

Supplement to: “Automated detection of glaucoma with interpretable machine learning using clinical data and multi-modal retinal images”

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Supplementary Information

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Supplementary Results and Methods

Reliability of self report

We ascertained the reliability of glaucoma labels. The labels that we used to determine whether a study participant did or did not have glaucoma were based on self-report. While previous studies have relied on self-report as labels[1], the reliability of these labels in the current cohort still needs to be ascertained. In particular, there is a concern of a high prevalence of false negatives as many cases of glaucoma go undetected [4, 5, 3, 2, 6]: there is a concern that there are many individuals who are labeled as healthy, while they already have glaucoma. In addition, there may be a concern of false positives: people who self-report that they have glaucoma but have other eye diseases. We relied on several different assessments: First, we looked at Test-retest reliability of self-reported labels. The total cohort had 96,020 participants. Of these, 12,397 (12.9%) had more than one visit (up to 3). Of these, only 49 (0.3%) had inconsistent self-reports of glaucoma across visits. That is, they reported glaucoma on one visit and reported that they did not have glaucoma on a subsequent visit. This means that 99.7% of individuals with repeated visits are consistent in their self-report of glaucoma, suggesting high test-retest reliability. Second, a subset of individuals in the UK Biobank dataset who were admitted as inpatients have clinical ICD-10 codes associated with them. These codes indicate a much higher level of confidence in a given label as they tell us that this individual was seen by a health-care provider and that the provider made a diagnostic decision to attach this diagnosis code to this individual. In the data we used for this study, only 38.46% of the subjects (45% of eyes) had an associated ICD-10 code. However, there are only 88 (11.61%) subjects (150 eyes) that have an ICD-10 code of glaucoma. All of these 88 subjects self-reported having glaucoma and none of the control (self-reported normal) had an ICD-10 code of glaucoma. This suggests a low prevalence of false negatives. Third, in addition to the self-report of glaucoma, participants could self-report on their use of medication. In our dataset, 296 (18.3%) subjects (515 (21%) eyes) reported that they take medication that is prescribed for glaucoma. Only one of these did not also self-report glaucoma. This is the one case we found using these three methods in which we might consider that we have in fact found a false negative (0.11%). In addition, in our dataset 8 subjects (1.05%) / 15 eyes (1.17%) are self-reported to have glaucoma and also take other eye medication (not used for glaucoma). This is an indication of a low false positive rate.

Statistical analysis of group differences

Statistical analysis of differences between glaucoma, healthy, PTG and PTG post-diagnosis demonstrates that pulmonary capacity variables differ between the groups. This is true even when controlling for age: an ANCOVA of FVC values for the three groups, using age as a covariate found a statistically significant effect of group identity (Supplementary Table 1). To further confirm this, we followed this ANCOVA with a pairwise Dunn's test (Supplementary Table 2 and Supplementary Table 3). We found that FVC in PTG significantly differed from FVC in patients with glaucoma (Supplementary Table 2). Likewise, FVC in normal vs. patients with glaucoma differed significantly (Supplementary Table 2), but we did not find a difference between normal and PTG (Supplementary Table 2). Values for PEF were similar: the ANCOVA using age as a covariate showed a statistically significant effect of group (Supplementary Table 1); Dunn's tests showed similar differences: glaucoma differ significantly from both PTG and healthy, but healthy and PTG do not significantly differ (Supplementary Table 3). In addition, a pairwise Dunn's test confirmed that the IOP difference between glaucoma and PTG groups was statistically significant ($Z=-10.74$, $p<0.05$). Post-diagnosis, the difference between PTG and glaucoma in FVC and PEF was no longer statistically significant. This was also true for IOP, but this is based on only a limited sample of PTG ($n=21$ retinas), for which there is a measurement of IOP post-diagnosis (see Methods).

Shuffle Test Results

Area under ROC curve(%): 53.625

Dependent Variable	dF	F Value	p value
FVC	1,2403	64.51	$1.49e - 15$
PEF	1,2403	50.8	$1.35e - 12$

Supplementary Table 1: Analysis of covariance (ANCOVA) of pulmonary capacity variables (forced vital capacity (FVC), peak expiratory capacity(PEF)) for group identity amongst the three groups (Healthy, Glaucoma and PTG), controlling for age.

Groups	Kruskal-Wallis Z	P (unadjusted)	P (adjusted)
Healthy vs. Glaucoma	7.03	$2.12e - 12$	$1.270017e - 11$
Healthy vs. PTG	-1.63	$1.03e - 01$	$6.17e - 01$
Glaucoma vs. PTG	-4.36	$1.28e - 05$	$7.66e - 05$
Healthy vs.PTG (post-diagnosis)	2.48	$1.32e - 02$	$7.93e - 02$
Glaucoma vs.PTG (post-diagnosis)	-0.26	$7.99e - 01$	1.0
PTG vs.PTG (post-diagnosis)	3.02	$2.51e - 03$	$1.50e - 02$

Supplementary Table 2: Dunn's test comparing **FVC** for Glaucoma, healthy, PTG and PTG (post-diagnosis) groups, with Bonferroni correction for p-values.

Groups	Kruskal-Wallis Z	P (unadjusted)	P (adjusted)
Healthy vs. Glaucoma	7.68	$1.54e - 14$	$9.25e - 14$
Healthy vs. PTG	-2.17	$3.02e - 02$	$1.81e - 01$
Glaucoma vs. PTG	-5.12	$3.01e - 07$	$1.81e - 06$
Healthy vs.PTG (post-diagnosis)	5.58	$2.38e - 08$	$1.43e - 07$
Glaucoma vs.PTG (post-diagnosis)	2.65	$8.12e - 03$	$4.86e - 02$
PTG vs.PTG (post-diagnosis)	5.70	$1.19e - 08$	$7.17e - 08$

Supplementary Table 3: Dunn's test comparing **PEF** for Glaucoma, healthy, PTG and PTG (post-diagnosis) groups, with Bonferroni correction for p-values.

Groups	Kruskal-Wallis Z	P (unadjusted)	P (adjusted)
Healthy vs. Glaucoma	-19.26	$1.10e - 82$	$6.61e - 82$
Healthy vs. PTG	-5.90	$3.53e - 09$	$2.12e - 08$
Glaucoma vs. PTG	1.47	$1.41e - 01$	$8.46e - 01$
Healthy vs. PTG (post-diagnosis)	-11.51	$1.16e - 30$	$6.96e - 30$
Glaucoma vs. PTG (post-diagnosis)	-4.15	$3.33e - 05$	$2.00e - 04$
PTG vs. PTG (post-diagnosis)	-4.12	$3.73e - 05$	$2.24e - 0$

Supplementary Table 4: Dunn's test comparing **Age** for Glaucoma, healthy, PTG and PTG (post-diagnosis) groups, with Bonferroni correction for p-values.

Groups	Kruskal-Wallis Z	P (unadjusted)	P (adjusted)
Healthy vs. Glaucoma	-6.09	$1.09e - 09$	$6.57e - 09$
Healthy vs. PTG	1.34	$1.80e - 01$	1.0
Glaucoma vs. PTG	3.69	$2.26e - 04$	$1.36e - 03$
Healthy vs. PTG (post-diagnosis)	1.70	$8.84e - 02$	$5.30e - 01$
Glaucoma vs. PTG (post-diagnosis)	4.05	$5.07e - 05$	$3.04e - 04$
PTG vs. PTG (post-diagnosis)	0.27	$7.89e - 01$	1.0

Supplementary Table 5: Dunn's test comparing **BMI** for Glaucoma, healthy, PTG and PTG (post-diagnosis) groups groups, with Bonferroni correction for p-values.

Groups	Kruskal-Wallis Z	P (unadjusted)	P (adjusted)
Healthy vs. Glaucoma	-14.31	$1.98e - 46$	$1.19e - 45$
Healthy vs. PTG	-10.74	$6.32e - 27$	$3.79e - 26$
Glaucoma vs. PTG	-5.20	$1.96e - 07$	$1.18e - 06$
Healthy vs. PTG (post-diagnosis)	-2.40	$1.64e - 02$	$9.84e - 02$
Glaucoma vs. PTG (post-diagnosis)	0.25	$7.99e - 01$	1.0
PTG vs. PTG (post-diagnosis)	2.50	$1.23e - 02$	$7.38e - 02$

Supplementary Table 6: Dunn’s test comparing **IOP** for Glaucoma, healthy, PTG and PTG (post-diagnosis) groups, with Bonferroni correction for p-values.

Groups	Predicted Normal	Predicted Glaucoma
True Normal	0.7096	0.2904
True Glaucoma	0.7011	0.2989

Supplementary Table 7: Normalized confusion matrix for shuffle test.

Measure	Category	Description
Gender	Demographic	Sex
Age	Demographic	Computed field based on visit date and birth month and year.
Ethnicity	Demographic	Ethnic background
BMI	Cardiovascular and Pulmonary	Body mass index
Diabetes Diagnosis	Cardiovascular and Pulmonary	Diabetes diagnosed by doctor
Peak Expiratory Flow (PEF)	Cardiovascular and Pulmonary	Peak expiratory flow during blow
Forced Vital Capacity (FVC))	Cardiovascular and Pulmonary	
Diastolic Pressure	Cardiovascular and Pulmonary	Diastolic blood pressure, automated reading
Systolic Pressure	Cardiovascular and Pulmonary	Systolic blood pressure, automated reading
Pulse Rate	Cardiovascular and Pulmonary	Pulse rate (during blood-pressure measurement)
Caffeine in last hour	Cardiovascular and Pulmonary	Caffeine drink within last hour
Smoke in last hour	Cardiovascular and Pulmonary	Smoked cigarette or pipe within last hour
Current eye infection	Cardiovascular and Pulmonary	Current eye infection
Intraocular Pressure	Ocular	Intra-ocular pressure, corneal-compensated
Corneal hysteresis	Ocular	Ocular measurement
Corneal resistance factor	Ocular	Ocular measurement

Supplementary Table 8: All factors used for building the baseline models.

UK Biobank coding	Medication Name
1140853180	chloromycetin redidrops 0.5% eye drops 5ml
1140853184	opulets chloramphenicol single-use eye drops 0.5ml
1140853186	chloramphenicol eye drops
1140853262	soframycin 0.5% eye drops 8ml
1140853270	albucid 2.5% eye ointment
1140853272	albucid 6% eye ointment
1140853274	albucid 10% eye ointment
1140853276	isopto cetamide eye drops
1140853278	minims sulphacetamide single-use eye drops 0.5ml
1140853282	sulphacetamide 10% eye drops
1140853336	ophthalmidine 0.1% eye drops

1140853338	ophthalmadine 0.5% eye ointment
1140853342	sulfomyl 5% eye drops
1140853344	mafee 5% eye drops
1140853370	albucid 20% eye drops
1140853424	opulets atropine single-use eye drops 0.5ml
1140853448	eumovate 0.1% eye drops 5ml
1140853480	cortucid eye ointment
1140853484	framygen eye ointment
1140853488	neo-cortef eye drops
1140853558	physostigmine+pilocarpine 0.25%+2% eye drops
1140853576	isopto epinal 1% eye drops
1140853676	opulets sodium chloride single-use eye drops 0.5ml
1140853678	minims thymoxamine single-use eye drops 0.5ml
1140853684	zincfrin 0.25% eye drops
1140853710	minims amethocaine hcl 0.5% single-use eye drops 0.5ml
1140864712	ciloxan 0.3% eye drops
1140864728	vividrin 2% eye drops
1140865010	viscotears liquid eye gel
1140875552	zovirax 3% eye ointment
1140875558	chloromycetin 1% eye ointment
1140875560	minims chloramphenicol 0.5% single-use eye drops
1140875562	sno phenicol 0.5% eye drops
1140875566	chloramphenicol 1% eye ointment
1140875568	aureomycin 1% eye ointment
1140875576	cidomycin eye ointment
1140875580	genticin eye ointment
1140875582	minims gentamicin 0.3% single-use eye drops
1140875590	idoxene 0.5% eye ointment
1140875650	minims neomycin sulphate 0.5% single-use eye drops
1140875652	neosporin eye drops
1140875658	polyfax eye ointment
1140875660	polytrim eye drops
1140875662	polytrim eye ointment
1140875664	polymyxin b sulphate+bacitracin zinc eye ointment
1140875666	polymyxin b sulphate+trimethoprim eye ointment
1140875668	chloromycetin hydrocortisone eye ointment
1140875684	minims prednisolone 0.5% single-use eye drops
1140875690	hay-crom aqueous eye drops
1140875696	lodoxamide
114087570	ocufen 0.03% single-use eye drops
1140875710	isopto atropine 1% eye drops
1140875712	minims atropine sulphate 1% single-use eye drops
1140875730	tobralax eye drops
1140875736	fucithalamic m/r eye drops
1140875740	noroxin 0.3% eye drops
1140875746	exocin 0.3% eye drops
1140875752	antazoline sulphate+xylometazoline hcl 0.5/0.05% eye drops
1140875754	antazoline phosphate+naphazoline hcl 0.5/0.05% eye drops
1140875766	fluorometholone
1140875768	fluorometholone+neomycin sulphate 0.1/0.5% eye drops
1140875852	tropicamide

1140876006	polyvinyl alcohol 1% eye drops
1140876026	simple eye ointment
1140876044	neomycin+hydrocortisone 0.5%/1.5% eye/ear ointment
1140876046	neomycin+hydrocortisone 0.5%/1.5% eye/ear drops
1140876806	sodium bicarbonate 2% preservative-free eye drops
1140877976	minims homatropine 2% single-use eye drops
1140877980	minims tropicamide 0.5% single-use eye drops
1140877984	mydriacyl 0.5% eye drops
1140878034	voltarol ophtha 0.1% single-use eye drops
1140878048	otrivine-antistin eye drops
1140878050	vasocon a eye drops
1140878052	fml eye drops
1140878056	fml-neo eye drops
1140878058	tanderil eye ointment
1140878060	alomide eye drops
1140878064	minims cyclopentolate 0.5% single-use eye drops
1140878068	mydrilate 0.5% eye drops
1140878116	hydroxypropylmethylcellulose
1140878122	h.p.m.c in balanced salt solution 2% eye drops
1140878140	citrate 6.5% preservative-free eye drops
1140878142	potassium ascorbate preservative-free eye drops
1140878170	hypotonic artificial tears eye drops
1140878172	tears naturale eye drops
1140878174	isopto plain 0.5% eye drops
1140878178	isopto frin eye drops
1140878180	hypromellose+phenylephrine
1140878182	hypotears eye drops
1140878184	sno-tears eye drops
1140878186	liquifilm tears 1.4% eye drops
1140878190	minims artificial tears single-use eye drops
1140878192	miochol intra-ocular irrigation
1140878194	lubrifilm eye ointment
1140878196	super soft paraffin eye ointment
1140878198	sootheye eye autodrop
1140878210	murine eye drops
1140878520	soframycin eye ointment
1140879518	opulets benoxinate eye drops
1140879844	phenylephrine
1140879848	phenylephrine eye drops
1140881472	lacri-lube eye ointment
1140882072	ilube eye drops
1140882506	achromycin 1% eye/ear ointment
1140882520	cidomycin eye/ear drops
1140882522	garamycin eye/ear drops
1140882538	chloramphenicol 0.25% eye drops
1140882624	vista-methasone 0.1% eye/ear/nose drops
1140882626	betnesol 0.1% eye/ear/nose drops
1140882718	maxitrol eye drops
1140882722	maxidex eye drops
1140882724	sofradex eye/ear drops
1140882768	vista-methasone n eye/ear/nose drops

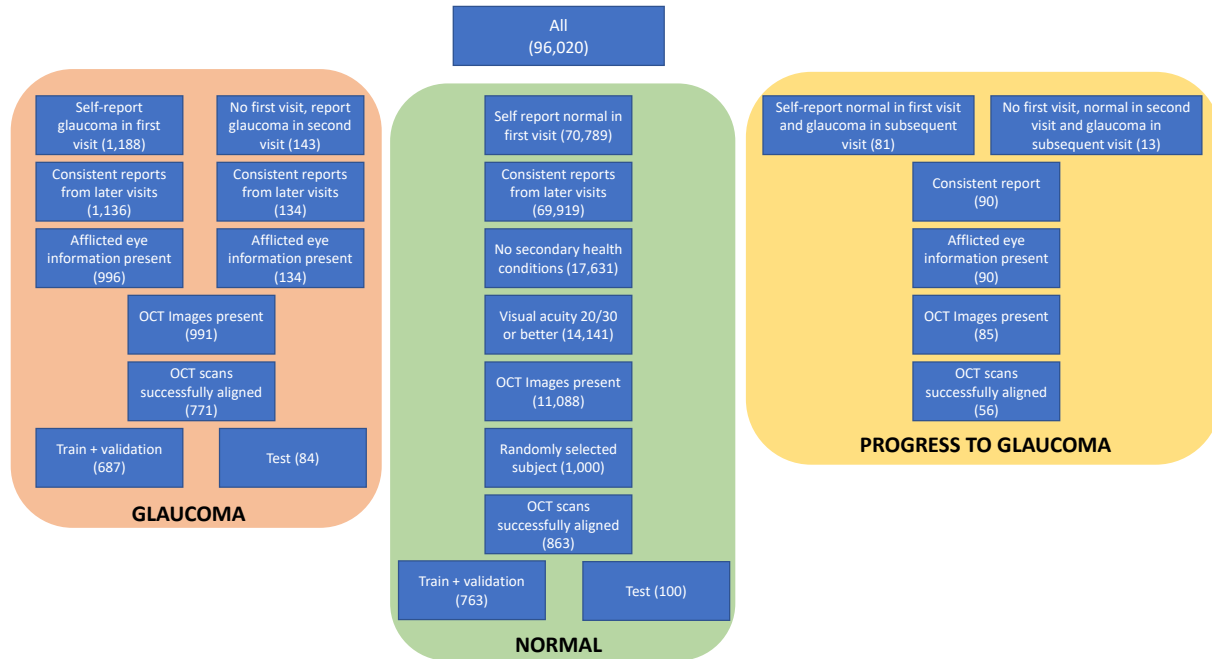
1140882808	cloburate eye drops
1140882892	neo-cortef eye/ear ointment
1140883028	predsol 0.5% eye/ear drops
1140883030	pred forte 1% eye drops
1140883522	alnide 0.5% eye drops
1140883586	opulets cyclopentolate eye drops
1140883904	bj6 eye drops
1140883984	framygen eye drops
1140884006	graneodin eye ointment
1140884048	framycort eye ointment
1140884050	framycort eye drops
1140884070	genticin 0.3% eye/ear drops
1140884118	achromycin 1% eye drops
1140884190	albucid 10% eye drops
1140884194	ocusol eye drops
1140884228	kerecid eye drops
1140884232	kerecid eye ointment
1140884238	vira-a eye ointment
1140888376	sodium chloride eye drops
1140909462	clariteyes eye drops
1140909466	bro-l-eze eye drops
1140909482	opticrom allergy eye drops
1140909484	hay-crom eye drops
1140910046	myciguent eye ointment
1140910906	eumovate eye drops
1140911572	eye-crom aqueous eye drops
1140912778	polymyxin b sulphate+trimethoprim eye drops
1140912910	chloromycetin 1% eye ointment 4g
1140912912	minims chloramphenicol 0.5% single-use eye drops 0.5ml
1140912914	sno phenicol 0.5% eye drops 10ml
1140912994	polymyxin b + bacitracin 10,000/500units/g eye ointment 4g
1140912998	polymyxin + trimethoprim 10ku/0.5%/g eye ointment 4g
1140916656	neo-cortef eye ointment
1140916830	normasol undine 0.9% eye irrigation solution
1140917204	cusilyn 2% eye drops
1140917432	rapitil 2% eye drops
1140921978	viz-on 2% eye drops
1140926178	livostin 0.5mg/ml eye drops
1140926516	optrex dry eye therapy eye drops
1140926848	moisture eyes eye drops
1141151184	aqisia eye irrigation solution
1141151196	bss eye irrigation solution
1141151424	hydrocortisone acetate+neomycin sulphate 1.5%/0.5% eye drops
1141153292	polymyxin b sulphate+trimethoprim eye drops 5ml
1141162532	minims dexamethasone na phosphate 0.1% s-d eye drops
1141162970	optilast 0.05% eye drops
1141163656	oculotect 5% single-use eye drops
1141164266	emadine 0.05% eye drops
1141165028	artelac 0.32% single-use eye drops
1141166502	okacyn 0.3% eye drops
1141166528	vexol 1% eye drops

1141169844	dexamethasone+hypromellose 0.1%/0.5% eye drops
1141172918	celluvisc 1% single-use eye drops
1141174552	tobradex eye drops
1141179744	clarityn allergy 2% eye drops
1141180040	zaditen 250micrograms/ml eye drops
1141181398	liposic eye gel
1141181944	vivicrom 2% eye drops
1141183482	dominion pharma hayfever eye drops
1141183866	virgan 0.15% eye gel
1141188504	pollenase allergy 2% eye drops
1141189040	brolene cool eyes eye drops
1141189252	optrex sore eyes eye drops
1141189626	liquivisc 0.25% eye gel
1141189696	relestat 0.5mg/ml eye drops
1141191198	optrex eye drops
1141191774	optrex allergy eye drops
1141192286	aller-eze 0.05% eye drops
1141192298	olopatadine
1141192302	opatanol 1mg/ml eye drops

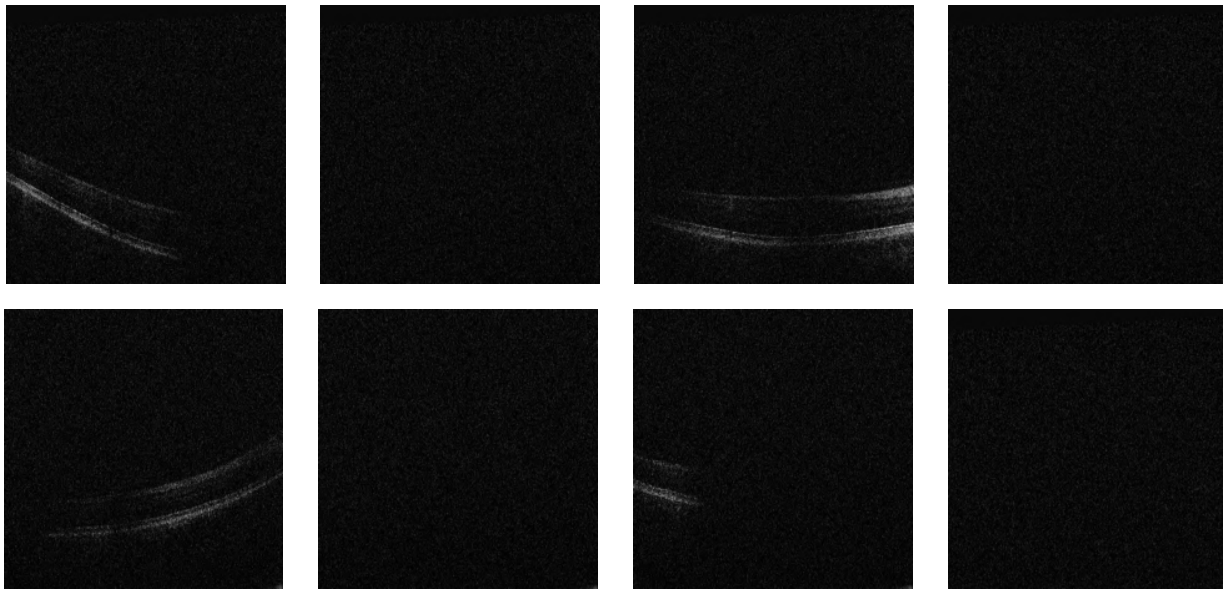
Supplementary Table 9: Other Eye medications.

UK Biobank coding	Medication Name
1140853574	opulets pilocarp-1% del 0.5ml
1140853596	tosmilen 0.25% eye drops
1140864342	glaucol 0.25% single-use eye drops
1140875816	pilocarpine
1140875828	ocusert pilo 20 ocular insert
1140875840	timolol 0.25% eye drops
1140875868	acetazolamide
1140875870	diamox 250mg tablet
1140875934	apraclonidine
1140877988	teoptic 1% eye drops
1140877992	propine eye drops
1140877994	minims metipranolol 0.1% single-use eye drops
1140877998	eserine sulphate 1.0% eye drops
1140878020	isopto carpine 0.5% eye drops
1140878080	sno pilo 1% eye drops
1140878092	minims pilocarpine nitrate 1% single-use eye drops
1140878098	betagan eye drops
1140878212	humorsol 0.25% eye drops
1140879828	glauine eye drops
1140881798	ismelin 5% eye drops
1140881800	ganda 1+0.2 eye drops
1140881864	guanethidine monosulphate+adrenaline 0.25%/0.05% eye drops
1140881882	timoptol 0.25% eye drops
1140881890	betoptic 0.5% eye drops
1140882070	eppy 1% eye drops
1140882170	simplene 0.5% eye drops
1140883158	isopto carbacol 3% eye drops
1140883470	lofexidine
1140883474	adrenaline eye drops
1140883528	epifrin 1% eye drops
1140888548	guanethidine eye drops
1140909420	phospholine iodide 0.03% eye drops
1140927928	pilogel 4% eye gel
1141145646	glau-opt 0.25% eye drops
1141146188	latanoprost
1141146198	xalatan 0.005% eye drops
1141150750	brimonidine tartrate
1141150754	alphagan 0.2% eye drops
1141169516	dorzolamide+timolol
1141169520	cosopt 2%/0.5% eye drops
1141176288	azopt 10mg/ml eye drops
1141179734	nyogel 0.1% liquid eye gel
1141179914	bimatoprost
1141179920	lumigan 0.3mg/ml eye drops
1141184722	latanoprost+timolol
1141184726	xalacom 0.005%/0.5% eye drops
1141185316	travoprost
1141185326	travatan 40micrograms/ml eye drops
1141190854	epinephrine eye drops

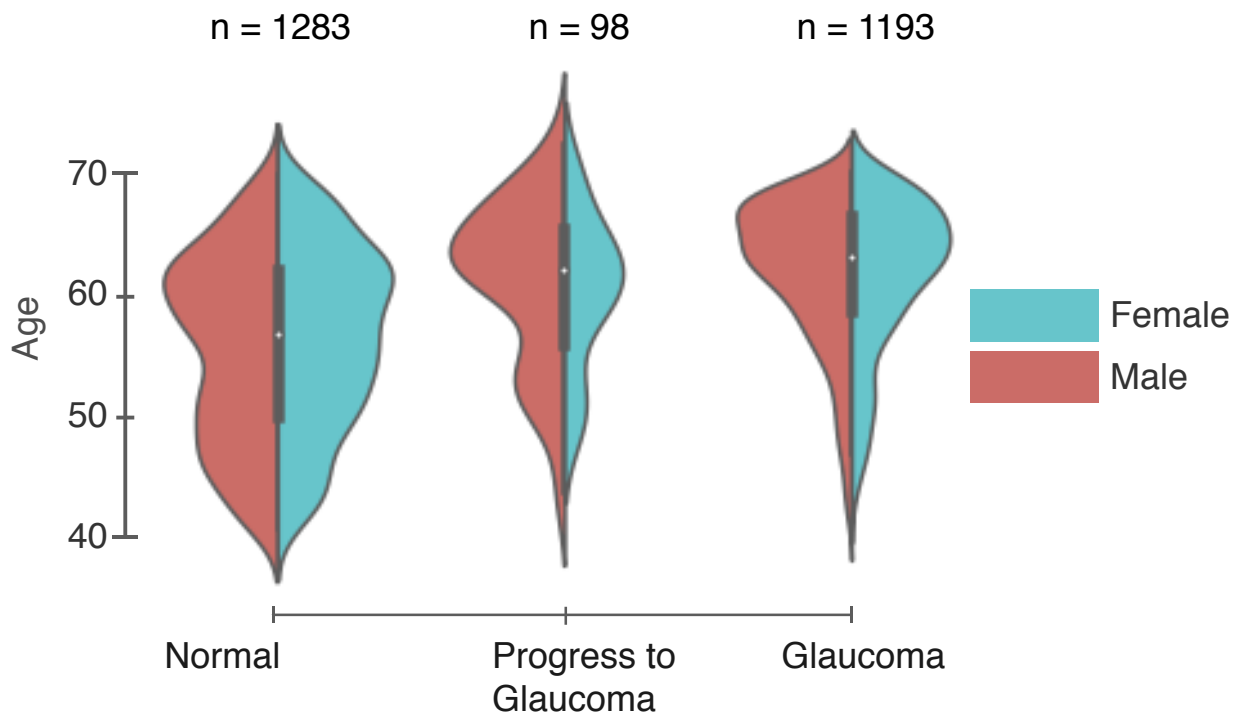
Supplementary Table 10: Glaucoma medications.



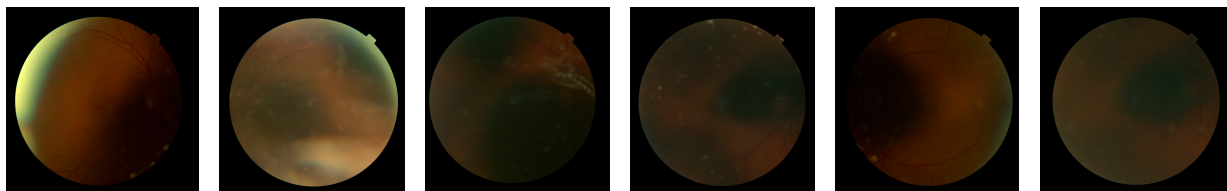
Supplementary Figure 1: Selection criteria for glaucoma and progress to glaucoma subjects from UK Biobank data set.



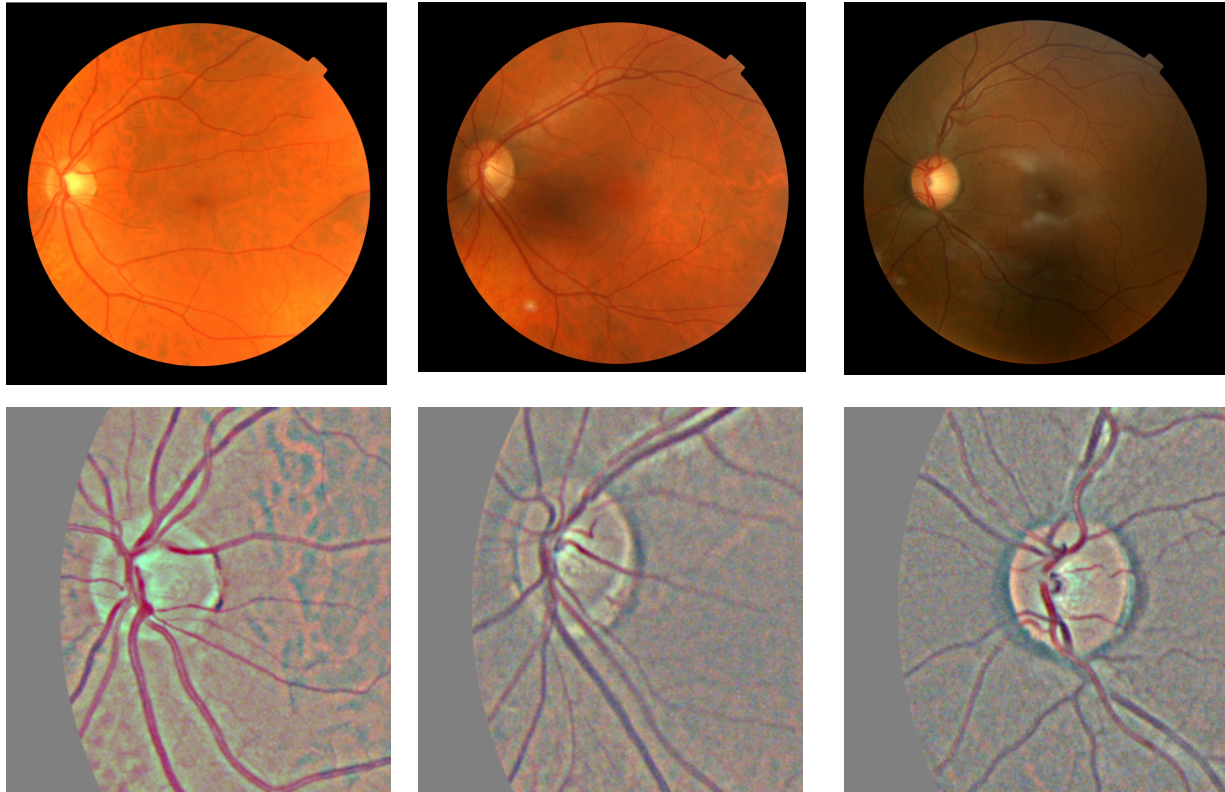
Supplementary Figure 2: Sample of OCT volumes eliminated due to alignment errors, this shows first two OCT slices for four retinas where alignment failure occurred. All OCT slices were eliminated for such retinas.



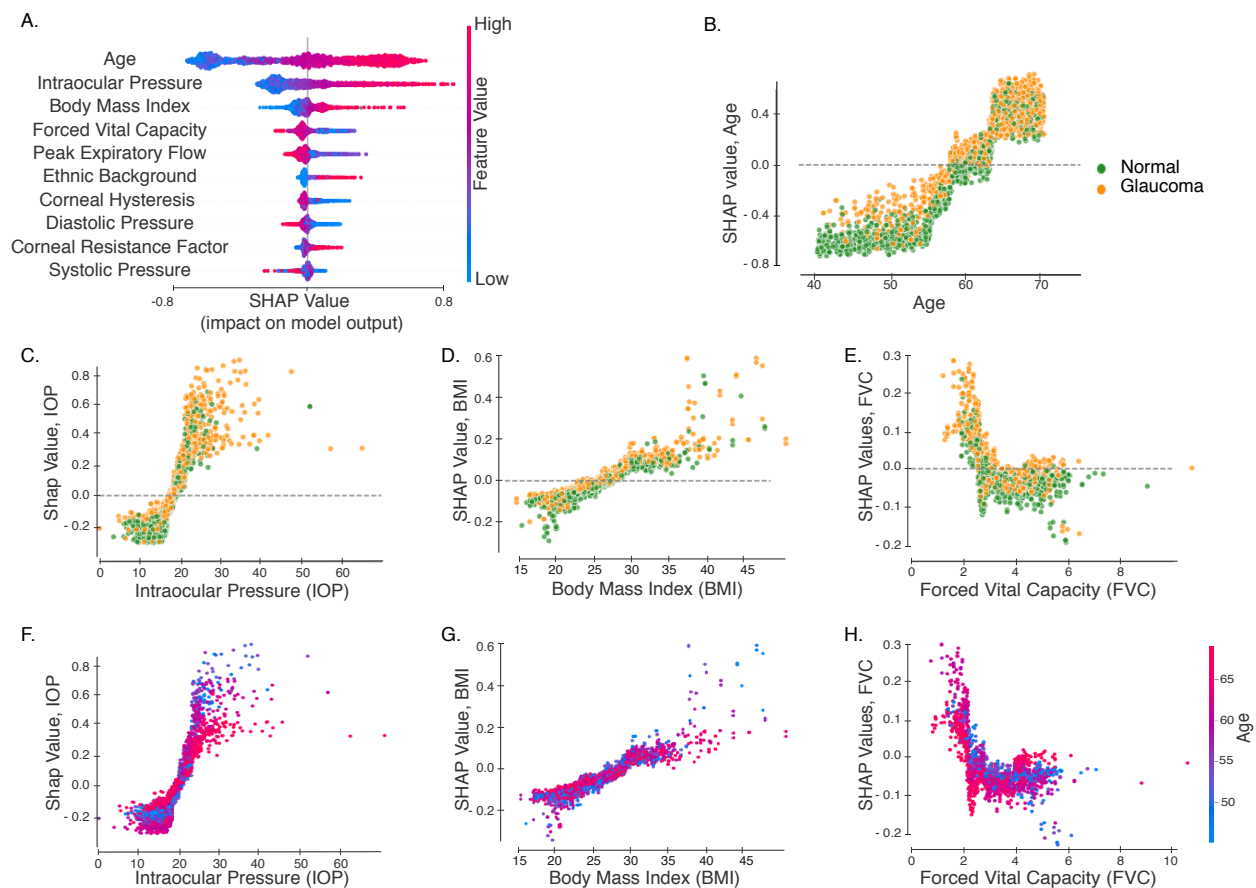
Supplementary Figure 3: **Data distribution:** Age and gender distributions as well as number of subjects in the Normal (left), progress to glaucoma (middle) and glaucoma (right) subject groups.



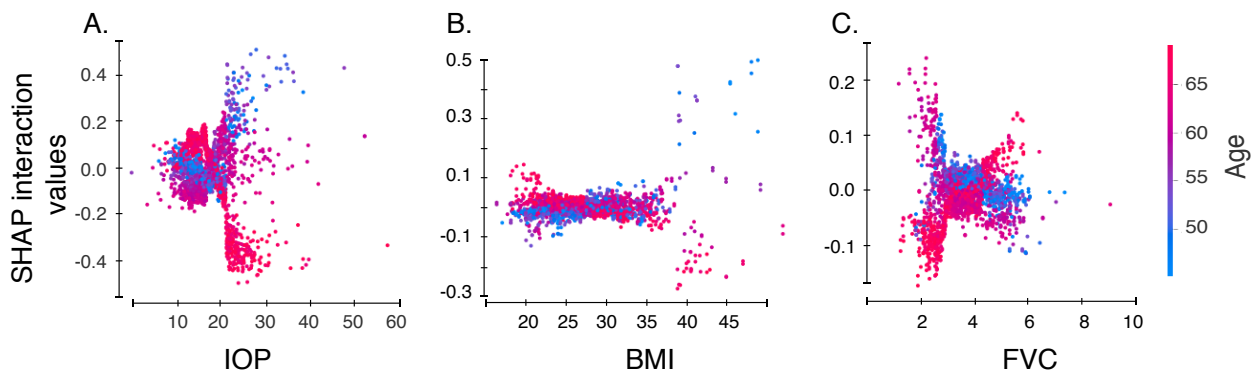
Supplementary Figure 4: Sample of CFP eliminated from test set due to bad quality.



Supplementary Figure 5: **Data processing for CFP images.** Top row shows original images, bottom row shows cropped and pre-processed images.



Supplementary Figure 6: **Interpreting model built on demographic, systemic and ocular data.** A) The ten most important features from BM3 based on SHAP values. B-E) SHAP values vs feature values for age, IOP, BMI, and FVC respectively. Each point represents an individual subject and the color denotes whether or not they have been diagnosed with glaucoma. F-H) SHAP values vs feature values for features IOP, BMI, and FVC respectively, with each point colored based on age of subject.



Supplementary Figure 7: **SHAP interaction values in BM3.** Interactions between age and each of the other top variables in model BM3: **A** SHAP interaction values for age and IOP. **B** SHAP interaction values for age and BMI. **C** SHAP interaction values for age and FVC.