nature medicine

Supplementary information

https://doi.org/10.1038/s41591-026-04359-w

AI framework for multidisease detection via retinal imaging

In the format provided by the authors and unedited

Supplementary Information

Supplementary Table 1. Ablation analysis of the Reti-Pioneer framework integrating quality-aware image assessment and clinical metadata.

Diseases	Models	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Brier scores	P value
T2DM	Metadata Only	0.811 (0.788-0.834)	0.802 (0.760-0.840)	0.682 (0.668-0.698)	0.182 (0.160-0.198)	0.975 (0.969-0.981)	0.067	**<0.001**
	Image Only	0.742 (0.711-0.772)	0.802 (0.765-0.835)	0.455 (0.435-0.469)	0.115 (0.105-0.126)	0.963 (0.953-0.970)	0.065	**<0.001**
	Good-quality Image Only	0.827 (0.804-0.849)	0.805 (0.764-0.846)	0.701 (0.688-0.712)	0.192 (0.174-0.209)	0.976 (0.970-0.981)	0.067	**0.011**
	Without Quality-aware Module	0.826 (0.803-0.848)	0.802 (0.764-0.842)	0.703 (0.686-0.719)	0.192 (0.173-0.211)	0.976 (0.971-0.981)	0.061	**0.021**
	Reti-Pioneer	0.833 (0.810-0.856)	0.802 (0.760-0.839)	0.706 (0.692-0.720)	0.194 (0.176-0.210)	0.976 (0.970-0.981)	0.066	1 [ref]
Hypertension	Metadata Only	0.723 (0.707-0.738)	0.800 (0.784-0.811)	0.524 (0.506-0.542)	0.621 (0.604-0.640)	0.729 (0.707-0.750)	0.213	**<0.001**
	Image Only	0.667 (0.651-0.684)	0.801 (0.786-0.819)	0.417 (0.398-0.438)	0.572 (0.555-0.591)	0.683 (0.653-0.706)	0.229	**<0.001**
	Good-quality Image Only	0.723 (0.708-0.739)	0.800 (0.783-0.814)	0.504 (0.484-0.520)	0.611 (0.591-0.625)	0.721 (0.701-0.746)	0.219	**<0.001**
	Without Quality-aware Module	0.739 (0.724-0.754)	0.801 (0.784-0.819)	0.546 (0.528-0.570)	0.632 (0.617-0.653)	0.737 (0.717-0.759)	0.207	0.085
	Reti-Pioneer	0.740 (0.726-0.755)	0.800 (0.783-0.819)	0.550 (0.531-0.573)	0.634 (0.616-0.649)	0.739 (0.720-0.764)	0.207	1 [ref]
Hyperlipidemia	Metadata Only	0.732 (0.716-0.747)	0.800 (0.782-0.820)	0.554 (0.534-0.573)	0.541 (0.522-0.559)	0.808 (0.791-0.826)	0.204	**0.027**
	Image Only	0.698 (0.682-0.714)	0.800 (0.784-0.817)	0.487 (0.465-0.508)	0.507 (0.487-0.523)	0.787 (0.769-0.809)	0.213	**<0.001**
	Good-quality Image Only	0.734 (0.719-0.749)	0.800 (0.781-0.818)	0.560 (0.543-0.577)	0.546 (0.529-0.567)	0.810 (0.795-0.829)	0.202	**0.037**
	Without Quality-aware Module	0.735 (0.720-0.750)	0.801 (0.782-0.824)	0.554 (0.536-0.573)	0.542 (0.523-0.561)	0.809 (0.787-0.829)	0.203	0.69
	Reti-Pioneer	0.736 (0.721-0.751)	0.800 (0.781-0.819)	0.564 (0.544-0.584)	0.546 (0.527-0.560)	0.810 (0.790-0.829)	0.201	1 [ref]
Gout	Metadata Only	0.769 (0.730-0.808)	0.810 (0.724-0.875)	0.633 (0.621-0.645)	0.043 (0.035-0.054)	0.994 (0.991-0.997)	0.024	**<0.001**
	Image Only	0.663 (0.599-0.727)	0.810 (0.716-0.892)	0.408 (0.394-0.424)	0.027 (0.022-0.033)	0.991 (0.986-0.995)	0.020	**<0.001**
	Good-quality Image Only	0.827 (0.792-0.861)	0.810 (0.740-0.887)	0.689 (0.676-0.703)	0.051 (0.039-0.062)	0.994 (0.991-0.997)	0.020	0.34

	Without Quality-aware Module	0.827 (0.793-0.861)	0.810 (0.738-0.871)	0.693 (0.678-0.704)	0.051 (0.040-0.063)	0.994 (0.992-0.998)	0.019	0.45
	Reti-Pioneer	0.832 (0.799-0.866)	0.810 (0.735-0.882)	0.697 (0.682-0.713)	0.052 (0.041-0.062)	0.994 (0.992-0.997)	0.019	1 [ref]
Osteoporosis	Metadata Only	0.725 (0.678-0.771)	0.800 (0.717-0.884)	0.542 (0.528-0.559)	0.037 (0.029-0.047)	0.992 (0.989-0.995)	0.026	**<0.001**
	Image Only	0.620 (0.560-0.679)	0.800 (0.719-0.863)	0.292 (0.279-0.305)	0.024 (0.019-0.029)	0.985 (0.979-0.992)	0.021	**<0.001**
	Good-quality Image Only	0.781 (0.736-0.825)	0.800 (0.735-0.880)	0.643 (0.627-0.660)	0.047 (0.036-0.056)	0.993 (0.990-0.996)	0.021	0.26
	Without Quality-aware Module	0.779 (0.735-0.823)	0.800 (0.716-0.872)	0.626 (0.614-0.639)	0.045 (0.038-0.056)	0.993 (0.990-0.996)	0.020	0.33
	Reti-Pioneer	0.787 (0.742-0.833)	0.800 (0.706-0.870)	0.647 (0.633-0.660)	0.047 (0.038-0.057)	0.993 (0.989-0.996)	0.021	1 [ref]
Thyroid diseases	Metadata Only	0.678 (0.646-0.710)	0.803 (0.759-0.843)	0.425 (0.412-0.441)	0.083 (0.072-0.093)	0.971 (0.963-0.978)	0.060	**0.05**
	Image Only	0.575 (0.539-0.611)	0.803 (0.757-0.852)	0.291 (0.275-0.307)	0.068 (0.059-0.079)	0.958 (0.947-0.970)	0.057	**<0.001**
	Good-quality Image Only	0.692 (0.660-0.724)	0.803 (0.750-0.850)	0.454 (0.438-0.469)	0.087 (0.078-0.101)	0.973 (0.966-0.980)	0.058	0.49
	Without Quality-aware Module	0.695 (0.663-0.726)	0.803 (0.757-0.847)	0.439 (0.427-0.455)	0.085 (0.074-0.096)	0.972 (0.965-0.978)	0.057	0.62
	Reti-Pioneer	0.699 (0.667-0.730)	0.803 (0.753-0.849)	0.490 (0.476-0.504)	0.093 (0.083-0.103)	0.975 (0.967-0.982)	0.056	1 [ref]

Performance comparisons against the full Reti-Pioneer framework (reference model). Metadata Only: Model utilizing structured clinical characteristics (age, sex, ethnicity, weight) without retinal images. Image Only: Reti-Pioneer framework trained and evaluated using bilateral retinal images without clinical metadata integration. Good-quality Image Only: Framework trained and evaluated exclusively on bilateral retinal images passing quality control, while low-quality images were excluded. Without Quality-Aware Module: Framework trained on all available bilateral retinal images without integration of the quality-assessment module. P values are derived from DeLong's test for AUROC comparisons. Bold indicates statistical significance ($P<0.05$). AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; T2DM, type 2 diabetes mellitus.

Supplementary Table 2. Sex-stratified performance of Reti-Pioneer in the internal test dataset.

Disease	Gender	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
T2DM	Female	0.839 (0.805-0.872)	0.801 (0.726-0.860)	0.739 (0.720-0.757)	0.187 (0.164-0.220)	0.980 (0.974-0.986)
	Male	0.816 (0.781-0.852)	0.801 (0.748-0.864)	0.649 (0.629-0.677)	0.180 (0.148-0.201)	0.972 (0.963-0.981)
Hypertension	Female	0.750 (0.730-0.770)	0.800 (0.784-0.833)	0.579 (0.552-0.603)	0.619 (0.595-0.636)	0.773 (0.748-0.800)
	Male	0.724 (0.701-0.748)	0.800 (0.780-0.820)	0.503 (0.465-0.536)	0.653 (0.629-0.676)	0.683 (0.651-0.709)
Hyperlipidemia	Female	0.742 (0.722-0.762)	0.801 (0.773-0.825)	0.576 (0.558-0.603)	0.560 (0.531-0.590)	0.811 (0.786-0.834)
	Male	0.716 (0.692-0.739)	0.804 (0.774-0.836)	0.518 (0.483-0.545)	0.529 (0.502-0.559)	0.797 (0.767-0.834)
Gout	Female	0.904 (0.827-0.982)	0.800 (0.585-1.000)	0.934 (0.922-0.944)	0.073 (0.041-0.112)	0.999 (0.997-1.000)
	Male	0.699 (0.634-0.765)	0.803 (0.683-0.879)	0.428 (0.407-0.449)	0.051 (0.037-0.063)	0.983 (0.973-0.991)
Osteoporosis	Female	0.753 (0.702-0.804)	0.808 (0.713-0.886)	0.549 (0.531-0.568)	0.055 (0.043-0.069)	0.989 (0.984-0.994)
	Male	0.713 (0.559-0.866)	0.800 (0.522-1.000)	0.403 (0.377-0.422)	0.011 (0.006-0.017)	0.996 (0.990-1.000)
Thyroid diseases	Female	0.624 (0.582-0.665)	0.803 (0.743-0.859)	0.339 (0.320-0.360)	0.102 (0.089-0.118)	0.949 (0.933-0.962)
	Male	0.685 (0.603-0.767)	0.808 (0.713-0.903)	0.369 (0.346-0.395)	0.037 (0.028-0.047)	0.985 (0.973-0.994)

AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; T2DM, type 2 diabetes mellitus.

Supplementary Table 3. Longitudinal risk stratification for endocrine and metabolic diseases using Reti-Pioneer.

Disease	Time intervals	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Brier scores
T2DM	5-year	0.752 (0.698-0.805)	0.891 (0.814-0.970)	0.478 (0.470-0.487)	0.009 (0.007-0.011)	0.999 (0.998-0.999)	0.006
	10-year	0.734 (0.691-0.777)	0.793 (0.719-0.865)	0.545 (0.537-0.553)	0.018 (0.015-0.022)	0.996 (0.995-0.997)	0.012
Hypertension	5-year	0.750 (0.694-0.805)	0.793 (0.719-0.871)	0.606 (0.590-0.617)	0.028 (0.022-0.035)	0.995 (0.993-0.997)	0.049
	10-year	0.717 (0.673-0.760)	0.705 (0.626-0.764)	0.638 (0.625-0.652)	0.049 (0.040-0.059)	0.988 (0.984-0.990)	0.024
Hyperlipidemia	5-year	0.745 (0.688-0.801)	0.726 (0.631-0.797)	0.655 (0.644-0.664)	0.023 (0.017-0.029)	0.995 (0.993-0.997)	0.011
	10-year	0.732 (0.690-0.775)	0.680 (0.597-0.744)	0.669 (0.658-0.682)	0.039 (0.032-0.046)	0.991 (0.988-0.993)	0.019
Gout	5-year	0.733 (0.636-0.830)	0.682 (0.500-0.878)	0.693 (0.684-0.701)	0.004 (0.002-0.006)	0.999 (0.999-1.000)	0.002
	10-year	0.753 (0.682-0.823)	0.705 (0.540-0.821)	0.704 (0.695-0.714)	0.009 (0.006-0.011)	0.998 (0.998-0.999)	0.004
Osteoporosis	5-year	0.796 (0.740-0.853)	0.765 (0.642-0.906)	0.759 (0.752-0.767)	0.013 (0.010-0.017)	0.999 (0.998-0.999)	0.004
	10-year	0.813 (0.772-0.854)	0.879 (0.819-0.924)	0.690 (0.681-0.698)	0.023 (0.018-0.027)	0.999 (0.998-0.999)	0.008
Thyroid diseases	5-year	0.665 (0.606-0.723)	0.658 (0.533-0.757)	0.623 (0.615-0.633)	0.012 (0.010-0.015)	0.996 (0.994-0.997)	0.007
	10-year	0.666 (0.620-0.712)	0.710 (0.628-0.778)	0.565 (0.555-0.574)	0.018 (0.015-0.021)	0.994 (0.992-0.996)	0.011

Performance metrics are shown for 5-year and 10-year prediction windows, based on a sensitivity analysis that excluded individuals diagnosed within the first year of follow-up. Performance metrics are reported as area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), with 95% confidence intervals (CIs) and brier scores. T2DM, type 2 diabetes mellitus.

Supplementary Table 4. Association between retinal latent features derived from OPLS-DA and endocrine-metabolic diseases.

Diseases	Model 1*		Model 2**	
	OR (95% CI)	*P*	OR (95% CI)	*P*
T2DM	1.08 (1.03-1.13)	**< 0.001**	0.85 (0.79-0.91)	**< 0.001**
Hypertension	0.94 (0.94-0.95)	**< 0.001**	1.15 (1.11-1.19)	**< 0.001**
Hyperlipemia	1.07 (1.05-1.08)	**< 0.001**	0.96 (0.94-0.98)	**< 0.001**
Gout	1.19 (1.14-1.25)	**< 0.001**	0.76 (0.67-0.87)	**< 0.001**
Osteoporosis	0.77 (0.72-0.82)	**< 0.001**	0.96 (0.85-1.08)	0.494
Thyroid Diseases	0.93 (0.92-0.95)	**< 0.001**	1.10 (1.05-1.14)	**< 0.001**

Retinal latent features were derived via orthogonal projections to latent structures-discriminant analysis (OPLS-DA). Logistic regression was used to assess associations. Model 1: unadjusted. Model 2: adjusted for baseline age and sex. OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus. Bold indicates P<0.05.

Supplementary Table 5. Associations between retinal latent features and top-ranked plasma proteins or polygenic risk scores.

Diseases	Protein/PRS	Number of cases	Number of controls	Model1		Model2	
				OR (95%CI)	*FDR-adjusted P value*	OR (95%CI)	*FDR-adjusted P value*
T2DM	NFASC	360	5,850	0.72 (0.57-0.92)	**0.007**	0.69 (0.53-0.90)	0.180
	SCARA5	360	5,850	0.77 (0.61-0.96)	**0.022**	0.75 (0.58-0.98)	**0.050**
	FN1	360	5,850	1.16 (0.87-1.55)	0.321	-	-
	PLA2G7	360	5,850	1.30 (1.06-1.59)	**0.013**	0.90 (0.71-1.14)	0.373
	CDH1	360	5,850	1.03 (0.86-1.25)	0.725	-	-
	PRS for HbA1c	360	5,850	0.98 (0.91-1.06)	0.574	-	-
	PRS for T2D	360	5,850	1.04 (0.95-1.13)	0.405	-	-
Hypertension	PTPRB	3,303	2,907	1.15 (0.88-1.50)	0.312	-	-
	SUSD5	3,303	2,907	1.09 (0.88-1.36)	0.440	-	-
	PODXL2	3,303	2,907	0.74 (0.57-0.96)	**0.026**	0.86 (0.66-1.12)	0..298
	ADGRG2	3,303	2,907	0.57 (0.45-0.72)	**<0.001**	0.87 (0.66-1.14)	0..298
	ADM	3,303	2,907	1.22 (0.98-1.52)	0.069	-	-
	PRS for hypertension	3,303	2,907	1.05 (0.96-1.14)	0.262	-	-
Hyperlipemia	PCSK9	2,817	3,393	0.75 (0.66-0.85)	**<0.001**	1.16 (0.97-1.40)	0.139
	PLA2G7	2,817	3,393	2.37 (1.99-2.81)	**<0.001**	2.33 (1.83-2.97)	**0.002**
	NRP1	2,817	3,393	0.78 (0.64-0.95)	**0.013**	1.12 (0.85-1.47)	0.433
	PTPRF	2,817	3,393	1.21 (1.01-1.44)	**0.040**	1.90 (1.46-2.47)	**0.002**
	APOM	2,817	3,393	0.77 (0.63-0.93)	**0.006**	1.61 (1.23-2.11)	**0.002**
	PRS for HDLC	2,817	3,393	0.98 (0.92-1.04)	0.491	-	-
	PRS for LDLC	2,817	3,393	0.93 (0.88-0.99)	**0.019**	0.94 (0.85-1.03)	0.190
Gout	UBQLN3	87	6,123	1.17 (0.96-1.42)	0.115	-	-
	ICOSLG	87	6,123	0.48 (0.33-0.70)	**<0.001**	0.53 (0.36-0.77)	**0.001**
	MENT	87	6,123	1.02 (0.72-1.45)	0.898	-	-
	FGFBP1	87	6,123	0.54 (0.43-0.68)	**<0.001**	0.59 (0.47-0.74)	**<0.001**
	GGT1	87	6,123	0.96 (0.84-1.09)	0.513	-	-
Osteoporosis	COLLA1	114	6,096	0.35 (0.29-0.43)	**<0.001**	0.38 (0.30-0.47)	**0.001**
	ELN	114	6,096	0.11 (0.10-0.13)	**<0.001**	0.15 (0.12-0.18)	**0.001**

	CHAD	114	6,096	0.41 (0.37-0.46)	**<0.001**	0.50 (0.44-0.57)	**0.001**
	F3	114	6,096	0.38 (0.32-0.45)	**<0.001**	0.85 (0.70-1.03)	0.105
	SPON1	114	6,096	0.33 (0.29-0.38)	**<0.001**	0.51 (0.43-0.61)	**0.001**
	PRS for EBMDT	114	6,096	1.03 (0.98-1.09)	0.241	-	-
	PRS for osteoporosis	114	6,096	0.99 (0.94-1.05)	0.819	-	-
	PDCD1	423	5,787	1.29 (0.82-2.03)	0.266	-	-
	SIL1	423	5,787	0.75 (0.33-1.75)	0.511	-	-
Thyroid diseases	TSHB	423	5,787	0.81 (0.63-1.04)	0.106	-	-
	TNFSF13B	423	5,787	1.29 (0.66-2.53)	0.454	-	-
	XG	423	5,787	3.05 (2.08-4.47)	**<0.001**	1.74 (1.02-2.97)	**0.040**

Proteins were selected via elastic net regression. Polygenic risk scores (PRS) were obtained from the UK Biobank. Logistic regression models were fitted with retinal latent features (OPLS-DA predictive components) as the outcome variable, dichotomized based on the optimal cutoff value of the predicted component derived from retinal features. Model 1: unadjusted. Model 2: adjusted for age, sex, ethnicity, weight, image quality, and assessment center. For associations between retinal latent features and polygenic risk scores, Model 2 was additionally adjusted for the top four ancestry principal components. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Bold font indicates statistical significance after false discovery rate (FDR) correction (FDR-adjusted P<0.05). OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; EBMDT, estimated bone mineral density. Bold indicates *P*<0.05.

Supplementary Table 6. Diagnostic performance of retinal specialists with and without Reti-Pioneer assistance.

Retina specialists	Years of experience	Methods	Correct guesses for T2DM	Correct guesses for hypertension	Correct guesses for hyperlipemia	Correct guesses for gout	Correct guesses for osteoporosis	Correct guesses for thyroid diseases
1	3	Without Reti-Pioneer	130(65.0%)	102 (51.0%)	99 (50.0%)	94 (47.0%)	110 (55.0%)	112 (56.0%)
		With Reti-Pioneer	170(85.0%)	116 (58.0%)	108 (54.0%)	143 (72.0%)	116 (58.0%)	121 (61.0%)
2	5	Without Reti-Pioneer	141(71.0%)	106 (53.0%)	101 (51.0%)	100 (50.0%)	114 (57.0%)	124 (62.0%)
		With Reti-Pioneer	176 (88.0%)	115 (58.0%)	108 (54.0%)	154 (77.0%)	118 (59.0%)	128 (64.0%)
3	10	Without Reti-Pioneer	154(77.0%)	106 (53.0%)	108 (54.0%)	109 (55.0%)	149 (75.0%)	140 (70.0%)
		With Reti-Pioneer	182(91.0%)	118 (59.0%)	112 (56.0%)	170 (85.0%)	164 (82.0%)	168 (84.0%)
Retina specialists' average		Without Reti-Pioneer	425 (71.0%)	314 (52.0%)	308 (51.0%)	303 (51.0%)	373 (62.0%)	376 (63.0%)
		With Reti-Pioneer	528 (88.0%)	349 (58.0%)	328 (55.0%)	467 (79.0%)	398 (66.0%)	417 (70.0%)

Three retinal specialists independently interpreted 200 bilateral fundus images per disease from an internal held-out test set. Correct guesses indicate the number of images correctly classified. Percentages are calculated as correct guesses/total images. T2DM, type 2 diabetes mellitus.

Supplementary Table 7. Characteristics of participants recruited for the silent trial and prospective pilot study from the primary care centre.

Characteristics	Silent Trial	Prospective pilot study
Total n participants	1,017	606
Age, mean (SD), years	54.4 (11.2)	52.7 (11.1)
Female sex (%)	664 (65.3%)	389 (64.2%)
Weight, mean (SD), kg	64.7 (34.7)	63.1 (11.8)
BMI, mean (SD), kg/m²	23.8 (3.9)	23.6 (3.2)
Waist circumference, mean (SD), cm	84.3 (10.6)	82.3 (10.3)
Regular exercise (%)*	584 (65.9%)	327 (63.9%)
Daily fruit and vegetable intake (%)*	803 (90.7%)	462 (90.4%)
High T2DM risk (%)*	143 (92.4%)	63 (92.6%)
Diagnosis of T2DM (%)	138 (13.6%)	53 (8.7%)
Diagnosis of hypertension (%)	245 (24.1%)	113 (18.6%)
Diagnosis of hyperlipidemia (%)	402 (39.5%)	250 (41.2%)
Diagnosis of gout (%)	158 (15.5%)	99 (16.3%)
Diagnosis of osteoporosis (%)	320 (31.5%)	160 (26.4%)
Diagnosis of thyroid disease (%)	252 (24.7%)	162 (26.7%)

*Based on the Finnish Diabetes Risk Score (FINDRISC) for T2DM risk assessment. Data are presented as mean ± SD or number (%). BMI, body mass index. T2DM, type 2 diabetes mellitus; SD, standard deviation; n, number.

Supplementary Table 8. Summary of variables from the UK Biobank dataset used in this study.

Measure	Field ID	Description
Prior type 2 diabetes mellitus	2443	Doctor diagnosed with diabetes previously.
	20002 (code 1220,1221,1222,1223, 1276,1468,1607)	Self-reported type 2 diabetesmellitus.
	6153 (code 3)	Use of insulin.
	20003	The use of diabetes-related medication.
	30750	HbA1c of at least 48 mmol/mol.
	41270 (code E10-E14,G590,G632, H280,H360,M142,N0 83,O24,T383,Y423)	Hospital in-patient records with T2DM as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Prior thyroid disorders	20002 (code 1610,1611,1224,1225, 1226,1228,1428,1522)	Self-reported thyroid disorders.
	41270 (code E01-E07)	Hospital in-patient records with thyroid disorders as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Prior hypertension	20002 (code 1065, 1072)	Self-reported hypertension.
	41270 (code I10-I15)	Hospital in-patient records with hypertension as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Prior osteoporosis	20002 (code 1309)	Self-reported osteoporosis.
	41270 (code M80-M82)	Hospital in-patient records with osteoporosis as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Prior gout	20002 (code 1466)	Self-reported gout.
	41270 (code M10,E790)	Hospital in-patient records with gout as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Prior hyperlipidemia	20002 (code 1473)	Self-reported hyperlipidemia.
	41270 (code E78)	Hospital in-patient records with hyperlipidemia as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident type 2 diabetes	41270 (code E10-E14,G590,G632, H280,H360,M142,N0 83,O24,T383,Y423)	Hospital in-patient records with type 2 diabetes as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).

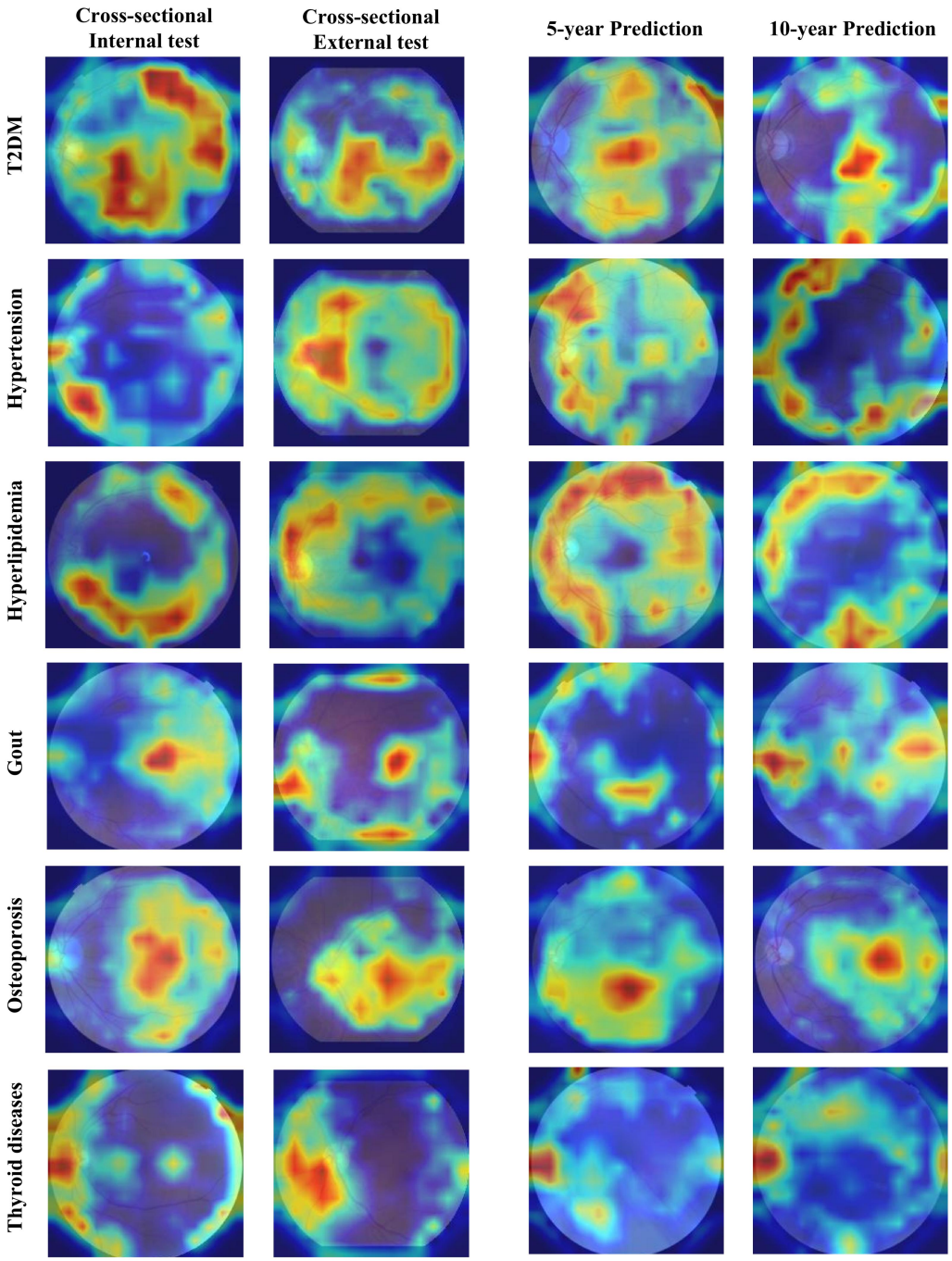
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident thyroid disorders	41270 (code E01-E07)	Hospital in-patient records with thyroid disorders as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident hypertension	41270 (code I10-I15)	Hospital in-patient records with hypertension as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident osteoporosis	41270 (code M80-M82)	Hospital in-patient records with osteoporosis as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident gout	41270 (code M10,E790)	Hospital in-patient records with gout as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.
Incident hyperlipidemia	41270 (code E78)	Hospital in-patient records with hyperlipidemia as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10).
	41280	The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.

Supplementary Table 9. Participant acceptance questionnaire.

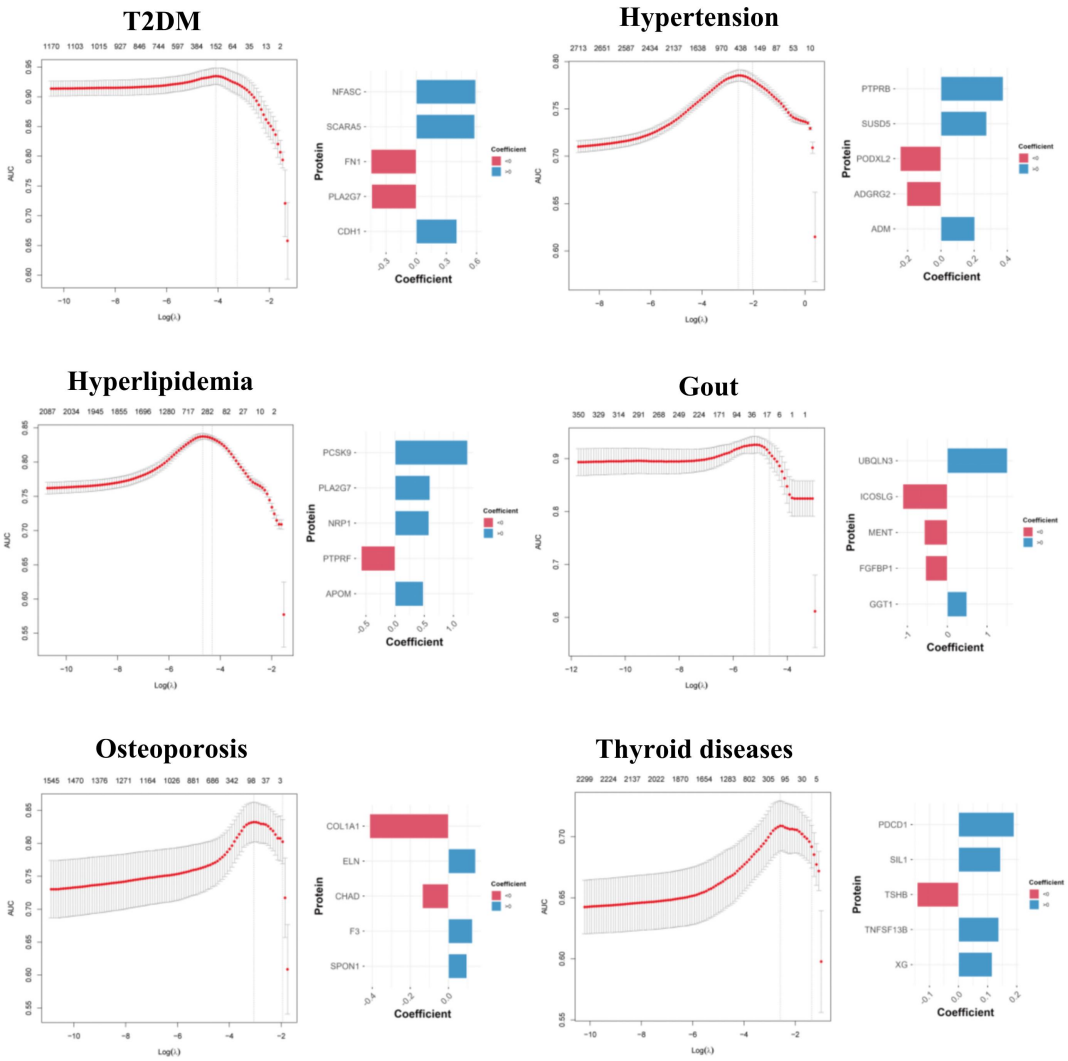
Instructions: Please indicate your level of agreement with the following statements based on your experience with the automated fundus photography and AI risk assessment system. **5-point Likert Scale:** 1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree
1. Perceived Ease of Use: I found the automated fundus photography and AI risk assessment system easy to operate. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
2. Report Understandability: The content of the AI-generated risk report was clear and easy to understand. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
3. Clarity of Management Plan: The health management recommendations in the report (e.g., follow-up timing) were clear and specific. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
4. Overall Satisfaction: Overall, I am satisfied with this AI-enabled fundus screening experience. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
5. Intention to Reuse: I would be willing to use this service again in the future if needed. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
6. Willingness to Recommend: I would recommend this screening to my friends or family. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
7. Perceived Value of Comprehensive Screening: Compared with screening for only one disease at a time, I find this one-time multi-disease risk assessment approach to be more efficient. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
8. Perceived Information Load: Receiving multiple disease risk results at once provided a manageable amount of information that I could understand and accept. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
9. Perceived Convenience: I believe this method of assessing systemic disease risk solely through fundus photography is more convenient than traditional methods like blood tests. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
10. Willingness to Pay: If this service required out-of-pocket payment, I would be willing to pay a reasonable fee for it. [Single Choice] ○ Yes (Please indicate an acceptable price range): _____ ○ No ○ It depends on the price
11. Primary Concerns: What was your biggest concern or worry regarding this screening experience? ____[Free Text]_____

Supplementary Table 10. Clinical physician acceptance questionnaire.

Instructions: Please indicate your level of agreement with the following statements by selecting the most appropriate option for each item, based on your experience with the Reti-Pioneer AI Multi-disease Screening System. **5-point Likert Scale:** 1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree
1. Overall Satisfaction: Overall, I am satisfied with the Reti-Pioneer AI Multi-disease Screening System. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
2. Intention to Integrate: I am willing to integrate this system into my future routine clinical practice. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
3. Willingness to Screen: The introduction of this system has increased my motivation to conduct multi-disease risk screening for patients. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
4. Workflow Impact: The system is highly compatible with my existing outpatient workflow and does not cause significant disruption. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
5. Decision Support: The AI-generated risk reports provide valuable reference for my patient communication and management plan development. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
6. Trust in Accuracy: I trust that the AI's predictions for the six disease risks have clinical reference value. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
7. Scenario Applicability: I believe this screening model is particularly suitable for promotion in primary care or community hospitals with relatively limited medical resources. [Single Choice] Strongly Disagree ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Strongly Agree
8. Perceived Barriers: In your opinion, what are the main potential obstacles to the clinical promotion of this system? [Multiple Choice] □ Equipment acquisition and maintenance costs □ Time and training requirements for operating personnel (nurses/technicians) □ Patient acceptance and trust in AI results □ My concerns regarding the accuracy of AI predictions □ Difficulty in integration with existing Hospital Information Systems (HIS) □ Regulatory and liability attribution issues □ Other (Please specify): _____
9. Model Preference: Please rank the following disease risk assessment models according to your preference (1 = Most Preferred, 2 = Second, 3 = Least Preferred). [Ranking Question - Please arrange the numbers 1, 2, 3 in the boxes below] [ ] Traditional model based on laboratory tests (blood tests) [ ] AI-based retinal image model (Reti-Pioneer) [ ] Traditional non-laboratory model (e.g., relying on BMI)



Supplementary Fig. 1 Saliency maps for individuals with endocrine-metabolic disorders. Gradient-based visual explanations (Integrated Gradients) for representative cases across six diseases in cross-sectional (internal and external test) and longitudinal (5-year and 10-year prediction) settings. T2DM, type 2 diabetes mellitus.



Supplementary Fig. 2 Identification and prioritization of disease-specific plasma protein signatures for endocrine-metabolic disorders. Elastic Net regression was used to select the top five protein biomarkers for each endocrine and metabolic disease from 2,920 plasma proteomic profiles. Proteins are ranked by permutation importance. Bar colors indicate the direction of association (red: negative; blue: positive). T2DM, type 2 diabetes mellitus.