

## Supplementary Material:

### Validation of a Deep Learning Model for Diabetic Retinopathy on Patients with Young-Onset Diabetes

#### Authors

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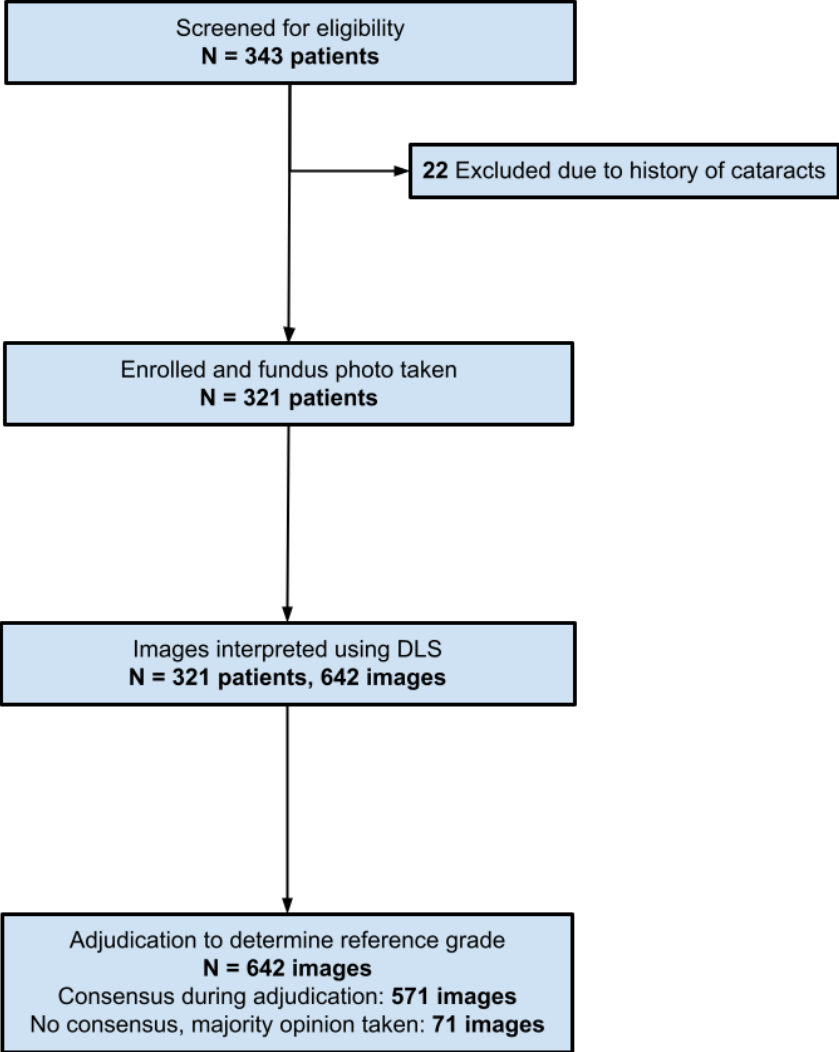
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Supplementary Figure 1: Flowchart of study workflow



**Supplementary Table 1: Confusion matrices (2-by-2 contingency tables) for (A) moderate+ DR and (B) DME status, stratified by sheen presence.** DME sensitivity differs substantially based on sheen presence (70% for sheen-positive vs. 100% for sheen-negative).

**A. Moderate+ DR reference grade and model predictions**

Sheen-positive (age mean 26.0, SD 6.1, 320 in younger cohort, 280 in older cohort)			Sheen-negative (age mean 33.3, SD 4.8, 1 in younger cohort, 33 in older cohort)		
	Ref. grade +	Ref. grade -		Ref. grade +	Ref. grade -
Predicted +	112	20	Predicted +	21	3
Predicted -	7	461	Predicted -	0	10

**B. DME reference grade and model predictions**

Sheen-positive (age mean 26.0, SD 6.1, 320 in younger cohort, 280 in older cohort)			Sheen-negative (age mean 33.4, SD 4.8, 1 in younger cohort, 34 in older cohort)		
	Ref. grade +	Ref. grade -		Ref. grade +	Ref. grade -
Predicted +	31	25	Predicted +	14	6
Predicted -	13	531	Predicted -	0	15

**Supplementary Table 2: Multivariable analyses for model performance for (A) moderate+ DR and (B) DME status, stratified by sheen presence.** Bold indicates p<0.05. The strongest significant association observed was between sheen presence and specificity (for both moderate+ DR and DME). Examples were excluded if they had invalid/missing sheen or hba1c values.

**A. Moderate+ DR**

		Sensitivity			Specificity		
Variable	Bucket	Counts	Log odds (95% CI)	P	Counts	Odds ratio (95% CI)	P
Hba1c (percentage)	4-8	52	Ref.		167	Ref.	
	8-18	81	0.726 (-0.855, 2.31)	0.368	304	-0.497 (-1.502, 0.507)	0.332
Duration of diabetes (years)	0-10	58	Ref.		144	Ref.	
	10-20	57	-0.041 (-1.738, 1.657)	0.963	233	<b>1.023 (0.045, 2.001)</b>	<b>0.040</b>
	20-40	18	0.091(-2.298, 2.479)	0.941	94	0.662 (-0.527, 1.852)	0.275
Age (years)	>25	94	Ref.		199	Ref.	
	18-25	39	1.283 (-0.896, 3.462)	0.249	272	<b>1.246 (0.267, 2.226)</b>	<b>0.013</b>
Sheen presence	No	20	Ref.		13	Ref.	
	Yes	113	-11.530 (-487.19, 464.135)	0.962	458	<b>1.543 (0.039, 3.047)</b>	<b>0.044</b>
Sex	Female	66	Ref.		238	Ref.	
	Male	67	1.027 (-0.689, 2.742)	0.241	233	-0.129 (-1.001, 0.743)	0.772

\* 33 examples were excluded due to invalid/missing hba1c or sheen values

## B. DME

		Sensitivity			Specificity		
Variable	Bucket	Counts	Log odds (95% CI)	P	Counts	Odds ratio (95% CI)	P
Hba1c (percentage)	4-8	25	Ref.		195	Ref.	
	8-18	31	0.756 (-0.690, 2.203)	0.305	354	0.348 (-0.438, 1.134)	0.386
Duration of diabetes (years)	0-10	22	Ref.		181	Ref.	
	10-20	28	0.263 (-1.380, 1.906)	0.754	262	0.233 (-0.694, 1.160)	0.622
	20-40	6	-1.420 (-3.730, 0.889)	0.228	106	-0.699 (-1.65, 0.252)	0.150
Age (years)	>25	38	Ref.		256	Ref.	
	18-25	18	0.782 (-0.674, 2.238)	0.292	293	<b>0.950 (0.080, 1.820)</b>	<b>0.032</b>
Sheen presence	No	13	Ref.		21	Ref.	
	Yes	43	-14.668 (-1045.883, 1016.547)	0.9778	528	<b>1.628 (0.522, 2.734)</b>	<b>0.004</b>
Sex	Female	26	Ref.		278	Ref.	
	Male	30	0.0864 (-1.470, 1.643)	0.913	271	0.454 (-0.341, 1.249)	0.263

\* 31 examples were excluded due to invalid/missing hba1c or sheen values

**Supplementary Table 3: Patient-level model performance**

<b>Endpoint</b>	<b>Metric</b>	<b>Full cohort (ages 18-45), N = 321</b>	<b>Younger cohort (ages 18-25) N = 162</b>	<b>Older cohort (ages 26-45) N = 159</b>	<b>P (younger vs. older cohort)</b>
Moderate-or-worse DR	Sensitivity	94.4% [87.5, 97.6]	100.0% [87.5, 100.0]	92.0% [82.5, 96.5]	0.073
	Specificity	95.2% [91.6, 97.3]	97.7% [93.6, 99.2]	91.7% [84.4, 95.7]	0.033
DME	Sensitivity	76.7% [62.3, 86.9]	78.6% [52.4, 92.4]	75.9% [57.9, 87.8]	0.851
	Specificity	94.1% [90.7, 96.4]	97.9% [94.1, 99.3]	89.8% [83.4, 94.0]	0.003
VTDR*	Clinically Important Miss Rate	7.41% [5.1, 21.8]	4.0% [0.1, 25.8]	8.9% [5.9, 28.0]	0.420
mtmDR*	Sensitivity	94.4% [87.5, 97.6]	100.0% [87.5, 100.0]	91.9% [82.5, 96.5]	0.066
	Specificity	94.8% [91.6, 97.3]	97.7% [93.6, 99.2]	90.6% [84.3, 95.7]	0.016

\*VTDR is severe NPDR, proliferative DR (PDR), or DME

\*mtmDR is moderate or severe NPDR or proliferative DR, or DME

**Supplementary Table 4: Confusion matrices (2-by-2 contingency tables) for (A) moderate+ DR vs sheen presence and (B) DME status vs sheen presence**

**A. DR Moderate+**

DR Moderate+	Sheen present	Sheen absent
Positive	119; 20%	21; 62%
Negative	481; 80%	13; 38%

A 2-tailed Fisher's exact test yields  $p < 0.0001$ .

**B. DME**

DME	Sheen present	Sheen absent
Present	44; 7%	14; 40%
Absent	556; 93%	21; 60%

A 2-tailed Fisher's exact test yields  $p < 0.0001$ .

**Supplementary Table 5.** Definitions of DR levels and DME.

<b>Lesions</b>	<b>Grades</b>
No lesions	No DR
Microaneurysms only	Mild
Hemorrhages*	Moderate
Hard exudates*	
Cotton wool spots*	
Focal laser scars	
Greater density/count of hemorrhages	Severe
Definite venous beading	
Prominent IRMAs	
Neovascularization at disc or elsewhere	Proliferative DR
Fibrovascular proliferation	
Preretinal hemorrhage	
Vitreous hemorrhage	
Tractional retinal detachment	
Panretinal photocoagulation scars	
Hard exudates* within 1 disc diameter	DME

\* Requires the presence of MA