Prognostic factors in the treatment of diabetic macular edema (DME) using aflibercept, ranibizumab and bevacizumab (DRCR.net protocol T*)

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2082 - B0314

Purpose

Anti-VEGF therapy has been established as the gold standard in the treatment of diabetic macular edema (**DME**) achieving **improvement** in best corrected visual acuity (**BCVA**) and **reduction** of central retinal thickness (**CRT**).

The consecutive aim is to **optimize treatment outcomes** and disease management by **identification of prognostic features** and substance characteristics of **aflibercept, ranibizumab** and **bevacizumab.**

Advanced analyses of optical coherence tomography (**OCT**) images from the **DRCR.net protocol T** study using **computational methods** allows to deduct **prognostic factors.**

Patients and Protocol

Post-hoc analyses were conducted in randomized trial data from **629 individuals** with **DME** involving the center of the macula and **BCVA from 78 to 24 ETDRS letters**. Participants were **randomized 1:1:1** to receive intravitreal therapy with **aflibercept** (2.0 mg), **ranibizumab** (0.3 mg) or **bevacizumab** (1.25 mg) according to a protocol-specified, as needed regimen.

According to the **protocol** patients were treated whenever a **change in OCT or BCVA** was visible meaning:
- One injection at baseline (BL)
- Retreatment as long as change is seen
- 1st re-visit without change: retreatment
- 2nd re-visit without change before week (W) 24:
  - no treatment if CRT <250μm and BCVA ≥20/20
  - treatment if CRT ≥250μm or BCVA <20/20
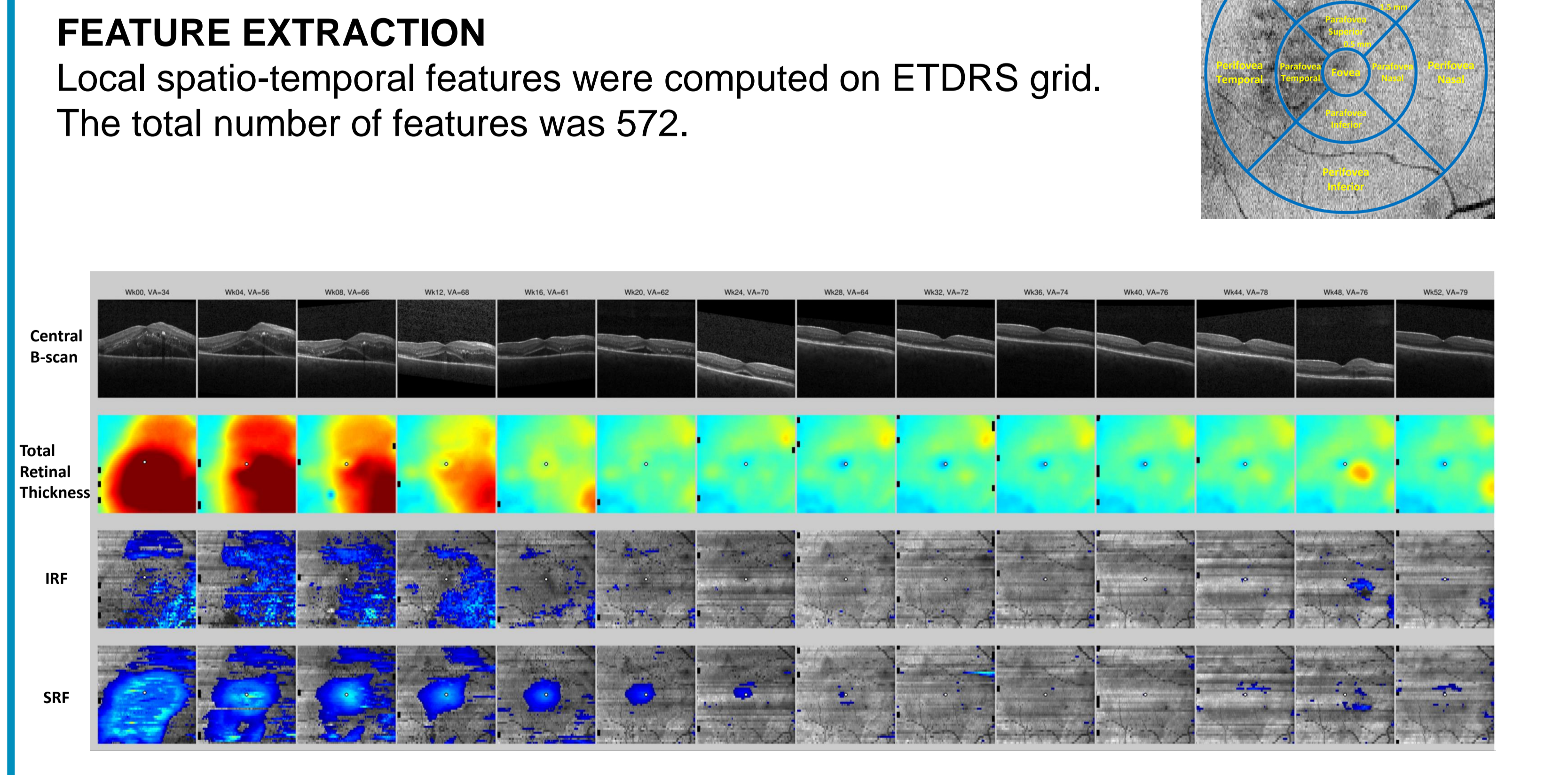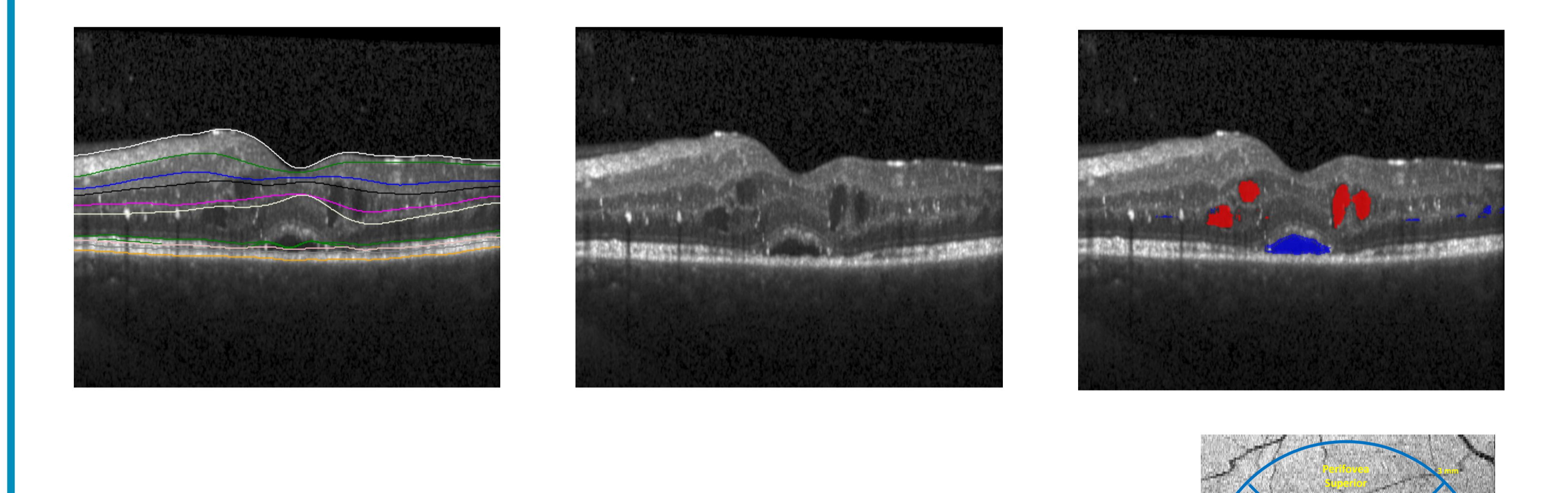- 2nd re-visit without change at and after W24
  - no treatment in any case

INITIAL PHASE   RETREATMENT PHASE

BL   W4   W8   W52
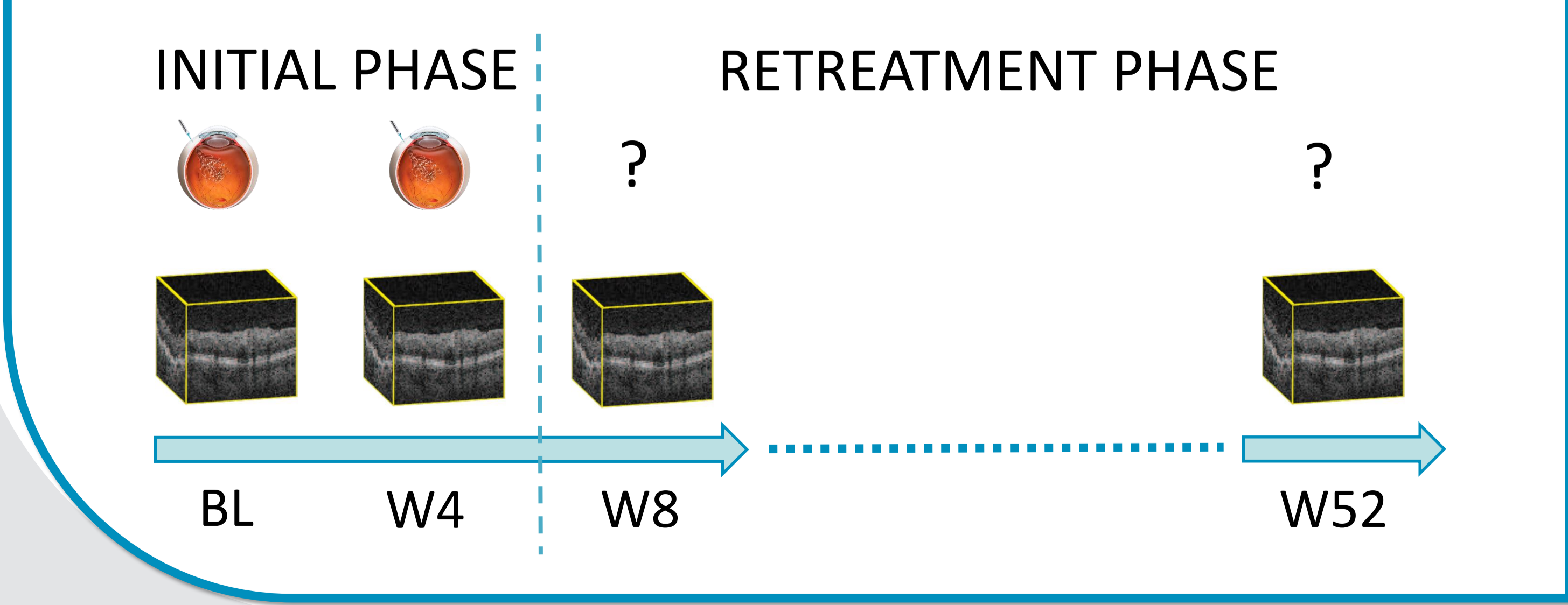
Methods

Spectral-domain OCT images of the **first study year** were analyzed using **automated algorithms** for **fluid quantification** and **retinal layer segmentation**. CRT was measured in μm in the central millimeter subfield, intraretinal cystoid fluid (**IRC**) and subretinal fluid (**SRF**) were measured as volume in mm^3 within the central 3 mm of the macula at baseline and weeks 4, 8, 12, and 24.

Predictive computerized modeling using **machine learning** (random forest classification, evaluation with 10-fold cross validation) was used for ranking of the most important predictive features for BCVA.

LAYER SEGMENTATION
Based on Iowa Reference algorithm [1], retinal layer thicknesses and total retinal thickness were calculated.

FLUID QUANTIFICATION
Intra- and subretinal fluid (**IRF** and **SRF**) volume and area were calculated using convolutional neural networks [2].

FEATURE EXTRACTION
Local spatio-temporal features were computed on ETDRS grid. The total number of features was 572.

Central B-scan
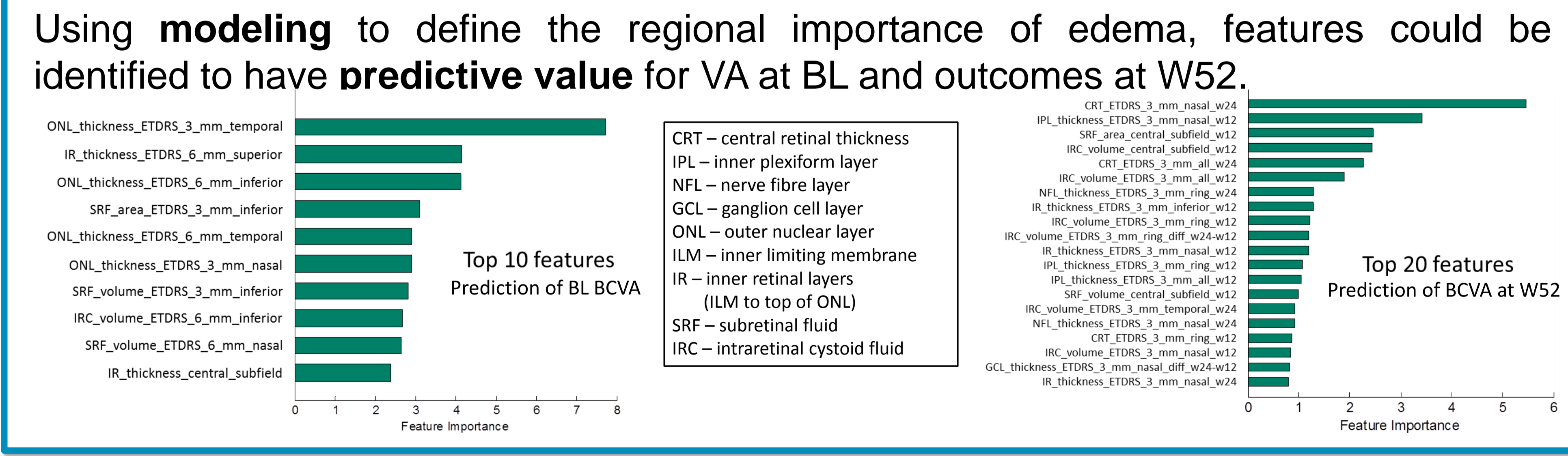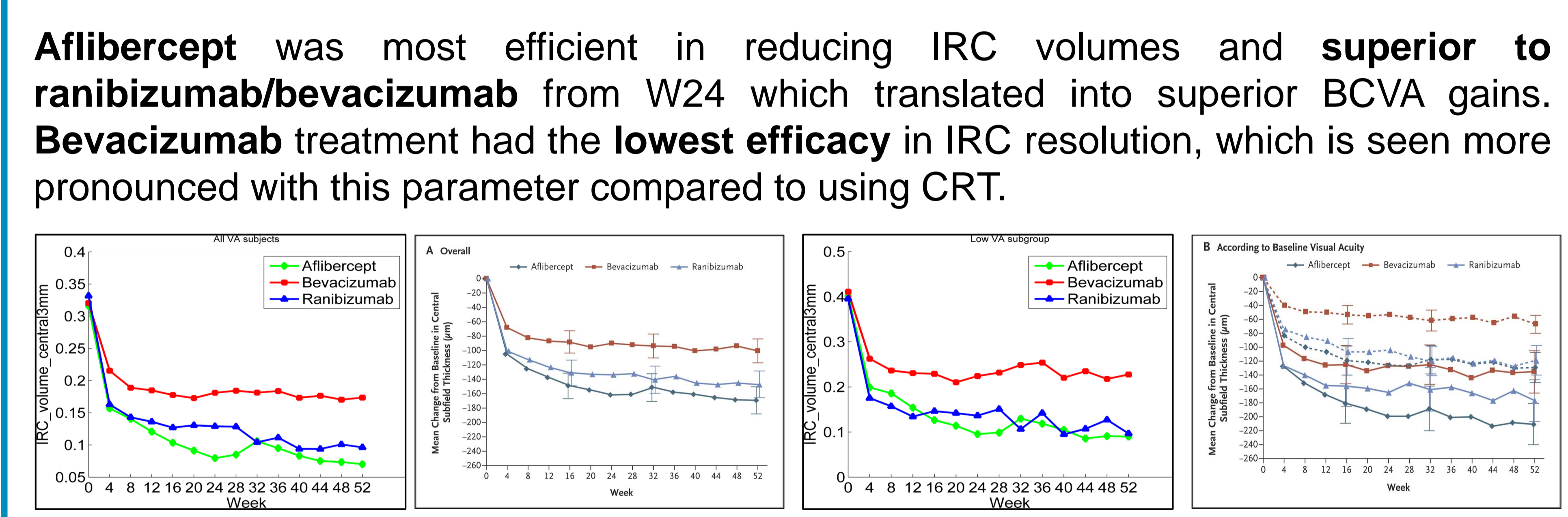
Total Retinal Thickness

IRF

SRF

References

[1] Garvin et al. Automated 3-D Intraretinal Layer Segmentation of Macular Spectral-Domain OCT Images. IEEE Trans Med. Imaging, 2009; 28(9):1436-47 [2] Schlegl et al. Predicting Semantic Descriptions from Medical Images with Convolutional Neural Networks. In Inf Process Med Imaging, 2015; 24:437-48 [3] The DRCR.net. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. N Engl J Med 2015;372:1193-1203.

Results

BL CRT in the **central millimeter** subfield and **BL IRC volume** in the **central 3mm** subfield showed a **moderate correlation** with **BCVA** letter score at BL (r = -0.35/-0.36) while **SRF** volume had **no relevant impact** on BL BCVA and **no prognostic value** for BCVA outcomes at W52.

BCVA outcomes at W52 were **predictable** from **IRC volume** already after the **first injection** (at W4) with a difference of +5/+7 letters in the overall/low VA at BL group whereas **persistent IRC** had a poor prognosis.

All patients	No IRC	IRC			Low VA patients	No IRC	IRC	
	Mean BCVA letter score at week 52		diff.			Mean BCVA letter score at week 52		diff.
Week 4	79.4	74.8	+4.6		Week 4	75.9	69.1	+6.8
Week 8	79.0	74.7	+4.3		Week 8	75.8	68.9	+6.9
Week 12	79.0	73.9	+5.1		Week 12	75.5	68.0	+7.5
Week 24	78.8	73.6	+5.2		Week 24	74.9	67.3	+7.6

*No cysts were defined as IRC volume of less than 5% of the maximal volume found in the population.

The impact of **morphological predictive features** were of **highest value** in the group with a **BL BCVA** letter score **< 69** (low VA patient group).

Aflibercept was most efficient in reducing IRC volumes and **superior to ranibizumab/bevacizumab** from W24 which translated into superior BCVA gains. **Bevacizumab** treatment had the **lowest efficacy** in IRC resolution, which is seen more pronounced with this parameter compared to using CRT.

Using **modeling** to define the regional importance of edema, features could be identified to have **predictive value** for VA at BL and outcomes at W52.

ONL_thickness_ETDRS_3_mm_temporal
IR_thickness_ETDRS_6_mm_superior
ONL_thickness_ETDRS_6_mm_inferior
SRF_area_ETDRS_3_mm_inferior
ONL_thickness_ETDRS_6_mm_temporal
ONL_thickness_ETDRS_3_mm_nasal
SRF_volume_ETDRS_3_mm_inferior
IRC_volume_ETDRS_6_mm_inferior
SRF_volume_ETDRS_6_mm_nasal
IR_thickness_central_subfield

Top 10 features Prediction of BL BCVA

CRT – central retinal thickness
IPL – inner plexiform layer
NFL – nerve fibre layer
GCL – ganglion cell layer
ONL – outer nuclear layer
ILM – inner limiting membrane
IR – inner retinal layers (ILM to top of ONL)
SRF – subretinal fluid
IRC – intraretinal cystoid fluid

Top 20 features Prediction of BCVA at W52

Conclusion

From treatment initiation, **IRC volume** appears to be the most relevant **predictive factor** determining **BCVA gains**. The choice of an anti-VEGF substance having an intense effect on **rapid IRC** reduction **enhances the functional benefit**.

Automated algorithms and **predictive modeling** offer promising tools to identify **predictive factors** at the level of **morphology**. This analysis path is able to detect relevant features and evaluate their **specific impact on the prognosis**.

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