

DYNAMIC RETINAL COMPETENCE: AN IDENTIFIABLE BIOPHYSICAL FRAMEWORK FOR PREDICTING RESPONSE TO CAUSAL THERAPY IN INHERITED RETINAL DEGENERATION

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Abstract. The response of inherited retinal degeneration to gene or genome-editing therapy depends not only on correction of the primary molecular defect but also on the biological state of the retina when treatment is delivered. I propose dynamic retinal competence (DRC) as an operational framework for testing whether a measurable change in retinal response to a standardized perturbation can provide information about later therapeutic rescue beyond conventional baseline measurements. The framework separates therapeutic accessibility, tissue recoverability, treatment interaction, and measurement uncertainty rather than treating a favorable final outcome as evidence for a single mechanism. To make the proposal falsifiable, I also report RETINA-DRC-00R, an exploratory secondary computational reconstruction from exact patient- or eye-level values published in three independent retinal pigment epithelium-specific 65 kDa protein (RPE65)/voretigene neparvovec cohorts, comprising 18 study-local patients and 32 eye-level records across the three source studies. Models were evaluated by leave-one-patient-out validation, keeping both eyes of each participant in the same fold; no missing values were imputed. A multidimensional baseline model did not robustly outperform the best single baseline predictor across the reconstructed cohorts. One eye-level Oxford sensitivity analysis favored the multidimensional model after exclusion of a one-month follow-up case, but the advantage disappeared after patient-level aggregation. These results do not validate DRC as a clinical predictor; instead, they delimit the conditions that a future confirmatory study must satisfy. The principal claim is therefore narrow: dynamic pre-therapeutic state is a testable candidate source of incremental predictive information, not an established causal mediator or validated clinical biomarker.

Key words: Inherited retinal degeneration, dynamic retinal competence, RPE65, voretigene neparvovec, optoretinography, gene therapy, identifiability, patient-grouped validation.

INTRODUCTION

Inherited retinal degenerations are genetically and mechanistically heterogeneous disorders characterized by progressive photoreceptor loss and

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secondary remodeling of retinal tissue. The development of gene supplementation and genome-editing therapies has changed the central question. It is no longer sufficient to ask whether a primary molecular defect can be corrected; one must also ask whether a retina at a particular biological stage can convert molecular correction into meaningful functional recovery.

Evidence from animal models shows that recovery is stage- and compartment-dependent. In a cyclic nucleotide-gated channel beta 1 (CNGB1) mouse model, genetic rescue after approximately 25 % or 50 % rod loss restored retinal output close to normal, whereas rescue after approximately 70 % rod loss left persistent gliosis, reduced sensitivity, and impaired retinal-ganglion-cell information fidelity [13]. In a separate phosphodiesterase 6 beta (Pde6b) rescue model, visually guided behavior could still be recovered after extensive rod loss, but not at a later disease stage [7]. These observations argue against a universal structural threshold that alone determines recoverability.

This article is an original theoretical and computational research contribution. The theoretical component defines a falsifiable biophysical framework for dynamic therapeutic competence and identifiability. The computational component, RETINA-DRC-00R, tests a restricted version of the central predictive claim using secondary reconstruction of exact numerical values published in independent human RPE65 treatment cohorts. It does not constitute a systematic review and does not claim that the reconstructed public data are equivalent to original individual-participant datasets.

TERMINOLOGY AND PREVIOUS RESEARCH CONTEXT

The expression “retinal competence” is not new. In developmental neurobiology, it has been used to describe the temporally restricted competence of retinal progenitor cells to generate particular cell types; for example, Liu *et al.* used the term in relation to Foxn4-dependent temporal identity during retinal development [10]. That developmental meaning is distinct from the present use.

Here, dynamic retinal competence (DRC) refers specifically to the measurable capacity of a mature or diseased retina to respond to a standardized perturbation and to change that response after a pre-therapeutic intervention. The adjective “dynamic” and the operational definition are essential: DRC does not describe developmental cell-fate competence, and it is not proposed as a synonym for tissue viability or treatment eligibility.

FROM STATIC BIOMARKERS TO DYNAMIC STATE

Clinical and experimental measurements provide partial observations of retinal state at particular times. Examples include outer nuclear layer (ONL) thickness, ellipsoid-zone integrity, fundus autofluorescence, electroretinography (ERG) amplitude, full-field stimulus threshold, and retinal sensitivity. These measurements

are indispensable, but they are neither complete nor error-free representations of the underlying biological system.

I represent a measured dynamic response by the vector:

$$D(t) = [A, \tau, R, H] \quad (1)$$

where $D(t)$ is the measured dynamic state at time t ; A is response magnitude to a standardized perturbation; τ is a response or recovery time constant; R is the fraction of the measured response recovered within a prespecified interval; and H is the residual deficit after that interval. These components are not collapsed into a weighted score before validation, because arbitrary weighting would increase model flexibility and weaken identifiability.

The framework does not assume that two equal measured vectors are biologically identical. A measured state is an incomplete and noisy projection of an underlying state. Measurement error, operator variability, temporal fluctuation, unmeasured biomarkers, and inability to sample all biological compartments simultaneously can all produce apparent equivalence between biologically different retinas. This alternative explanation is treated as a core limitation rather than as evidence for DRC.

BIOPHYSICAL RATIONALE FOR A DYNAMIC PROBE

Ding *et al.* [3] used intrinsic-signal optoretinography, based on functional optical coherence tomography, to characterize dark adaptation in retinal degeneration 10 (rd10) mice. At postnatal day 14, before obvious morphological abnormalities, dynamic optical responses already differed from wild type. After 30 minutes of dark adaptation, the reported change in external limiting membrane-to-retinal pigment epithelium thickness was $2.64 \pm 0.86 \mu\text{m}$ in rd10 and $1.13 \pm 0.69 \mu\text{m}$ in wild type [3]. The result supports the narrower proposition that dynamic physiology can reveal information not obvious from a single structural snapshot.

A human precedent is provided by retinaldehyde-binding protein 1 (RLBP1)-associated retinal dystrophy. Kvanta *et al.* [9] used dark-adaptation recovery as a primary endpoint in a phase 1/2 gene-therapy trial involving 12 patients with follow-up extending to three years. Dynamic recovery therefore has both experimental and clinical measurement precedent, although this does not by itself validate DRC as a predictor.

GENETIC CORRECTION, TISSUE STATE, AND COMPARTMENTAL RECOVERY

Genetic rescue does not guarantee normalization of the entire retinal system. In the CNGB1 model, late rescue improved function but failed to restore retinal-ganglion-cell sensitivity and information fidelity to wild-type levels, and gliosis persisted [13]. In the Pde6b model studied by Kajtna *et al.* [7], rescue at 12 or 16 weeks improved visually guided behavior, whereas treatment at 24 weeks did not. Endpoint-specific group sizes were generally small, commonly in the range of three to nine animals, and the study did not report a single *a priori* power calculation for all endpoints.

Large-animal evidence adds an important qualification. Beckwith-Cohen *et al.* [1] showed that adeno-associated-virus (AAV)-mediated calcium-binding protein 4 (CaBP4) augmentation in adult dogs could restore synaptic function and vision and induce maturation and reorganization of the outer plexiform layer. Several quantitative comparisons used small animal groups or within-retina treated/untreated regions; for example, one postsynaptic puncta comparison reported $n = 4$ per group [1]. The finding therefore supports mechanism- and stage-dependent synaptic recoverability, not a universal rule of reversibility.

THE THERAPEUTIC MICROENVIRONMENT CAN BE MODIFIED

Wu *et al.* [15] identified oxidative stress as an important barrier to Pde6b-directed gene supplementation in rd10 mice. Their AAV-CoG4 construct combined Pde6b supplementation with a self-contained catalytic G-quadruplex-hemin DNAzyme antioxidant strategy (CoG4). Key treatment panels used $n = 5$ biologically independent samples, and the authors state that sample sizes were based on prior variance and preliminary power calculations. Functional and structural outcomes were assessed from postnatal day 33 to day 153 [15]. The study provides direct evidence that modifying the diseased microenvironment can enhance gene-therapy efficacy, but it does not test whether a measured pre-rescue dynamic change predicts subsequent benefit.

O'Hara-Wright *et al.* [11] showed in human induced-pluripotent-stem-cell retinal organoids that BrainPhys culture medium increased AAV transduction across retinal cell types. For one principal flow-cytometry comparison, $n = 5$ organoids per batch across three independent differentiation batches; a second capsid experiment used $n = 6$ organoids per batch across three batches, and proteomic analyses used four differentiation batches per condition [11]. This finding motivates a distinction between therapeutic accessibility – the ability of a vector to reach, enter, traffic within, and express in target cells – and biological rescue competence after effective delivery.

DYNAMIC RETINAL COMPETENCE HYPOTHESIS

I propose a four-step experimental logic: first probe the retinal response; then apply a conditioning intervention; then repeat the same probe; and only afterwards apply the causal rescue. The key measured quantity is the change between the two pre-rescue dynamic observations, defined as

$$\Delta D = D_{\text{post-condition}} - D_{\text{baseline}} \quad (2)$$

where ΔD is the conditioning-induced change in the prespecified dynamic component or vector, D_{baseline} is the pre-conditioning measurement, and $D_{\text{post-condition}}$ is the repeated measurement after conditioning but before causal rescue. The primary predictive hypothesis is that ΔD contains incremental information about later therapeutic outcome after accounting for baseline reserve and effective target engagement. DRC is therefore initially a predictive construct, not a demonstrated causal mediator.

IDENTIFIABILITY AND FACTORIAL TESTING

A better final outcome after combined conditioning and gene therapy does not identify the mechanism that produced it. The difference can arise from increased cell survival, improved vector delivery or editing efficiency, a direct effect of the conditioning intervention, or a genuine interaction between conditioning and causal rescue. The confirmatory experimental design must therefore separate these components.

For a two-by-two factorial experiment, I define the interaction on an additive outcome scale as:

$$I = (Y_{11} - Y_{10}) - (Y_{01} - Y_{00}) \quad (3)$$

where Y_{00} is the mean outcome without conditioning and without causal rescue, Y_{01} is the outcome with causal rescue alone, Y_{10} is the outcome with conditioning alone, Y_{11} is the combined-treatment outcome, and I is the interaction contrast. A positive I on a prespecified scale supports an interaction beyond simple additivity on that scale; it does not by itself prove that DRC mediates the interaction.

METHODS: RETINA-DRC-00R PUBLISHED-DATA RECONSTRUCTION

STUDY TYPE

RETINA-DRC-00R is an exploratory secondary computational analysis of numerical values already published in peer-reviewed human studies. No new human

or animal experiment was performed. I used only values explicitly reported in article tables or text for the primary reconstruction; values that would require digitization of figures were excluded from the principal numerical analysis.

COHORTS

Three independent RPE65/voretigene neparvovec cohorts provided sufficient exact patient- or eye-level information for restricted reconstruction. The Oxford cohort included 12 eyes from six patients and reported age, baseline and follow-up best-corrected visual acuity (BCVA), white full-field stimulus threshold (FST), central retinal thickness (CRT), and follow-up duration [8]. The Tübingen cohort provided blue and red baseline FST and three-month blue FST for seven eyes from five patients [14]. The Michigan pediatric report provided exact baseline and follow-up Goldmann visual-field (GVF) values for 13 eyes from seven patients in the subset with paired field data [2].

OUTCOME DEFINITIONS

For Oxford and Tübingen, FST improvement was defined as baseline FST minus follow-up FST, so that a positive value represented improved sensitivity. For Michigan, improvement was defined as follow-up minus baseline GVF. I did not pool endpoints across studies because units, follow-up times, populations, and measurement procedures differed.

MODELS

M0 was a reference model that predicted the training-set mean. M1 was the best single baseline predictor selected exclusively within the training data. M2 was a prespecified multivariable baseline model. Oxford M2 used age, baseline BCVA, baseline FST, and baseline CRT. Tübingen M2 used baseline blue and red FST. Michigan M2 used the two published baseline GVF representations (sum-degrees and area) and therefore functions mainly as a redundancy stress test rather than as a complete biological DRC model.

VALIDATION AND LEAKAGE CONTROL

The outer validation was leave-one-patient-out: both eyes of the same participant always remained in the same fold. M1 feature selection was repeated only inside the outer training fold by grouped inner leave-one-patient-out validation. M2 used standardized ridge regression, with the ridge penalty selected only inside the outer training fold from $\alpha = 0.1, 1, 10, \text{ or } 100$ using the same patient-grouped inner validation. Performance was assessed by root mean squared error (RMSE); lower RMSE indicates better out-of-sample prediction. For M2, an out-of-sample coefficient of determination (R^2) was also calculated.

SOFTWARE AND NUMERICAL VERIFICATION

The reconstruction was reproduced in Python 3.13.5 using NumPy 2.3.5, pandas 2.2.3, and scikit-learn 1.8.0. The analysis script and reconstructed-data workbook accompany the revised manuscript as supplementary computational material. Every patient identifier in the reconstruction is study-local and contains no information beyond what the source publications already disclosed.

REPORTING TRANSPARENCY AND DATA COMPLETENESS

All exact publicly reported records that contained the variables required for each cohort-specific analysis were used; no formal sample-size calculation was performed because RETINA-DRC-00R is an exploratory reconstruction rather than a confirmatory model-development study. No missing value was imputed. Standardization parameters, single-predictor selection, and ridge-penalty tuning were estimated only within training data. The analysis was not prospectively registered and no separate protocol was prepared before the exploratory reconstruction. No patient or public involvement occurred in the design or conduct of this secondary analysis. The very small samples and incomplete sociodemographic information in the source reports do not permit a meaningful model-fairness analysis; therefore, no fairness or subgroup-performance claim is made.

AUTHOR CONTRIBUTION STATEMENT

The scientific question, conceptual framework, source integration, design of the identifiability audit, definition of RETINA-DRC-00R, model-comparison rules, interpretation, falsification criteria, and final scientific responsibility belong to the author. Computational analyses and numerical checks were executed with the software specified in the Methods section under the author's methodological control and were independently rechecked before resubmission.

DATA AVAILABILITY

No new experimental dataset was generated. RETINA-DRC-00R uses exact numerical values published in the cited source articles. The reconstructed-data workbook and the analysis script used for the revised manuscript are supplied as supplementary computational material. They must not be interpreted as original individual-participant datasets from the source investigators.

PROTOCOL AND REGISTRATION

RETINA-DRC-00R was an exploratory secondary reconstruction and was not prospectively registered. No separate protocol was prepared before the reconstruction. The analysis rules, reconstructed data, and executable script are supplied with the resubmission so that the reported calculations can be independently checked.

RESULTS: RETINA-DRC-00R

The reconstructed public data did not provide robust evidence that the multivariable model outperformed the strongest simple comparator. Table 1 reports patient-grouped out-of-sample results. In the complete Oxford reconstruction, M2 was worse than both the mean-reference model and M1. Excluding the patient whose last available follow-up was only one month produced an eye-level sensitivity analysis in which M2 had lower RMSE than M0 and M1; however, this apparent advantage disappeared after outcomes were conservatively averaged at the patient level. Tübingen showed no M2 advantage. In Michigan, M1 modestly improved prediction for both visual-field endpoints, whereas the two-variable M2 was worse than M1.

Table 1

RETINA-DRC-00R patient-grouped out-of-sample reconstruction

Analysis	Patients / units	Endpoint	RMSE M0	RMSE M1	RMSE M2	Verdict
Oxford, all follow-ups	6 / 12 eyes	Δ FST	16.90	17.22	18.75	No M2 superiority
Oxford, excluding 1-month case	5 / 10 eyes	Δ FST	18.34	30.95	14.22	Weak eye-level M2 signal only
Oxford, patient-mean sensitivity	5 / 5 patients	Δ FST	18.31	33.74	18.36	Eye-level signal does not survive
Tübingen, 3 months	5 / 7 eyes	Δ FST blue	10.60	11.32	11.18	No M2 superiority
Michigan	7 / 13 eyes	Δ GVF sum-degrees	132.13	127.75	136.09	M1 > M2
Michigan	7 / 13 eyes	Δ GVF area	1672.31	1324.38	1841.57	M1 > M2

Lower RMSE is better.

The result is deliberately negative with respect to the strong predictive claim: RETINA-DRC-00R does not validate DRC as a clinical predictor and does not establish superiority of a multivariable baseline state over the best single marker. The analysis instead demonstrates why comparator supremacy and patient-grouped leakage control are necessary. A correlation or apparent eye-level improvement can

disappear when biological dependence and out-of-sample performance are respected.

PREDICTOR VERSUS CAUSAL MEDIATOR

The proposed confirmatory model for a future adequately powered dataset is

$$\Delta Y_i = \beta_0 + \beta_1 \Delta D_i + \beta_2 \text{ONL}_{0,i} + \beta_3 \text{ERG}_{0,i} + \beta_4 \text{Target}_i + \beta_5 \text{State}_i + \epsilon_i \quad (4)$$

where ΔY_i is the prespecified therapeutic outcome for unit i ; β_0 is the intercept; β_1 quantifies the incremental association of the pre-rescue dynamic change ΔD_i ; $\text{ONL}_{0,i}$ is baseline outer nuclear layer reserve or an equivalent structural measure; $\text{ERG}_{0,i}$ is baseline electroretinographic function or another prespecified functional measure; Target_i is effective target engagement, such as editing or transduction efficiency; State_i is an orthogonal biological state measure such as redox or mitochondrial status; β_2 to β_5 are the corresponding regression coefficients; and ϵ_i is the residual error. The exact covariates must be prespecified for the cohort under study and selected without access to held-out outcomes.

Even if β_1 is non-zero out of sample, DRC would initially be an independent predictor, not necessarily a causal mediator. Causal mediation would require stronger intervention-based evidence, ideally using mechanistically distinct conditioning interventions that shift the same prespecified dynamic measure and reproduce a common relation between that shift and later rescue.

Novelty boundary. Within the retinal literature considered for this article, previous studies establish separate precedents for dynamic retinal endpoints, baseline-state/outcome analyses, stage-dependent rescue, and interventions that modify the therapeutic microenvironment. I did not identify a prior retinal study in this evidence set that prospectively treats a conditioning-induced pre-rescue change in retinal dynamics as an incremental predictor of later causal rescue while also requiring patient-grouped out-of-sample superiority over the best simple baseline comparator and separating predictive performance from mechanistic identifiability. This is a bounded methodological novelty claim, not a claim that DRC is already a validated biomarker or that the underlying concept of retinal competence is new.

CRITICAL APPRAISAL OF THE EVIDENCE BASE

The studies used to motivate the framework are heterogeneous and cannot be summed as though they were one experiment. None of the key preclinical studies cited here used rats; the animal models are predominantly mice, with one recent dog model, while other evidence comes from human participants and human retinal organoids. A single total animal count would therefore be scientifically misleading

because sample units, endpoints, repeated measures, and within-animal comparisons differ. Table 2 summarizes the most relevant limitations instead.

Table 2

Selected evidence base and limitations relevant to interpretation of DRC

Study	Model / reported unit	Relevant sample-size information	Follow-up / replication note
Kajtna <i>et al.</i> 2022 [7]	Pde6b mouse	Endpoint-specific groups commonly $n = 3-9$ animals	Rescue evaluated to 30–40 weeks; exact late-stage threshold has limited independent replication
Qin <i>et al.</i> 2023 [12]	rd10 mouse prime editing	Key molecular endpoints $n = 3-4$; ERG panels $n = 6$; experiments independently repeated ≥ 3 times	Functional assessment to postnatal day 120; no reported universal <i>a priori</i> power analysis
Scalabrino <i>et al.</i> 2023 [13]	CNGB1 mouse	Retinal ganglion cell analyses across 48 retinas; information analyses used 2–6 retinas per condition/time	Longitudinal months after rescue; stage dependence consistent with earlier CNGB1 literature
Kvanta <i>et al.</i> 2024 [9]	Human RLBP1 trial	12 patients	Prespecified interim follow-up up to 3 years; phase 1/2, not a DRC prediction study
Wu <i>et al.</i> 2026 [15]	rd10 mouse	Key treatment panels $n = 5$ biological samples; authors report preliminary power calculations	Postnatal days 33–153; independent replication of the 2026 platform not yet established
Beckwith-Cohen <i>et al.</i> 2026 [1]	CaBP4 dog	Endpoint-dependent; one synaptic comparison $n = 4$ per group plus within-retina treated/untreated regions	Examples followed up to 38 months; independent replication not yet established
O'Hara-Wright <i>et al.</i> 2026 [11]	Human retinal organoids	Transduction: $n = 5-6$ organoids per batch, $N = 3$ batches; proteomics $N = 4$ batches	<i>In vitro</i> model; no clinical follow-up; independent replication not yet established

Several mechanistic studies rely on small endpoint-specific sample sizes and conventional null-hypothesis significance testing. Reporting of standardized effect sizes and *a priori* statistical power is inconsistent across the literature. Recent 2026 findings are too new to have accumulated substantial independent replication.

Consequently, these studies support plausibility and boundary conditions, not clinical certification of DRC.

RELATION TO CLASSICAL BIOPHYSICAL MODELS OF PHOTOTRANSDUCTION

Classical biophysical work, including Herman and Dimoftache [5, 6], modeled transformation of light into biochemical and electrical photoreceptor responses involving rhodopsin, transducin, phosphodiesterase, cyclic guanosine monophosphate, cyclic-nucleotide-gated channels, and membrane current. DRC does not replace these models. It asks a different systems-level question: which measured properties of a diseased retina add information about whether restoration of a molecular mechanism will translate into later functional recovery?

LIMITATIONS

The most fundamental limitation is observability. A measured retinal state is not the complete biological state. Measurements contain methodological error, biological fluctuation, operator and instrument variability, and sampling uncertainty. Moreover, all relevant biomarkers cannot be measured simultaneously at every spatial scale and biological compartment. Therefore, two retinas that appear similar at baseline may differ because the measurements are noisy or incomplete, not because a separate latent “competence” state necessarily exists. Any future DRC claim must show incremental prediction beyond the best measured comparator and must quantify measurement reliability where possible.

RETINA-DRC-00R is a small-sample secondary reconstruction, not a validation cohort. The Oxford analysis includes heterogeneous last-follow-up times from one to twelve months. The Tübingen dataset contains only five patients. The Michigan reconstruction is pediatric and includes related participants in the original report, while its two baselines visual-field representations are partly redundant. These constraints make model selection unstable and limit statistical power. The analysis is deliberately used as a falsification-oriented stress test rather than as evidence of clinical utility. Point estimates of predictive error are therefore reported descriptively; confidence intervals around model performance were not used to support inference because the number of independent patients is too small for stable interval estimation. This is a reporting limitation and another reason the analysis cannot certify clinical performance.

The broader biological evidence is also heterogeneous across genes, diseases, species, interventions, and endpoints. Findings from *Pde6b*, *CNGB1*, *CaBP4*, *RLBP1*, *RPE65*, or retinal organoids cannot be transferred directly to another

genotype or therapy without a separate test. Recent preclinical studies often use small endpoint-specific groups, and formal effect-size and power reporting is incomplete. The newest 2026 studies have not yet accumulated independent replication. No universal recovery window or universal dynamic biomarker is established.

Finally, optoretinography and other dynamic measurements are not specific to one molecular process. A dynamic optical signal can reflect phototransduction, osmotic or water movement, metabolism, mitochondrial activity, and retinal-pigment-epithelium transport. A DRC experiment therefore requires orthogonal target-engagement or state measurements and cannot identify mechanism from optical dynamics alone.

CONCLUSION

The evidence reviewed here supports a bounded proposition: retinal recovery is compartment- and stage-dependent, and correction of a molecular defect does not guarantee normalization of all downstream retinal functions. Dynamic measurements can reveal physiology not evident from a single structural observation, and the therapeutic microenvironment can modify response to gene therapy. These facts make a dynamic predictive experiment biologically plausible.

The new computational reconstruction adds an equally important negative result. In the limited exact public human data currently reconstructable, a multivariable baseline model did not robustly outperform the strongest simple comparator under patient-grouped out-of-sample validation. DRC is therefore not validated as a clinical predictor. The next legitimate test is prospective or original individual-participant-data validation with prespecified endpoints, strict patient-level leakage control, and explicit comparison against the best single baseline marker. The framework succeeds only if it survives that comparison.

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Ethics statement. No new experiments involving animals or human participants were conducted as part of this study. The computational reconstruction uses only information already publicly reported in peer-reviewed publications.

Patient and public involvement. No patients or members of the public were involved in the design, conduct, reporting, interpretation, or dissemination planning of this secondary computational reconstruction.

Declaration of generative AI and AI-assisted technologies in the writing process. During manuscript preparation, the author used OpenAI ChatGPT to assist with language editing, document organization, and generation/checking of analysis code. The author independently defined the scientific questions, verified source data and numerical results, revised the manuscript line by line, and takes full responsibility for the final scientific content.

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