

Online-only material

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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.

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eTable 1. Selection Criteria for the Real-World Cohort

Inclusion Criteria	Exclusion Criteria
<p>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</p>	<p>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</p>
<p>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.)</p>	<p>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)</p>
<p>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</p>	
<p>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.</p>	

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.

^aPANORAMA 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.

^aA positive β coefficient indicates an increase in risk of PDR progression.

^bContinuous 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)

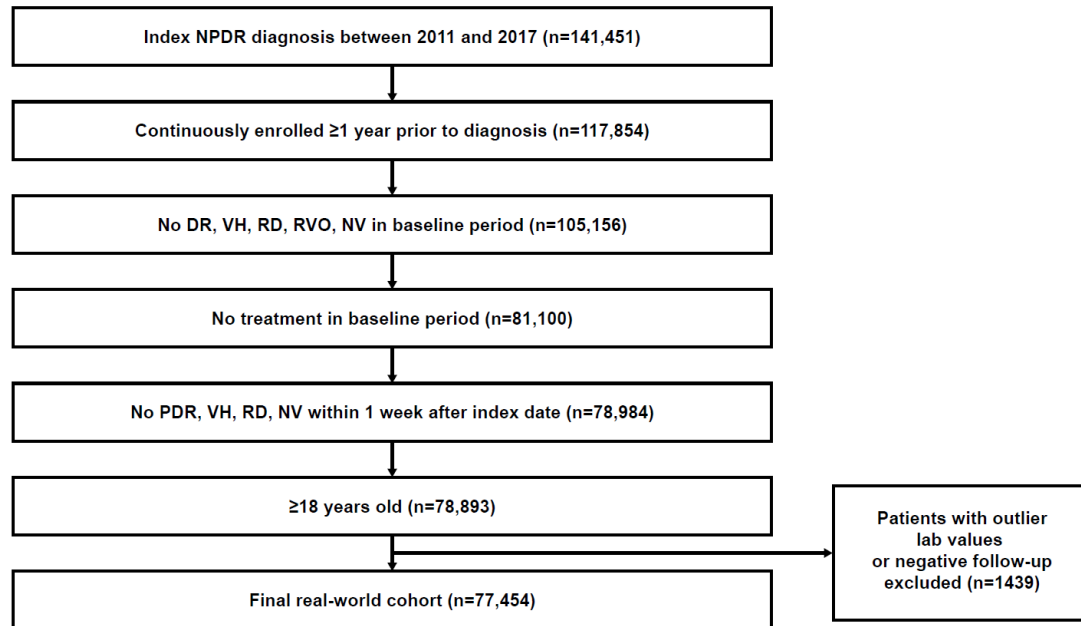
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; DME, diabetic macular edema; NPDR, non-proliferative diabetic retinopathy.

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

	N	No. of PDR events (%)			Absolute Risk Reduction, %	Number Needed to Treat, %
		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

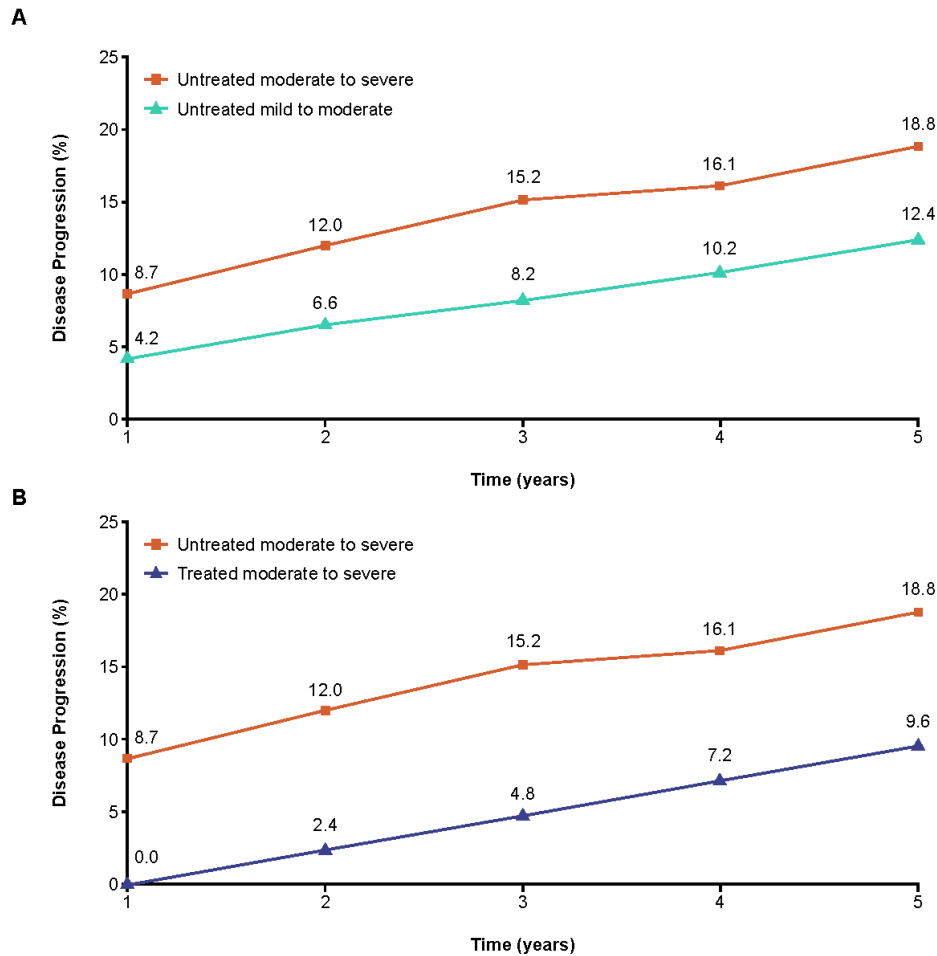
Type 2 diabetes	1,866,697	275,349	246,371	28,978 (10.5)	1.6	64.42
Mild NPDR	1,550,514	184,013	181,793	2219 (1.2)	0.1	698.71
Moderate NPDR	362,815	83,579	71,674	11,905 (14.2)	3.3	30.48
Severe NPDR	86,671	32,488	15,704	16,784 (51.7)	19.4	5.16
Total	2,000,000	300,080	269,172	30,908 (10.3)	1.5	64.71

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

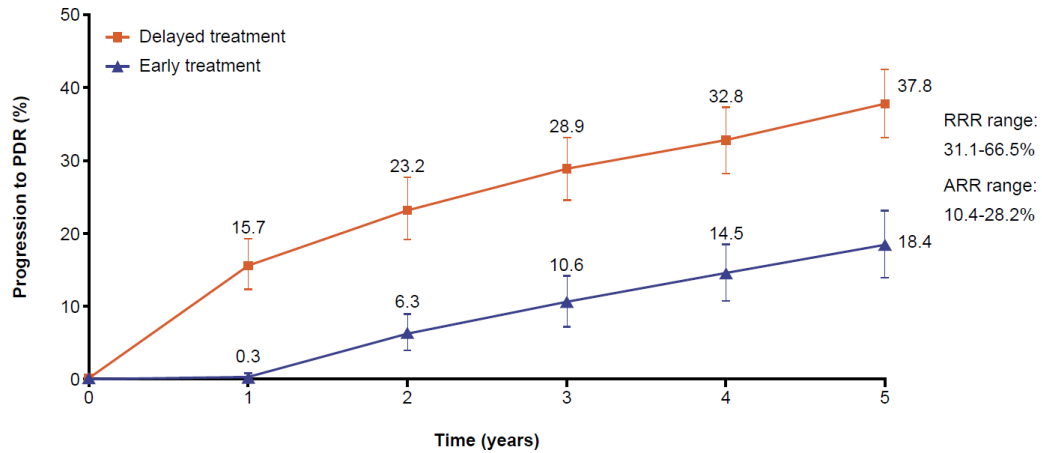
Abbreviations: NPDR, non-proliferative diabetic retinopathy; NV, neovascularization; PDR, proliferative diabetic retinopathy; RD, retinal detachment; RVO, retinal vein occlusion; VH, vitreous hemorrhage.

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.

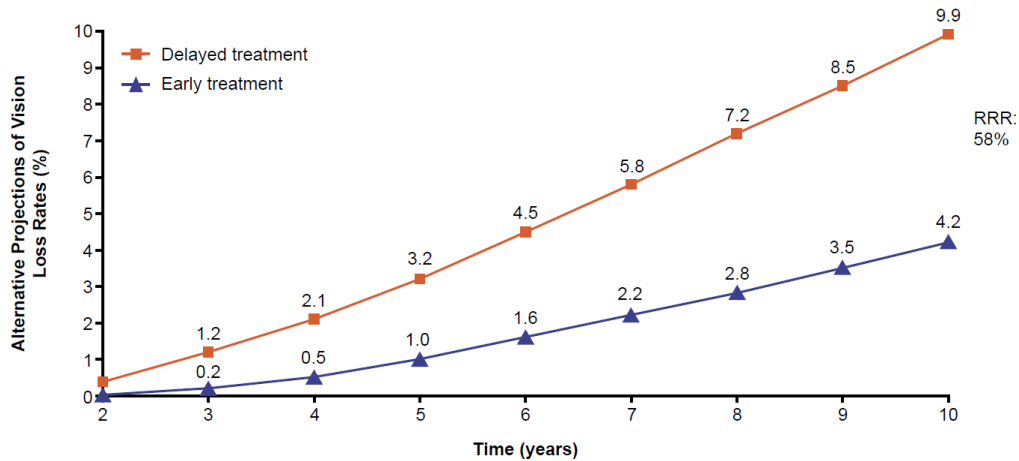
^aTreated patients with moderate NPDR are the patients with severe NPDR who experienced ≥ 2 -step improvement after treatment. For the treated population, data for years 1 and 2 are based on the PANORAMA trial and for years 3-5 are based on a linear projection of disease progression as observed in the 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 $\pm 5\%$ 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.

^aEstimated based on a linear projection of the DRS.¹²