

Supplementary information

**Detection of signs of disease in external
photographs of the eyes via deep learning**

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Supplementary Note 1. Pupil / iris pupil segmentation model.

A deep learning model was trained for pupil / iris pupil segmentation because most existing methods were developed to detect either the pupil or iris, and not for these magnified images with circular cutouts. The iris and pupils were each modeled as axis-aligned ellipses with 4 parameters each: x / y center coordinates and x / y dimensions. All 8 parameters were represented as floating point numbers in the range [0,1], representing the fraction of the image width or height. A deep learning model was trained using a L2 regression loss to take as input the external eye image and output these 8 parameters. The architecture was otherwise identical to the disease prediction models. This model's hyperparameters are detailed in Supplementary Table 14, and results are presented in Supplementary Figure 6.

Supplementary Table 1 | Area under receiver operating characteristics curve (AUC) of our models for the four validation sets.

(A) validation set A, (B) validation set B, (C) validation set C, and (D) Validation set D. Bold indicates $p < 0.05$. †:prespecified primary prediction tasks.

A

Target	Total	Positive (%)	Baseline characteristics	External image	Improvement	P-value
HbA1c $\geq 7\%$	21183	13544 (63.9%)	65.0 (64.3-65.8)	66.9 (66.1-67.6)	1.8 (1.0-2.7)	p < 0.001
HbA1c $\geq 8\%$	21183	9347 (44.1%)	65.2 (64.5-66.0)	69.1 (68.4-69.8)	3.9 (3.1-4.6)	p < 0.001
HbA1c $\geq 9\%$ †	21183	6537 (30.9%)	64.8 (64.0-65.6)	70.0 (69.3-70.8)	5.2 (4.5-6.0)	p < 0.001
Tch ≥ 200	9318	2913 (31.3%)	55.5 (54.3-56.8)	57.3 (56.1-58.6)	1.8 (0.4-3.3)	p = 0.007
Tch ≥ 240	9318	984 (10.6%)	55.1 (53.3-56.9)	59.1 (57.3-61.0)	4.0 (1.8-6.3)	p < 0.001
Tg ≥ 150	9104	4674 (51.3%)	60.9 (59.7-62.0)	63.3 (62.1-64.4)	2.4 (1.4-3.4)	p < 0.001
Tg ≥ 200	9104	2894 (31.8%)	61.7 (60.5-62.9)	63.6 (62.4-64.8)	1.9 (0.9-2.9)	p < 0.001
Tg ≥ 500	9104	323 (3.5%)	66.3 (63.4-69.1)	68.1 (65.3-70.9)	1.8 (-0.3-3.9)	p = 0.045
Mild+ DR	26950	5144 (19.1%)	68.9 (68.1-69.7)	70.5 (69.7-71.3)	1.6 (0.6-2.6)	p = 0.001
Moderate+ DR†	26950	3247 (12.0%)	71.0 (70.0-72.0)	75.0 (74.1-75.9)	4.0 (2.8-5.2)	p < 0.001
Severe+ DR	26950	404 (1.5%)	74.5 (72.0-76.9)	82.4 (80.6-84.3)	8.0 (5.0-11.0)	p < 0.001
DME†	26950	797 (3.0%)	71.2 (69.4-73.0)	77.9 (76.3-79.5)	6.7 (4.6-8.9)	p < 0.001
VTDR†	26950	1042 (3.9%)	72.7 (71.1-74.2)	79.2 (77.9-80.5)	6.5 (4.6-8.4)	p < 0.001
Cataract	27415	639 (2.3%)	76.5 (74.7-78.2)	86.4 (84.9-87.8)	9.9 (8.2-11.6)	p < 0.001

B

Target	Total	Positive (%)	Baseline characteristics	External image	Improvement	P-value
HbA1c ≥ 7%	4120	2819 (68.4%)	69.6 (67.9-71.3)	74.5 (73.0-76.1)	5.0 (3.1-6.8)	p < 0.001
HbA1c ≥ 8%	4120	1991 (48.3%)	68.4 (66.8-70.0)	73.7 (72.2-75.2)	5.3 (3.7-6.9)	p < 0.001
HbA1c ≥ 9%†	4120	1455 (35.3%)	66.5 (64.8-68.2)	73.4 (71.8-75.0)	6.9 (5.3-8.5)	p < 0.001
Tch ≥ 200	859	219 (25.5%)	54.3 (50.1-58.6)	58.5 (54.1-63.0)	4.2 (-0.9-9.3)	p = 0.053
Tch ≥ 240	859	82 (9.5%)	57.3 (50.8-63.8)	57.9 (51.1-64.7)	0.6 (-8.3-9.5)	p = 0.451
Tg ≥ 150	843	414 (49.1%)	58.2 (54.4-62.1)	61.9 (58.2-65.7)	3.7 (-0.0-7.4)	p = 0.026
Tg ≥ 200	843	260 (30.8%)	59.2 (55.1-63.3)	62.7 (58.7-66.7)	3.5 (-0.4-7.3)	p = 0.038
Tg ≥ 500	843	21 (2.5%)*	69.3 (57.2-81.4)	63.1 (50.1-76.2)	-6.1 (-16.1-3.8)	p = 0.887
Mild+ DR	4982	1509 (30.3%)	75.0 (73.6-76.5)	80.2 (78.9-81.6)	5.2 (3.5-6.9)	p < 0.001
Moderate+ DR†	4982	1172 (23.5%)	77.2 (75.7-78.8)	84.0 (82.7-85.3)	6.8 (5.0-8.5)	p < 0.001
Severe+ DR	4982	455 (9.1%)	76.3 (74.1-78.5)	88.7 (87.3-90.1)	12.4 (10.0-14.8)	p < 0.001
DME†	4982	394 (7.9%)	76.8 (74.5-79.1)	84.7 (82.9-86.5)	7.9 (5.1-10.6)	p < 0.001
VTDR†	4982	617 (12.4%)	76.9 (75.0-78.8)	86.7 (85.3-88.2)	9.8 (7.6-12.0)	p < 0.001
Cataract	5058	268 (5.3%)	74.3 (71.5-77.2)	93.2 (91.6-94.8)	18.9 (16.0-21.8)	p < 0.001

C

Target	Total	Positive (%)	Baseline characteristics	External image	Improvement	P-value
HbA1c ≥ 7%	8995	5119 (56.9%)	57.8 (56.6-58.9)	64.0 (62.9-65.1)	6.2 (4.9-7.6)	p < 0.001
HbA1c ≥ 8%	8995	2947 (32.8%)	61.9 (60.6-63.1)	66.3 (65.1-67.5)	4.5 (3.2-5.7)	p < 0.001
HbA1c ≥ 9%†	8995	1766 (19.6%)	65.2 (63.8-66.6)	69.3 (68.0-70.7)	4.2 (2.8-5.5)	p < 0.001
Tch ≥ 200	9304	1935 (20.8%)	61.0 (59.6-62.4)	60.8 (59.3-62.2)	-0.3 (-1.4-0.8)	p = 0.679
Tch ≥ 240	9304	580 (6.2%)	62.7 (60.3-65.0)	62.3 (60.0-64.7)	-0.3 (-2.1-1.5)	p = 0.639
Tg ≥ 150	9280	3825 (41.2%)	53.4 (52.2-54.6)	65.4 (64.3-66.5)	12.0 (10.4-13.6)	p < 0.001
Tg ≥ 200	9280	2261 (24.4%)	55.5 (54.2-56.9)	66.3 (65.1-67.6)	10.8 (9.1-12.5)	p < 0.001
Tg ≥ 500	9280	205 (2.2%)	65.2 (61.6-68.8)	70.4 (66.9-74.0)	5.3 (1.6-8.9)	p = 0.002
Mild+ DR	9518	992 (10.4%)	52.9 (51.0-54.8)	71.5 (69.7-73.3)	18.6 (16.0-21.2)	p < 0.001
Moderate+ DR†	9518	454 (4.8%)	55.1 (52.4-57.8)	76.8 (74.6-79.0)	21.7 (18.2-25.2)	p < 0.001
Severe+ DR	9518	203 (2.1%)	54.5 (50.7-58.4)	79.5 (76.6-82.5)	25.0 (19.9-30.1)	p < 0.001
DME†	9528	119 (1.2%)	66.3 (61.6-71.0)	79.5 (75.5-83.6)	13.3 (7.7-18.9)	p < 0.001
VTDR†	9528	287 (3.0%)	57.8 (54.6-61.1)	81.1 (78.6-83.6)	23.3 (19.2-27.4)	p < 0.001

D

Target	Total	Positive (%)	Baseline characteristics	External image	Improvement	P-value
HbA1c ≥ 7%	3200	1152 (36.0%)	55.9 (53.9-57.9)	64.3 (62.3-66.3)	8.4 (5.3-11.5)	p < 0.001
HbA1c ≥ 8%	3200	623 (19.5%)	55.9 (53.4-58.4)	66.0 (63.6-68.3)	10.1 (7.1-13.0)	p < 0.001
HbA1c ≥ 9%	3200	357 (11.2%)	59.8 (56.7-62.8)	67.6 (64.7-70.5)	7.8 (4.5-11.1)	p < 0.001
Tch ≥ 200	4561	1171 (25.7%)	62.4 (60.6-64.2)	60.5 (58.6-62.3)	-1.9 (-3.4--0.4)	p = 0.993
Tch ≥ 240	4561	343 (7.5%)	60.5 (57.4-63.6)	58.1 (55.0-61.3)	-2.4 (-5.1-0.4)	p = 0.954
Tg ≥ 150	4590	1332 (29.0%)	55.9 (54.1-57.7)	65.3 (63.6-67.1)	9.5 (7.1-11.8)	p < 0.001
Tg ≥ 200	4590	726 (15.8%)	56.3 (54.1-58.5)	67.1 (64.9-69.2)	10.8 (8.0-13.6)	p < 0.001
Tg ≥ 500	4590	49 (1.1%)*	64.6 (57.2-71.9)	65.7 (58.1-73.4)	1.2 (-6.0-8.3)	p = 0.374

Abbreviations: DR = diabetic retinopathy; DME = diabetic macular edema; HbA1c = hemoglobin A1c (glycated hemoglobin). *Note: fewer than 50 positive examples.

Supplementary Table 2 | Performance of adding predicted pupil size to baseline characteristics models for prespecified primary prediction tasks and lipids in (A) validation set A, (B) validation set B, (C) validation set C and (D) validation set D.

Note that per the other analyses, validation sets C and D had the baseline models fit directly on the validation set, and so the corresponding AUCs are over-estimates. Bold indicates $p < 0.05$. †:prespecified primary prediction tasks.

A

Target	Total	Positive (%)	Baseline characteristics	Baseline characteristics + pupil size	DLS (external eye image)	Improvement	P-value for improvement
HbA1c > 9%†	21183	6537 (30.9%)	64.8 (64.0-65.6)	65.1 (64.3-65.8)	70.1 (69.3-70.8)	5.0 (4.3-5.7)	p < 0.001
Tch ≥ 240	9320	986 (10.6%)	55.0 (53.2-56.9)	54.6 (52.8-56.4)	59.1 (57.3-61.0)	4.5 (2.2-6.8)	p < 0.001
Tg ≥ 200	9106	2894 (31.8%)	61.7 (60.5-62.9)	61.8 (60.5-63.0)	63.6 (62.4-64.8)	1.8 (0.8-2.9)	p < 0.001
Moderate+ DR†	26950	3249 (12.1%)	71.0 (70.0-71.9)	71.5 (70.5-72.4)	75.0 (74.1-75.9)	3.5 (2.4-4.7)	p < 0.001
DME†	26950	797 (3.0%)	71.2 (69.4-73.0)	71.8 (70.1-73.5)	77.9 (76.3-79.5)	6.2 (4.1-8.2)	p < 0.001
VTDR†	26950	1042 (3.9%)	72.7 (71.1-74.2)	73.4 (72.0-74.9)	79.2 (77.9-80.5)	5.8 (4.0-7.5)	p < 0.001
Cataract	27415	640 (2.3%)	76.4 (74.7-78.1)	76.1 (74.4-77.8)	86.4 (84.9-87.8)	10.3 (8.6-12.0)	p < 0.001

B

Target	Total	Positive (%)	Baseline characteristics	Baseline characteristics + pupil size	DLS (external eye image)	Improvement	P-value for improvement
HbA1c > 9%†	4119	1457 (35.4%)	66.5 (64.8-68.2)	66.8 (65.1-68.5)	73.5 (71.9-75.1)	6.7 (5.1-8.3)	p < 0.001
Tch ≥ 240	859	82 (9.5%)	57.3 (50.8-63.8)	57.3 (51.1-63.5)	57.9 (51.1-64.7)	0.5 (-8.1-9.2)	p = 0.451
Tg ≥ 200	843	260 (30.8%)	59.2 (55.1-63.3)	59.2 (55.1-63.3)	62.7 (58.7-66.7)	3.5 (-0.4-7.4)	p = 0.038
Moderate+ DR†	4982	1174 (23.6%)	77.3 (75.8-78.8)	78.1 (76.7-79.6)	84.1 (82.8-85.3)	5.9 (4.2-7.6)	p < 0.001
DME†	4982	397 (8.0%)	77.0 (74.7-79.3)	78.3 (76.1-80.4)	84.7 (82.9-86.5)	6.4 (3.8-9.1)	p < 0.001
VTDR†	4982	618 (12.4%)	77.0 (75.1-78.9)	78.2 (76.4-80.0)	86.7 (85.3-88.2)	8.5 (6.5-10.6)	p < 0.001
Cataract	5058	268 (5.3%)	74.1 (71.3-77.0)	75.2 (72.4-78.0)	93.2 (91.5-94.8)	18.0 (15.1-20.8)	p < 0.001

C

Target	Total	Positive (%)	Baseline characteristics	Baseline characteristics + pupil size	DLS (external eye image)	Improvement	P-value for improvement
HbA1c > 9%†	8995	1766 (19.6%)	65.2 (63.8-66.6)	65.6 (64.2-67.0)	69.3 (68.0-70.7)	3.7 (2.4-5.0)	p < 0.001
Tch ≥ 240	9304	580 (6.2%)	62.7 (60.3-65.0)	62.6 (60.3-65.0)	62.3 (60.0-64.7)	-0.3 (-2.1-1.5)	p = 0.630
Tg ≥ 200	9280	2261 (24.4%)	55.5 (54.2-56.9)	56.5 (55.2-57.9)	66.3 (65.1-67.6)	9.8 (8.1-11.5)	p < 0.001
Moderate+ DR†	9513	457 (4.8%)	55.1 (52.4-57.7)	56.9 (54.3-59.5)	77.0 (74.8-79.2)	20.1 (16.9-23.3)	p < 0.001
DME†	9525	135 (1.4%)	65.7 (61.1-70.2)	66.5 (62.0-71.0)	77.7 (73.6-81.9)	11.2 (5.4-17.0)	p < 0.001
VTDR†	9525	311 (3.3%)	57.7 (54.6-60.9)	61.1 (58.0-64.2)	80.8 (78.4-83.3)	19.7 (16.0-23.5)	p < 0.001

D

Target	Total	Positive (%)	Baseline characteristics	Baseline characteristics + pupil size	DLS (external eye image)	Improvement	P-value for improvement
HbA1c > 9%†	3200	357 (11.2%)	59.8 (56.7-62.8)	61.6 (58.6-64.6)	67.6 (64.7-70.5)	6.0 (2.8-9.2)	p < 0.001
Tch ≥ 240	4561	343 (7.5%)	60.5 (57.4-63.6)	60.6 (57.5-63.6)	58.1 (55.0-61.3)	-2.5 (-5.3-0.3)	p = 0.961
Tg ≥ 200	4590	726 (15.8%)	56.3 (54.1-58.5)	56.2 (54.0-58.4)	67.1 (64.9-69.2)	10.8 (8.1-13.6)	p < 0.001

Supplementary Table 3 | Adjusted analysis including pupil size for (A) validation set A, (B) validation set B, (C) validation set C, and (D) validation set D.

Similar to Table 2. †:prespecified primary prediction tasks.

A

Prediction target	Total	Positive (%)	Age (per decade)	Years with diabetes (per 5 years)	Male	White	Black	Asian / Pacific islander	Pupil radius relative to iris	DLS (external eye image)
HbA1c > 7%	21183	13544 (63.9)	0.890 (0.864-0.917) p < 0.001	1.105 (1.041-1.174) p = 0.001	0.962 (0.891-1.037) p = 0.311	0.974 (0.889-1.067) p = 0.567	1.077 (0.976-1.188) p = 0.141	1.451 (1.407-1.496) p < 0.001	0.994 (0.954-1.036) p = 0.782	1.718 (1.657-1.781) p < 0.001
HbA1c > 8%	21183	9347 (44.1)	0.910 (0.882-0.939) p < 0.001	1.068 (1.007-1.133) p = 0.029	0.906 (0.841-0.975) p = 0.009	0.914 (0.836-1.000) p = 0.049	1.026 (0.930-1.132) p = 0.607	1.325 (1.289-1.362) p < 0.001	0.967 (0.929-1.006) p = 0.099	1.944 (1.872-2.020) p < 0.001
HbA1c > 9%†	21183	6537 (30.9)	0.924 (0.894-0.956) p < 0.001	1.065 (1.000-1.134) p = 0.051	0.910 (0.841-0.984) p = 0.018	0.949 (0.863-1.044) p = 0.279	0.939 (0.843-1.046) p = 0.252	1.209 (1.175-1.244) p < 0.001	0.950 (0.910-0.991) p = 0.019	1.957 (1.880-2.036) p < 0.001
Tch ≥ 200	9318	2913 (31.3)	0.964 (0.923-1.008) p = 0.107	0.919 (0.838-1.008) p = 0.073	0.964 (0.861-1.079) p = 0.522	0.873 (0.775-0.983) p = 0.025	0.839 (0.700-1.006) p = 0.058	0.915 (0.878-0.953) p < 0.001	0.984 (0.926-1.045) p = 0.595	1.251 (1.187-1.318) p < 0.001
Tch ≥ 240	9318	984 (10.6)	0.975 (0.914-1.040) p = 0.443	0.941 (0.822-1.076) p = 0.374	1.067 (0.903-1.261) p = 0.449	0.842 (0.702-1.011) p = 0.065	0.829 (0.620-1.110) p = 0.208	0.914 (0.858-0.973) p = 0.005	0.944 (0.862-1.033) p = 0.212	1.328 (1.241-1.420) p < 0.001
Tg ≥ 150	9104	4674 (51.3)	0.985 (0.947-1.024) p = 0.434	1.045 (0.959-1.138) p = 0.312	1.055 (0.945-1.178) p = 0.342	0.802 (0.699-0.921) p = 0.002	0.827 (0.703-0.972) p = 0.021	0.911 (0.877-0.947) p < 0.001	0.944 (0.891-1.001) p = 0.056	1.514 (1.426-1.608) p < 0.001
Tg ≥ 200	9104	2894 (31.8)	0.935 (0.895-0.976) p = 0.002	1.135 (1.035-1.244) p = 0.007	1.026 (0.913-1.153) p = 0.664	0.710 (0.613-0.821) p < 0.001	0.795 (0.662-0.954) p = 0.014	0.933 (0.894-0.973) p = 0.001	0.947 (0.890-1.008) p = 0.086	1.442 (1.357-1.533) p < 0.001
Tg ≥ 500	9104	323 (3.5)	0.851 (0.758-0.956) p = 0.006	1.746 (1.362-2.239) p < 0.001	1.121 (0.853-1.472) p = 0.412	0.579 (0.401-0.835) p = 0.003	0.750 (0.456-1.234) p = 0.257	0.902 (0.809-1.006) p = 0.064	0.898 (0.771-1.045) p = 0.165	1.227 (1.100-1.370) p < 0.001
Mild+ DR	26950	5144 (19.1)	0.889 (0.863-0.916) p < 0.001	1.141 (1.067-1.220) p < 0.001	0.782 (0.719-0.850) p < 0.001	1.007 (0.915-1.109) p = 0.882	1.296 (1.159-1.448) p < 0.001	1.635 (1.590-1.683) p < 0.001	0.890 (0.852-0.931) p < 0.001	1.789 (1.734-1.846) p < 0.001
Moderate+ DR†	26950	3247 (12.0)	0.887 (0.856-0.919) p < 0.001	1.176 (1.084-1.275) p < 0.001	0.785 (0.709-0.870) p < 0.001	0.789 (0.699-0.889) p < 0.001	1.131 (0.988-1.295) p = 0.074	1.674 (1.619-1.730) p < 0.001	0.843 (0.798-0.891) p < 0.001	1.864 (1.803-1.927) p < 0.001
Severe+ DR	26950	404 (1.5)	0.851 (0.780-0.930) p < 0.001	1.466 (1.192-1.804) p < 0.001	0.804 (0.614-1.054) p = 0.114	1.019 (0.746-1.392) p = 0.905	2.192 (1.633-2.943) p < 0.001	1.825 (1.680-1.983) p < 0.001	0.809 (0.702-0.933) p = 0.003	1.433 (1.373-1.495) p < 0.001
DME†	26950	797 (3.0)	0.882 (0.826-0.940) p < 0.001	1.207 (1.041-1.399) p = 0.013	0.635 (0.521-0.774) p < 0.001	0.934 (0.761-1.147) p = 0.516	1.195 (0.939-1.521) p = 0.147	1.651 (1.556-1.751) p < 0.001	0.830 (0.751-0.918) p < 0.001	1.471 (1.413-1.532) p < 0.001
VTDR†	26950	1042 (3.9)	0.886 (0.836-0.938) p < 0.001	1.214 (1.063-1.385) p = 0.004	0.692 (0.581-0.823) p < 0.001	0.988 (0.820-1.191) p = 0.001	1.408 (1.143-1.734) p < 0.001	1.719 (1.631-1.812) p < 0.001	0.850 (0.777-0.931) p < 0.001	1.563 (1.506-1.622) p < 0.001

			p < 0.001		p < 0.001	p = 0.898	p = 0.001			
Cataract	27415	639 (2.3)	1.683 (1.547-1.831) p < 0.001	0.828 (0.694-0.988) p = 0.036	1.617 (1.272-2.054) p < 0.001	1.351 (1.015-1.800) p = 0.039	3.753 (2.954-4.768) p < 0.001	1.073 (0.999-1.151) p = 0.052	0.889 (0.786-1.004) p = 0.058	1.617 (1.555-1.681) p < 0.001

B

Prediction target	Total	Positive (%)	Age (per decade)	Years with diabetes (per 5 years)	Male	White	Black	Asian / Pacific islander	Pupil radius relative to iris	DLS (external eye image)
HbA1c > 7%	4120	2819 (68.4)	0.864 (0.799-0.933) p < 0.001	1.159 (0.995-1.350) p = 0.058	0.809 (0.604-1.083) p = 0.154	0.827 (0.633-1.081) p = 0.165	1.519 (0.810-2.848) p = 0.192	1.416 (1.317-1.523) p < 0.001	0.987 (0.897-1.087) p = 0.795	2.240 (2.048-2.451) p < 0.001
HbA1c > 8%	4120	1991 (48.3)	0.913 (0.846-0.985) p = 0.018	1.208 (1.049-1.391) p = 0.009	0.847 (0.637-1.127) p = 0.254	0.697 (0.542-0.896) p = 0.005	1.492 (0.821-2.709) p = 0.189	1.317 (1.236-1.402) p < 0.001	1.022 (0.934-1.119) p = 0.632	2.302 (2.106-2.516) p < 0.001
HbA1c > 9%†	4120	1455 (35.3)	0.948 (0.875-1.027) p = 0.188	1.177 (1.018-1.360) p = 0.028	0.837 (0.617-1.135) p = 0.252	0.792 (0.610-1.027) p = 0.078	1.422 (0.756-2.676) p = 0.275	1.198 (1.125-1.275) p < 0.001	1.012 (0.922-1.112) p = 0.796	2.247 (2.053-2.459) p < 0.001
Tch ≥ 200	859	219 (25.5)	1.080 (0.923-1.264) p = 0.337	0.868 (0.626-1.205) p = 0.399	1.923 (1.170-3.160) p = 0.010	1.372 (0.927-2.030) p = 0.114	3.092 (1.202-7.952) p = 0.019	0.920 (0.806-1.051) p = 0.221	1.014 (0.853-1.207) p = 0.872	1.419 (1.179-1.708) p < 0.001
Tch ≥ 240	859	82 (9.5)	1.078 (0.859-1.353) p = 0.517	0.791 (0.492-1.271) p = 0.333	1.719 (0.855-3.455) p = 0.128	1.326 (0.751-2.342) p = 0.331	0.685 (0.087-5.396) p = 0.719	0.822 (0.671-1.008) p = 0.059	1.018 (0.787-1.317) p = 0.892	1.316 (1.032-1.680) p = 0.027
Tg ≥ 150	843	414 (49.1)	1.136 (0.995-1.296) p = 0.059	1.119 (0.843-1.485) p = 0.437	1.162 (0.718-1.880) p = 0.540	0.833 (0.538-1.292) p = 0.415	0.726 (0.296-1.778) p = 0.483	0.884 (0.786-0.994) p = 0.040	1.052 (0.903-1.226) p = 0.515	1.459 (1.208-1.762) p < 0.001
Tg ≥ 200	843	260 (30.8)	1.063 (0.916-1.233) p = 0.422	1.141 (0.837-1.555) p = 0.403	1.273 (0.779-2.080) p = 0.335	0.618 (0.381-1.002) p = 0.051	0.694 (0.245-1.971) p = 0.493	0.921 (0.810-1.046) p = 0.204	0.962 (0.816-1.135) p = 0.646	1.404 (1.156-1.705) p < 0.001
Tg ≥ 500	843	21 (2.5)*	0.724 (0.447-1.174) p = 0.190	2.261 (0.838-6.104) p = 0.107	2.884 (0.840-9.899) p = 0.092	0.451 (0.095-2.132) p = 0.315	1.652 (0.187-14.554) p = 0.651	0.787 (0.525-1.179) p = 0.245	0.735 (0.469-1.151) p = 0.179	0.897 (0.527-1.527) p = 0.688
Mild+ DR	4982	1509 (30.3)	0.927 (0.863-0.996) p = 0.038	1.340 (1.153-1.558) p < 0.001	0.770 (0.579-1.025) p = 0.073	0.736 (0.564-0.960) p = 0.024	1.853 (1.003-3.423) p = 0.049	1.700 (1.595-1.812) p < 0.001	0.919 (0.838-1.008) p = 0.075	2.875 (2.646-3.124) p < 0.001
Moderate+ DR†	4982	1172 (23.5)	0.881 (0.813-0.954) p = 0.002	1.399 (1.184-1.655) p < 0.001	0.629 (0.449-0.880) p = 0.007	0.667 (0.497-0.896) p = 0.007	1.559 (0.791-3.074) p = 0.200	1.749 (1.632-1.874) p < 0.001	0.820 (0.741-0.908) p < 0.001	3.047 (2.793-3.324) p < 0.001
Severe+ DR	4982	455 (9.1)	0.833 (0.743-0.934) p = 0.002	1.378 (1.091-1.740) p = 0.007	0.466 (0.264-0.820) p = 0.008	0.492 (0.295-0.819) p = 0.006	0.178 (0.025-1.246) p = 0.082	1.606 (1.462-1.765) p < 0.001	0.842 (0.731-0.970) p = 0.017	2.457 (2.241-2.695) p < 0.001
DME†	4982	394 (7.9)	1.011 (0.899-1.136) p = 0.857	1.558 (1.231-1.972) p < 0.001	0.303 (0.161-0.573) p < 0.001	0.464 (0.288-0.748) p = 0.002	0.641 (0.197-2.090) p = 0.461	1.702 (1.549-1.870) p < 0.001	0.766 (0.667-0.879) p < 0.001	1.932 (1.778-2.100) p < 0.001
VTDR†	4982	617 (12.4)	0.895 (0.809-0.990) p = 0.032	1.465 (1.191-1.804) p < 0.001	0.413 (0.253-0.676) p < 0.001	0.501 (0.334-0.752) p < 0.001	0.585 (0.187-1.833) p = 0.358	1.695 (1.560-1.842) p < 0.001	0.777 (0.686-0.880) p < 0.001	2.523 (2.311-2.754) p < 0.001

Cataract	5058	268 (5.3)	1.406 (1.206-1.639) p < 0.001	1.224 (0.888-1.688) p = 0.216	1.267 (0.727-2.208) p = 0.403	0.545 (0.293-1.013) p = 0.055	3.095 (1.378-6.951) p = 0.006	1.210 (1.072-1.366) p = 0.002	0.657 (0.549-0.785) p < 0.001	2.699 (2.453-2.970) p < 0.001
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***Note: fewer than 50 positive examples.**

C

Prediction target	Total	Positive (%)	Age (per decade)	Male	Pupil radius relative to iris	DLS (external eye image)
HbA1c > 7%	8995	5119 (56.9)	0.889 (0.847-0.933) p < 0.001	1.175 (0.953-1.449) p = 0.130	1.050 (0.997-1.106) p = 0.065	1.638 (1.558-1.722) p < 0.001
HbA1c > 8%	8995	2947 (32.8)	0.834 (0.790-0.880) p < 0.001	1.176 (0.946-1.462) p = 0.145	1.032 (0.976-1.092) p = 0.265	1.720 (1.627-1.817) p < 0.001
HbA1c > 9%†	8995	1766 (19.6)	0.810 (0.758-0.865) p < 0.001	1.002 (0.787-1.277) p = 0.985	1.016 (0.950-1.086) p = 0.644	1.778 (1.668-1.895) p < 0.001
Tch ≥ 200	9304	1935 (20.8)	0.806 (0.755-0.860) p < 0.001	0.801 (0.645-0.996) p = 0.046	1.011 (0.953-1.073) p = 0.717	1.254 (1.173-1.340) p < 0.001
Tch ≥ 240	9304	580 (6.2)	0.768 (0.694-0.851) p < 0.001	0.812 (0.584-1.129) p = 0.216	1.011 (0.916-1.116) p = 0.827	1.272 (1.153-1.403) p < 0.001
Tg ≥ 150	9280	3825 (41.2)	0.945 (0.905-0.988) p = 0.013	1.531 (1.226-1.912) p < 0.001	1.037 (0.986-1.091) p = 0.162	1.735 (1.658-1.816) p < 0.001
Tg ≥ 200	9280	2261 (24.4)	0.913 (0.867-0.961) p < 0.001	1.943 (1.459-2.587) p < 0.001	1.055 (0.995-1.118) p = 0.074	1.747 (1.662-1.838) p < 0.001
Tg ≥ 500	9280	205 (2.2)	0.793 (0.680-0.925) p = 0.003	1.368 (0.630-2.973) p = 0.429	1.072 (0.907-1.268) p = 0.415	1.572 (1.412-1.750) p < 0.001
Mild+ DR	9518	992 (10.4)	0.941 (0.878-1.010) p = 0.090	1.607 (1.075-2.404) p = 0.021	0.934 (0.862-1.012) p = 0.095	1.991 (1.883-2.105) p < 0.001
Moderate+ DR†	9518	454 (4.8)	0.829 (0.749-0.916) p < 0.001	1.815 (0.992-3.322) p = 0.053	0.857 (0.764-0.960) p = 0.008	2.022 (1.891-2.162) p < 0.001
Severe+ DR	9518	203 (2.1)	0.777 (0.674-0.896) p < 0.001	2.670 (0.973-7.327) p = 0.057	0.728 (0.620-0.855) p < 0.001	1.592 (1.480-1.714) p < 0.001
DME†	9528	119 (1.2)	0.579 (0.482-0.696) p < 0.001	2.217 (0.761-6.463) p = 0.145	0.744 (0.601-0.920) p = 0.006	1.717 (1.556-1.894) p < 0.001
VTDR†	9528	287 (3.0)	0.712 (0.628-0.807) p < 0.001	2.143 (0.992-4.632) p = 0.053	0.768 (0.667-0.884) p < 0.001	1.920 (1.787-2.063) p < 0.001

D

Prediction target	Total	Positive (%)	Age (per decade)	BMI (per 5 kg/m ²)	Male	White	Other	Pupil radius relative to iris	DLS (external eye image)
HbA1c > 7%	2949	1045 (35.4)	1.233 (1.139-1.336) p < 0.001	1.343 (1.256-1.436) p < 0.001	2.592 (1.933-3.476) p < 0.001	0.856 (0.716-1.023) p = 0.088	0.797 (0.551-1.151) p = 0.226	0.764 (0.691-0.845) p < 0.001	1.759 (1.612-1.920) p < 0.001
HbA1c > 8%	2949	572 (19.4)	1.262 (1.142-1.395) p < 0.001	1.215 (1.126-1.310) p < 0.001	1.651 (1.181-2.308) p = 0.003	0.665 (0.535-0.826) p < 0.001	0.617 (0.387-0.984) p = 0.043	0.815 (0.723-0.919) p < 0.001	1.946 (1.752-2.162) p < 0.001
HbA1c > 9%†	2949	331 (11.2)	1.127 (0.994-1.278) p = 0.063	1.146 (1.046-1.256) p = 0.003	1.443 (0.990-2.104) p = 0.056	0.414 (0.311-0.551) p < 0.001	0.319 (0.158-0.648) p = 0.002	0.739 (0.638-0.856) p < 0.001	1.832 (1.619-2.073) p < 0.001
Tch ≥ 200	3866	1029 (26.6)	0.953 (0.881-1.030) p = 0.226	0.880 (0.827-0.936) p < 0.001	0.628 (0.512-0.769) p < 0.001	1.016 (0.865-1.194) p = 0.845	1.046 (0.758-1.443) p = 0.785	1.070 (0.979-1.169) p = 0.137	1.298 (1.185-1.421) p < 0.001
Tch ≥ 240	3866	301 (7.8)	0.940 (0.834-1.060) p = 0.315	0.803 (0.723-0.893) p < 0.001	0.577 (0.425-0.782) p < 0.001	1.177 (0.905-1.532) p = 0.225	1.404 (0.864-2.281) p = 0.171	0.969 (0.840-1.119) p = 0.672	1.223 (1.072-1.396) p = 0.003
Tg ≥ 150	3891	1102 (28.3)	0.974 (0.905-1.048) p = 0.485	1.144 (1.077-1.216) p < 0.001	1.815 (1.405-2.345) p < 0.001	1.443 (1.145-1.820) p = 0.002	1.170 (0.832-1.646) p = 0.367	0.831 (0.759-0.909) p < 0.001	1.512 (1.356-1.687) p < 0.001
Tg ≥ 200	3891	612 (15.7)	0.966 (0.883-1.057) p = 0.455	1.160 (1.079-1.247) p < 0.001	1.543 (1.119-2.128) p = 0.008	1.386 (1.050-1.830) p = 0.021	1.618 (1.096-2.387) p = 0.015	0.927 (0.830-1.035) p = 0.177	1.537 (1.362-1.734) p < 0.001
Tg ≥ 500	3891	43 (1.1)*	0.715 (0.536-0.953) p = 0.022	0.959 (0.751-1.224) p = 0.736	5.696 (1.013-32.028) p = 0.048	1.611 (0.752-3.454) p = 0.220	1.036 (0.251-4.277) p = 0.961	0.820 (0.576-1.168) p = 0.271	1.200 (0.938-1.536) p = 0.147

*Note: fewer than 50 positive examples.

Supplementary Table 4 | Adjusted analysis for diabetic eye disease targets including HbA1c.

†:prespecified primary prediction tasks.

A

Prediction target	Total	Positive (%)	Age (per decade)	Years with diabetes (per 5 years)	Male	White	Black	Asian / Pacific islander	HbA1c (per 5%)	DLS (external eye image)
Mild+ DR	21142	4075 (19.3)	0.954 (0.922-0.987) p = 0.007	1.144 (1.061-1.233) p < 0.001	0.784 (0.711-0.864) p < 0.001	1.168 (1.049-1.301) p = 0.005	1.230 (1.090-1.389) p < 0.001	1.594 (1.543-1.647) p < 0.001	2.077 (1.914-2.254) p < 0.001	1.695 (1.636-1.757) p < 0.001
Moderate+ DR†	21142	2535 (12.0)	1.001 (0.961-1.043) p = 0.958	1.155 (1.054-1.267) p = 0.002	0.779 (0.691-0.878) p < 0.001	0.922 (0.806-1.055) p = 0.239	1.175 (1.015-1.360) p = 0.030	1.616 (1.555-1.680) p < 0.001	2.509 (2.275-2.767) p < 0.001	1.764 (1.698-1.832) p < 0.001
Severe+ DR	21142	335 (1.6)	0.996 (0.902-1.101) p = 0.944	1.373 (1.094-1.725) p = 0.006	0.838 (0.616-1.142) p = 0.263	1.100 (0.776-1.560) p = 0.592	2.136 (1.552-2.941) p < 0.001	1.818 (1.658-1.993) p < 0.001	2.343 (1.844-2.978) p < 0.001	1.460 (1.392-1.533) p < 0.001
DME†	21142	618 (2.9)	1.036 (0.961-1.117) p = 0.355	1.267 (1.071-1.499) p = 0.006	0.649 (0.515-0.817) p < 0.001	1.010 (0.800-1.274) p = 0.934	1.131 (0.868-1.473) p = 0.363	1.565 (1.462-1.675) p < 0.001	2.662 (2.241-3.163) p < 0.001	1.409 (1.348-1.473) p < 0.001
VTDR†	21142	825 (3.9)	1.042 (0.975-1.114) p = 0.227	1.233 (1.062-1.431) p = 0.006	0.714 (0.583-0.874) p = 0.001	1.052 (0.850-1.301) p = 0.641	1.391 (1.109-1.746) p = 0.004	1.664 (1.566-1.768) p < 0.001	2.571 (2.199-3.005) p < 0.001	1.550 (1.487-1.617) p < 0.001
Cataract	21478	537 (2.5)	1.745 (1.587-1.918) p < 0.001	0.855 (0.704-1.038) p = 0.113	1.459 (1.120-1.900) p = 0.005	1.335 (0.979-1.820) p = 0.068	2.807 (2.158-3.652) p < 0.001	1.124 (1.039-1.216) p = 0.004	1.389 (1.105-1.746) p = 0.005	1.667 (1.594-1.743) p < 0.001

B

Prediction target	Total	Positive (%)	Age (per decade)	Years with diabetes (per 5 years)	Male	White	Black	Asian / Pacific islander	HbA1c (per 5%)	DLS (external eye image)
Mild+ DR	4094	1217 (29.7)	0.999 (0.920-1.085) p = 0.980	1.396 (1.176-1.657) p < 0.001	0.890 (0.626-1.264) p = 0.515	0.676 (0.501-0.914) p = 0.011	1.942 (0.999-3.773) p = 0.050	1.669 (1.551-1.796) p < 0.001	2.265 (1.866-2.749) p < 0.001	2.884 (2.622-3.172) p < 0.001
Moderate+ DR†	4094	960 (23.4)	0.966 (0.881-1.059) p = 0.461	1.490 (1.231-1.803) p < 0.001	0.813 (0.540-1.223) p = 0.321	0.659 (0.472-0.919) p = 0.014	1.989 (0.968-4.083) p = 0.061	1.663 (1.536-1.800) p < 0.001	2.549 (2.062-3.152) p < 0.001	3.205 (2.897-3.545) p < 0.001
Severe+ DR	4094	401 (9.8)	0.968 (0.856-1.096) p = 0.610	1.473 (1.149-1.888) p = 0.002	0.643 (0.346-1.193) p = 0.161	0.877 (0.557-1.379) p = 0.569	0.597 (0.136-2.628) p = 0.496	1.568 (1.417-1.734) p < 0.001	1.811 (1.384-2.370) p < 0.001	2.391 (2.162-2.646) p < 0.001
DME†	4094	321 (7.8)	1.127 (0.986-1.288) p = 0.080	1.482 (1.141-1.924) p = 0.003	0.516 (0.255-1.044) p = 0.066	0.563 (0.338-0.940) p = 0.028	1.584 (0.584-4.299) p = 0.367	1.533 (1.380-1.703) p < 0.001	2.311 (1.749-3.055) p < 0.001	1.992 (1.812-2.190) p < 0.001
VTDR†	4094	514 (12.6)	1.023 (0.914-1.146) p = 0.689	1.463 (1.164-1.840) p = 0.001	0.660 (0.385-1.132) p = 0.131	0.632 (0.415-0.963) p = 0.033	1.056 (0.376-2.968) p = 0.918	1.618 (1.474-1.775) p < 0.001	2.222 (1.733-2.849) p < 0.001	2.549 (2.309-2.814) p < 0.001
Cataract	4169	218 (5.2)	1.520 (1.272-1.816) p < 0.001	1.320 (0.922-1.892) p = 0.130	0.913 (0.422-1.972) p = 0.816	0.859 (0.434-1.701) p = 0.663	3.115 (1.249-7.772) p = 0.015	1.200 (1.046-1.375) p = 0.009	1.540 (1.037-2.287) p = 0.032	2.748 (2.464-3.066) p < 0.001

C

Prediction target	Total	Positive (%)	Age (per decade)	Male	HbA1c (per 5%)	DLS (external eye image)
Mild+ DR	8454	908 (10.7)	1.051 (0.973-1.137) p = 0.206	1.308 (0.882-1.941) p = 0.182	2.686 (2.252-3.205) p < 0.001	1.940 (1.828-2.060) p < 0.001
Moderate+ DR†	8454	414 (4.9)	0.973 (0.870-1.087) p = 0.628	1.440 (0.801-2.590) p = 0.223	2.848 (2.244-3.614) p < 0.001	1.937 (1.805-2.079) p < 0.001
Severe+ DR	8454	195 (2.3)	0.862 (0.740-1.003) p = 0.055	1.662 (0.716-3.860) p = 0.237	2.375 (1.704-3.311) p < 0.001	1.613 (1.498-1.736) p < 0.001
DME†	8471	131 (1.5)	0.694 (0.578-0.833) p < 0.001	3.182 (0.964-10.501) p = 0.057	4.025 (2.813-5.759) p < 0.001	1.599 (1.465-1.746) p < 0.001
VTDR†	8471	291 (3.4)	0.812 (0.713-0.924) p = 0.002	1.847 (0.902-3.783) p = 0.093	2.775 (2.116-3.638) p < 0.001	1.778 (1.658-1.907) p < 0.001

Supplementary Table 5 | Subgroup analysis for HbA1c \geq 9% in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. None of the subgroups' DLS AUC decreased by >5% compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		21183	6537 (30.9%)	64.8 (64.0-65.6)	70.0 (69.3-70.8)	5.2 (4.5-6.0)	p < 0.001
Age	≤50 years old	8081	3198 (39.6%)	61.0 (59.7-62.3)	67.9 (66.8-69.1)	6.9 (5.6-8.3)	p < 0.001
	50-60 years old	6989	2126 (30.4%)	60.8 (59.4-62.2)	66.7 (65.3-68.1)	5.9 (4.3-7.6)	p < 0.001
	>60 years old	6542	1339 (20.5%)	61.8 (60.1-63.5)	67.3 (65.7-68.9)	5.5 (3.6-7.4)	p < 0.001
Sex	Male	10019	3344 (33.4%)	64.1 (63.0-65.2)	69.4 (68.3-70.4)	5.3 (4.2-6.4)	p < 0.001
	Female	11154	3241 (29.1%)	65.1 (64.0-66.2)	70.2 (69.1-71.2)	5.1 (4.0-6.2)	p < 0.001
Race / ethnicity	Hispanic	8687	3107 (35.8%)	63.6 (62.4-64.8)	70.1 (69.0-71.3)	6.5 (5.3-7.7)	p < 0.001
	White	5559	1579 (28.4%)	63.0 (61.4-64.6)	66.1 (64.5-67.7)	3.1 (1.6-4.6)	p < 0.001
	Black	3147	914 (29.0%)	65.5 (63.4-67.6)	65.7 (63.6-67.8)	0.2 (-2.0-2.4)	p = 0.428
	Asian / Pacific islander	2615	627 (24.0%)	66.3 (63.9-68.8)	76.5 (74.4-78.6)	10.1 (7.8-12.5)	p < 0.001
No. years with diabetes	≤5	12095	3247 (26.8%)	63.4 (62.3-64.5)	69.5 (68.4-70.5)	6.1 (5.1-7.1)	p < 0.001
	5-10	5557	1872 (33.7%)	65.0 (63.5-66.5)	71.4 (70.0-72.8)	6.3 (5.0-7.7)	p < 0.001
	>10	4914	1859 (37.8%)	63.5 (61.9-65.1)	69.6 (68.1-71.1)	6.1 (4.6-7.6)	p < 0.001
Cataract*	Present	578	158 (27.3%)	66.2 (61.2-71.2)	69.5 (64.6-74.4)	3.3 (-1.7-8.4)	p = 0.099
	Absent	20702	6402 (30.9%)	64.7 (63.9-65.5)	69.0 (68.3-69.8)	4.4 (3.6-5.2)	p < 0.001
Pupil diameter*	Small pupil	9759	3084 (31.6%)	64.3 (63.2-65.5)	69.3 (68.2-70.4)	5.0 (3.8-6.2)	p < 0.001
	Medium pupil	12395	3817 (30.8%)	65.2 (64.2-66.2)	69.5 (68.5-70.5)	4.3 (3.3-5.3)	p < 0.001
	Large pupil	6809	1993 (29.3%)	65.4 (64.0-66.8)	69.2 (67.8-70.5)	3.8 (2.5-5.1)	p < 0.001
Site by camera type	Model A	9044	2827 (31.3%)	66.3 (65.1-67.5)	71.4 (70.3-72.6)	5.1 (4.0-6.2)	p < 0.001
	Model B	2162	610 (28.2%)	67.4 (64.9-70.0)	68.2 (65.7-70.8)	0.8 (-1.9-3.6)	p = 0.284

*Because two eyes of the same patient can have different cataract statuses and pupil sizes, for this analysis we selected a random eye that fit this criteria per patient. In other words, in contrast to other analysis in this paper, these HbA1c predictions are from a single eye instead of being the average of two eyes.

Supplementary Table 6 | Subgroup analysis for Tch ≥ 240 in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. None of the subgroups' DLS AUC decreased by >5% compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		9318	984 (10.6%)	55.1 (53.3-56.9)	59.1 (57.3-61.0)	4.0 (1.8-6.3)	p < 0.001
Age	≤50 years old	3272	391 (11.9%)	49.4 (46.4-52.5)	59.4 (56.3-62.5)	10.0 (5.7-14.2)	p < 0.001
	50-60 years old	3184	371 (11.7%)	56.0 (53.0-58.9)	58.2 (55.2-61.3)	2.3 (-1.6-6.1)	p = 0.123
	>60 years old	3044	238 (7.8%)	54.7 (50.8-58.6)	56.6 (52.9-60.3)	1.9 (-2.8-6.6)	p = 0.209
Sex	Male	4357	440 (10.1%)	56.1 (53.5-58.8)	62.3 (59.7-65.0)	6.2 (3.2-9.2)	p < 0.001
	Female	4955	534 (10.8%)	54.2 (51.7-56.8)	57.6 (55.0-60.1)	3.3 (0.1-6.6)	p = 0.021
Race / ethnicity	Hispanic	3699	397 (10.7%)	56.0 (53.0-58.9)	61.3 (58.4-64.2)	5.4 (1.7-9.1)	p = 0.002
	White	2355	287 (12.2%)	54.0 (50.6-57.4)	57.7 (54.2-61.2)	3.7 (-0.5-8.0)	p = 0.043
	Black	2102	204 (9.7%)	53.9 (49.8-57.9)	54.2 (49.9-58.5)	0.3 (-4.9-5.5)	p = 0.455
	Asian / Pacific islander	809	60 (7.4%)	58.5 (50.2-66.7)	64.5 (57.5-71.6)	6.1 (-3.7-15.9)	p = 0.113
No. years with diabetes	≤5	5146	583 (11.3%)	53.1 (50.7-55.5)	58.1 (55.6-60.5)	4.9 (2.1-7.8)	p < 0.001
	5-10	2559	249 (9.7%)	55.7 (51.9-59.5)	58.8 (55.3-62.4)	3.1 (-1.1-7.4)	p = 0.074
	>10	2262	206 (9.1%)	56.6 (52.6-60.7)	63.1 (59.0-67.1)	6.4 (1.7-11.1)	p = 0.004
Cataract	Present	229	19 (8.3%)*	50.1 (36.5-63.7)	69.2 (59.4-79.1)	19.1 (5.9-32.3)	p = 0.002
	Absent	9150	984 (10.8%)	55.3 (53.4-57.1)	59.1 (57.3-61.0)	3.9 (1.6-6.1)	p < 0.001
HbA1c (%)	≤7	3698	277 (7.5%)	54.4 (51.1-57.7)	57.3 (53.8-60.7)	2.9 (-1.0-6.7)	p = 0.072
	7-9	3445	310 (9.0%)	56.3 (53.0-59.5)	60.2 (56.8-63.6)	3.9 (0.2-7.6)	p = 0.018
	>9	2806	454 (16.2%)	55.4 (52.6-58.2)	57.7 (54.9-60.5)	2.3 (-1.4-6.0)	p = 0.109
Pupil diameter	Small pupil	4682	499 (10.7%)	54.1 (51.5-56.8)	56.8 (54.1-59.5)	2.6 (-0.6-5.9)	p = 0.053
	Medium pupil	5334	549 (10.3%)	55.7 (53.3-58.1)	59.5 (57.1-62.0)	3.8 (0.7-6.9)	p = 0.008
	Large pupil	2842	317 (11.2%)	58.1 (55.0-61.1)	60.5 (57.3-63.8)	2.5 (-1.4-6.3)	p = 0.106
Site by camera type	Model A	3469	322 (9.3%)	56.0 (52.9-59.1)	63.2 (60.0-66.4)	7.2 (3.5-10.8)	p < 0.001
	Model B	2069	221 (10.7%)	51.0 (47.2-54.9)	52.9 (48.7-57.1)	1.8 (-3.4-7.1)	p = 0.244

*Note: fewer than 50 positive examples.

Supplementary Table 7 | Subgroup analysis for Tg ≥ 200 in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		9104	2894 (31.8%)	61.7 (60.5-62.9)	63.6 (62.4-64.8)	1.9 (0.9-2.9)	p < 0.001
Age	≤50 years old	3144	1160 (36.9%)	58.4 (56.4-60.4)	60.0 (58.0-62.1)	1.6 (-0.2-3.5)	p = 0.037
	50-60 years old	3111	994 (32.0%)	61.7 (59.6-63.7)	64.7 (62.7-66.8)	3.1 (1.3-4.8)	p < 0.001
	>60 years old	3037	799 (26.3%)	61.6 (59.4-63.8)	63.8 (61.7-66.0)	2.2 (0.3-4.1)	p = 0.012
Sex	Male	4247	1461 (34.4%)	61.1 (59.4-62.9)	64.4 (62.7-66.2)	3.3 (1.9-4.7)	p < 0.001
	Female	4849	1451 (29.9%)	61.9 (60.2-63.6)	62.5 (60.9-64.2)	0.7 (-0.8-2.1)	p = 0.190
Race / ethnicity	Hispanic	3502	1229 (35.1%)	56.2 (54.2-58.2)	58.9 (57.0-60.9)	2.7 (0.5-5.0)	p = 0.009
	White	2338	924 (39.5%)	55.2 (52.9-57.6)	59.8 (57.4-62.1)	4.5 (1.7-7.3)	p < 0.001
	Black	2105	421 (20.0%)	61.5 (58.5-64.5)	58.2 (55.2-61.1)	-3.3 (-7.0-0.4)	p = 0.960
	Asian / Pacific islander	813	198 (24.4%)	58.2 (53.6-62.8)	59.5 (54.9-64.1)	1.3 (-3.6-6.2)	p = 0.303
No. years with diabetes	≤5	5041	1722 (34.2%)	61.7 (60.1-63.3)	62.3 (60.7-63.9)	0.7 (-0.6-1.9)	p = 0.157
	5-10	2497	742 (29.7%)	61.9 (59.5-64.2)	65.1 (62.8-67.4)	3.2 (1.3-5.2)	p < 0.001
	>10	2212	641 (29.0%)	61.3 (58.8-63.8)	64.8 (62.3-67.3)	3.5 (1.4-5.6)	p < 0.001
Cataract	Present	224	58 (25.9%)	68.7 (61.2-76.2)	72.3 (65.1-79.5)	3.6 (-3.4-10.6)	p = 0.156
	Absent	8936	2870 (32.1%)	61.6 (60.4-62.8)	63.3 (62.1-64.5)	1.7 (0.7-2.8)	p < 0.001
HbA1c (%)	≤7	3634	880 (24.2%)	61.7 (59.7-63.8)	63.0 (61.0-65.1)	1.3 (-0.4-2.9)	p = 0.066
	7-9	3380	1116 (33.0%)	61.2 (59.2-63.1)	63.0 (61.1-65.0)	1.9 (0.2-3.5)	p = 0.012
	>9	2703	1115 (41.3%)	61.0 (58.9-63.2)	61.9 (59.7-64.0)	0.8 (-1.0-2.7)	p = 0.188
Pupil diameter	Small pupil	4567	1399 (30.6%)	62.9 (61.2-64.6)	64.2 (62.5-65.9)	1.3 (-0.1-2.7)	p = 0.035
	Medium pupil	5217	1655 (31.7%)	61.1 (59.5-62.7)	62.2 (60.6-63.8)	1.1 (-0.3-2.5)	p = 0.061
	Large pupil	2776	955 (34.4%)	60.5 (58.3-62.7)	62.2 (60.0-64.4)	1.7 (-0.2-3.6)	p = 0.042
Site by camera type	Model A	3421	1161 (33.9%)	60.4 (58.5-62.4)	62.2 (60.3-64.2)	1.8 (-0.0-3.6)	p = 0.027
	Model B	2068	587 (28.4%)	62.4 (59.8-65.1)	62.1 (59.4-64.8)	-0.3 (-2.4-1.7)	p = 0.624

Supplementary Table 8 | Subgroup analysis for moderate+ diabetic retinopathy (DR) in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		26950	3247 (12.0%)	71.0 (70.0-72.0)	75.0 (74.1-75.9)	4.0 (2.8-5.2)	p < 0.001
Age	≤50 years old	10075	1198 (11.9%)	74.1 (72.6-75.6)	77.0 (75.6-78.4)	2.9 (1.1-4.7)	p < 0.001
	50-60 years old	8937	1118 (12.5%)	69.8 (68.1-71.5)	73.6 (72.0-75.1)	3.8 (1.8-5.8)	p < 0.001
	>60 years old	8415	911 (10.8%)	69.6 (67.8-71.4)	73.9 (72.3-75.6)	4.3 (2.0-6.6)	p < 0.001
Sex	Male	12659	1650 (13.0%)	70.2 (68.8-71.6)	75.0 (73.8-76.2)	4.8 (3.1-6.5)	p < 0.001
	Female	14301	1520 (10.6%)	71.1 (69.6-72.5)	75.8 (74.6-77.1)	4.8 (3.1-6.5)	p < 0.001
Race / ethnicity	Hispanic	11177	1456 (13.0%)	71.6 (70.1-73.0)	77.1 (75.8-78.3)	5.5 (3.8-7.2)	p < 0.001
	White	7528	715 (9.5%)	72.2 (70.1-74.2)	73.9 (72.0-75.8)	1.7 (-0.8-4.3)	p = 0.087
	Black	4094	470 (11.5%)	68.2 (65.7-70.8)	68.7 (66.1-71.3)	0.5 (-2.7-3.7)	p = 0.386
	Asian / Pacific islander	2882	354 (12.3%)	65.5 (62.3-68.6)	77.7 (75.2-80.3)	12.3 (8.6-16.0)	p < 0.001
No. years with diabetes	≤5	15059	922 (6.1%)	59.7 (57.8-61.6)	74.8 (73.1-76.4)	15.1 (12.8-17.3)	p < 0.001
	5-10	7023	882 (12.6%)	60.2 (58.2-62.2)	73.5 (71.8-75.3)	13.3 (10.9-15.8)	p < 0.001
	>10	6457	1565 (24.2%)	60.0 (58.4-61.5)	71.8 (70.4-73.3)	11.9 (9.9-13.8)	p < 0.001
Cataract	Present	656	71 (10.8%)	66.4 (59.3-73.5)	73.5 (67.9-79.1)	7.1 (-1.3-15.6)	p = 0.049
	Absent	26413	3099 (11.7%)	71.1 (70.2-72.1)	75.5 (74.6-76.4)	4.4 (3.2-5.6)	p < 0.001
HbA1c (%)	≤7	8130	360 (4.4%)	66.8 (63.7-69.8)	71.8 (68.9-74.6)	5.0 (1.5-8.5)	p = 0.003
	7-9	7972	990 (12.4%)	68.7 (66.9-70.5)	73.7 (72.0-75.4)	5.0 (2.7-7.2)	p < 0.001
	>9	6665	1361 (20.4%)	67.8 (66.2-69.4)	72.1 (70.6-73.6)	4.3 (2.3-6.3)	p < 0.001
Pupil diameter	Small pupil	12120	1630 (13.4%)	69.2 (67.9-70.6)	73.9 (72.6-75.2)	4.7 (3.0-6.4)	p < 0.001
	Medium pupil	15819	1938 (12.3%)	70.7 (69.4-71.9)	75.3 (74.2-76.5)	4.7 (3.1-6.2)	p < 0.001
	Large pupil	8756	744 (8.5%)	72.9 (70.9-74.9)	75.8 (74.0-77.6)	2.8 (0.5-5.2)	p = 0.009
Site by camera type	Model A	12114	1431 (11.8%)	71.8 (70.4-73.3)	76.5 (75.2-77.7)	4.6 (2.9-6.4)	p < 0.001
	Model B	2384	249 (10.4%)	69.5 (66.0-73.0)	73.4 (70.2-76.5)	3.8 (-0.4-8.1)	p = 0.038

Supplementary Table 9 | Subgroup analysis for diabetic macular edema (DME) in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. None of the subgroups' DLS AUC decreased by >5% compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		26950	797 (3.0%)	71.2 (69.4-73.0)	77.9 (76.3-79.5)	6.7 (4.6-8.9)	p < 0.001
Age	≤50 years old	10075	280 (2.8%)	73.5 (70.5-76.5)	78.0 (75.3-80.6)	4.5 (1.0-8.0)	p = 0.006
	50-60 years old	8937	301 (3.4%)	69.5 (66.6-72.4)	77.7 (75.0-80.4)	8.2 (4.6-11.8)	p < 0.001
	>60 years old	8415	230 (2.7%)	68.3 (64.9-71.7)	74.6 (71.2-77.9)	6.3 (1.9-10.7)	p = 0.003
Sex	Male	12659	426 (3.4%)	67.7 (65.1-70.4)	76.5 (74.3-78.7)	8.8 (5.7-11.9)	p < 0.001
	Female	14301	404 (2.8%)	72.6 (70.2-75.0)	77.8 (75.5-80.1)	5.2 (2.2-8.2)	p < 0.001
Race / ethnicity	Hispanic	11177	361 (3.2%)	70.5 (67.8-73.1)	79.4 (77.1-81.7)	8.9 (5.8-12.0)	p < 0.001
	White	7528	153 (2.0%)	72.2 (68.3-76.1)	74.6 (70.6-78.6)	2.4 (-2.6-7.5)	p = 0.171
	Black	4094	146 (3.6%)	69.9 (65.5-74.2)	74.5 (70.5-78.4)	4.6 (-0.9-10.1)	p = 0.051
	Asian / Pacific islander	2882	93 (3.2%)	69.2 (63.8-74.6)	80.4 (75.6-85.3)	11.3 (5.0-17.5)	p < 0.001
No. years with diabetes	≤5	15059	219 (1.5%)	61.5 (57.7-65.3)	78.3 (75.3-81.4)	16.8 (12.2-21.4)	p < 0.001
	5-10	7023	204 (2.9%)	56.9 (52.9-60.9)	77.5 (74.6-80.5)	20.7 (16.1-25.3)	p < 0.001
	>10	6457	412 (6.4%)	58.3 (55.5-61.2)	73.1 (70.7-75.6)	14.8 (11.4-18.1)	p < 0.001
Cataract	Present	656	14 (2.1%)*	61.6 (45.4-77.8)	74.9 (59.9-89.8)	13.3 (-6.7-33.3)	p = 0.097
	Absent	26413	798 (3.0%)	71.5 (69.7-73.3)	77.5 (75.9-79.1)	6.0 (3.9-8.1)	p < 0.001
HbA1c (%)	≤7	8130	62 (0.8%)	68.2 (61.0-75.3)	74.2 (68.1-80.4)	6.1 (-1.9-14.1)	p = 0.067
	7-9	7972	233 (2.9%)	68.1 (64.6-71.5)	78.0 (75.0-81.0)	9.9 (5.7-14.2)	p < 0.001
	>9	6665	340 (5.1%)	66.8 (64.0-69.7)	75.2 (72.6-77.8)	8.4 (4.9-11.9)	p < 0.001
Pupil diameter	Small pupil	12120	407 (3.4%)	68.1 (65.6-70.7)	77.4 (75.2-79.6)	9.3 (6.1-12.5)	p < 0.001
	Medium pupil	15819	488 (3.1%)	69.7 (67.4-72.1)	76.9 (74.8-79.1)	7.2 (4.4-10.0)	p < 0.001
	Large pupil	8756	160 (1.8%)	74.7 (70.7-78.7)	78.3 (74.4-82.1)	3.6 (-1.0-8.1)	p = 0.064
Site by camera type	Model A	12114	346 (2.9%)	70.9 (68.1-73.6)	79.6 (77.2-82.0)	8.7 (5.4-12.0)	p < 0.001
	Model B	2384	62 (2.6%)	68.5 (61.6-75.4)	74.3 (68.2-80.3)	5.8 (-2.0-13.6)	p = 0.074

*Note: fewer than 50 positive examples.

Supplementary Table 10 | Subgroup analysis for vision-threatening diabetic retinopathy (VTDR) in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		26950	1042 (3.9%)	72.7 (71.1-74.2)	79.2 (77.9-80.5)	6.5 (4.6-8.4)	p < 0.001
Age	≤50 years old	10075	368 (3.7%)	75.5 (73.0-78.1)	80.1 (77.9-82.4)	4.6 (1.6-7.7)	p = 0.001
	50-60 years old	8937	381 (4.3%)	70.2 (67.5-72.8)	79.2 (76.9-81.5)	9.1 (5.9-12.3)	p < 0.001
	>60 years old	8415	313 (3.7%)	71.8 (69.0-74.7)	76.1 (73.3-78.8)	4.2 (0.6-7.9)	p = 0.011
Sex	Male	12659	565 (4.5%)	70.7 (68.5-72.9)	77.4 (75.5-79.3)	6.7 (4.0-9.4)	p < 0.001
	Female	14301	514 (3.6%)	73.4 (71.2-75.6)	79.7 (77.7-81.6)	6.3 (3.6-8.9)	p < 0.001
Race / ethnicity	Hispanic	11177	457 (4.1%)	71.4 (69.0-73.8)	80.6 (78.7-82.6)	9.2 (6.4-12.0)	p < 0.001
	White	7528	211 (2.8%)	74.7 (71.4-78.0)	77.5 (74.3-80.6)	2.7 (-1.5-6.9)	p = 0.101
	Black	4094	176 (4.3%)	70.8 (66.9-74.8)	74.2 (70.6-77.7)	3.4 (-1.6-8.3)	p = 0.093
	Asian / Pacific islander	2882	141 (4.9%)	69.1 (64.5-73.8)	81.9 (78.2-85.6)	12.7 (7.6-17.9)	p < 0.001
No. years with diabetes	≤5	15059	265 (1.8%)	61.7 (58.3-65.1)	79.9 (77.3-82.6)	18.2 (14.1-22.4)	p < 0.001
	5-10	7023	253 (3.6%)	56.9 (53.3-60.6)	77.6 (75.0-80.3)	20.7 (16.4-25.0)	p < 0.001
	>10	6457	570 (8.8%)	60.8 (58.4-63.2)	74.0 (72.0-76.1)	13.2 (10.3-16.1)	p < 0.001
Cataract	Present	656	20 (3.0%)*	68.5 (54.8-82.1)	74.6 (63.4-85.9)	6.2 (-10.0-22.3)	p = 0.227
	Absent	26413	1039 (3.9%)	72.5 (70.9-74.1)	79.3 (77.9-80.6)	6.8 (4.9-8.7)	p < 0.001
HbA1c (%)	≤7	8130	93 (1.1%)	69.3 (63.2-75.4)	76.9 (72.1-81.7)	7.6 (0.7-14.6)	p = 0.016
	7-9	7972	297 (3.7%)	70.4 (67.4-73.5)	79.4 (76.9-82.0)	9.0 (5.3-12.7)	p < 0.001
	>9	6665	446 (6.7%)	68.4 (65.9-71.0)	75.6 (73.4-77.9)	7.2 (4.1-10.4)	p < 0.001
Pupil diameter	Small pupil	12120	548 (4.5%)	70.0 (67.7-72.2)	78.1 (76.3-80.0)	8.2 (5.4-10.9)	p < 0.001
	Medium pupil	15819	632 (4.0%)	72.2 (70.2-74.2)	78.5 (76.6-80.3)	6.3 (3.8-8.7)	p < 0.001
	Large pupil	8756	203 (2.3%)	74.0 (70.4-77.7)	80.3 (77.1-83.5)	6.3 (2.1-10.5)	p = 0.002
Site by camera type	Model A	12114	428 (3.5%)	72.4 (69.9-74.8)	79.8 (77.7-81.9)	7.4 (4.5-10.4)	p < 0.001
	Model B	2384	84 (3.5%)	71.1 (65.4-76.8)	76.2 (71.2-81.3)	5.1 (-1.4-11.7)	p = 0.063

*Note: fewer than 50 positive examples.

Supplementary Table 11 | Subgroup analysis for cataract in validation set A.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		27415	639 (2.3%)	76.5 (74.7-78.2)	86.4 (84.9-87.8)	9.9 (8.2-11.6)	p < 0.001
Age	≤50 years old	10198	56 (0.5%)	63.8 (56.1-71.4)	87.3 (81.3-93.2)	23.5 (14.3-32.7)	p < 0.001
	50-60 years old	9093	150 (1.6%)	62.3 (57.8-66.8)	78.7 (74.6-82.9)	16.5 (10.9-22.0)	p < 0.001
	>60 years old	8625	448 (5.2%)	62.9 (60.4-65.5)	79.5 (77.2-81.7)	16.5 (13.8-19.3)	p < 0.001
Sex	Male	12890	247 (1.9%)	74.1 (71.0-77.1)	83.9 (81.4-86.5)	9.9 (6.7-13.0)	p < 0.001
	Female	14525	390 (2.7%)	77.5 (75.5-79.6)	87.7 (85.9-89.4)	10.2 (8.1-12.2)	p < 0.001
Race / ethnicity	Hispanic	11393	167 (1.5%)	77.2 (73.7-80.7)	88.9 (86.4-91.4)	11.7 (8.1-15.3)	p < 0.001
	White	7621	162 (2.1%)	72.2 (68.1-76.2)	82.8 (79.3-86.4)	10.7 (6.6-14.7)	p < 0.001
	Black	4140	90 (2.2%)	76.5 (72.4-80.7)	83.5 (79.2-87.8)	6.9 (2.7-11.2)	p < 0.001
	Asian / Pacific islander	2949	184 (6.2%)	72.9 (69.7-76.1)	85.9 (83.3-88.5)	13.0 (9.6-16.5)	p < 0.001
No. years with diabetes	≤5	15204	284 (1.9%)	78.8 (76.1-81.5)	88.2 (86.1-90.4)	9.4 (6.8-12.0)	p < 0.001
	5-10	7137	171 (2.4%)	72.7 (69.0-76.4)	85.5 (82.6-88.4)	12.8 (9.0-16.6)	p < 0.001
	>10	6677	214 (3.2%)	71.5 (68.3-74.6)	82.4 (79.6-85.2)	10.9 (7.5-14.4)	p < 0.001
HbA1c (%)	≤7	8214	223 (2.7%)	78.7 (76.0-81.5)	88.3 (86.0-90.7)	9.6 (7.0-12.2)	p < 0.001
	7-9	8080	194 (2.4%)	76.0 (72.6-79.4)	87.8 (85.5-90.1)	11.7 (8.5-15.0)	p < 0.001
	>9	6825	150 (2.2%)	75.9 (72.5-79.4)	84.8 (81.6-87.9)	8.8 (4.8-12.8)	p < 0.001
Pupil diameter	Small pupil	12488	308 (2.5%)	73.0 (70.5-75.5)	79.9 (77.4-82.3)	6.9 (4.3-9.4)	p < 0.001
	Medium pupil	16009	407 (2.5%)	75.8 (73.5-78.2)	87.6 (85.9-89.4)	11.8 (9.5-14.1)	p < 0.001
	Large pupil	8798	173 (2.0%)	80.7 (77.6-83.9)	91.1 (88.5-93.6)	10.3 (7.4-13.2)	p < 0.001
Site by camera type	Model A	12413	335 (2.7%)	77.1 (74.8-79.4)	88.1 (86.4-89.9)	11.1 (8.8-13.4)	p < 0.001
	Model B	2384	35 (1.5%)*	76.1 (67.8-84.5)	78.2 (71.0-85.4)	2.1 (-5.3-9.4)	p = 0.292

*Note: fewer than 50 positive examples.

Supplementary Table 12 | Subgroup analysis for HbA1c ≥ 7 in validation set D.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		3200	1152 (36.0%)	55.9 (53.9-57.9)	64.3 (62.3-66.3)	8.4 (5.3-11.5)	p < 0.001
Diabetes status	Diabetic	1902	1102 (57.9%)	45.0 (42.3-47.6)	62.6 (60.1-65.1)	17.6 (13.7-21.6)	p < 0.001
	Non-diabetic	1303	52 (4.0%)	53.7 (45.8-61.6)	57.6 (49.2-65.9)	3.9 (-8.6-16.3)	p = 0.271
BMI range	Normal	358	77 (21.5%)	56.1 (49.0-63.2)	71.8 (65.4-78.2)	15.8 (4.8-26.7)	p = 0.002
	Overweight	981	285 (29.1%)	55.0 (51.1-58.9)	62.3 (58.5-66.2)	7.3 (1.4-13.3)	p = 0.008
	Obesity I	916	364 (39.7%)	59.8 (56.1-63.5)	64.6 (61.0-68.3)	4.9 (-0.7-10.4)	p = 0.043
	Obesity II+	711	327 (46.0%)	59.1 (55.0-63.3)	62.7 (58.6-66.8)	3.5 (-2.6-9.7)	p = 0.132
IOL history	Yes	460	209 (45.4%)	46.9 (41.6-52.2)	64.9 (59.8-69.9)	18.0 (9.7-26.2)	p < 0.001
	No	2740	942 (34.4%)	55.9 (53.7-58.1)	63.7 (61.5-65.9)	7.8 (4.4-11.2)	p < 0.001
Race / ethnicity	Black	1733	599 (34.6%)	57.3 (54.5-60.0)	66.0 (63.3-68.7)	8.7 (4.6-12.9)	p < 0.001
	White	1283	488 (38.0%)	53.1 (49.8-56.3)	62.1 (58.9-65.2)	9.0 (4.0-14.0)	p < 0.001

Supplementary Table 13 | Subgroup analysis for HbA1c ≥ 9 in validation set D.

Note that the sum of some subgroups can exceed the total because some patients have multiple visits over time that can fall under different groups. Bold indicates there is a >5% decrease in AUC for the DLS in that subgroup compared to the entire cohort.

Category	Subgroup	No. of visits		AUC (%) (95% CI)			
		Total	Positive (%)	Baseline characteristics	DLS (external eye image)	Improvement	P-value for improvement
All		3200	357 (11.2%)	59.8 (56.7-62.8)	67.6 (64.7-70.5)	7.8 (4.5-11.1)	p < 0.001
Diabetes status	Diabetic	1902	346 (18.2%)	65.6 (62.4-68.9)	67.9 (64.9-71.0)	2.3 (-1.2-5.8)	p = 0.099
	Non-diabetic	1303	9 (0.7%)*	60.8 (44.6-77.0)	62.4 (46.9-78.0)	1.6 (-19.4-22.7)	p = 0.440
BMI range	Normal	358	30 (8.4%)*	57.6 (47.2-68.0)	73.1 (64.7-81.5)	15.5 (6.2-24.9)	p < 0.001
	Overweight	981	84 (8.6%)	59.3 (52.4-66.2)	65.7 (59.7-71.8)	6.4 (-0.5-13.3)	p = 0.034
	Obesity I	916	107 (11.7%)	57.7 (52.3-63.0)	71.7 (66.8-76.7)	14.1 (8.1-20.1)	p < 0.001
	Obesity II+	711	110 (15.5%)	59.5 (54.0-65.0)	63.6 (57.9-69.4)	4.2 (-2.2-10.6)	p = 0.100
IOL history	Yes	460	51 (11.1%)	66.0 (57.5-74.4)	67.0 (59.4-74.7)	1.1 (-7.7-9.9)	p = 0.406
	No	2740	307 (11.2%)	59.3 (56.1-62.6)	67.7 (64.6-70.9)	8.4 (4.8-12.0)	p < 0.001
Race / ethnicity	Black	1733	243 (14.0%)	56.2 (52.4-60.0)	65.9 (62.2-69.6)	9.6 (5.4-13.9)	p < 0.001
	White	1283	100 (7.8%)	64.6 (58.8-70.3)	70.0 (64.9-75.2)	5.4 (0.1-10.8)	p = 0.023

***Note: fewer than 50 positive examples. Please see analysis on HbA1c ≥ 7 in Supplementary Table 12 for a better powered analysis.**

Supplementary Table 14 | Hyperparameters.

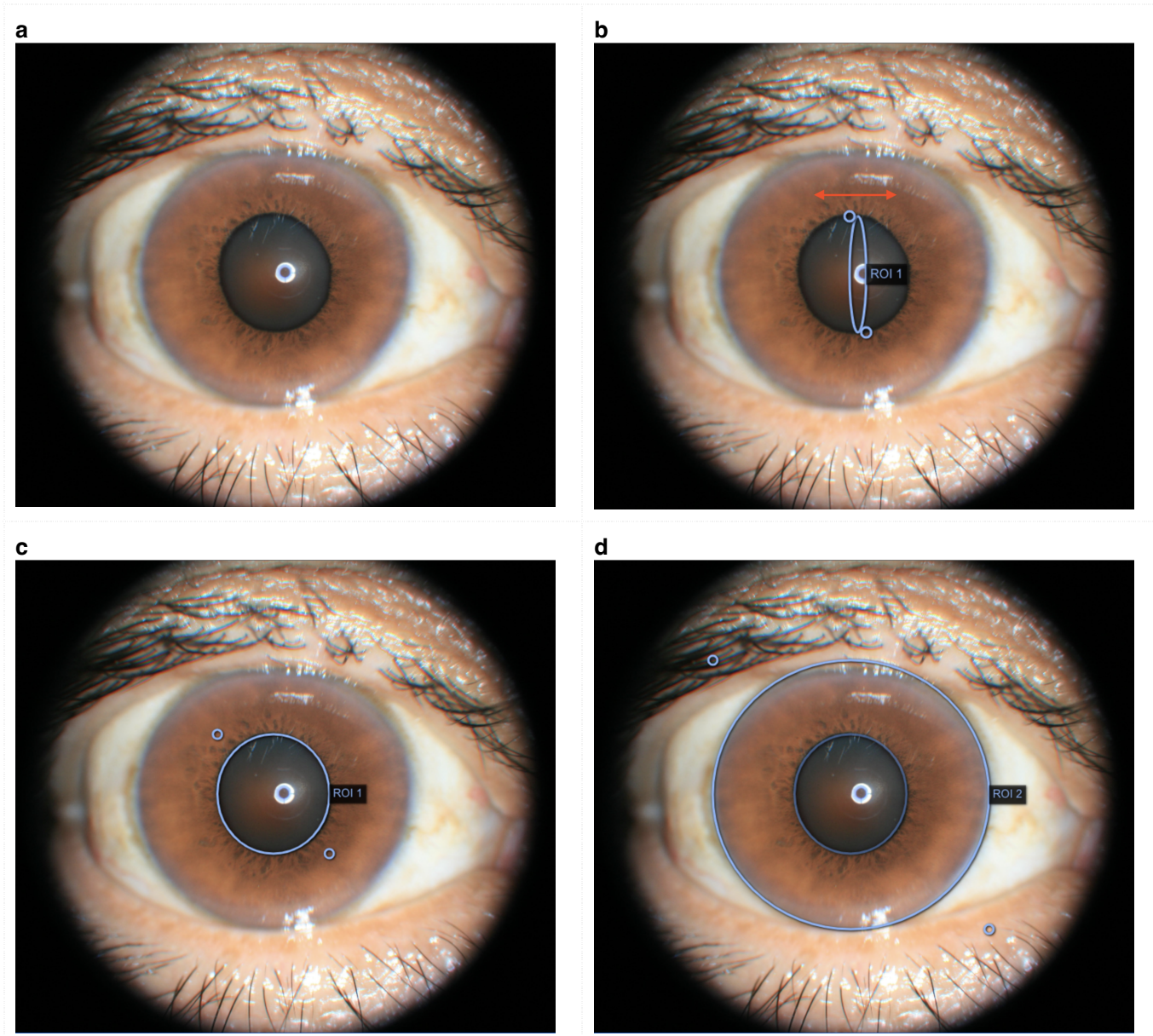
(A) common across models and (B) specific to each selected model.

A

Hyperparameter	DLS (external eye image)	Pupil / iris model
Batch size per TPU core	8	8
Number of TPU cores	8	2
Effective batch size	64	16
Moving average decay rate	0.9999	0.9999
Max training steps	300000	300000
Input image size [pixels]	587 × 587	587 × 587
Random flip	Horizontal and vertical	-
Random brightness max delta	0.1148	0.1148
Random hue max delta	0.0251	0.0251
Random saturation range	0.5597 - 1.2749	0.5597 - 1.2749
Random contrast range	0.9997 - 1.7705	0.9997 - 1.7705
Random scale factors	1.0X (60%), 1.3X (20%), 1.5X (20%)	1.0X (100%)
Dropout rate at final layer	0.2	0.2
Weight decay rate (L2 regularization)	4.0e-05	4.0e-05
Model architecture	Inception V3	Inception V3
Preinitialization	ImageNet	ImageNet

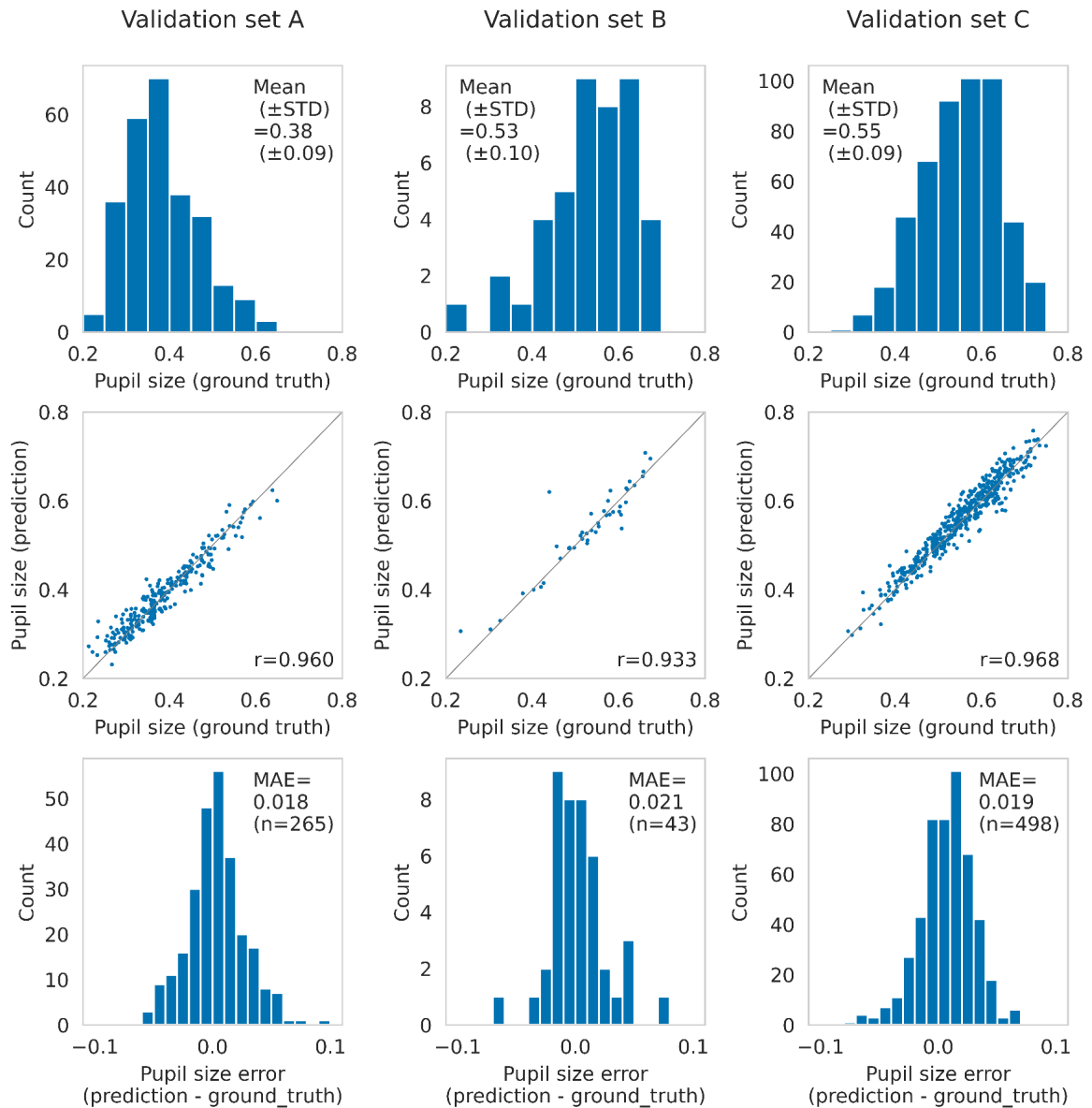
B

Hyperparameter	DLS 1	DLS 2	DLS 3	DLS 4	DLS 5	Pupil / iris model
Optimizer	Momentum	Momentum	Momentum	Momentum	Momentum	Momentum
Initial learning rate	1.39e-02	2.53e-02	2.17e-02	3.58e-03	1.38e-02	4.57e-02
Decay steps	10000	20000	10000	50000	50000	50000
Decay rate	0.662	0.545	0.610	0.956	0.685	0.725
Pre warm-up learning rate	1.39e-03	2.53e-03	2.17e-03	3.58e-04	1.38e-03	1.39e-03
Warm up steps	4000	4000	4000	4000	4000	4000
Training steps (early stopping)	52000	90000	78000	80000	136000	298000



Supplementary Figure 1. Pupil / iris segmentation tool.

The segmentation tool involved drawing ellipses using a custom click and drag interface (A-C), to produce two ellipses: one around the pupil and another around the iris (D).



Supplementary Figure 2. Accuracy of pupil size predictions by pupil/iris segmentation model.

Pupil size is represented as a fraction: the pupil radius divided by the iris radius. (Top row) Distribution of ground truth pupil size in each dataset. Note that validation set A contained non-dilated pupils, whereas pupils in validation sets B and C were dilated. (Middle row) Joint distribution of ground truth and predicted pupil size. Text indicates Pearson’s correlation coefficient (r). (Bottom row) Distribution of errors (difference between predicted and ground truth pupil size). Abbreviations: STD = standard deviation, MAE = mean absolute error.