+8.1%** and reduced HbA1c by **−0.6%** at 6 months.
Non-inferiority	Smart MDI was non-inferior to standard MDI + CGM for the primary outcome.
Engagement effect	Among users, high engagement with alerts and recommendations led to markedly better outcomes.
Clinical relevance	Combining insulin pen, CGM and decision support can enhance self-management in type 2 diabetes treated with MDI.

Take-Home Message

In people with type 2 diabetes using multiple daily injections, an integrated system of a smart insulin pen, CGM and decision support improved glycemic outcomes, particularly in patients who actively engaged with the system. Smart MDI offers a practical, technology-enabled approach to enhance insulin self-management.

Separating AI Capability from Autonomous Action

Status: Mixed / Domain Dependent



Core Directive: Separate screening, forecasting, decision support, and autonomous action. Evidence for one function cannot be transferred to another.

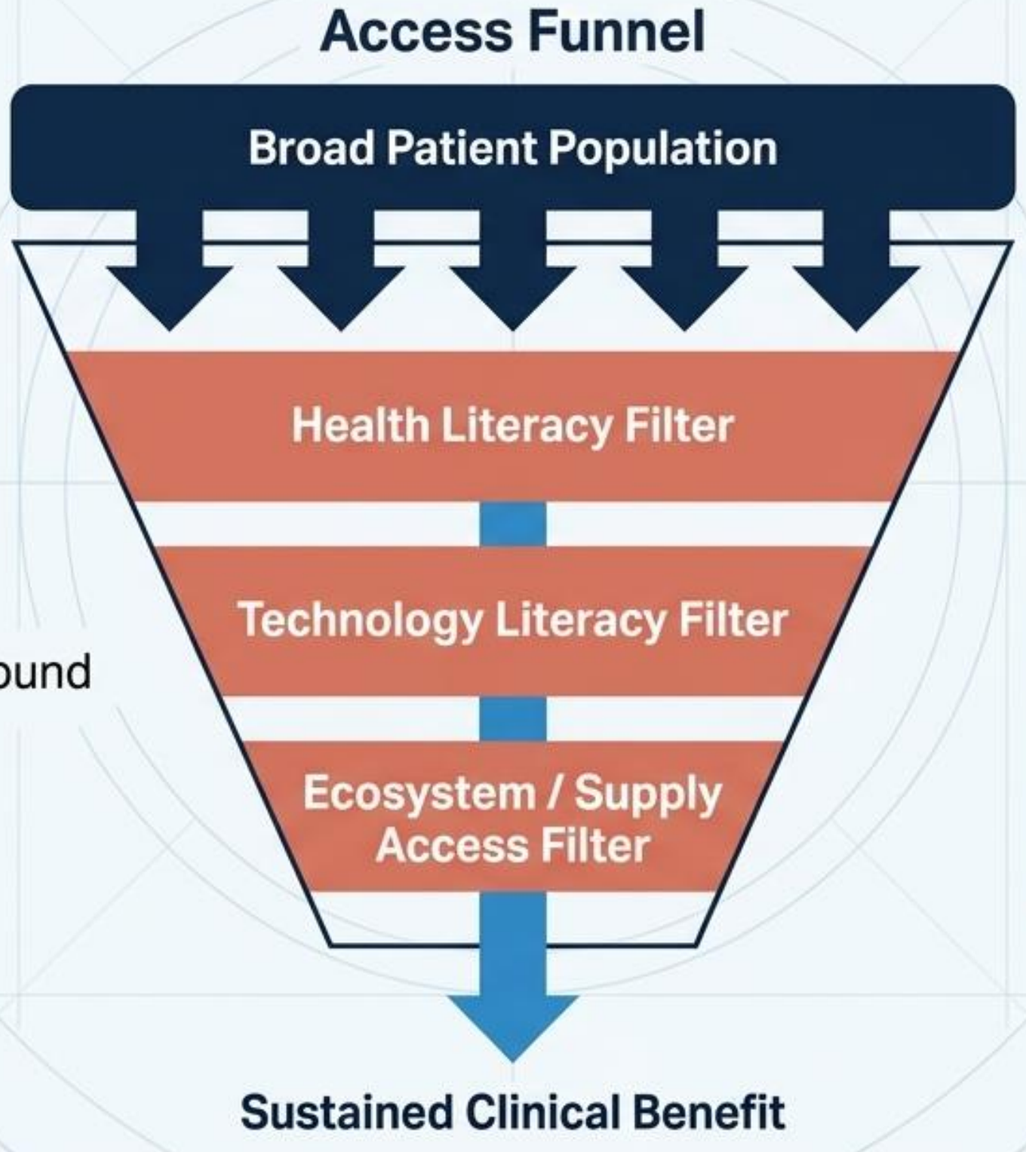
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The Human Component: Ecosystem Over Hardware

Status: ADA/EASD Consensus

Context:
Dexcom T2D global survey reveals 55% of respondents have limited CGM knowledge.

ADA/EASD consensus emphasizes device selection around personal capabilities, not just clinical algorithms.



Strategic Directive:

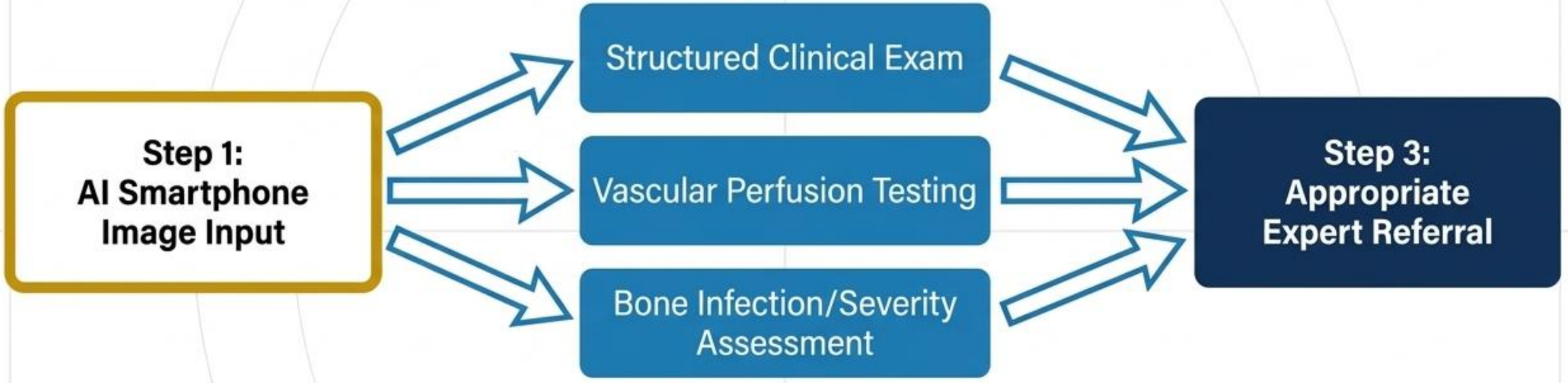
A technology service requires onboarding, language-appropriate education, and escalation.

Measure who cannot participate, not just outcomes among those who complete the program.

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Special Settings: Optimizing DFU AI Triage at IEMRC

Status: IEMRC Local Application



Clinical Reality:

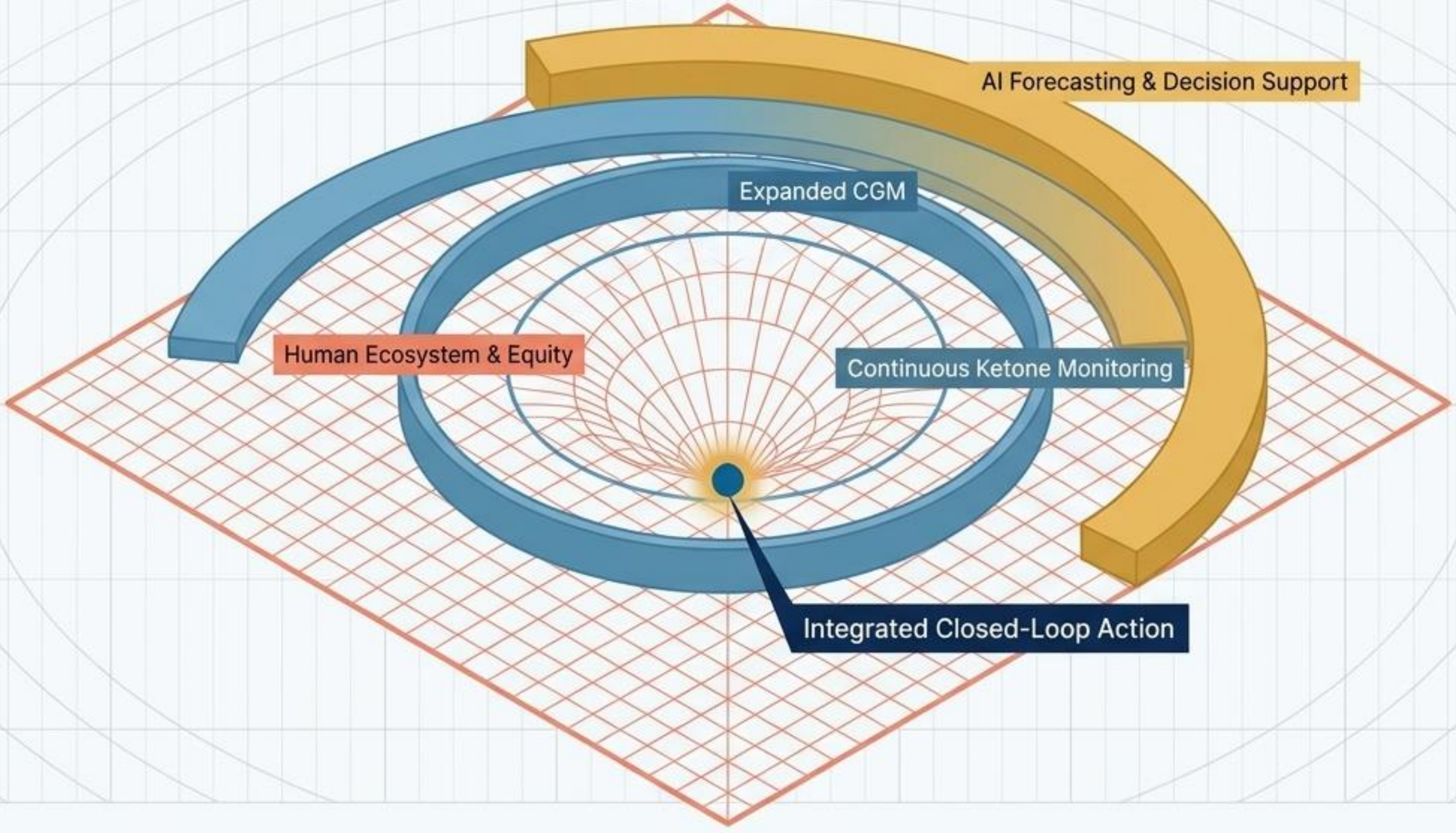
A photograph alone cannot establish vascular perfusion or protective sensation.

Project Directive:

For the IEMRC/Khorshid evaluation tool, success must be measured by referral appropriateness, zero missed urgent cases, and clinician time saved—not merely image-classification accuracy. AI is a support node, not the entire pathway.

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Synthesis: The Complete Metabolic Picture

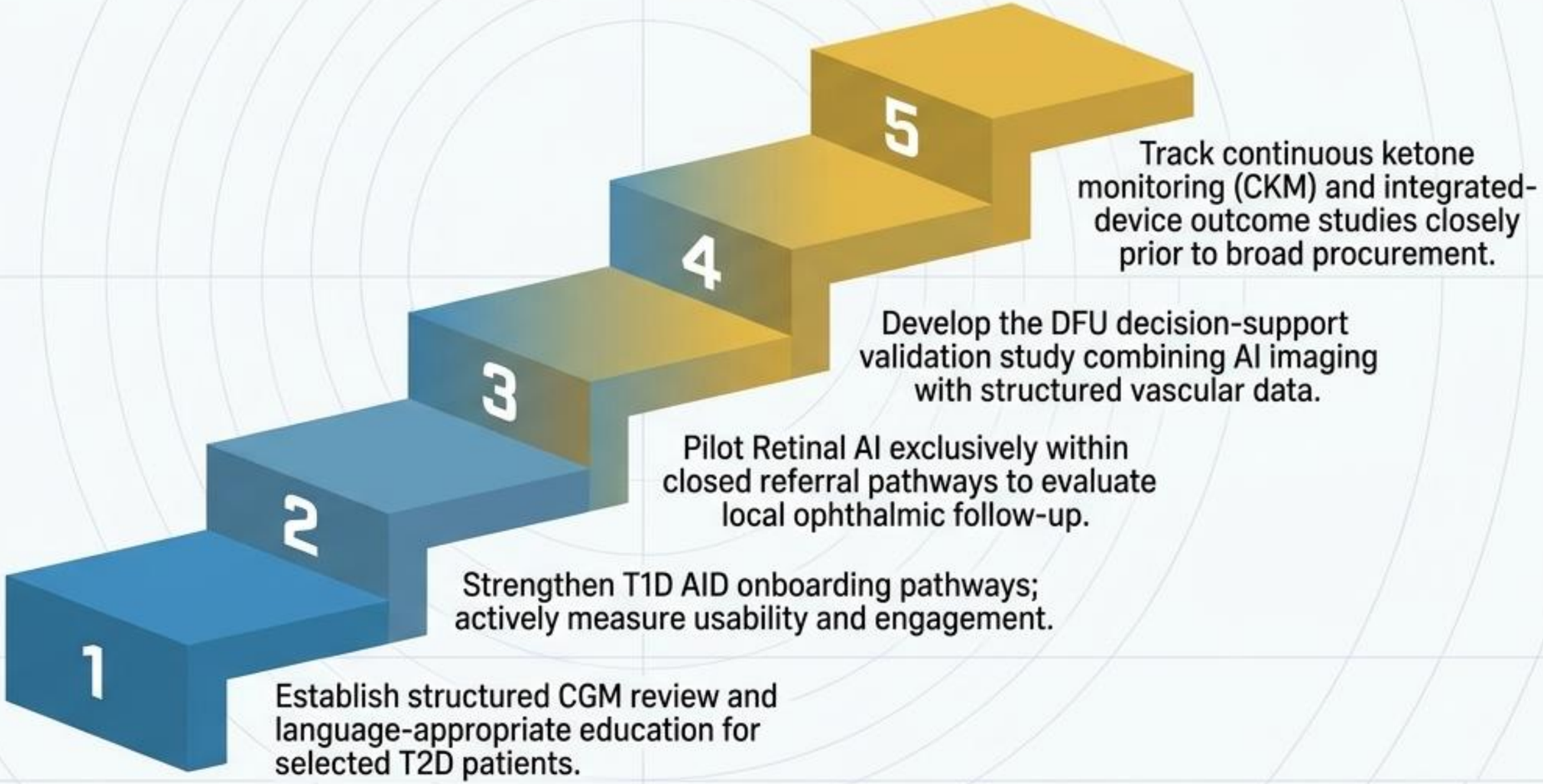


The Complete Picture: The future of diabetes care relies on layering continuous metabolic anticipation over a foundation of equitable human access and robust clinical triage.

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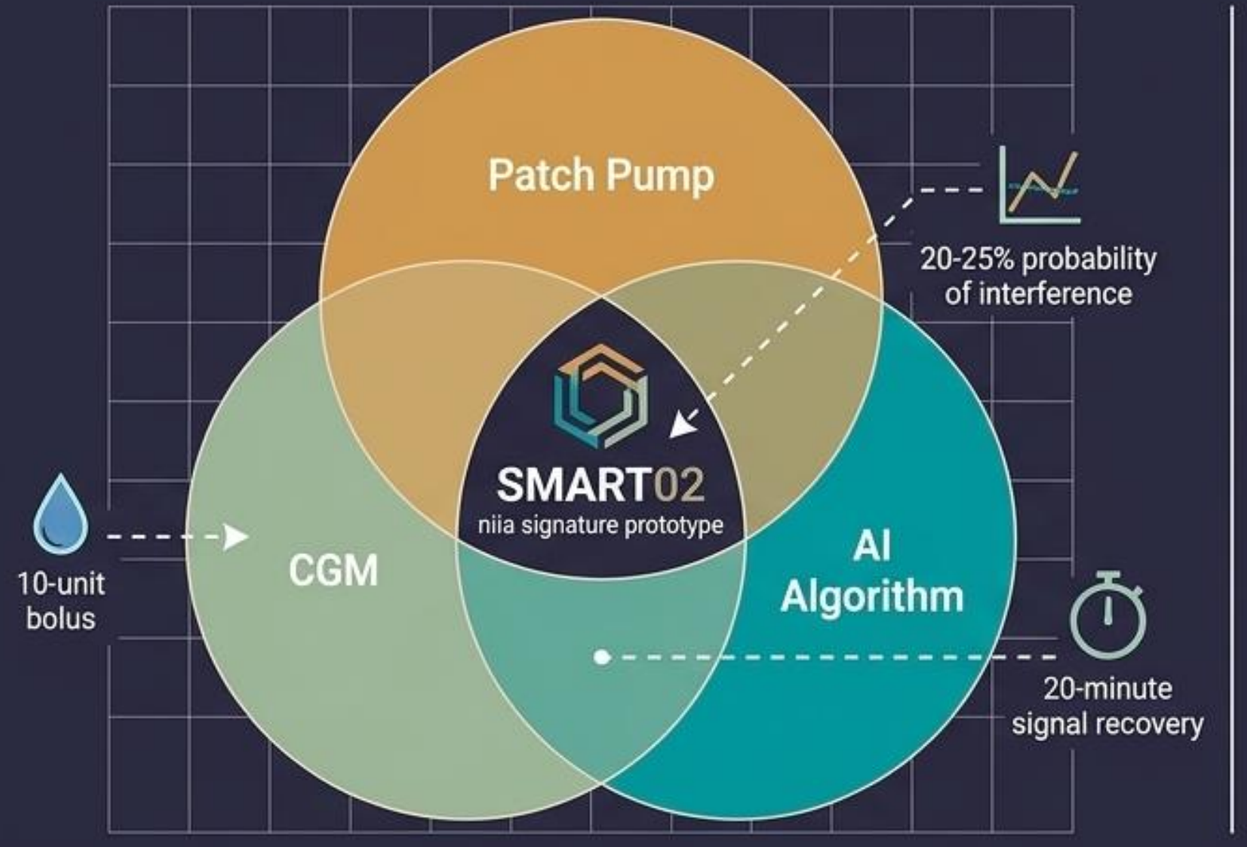
IEMRC Strategic Action Roadmap

Priority Roadmap for Implementation & Research

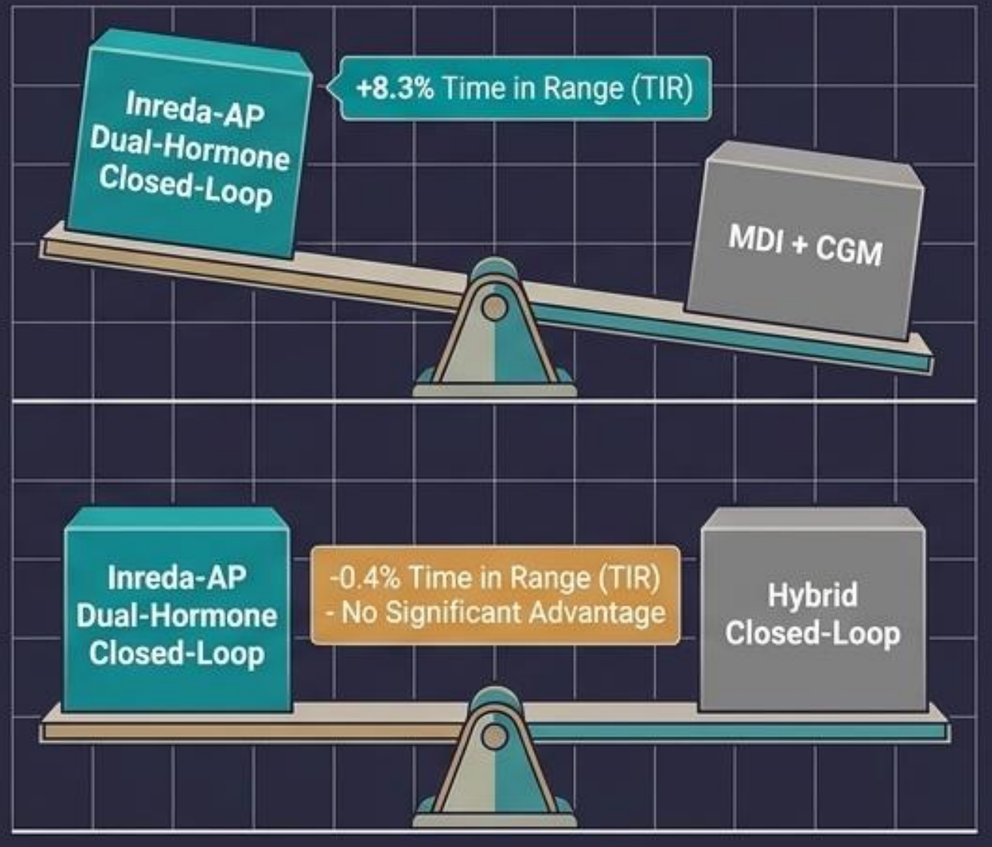


Gemini Notebook

System-Level Engineering & AID Context



Hardware Integration (SMART02): Combining a patch pump, CGM, and AI algorithm into a single wearable prototype reduces insertion burden. However, nearby insulin infusion (boluses ≥10 units) temporarily disturbs sensor readings. Sensing and delivery failures are now linked.

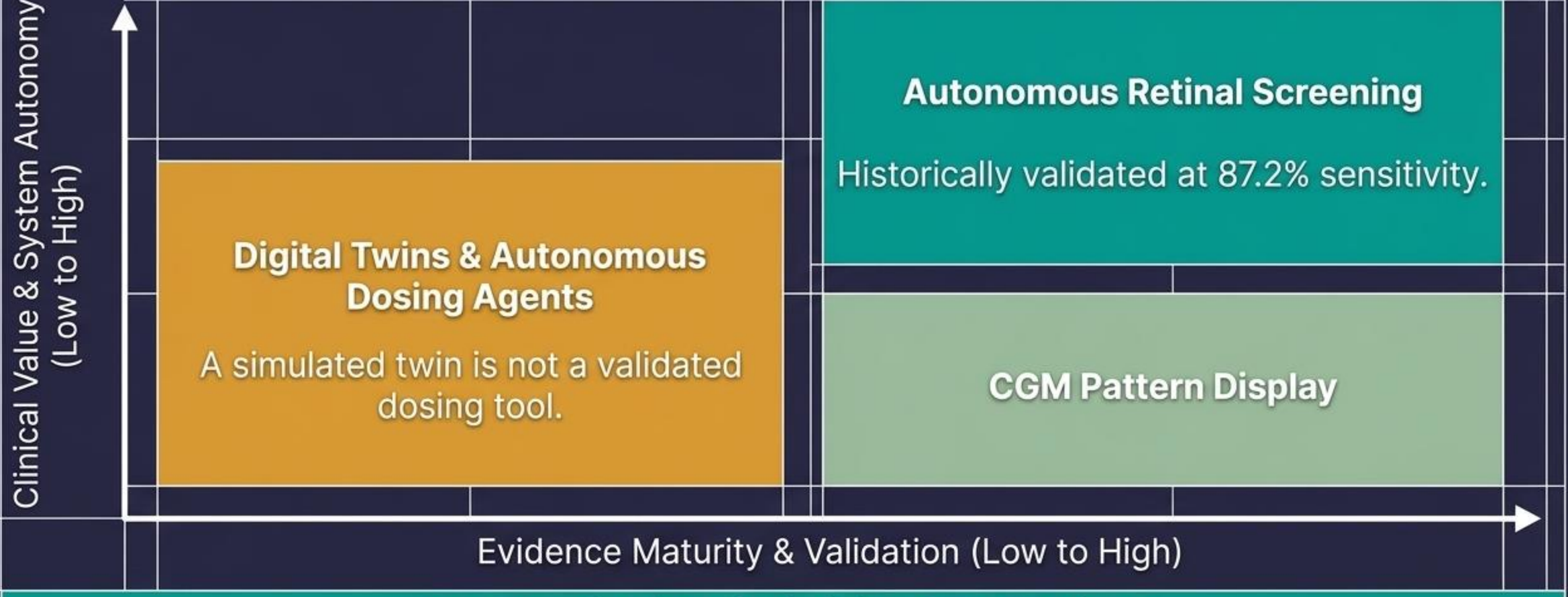


AID Efficacy Context (DARE Trial): Greater automation is not synonymous with clinical superiority. Fully closed-loop dual-hormone systems dominate standard MDI (+8.3% TIR) but plateau when compared to modern hybrid closed-loop systems (-0.4% TIR). The comparator dictates the conclusion.

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Separating AI Capability from Autonomous Action

Core Directive: Evidence for screening cannot be transferred to autonomous treatment.

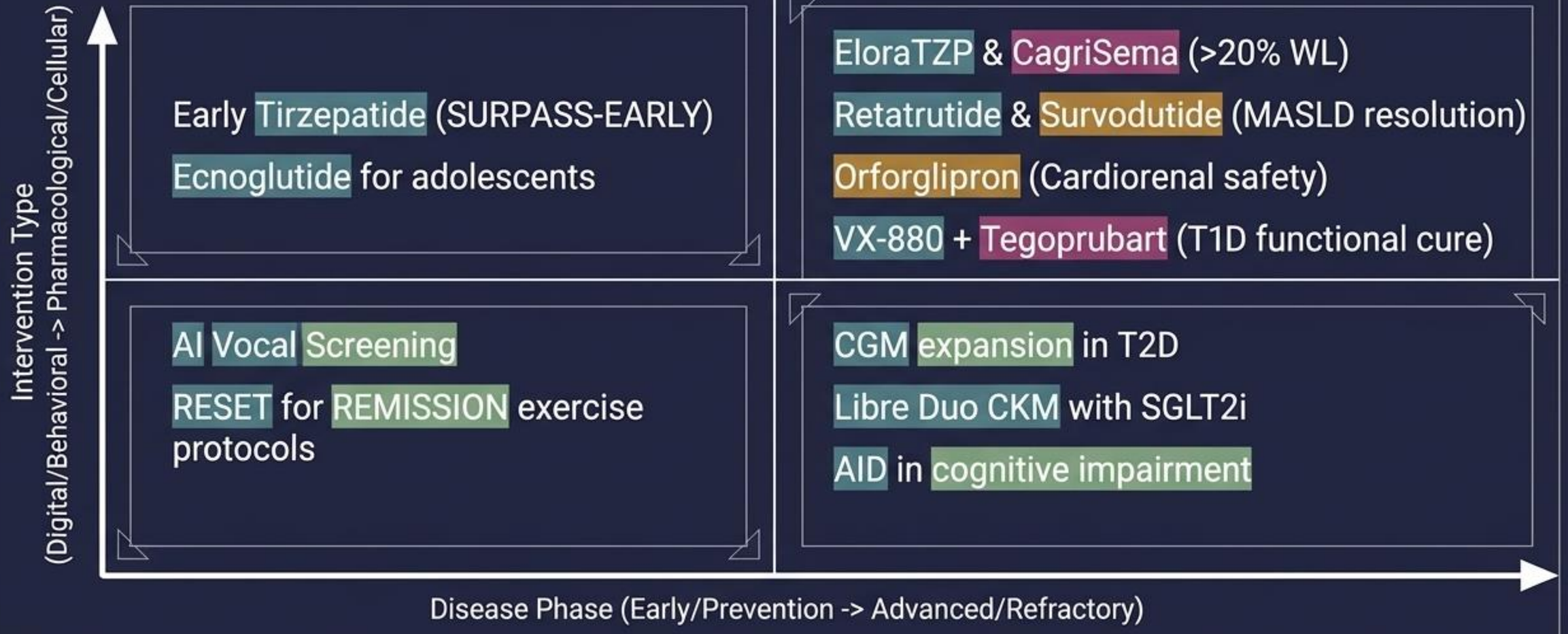


Local Application: Optimizing DFU AI Triage

A smartphone image alone cannot establish perfusion. AI is a support node; success is measured by zero missed urgent vascular/infection referrals, not just image accuracy.

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The 2026 Endocrinologist's Toolkit

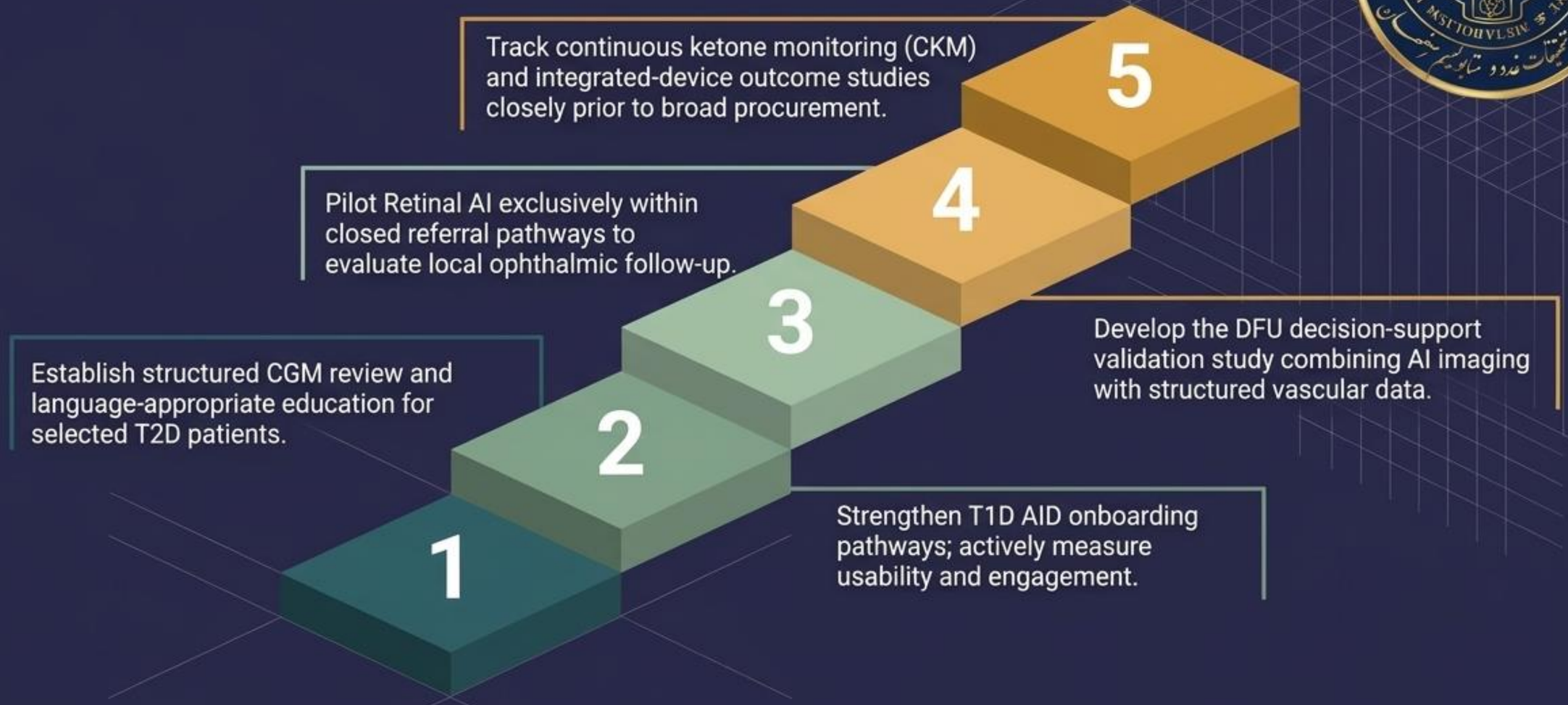


Precision matching of modality to disease phase.

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The future of diabetes care relies on layering continuous metabolic anticipation over a foundation of equitable human access and robust clinical triage.

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Thank you

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Which research question should we answer next?