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A translational mathematical model linking systemic biomarkers to disease recurrence in diabetic macular edema: a proof-of-concept analysis

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Abstract

This study aimed to develop a translational mathematical model that links systemic biomarkers to diabetic macular edema (DME) dynamics and to provide a proof-of-concept assessment of its plausibility for informing anti-vascular endothelial growth factor (anti-VEGF) treatment strategies. A hybrid modeling approach was employed, combining mechanistic reasoning with a retrospective analysis of DRCR.net Protocol H data. A mechanistic model formalized the biological interaction between systemic drivers -glycated hemoglobin (HbA1c), systolic blood pressure (BP), and glycemic variability- and retinal VEGF dynamics, while an empirical penalty model translated these drivers into a framework for estimating personalized injection intervals (I_{model}). Using data from 97 eyes treated with bevacizumab, we assessed the association between I_{model} and a theoretical time to disease recurrence (T_{rec}), defined as a >10% increase in central subfield thickness or a >5-letter loss in visual acuity. The model's hierarchical structure, which prioritized HbA1c, produced a shorter or equivalent interval compared to T_{rec} in 63.6% of the overall cohort, and in a targeted subgroup where the model's logic was fully applicable, the concordance rate was 77.6%. In Group E, simulating a post-loading phase with two injections plus laser, the mean deviation between I_{model} and T_{rec} was minimal (-0.1 weeks) with reduced variability (SD=5.6 weeks). Sensitivity analysis confirmed the designed hierarchy, showing HbA1c exerted a 36-fold greater influence on the model's output than BP. These findings present a novel mathematical framework linking systemic metabolic and hemodynamic control to DME progression. The proof-of-concept analysis supports the biological plausibility of using HbA1c and BP to stratify recurrence risk and provides a transparent, interpretable foundation for future research. This model bridges systemic and ocular care and proposes a structured hypothesis for personalized treatment scheduling that warrants prospective validation in appropriately designed clinical cohorts.

Key words: diabetic macular edema; anti-vascular endothelial growth factor; mathematical model; glycemic variability.

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Introduction

Diabetic macular edema (DME), a vision-threatening complication of diabetes mellitus, arises from chronic hyperglycemia and associated vascular dysfunction. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is a cornerstone of treatment, yet its management presents a significant challenge: balancing therapeutic efficacy against the substantial burden of frequent injections and monitoring.[1] Current treatment protocols, such as treat-and-extend or pro re nata (PRN), are predominantly reactive, driven by anatomic changes on optical coherence tomography (OCT). This ocular-centric approach, however, may overlook the fundamental systemic drivers of the disease.

Landmark trials have unequivocally established that intensive control of glycated hemoglobin (HbA1c) and blood pressure (BP) reduces the risk and progression of microvascular complications, including retinopathy.[2,3] Beyond average glucose levels, emerging evidence implicates glycemic variability as an independent contributor to retinal damage, potentiating oxidative stress, inflammation, and breakdown of the blood-retinal barrier.[4-7] Clinically, poor systemic control has been associated with suboptimal anti-VEGF responses and greater treatment demand.[8-9] This creates a compelling rationale for integrating systemic risk stratification into DME management paradigms, potentially enabling more personalized and proactive care.

Existing mathematical models in DME have primarily focused on long-term prognosis or simulated general disease mechanisms.[10] A critical gap remains in developing a clinically actionable framework that dynamically links modifiable systemic parameters (HbA1c, BP, and glycemic variability) to the kinetics of disease recurrence and the required frequency of therapeutic intervention. Such a tool could bridge the divide between systemic diabetes management and ocular treatment, optimizing resource use and reducing patient burden.

To address this gap, we present a hybrid translational modeling study. First, we develop a mechanistic model (Model 1) that formalizes the biological pathways through which systemic drivers influence VEGF dynamics and macular thickness. Second, we derive an empirical, clinically-feasible model (Model 2) that trans-

lates these drivers into a structured framework for considering anti-VEGF injection intervals. Finally, we perform a proof-of-concept analysis using retrospective data from the DRCR.net Protocol H to assess the biological plausibility of this framework by examining the association between model-derived intervals and the theoretical time to disease recurrence. The aim of this work is not to present a validated clinical tool, but to establish a novel, transparent mathematical foundation and generate hypotheses for future research into personalized, systemically-informed DME therapy.

Model 1 (mechanistic model): dynamic systems framework for DME

Model rationale and scope

Model 1 establishes a mechanistic, dynamic systems framework to formalize the hypothesized biological interplay between systemic metabolic control, vascular endothelial growth factor (VEGF) signaling, and the progression of DME. Grounded in established retinal vascular biology,[11] the model conceptualizes central macular thickness as a dynamic state variable governed by the balance between VEGF-driven vascular leakage and physiological (and treatment-enhanced) fluid clearance. The core innovation of this model is the explicit integration of three key systemic modulators -glycated hemoglobin (HbA1c), systolic blood pressure (BP), and glycemic variability- as upstream drivers of the ocular pathological process (Figure 1).

These parameters were selected based on three criteria: i) robust mechanistic links to DME pathogenesis via distinct pathways,[12-14] ii) routine availability in standard diabetes care, and iii) their status as primary, modifiable treatment targets in systemic management. While other factors (e.g., renal function, lipid profile) may contribute to overall risk, their connection to the *kinetics* of DME recurrence and anti-VEGF demand is less direct and not consistently utilized in ophthalmic clinical decision-making; thus, they are excluded from this foundational model.

Model formulation

The model consists of two coupled ordinary differential equations describing the dynamics of intraocular VEGF concentration, $V(t)$, and central subfield thickness, $C(t)$.

Equation (1): VEGF dynamic

The rate of change in VEGF concentration is modeled as:

$$\frac{dV(t)}{dt} = P_{sys}\,(H(t),B(t),G(t))-\delta_V\,V(t)-R_{anti}\,(V(t),I(t))$$

Where:

P_{sys} represents the **systemic driver-induced VEGF production rate**, a function of HbA1c (H), blood pressure (B), and glycemic variability (G). This term aggregates contributions from:

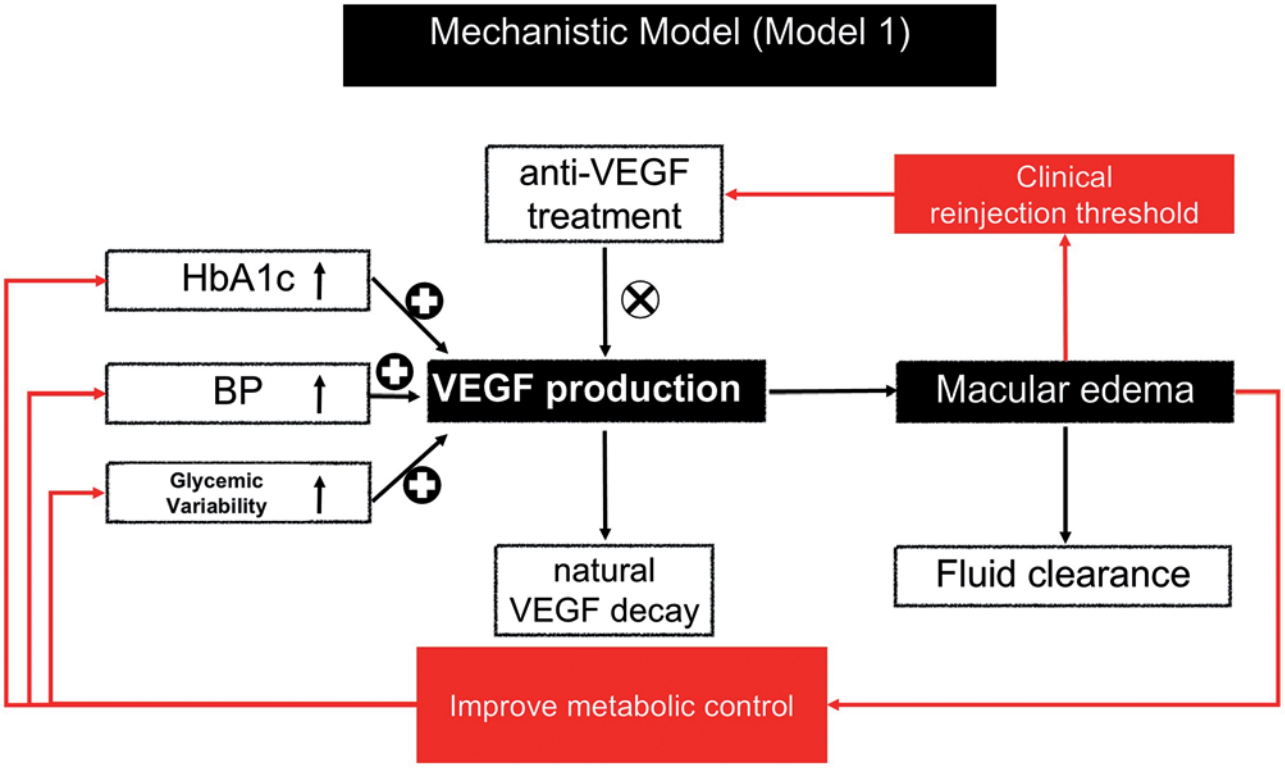

Figure 1. Mechanistic model (Model 1) of DME progression and anti-VEGF response. Systemic drivers (HbA1c, blood pressure, glycemic variability) increase VEGF production, which drives macular thickening. Anti-VEGF injections reduce VEGF in a saturable manner, while natural decay and fluid clearance provide additional regulation. The occurrence of macular edema highlights the importance of optimizing metabolic control; however, once the clinical threshold for reinjection is reached, administration of anti-VEGF therapy becomes warranted.

i) HbA1c-mediated advanced glycation end-product (AGE) signaling (AGE–RAGE–NF-κB pathway);[12] ii) BP-induced hydrostatic and mechanical stress on the vasculature;[13] and iii) oxidative stress from glycemic variability, which amplifies VEGF transcription and signaling.[14]

δ_V is the natural decay rate constant of VEGF.

R_{anti} (V) models the saturable anti-VEGF drug effect, formulated using Michaelis-Menten kinetics ($R_{anti}(V) \propto \frac{V(t)}{K_M + V(t)}$) to reflect the finite binding capacity of VEGF ligands.[11]

Equation (2): macular edema dynamics

The rate of change in central macular thickness is modeled as:

$$\frac{dC(t)}{dt} = L(V(t),G(t)) - F_{clear}(B(t),I(t)) \cdot C(t)$$

where:

$L(V,G)$ is the total leakage function into the retina, which depends on VEGF and glycemic variability.[11,14]

F_{clear} is the total fluid clearance rate function, which depends on systemic blood pressure and anti-VEGF treatment.[8]

From mechanisms to intervals: a conceptual link

Within this framework, the need for therapeutic re-intervention is conceptually defined as the time point at which the simulated trajectory of $C(t)$ crosses a pre-defined recurrence threshold (e.g., a >10% increase from a treated baseline).[15] By simulating the system under different initial conditions of H, B, and G, Model 1 provides a *theoretical* injection interval based on the inherent pharmacodynamics of anti-VEGF agents and the patient-specific systemic driver profile. Detailed derivations, parameter definitions, and phase-plane analyses illustrating system stability and bifurcations are provided in *Appendix A*.

Model 1 serves as a causal, biological scaffold. Its purpose is to articulate and formalize the hypothesized pathways, thereby providing the mechanistic justification for the structure and variable selection of the more tractable, empirical Model 2 presented in the following section.

Bridging mechanistic theory and clinical translation

Model 1 provides a comprehensive, causal description of DME dynamics rooted in vascular biology. However, its utility for direct clinical decision support is limited by its complexity and substantial data requirements (e.g., precise kinetic parameters for VEGF production and clearance, continuous systemic variable measurements). These requirements render it primarily a conceptual tool for exploring system behavior and validating biological hypotheses *in silico*.

To translate the mechanistic insights of Model 1 into a format suitable for clinical consideration, a simplified, empirical counterpart was developed. Model 2 serves as the translational bridge. It distills the core causal pathways of Model 1 - where systemic drivers (HbA1c, BP, glycemic variability) upregulate pathological VEGF activity - into a pragmatic, algebraic framework. This framework outputs a model-derived interval estimate, designed not as a deterministic prediction but as a structured, personalized risk assessment to inform scheduling logic within existing clinical protocols.

While Model 2 sacrifices some biological granularity, it retains the essential hierarchical and nonlinear logic of the mechanistic model. This two-model approach -a detailed *explanatory* system (Model 1) and a simplified *operational* framework (Model 2) creates a coherent pipeline from biological principle to clinical application, supporting the development of a more personalized, systemically-informed strategy for DME management.

Model 2 (empirical model): a clinical decision framework

Model structure and formulation

To translate the mechanistic insights of Model 1 into a clinically-actionable tool, we developed an empirical penalty model. This model estimates a personalized treatment interval I_{model}, by starting from a defined maximum interval, I_{max}, and applying conditional penalties proportional to the deviation of systemic parameters from their clinical targets (Figure 2).

The core model is defined by the following equation:

$$I_{model} = \frac{I_{max}}{1 + \alpha \cdot max(H - H_{target}, 0) + \beta \cdot max(B - B_{target}, 0) + \gamma \cdot \Delta G \cdot 1_A}$$

where:

I_{max} is the maximum interval when $H \leq H_{target}$, $B \leq B_{target}$, $G = 0$

H is the HbA1c level (%),

B is the systolic blood pressure (mm Hg),

G is a measure of glycemic variability (%),

$\Delta G = max(G - G_{target}, 0) \cdot \left(\frac{average\ glucose\ (mg/dL)}{100} \right)$ scales the glycemic variability penalty.

H_{target}, B_{target} and G_{target} are clinical target values (e.g., 7%, 140 mm Hg, and 36% respectively),[16-18]

1_A is an indicator function where $1_A = 1$ if $H \leq H_{target}$ and $B \leq B_{target}$, and 0 otherwise. This encodes the conditional activation of the glycemic variability penalty.

α, β, γ are empirical penalty coefficients, with preliminary values set at, $\alpha = 0.54$ per %, $\beta = 0.015$ per mm Hg, and $\gamma = 0.01$ per mg/dL.

It is important to emphasize that Model 2 is presented as a proof-of-concept framework. The clinical thresholds (H_{target}, B_{target} and G_{target}) align with established diabetes management guidelines (e.g., ADA, IDF) and reflect levels beyond which microvascular risk escalates.[16-18]

The penalty coefficients were derived from published risk associations:

- $\alpha = 0.54$ per % HbA1c was scaled from the UKPDS 35 risk gradient for microvascular complications.[19]
- $\beta = 0.015$ per mm Hg was informed by hypertension severity data from Angaramo *et* al.[20]
- $\gamma = 0.01$ per mg/dL was estimated from fasting glucose variability risk ratios reported by Hsieh and Hsieh.[14]

These coefficients are proof-of-concept placeholders based on epidemiological risk gradients and are not empirically validated for interval prediction. Their primary purpose is to illustrate the model's structure and hierarchical logic—not to serve as definitive clinical parameters; they are not empirically validated and must be re-calibrated using prospective clinical data before any clinical application.

Rationale for the penalty-based architecture

The mathematical structure was chosen to mirror the pathophysiological logic formalized in Model 1. The denominator represents a "risk multiplier" that increases from a baseline of 1. Each additive penalty term corresponds to a systemic driver upregulating VEGF burden, thereby shortening the time to likely recurrence.

This approach offers several advantages:

i) *Clinical interpretability*: each term directly corresponds to a modifiable clinical parameter, and its contribution to shortening the interval is transparent.

ii) *Non-linearity and thresholds*: the *max*(… .,0) functions impose thresholds, reflecting the established clinical concept that risk accelerates beyond specific targets.

iii) *Hierarchical prioritization*: the model architecture inherently prioritizes HbA1c and BP as primary drivers, consistent with the strongest clinical evidence base.[2,3,8,13]

iv) *Conditional role of glycemic variability*: the indicator function 1_A encodes a specific hypothesis: that glycemic variability exerts a significant effect primarily in patients with otherwise good HbA1c and BP control, acting as a residual risk modulator. This reflects emerging biological understanding and prevents double-penalizing patients already identified as high-risk by HbA1c and BP.[4,14]

Operational interpretation and parameterization

The model operates as a structured risk calculator:

- Optimal control: when $H \leq H_{target}$, $B \leq B_{target}$ and $G \leq G_{target}$, the denominator equals 1, and $I_{model} = I_{max}$, suggesting the longest feasible interval.
- Suboptimal HbA1c or BP: deviations above target directly increase the denominator, shortening I_{model} in proportion to the coefficients α and β. The larger value of α reflects the dominant influence of hyperglycemia in microvascular pathophysiology.
- Isolated elevated glycemic variability: The glycemic variability penalty term $\gamma \Delta G$ activates **only** if HbA1c and BP are at target, providing a mechanism to identify "high-risk among the well-controlled."

The empirical coefficients (α, β, γ) and the value of I_{max} (e.g., 12 weeks) are model parameters. Their preliminary values were established through a combination of theoretical constraints (e.g., ensuring intervals remain within plausible clinical bounds) and calibration to reflect observed clinical logic; detailed derivation of the penalty coefficients and threshold selection is provided in *Appendix B*. Importantly, these parameters are presented as a proof-of-concept calibration and are the primary target for future empirical refinement and validation in prospective cohorts. The coefficients and thresholds are presented as a theoretical calibration for demonstration only. They were derived from published risk studies and preliminary mechanistic scaling, but require prospective, data-driven re-calibration before any clinical application.

Synthesizing the mechanistic and empirical frameworks

The hybrid modeling approach presented here - a detailed dynamic system (Model 1) and a simplified penalty model (Model 2) - is designed to create a coherent translational pipeline. This sec-

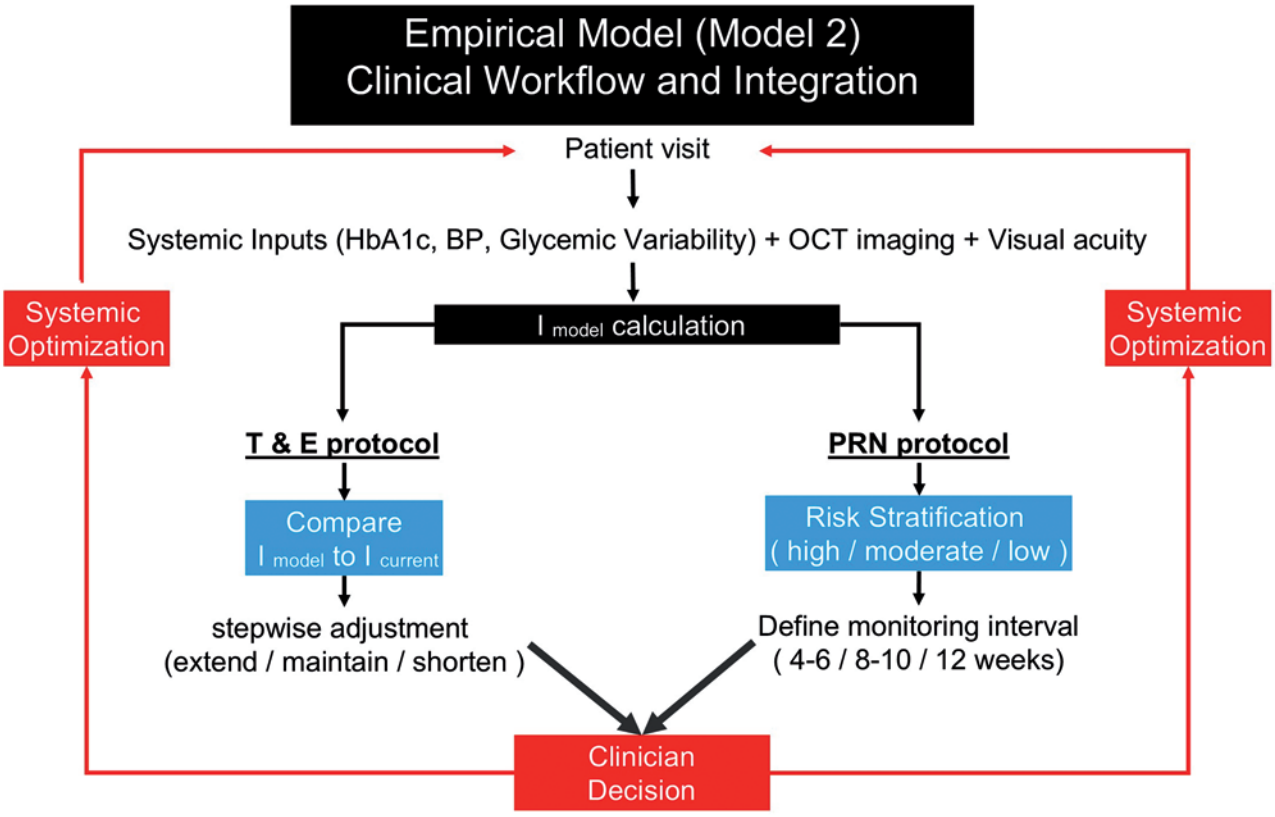

Figure 2. Empirical model (Model 2). The empirical penalty model estimates personalized injection intervals and integrates directly into clinical workflows. It provides a simplified yet clinically actionable approximation of the mechanistic model (Model 1). The systemic drivers—HbA1c, blood pressure, and glycemic variability—are incorporated through penalty terms, and the model outputs decision-support recommendations for treatment interval adjustment. In addition, the model provides feedback regarding the need for systemic optimization.

tion explicitly synthesizes the conceptual and structural linkages between the two models, demonstrating how Model 2 is a principled derivation of Model 1's core logic for clinical application.

Unified systemic drivers

Both models are founded on the same triad of modifiable systemic parameters: HbA1c (H), blood pressure (B), and glycemic variability (G). In Model 1, these are explicit inputs into the VEGF production function, P_{sys} (H, B, G), where they operate via distinct biological pathways (AGE-RAGE signaling, hydrostatic stress, oxidative synergy).[12-14] Model 2 adopts these identical drivers as direct clinical inputs, preserving their identity as the primary levers for personalized risk assessment.

Threshold and non-linear behavior

A key non-linearity captured in both models is the threshold effect. Model 1 implements this through activation functions (e.g., Hill kinetics), where the influence of a systemic driver on VEGF production becomes significant only after surpassing a physiological cutoff. Model 2 translates this concept into the clinical domain through the $max(H - H_{target},0)$ and $max(B - B_{target},0)$ operators. These impose a treatment-relevant threshold, ensuring interval shortening occurs only when parameters deviate from accepted clinical targets, mirroring the biological switch.

Pharmacodynamic saturation

The saturable nature of anti-VEGF therapy is a critical pharmacodynamic feature. Model 1 represents this explicitly via Michaelis-Menten kinetics in the drug removal term $R_{anti}(V)$, modeling diminishing returns at high drug concentrations. Model 2 captures the clinical consequence of this saturation through its inverse penalty structure. A small deviation from systemic targets (representing a small increase in underlying VEGF burden) leads to a proportionally larger reduction in the safe interval early on, mimicking the steep initial efficacy of anti-VEGF treatment that plateaus with continued use.

Hierarchical and conditional influence of glycemic variability

Both models assign glycemic variability a conditional, amplifying role. In Model 1, glycemic variability -induced oxidative stress is modeled to synergistically enhance VEGF signaling and its effect on vascular permeability, particularly when other drivers are active. Model 2 operationalizes this by applying the glycemic variability penalty via the indicator function , which activates only when HbA1c and BP are at target. This encodes the hypothesis that glycemic variability represents a residual risk factor, most relevant for stratifying patients who otherwise appear well-controlled.

Model 2 as a steady-state projection

A formal mathematical link can be established by considering Model 1 under quasi-steady-state assumptions. Assuming the fast dynamics of VEGF concentration reach equilibrium ($\frac{dV}{dt} \approx 0$) relative to slower changes in systemic drivers, the steady-stateVEGF level, V_{ss} , becomes a function of H, B, and G. If the need for re-injection is triggered when macular thickness $C(t)$ crosses a threshold, and $C(t)$ itself is driven by V_{ss}, then the time to this event is approximately inversely proportional to the systemic driver function. Model 2's penalty-based denominator $(1+\alpha\Delta H+\beta\Delta B+\gamma\Delta G\cdot 1_A)$ can be viewed as a linearized, empirical approximation of this inverse relationship, where the coefficients α, β, γ aggregate the complex kinetic parameters from Model 1.

The translational bridge

In summary, Model 1 provides the causal biological narrative: $(H, B, G) \rightarrow \uparrow P_{sys} \rightarrow \uparrow V(t) \rightarrow \uparrow C(t) \rightarrow recurrence$. Model 2 provides the actionable clinical calculus: $(H, B, G) \rightarrow risk\ multiplier \rightarrow I_{model}$. The latter is achieved by replacing continuous differential equations with discrete thresholds, kinetic parameters with empirical penalties, and dynamic simulation with algebraic calculation.

This synthesis demonstrates that Model 2 is not an arbitrary construct but a deliberate, simplified projection of Model 1's logic into a clinical decision-support format. This foundational consistency strengthens the biological plausibility of the empirical model and provides a clear roadmap for its future refinement using data-informed parameter estimation.

Illustrating clinical integration: a model-informed treat-and-extend framework

To demonstrate how the empirical model (Model 2) could interact with established clinical workflows, we describe a hypothetical **Model-Informed Treat-and-Extend (T&E) Protocol**. This framework illustrates how systemic biomarker data could be logically incorporated into the stepwise extension logic of standard T&E to create a more personalized, risk-adjusted approach.

Conceptual principles of integration

The core concept is to use the model-derived interval estimate, I_{model}, as an additional, quantitative decision-support metric alongside traditional anatomic (OCT) and functional (visual acuity) criteria. The protocol adheres to standard T&E principles: intervals are adjusted in discrete steps (e.g., 2-week increments), extension requires anatomic stability, and treatment is administered at every visit. The innovation lies in allowing I_{model}, which reflects systemic risk, to influence the direction (extend, maintain, or shorten) and magnitude of interval adjustments. This integration enforces the hierarchical logic of Model 2, where HbA1c and BP are primary drivers, and glycemic variability is considered a conditional modifier.

A proposed decision algorithm

At each treatment visit, following confirmation of anatomic stability, the clinician would:

1. Calculate I_{model} using the latest systemic parameters.
2. Compare I_{model} to the current treatment interval, $I_{current}$.
3. Apply the following adjustment rules:

- Extend: If $I_{model} > I_{current}+2$ *weeks*, the interval is extended by one discrete step (e.g., from 8 to 10 weeks).
- Maintain: If $I_{current} \leq I_{model} \leq I_{current}+2$ *weeks*, the interval is unchanged.
- Shorten: If $I_{model} < I_{current}$, the interval is reduced to $max(4,\lfloor I_{model} \rfloor)$ weeks, ensuring a minimum interval of 4 weeks.

As per conventional T&E, permissible intervals are typically constrained to discrete values (e.g., 4, 6, 8, 10, 12 weeks), and extensions occur one step at a time.

Illustrative clinical scenarios

The following scenarios demonstrate the algorithm's logic in practice, assuming $I_{max}=12$ *weeks*, $H_{target}=7\%$, $B_{target}=140$ *mm Hg*, and the proof-of-concept coefficients $\alpha=0.54$, $\beta=0.015$, $\gamma=0.01$.

- Scenario A (optimal control): a patient with H=6.5%, B=120 *mm Hg*, ΔG=0 has I_{model}=12 *weeks*. With $I_{current}$=8 *weeks*, the rule supports extension to 10 weeks.
- Scenario B (Elevated HbA1c): a patient with H=9%, B=130 *mm Hg*, has $I_{model} \approx 5.7$ *weeks*. With $I_{current}$=6 *weeks*, the rule triggers a shortening to 4 weeks, overriding a potentially stable OCT based on high systemic risk.
- Scenario C (isolated elevated glycemic variability): a patient with controlled H and B but significant glycemic variability (ΔG=40) has $I_{model} \approx 8.6$ *weeks*. With $I_{current}$=8 *weeks*, the rule recommends maintenance, preventing extension despite good HbA1c/BP.

Potential advantages and clinical implications

This illustrative framework highlights several hypothetical benefits of integrating systemic data:

- Risk-adjusted personalization: it provides a structured method to modulate treatment intensity based on individual systemic risk profiles, moving beyond a one-size-fits-all extension strategy.
- Prevention of premature extension: in scenarios like B and C, the model introduces caution, potentially preventing extension in patients with high or residual systemic risk that may not be evident on OCT alone.
- Promotion of systemic-ocular care integration: it creates a tangible workflow that encourages communication between retina specialists and diabetes care teams, as systemic parameters directly influence ocular treatment frequency.

It is crucial to emphasize that this is a proof-of-concept illustration. The proposed algorithm and coefficients require rigorous prospective clinical evaluation to assess their safety, efficacy, and impact on outcomes compared to standard T&E. This section serves to translate the mathematical framework of Model 2 into a concrete clinical use case, demonstrating its potential to bridge systemic medicine and ophthalmology.

Illustrating clinical integration: a model-informed PRN monitoring framework

To further demonstrate the versatility of Model 2, we extend its application to a Pro Re Nata (PRN) treatment paradigm. In standard PRN, follow-up intervals are often fixed (e.g., every 4-12 weeks), and treatment is administered reactively upon detection of disease activity. We propose a *model-informed PRN monitoring framework* that leverages systemic biomarkers to personalize *monitoring frequency*, creating a dynamic, risk-adapted surveillance schedule while preserving the core PRN principle of activity-driven treatment.

Conceptual principles of integration

In this framework, the model-derived interval, I_{model}, is repurposed to determine the *risk-based monitoring interval* between evaluations, not the injection interval itself. Injections remain strictly contingent on anatomic evidence of active DME. The central innovation is that patients with poorer systemic control (shorter I_{model}) are monitored more closely, allowing for earlier detection of recurrence, while those with excellent control (longer I_{model}) can safely be monitored less frequently. This protocol explicitly encourages the intensification of systemic therapy (for HbA1c and BP) at ophthalmology visits when targets are not met, fostering integrated care.

A proposed risk - Adaptive monitoring algorithm

- Step 1: baseline risk stratification. Calculate I_{model} using the patient's current systemic parameters. Stratify the patient into a monitoring risk category:
  - High risk: I_{model}<6 *weeks*→Schedule next evaluation in 4-6 weeks.
  - Moderate risk: 6 *weeks*≤I_{model}≤10 *weeks*→Schedule next evaluation in 8-10 weeks.
  - Low risk: I_{model}>10 *weeks*→Schedule next evaluation in 12 weeks.
- Step 2: visit workflow. At each scheduled evaluation, perform standard OCT and visual acuity assessment.
  - If DME is active, administer an anti-VEGF injection and schedule the next visit in 4-6 weeks (standard PRN).
  - If DME is inactive, recalculate I_{model} with updated systemic parameters. Re-stratify the patient and schedule the next monitoring visit according to the new risk category. Counsel the patient and/or their primary care physician if HbA1c or BP is above target.
- Step 3: dynamic re-stratification. The monitoring interval is dynamically adjusted over time in response to changes in systemic control, allowing for escalation or de-escalation of surveillance intensity.

Illustrative clinical scenarios

Using the same proof-of-concept coefficients and I_{max}=12 *weeks*:

- Scenario A (high systemic risk): a patient with H=9%, B=130 *mm Hg*, has $I_{model} \approx 5.7$ *weeks*. They are classified as *high risk* and scheduled for follow-up in 4-6 weeks, regardless of a currently inactive OCT, to allow for close surveillance and emphasis on systemic management.
- Scenario B (low systemic risk): a patient with excellent HbA1c and BP but moderate glycemic variability (ΔG=10) has $I_{model} \approx$ 10.9 *weeks*. They are classified as *low risk* and can be scheduled for follow-up in 12 weeks, reducing clinic visit burden.

Implementation considerations

This framework uses I_{max}=12 *weeks* as the default anchor for a stable patient, consistent with common PRN practices. The proof-of-concept coefficients and risk category thresholds are illustrative and would require calibration in future studies. Crucially, this algorithmic approach does not override clinical judgment; conditions such as sudden vision loss or poor compliance necessitate immediate intervention or more conservative monitoring.

Potential advantages and implications

This illustrative framework highlights how Model 2 could hypothetically enhance PRN management:

- Efficient resource allocation: it rationalizes monitoring frequency, directing more frequent evaluations toward patients at highest risk of recurrence, potentially improving detection timelines.
- Proactive systemic engagement: by tying ophthalmic visit frequency to systemic parameters, it creates a natural feedback loop that emphasizes the importance of metabolic and hemodynamic control at every eye appointment.
- Adaptive and flexible: it retains the fundamental flexibility of the PRN approach while adding a structured, personalized layer for determining *when* to look for disease.

As with the T&E framework, this PRN monitoring model is pre-

sented as a *proof-of-concept illustration*. Its safety, impact on visual outcomes, and effectiveness in optimizing healthcare utilization require formal prospective evaluation. This exercise demonstrates the potential of a simple mathematical framework to inform and personalize different aspects of DME clinical management.

Proof-of-concept analysis using DRCR.net Protocol H data

To assess the biological plausibility of the proposed framework, we conducted a proof-of-concept analysis using publicly available, anonymized data from the DRCR.net Protocol H study. This analysis aimed to evaluate whether the model's output, based on systemic parameters, showed a coherent association with the theoretical time to disease recurrence in a retrospective cohort. A detailed description of the analytical process is provided in *Appendix C*.

Data source and cohort

We analyzed data from 97 eyes of patients enrolled in DRCR.net Protocol H who were treated with bevacizumab for DME. Protocol H was selected as it was the sole publicly available anti-VEGF trial that collected systolic blood pressure measurements at every study visit. Protocol H utilized a fixed regimen of two intravitreal bevacizumab injections administered six weeks apart, in contrast to reactive or extension-based approaches. Moreover, the study population was defined by stringent inclusion and exclusion criteria, yielding a more homogeneous phenotype than is typically observed in real-world DME cohorts. Consequently, these design elements constrain the direct applicability of our results to more flexible treatment paradigms such as treat-and-extend (T&E) or pro-re-nata (PRN).

Analytical method

For each eye, the model-derived interval (I_{model}) was calculated using baseline HbA1c and the blood pressure measured at the final anti-VEGF treatment visit. Glycemic variability was not available in this dataset and was set to zero, focusing the analysis on the HbA1c and BP components. This absence precluded a full evaluation of the model's three-driver logic, particularly the conditional role of glycemic variability as a residual risk modulator in otherwise well-controlled patients.

We then calculated a theoretical time to recurrence (T_{rec}) for each eye. Recurrence was defined by a pre-defined activity threshold (>10% increase in central subfield thickness or >5-letter loss in visual acuity)[15]. For eyes that met this threshold at a follow-up visit, T_{rec} was operationally defined as the midpoint (in weeks) between that visit and the immediately preceding visit. For example, if the final anti-VEGF injection was at week 6, and the recurrence threshold was first met at week 18 but not at week 12, then $T_{rec} = \frac{12+18}{2} - 6 = 9$ *weeks*. This midpoint method estimates the time the continuous process of recurrence crossed the threshold between two discrete measurement points. T_{rec} thus serves as a *biologically-imputed proxy* for the time at which a treatment effect may have waned, acknowledging tha Protocol H itself did not use these thresholds to trigger injections.

The association between the model and this biological proxy was evaluated by calculating: 1) the *concordance rate* (percentage of eyes where $I_{model} \leq T_{rec}$), indicating alignment between the model's risk ranking and the observed disease course; and 2) the *interval deviation* ($\Delta I = T_{rec} - I_{model}$), where a positive value indicates a conservative model estimate. Analyses were performed across protocol subgroups (B-E).

Main outcome measures

Primary outcomes were the concordance rate and the mean interval deviation (ΔI) with associated variability. A secondary outcome was the relative influence of HbA1c *vs* BP on I_{model}, quantified *via* sensitivity analysis.

Results

Table 1 presents an overview of the analysis results. In the pooled cohort (n=77 eyes with calculable T_{rec}, the model's interval was concordant with or shorter than T_{rec} in 63.6% of cases (49/77; 95% CI: 52.5–73.8). The mean ΔI was +4.7 weeks (95% CI: +1.2 to +8.3; SD=13.1 weeks), indicating that, on average, the model's suggested interval was more conservative than the imputed recurrence time.

In a targeted subgroup (n=49) where the model's conditional glycemic variability logic was not invoked (i.e., HbA1c or BP above target), the concordance rate was 77.6% (38/49; 95% CI: 63.4–87.6) with a mean ΔI of +5.0 weeks (SD=9.6 weeks). This subgroup analysis was necessarily limited to the HbA1c/BP components due to the lack of glycemic variability data, and thus does not reflect the model's complete intended behavior. In Group E (which received two injections plus laser, approximating a loading phase), the mean ΔI was -0.1 weeks (95% CI: -4.4 to +4.2; SD=5.6 weeks), suggesting a close alignment between model output and T_{rec} in this specific context.

The concordance rates observed (63.6% overall, 77.6% in selected subgroups) reflect the *limited predictive precision of the current proof-of-concept parameterization*. These results underscore that the model in its present form is not a validated predictive tool, but a structured hypothesis requiring refinement through prospective coefficient optimization.

Sensitivity analysis confirmed the model's designed hierarchy,

Table 1. Overview results of the proof-of-concept analysis.

Group	B	C	D	E	Pooled (B-E)	Pooled (B-E), *G* not triggerred
Concordance rate (%, 95%CI)	75.0 (53.1-88.8)	52.4 (32.4-71.7)	63.2 (41.8-81.5)	64.7 (41.3-82.7)	63.6 (52.5-73.8)	77.6 (63.4-87.6)
Mean (week, 95%CI)	8.7 (0.14-17.4)	4.5 (-2.2-11.2)	4.1 (-4.09-1.25)	-0.1 (-4.39-4.24)	4.7 (1.19-8.27)	5.0 (1.55-8.45)
Standard deviation (week, 95%CI)	14.9 (10.8-24.0)	13.9 (19.5-20.6)	13.5 (9.7-22.32)	5.6 (3.79-10.76)	13.1 (11.03-16.14)	9.6 (7.67-12.72)

showing HbA1c exerted approximately 36 times greater influence on I_{model} than systolic blood pressure.

This analysis demonstrates that the model's structure produces outputs broadly aligned with the theoretical recurrence kinetics in this retrospective dataset. The results, particularly in subgroups where the model's logic is fully engaged, support its biological plausibility and warrant further investigation. They should be interpreted as hypothesis-generating, providing preliminary associative evidence rather than definitive proof of clinical predictive utility. The penalty coefficients used remain theoretical and require prospective re-calibration.

The use of Protocol H data -with its fixed regimens and selected population- means that our proof-of-concept analysis primarily tests the *biological plausibility* of the model's systemic logic, rather than its operational performance in dynamic clinical settings. The observed associations between I_{model} and T_{rec} should be interpreted as hypothesis-generating for systemic risk stratification, not as evidence of predictive utility in T&E or PRN workflows.

Sensitivity analysis

A detailed description is provided in the *Appendix D*.

Discussion

This study presents a novel translational modeling framework designed to formally link systemic metabolic and hemodynamic control with the dynamics of diabetic macular edema (DME). By integrating a mechanistic model of pathophysiology (Model 1) with an empirically-structured clinical calculator (Model 2), we provide a transparent, mathematically-grounded hypothesis for personalizing anti-VEGF management. The core innovation lies in its hierarchical penalty structure, which quantitatively prioritizes HbA1c and systolic BP—parameters with the strongest evidence base for microvascular complications—while conditionally incorporating glycemic variability as a modulator of residual risk in otherwise well-controlled patients.

We wish to underscore that Model 2 is a *proof-of-concept empirical model*. Its penalty coefficients (α, β, γ) are theoretically derived and have not been validated prospectively. Their values are illustrative and intended to demonstrate the model's structure and logic rather than to serve as clinically applicable parameters. Future studies must focus on empirical re-calibration of these coefficients using data from prospective cohorts managed under real-world treat-and-extend or PRN protocols.

Our proof-of-concept analysis using DRCR.net Protocol H data offers preliminary associative evidence supporting this framework's biological plausibility. The model demonstrated a coherent association with the theoretical time to disease recurrence, particularly in subgroups where its logic was fully engaged. For instance, the close alignment between model output and recurrence time in Group E (which approximated a post-loading phase) suggests the framework may be most relevant after initial disease stabilization, a hypothesis meriting direct testing. The analysis also empirically confirmed the designed hierarchy, with HbA1c exerting a substantially greater influence on the model's output than blood pressure, reflecting its pathophysiological primacy.

Interpretation and clinical implications

The primary contribution of this work is the provision of a structured, interpretable *decision-support framework*, not a validated clinical algorithm. It challenges the current, predominantly ocular-centric paradigm by demonstrating how routine systemic data can be quantitatively integrated into DME management logic.[1] This approach aligns with the philosophy of composite risk engines like the UKPDS model,[21] applying it to a dynamic, treatment-focused context. By creating a tangible link between HbA1c/BP values and suggested management intensity, the model can serve as a communication tool to emphasize systemic control during ophthalmology visits and may help rationalize monitoring schedules in both treat-and-extend and PRN settings, as illustrated in previous sections.

We deliberately excluded parameters like dyslipidemia, as major trials (ACCORD Eye,[22] and FIELD[23]) have not demonstrated a strong, consistent effect on DME progression or anti-VEGF response comparable to hyperglycemia and hypertension, though systemic management per the American Diabetic Association guidelines remains paramount.

Limitations and future refinement

The analysis has important limitations that define its status as hypothesis-generating. The "concordance rate" of up to 77.6% and the observed instances where the model's interval exceeded the recurrence time (up to 47.6% in some subgroups) underscore that the current proof-of-concept parameterization is not sufficiently reliable for standalone clinical use. These discrepancies highlight the need to incorporate additional variables (such as retinal perfusion metrics, genetic factors, or detailed treatment history) and, crucially, to calibrate the model's coefficients through prospective, data-driven fitting.

A key limitation of this proof-of-concept analysis is the *absence of glycemic variability data* in the DRCR.net Protocol H dataset. Our model's design incorporates glycemic variability as a conditional modulator of recurrence risk, particularly in patients with otherwise controlled HbA1c and BP. The inability to test this component means the model's full hierarchical and conditional logic could not be evaluated. Future validation studies must include glycemic variability measurements (e.g., from continuous glucose monitoring) to properly assess the model's integrated performance.

The model's structure, however, is designed for such evolution. Its transparency and modularity allow for the integration of new biomarkers and the refinement of coefficients (α, β, γ) as more robust data become available. Future validation must occur in prospective cohorts managed with true treat-and-extend or PRN protocols, where the model's suggested intervals can be compared against actual clinical decisions and time-to-retreatment outcomes.

Parameter justification and sensitivity

The penalty coefficients (α, β, γ) were informed by established risk gradients: HbA1c from UKPDS 35,[19] blood pressure from hypertension severity studies,[20] and glycemic variability from prospective cohort data.[14] While these sources provide biological plausibility, the coefficients remain *theoretical placeholders* without validation in the context of anti-VEGF interval prediction. Future work must focus on systematic sensitivity analysis and data-driven re-calibration in diverse cohorts.

Predictive accuracy

The observed concordance rates, while supportive of biological plausibility, highlight the model's current *limited predictive*

precision. This is expected given the proof-of-concept nature of the coefficient calibration. Prospective studies should aim not only to validate the model structure but also to iteratively refine coefficients using real-world treatment and outcome data.

Limitations in generalizability

Our analysis relied on DRCR.net Protocol H, which used fixed dosing schedules and enrolled a relatively narrow phenotype spectrum. Consequently, the model's performance in real-world T&E or PRN settings -where intervals are adjusted dynamically based on anatomical response- remains untested. Furthermore, all patients received bevacizumab; whether the model generalizes to other anti-VEGF agents (e.g., aflibercept, ranibizumab) with differing pharmacokinetic and binding properties is uncertain. Future validation should prioritize prospective cohorts managed under T&E/PRN protocols and include patients treated with a range of anti-VEGF therapies to assess broader applicability.

Data availability

While recent prospective studies such as DRCR.net Protocol V and real-world T&E cohorts provide valuable insights into anti-VEGF management and outcomes,[24-26] our model's validation in this proof-of-concept phase was necessarily constrained by data availability. Specifically, Protocol V (though offering rich outcome data) did not systematically collect systolic blood pressure measurements at follow-up visits, a variable central to our model's logic. Similarly, many real-world T&E registries lack granular, visit-by-visit systemic biomarker data (e.g., HbA1c, glycemic variability, BP), which limits their utility for testing a dynamic, systemically-driven interval model. Future validation efforts should prioritize datasets that capture both ocular response and serial systemic parameters to properly evaluate the model's clinical applicability.

Future directions and the path to AI-enhanced personalization

The proof-of-concept framework presented here opens several promising avenues for translational research and clinical implementation. The models are fundamentally interpretable, rule-based systems derived from mechanistic reasoning and structured empirical penalties. This design prioritizes transparency and clinical plausibility, providing a strong foundation for future enhancement through adaptive computational techniques, including AI. We propose the following specific research directions, which align with both the translational vision of this work and the reviewer's constructive suggestions:

1. Prospective validation in real-world T&E and PRN cohorts
   The highest priority is to prospectively validate and refine the model in multi-center cohorts managed under treat-and-extend (T&E) or pro re nata (PRN) protocols, with systematic capture of serial systemic biomarkers (HbA1c, blood pressure, glycemic variability). Such studies would enable empirical recalibration of the penalty coefficients (α, β, γ) and directly assess the model's impact on visual outcomes, treatment burden, and safety compared to standard protocols. Validation across multiple anti-VEGF agents will clarify whether systemic risk stratification is equally informative across different pharmacodynamic profiles.
2. Expansion with novel biomarkers and imaging metrics
   The modular structure of Model 1 allows for the integration of emerging biomarkers. Retinal perfusion metrics from OCT angiography (OCTA), systemic inflammatory markers, or renal function parameters could be incorporated as additional drivers, enhancing biological fidelity and predictive accuracy. Similarly, the inclusion of continuous glucose monitoring data could refine the representation of glycemic variability.
3. From static to dynamic learning systems
   The natural progression of this work is toward greater personalization and accuracy by transforming the static framework into a dynamic learning system. This could involve:
   - *Adaptive coefficient calibration:* using reinforcement learning to dynamically optimize penalty coefficients based on continuous outcome feedback from real-world treatment cohorts.[27]
   - *Multimodal data integration:* leveraging neural networks -such as Long Short-Term Memory (LSTM) networks for continuous glucose monitor data or Convolutional Neural Networks (CNNs) for detailed OCT biomarkers- to process high-dimensional data streams and refine risk assessments.[28]
   - *Scalable and private validation:* employing federated learning frameworks to validate and refine models across multiple institutions without centralizing sensitive patient data, ensuring robust generalizability while preserving privacy.[29]
4. Implementation science and electronic health record (EHR) integration
   To transition from theory to practice, pilot implementation studies within electronic health record (EHR) systems are warranted. Embedding the model as a clinical decision support tool could enable dynamic, personalized scheduling recommendations at the point of care, while facilitating continuous data capture for iterative model refinement.
5. Comparison of modeling paradigms
   Future work should compare the performance of this interpretable, rule-based approach against purely data-driven methods (e.g., neural networks) in predicting DME recurrence and optimal treatment intervals. Hybrid strategies, where mechanistic constraints guide AI training, may offer an optimal balance between clinical plausibility and predictive power.

In this envisioned pathway, the current mechanistic-empirical framework provides the essential, interpretable "scaffold" and causal logic. AI methodologies would then augment this scaffold by enabling dynamic tuning, sophisticated data fusion, and learning from heterogeneous real-world evidence. Therefore, this work is not an AI model but is intentionally architected for AI integration, positioning it as a transparent, hypothesis-driven foundation upon which more complex, data-driven learning systems can be built to advance precision medicine in DME.

Conclusions

In summary, this study establishes a principled mathematical foundation for systemically-informed DME management. It moves beyond qualitative associations to propose a quantitative, causal framework that bridges diabetes care and retina specialty practice. While not yet a clinical tool, it provides a clear, testable hypothesis and a flexible structure for future research aimed at truly personalized, efficient, and holistic patient care.

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Online supplementary material:

Appendix A. Model 1 (mechanistic model): Dynamic model of DME progression and anti-VEGF response.

Appendix B. Model 2 (empirical model): reconciling mechanistic dynamics with clinical feasibility. This appendix details the theoretical derivation and preliminary calibration of the penalty coefficients (α, β, γ) used in Model 2. It is reiterated that these coefficients are proof-of-concept and require prospective empirical validation before clinical use.

Appendix C. Proof-of-concept analysis and data (Microsoft Excel).

Appendix D. Sensitivity analysis.

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Declaration of generative artificial intelligent and artificial intelligent-assisted technologies in the writing process: in the preparation of this manuscript, the author utilized an artificial intelligence tool (ChatGPT, OpenAI GPT-5o and DeepSeek V3.2) to enhance the efficiency, clarity, and precision of the work. AI assistance was employed in several areas: generating preliminary drafts for sections such as the Methods and Discussion based on structured prompts; refining the mathematical model, including the development of piecewise functions and calibration of coefficients; and synthesizing relevant literature to contextualize model design. Additionally, AI was used to improve readability by rephrasing complex sentences and ensuring consistency in terminology. All AI-generated content was rigorously reviewed, edited, and validated by the author to ensure scientific accuracy and originality. The final manuscript reflects the author's intellectual input, clinical expertise, and critical analysis. No patient data or confidential information was entered into the AI system. AI was used solely as a productivity-enhancing tool to support, not a substitute for human reasoning and academic integrity.

Availability of data and material: all datasets used in this study are publicly available through the DRCR Retinal Network Public Site (https://public.jaeb.org/drcrnet/stdy). Specifically, protocol H data were accessed in compliance with the site's data usage agreement. As the data are fully anonymized and collected through a previously approved clinical trial, no additional ethical approval or registration as a clinical trial was required for secondary analysis. Nevertheless, the study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice.

Conference presentation: this paper has been accepted as a free paper presentation at the 41st Asia-Pacific Academy of Ophthalmology (APAO) Congress, held in conjunction with the 37th Annual Scientific Meeting of the Hong Kong Ophthalmological Symposium, which took place in Hong Kong 5-8 February 2026.