BMJ Open Ophthalmology

Simulation of long-term impact of intravitreal anti-VEGF therapy on patients with severe non-proliferative diabetic retinopathy

Quan Dong Nguyen ,[1] Andrew A Moshfeghi,[2] Jennifer I Lim,[3] Ekaterina Ponomareva,[4] Ankita Chauhan,[4] Rohini Rao,[5] Steven Sherman[5]

To cite: Nguyen QD, Moshfeghi AA, Lim JI, *et al*. Simulation of long-term impact of intravitreal anti-VEGF therapy on patients with severe non-proliferative diabetic retinopathy. *BMJ Open Ophthalmology* 2023;**8**:e001190. doi:10.1136/bmjophth-2022-001190

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2022-001190).

The results of this study were presented in parts at the 44th Macula Society 2021 Virtual Annual Meeting, 6–7 February 2021; the Association for Research in Vision and Ophthalmology 2021 Annual Meeting, 1–7 May 2021, Rockville, Maryland; and the American Academy of Ophthalmology 2021 Annual Meeting, 12–15 November 2021, New Orleans, Louisiana.

Received 21 October 2022
Accepted 1 March 2023

For numbered affiliations see end of article.

Correspondence to
Dr Quan Dong Nguyen; ndquan@stanford.edu

ABSTRACT

Objective A simulation model was constructed to assess long-term outcomes of proactively treating severe non-proliferative diabetic retinopathy (NPDR) with anti-vascular endothelial growth factor (anti-VEGF) therapy versus delaying treatment until PDR develops.

Methods and analysis Simulated patients were generated using a retrospective real-world cohort of treatment-naive patients identified in an electronic medical records database (IBM Explorys) between 2011 and 2017. Impact of anti-VEGF treatment was derived from clinical trial data for intravitreal aflibercept (PANORAMA) and ranibizumab (RISE/RIDE), averaged by weighted US market share. Real-world risk of PDR progression was modelled using Cox multivariable regression. The Monte Carlo simulation model examined rates of progression to PDR and sustained blindness (visual acuity <20/200) for 2 million patients scaled to US NPDR disease prevalence. Simulated progression rates from severe NPDR to PDR over 5 years and blindness rates over 10 years were compared for delayed versus early-treatment patients.

Results Real-world data from 77 454 patients with mild-to-severe NPDR simulated 2 million NPDR patients, of which 86 680 had severe NPDR. Early treatment of severe NPDR with anti-VEGF therapy led to a 51.7% relative risk reduction in PDR events over 5 years (15 704 early vs 32 488 delayed), with a 19.4% absolute risk reduction (18.1% vs 37.5%). Sustained blindness rates at 10 years were 4.4% for delayed and 1.9% for early treatment of severe NPDR.

Conclusion The model suggests treating severe NPDR early with anti-VEGF therapy, rather than delaying treatment until PDR develops, could significantly reduce PDR incidence over 5 years and sustained blindness over 10 years.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a lack of long-term clinical trial data and real-world evidence on the impact of anti-vascular endothelial growth factor (anti-VEGF) treatment at the severe non-proliferative diabetic retinopathy (NPDR) stage on progression to PDR and long-term visual outcomes in this population.

WHAT THIS STUDY ADDS

⇒ Monte Carlo simulation model results suggest that anti-VEGF treatment at the severe NPDR stage could significantly reduce incidence of PDR over 5 years and sustained blindness over 10 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides an estimation of the impact of treatment at the severe NPDR stage in a large simulated NPDR population derived from a real-world database.

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of vision loss and blindness in people aged 20–65 years.[1 2] With progression from non-proliferative DR (NPDR) to PDR, risks of ocular complications increase, including retinal detachment, vitreous haemorrhage and diabetic macular oedema (DMO), which can lead to severe vision loss and blindness.[2–4]

Greater DR severity is associated with faster PDR progression[5 6] and sustained blindness when untreated.[7] In the Early Treatment Diabetic Retinopathy Study, progression rates from NPDR to PDR in untreated eyes increased with greater baseline DR severity.[5] Recent US clinical practice data showed 46.8% of untreated eyes with severe NPDR progressed to PDR within 4 years. The probability of sustained blindness over 2 years increased with DR severity; eyes with severe NPDR and PDR at diagnosis were 3.6 and 4.0 times more likely, respectively, to develop sustained blindness than those with mild NPDR.[7] Anti-vascular endothelial growth factor (anti-VEGF) treatment slows progression to PDR, development of vision-related complications and centre-involved DMO (CI-DMO) with vision loss in patients with NPDR.[8–10] For patients with moderately severe or severe NPDR at baseline, intravitreal aflibercept improved Diabetic Retinopathy

Severity Scale (DRSS) score and reduced risk of developing a vision-threatening complication (PDR/anterior segment neovascularisation) or CI-DMO over 100 weeks versus sham.[8] In patients with moderately severe to severe NPDR, lower DR worsening rates were observed following ranibizumab treatment versus sham through month 36.[9] In Protocol W, intravitreal aflibercept-treated patients with moderate-to-severe NPDR had lower rates of PDR or CI-DMO with vision loss through 2 years versus sham.[10]

Long-term clinical trial data and real-world evidence examining the impact of early anti-VEGF treatment on progression of severe NPDR to PDR and visual outcomes in this population are lacking. We developed a Monte Carlo simulation (MCS) model to assess the impact of initiating anti-VEGF therapy when mild or moderate NPDR progresses to severe NPDR (DRSS 47–53)—rather than delaying until PDR develops—on the rate of PDR progression and incidence of associated blindness.

MATERIALS AND METHODS

A real-world cohort of treatment-naive patients with mild-to-severe NPDR was identified using IBM Explorys, a database of deidentified, longitudinal patient-level data from over 53 million patients, from electronic health records (EHR) and billing sources within participating Integrated Delivery Networks, Clinically Integrated Networks and Care Collaborative Networks. This cohort was used to estimate real-world rates of PDR progression, and provided patient profiles to generate a larger population of simulated patients, weighted to reflect NPDR prevalence in the US, used in an MCS model (online supplemental eMethods). This model followed a simulated cohort of patients to evaluate PDR progression rates and subsequent development of sustained blindness through 2 scenarios: early treatment during severe NPDR or delayed treatment when PDR developed.

Identification of a real-world cohort of patients with NPDR

The real-world cohort comprised patients aged ≥18 years with an incident NPDR diagnosis (mild, moderate, severe or unspecified) between 2011 and 2017 (diagnosis date referred to as index date). Briefly, patients had not received anti-VEGF, pan-retinal photocoagulation or steroid medications 1 year before index date; had no vitreous haemorrhage, retinal detachment, retinal vein occlusion or neovascularisation in the year before or week after NPDR diagnosis; and had no PDR diagnosis within 1 week after index date (online supplemental eTable 1).

NPDR diagnosis was determined based on Systematized Nomenclature of Medicine codes (online supplemental eMethods).

Simulation model

The real-world cohort was developed using MySQL Workbench V.8.0. Cox proportional hazards and MCS models were coded/analysed using Python programming language in Spyder V.3.6. A simulated cohort of 2 million patients with mild-to-severe NPDR was generated by random sampling with replacement (bootstrapping) from the real-world cohort. The greater size of the simulation cohort relative to the database cohort is consistent with principles of MCS, with bootstrapping allowing for multiple replications per individual.[11] With a sample size of 2 million, diagnostic plots representing key summary results from simulation versus sample size were stable (variation <0.1% with successive runs) and insensitive to further cohort size increases. Sampling weights were used in bootstrapping to account for quantifiable differences in characteristics of the real-world cohort relative to the overall US NPDR population (online supplemental eMethods).

In the MCS model, to ensure the only difference between groups was treatment effect, patients developing severe NPDR were 'cloned' into two identical subcohorts: early anti-VEGF treatment at the severe NPDR stage and delayed treatment until PDR development (figure 1). Patients in the simulated cohort followed their own probabilistic path through NPDR progression to PDR based on their risk profile applied to the Cox regression risk equation. Anti-VEGF treatment impact was derived from efficacy estimates of clinical trial data for intravitreal aflibercept 2 mg dosed every 8 weeks after 5 monthly

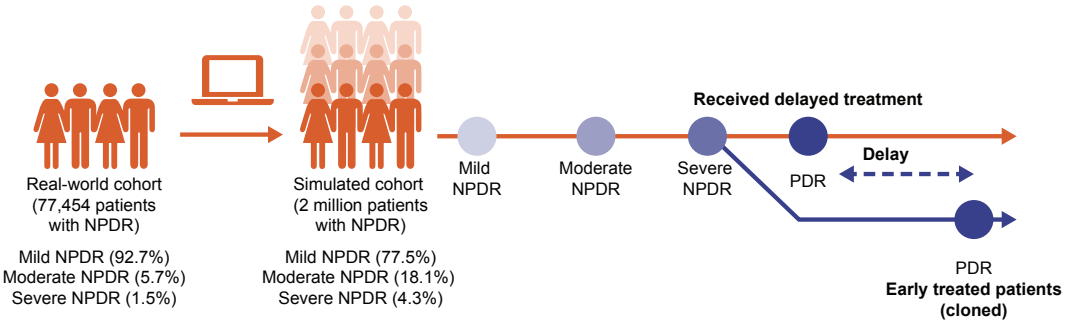


Figure 1 Flow of the simulation model. Circles represent first respective diagnosis. Patients receiving delayed treatment were followed from the index diagnosis through all stages of NPDR progression up to the first PDR event. NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

doses (2q8; PANORAMA)[8] and intravitreal ranibizumab 0.3 mg dosed monthly (post-hoc analysis of RISE/RIDE)[9] (online supplemental eTable 5), in both separate and combined scenarios. Only year 1 data were used, as the 2q8 group in PANORAMA received treatment as needed in year 2. Variability in risk of PDR progression was estimated in the combined treatment scenario using bootstrapping (online supplemental eMethods).

Outcomes

The simulated rate of PDR progression was assessed in untreated patients with mild, moderate or severe NPDR over 5 years. The impact of early anti-VEGF treatment on rates of PDR progression was assessed for patients with severe NPDR projected over 5 years. Rates of sustained blindness with PDR projected over 10 years were assessed in patients who received anti-VEGF for severe NPDR (early treatment) versus those who were treated after PDR developed (delayed treatment). Sustained blindness was defined as visual acuity (VA) of ≤20/200 in the study eye at 2 visits ≥3 months apart, with no improvement >20/100 since the first ≤20/200 reading.

Statistical analysis

A Cox proportional hazard model was used to estimate individual patient risk of PDR progression, calibrated to match with average cohort risks obtained by Kaplan-Meier analysis (online supplemental eTable 6 and eMethods). Estimated rates of PDR progression were based on specific patient demographic and clinical characteristics. Patients' annual risks could vary over the projected 5-year model if impacted by changes in their age group or NPDR severity.

The EHR database cannot fully capture progression through mild, moderate and severe NPDR. Therefore, differences in PDR progression hazards were used to estimate disease progression rates for untreated patients with mild-to-moderate and moderate-to-severe NPDR in the real-world cohort. Rates of disease progression post-treatment were linearly projected to 5 years for patients with severe NPDR using year 1 data for the intravitreal aflibercept 2q8 arm of the 2-year PANORAMA trial.[8]

Sustained blindness rates over 10 years were estimated based on rates reported by Wykoff *et al* for PDR[7] and projected based on PDR event rates in early and delayed treatment groups over 5 years (with treatment effect from clinical trials not applied beyond 5 years). Alternative estimates of blindness were based on linear projections of the Diabetic Retinopathy Study (DRS) (VA <5/200 at ≥2 consecutive 4-month follow-up visits).[12]

Model assumptions

Patients would not be treated earlier than the severe NPDR stage, not accounting for other reasons for anti-VEGF treatment. The real-world population was scaled to reflect quantifiable differences with the US population using IBM Market Scan 2018 data, however, demographics and clinical characteristics are likely to change over 10 years. Patients were assumed to receive the same dosing regimen as the clinical trials, although in real life there may be altered dosing, missed treatments, patients lost to follow-up and treatment interruptions or discontinuation. The US market share data for anti-VEGF agents was assumed valid over 10 years (confounding factors may include new treatments and generics). Data from the clinical trials (PDR progression risk and treatment impact) at year 1 were assumed to be applicable over 1–5 years. Results from the trials were assumed to be applicable to the simulated cohort, despite inclusion/exclusion criteria differing from the real-world population, the basis of the simulated population. For example, the real-world cohort included patients with DMO, while PANORAMA did not. Since moderately severe NPDR is not captured in the IBM Explorys database, severe NPDR would be a combination of moderately severe and severe NPDR. Patients included in the Wykoff *et al* study[7] used for blindness risk estimates were treated appropriately. Finally, the model assumed patients developed PDR before sustained blindness.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research in any way.

RESULTS

Of 141 451 patients with NPDR identified from IBM Explorys between 2011 and 2017, 77 454 were included in the real-world cohort (online supplemental eFigure 1). Most were classified as mild or unspecified NPDR (92.7%), followed by moderate (5.7%) and severe (1.5%) NPDR (online supplemental eTable 7).

Compared with the real-world cohort, the simulated cohort had a higher proportion of patients aged 65–74 years (32.4%), with DMO (23.0%), and with moderate (18.1%) and severe (4.3%) NPDR.

Risk factors for PDR events

Risk factors for PDR included greater baseline NPDR severity, DMO, certain comorbidities (eg, diabetic nephropathy, diabetic neuropathy), medications (eg, beta blockers) and laboratory results (eg, glycated haemoglobin, insulin) (online supplemental eTable 6). Diabetic nephropathy at baseline was associated with a 23% increase in hazard of progressing to PDR versus no diabetic nephropathy. Age ≥55 years, male sex, better glucose management, lower rates of hypertriglyceridaemia, hypertension, cerebrovascular accident or amputation were associated with decreased risks of PDR events.

Rate of disease progression in the real-world cohort

In the real-world cohort, there was a steady increase in estimated cumulative disease progression risk in untreated patients from mild-to-moderate (12.4%) and

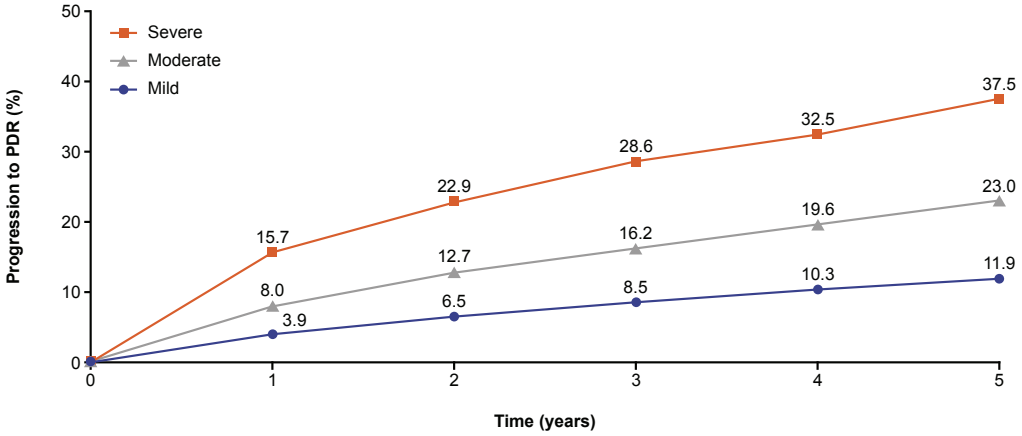


Figure 2 Risk of progression to PDR in untreated simulated patients by NPDR severity over 5 years. NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

moderate-to-severe NPDR (18.8%) at 5 years (online supplemental eFigure 2A).

Based on PANORAMA year 1 data, patients with moderately severe to severe NPDR had a lower estimated cumulative risk of disease progression when treated with intravitreal aflibercept (9.6%) versus no treatment (18.8%) projected at 5 years (online supplemental eFigure 2B).

Rate of progression to PDR in the simulated cohort

In the simulated cohort, PDR progression rates projected over 5 years were higher in untreated patients with severe NPDR (37.5%) versus moderate (23.0%) or mild (11.9%) NPDR (figure 2).

Based on PANORAMA year 1 results, early intravitreal aflibercept treatment reduced PDR progression risk projected over 5 years in simulated patients with severe NPDR by 51.5% (18.2% vs 37.5% with delayed treatment; absolute risk reduction 19.3%) (figure 3A). Comparable results were obtained from a post hoc analysis of RISE/RIDE year 1 data projected over 5 years, in which early treatment of severe NPDR with intravitreal ranibizumab resulted in a 51.7% reduction in PDR event risk versus delayed treatment (figure 3B).

Impact of early anti-VEGF treatment on the rate of progression to PDR

In the composite treatment scenario (projected over 5 years based on PANORAMA and RISE/RIDE year 1 data), 16 784 (51.7%) PDR events were avoided over 5 years with early anti-VEGF treatment (15 704 PDR events vs 32 488 with delayed treatment) in patients with severe NPDR, a 19.4% absolute risk reduction (figure 4A, online supplemental eTable 8). Additionally, 3185 (9.8%) PDR events were delayed over 5 years with early versus delayed treatment (figure 4B). When stratified by diabetes type, a higher proportion of PDR events were avoided in early treated patients with type 2 diabetes (10.5%; 28 978 of 275 349 events avoided) versus type 1 diabetes (7.8%; 1930 of 24 731 events avoided), an absolute risk reduction of 1.6% versus 1.4%, respectively (online supplemental eTable 8).

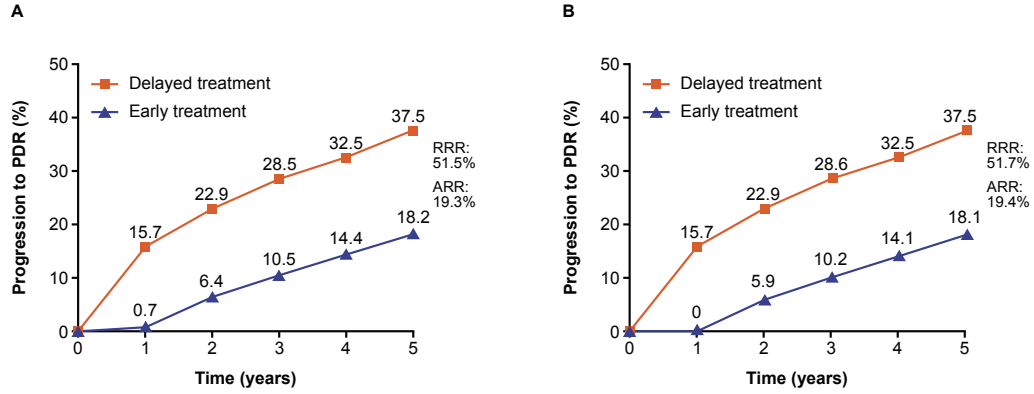
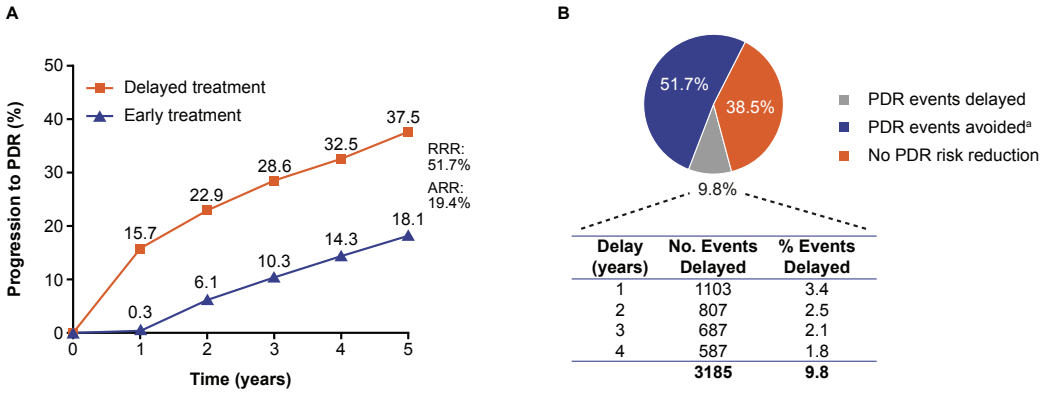


Figure 3 Risk of progression to PDR in delayed versus early treated simulated patients with severe NPDR projected over 5 years based on year 1 data in the (A) PANORAMA and (B) RISE/RIDE trials. ARR, absolute risk reduction; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RRR, relative risk reduction.



Delay (years)	No. Events Delayed	% Events Delayed
1	1103	3.4
2	807	2.5
3	687	2.1
4	587	1.8
	3185	**9.8**

Figure 4 Composite treatment scenario (based on year 1 data from PANORAMA and RISE/RIDE trials) of patients with severe NPDR: impact of early anti-VEGF treatment on (A) risk of progression to PDR and (B) PDR events projected over 5 years. [a]'PDR events avoided' refers to percentage of patients who did not experience a PDR event with early treatment compared with what would be expected with delayed treatment. ARR, absolute risk reduction; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RRR, relative risk reduction; VEGF, vascular endothelial growth factor.

Rate of sustained blindness

In simulated patients with severe NPDR, sustained blindness events with PDR were reduced by 57.7% projected over 10 years with early versus delayed anti-VEGF treatment (1.9% vs 4.4%, respectively), a 2.5% absolute risk reduction (figure 5).

Sensitivity analysis

A sensitivity analysis, conducted to examine variability in risk estimates for the composite treatment scenario (using ±5% variability), found that PDR progression risk projected over 5 years was reduced to half in early treated patients with severe NPDR versus delayed treatment. Relative risk reductions ranged from 31.1% to 66.5% and absolute risk reductions from 10.4% to 28.2% (online supplemental eFigure 3). The 95% CIs for early and delayed treatment groups did not overlap, suggesting that, after accounting for variability, PDR progression was significantly reduced with early anti-VEGF treatment.

An additional sensitivity analysis was performed using alternative estimates for blindness (VA <5/200) based on the DRS study.[12] Rerunning the model with this input, the projected incidence of blindness with early treatment (4.2%) versus delayed treatment (9.9%) in patients with severe NPDR decreased 58.0% over 10 years (online supplemental eFigure 4).

DISCUSSION

Long-term clinical trial data and real-world evidence are lacking regarding effects of early anti-VEGF treatment as a function of baseline NPDR stage on PDR progression and long-term visual outcomes in this population. This study aimed to improve current understandings

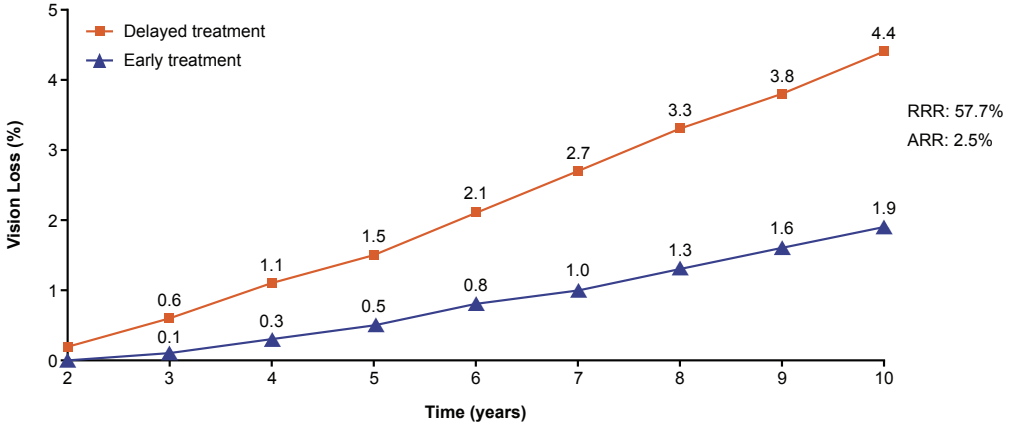


Figure 5 Impact of anti-VEGF treatment initiation (early vs delayed) on the rate of sustained blindness[a] over 10 years. [a]Sustained blindness defined as ≥2 VA readings of 20/200 or worse ≥3 months apart, and no improvement beyond 20/100 after the first 20/200 reading. First data point simulated 2 years after model start. Projections of sustained blindness rates based on PDR events estimated by Wykoff *et al*.[7] ARR, absolute risk reduction; PDR, proliferative diabetic retinopathy; RRR, relative risk reduction; VA, visual acuity; VEGF, vascular endothelial growth factor.

of impacts of early treatment in a large simulated mild, moderate and severe NPDR population derived from a real-world EHR database and adjusted to represent the US NPDR population. This provided a more generalisable characterisation of impacts and clinical value of early anti-VEGF treatment beyond what is captured in clinical trials.

In this simulation model, early treated patients with severe NPDR had a significantly lower risk of PDR progression and blindness than patients receiving delayed treatment. PDR progression rates projected over 5 years increased with NPDR severity and were higher in patients with severe (37.5%) versus mild (11.9%) or moderate (23.0%) NPDR. Left untreated, the projected 4-year risk of PDR progression from severe NPDR in this study (32.5%) was lower than that observed in a recent retrospective study (46.8%), possibly due to patient population differences (eg, fewer patients with type 1 diabetes and moderate or severe NPDR).

Furthermore, a sensitivity analysis using a ±5% variability in risk estimates confirmed a 37.8%–18.4% reduction in the projected 5-year risk of PDR development with early treatment in patients with severe NPDR. An additional 9.8% of PDR events were delayed 1–4 years within the same period. A 0.5% variation in mean risk estimates was acceptable due to stochasticity in the model. The alternative projections for blindness, evaluated using DRS estimates,[12] confirmed a considerable reduction in blindness risk with early treatment of patients with severe NPDR projected over 10 years.

Early treatment of patients with severe NPDR projected over 10 years was associated with a ~58% reduction in sustained blindness. The estimated 10-year sustained blindness risk with PDR was 4.4% with delayed treatment, decreasing to 1.9% with early anti-VEGF treatment.

Findings from this study are broadly consistent with prior studies in DR progression that highlight the importance of close monitoring and early treatment at the NPDR stage to reduce PDR progression.[6 8 9] One recent retrospective analysis found the risk of progression to severe NPDR or PDR within 5 years of diagnosis was approximately 3-fold greater in treatment-naive patients with moderate (17.6%) versus mild (5.8%) NPDR, highlighting the importance of closely monitoring these patients.[6] In Protocol W, the 2-year cumulative rate of developing PDR among eyes with moderate-to-severe NPDR was reduced with intravitreal aflibercept treatment versus sham (13.5% vs 33.2%, respectively).[10]

The estimated impact of early anti-VEGF intervention observed in this model may help fill the data gap in the existing evidence from controlled clinical trials that report data up to 2 years.[8–10] Since each sampled patient traced a unique probabilistic path and treatment response over the model time horizon, the study outcomes may exaggerate treatment effect estimates possibly observed in real-world settings. The MCS model is widely used as a standard for modelling disease progression and understanding optimal treatment strategies and practice patterns in other therapeutic areas.[13–16] Intrinsic features of flexibility and scalability of this model allow for future adaptations to account for real-world challenges like non-adherence or payer restrictions. Model findings could stimulate clinical discussions about benefits of early anti-VEGF interventions for severe NPDR and potentially be of value to inform clinical practice patterns.

Use of an EHR database for developing the study cohort may introduce specific biases as data related to NPDR severity, clinical management (eg, treatment adherence, anti-VEGF injection frequency) and disease progression may not be fully captured. Adjusted sampling methodology helped ensure summary characteristics of the simulation cohort were similar to the representative US NPDR population. Although this study accounted for quantifiable biases based on age, sex and clinical conditions, not all biases can be measured or corrected. For example, the population-adjusted cohort had a higher proportion of patients with DMO versus the real-world cohort (23% vs 1%, respectively), likely due to exclusion of treated patients at baseline in the real-world cohort. Differences in patient population and clinical management of NPDR may result in lower treatment efficacy in real life compared with results observed in PANORAMA and RISE/RIDE.

Other limitations include a high proportion of patients with mild or unspecified NPDR, likely due to incomplete EHR entries in the database. Since intermediate NPDR stages were not always captured, progression rates from mild-to-moderate and moderate-to-severe NPDR were estimated based on PDR progression hazard differences. For PANORAMA, NPDR progression rates post-treatment were linearly projected to 5 years using year 1 data as 2q8 dosing during year 2 was as needed.[8] Since moderately severe NPDR is not captured in the IBM Explorys database, severe NPDR was assumed a combination of moderately severe and severe NPDR. Yet, in treatment scenarios, anti-VEGF efficacy in patients with moderately severe to severe NPDR was applied to the severe NPDR cohort. Risk of PDR progression may be underestimated, as only PDR events during follow-up periods were tracked. Due to lack of VA data in the real-world cohort, vision loss rates were estimated using projections from previously published literature.[7] However, the study by Wykoff *et al* did not account for treatment of diabetes or DR in their study[7]; we assumed patients included were treated appropriately. The MCS model relied on data from PANORAMA and RISE/RIDE, and did not account for patient compliance and clinical management of NPDR in a real-world setting.

The MCS model suggests early treatment of severe NPDR with intravitreal anti-VEGF therapy, rather than delaying until PDR develops, could significantly decrease PDR occurrence over 5 years and reduce incidence of sustained blindness with PDR over 10 years. This simulation may provide a reasonable alternative for estimating the impact of initiating treatment at the severe NPDR stage in the absence of long-term clinical trial data.

Author affiliations
[1]Byers Eye Institute, Stanford University, Palo Alto, California, USA
[2]Department of Ophthalmology, Keck School of Medicine, Roski Eye Institute, University of Southern California, Los Angeles, California, USA
[3]Department of Ophthalmology, University of Illinois at Chicago, Illinois Eye and Ear Infirmary, Chicago, Illinois, USA
[4]Axtria Inc, Berkeley Heights, New Jersey, USA
[5]Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA

Acknowledgements Medical writing support under guidance of the authors was provided by Rhutika Dessai, MSc, and Rob Campbell, PhD, and editing support was provided by Joe Alling, BSc, all of Core, London, UK, in accordance with Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460), and funded by Regeneron Pharmaceuticals, Inc.

Contributors All authors contributed to the concept, design, data collection, interpretation, analysis and drafting of the manuscript. QDN and SS act as guarantors, and take full responsibility for the work, had access to the data, and controlled the decision to publish.

Funding The study was funded by Regeneron Pharmaceuticals, Inc, Tarrytown, New York. The sponsor participated in the design and conduct of the study, analysis of the data and preparation of this manuscript.

Competing interests QDN: Scientific advisory boards for Bausch + Lomb, Genentech, Regeneron Pharmaceuticals, Inc, Santen and Unity. AAM: Consultant to Allergan, Genentech/Roche, Graybug, Novartis, Ocular Therapeutix, Regeneron Pharmaceuticals, Inc, Pr3vent, Waldo, Valitor and Regenxbio; contracted research with Genentech/Roche, Novartis and Regeneron Pharmaceuticals, Inc; and ownership interest in Ocular Therapeutix, PLACIDO, Waldo and Pr3vent. JIL: Consultant to Allergan, Aura Biosciences, Cognition, Eyenuk, Genentech, Luxa, Novartis, Opthea, Quark, Santen, Unity, and Viridian; research funds from Aldeyra Therapeutics, Chengdu, Genentech, Regeneron Pharmaceuticals, Inc, NGM, Stealth and Graybug; and honoraria from Iveric Bio. EP: Consultant to Regeneron Pharmaceuticals, Inc. AC: Consultant to Regeneron Pharmaceuticals, Inc. RR: Employee of and stockholder in Regeneron Pharmaceuticals, Inc. SS: Employee of and stockholder in Regeneron Pharmaceuticals, Inc.

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 This study did not enrol human participants and used deidentified patient data; institutional review board approval or patient informed consent was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD
Quan Dong Nguyen http://orcid.org/0000-0001-9033-8117

REFERENCES

1 International Diabetes Federation. Clinical practice recommendations for managing diabetic macular edema. 2019. Available: www.idf.org/e-library/guidelines/161-dme-clinical-practice-recommendations.html [Accessed 10 Mar 2023].
2 American Academy of Ophthalmology. Diabetic retinopathy preferred practice pattern. 2019. Available: www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp [Accessed 10 Mar 2023].
3 Early Treatment of Diabetic Retinopathy Study Research Group. Fluorescein angiographic risk factors for progression of diabetic retinopathy. ETDRS report number 13. *Ophthalmology* 1991;98:834–40.
4 Solomon SD, Chew E, Duh EJ, *et al*. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:412–8.
5 Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* 1991;98:823–33.
6 Moshfeghi A, Garmo V, Sheinson D, *et al*. Five-year patterns of diabetic retinopathy progression in US clinical practice. *Clin Ophthalmol* 2020;14:3651–9.
7 Wykoff CC, Khurana RN, Nguyen QD, *et al*. Risk of blindness among patients with diabetes and newly diagnosed diabetic retinopathy. *Diabetes Care* 2021;44:748–56.
8 Brown DM, Wykoff CC, Boyer D, *et al*. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol* 2021;139:946–55.
9 Wykoff CC, Eichenbaum DA, Roth DB, *et al*. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. *Ophthalmol Retina* 2018;2:997–1009.
10 Maturi RK, Glassman AR, Josic K, *et al*. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol* 2021;139:701–12.
11 Press WHT, Saul A, Vetterling W, *et al*. *Numerical recipes: the art of scientific computing*. Third ed. Cambridge, England: Cambridge University Press, 2007.
12 Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–96.
13 Orlando LA, Belasco EJ, Patel UD, *et al*. The chronic kidney disease model: a general purpose model of disease progression and treatment. *BMC Med Inform Decis Mak* 2011;11:41.
14 Barhak J, Isaman DJM, Ye W, *et al*. Chronic disease modeling and simulation software. *J Biomed Inform* 2010;43:791–9.
15 Xie G. A novel Monte Carlo simulation procedure for modelling COVID-19 spread over time. *Sci Rep* 2020;10:13120.
16 Cannon CP, Khan I, Klimchak AC, *et al*. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2017;2:959–66.

Online-only material

eMethods

Unspecified Index NPDR Diagnoses

NPDR diagnosis was determined based on SNOMED (Systematized Nomenclature of Medicine) codes. Unspecified index NPDR diagnoses using SNOMED codes were updated if there was an International Classification of Diseases (ICD) code indicating a specific diagnosis (mild/moderate/severe), or if a patient had a specific SNOMED or ICD diagnosis within 30 days of the index date. If a patient received a second mild NPDR diagnosis, the index diagnosis was updated to mild. Diagnosis codes were used to identify different stages of DR (eTable 2), all other ocular complications (eTable 3), and PDR and PDR-related events during follow-up (eTable 4).

Simulation Model

Patients' annual risks could vary over the 5-year model horizon if they were impacted by changes in their age group and/or severity of NPDR. Patients' age groups were updated if they aged beyond the group cut off (ages were grouped in 35-44, 45-54, etc). NPDR stage was updated based on the risk of disease progression in the study cohort. Patients in the model had competing risks of NPDR stage progression and PDR progression, which could occur at any NPDR stage and was more likely the more severe the NPDR stage. In the simulation, the risk of PDR progression was adjusted accordingly for patients who improved (ie, reverted to moderate NPDR) following anti-VEGF treatment. Although reduced, these patients were still at a risk of NPDR and PDR progression through the end of the model horizon.

The simulation model leveraged stochasticity, including the random selection of patients from the cohort, the patient-specific response to stage progression, and the uncertain time until a PDR event. Stochasticity was fixed between untreated and treated scenarios, so that the simulated cohorts and their progression through NPDR stages were identical up until the point they reach severe NPDR stage.

Estimation of Sampling Weights for Bootstrap Sampling

Sampling weights were utilized in the bootstrap sampling methodology to account for quantifiable differences in the characteristics of the real-world cohort relative to IBM MarketScan, and to allow for findings that were more representative of the overall US population. These weights were calculated by first segmenting patients from the real-world cohort into distinct groups (or strata) based on age, sex, non-proliferative diabetic retinopathy (NPDR) stage, and diabetic macular edema (DME) status. Discrete scaling factors were then determined for each of these strata based on the 2018 US NPDR prevalence obtained using IBM MarketScan.

Risk of Progression to PDR

Variability of the risk of progression to PDR was estimated in the combined treatment scenario using the bootstrap method. Confidence intervals were estimated for the lower and upper limits of the treatment effect as reported in PANORAMA and RISE/RIDE,[8, 9] and then were combined into 1 confidence interval. Calculations were based on 500 model iterations, with each iteration including 10,000 resampled observations from the simulated cohort. A margin of error was estimated to be within 1-5% points for all years of the simulation model. The combined treatment effect in this model was averaged by weighted US market shares of intravitreal aflibercept (39%) and intravitreal ranibizumab (61%) for DR without DME, estimated based on data provided by Vestrum Health (Naperville, Illinois).

Cox Model Specification

A Cox proportional hazards model, adjusted for demographic and clinical characteristics, was used to estimate patient-specific composite proliferative diabetic retinopathy (PDR) risk and time to PDR event. The model was further calibrated to ensure the average patient risk predicted by the model corresponded with that of an average patient with NPDR in the real-world cohort. Calibration constants were estimated using Excel Solver optimization, which minimizes the error between average actual cohort PDR risk by NPDR stage and the average risk resulting from a manual calculation using Cox proportional hazards coefficients.

For this analysis, a PDR event was defined as any of the following diagnoses: PDR, vitreous hemorrhage, retinal detachment, or neovascularization.

The variables were selected using a backwards elimination process and evaluated for best fit within the regression model (i.e., $P<.1$). The reference patient in the mathematical model was a female with mild/unspecified NPDR, no comorbidities, and no DME. Because the reference patient did not correspond to an average patient in the cohort, the 1-year risk estimates from the Cox model were compared and calibrated to match with the average cohort risks obtained via Kaplan-Meier analysis.

The final Cox model included age, sex, diabetic nephropathy, hypertension, cerebrovascular accident, diabetic ulcer, amputation, calcium blocker use, beta blocker use, baseline NPDR severity, diabetes control regimen, dyslipidemia, glycated hemoglobin, and DME presence. This 1-year Cox model was used iteratively over the model time horizon of 5 years. During each year of the simulation, patients' age group, NPDR stage, and NPDR stage interaction with DME were updated to reflect aging, disease progression, or response to treatment. The patients' risk of progression from mild to moderate and moderate to severe NPDR stages was estimated. Untreated cohort progression risks were obtained by subtracting hazard rates of cohort progression to PDR for the 3 NPDR stages.

Patients' variable and baseline characteristics were fed into calculation of their annual risks and the estimation of time to PDR event in each year of the simulation model. For any iteration in which the resulting time to PDR event was <1 year, the patient was recorded to experience a PDR event that year; otherwise, the patient's risk was recalculated for each consecutive year until experiencing a PDR event or the end of the model horizon, whichever came first.

eReferences

1. International Diabetes Federation. Clinical practice recommendations for managing diabetic macular edema. Accessed May 5, 2022. https://www.idf.org/e-library/guidelines/161-dme-clinical-practice-recommendations.html

2. American Academy of Ophthalmology. Diabetic retinopathy preferred practice pattern 2019. Accessed July 12, 2022. https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp

3. Early Treatment Diabetic Retinopathy Study Research Group. Fluorescein angiographic risk factors for progression of diabetic retinopathy. Early Treatment Diabetic Retinopathy Study report number 13. *Ophthalmology*. May 1991;98(5 Suppl):834-40.

4. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. Mar 2017;40(3):412-418. doi:10.2337/dc16-2641

5. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. May 1991;98(5 Suppl):823-33. doi:10.1016/S0161-6420(13)38014-2

6. Moshfeghi A, Garmo V, Sheinson D, Ghanekar A, Abbass I. Five-year patterns of diabetic retinopathy progression in US clinical practice. *Clin Ophthalmol*. 2020;14:3651-3659.

7. Wykoff CC, Khurana RN, Nguyen QD, et al. Risk of blindness among patients with diabetes and newly diagnosed diabetic retinopathy. *Diabetes Care*. Mar 2021;44(3):748-756. doi:10.2337/dc20-0413

8. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol*. Aug 5 2021;139(9):946-955. doi:10.1001/jamaophthalmol.2021.2809

9. Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. *Ophthalmol Retina*. Oct 2018;2(10):997-1009. doi:10.1016/j.oret.2018.06.005

10. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol*. Mar 30 2021;139(7):701-712. doi:10.1001/jamaophthalmol.2021.0606

11. Press WHT, Saul A; Vetterling, William T; Flannery, Brian P. *Numerical Recipes: The Art of Scientific Computing*. Third ed. Cambridge University Press; 2007.

12. Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol*. 1976;81(4):383-396. doi:10.1016/0002-9394(76)90292-0

13. Orlando LA, Belasco EJ, Patel UD, Matchar DB. The chronic kidney disease model: a general purpose model of disease progression and treatment. *BMC Med Inform Decis Mak*. Jun 16 2011;11:41. doi:10.1186/1472-6947-11-41

14. Barhak J, Isaman DJ, Ye W, Lee D. Chronic disease modeling and simulation software. *J Biomed Inform*. Oct 2010;43(5):791-9. doi:10.1016/j.jbi.2010.06.003

15. Xie G. A novel Monte Carlo simulation procedure for modelling COVID-19 spread over time. *Sci Rep*. Aug 4 2020;10(1):13120. doi:10.1038/s41598-020-70091-1

16. Cannon CP, Khan I, Klimchak AC, Reynolds MR, Sanchez RJ, Sasiela WJ. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. *JAMA Cardiol*. Sep 1 2017;2(9):959-966. doi:10.1001/jamacardio.2017.2289

eTable 1. Selection Criteria for the Real-World Cohort

Inclusion Criteria	Exclusion Criteria
Patients aged ≥18 years diagnosed with NPDR at any stage (mild/unspecified, moderate, or severe) with or without DME and with a first-time diagnosis (SNOMED coded) between 2011 and 2017 Patients continuously enrolled ≥1 year before the study period. Patient enrollment continuity was approximated using the first and last observed date for patient ID across all encounter tables in the database (drug, hospital admissions, medical history, health maintenance, procedures, problem list, etc.) Patients were included if an unspecified SNOMED NPDR diagnosis was updated, if they also had an ICD code indicating a specific diagnosis (mild/moderate/severe), or if they had a specific SNOMED or ICD diagnosis within 30 days of the index date. If the patient's second diagnosis was mild NPDR, index diagnosis was updated to mild	Patients aged <18 years who had received treatment (anti-VEGF, PRP laser, and steroid medications), accompanied with PDR, RD, NV, VH, RVD, or RVO in the baseline period or developed PDR, RD, NV, or VH within 1 week of NPDR diagnosis Patients with outlier values in lab measurements (HbA1c >13.5%, LDL-C >1000 mg/dL, HDL-C >90 mg/dL, triglycerides >2000 mg/dL) and negative follow-up (referred to when index diagnosis was after the last follow-up date)

Abbreviations: DME, diabetic macular edema; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; ICD, International Classification of Diseases; LDL-C, low-density lipoprotein cholesterol; NPDR, non-proliferative diabetic retinopathy; NV, neovascularization; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; RD, retinal detachment; RVD, retinal vascular disease; RVO, retinal vein occlusion; SNOMED, Systematized Nomenclature of Medicine; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

eTable 2. Diagnosis Codes Used to Identify Patients With NPDR From the IBM Explorys™ Database

SNOMED ID	Description	Clinical Classification
4855003	Retinopathy due to diabetes mellitus	Unspecified DR
311782002	Advanced retinal disease due to diabetes mellitus (disorder)	Unspecified DR
232020009	Disorder of macula due to diabetes mellitus (disorder)	Unspecified DR
193350004	Advanced maculopathy due to diabetes mellitus (disorder)	Unspecified DR
769245002	Disorder of left macula due to diabetes mellitus (disorder)	Unspecified DR
769218003	Macular edema of left eye due to diabetes mellitus (disorder)	DME
769222008	Clinically significant macular edema of left eye due to diabetes mellitus (disorder)	DME
769244003	Disorder of right macula due to diabetes mellitus (disorder)	Unspecified DR
769217008	Macular edema of right eye due to diabetes mellitus (disorder)	DME
769221001	Clinically significant macular edema of right eye due to diabetes mellitus (disorder)	DME
314014002	Ischemic maculopathy due to diabetes mellitus (disorder)	Unspecified DR
314015001	Mixed maculopathy due to diabetes mellitus (disorder)	Unspecified DR
312912001	Macular edema due to diabetes mellitus (disorder)	DME
770097006	Clinically significant macular edema due to diabetes mellitus (disorder)	DME
399872003	Severe nonproliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	Severe NPDR with DME
399877009	Very severe nonproliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	Severe NPDR with DME
314010006	Diffuse exudative maculopathy due to diabetes mellitus (disorder)	Unspecified DR
314011005	Focal exudative maculopathy due to diabetes mellitus (disorder)	DME
399874002	High risk proliferative retinopathy with clinically significant macula edema due to diabetes mellitus (disorder)	PDR with DME
769219006	Macular edema due to type 1 diabetes mellitus (disorder)	DME
420486006	Exudative maculopathy due to type 1 diabetes mellitus (disorder)	DME
769220000	Macular edema due to type 2 diabetes mellitus (disorder)	DME
421779007	Exudative maculopathy due to type 2 diabetes mellitus (disorder)	DME
399864000	Macular edema not clinically significant due to diabetes mellitus (disorder)	DME
314015001	Mixed maculopathy due to diabetes mellitus (disorder)	Unspecified DR

399875001	Non-high-risk proliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	PDR with DME
399868002	Intraretinal microvascular anomaly due to diabetes mellitus (disorder)	Unspecified DR
770324004	Ischemia of retina due to diabetes mellitus (disorder)	Unspecified DR
104941000119109	Ischemia of retina due to type 1 diabetes mellitus (disorder)	Unspecified DR
104961000119108	Ischemia of retina due to type 2 diabetes mellitus (disorder)	Unspecified DR
25412000	Microaneurysm of retinal artery due to diabetes mellitus (disorder)	Unspecified DR
770582001	Microaneurysm of left retinal artery due to diabetes mellitus (disorder)	Unspecified DR
770581008	Microaneurysm of right retinal artery due to diabetes mellitus (disorder)	Unspecified DR
390834004	Nonproliferative retinopathy due to diabetes mellitus	NPDR
312903003	Mild nonproliferative retinopathy due to diabetes mellitus (disorder)	Mild NPDR
368711000119106	Mild nonproliferative retinopathy due to secondary diabetes mellitus	Mild NPDR
138881000119106	Mild nonproliferative retinopathy due to type 1 diabetes mellitus (disorder)	Mild NPDR
138911000119106	Mild nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	Mild NPDR
769184004	Mild nonproliferative retinopathy of left eye due to diabetes mellitus (disorder)	Mild NPDR
769183005	Mild nonproliferative retinopathy of right eye due to diabetes mellitus (disorder)	Mild NPDR
312904009	Moderate nonproliferative retinopathy due to diabetes mellitus (disorder)	Moderate NPDR
368741000119105	Moderate non-proliferative retinopathy due to secondary diabetes mellitus (disorder)	Moderate NPDR
138891000119109	Moderate nonproliferative retinopathy due to type 1 diabetes mellitus (disorder)	Moderate NPDR
138921000119104	Moderate nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	Moderate NPDR
769186002	Moderate nonproliferative retinopathy of left eye due to diabetes mellitus (disorder)	Moderate NPDR
769185003	Moderate nonproliferative retinopathy of right eye due to diabetes mellitus (disorder)	Moderate NPDR
368721000119104	Non-proliferative retinopathy due to secondary diabetes mellitus (disorder)	NPDR
368711000119106	Mild nonproliferative retinopathy due to secondary diabetes mellitus (disorder)	Mild NPDR
60961000119107	Nonproliferative diabetic retinopathy due to type 1 diabetes mellitus (disorder)	NPDR
138881000119106	Mild nonproliferative retinopathy due to type 1 diabetes mellitus (disorder)	Mild NPDR
1551000119108	Nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	NPDR
138911000119106	Mild nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	Mild NPDR
816177009	Nonproliferative retinopathy of left eye due to diabetes mellitus (disorder)	NPDR
408410002	On examination - left eye background diabetic retinopathy (disorder)	NPDR
408412005	On examination - left eye preproliferative diabetic retinopathy (disorder)	Severe NPDR
769182000	Preproliferative retinopathy of left eye due to diabetes mellitus (disorder)	Severe NPDR

769188001	Severe nonproliferative retinopathy of left eye due to diabetes mellitus (disorder)	Severe NPDR
769191001	Very severe nonproliferative retinopathy of left eye due to diabetes mellitus (disorder)	Severe NPDR
816178004	Nonproliferative retinopathy of right eye due to diabetes mellitus (disorder)	NPDR
408409007	On examination - right eye background diabetic retinopathy (disorder)	NPDR
408411003	On examination - right eye preproliferative diabetic retinopathy (disorder)	Severe NPDR
769181007	Preproliferative retinopathy of right eye due to diabetes mellitus (disorder)	Severe NPDR
769187006	Severe nonproliferative retinopathy of right eye due to diabetes mellitus (disorder)	Severe NPDR
769190000	Very severe nonproliferative retinopathy of right eye due to diabetes mellitus (disorder)	Severe NPDR
193349004	Preproliferative retinopathy due to diabetes mellitus (disorder)	Severe NPDR
312905005	Severe nonproliferative retinopathy due to diabetes mellitus (disorder)	Severe NPDR
399872003	Severe nonproliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	Severe NPDR with DME
399873008	Severe nonproliferative retinopathy without macular edema due to diabetes mellitus (disorder)	Severe NPDR without DME
399876000	Very severe nonproliferative retinopathy due to diabetes mellitus (disorder)	Severe NPDR
399877009	Very severe nonproliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	Severe NPDR with DME
399863006	Very severe nonproliferative retinopathy without macular edema due to diabetes mellitus (disorder)	Severe NPDR without DME
59276001	Proliferative retinopathy due to diabetes mellitus (disorder)	PDR
312907002	High risk proliferative retinopathy due to diabetes mellitus (disorder)	PDR
399869005	High risk proliferative retinopathy not amenable to photocoagulation due to diabetes mellitus (disorder)	PDR
399862001	High risk proliferative retinopathy without macular edema due to diabetes mellitus (disorder)	PDR without DME
399865004	Very severe proliferative retinopathy due to diabetes mellitus (disorder)	PDR
312906006	Non-high-risk proliferative retinopathy due to diabetes mellitus (disorder)	PDR
399870006	Non-high-risk proliferative retinopathy with no macular edema due to diabetes mellitus (disorder)	PDR without DME
312908007	Quiescent proliferative retinopathy due to diabetes mellitus (disorder)	PDR
60971000119101	Proliferative retinopathy due to type 1 diabetes mellitus (disorder)	PDR
1501000119109	Proliferative retinopathy due to type 2 diabetes mellitus (disorder)	PDR
97341000119105	Proliferative retinopathy with retinal edema due to type 2 diabetes mellitus (disorder)	PDR with DME
770766000	Proliferative retinopathy of left eye due to diabetes mellitus (disorder)	PDR
408414006	On examination - left eye proliferative diabetic retinopathy (disorder)	PDR
414894003	On examination - left eye stable treated proliferative diabetic retinopathy (disorder)	PDR
816962002	Stable treated proliferative retinopathy of left eye due to diabetes mellitus (disorder)	PDR
103981000119101	Proliferative retinopathy following surgery due to diabetes mellitus (disorder)	PDR

770765001	Proliferative retinopathy of right eye due to diabetes mellitus (disorder)	PDR
408413000	On examination - right eye proliferative diabetic retinopathy (disorder)	PDR
414910007	On examination - right eye stable treated proliferative diabetic retinopathy (disorder)	PDR
816961009	Stable treated proliferative retinopathy of right eye due to diabetes mellitus (disorder)	PDR
312909004	Proliferative retinopathy with iris neovascularization due to diabetes mellitus (disorder)	PDR with neovascularization
232022001	Proliferative retinopathy with neovascularization elsewhere than the optic disc due to diabetes mellitus (disorder)	PDR with neovascularization
232021008	Proliferative retinopathy with optic disc neovascularization due to diabetes mellitus (disorder)	PDR with neovascularization
770323005	Retinal edema due to diabetes mellitus (disorder)	Unspecified DR
97331000119101	Macular edema and retinopathy due to type 2 diabetes mellitus (disorder)	Unspecified DR with DME
314537004	Optic papillopathy due to diabetes mellitus (disorder)	Unspecified DR
109171000119104	Retinal edema due to type 1 diabetes mellitus (disorder)	Unspecified DR
28331000119107	Retinal edema due to type 2 diabetes mellitus (disorder)	Unspecified DR
421779007	Exudative maculopathy due to type 1 diabetes mellitus (disorder)	DME
420789003	Retinopathy due to type 1 diabetes mellitus (disorder)	Unspecified DR
60961000119107	Nonproliferative diabetic retinopathy due to type 1 diabetes mellitus (disorder)	NPDR
138891000119109	Moderate nonproliferative retinopathy due to type 1 diabetes mellitus (disorder)	Moderate NPDR
60971000119101	Proliferative diabetic retinopathy due to type 1 diabetes mellitus (disorder)	PDR
706894000	Retinopathy due to unstable diabetes mellitus type 1 (disorder)	Unspecified DR
82571000119107	Traction detachment of retina due to type 1 diabetes mellitus (disorder)	Retinal detachment
422034002	Retinopathy due to type 2 diabetes mellitus (disorder)	Unspecified DR
1551000119108	Nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	NPDR
138911000119106	Mild nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	NPDR
138921000119104	Moderate nonproliferative retinopathy due to type 2 diabetes mellitus (disorder)	Moderate NPDR
1501000119109	Proliferative retinopathy due to type 2 diabetes mellitus (disorder)	PDR
769220000	Macular edema due to type 2 diabetes mellitus (disorder)	DME
97341000119105	Proliferative retinopathy with retinal edema due to type 2 diabetes mellitus (disorder)	PDR with DME
82541000119100	Traction detachment of retina due to type 2 diabetes mellitus (disorder)	Retinal detachment
232023006	Traction detachment of retina due to diabetes mellitus (disorder)	Retinal detachment
82571000119107	Traction detachment of retina due to type 1 diabetes mellitus (disorder)	Retinal detachment
82541000119100	Traction detachment of retina due to type 2 diabetes mellitus (disorder)	Retinal detachment

399866003	Venous beading of retina due to diabetes mellitus (disorder)	Unspecified DR
770600002	Venous beading of left retina due to diabetes mellitus (disorder)	Unspecified DR
770599000	Venous beading of right retina due to diabetes mellitus (disorder)	Unspecified DR
399871005	Visually threatening retinopathy due to diabetes mellitus (disorder)	PDR
417677008	On examination - sight threatening diabetic retinopathy (disorder)	PDR

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

eTable 3. Diagnosis Codes Used for Identifying All Other Complications From the IBM Explorys™ Database

SNOMED ID	Description	Clinical Classification
51995000	Iris neovascularization	Neovascularization
713457002	Neovascular glaucoma due to diabetes mellitus (disorder)	Neovascularization
416328002	On examination - left eye rubeosis iridis (disorder)	Neovascularization
416650005	On examination - right eye rubeosis iridis (disorder)	Neovascularization
312909004	Proliferative retinopathy with iris neovascularization due to diabetes mellitus (disorder)	Neovascularization
82581000119105	Rubeosis iridis due to type 1 diabetes mellitus (disorder)	Neovascularization
82551000119103	Rubeosis iridis due to type 2 diabetes mellitus (disorder)	Neovascularization
678201000119103	Rubeosis iridis of left eye (disorder)	Neovascularization
678191000119101	Rubeosis iridis of bilateral eyes (disorder)	Neovascularization
678211000119100	Rubeosis iridis of right eye (disorder)	Neovascularization
246925003	Vascularization of cornea (finding)	Neovascularization
373431007	Corneal ghost vessels (finding)	Neovascularization
35666006	Corneal pannus (disorder)	Neovascularization
341221000119109	Corneal pannus of left eye (disorder)	Neovascularization
346471000119103	Corneal pannus of bilateral eyes (disorder)	Neovascularization
2102007	Deep vascularization of cornea (disorder)	Neovascularization
4873000	Localized vascularization of cornea (disorder)	Neovascularization
341231000119107	Neovascularization of left cornea (disorder)	Neovascularization
341221000119109	Corneal pannus of left eye (disorder)	Neovascularization
346471000119103	Corneal pannus of bilateral eyes (disorder)	Neovascularization
346481000119100	Neovascularization of bilateral corneas	Neovascularization
346471000119103	Corneal pannus of bilateral eyes (disorder)	Neovascularization
335621000119105	Neovascularization of right cornea (disorder)	Neovascularization
335611000119103	Corneal pannus of right eye (disorder)	Neovascularization
346471000119103	Corneal pannus of bilateral eyes (disorder)	Neovascularization
346481000119100	Neovascularization of bilateral corneas	Neovascularization

346471000119103	Corneal pannus of bilateral eyes (disorder)	Neovascularization
418252000	Salmon patch cornea (disorder)	Neovascularization
246926002	Superficial contact lens-induced peripheral corneal vascularization (finding)	Neovascularization
231911000	Superficial corneal vascularization (disorder)	Neovascularization
61267008	Retinal neovascularization (disorder)	Neovascularization
314265001	Classic choroidal neovascular membrane (disorder)	Neovascularization
314267009	Extramacular choroidal neovascular membrane (disorder)	Neovascularization
314269007	Idiopathic choroidal neovascular membrane (disorder)	Neovascularization
314266000	Occult choroidal neovascular membrane (disorder)	Neovascularization
232071006	Occult neovascularization of macula (disorder)	Neovascularization
163989008	On examination - retinal vascular proliferation (disorder)	Neovascularization
247099009	Optic disc neovascularization (disorder)	Neovascularization
314268004	Peripapillary choroidal neovascular membrane (disorder)	Neovascularization
247100001	Peripheral retinal neovascularization (disorder)	Neovascularization
792908009	Retinal angiomatous proliferation (disorder)	Neovascularization
16711551000119108	Retinal neovascularization due to occlusion of branch of retinal vein of left eye (disorder)	Neovascularization
16711591000119103	Retinal neovascularization due to occlusion of branch of retinal vein of right eye (disorder)	Neovascularization
16711071000119107	Retinal neovascularization due to occlusion of central retinal vein of left eye (disorder)	Neovascularization
16711031000119109	Retinal neovascularization due to occlusion of central retinal vein of right eye (disorder)	Neovascularization
251732007	Neovascularization of angle (finding)	Neovascularization
232086000	Neovascular glaucoma (disorder)	Neovascularization
713457002	Neovascular glaucoma due to diabetes mellitus (disorder)	Neovascularization
698840003	Neovascular glaucoma due to hyphema (disorder)	Neovascularization
75971007	Choroidal retinal neovascularization (disorder)	Neovascularization
314265001	Classic choroidal neovascular membrane (disorder)	Neovascularization
314267009	Extramacular choroidal neovascular membrane (disorder)	Neovascularization
314269007	Idiopathic choroidal neovascular membrane (disorder)	Neovascularization
733124000	Myopic choroidal neovascularization (disorder)	Neovascularization
677651000119102	Neovascularization of choroid of left eye (disorder)	Neovascularization
677211000119101	Histoplasmosis syndrome of left eye (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization

677621000119105	Neovascularization of choroid of bilateral eyes (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
677681000119109	Neovascularization of choroid of right eye (disorder)	Neovascularization
677221000119108	Histoplasmosis syndrome of right eye (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
677621000119105	Neovascularization of choroid of bilateral eyes (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
314266000	Occult choroidal neovascular membrane (disorder)	Neovascularization
416770009	Ocular histoplasmosis syndrome (disorder)	Neovascularization
677211000119101	Histoplasmosis syndrome of left eye (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
677621000119105	Neovascularization of choroid of bilateral eyes (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
677221000119108	Histoplasmosis syndrome of right eye (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
677621000119105	Neovascularization of choroid of bilateral eyes (disorder)	Neovascularization
677201000119104	Histoplasmosis syndrome of bilateral eyes (disorder)	Neovascularization
314268004	Peripapillary choroidal neovascular membrane (disorder)	Neovascularization
76309006	Cataract with neovascularization	Neovascularization
232046008	Branch retinal vein occlusion with neovascularization (disorder)	Neovascularization
232038007	Central retinal vein occlusion with neovascularization (disorder)	Neovascularization
232044006	Hemispheric retinal vein occlusion with neovascularization (disorder)	Neovascularization
312909004	Proliferative retinopathy with iris neovascularization due to diabetes mellitus (disorder)	Neovascularization
232041003	Central retinal vein occlusion - juvenile with neovascularization (disorder)	Neovascularization
232021008	Proliferative retinopathy with optic disc neovascularization due to diabetes mellitus (disorder)	Neovascularization
232022001	Proliferative retinopathy with neovascularization elsewhere than the optic disc due to diabetes mellitus (disorder)	Neovascularization
770437002	Fundus pulverulentus (disorder)	Neovascularization
783090002	Idiopathic retinal vasculitis, aneurysms, neuroretinitis syndrome (disorder)	Neovascularization
773991005	Idiopathic posterior uveitis (disorder)	Neovascularization
723502001	Reticular dystrophy of retinal pigment epithelium (disorder)	Neovascularization
719431007	Autosomal dominant late-onset retinal degeneration (disorder)	Neovascularization

719297006	Persistent placoid maculopathy (disorder)	Neovascularization
770791000	Autosomal dominant neovascular inflammatory vitreoretinopathy (disorder)	Neovascularization
31056006	Orbital hemorrhage (disorder)	Vitreous hemorrhage
21117005	Conjunctival hemorrhage (disorder)	Vitreous hemorrhage
339041000119109	Hemorrhage of left orbit (disorder)	Vitreous hemorrhage
333431000119106	Hemorrhage of right orbit (disorder)	Vitreous hemorrhage
194179009	Retrobulbar hemorrhage (disorder)	Vitreous hemorrhage
733308009	Traumatic orbital hemorrhage (disorder)	Vitreous hemorrhage
31341008	Vitreous hemorrhage (disorder)	Vitreous hemorrhage
336981000119105	Hemorrhage of left vitreous body (disorder)	Vitreous hemorrhage
343091000119103	Hemorrhage of bilateral vitreous bodies (disorder)	Vitreous hemorrhage
678071000119103	Preretinal hemorrhage of left eye (disorder)	Vitreous hemorrhage
770362001	Vitreous hemorrhage of left eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
331371000119103	Hemorrhage of right vitreous body (disorder)	Vitreous hemorrhage
343091000119103	Hemorrhage of bilateral vitreous bodies (disorder)	Vitreous hemorrhage
678091000119102	Preretinal hemorrhage of right eye (disorder)	Vitreous hemorrhage
770361008	Vitreous hemorrhage of right eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
163990004	On examination - vitreous hemorrhages (disorder)	Vitreous hemorrhage
312910009	Vitreous hemorrhage due to diabetes mellitus (disorder)	Vitreous hemorrhage
104951000119106	Vitreous hemorrhage due to type 1 diabetes mellitus (disorder)	Vitreous hemorrhage
1491000119102	Vitreous hemorrhage due to type 2 diabetes mellitus (disorder)	Vitreous hemorrhage
770362001	Vitreous hemorrhage of left eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
770361008	Vitreous hemorrhage of right eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
73757007	Retinal vascular occlusion (disorder)	Retinal vascular occlusion
68478007	Central retinal vein occlusion (disorder)	Retinal vascular occlusion
312997008	Central retinal vein occlusion - ischemic (disorder)	Retinal vascular occlusion
232040002	Central retinal vein occlusion - juvenile (disorder)	Retinal vascular occlusion
232042005	Central retinal vein occlusion - juvenile with macular edema (disorder)	Retinal vascular occlusion
232041003	Central retinal vein occlusion - juvenile with neovascularization (disorder)	Retinal vascular occlusion
312998003	Central retinal vein occlusion - non-ischemic (disorder)	Retinal vascular occlusion
232039004	Central retinal vein occlusion with macular edema (disorder)	Retinal vascular occlusion

232038007	Central retinal vein occlusion with neovascularization (disorder)	Retinal vascular occlusion
232043000	Hemispheric retinal vein occlusion (disorder)	Retinal vascular occlusion
232045007	Hemispheric retinal vein occlusion with macular edema (disorder)	Retinal vascular occlusion
232044006	Hemispheric retinal vein occlusion with neovascularization (disorder)	Retinal vascular occlusion
733325006	Combined occlusion by thrombus of retinal artery and retinal vein (disorder)	Retinal vascular occlusion
193379006	Retinal venous engorgement (disorder)	Retinal vascular occlusion
24596005	Venous retinal branch occlusion (disorder)	Retinal vascular occlusion
232048009	Branch retinal vein occlusion with macular edema (disorder)	Retinal vascular occlusion
232046008	Branch retinal vein occlusion with neovascularization (disorder)	Retinal vascular occlusion
314000002	Branch retinal vein occlusion with no neovascularization (disorder)	Retinal vascular occlusion
232068003	Retinal pigment epithelial detachment with vascularization (disorder)	Retinal vascular occlusion
420308006	Retinal vascular changes associated with acquired immunodeficiency syndrome (disorder)	Retinal vascular occlusion
46085004	Retinal vein occlusion	Retinal vein occlusion
68478007	Central retinal vein occlusion (disorder)	Retinal vein occlusion
312997008	Central retinal vein occlusion - ischemic (disorder)	Retinal vein occlusion
232040002	Central retinal vein occlusion - juvenile (disorder)	Retinal vein occlusion
232042005	Central retinal vein occlusion - juvenile with macular edema (disorder)	Retinal vein occlusion
232041003	Central retinal vein occlusion - juvenile with neovascularization (disorder)	Retinal vein occlusion
312998003	Central retinal vein occlusion - non-ischemic (disorder)	Retinal vein occlusion
232039004	Central retinal vein occlusion with macular edema (disorder)	Retinal vein occlusion
232038007	Central retinal vein occlusion with neovascularization (disorder)	Retinal vein occlusion
232043000	Hemispheric retinal vein occlusion (disorder)	Retinal vein occlusion
232045007	Hemispheric retinal vein occlusion with macular edema (disorder)	Retinal vein occlusion
232044006	Hemispheric retinal vein occlusion with neovascularization (disorder)	Retinal vein occlusion
733325006	Combined occlusion by thrombus of retinal artery and retinal vein (disorder)	Retinal vein occlusion
71719003	Thrombophlebitis of retinal vein (disorder)	Retinal vein occlusion
24596005	Venous retinal branch occlusion (disorder)	Retinal vein occlusion
232048009	Branch retinal vein occlusion with macular edema (disorder)	Retinal vein occlusion
232046008	Branch retinal vein occlusion with neovascularization (disorder)	Retinal vein occlusion
314000002	Branch retinal vein occlusion with no neovascularization (disorder)	Retinal vein occlusion
65593009	Partial occlusion of retinal vein (disorder)	Retinal vein occlusion

677821000119109	Partial occlusion of left retinal vein (disorder)	Retinal vein occlusion
677831000119107	Partial occlusion of right retinal vein (disorder)	Retinal vein occlusion
28578008	Incipient occlusion of retinal vein (disorder)	Retinal vein occlusion
247121001	Macular branch retinal vein occlusion (disorder)	Retinal vein occlusion
427902001	History of branch retinal vein occlusion (situation)	Retinal vein occlusion
432006000	History of occlusion of central retinal vein (situation)	Retinal vein occlusion
42059000	Retinal detachment (disorder)	Retinal detachment
232012007	Combined traction and rhegmatogenous retinal detachment (disorder)	Retinal detachment
713345005	Partial retinal detachment (disorder)	Retinal detachment
314494006	Pseudophakic retinal detachment (disorder)	Retinal detachment
56202001	Retinal detachment with retinal defect (disorder)	Retinal detachment
51987004	Retinal detachment without retinal defect (disorder)	Retinal detachment
19620000	Rhegmatogenous retinal detachment (disorder)	Retinal detachment
331111000119108	Total retinal detachment (disorder)	Retinal detachment
34711008	Traction detachment of retina (disorder)	Retinal detachment
50821009	Arterial retinal branch occlusion (disorder)	Retinal vascular disease
312937006	Cavernous hemangioma of retina (disorder)	Retinal vascular disease
232036006	Cilioretinal artery occlusion (disorder)	Retinal vascular disease
789700005	Congenital racemose hemangioma of retina (disorder)	Retinal vascular disease
28578008	Incipient occlusion of retinal vein (disorder)	Retinal vascular disease
247121001	Macular branch retinal vein occlusion (disorder)	Retinal vascular disease
786049007	Occlusion of branch of retinal vein of left eye (disorder)	Retinal vascular disease
786050007	Occlusion of branch of retinal vein of right eye (disorder)	Retinal vascular disease
786055002	Occlusion of central retinal vein of left eye (disorder)	Retinal vascular disease
786054003	Occlusion of central retinal vein of right eye (disorder)	Retinal vascular disease
776009	Partial occlusion of retinal artery (disorder)	Retinal vascular disease
65593009	Partial occlusion of retinal vein (disorder)	Retinal vascular disease
95501007	Retinal arteriovenous malformation (disorder)	Retinal vascular disease
232035005	Retinal artery occlusion (disorder)	Retinal vascular disease
64959007	Retinal artery spasm (disorder)	Retinal vascular disease
404667009	Retinal embolus (disorder)	Retinal vascular disease

76975009	Retinal microembolism (disorder)	Retinal vascular disease
61267008	Retinal neovascularization (disorder)	Retinal vascular disease
84884003	Retinal telangiectasia (disorder)	Retinal vascular disease
420308006	Retinal vascular changes associated with acquired immunodeficiency syndrome (disorder)	Retinal vascular disease
73757007	Retinal vascular occlusion (disorder)	Retinal vascular disease
77628002	Retinal vasculitis (disorder)	Retinal vascular disease
783787000	Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (disorder)	Retinal vascular disease
429397000	Rouleaux formation in retinal artery (disorder)	Retinal vascular disease
3506008	Stenosis of retinal artery (disorder)	Retinal vascular disease
26214006	Thrombosis of retinal artery (disorder)	Retinal vascular disease
46085004	Thrombosis of retinal vein (disorder)	Retinal vascular disease
87224000	Transient arterial retinal occlusion (disorder)	Retinal vascular disease
52539004	Vascular sheathing of retina (disorder)	Retinal vascular disease
771235001	Vasoproliferative tumor of retina (disorder)	Retinal vascular disease
359957005	Photocoagulation of eye (procedure)	Laser and steroid procedures
49257005	Destruction of chorioretinal lesion by laser photocoagulation (procedure)	Laser and steroid procedures
64943007	Destruction of lesion of choroid by photocoagulation (procedure)	Laser and steroid procedures
420029005	Endolaser photocoagulation (procedure)	Laser and steroid procedures
398874009	Focal photocoagulation (procedure)	Laser and steroid procedures
398750002	Grid photocoagulation (procedure)	Laser and steroid procedures
35137007	Photocoagulation of ciliary body (procedure)	Laser and steroid procedures
76458006	Photocoagulation of iris (procedure)	Laser and steroid procedures
231762005	Photocoagulation to retina (procedure)	Laser and steroid procedures
81924001	Destruction of lesion of retina by photocoagulation (procedure)	Laser and steroid procedures
399867007	Laser photocoagulation to retina (procedure)	Laser and steroid procedures
312713003	Panretinal photocoagulation (procedure)	Laser and steroid procedures
172586003	Panretinal photocoagulation for glaucoma (procedure)	Laser and steroid procedures
413180006	Pan retinal photocoagulation for diabetes (procedure)	Laser and steroid procedures
440578004	Photocoagulation of macular drusen (procedure)	Laser and steroid procedures
78917001	Repair of retina for retinal detachment by photocoagulation (procedure)	Laser and steroid procedures
66208000	Repair of retina for retinal tear or defect by photocoagulation (procedure)	Laser and steroid procedures

398952004	Sectoral photocoagulation (procedure)	Laser and steroid procedures
425431007	Injection of steroid into posterior segment of eye (procedure)	Laser and steroid procedures
410572008	Intravitreal steroid injection (procedure)	Laser and steroid procedures

eTable 4. Diagnosis Codes Used for Identification of PDR and PDR-Related Events From the IBM Explorys™ Database

SNOMED ID	Description	Clinical Classification
59276001	Proliferative retinopathy due to diabetes mellitus (disorder)	PDR
232021008	Proliferative retinopathy with optic disc neovascularization due to diabetes mellitus (disorder)	PDR
232022001	Proliferative retinopathy with neovascularization elsewhere than the optic disc due to diabetes mellitus (disorder)	PDR
312906006	Non-high-risk proliferative retinopathy due to diabetes mellitus (disorder)	PDR
312907002	High risk proliferative retinopathy due to diabetes mellitus (disorder)	PDR
312908007	Quiescent proliferative retinopathy due to diabetes mellitus (disorder)	PDR
312909004	Proliferative retinopathy with iris neovascularization due to diabetes mellitus (disorder)	PDR
399862001	High risk proliferative retinopathy without macular edema due to diabetes mellitus (disorder)	PDR
399865004	Very severe proliferative retinopathy due to diabetes mellitus (disorder)	PDR
399869005	High risk proliferative retinopathy not amenable to photocoagulation due to diabetes mellitus	PDR
399870006	Non-high-risk proliferative retinopathy with no macular edema due to diabetes mellitus (disorder)	PDR
399871005	Visually threatening retinopathy due to diabetes mellitus (disorder)	PDR
399874002	High risk proliferative retinopathy with clinically significant macula edema due to diabetes mellitus (disorder)	PDR
399875001	Non-high-risk proliferative retinopathy with clinically significant macular edema due to diabetes mellitus (disorder)	PDR
408413000	On examination - right eye proliferative diabetic retinopathy (disorder)	PDR
408414006	On examination - left eye proliferative diabetic retinopathy (disorder)	PDR
414894003	On examination - left eye stable treated proliferative diabetic retinopathy (disorder)	PDR
414910007	On examination - right eye stable treated proliferative diabetic retinopathy (disorder)	PDR
417677008	On examination - sight threatening diabetic retinopathy (disorder)	PDR
770765001	Proliferative retinopathy of right eye due to diabetes mellitus (disorder)	PDR
770766000	Proliferative retinopathy of left eye due to diabetes mellitus (disorder)	PDR
816961009	Stable treated proliferative retinopathy of right eye due to diabetes mellitus (disorder)	PDR
816962002	Stable treated proliferative retinopathy of left eye due to diabetes mellitus (disorder)	PDR
1501000119109	Proliferative retinopathy due to type 2 diabetes mellitus (disorder)	PDR
60971000119101	Proliferative retinopathy due to type 1 diabetes mellitus (disorder)	PDR
60971000119101	Proliferative diabetic retinopathy due to type 1 diabetes mellitus (disorder)	PDR

97341000119105	Proliferative retinopathy with retinal edema due to type 2 diabetes mellitus (disorder)	PDR
103981000119101	Proliferative retinopathy following surgery due to diabetes mellitus (disorder)	PDR
251732007	Neovascularization of angle (finding)	Neovascularization
232086000	Neovascular glaucoma (disorder)	Neovascularization
713457002	Neovascular glaucoma due to diabetes mellitus (disorder)	Neovascularization
698840003	Neovascular glaucoma due to hyphema (disorder)	Neovascularization
247100001	Peripheral retinal neovascularization (disorder)	Neovascularization
163989008	On examination - retinal vascular proliferation (disorder)	Neovascularization
247099009	Optic disc neovascularization (disorder)	Neovascularization
61267008	Retinal neovascularization	Neovascularization
51995000	Iris neovascularization	Neovascularization
713457002	Neovascular glaucoma due to diabetes mellitus (disorder)	Neovascularization
416328002	On examination - Left eye rubeosis iridis (disorder)	Neovascularization
416650005	On examination - Right eye rubeosis iridis (disorder)	Neovascularization
312909004	Proliferative retinopathy with iris neovascularization due to diabetes mellitus (disorder)	Neovascularization
82581000119105	Rubeosis iridis due to type 1 diabetes mellitus (disorder)	Neovascularization
82551000119103	Rubeosis iridis due to type 2 diabetes mellitus (disorder)	Neovascularization
678201000119103	Rubeosis iridis of left eye (disorder)	Neovascularization
678191000119101	Rubeosis iridis of bilateral eyes (disorder)	Neovascularization
678211000119100	Rubeosis iridis of right eye (disorder)	Neovascularization
31056006	Orbital hemorrhage (disorder)	Vitreous hemorrhage
21117005	Conjunctival hemorrhage (disorder)	Vitreous hemorrhage
339041000119109	Hemorrhage of left orbit (disorder)	Vitreous hemorrhage
333431000119106	Hemorrhage of right orbit (disorder)	Vitreous hemorrhage
194179009	Retrobulbar hemorrhage (disorder)	Vitreous hemorrhage
733308009	Traumatic orbital hemorrhage (disorder)	Vitreous hemorrhage
31341008	Vitreous hemorrhage (disorder)	Vitreous hemorrhage
336981000119105	Hemorrhage of left vitreous body (disorder)	Vitreous hemorrhage
343091000119103	Hemorrhage of bilateral vitreous bodies (disorder)	Vitreous hemorrhage
678071000119103	Preretinal hemorrhage of left eye (disorder)	Vitreous hemorrhage
770362001	Vitreous hemorrhage of left eye due to diabetes mellitus (disorder)	Vitreous hemorrhage

331371000119103	Hemorrhage of right vitreous body (disorder)	Vitreous hemorrhage
343091000119103	Hemorrhage of bilateral vitreous bodies (disorder)	Vitreous hemorrhage
678091000119102	Preretinal hemorrhage of right eye (disorder)	Vitreous hemorrhage
770361008	Vitreous hemorrhage of right eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
163990004	On examination - vitreous hemorrhages (disorder)	Vitreous hemorrhage
312910009	Vitreous hemorrhage due to diabetes mellitus (disorder)	Vitreous hemorrhage
104951000119106	Vitreous hemorrhage due to type 1 diabetes mellitus (disorder)	Vitreous hemorrhage
1491000119102	Vitreous hemorrhage due to type 2 diabetes mellitus (disorder)	Vitreous hemorrhage
770362001	Vitreous hemorrhage of left eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
770361008	Vitreous hemorrhage of right eye due to diabetes mellitus (disorder)	Vitreous hemorrhage
42059000	Retinal detachment (disorder)	Retinal detachment
232012007	Combined traction and rhegmatogenous retinal detachment (disorder)	Retinal detachment
713345005	Partial retinal detachment (disorder)	Retinal detachment
314494006	Pseudophakic retinal detachment (disorder)	Retinal detachment
31191000119102	Recent retinal detachment (disorder)	Retinal detachment
56202001	Retinal detachment with retinal defect (disorder)	Retinal detachment
51987004	Retinal detachment without retinal defect (disorder)	Retinal detachment
19620000	Rhegmatogenous retinal detachment (disorder)	Retinal detachment
331111000119108	Total retinal detachment (disorder)	Retinal detachment
34711008	Traction detachment of retina (disorder)	Retinal detachment

Abbreviations: PDR, proliferative diabetic retinopathy.

eTable 5. Effect of Anti-VEGF Therapies on Progression to PDR in Patients With DRSS of 47 and 53 and Moderately Severe or Severe NPDR Over a Period of 12 Months

Clinical Trial	Treatment	Patients Achieving a ≥2-Step DRSS Improvement at 12 Months, % (95% CI)	Progression to PDR at 12 Months, %
PANORAMA[8,a]	Intravitreal aflibercept 2q8	79.9 (73.1-86.7)	0.7
RISE/RIDE[9]	Intravitreal ranibizumab 0.3 mg monthly	76.1 (67.9-84.3)	0.0

Abbreviations: 2q8, 2 mg every 8 weeks; CI, confidence interval; DRSS, Diabetic Retinopathy Severity Scale; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.
[a]PANORAMA estimates are calculated as last observation carried forward.

eTable 6. Baseline Factors Associated With PDR Progression Estimated Using a Cox Proportional Hazards Model

Variable	β Coefficient[a]	Hazard Ratio	*P* Value
Age, years			
18-34 (reference)			
35-44	–0.11	0.89	.1
45-54	–0.13	0.88	.04
55-64	–0.22	0.8	<.005
65-74	–0.32	0.73	<.005
≥75	–0.46	0.63	<.005
Sex			
Female (reference)			
Male	–0.07	0.93	<.005
Diabetes type			
Type 2 diabetes (reference)			
Type 1 diabetes	0.12	1.13	<.005
NPDR severity			
Mild (reference)			
Moderate	0.67	1.95	<.005
Severe	1.29	3.62	<.005
NPDR severity and DME status			
Mild NPDR and no DME (reference)			
Moderate NPDR and DME	–0.53	0.59	.01
Severe NPDR and DME	–0.89	0.41	.01
Comorbid conditions (yes vs no)			
Amputation	–0.18	0.83	<.005
Cerebrovascular accident	–0.75	0.47	<.005

Diabetic nephropathy	0.21	1.23	<.005
Diabetic neuropathy	0.16	1.17	<.005
DME	0.85	2.34	<.005
Hypertension	–0.1	0.91	<.005
Lower-extremity ulcer	0.26	1.29	<.005
Medication use (yes vs no)			
Beta blockers	0.10	1.11	<.005
Calcium channel blockers	0.07	1.08	.03
Blood glucose management	−0.31	0.73	<.005
Insulin	0.17	1.18	<.005
Laboratory measurements			
Hypertriglyceridemia (>150 mg/dL vs ≤150 mg/dL)	–0.12	0.8989	<.005
Dyslipidemia in LDL-C (>100 mg/dL vs ≤100 mg/dL)	0.05	1.06	.09
No HbA1c measurement (vs HbA1c measurement present)	0.62	1.87	<.005
HbA1c[b] (%)	0.09	1.09	<.005

Abbreviations: DME, diabetic macular edema; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
[a]A positive β coefficient indicates an increase in risk of PDR progression.
[b]Continuous variable.

eTable 7. Baseline Demographic and Disease Characteristics

Characteristic	Real-World Cohort (n=77,454)	Simulated Cohort (n=2,000,000)
Age, years, no. (%)		
18-24	351 (0.5)	5613 (0.3)
25-34	1886 (2.4)	35,116 (1.8)
35-44	4808 (6.2)	90,404 (4.5)
45-54	11,458 (14.8)	261,829 (13.1)
55-64	19,976 (25.8)	484,804 (24.2)
65-74	22,286 (28.8)	647,357 (32.4)
≥75	16,689 (21.5)	474,877 (23.7)
Male, no. (%)	38,218 (49.3)	1,072,439 (53.6)
NPDR severity, no. (%)		
Mild	71,827 (92.7)	1,550,658 (77.5)
Moderate	4453 (5.7)	362,662 (18.1)
Severe	1174 (1.5)	86,680 (4.3)
Comorbid conditions, no. (%)		
Type 1 diabetes	6194 (8.0)	133,262 (6.7)
Type 2 diabetes	71,260 (92.0)	1,866,738 (93.3)
Hypertension	47,075 (60.8)	1,195,855 (59.8)
DME	759 (1.0)	460,160 (23.0)
Diabetic neuropathy	10,414 (13.4)	254,512 (12.7)
Diabetic nephropathy	9828 (12.7)	252,776 (12.6)
Cataract	5117 (6.6)	214,914 (10.7)
Lower-extremity ulcer	4590 (5.9)	119,728 (6.0)
Myocardial infarction	4573 (5.9)	110,480 (5.5)
Amputation	4298 (5.5)	100,868 (5.0)

Hemiplegia	865 (1.1)	18,480 (0.9)
Cerebrovascular accident	321 (0.4)	7146 (0.4)
Medication use, no. (%)		
Lipid-modifying agent	28,385 (36.6)	697,714 (34.9)
Insulin	25,813 (33.3)	633,270 (31.7)
Blood glucose management	24,251 (31.3)	613,948 (30.7)
ACEi	20,128 (26.0)	513,328 (25.7)
Beta blockers	19,689 (25.4)	500,382 (25.0)
Diuretics	19,803 (25.6)	493,868 (24.7)
Calcium channel blockers	12,985 (16.8)	328,402 (16.4)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; DME, diabetic macular edema; NPDR, non-proliferative diabetic retinopathy.

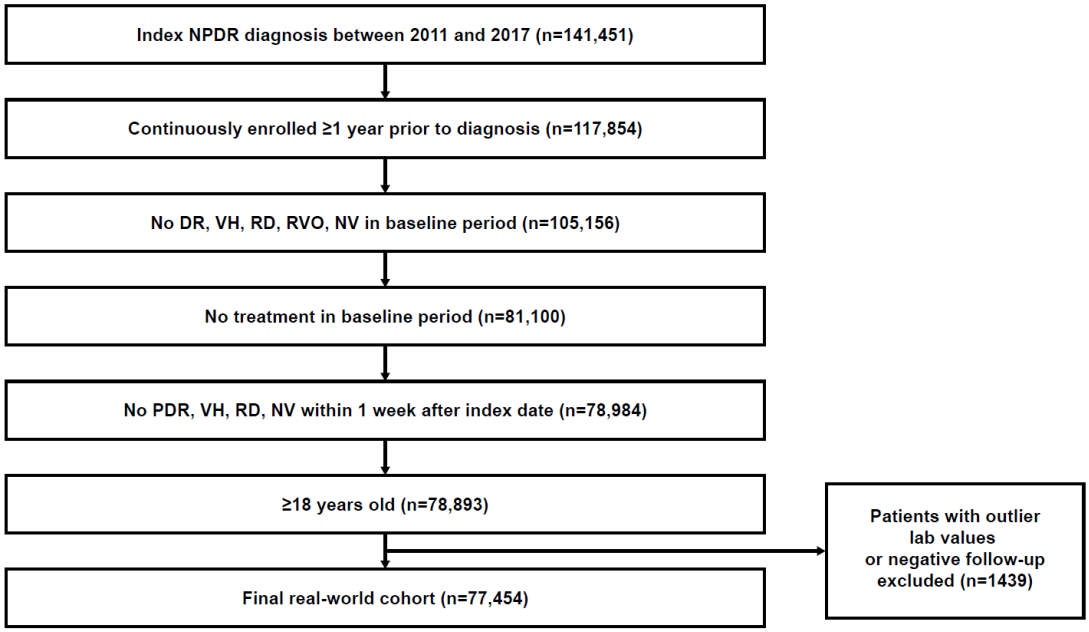
eTable 8. Absolute Risk Reduction in PDR Events Projected From Year 1 Clinical Trial Data Over 5 Years Based on Anti-VEGF Treatment Scenario

		No. of PDR events (%)			Absolute Risk Reduction, %	Number Needed to Treat, %
	N	Before Treatment	After Treatment	Avoided		
PANORAMA Treatment Scenario						
Diabetes status						
Type 1 diabetes	133,262	24,734	22,814	1920 (7.8)	1.4	69.41
Type 2 diabetes	1,866,738	275,298	246,638	28,660 (10.4)	1.5	65.13
NPDR severity						
Mild	1,550,658	184,026	181,863	2163 (1.2)	0.1	716.90
Moderate	362,663	83,527	71,809	11,718 (14.0)	3.2	30.95
Severe	86,679	32,479	15,780	16,699 (51.4)	19.3	5.19
Total	**2,000,000**	**300,032**	**269,452**	**30,580 (10.2)**	**1.5**	**65.40**
RISE/RIDE Treatment Scenario						
Type 1 diabetes	133,329	24,729	22,792	1937 (7.8)	1.5	68.83
Type 2 diabetes	1,866,671	275,382	246,201	29,181 (10.6)	1.6	63.97
Mild NPDR	1,550,422	184,004	181,749	2255 (1.2)	0.1	687.55
Moderate NPDR	362,912	83,613	71,588	12,025 (14.4)	3.3	30.18
Severe NPDR	86,666	32,494	15,656	16,838 (51.8)	19.4	5.15
Total	**2,000,000**	**300,111**	**268,993**	**31,118 (10.4)**	**1.6**	**64.27**
Composite Anti-VEGF Treatment Scenario						
Type 1 diabetes	133,303	24,731	22,801	1930 (7.8)	1.4	69.06

Type 2 diabetes	1,866,697	275,349	246,371	28,978 (10.5)	1.6	64.42
Mild NPDR	1,550,514	184,013	181,793	2219 (1.2)	0.1	698.71
Moderate NPDR	362,815	83,579	71,674	11,905 (14.2)	3.3	30.48
Severe NPDR	86,671	32,488	15,704	16,784 (51.7)	19.4	5.16
Total	**2,000,000**	**300,080**	**269,172**	**30,908 (10.3)**	**1.5**	**64.71**

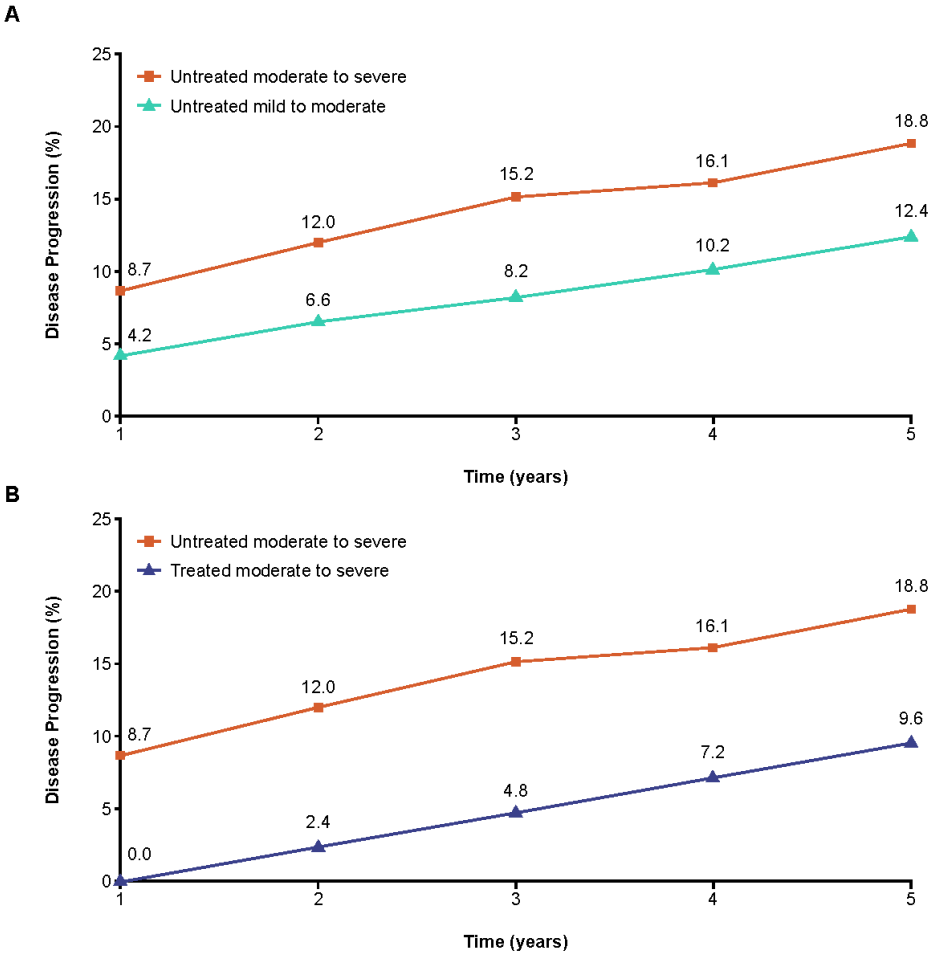
Abbreviations: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

eFigure 1. Selection of Treatment-Naive Patients With NPDR From the IBM Explorys™ Database



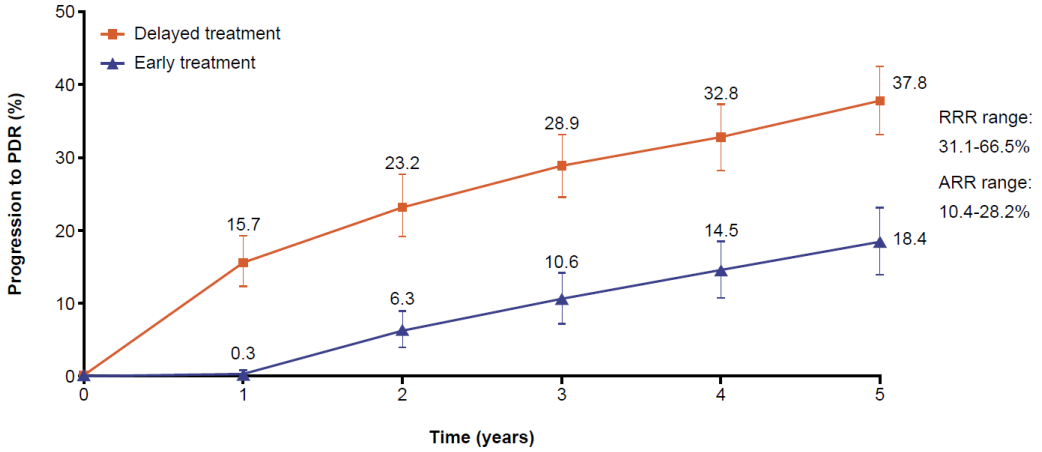
Abbreviations: NPDR, non-proliferative diabetic retinopathy; NV, neovascularization; PDR, proliferative diabetic retinopathy; RD, retinal detachment; RVO, retinal vein occlusion; VH, vitreous hemorrhage.

eFigure 2. (A) Five-Year Cumulative Rate of Disease Progression in Untreated Patients From the Real-World Cohort and (B) Impact of Intravitreal Aflibercept on the Rate of Disease Progression in Patients With Moderate to Severe NPDR From the PANORAMA Trial Projected Over 5 Years[a]



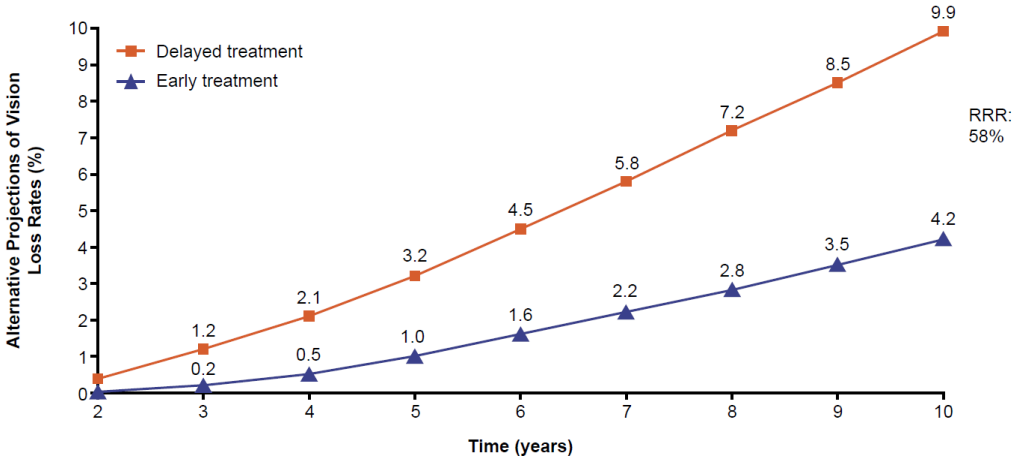
Abbreviations: 2q8, 2 mg every 8 weeks; NPDR, non-proliferative diabetic retinopathy.
[a]Treated patients with moderate NPDR are the patients with severe NPDR who experienced ≥2-step improvement after treatment. For the treated population, data for years 1 and 2 are based on the PANORAMA trial and for years 3-5 are based on a linear projection of disease progression as observed in the intravitreal aflibercept 2q8 arm at week 100.

eFigure 3. Treatment Effect Variability on the Risk of PDR Progression Among Patients With Severe NPDR



Abbreviations: ARR, absolute risk reduction; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RRR, relative risk reduction.
Error bars represent 95% confidence intervals. Margin of error within ±5% for each simulation year.

eFigure 4. Impact of Early Versus Delayed Anti-VEGF Treatment on the Estimated Incidence of Blindness[a] Over a 10-Year Period



Abbreviations: DRS, Diabetic Retinopathy Study; NPDR, non-proliferative diabetic retinopathy; RRR, relative risk reduction; VEGF, vascular endothelial growth factor.
[a]Estimated based on a linear projection of the DRS.[12]