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Predictive value of early treatment response for long-term outcomes after seven years on low-dose atropine

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ABSTRACT

Background/Aims To determine whether first-year response to low-dose atropine predicts long-term myopia control and may guide treatment escalation in myopic children.

Methods A retrospective chart review (2012–2025) identified children treated with atropine 0.01%–0.05% at a single practice with ≥54 months of treatment. Children were excluded with insufficient follow-up (<54 months of treatment), comorbidities that might affect myopia progression or concurrent baseline optical myopia-control therapy. First-year response was modelled as the spherical equivalent refraction (SER) progression rate (diopters (D)/year, continuous, positive values indicating worsening myopia) and by responder status (defined as≤0.25D total progression at 12±3 months). The primary outcome was successful control maintaining≤0.25 D/year over follow-up. Key secondary outcomes were total SER progression and time-to-treatment escalation. Eye-level models accounted for correlation between fellow eyes and adjusted for baseline age and baseline SER.

Results 71 children (142 eyes) had a mean follow-up of 6.8±2.0 years. First-year responders included 101/142 eyes (71%) with higher odds of successful control (adjusted OR 2.66, 95% CI 1.11 to 6.35, p=0.028) and less total SER progression (adjusted difference 0.57D, 95% CI 0.28 to 0.86, p<0.001). Each additional 0.25 D/year of year-1 progression was associated with lower odds of successful control (OR 0.73, 95% CI 0.59 to 0.89, p=0.002) and greater total progression (0.22 D more, 95% CI 0.16 to 0.29, p<0.001). Dose escalation occurred earlier in nonresponders; responders had a lower hazard of escalation (HR 0.27, 95% CI 0.14 to 0.52).

Conclusion First-year SER change is strongly predictive of long-term outcomes; despite earlier treatment escalation in nonresponders, responders had a much higher likelihood of sustained long-term control. Early response assessment may help identify high-risk patients for closer monitoring and/or treatment intensification.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low-dose atropine slows myopia on average, but long-term outcomes vary and early response is used pragmatically to guide escalation.

WHAT THIS STUDY ADDS

⇒ First-year spherical equivalent refraction progression, either modelled continuously or dichotomised into responders/nonresponders, strongly predicted 7 year refractive outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ First-year spherical equivalent refraction change may help risk-stratify patients for closer monitoring and/or treatment intensification and provides targets for prospective validation with axial length.

INTRODUCTION

Myopia has grown at an unprecedented rate over the past few decades, with projections indicating that nearly five billion people will be affected by 2050.[1] Environmental exposures (less time outdoors and more near work) and genetics are thought to contribute, with substantial ethnic differences in prevalence and severity.[2–4] Myopia is not a benign condition: it increases the risk of glaucoma, cataract, retinal detachment and myopic maculopathy and is now a leading cause of uncorrectable visual impairment worldwide, making effective strategies to slow progression clinically important.[5]

Many interventions, including orthokeratology,[6 7] contact lenses,[8] multifocal spectacles[9] and low-dose atropine eye drops,[10–26] have shown some benefit in reducing childhood myopia progression.[27 28] For low-dose atropine, randomised controlled trials such as Atropine for the Treatment of Myopia 2,[23 24] the Low-Concentration Atropine for Myopia Progression study[20–22] and the Childhood Atropine for Myopia Progression trial[18] have demonstrated safety and efficacy in multiple settings, with variable effect sizes by population, atropine concentration and trial endpoints. Yet, every major trial has also demonstrated wide variability in outcomes: some children progress very little, while others continue to advance at rates exceeding 0.50 diopters (D) per year.[4 27 28]

Early studies framed results around 'responders/slow progressors' and 'nonresponders/fast progressors' to account for

this variability, commonly defining responders as those averaging ≤0.25D/year or 0.50D/year of progression and nonresponders as those with faster progression.[15 29–31] This classification could help explain inconsistent efficacy estimates across studies, reduce outcome variability caused by mixing faster and slower progressors and provide a pragmatic guide for management—maintaining therapy in responders and escalating treatment in nonresponders. However, others have argued that these categories are artificial, merely distinguishing children who naturally progress at different rates but derive similar absolute benefit from atropine.[32]

In this retrospective cohort, we evaluated whether the first-year response to low-dose atropine predicted long-term myopia control. We evaluated whether classifying children as responders or nonresponders after the first year provides clinically useful prognostic information—reflecting a true differential pharmacologic effect versus simply uncovering inherently different progression rates—and whether this framework can help guide decisions about treatment escalation.

METHODS

We performed a retrospective cohort study at a single clinical practice, identifying eligible children as those who received atropine prescriptions (0.01%–0.05%) dispensed by compounding pharmacies between 19 February 2012 and 3 July 2025. Charts were located for 787 of 802 unique patients identified from pharmacy records as having received an atropine prescription under the corresponding author's NPI number; 15 paper charts could not be located after the practice's conversion to an electronic medical record. 71 children met the inclusion criteria: ≥54 months of treatment with low-dose atropine, no discontinuation intervals >18 months and at least annual spherical equivalent refraction (SER) measurements. Excluded children included six with systemic diseases known to affect SER (congenital glaucoma, Marfan, Ehlers-Danlos and Down syndromes), two on orthokeratology without SER data, one on prior long-term atropine 1% and 654 with insufficient duration of treatment (figure 1). Comorbidities such as amblyopia, anisometropia, high astigmatism (≥1.5 D cylinder in either eye) and history of retinopathy of prematurity (ROP) were also excluded, plus three additional children who started atropine concurrently with optical myopia-control therapy at baseline. Baseline characteristics for included subjects are summarised in table 1.

Initial therapy was at the physician's discretion using atropine 0.01%–0.05% eye drops for all children without

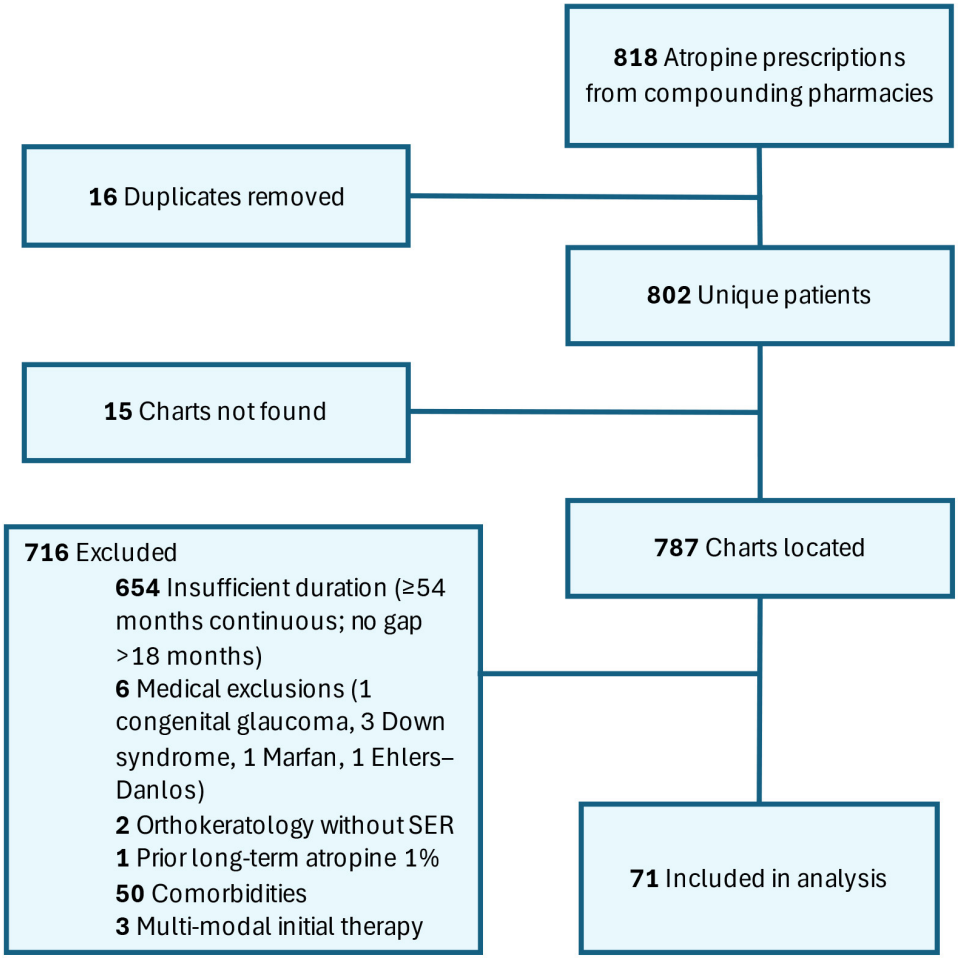

Figure 1 Flow diagram of participants. D, diopters; ROPretinopathy of prematurity; SER, spherical equivalent refraction.

Table 1 Baseline characteristics and follow-up (n=71 children).

Characteristic	Value
Age at baseline (years)	9.5±2.1
Baseline SER (D), average between eyes	−1.97±1.94
Final SER (D) average between eyes	−3.61±2.36
Sex (female/male)	36/35
Follow-up (years)	6.8±2.0 (range 4.7–12.4)
Initial atropine concentration	0.01%, 69 (97.2%); 0.02%, 2 (2.8%)
Inter-eye correlation (baseline SER)	0.94
Any side effect reported	7 (9.9%)
Discontinued due to side effects	1 (1.4%)

Values are mean±SD or n (%), unless otherwise specified.
D, diopter; SER, spherical equivalent refraction.

concurrent optical treatment. During follow-up, treatment escalation also occurred at physician discretion by increasing the atropine concentration and/or adding peripheral defocus contact lenses (PD-CTL) (MiSight, CooperVision, Inc., San Ramon, CA, United States)[8] or peripheral defocus glasses (PD-Glasses) (MyoZoom, Riccino Optical, Inc., Xiamen, China).

SER (sphere + ½ cylinder) was the primary variable. Refraction was obtained by objective retinoscopy, cycloplegic or non-cycloplegic per routine clinical practice, in most cases; a small subset of older children had manifest refractions only that were used as recorded. Within each subject, the type of refraction (retinoscopy or manifest) was consistent across study visits. Myopia progression was defined as $SER_{(start)} - SER_{(end)}$, reported as positive values for worsening myopia. Eye-level responders were defined by an increase ≤0.25D at 12±3 months from baseline or, if the first follow-up was longer than 15 months, an increase ≤0.25D/year (annualised rate); otherwise, the eyes were defined as nonresponders. In this context, responders/nonresponders were operational labels based on observed on-treatment progression at 12 months; they did not imply identification of an individual treatment effect, which cannot be estimated without an untreated control. Subject-level categories were responsive (both eyes responders), partially responsive (one eye responder) and unresponsive (neither eye responder). Safety was recorded as 1=any reported adverse symptom attributable to therapy (eg, photophobia, irritation) or 0=no reported adverse symptoms. Any adverse event at the subject level was defined as ≥1 visit with safety=1.

The primary outcome was successful control, prespecified as ≤0.25 D/year progression across the duration of follow-up. Secondary outcomes included total SER progression (baseline SER minus final SER, averaged between eyes), time-to-treatment escalation and safety. Prespecified modifiers for eye-level modelling included baseline SER and baseline age. Finally, to provide a cohort-level comparator of untreated SER progression for context only, we used the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study's multivariate cubic mixed-effects model for cycloplegic spherical-equivalent refraction.[4]

Statistical analysis was performed in R (v4.5.1)[33 34] with continuous variables presented as mean±SD and compared using analysis of variance (ANOVA) and Fisher's exact or χ^2 for group comparisons and one-sample t-tests for the contextual CLEERE comparison, reported as the mean difference with a 95% CI. Primary prognostic models were fit at the eye level (two eyes per child) with correlation between fellow eyes handled by subject-level clustering: (1) generalised estimating equation (GEE) logistic regression for successful control, using subject as the clustering variable, an exchangeable working correlation structure and robust (sandwich) standard errors, and (2) linear mixed-effects regression for total SER progression, with a random intercept for subject and maximum-likelihood estimation (reported as positive for worsening myopia).[33–36] Models were fit using two alternative representations of early response: (a) continuous first-year progression rate (scaled per 0.25 D/year) and (b) binary responder status (≤0.25 D progression at 12±3 months). Covariates included baseline age and baseline SER. We report adjusted ORs and adjusted mean differences with 95% CIs. Predictive performance of the binary responder classification was summarised using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Kaplan-Meier curves and Cox proportional-hazards models assessed time-to-escalation.[33–36] Statistical significance was two-sided α=0.05 with no adjustment for multiple comparisons. A priori power was estimated at 69% for moderate effect sizes.

Because treatment escalation is usually introduced in response to faster myopia progression, analyses involving escalation are vulnerable to confounding by indication. We therefore performed two post hoc checks to test whether the primary prognostic findings were driven by threshold artefact or by nonspecific measurement variability rather than by SER itself. First, we repeated the binary responder analysis after excluding eyes whose first-year progression lay close to the responder threshold so that small measurement differences around the cut-point would be less likely to determine classification. Second, we performed a negative-control analysis using change in cylinder rather than SER progression. If the responder framework were primarily reflecting general noise or instability in refraction measurements, a similar

Table 2 First-year response category and long-term outcomes (subject-level).

Characteristic	Responsive (n=45)	Partially responsive (n=11)	Unresponsive (n=15)	P value
Baseline age (years)	9.8±2.2	8.8±1.3	9.4±2.3	0.33
Baseline SER (D)	−1.85±1.94	−1.65±1.27	−2.57±2.30	0.39
Final SER on atropine (D)	−3.15±2.19	−2.99±1.70	−5.42±2.53	0.0026
Total SER progression (D)	1.30±0.97	1.35±0.91	2.85±1.77	<0.001
Successful control (both eyes), n (%)	26 (57.8%)	6 (54.5%)	2 (13.3%)	0.010

Response categories are based on first-year responder status in each eye: responsive = both eyes responders; partially responsive = one eye responder; unresponsive = neither eye responder. Total SER progression is baseline SER minus final SER on atropine (positive = worsening myopia). Successful control indicates both eyes maintained ≤0.25 D/year over follow-up.
SER, spherical equivalent refraction .

association would be expected for cylinder; failure to observe such an association would support specificity of the SER-based prognostic signal.

RESULTS

Subjects included 71 children (142 eyes) with a mean follow-up of 6.8±2.0 years (range 4.7 to 12.4 years). Initial atropine concentration was 0.01% in 69/71 (97.2%) and 0.02% in 2/71 (2.8%). Average baseline SER was −1.97±1.94 D, and average final SER was −3.61±2.36 D. Adverse events occurred in 7/71 subjects (9.9%), primarily light sensitivity and irritation, but only 1/71 (1.4%) discontinued treatment after almost 10 years on treatment (table 1).

At 1 year, 45/71 (63.4%) children were responsive, 11/71 (15.5%) were partially responsive and 15/71 (21.1%) were unresponsive. Successful control (≤ 0.25 D/year over total follow-up) was achieved in 26/45 (57.8%) responsive, 6/11 (54.5%) partially responsive and 2/15 (13.3%) unresponsive subjects (χ^2 p=0.01). Total SER progression (baseline SER minus final SER, averaged between eyes) was 1.30±0.97D (responsive), 1.35±0.91D (partially responsive) and 2.85±1.77D (unresponsive) (ANOVA p=0.0001) (table 2). At eye level, 101/142 eyes (71.1%) were responders and 41/142 (28.9%) were nonresponders. In adjusted eye-level models, responders had higher odds of successful control (OR 2.66, 95% CI 1.11 to 6.35; p=0.028) and 0.57 D less total SER progression than nonresponders (95% CI 0.28 to 0.86, p<0.001). When modelled continuously, each additional 0.25 D/year of first-year progression was associated with lower odds of successful control (OR 0.73, 95% CI 0.59 to 0.89; p=0.002) and greater total SER progression (0.22 D more, 95% CI 0.16 to 0.29; p<0.001). First-year status had a PPV of 0.67 (95% CI 0.58 to 0.76) for responsive children achieving successful control and NPV of 0.66 (95% CI 0.51 to 0.78) for unresponsive children not achieving successful control. Sensitivity and specificity were 0.83 and 0.45, respectively.

As clinically expected, treatment was escalated sooner and more often by the end of follow-up in initially unresponsive children. Atropine concentration was increased in 15/15 (100.0%) unresponsive, 8/11 (72.7%) partially responsive and 34/45 (75.6%) responsive children. Because cumulative ('ever') escalation proportions reflect opportunity over long follow-up, we emphasise escalation timing: median time to escalation reflected clinical urgency, occurring much earlier in unresponsive (24.4 months) and partially responsive (24.0 months) subjects compared with responsive subjects (37.4 months) (table 3). The global log-rank test showed significant separation among groups (χ^2=13.1, df=2, p=0.0014). In a Cox model (reference=unresponsive), responsive subjects had a significantly lower hazard of escalation (HR 0.27, 95% CI 0.14 to 0.52; p<0.001). Partially responsive subjects also had a lower hazard of escalation (HR 0.28, 95% CI 0.11 to 0.69; p=0.006). In exploratory, observational modelling aligned to the escalation event, the modelled progression rate improved from 0.55 to 0.22 D/year in nonresponders but remained similar (0.21 vs 0.18 D/year) in responders.

Table 3 Treatment escalation and adjunct therapies by first-year response category (subject-level).

First-year response	Any escalation, n (%)	Median time to escalation (months)	Cox HR for escalation (95% CI)	Any PD-CTL, n (%)	Any PD-Glasses, n (%)
Unresponsive (n=15)	15 (100.0%)	24.4	1.00 (ref)	8 (53.3%)	1 (6.7%)
Partially responsive (n=11)	8 (72.7%)	24.0	0.28 (0.11 to 0.69)	1 (9.1%)	2 (18.2%)
Responsive (n=45)	34 (75.6%)	37.4	0.27 (0.14 to 0.52)	13 (28.9%)	4 (8.9%)

Escalation defined as the first recorded treatment increase (atropine dose increase and/or addition of PD-CTL or PD-Glasses). Median time is the Kaplan-Meier median. HR = hazard ratio from Cox proportional-hazards model with unresponsive as the reference group. PD-CTL = MiSight® contact lens; PD-Glasses = MyoZoom® spectacle lenses.
PD=CTL, peripheral defocus contact lenses.

Adjunct optical defocus (PD-CTL) was prescribed to a subset of children across all groups: 8/15 (53.3%) unresponsive, 1/11 (9.1%) partially responsive and 13/45 (28.9%) responsive children. The frequency of PD-CTL usage differed across response categories (χ^2 p=0.048), consistent with preferential use in children with poorer initial control. In exploratory longitudinal modelling, its addition was associated with an estimated 0.20 D/year slower interval progression in nonresponders with little change in responders. PD-Glasses were used infrequently, and no statistically significant association with interval progression was detected. Because escalation and add-ons are triggered by worsening progression (confounding by indication) and regression to the mean, these event-aligned estimates should be interpreted as observational associations rather than causal effects; our primary responder inferences were unchanged in post hoc sensitivity checks (near-threshold restriction and a negative-control outcome using cylinder).

For context, the treated cohort had 1.66 D (95% CI 1.28 to 1.92 D; p<0.0001) less final SER than the predicted untreated CLEERE estimate of −5.27±2.20 D. Because this is an external, model-based benchmark rather than a concurrent control group, this result is presented to illustrate clinical scale rather than to infer causal treatment effect.

DISCUSSION

In this cohort of myopic children treated with low-dose atropine from childhood into adolescence, children who demonstrated minimal first-year progression ≤0.25D were substantially more likely to achieve successful long-term control and had markedly less total SER progression than those who did not. At the subject level, initially responsive children were more than four times more likely to average ≤0.25D/year across follow-up compared with unresponsive children (57.8% vs 13.3%). At the eye level, responder eyes had greater odds for successful control (OR 2.66, 95% CI 1.11 to 6.35) and progressed ~0.57 D less than nonresponder eyes. The PPV and NPV of first-year status for successful control were 0.67/0.66, supporting the clinical utility of classifying children after 12 months and using that classification to guide subsequent management. These results are prognostic rather than causal—early on-treatment progression stratifies the risk of later good versus poor control.

Escalation patterns aligned with clinical expectations: unresponsive children escalated earlier (shorter time-to-escalation) and were more likely to have escalation by the end of follow-up (table 3). PD-CTL prescription frequency differed significantly by responder category, and exploratory observational estimates suggested larger slowing among nonresponders than responders; these escalation/add-on findings should be interpreted as descriptive rather than causal given possible confounding by indication. Adverse effects were uncommon (9.9% reported at any visit), and discontinuations due to side effects were rare (1.4%) and occurred only after many years on treatment.

Randomised trials demonstrate efficacy of low-dose atropine on average, yet outcomes vary widely between individuals. Our design cannot estimate individual counterfactual treatment effects; instead, these data show that early on-treatment SER change may provide clinically useful prognostic information for identifying children more likely to achieve long-term control under routine care and those at higher risk of continued progression who may warrant closer monitoring and consideration of intensification.

The CLEERE-based projection of untreated final SER anchored to our cohort's baseline age, SER, sex and ethnic mix was included to provide context and scale to the treatment benefit.[4] This analysis is intentionally labelled context-only, not an outcome, because the comparison is not controlled for population and historical differences in myopia progression rates. Nonetheless, the magnitude of the benefit observed on treatment, −3.61±2.36 D versus −5.27±2.20 D projected without treatment, provides a validated external reference supporting a clinically meaningful reduction in final myopic SER using low-dose atropine.

Key study strengths are the long follow-up (mean 6.8 years, range up to ~12 years) and quantification of the effects of real-world management decisions that are difficult to capture in a fixed-protocol clinical trial, especially the inclusion of multiple treatment modalities like PD-CTL and PD-Glasses in addition to increasing concentrations of atropine. Limitations include the absence of a concurrent control group, lack of axial length measurements and non-uniform use of cycloplegia across all visits. Additionally, SER measurements were obtained using retinoscopy or manifest refraction rather than automated refraction. Because the test-retest variability of non-cycloplegic refraction can approach ±0.50 D in children,[37] there is a risk of classification error when categorising first-year response using a single ≤0.25D threshold. We mitigated that risk by modelling the first-year response continuously and performing sensitivity checks using alternative responder thresholds and excluding eyes near the cut-point. While the extensive duration of our follow-up mitigates the impact of individual visit-to-visit measurement noise on the long-term progression rates, initial misclassification remains an important limitation. In addition, treatment escalations may have compressed outcome differences (confounding by indication) because faster-progressing children experienced more treatment escalations than slower-progressing children. These factors should have diminished, not increased, any treatment benefit, however, by preferentially improving outcomes in unresponsive children. Finally, the use of compounded low-dose atropine introduces potential variability in medication stability and concentration over time,[38] as we do not possess independent stability data for dispensed bottles. Patients were instructed to replace bottles regularly per standard pharmacy guidance; nevertheless, any unmeasured degradation would be expected to reduce delivered

dose and diminish the observed treatment effect, representing an additional source of real-world variability.

Clinically, these findings support a pragmatic framework: assess first-year on-treatment SER change around 12 months to risk-stratify children, maintain therapy in well-controlled children and consider earlier intensification and closer monitoring in those with continued rapid progression. Future research could prospectively validate SER-based early response with axial length measures, evaluate potential synergies between atropine and optical interventions and further explore astigmatism and ROP as potential modifiers.

During preparation of this work, the authors used ChatGPT-5 to improve the language and readability of the manuscript. After using the service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Competing interests Robert A. Clark consulted for Vyluma®, Inc., Sydnexis®, Inc., and CooperVision®, Inc. on myopia control. Karenna Mehta declares no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Providence Institutional Review Board (Study ID: STUDY2024000577). A waiver of informed consent was granted for this retrospective chart review. All procedures adhered to the tenets of the Declaration of Helsinki and applicable privacy regulations.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. De-identified data that support the findings of this study are available from the corresponding author upon reasonable request, subject to any required approvals and data use agreement requirements.

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