Using AI to Discover Baseline Predictors of Anti-VEGF Treatment Intervals in nAMD From Real World Canadian Ophthalmology Electronic Health Record Data

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Introduction

- Treat & Extend (T&E) is the preferred treatment protocol for anti-VEGF therapies, but ~ 1/3 of patients with nAMD still require dosing every 8 weeks or more frequently[1].
- The ability to predict which patients would most likely extend treatment intervals could substantially improve clinical outcomes and efficiency[2].
- Traditional studies have been unsuccessful in describing baseline demographics and clinical characteristics predictive of outcomes for patients on anti-VEGF treatment[3].
- DARWEN™ is an artificial intelligence (AI) engine, designed to quickly and economically extract real-world evidence trapped in large repositories of existing unstructured healthcare data and transform it into reports that can be easily interpreted by the clinician[4].
- DARWEN™ – which has been previously described and validated in detail – combines multiple state of the art approaches to extract relevant data from structured and unstructured EHR fields[4].
- DARWEN™ uses a "twin-engine design" which allows model training to begin on one task, while learnings and adjustments can be made quickly and easily for adjacent tasks. This provides knowledge transfer between tasks, flexibility and adaptability, reducing the overall number of models required and hence the compound error, thus achieving high accuracy with results that are aligned with clinician expertise[4].

Purpose

- This study is designed to validate a machine learning model to predict treatment outcomes for patients receiving continued anti-VEGF injections for nAMD.

Methods

- A total of 206,989 clinical documents from **41,849** patients (EyeDoc®) at Ivey Eye Institute in London, Ontario diagnosed with nAMD between Jan 1, 2009 and May 31, 2023 and treated with anti-VEGF therapy were analyzed through a retrospective chart review using the machine learning model DARWEN™. Ethics approval was obtained.
- DARWEN™ utilizes a supervised Machine Learning Model (MLM).
- 1,122 patients were analyzed by DARWEN™ and classified based on whether anti-VEGF treatment intervals could be extended to ≥8 week, based on demographics, disease characteristics, and documented OCT reports.
- Of 1122 patients, 44% received aflibercept, 54% received ranibizumab and 2% received other treatment. 58% were injection non-intensive (≥ 8 weeks between doses) vs. 32% injection-intensive (< 8 weeks between doses)
- 426 Patients with nAMD who were anti-VEGF naïve, and who started treatment after Eylea 2mg was publicly reimbursed in Ontario in July 2015 were clustered based on probability of having frequent injections. This timeframe was chosen to ensure standardization in the availability of treatment to patients for nAMD
- ~10% of patients were randomly excluded from model development to assess the accuracy of the final patient clusters.
- In line with standard Machine Learning protocols, DARWEN™ was trained on 389 patients and then tested on a sample of 37 patients not seen by the model.
- Statistical analysis of demographic variable differences was performed using Fisher's exact test and Kruskal wallis test for categorical and continuous variables respectively.

Results

Table 1. DARWEN™ Performance for Various Parameters of anti-VEGF Treatment

Results for 100 Patients	Precision	Recall	F1
Diagnosis of nAMD	0.92	1.00	0.96
nAMD extending intervals	1.00	0.92	0.96
nAMD frequent injections	0.92	1.00	0.96

- **Precision**: True positive divided by the test positive (true positive + false positive). Analogous to positive predictive value.
- **Recall**: True positive divided by the condition positive (true positive + false negative). Analogous to sensitivity.
- **F1**: Combination of precision and recall in a single metric. Mean of precision and recall.
- A high F1 (~1) demonstrates high predictive validity of the model.

Figure 1. DARWEN™ Clustering of Patients into Discrete Groups Based on Baseline Characteristics

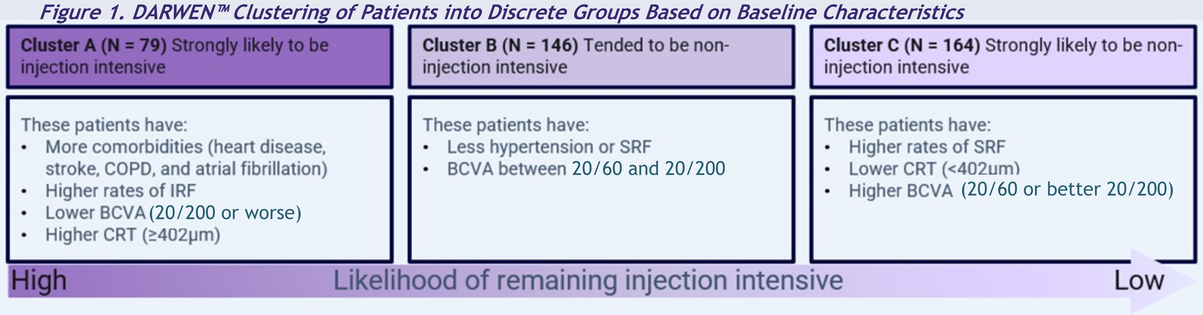

Table 2. Patient Baseline Characteristics

	A (N=79)	B (N=146)	C (N=164)	Total (N=389)	p value
Baseline Patient Demographics					
Age					0.813
Mean (SD)	81.94 (8.12)	82.16 (8.03)	82.59 (7.65)	82.30 (7.87)	
Median (Range)	82.05 (57.28, 96.19)	82.62 (51.31, 97.60)	82.93 (60.51, 96.61)	82.75 (51.31, 97.60)	
Patient Sex					0.828
Female	46 (58%)	90 (62%)	96 (59%)	232 (60%)	
Male	33 (42%)	56 (38%)	68 (41%)	157 (40%)	
Baseline Ophthalmology characteristics					
Central retinal thickness (CRT) (µm)					< 0.001
Mean (SD)	398.27 (113.53)	369.57 (115.75)	313.33 (80.08)	357.52 (108.88)	
Median (Range)	409.00 (205.00, 677.00)	365.00 (187.00, 701.00)	307.00 (100.00, 632.00)	337.00 (100.00, 701.00)	
N-Miss	24	79	95	198	
CRT (µm) divided based on tertiles					< 0.001
<296.7	14 (25%)	22 (33%)	28 (41%)	64 (34%)	
296.7-402	10 (18%)	18 (27%)	34 (49%)	62 (32%)	
≥402	31 (56%)	27 (40%)	7 (10%)	65 (34%)	
N-Miss	24	79	95	198	

Table 3. Patient Ophthalmic Characteristics

	A (N=79)	B (N=146)	C (N=164)	Total (N=389)	p value
Best corrected visual acuity BCVA (20/X)					< 0.001
Mean (SD)	656.53 (793.41)	467.15 (703.97)	139.36 (334.52)	373.52 (638.46)	
Median (Range)	200.00 (30.00, 2000.00)	100.00 (20.00, 2000.00)	50.00 (20.00, 2000.00)	80.00 (20.00, 2000.00)	
N-Miss	7	16	25	48	
BCVA (20/X) divided based on tertiles					< 0.001
20/60 or better	4 (6%)	15 (12%)	80 (58%)	99 (29%)	
20/60 - 20/200	19 (26%)	51 (39%)	38 (27%)	108 (32%)	
20/200 or worse	49 (68%)	64 (49%)	21 (15%)	134 (39%)	
N-Miss	7	16	25	48	
Hemorrhage					< 0.001
absent	29 (37%)	78 (53%)	110 (67%)	217 (56%)	
present	50 (63%)	68 (47%)	54 (33%)	172 (44%)	
Intraretinal Fluid (IRF)					< 0.001
absent	50 (63%)	121 (83%)	147 (90%)	318 (82%)	
present	29 (37%)	25 (17%)	17 (10%)	71 (18%)	
Subretinal fluid (SRF)					0.042
absent	64 (81%)	126 (86%)	123 (75%)	313 (80%)	
present	15 (19%)	20 (14%)	41 (25%)	76 (20%)	

Table 4. Patient Medical History Characteristics

	A (N=79)	B (N=146)	C (N=164)	Total (N=389)	p value
Dry AMD	16 (20%)	14 (10%)	12 (7%)	42 (11%)	**0.013**
Cataract Extraction with implant of Intraocular Lens	53 (67%)	99 (68%)	124 (76%)	276 (71%)	0.211
Other Comorbidities					
Hypertension	26 (33%)	27 (18%)	37 (23%)	90 (23%)	0.053
Heart Disease	14 (18%)	6 (4%)	0 (0%)	20 (5%)	**< 0.001**
Stroke	13 (16%)	8 (5%)	4 (2%)	25 (6%)	**< 0.001**
Diabetes	9 (11%)	25 (17%)	28 (17%)	62 (16%)	0.492
Kidney disease	2 (3%)	1 (1%)	2 (1%)	5 (1%)	0.440
Hypothyroidism	8 (10%)	9 (6%)	12 (7%)	29 (7%)	0.556
Hyperlipidemia/Hypercholesterolemia	4 (5%)	4 (3%)	7 (4%)	15 (4%)	0.581
COPD	6 (8%)	1 (1%)	0 (0%)	7 (2%)	**< 0.001**
Atrial fibrillation	6 (8%)	3 (2%)	1 (1%)	10 (3%)	**0.009**
Cancer	7 (9%)	26 (18%)	35 (21%)	68 (17%)	**0.047**
Family history					
Family history of amblyopia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Family history of blindness	0 (0%)	5 (3%)	9 (5%)	14 (4%)	0.077
Family history of cataracts	21 (27%)	28 (19%)	8 (5%)	57 (15%)	**< 0.001**

Table 5. Patient Family History Characteristics

	A (N=79)	B (N=146)	C (N=164)	Total (N=389)	p value
Family history of crossed eyes	0 (0%)	0 (0%)	1 (1%)	1 (0%)	1.000
Family history of diabetic retinopathy	2 (3%)	0 (0%)	0 (0%)	2 (1%)	**0.041**
Family history of glaucoma	6 (8%)	12 (8%)	9 (5%)	27 (7%)	0.636
Family history of macular degeneration	14 (18%)	21 (14%)	25 (15%)	60 (15%)	0.813
Family history of retinal detachment	1 (1%)	1 (1%)	5 (3%)	7 (2%)	0.333
Family history of cancer	13 (16%)	25 (17%)	29 (18%)	67 (17%)	0.984
Family history of diabetes	11 (14%)	16 (11%)	13 (8%)	40 (10%)	0.322
Family history of heart disease	13 (16%)	15 (10%)	12 (7%)	40 (10%)	0.095
Family history of high blood pressure	18 (23%)	11 (8%)	1 (1%)	30 (8%)	**< 0.001**
Family history of stroke	15 (19%)	4 (3%)	4 (2%)	23 (6%)	**< 0.001**

Results (Cont'd)

- AI clustering of patients into groups based on likelihood of requiring frequent injections was found to determine categorization based on Intraretinal fluid being present, Low BCVA (20/200 or worse), High CRT (≥402µm), and having more comorbidities (such as heart disease, stroke, COPD, and atrial fibrillation).

Table 6. **Proportion** *of Treatment Intervals in Each Cluster*

Training dataset (n=389)

	A (N=79)	B (N=146)	C (N=164)	Total (N=389)	p value
Response to anti-VEGF therapy					< 0.001
Require frequent treatment intervals	34 (43%)	32 (22%)	16 (10%)	82 (21%)	
Extend treatment intervals	45 (57%)	114 (78%)	148 (90%)	307 (79%)	

Conclusions

- DARWEN™ accuracy is consistent with other published studies on clinically verified MLMs.
- Patients with the following characteristics were most likely to be injection intensive – more comorbidities (heart disease, stroke, COPD, and atrial fibrillation), IRF present, Low BCVA (20/200 or worse), High CRT (≥402µm).
- DARWEN™ was able to successfully categorize patients by disease and treatment response and predict which patients will be able to extend anti-VEGF injections.
- AI can be used to identify patients with nAMD from EHRs and identify baseline predictors of anti-VEGF treatment intervals to enable clinicians to optimize treatment for patients.

Limitations and Future work

- This study was conducted at a single site and results may not be consistent with the entire Canadian population
- Future work will aim to further refine the models and validate the results with additional sites.

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