A Post Hoc Analysis of Intravitreal Aflibercept–Treated nAMD Patients from ARIES & ALTAIR: Predicting Patient-Individualized Treatment Interval for Aflibercept Treat-and-Extend Therapy Regimen by Adapting AI Algorithms Trained on Pro Re Nata Data

Matthias Gutfleisch, MD[1,2], Sökmen Aydin[2,3], Ratko Petrovic[3], Alexander Loktyushin[3], Paula Scholz, MD[4], Hossam Youssef[5], Ulrike Bauer-Steinhusen[4], Kristian T. Johnson, MD[6], Britta Heimes-Bussmann, MD[1,2], Kai Rothaus[1,2], Albrecht Lommatzsch, MD[1,2,7,8]

[1]Department of Ophthalmology, St. Franziskus-Hospital, Münster, Germany; [2]M3 Macula Monitor Münster GmbH & Co KG, Münster, Germany; [3]deepeye Medical GmbH, Munich, Germany; [4]Bayer Vital GmbH, Leverkusen, Germany; [5]Bayer Middle East FZE, Dubai, United Arab Emirates; [6]Bayer US LLC, Cambridge, MA, USA; [7]Department of Ophthalmology, University Duisburg-Essen, Essen, Germany; [8]Achim Wessing Institute of Ophthalmic Diagnostic, University Duisburg-Essen, Essen, Germany

23rd Euretina Congress, Amsterdam, September 5-8, 2023

Disclosures

Disclosures: Presenting author

Matthias Gutfleisch: Study participation: Amgen, Apellis, Iveric Bio, Kodiak, Neurotech, Novartis, Regeneron, Roche; Shareholder: deepeye Medical GmbH; Travel support: DORC; Consultant: Bayer.

Disclosures: Co-author group

PS: Employee: Bayer; **HY:** Employee: Bayer; **UBS:** Employee: Bayer; **KTJ:** Employee: Bayer; **KR:** No financial disclosures;
BHB: Study participation: Roche, Amgen, Iveric Bio, Kodiak, Novartis, Novo Nordisk; **ALom:** Study participation & consulting: Roche, Iveric Bio, Kodiak, Amgen, Novartis, Boehringer Ingelheim, Apellis, Ohthea, Alexion; Sharholder deepeye Medical GmbH **RP:** Employee: deepeye Medical GmbH;
ALok: Employee: deepeye Medical GmbH; **SA:** No financial disclosures

Purpose

- Prediction of potential treatment need/expected therapy response and neovascular age-related macular degeneration (nAMD) disease course using artificial intelligence (AI)
- ARIES[1] and ALTAIR[2]
  - Randomized, controlled, Phase 3b/4 trials
  - Treat & Extend (T&E) regimens in newly diagnosed nAMD patients
  - Three loading doses (initial monthly injections), followed by injection after 8 weeks with 2 mg intravitreal aflibercept (IVT-AFL)
  - Treatment intervals assessed based on prespecified spectral domain optical coherence tomography (SD-OCT) criteria at each injection visit over 2 years

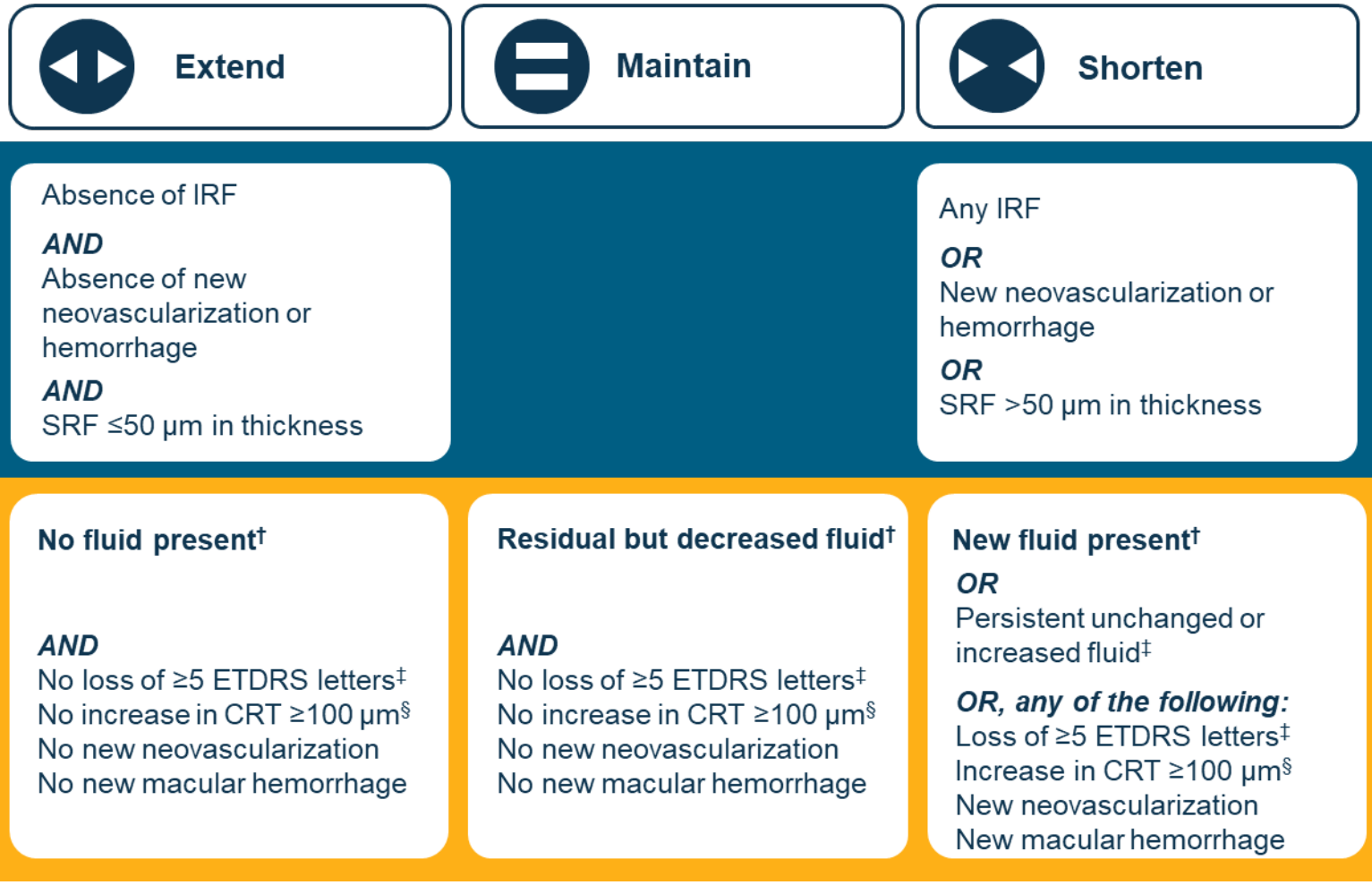
Methods – Data

- AI analysis based on available SD-OCT images at Weeks 8 and 16
  - ARIES: SD-OCT images from 224 of 237 patients
  - ALTAIR: SD-OCT images from 112 of 246 patients
- Clinical patient documentation (visit intervals and injections as prediction targets)

1. Mitchell P, et al. *Retina*. 2021;41:1911–1920. Erratum in: *Retina*. 2022;42:e43.
2. Okada AA, et al. *Adv Ther*. 2022;39:2984–2998.

Methods – criteria for interval adaptation

Criteria for interval adaptation for ARIES & ALTAIR interventional studies (see Table)



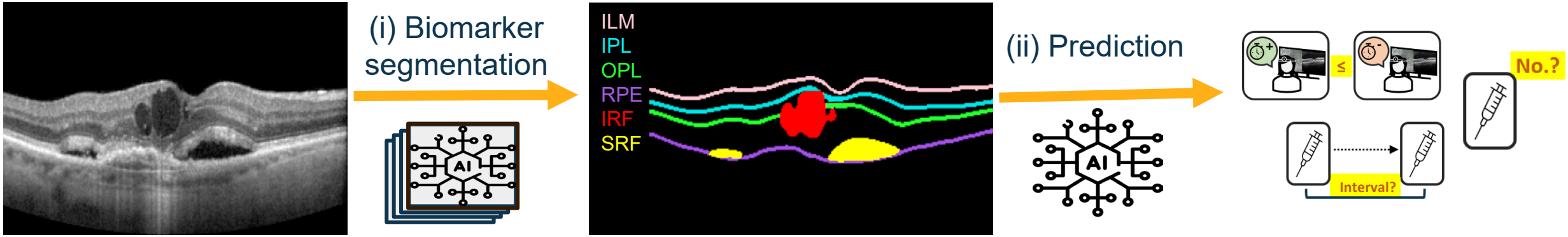
*Patients could receive more frequent treatment if identified as injection-intensive and were excluded from the per-protocol set; †Assessed by OCT; ‡Loss of ≥5 ETDRS letters from the last treatment visit, in conjunction with recurrent fluid on OCT; §Increase in CRT of ≥100 µm compared with the lowest previous value by OCT.

CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; SRF, subretinal fluid.

1. Ohji M, et al. *Adv Ther*. 2020;37:1173–1187.

Methods – AI pipeline

- Evaluation and adaptation of the existing AI models in the deepeye® research tool[1–3]
- AI architecture
  - Input: SD-OCT images from Weeks 8 and 16 from ARIES & ALTAIR studies
  - Two AI networks: Biomarker segmentation (i) and prediction model (ii)
  - Use of AI model trained on SD-OCT data of real-world pro re nata (PRN) cohort[1]
  - Retrain model (ii) and apply AI model to T&E datasets from ARIES & ALTAIR SD-OCT
- Assess agreement between AI model and study results (5-fold cross-validation)



ILM, internal limiting membrane, IPL, inner plexiform layer; OPL, outer plexiform layer, RPE, retinal pigment epithelium; IRF, intraretinal fluid; SRF, subretinal fluid

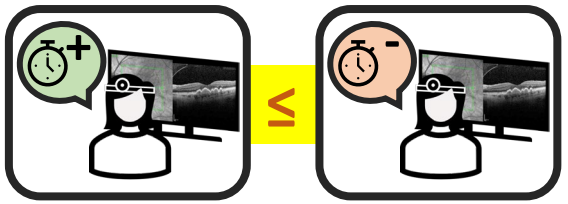
1. Gutfleisch M, et al. *Graefes Arch Clin Exp Ophthalmol*. 2022;260:2217–2230. 2. Gutfleisch M, et al. Poster (PFr05-05) presented at DOG 2022. 3. Rothaus K, et al. Poster (PDo04-11) presented at DOG 2022.

Methods – experiments

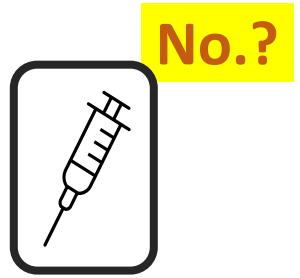
- Prediction of treatment frequency and interval
  - Experiment 1: Prediction of potential adequate first injection interval: <3 vs ≥3 interval extensions in the first four visits after initiation*
  - Experiment 2: Prediction of injection frequency in first and second years
  - Experiment 3: Prediction of treatment interval after second year (end of study)
- Documented study data served as ground-truth

- **In this presentation, we show detailed results of Experiment 3:**
  - Ground-truth: Intended patient individual treatment interval after 2 years
  - AI task: Prediction of this interval (see above), binarized into two classes
    - Short intervals (<12 weeks)
    - Long intervals (≥12 weeks)

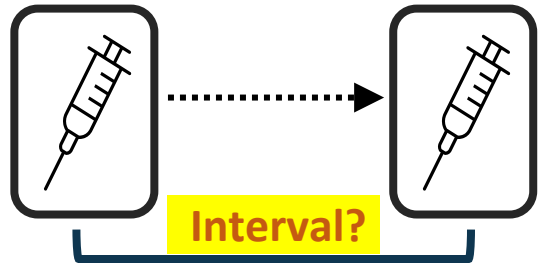
Experiment 1:



Experiment 2:

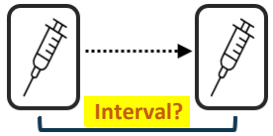


Experiment 3:

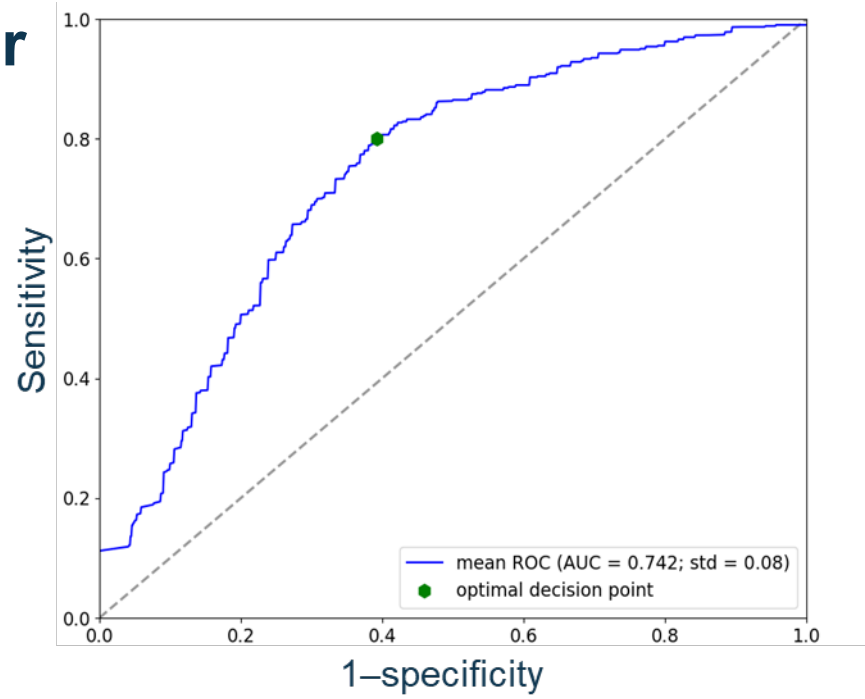


*Initial monthly injections of three loading doses.

Results of Experiment 3 – interval after second year



- ARIES:
  - **Sensitivity:** Patients identified as needing a **'short'** interval: From study data: 116 patients; from model: 93 patients (80% sensitivity)
  - **Specificity:** Patients identified as needing a **'long'** interval: From study data: 105 patients; from model: 66 patients (63% specificity)
  - **Overall accuracy** of the algorithm in this case was 71%
- ALTAIR: Results with machine learning (not deep learning) approaches
  - **Sensitivity:** 34 of 43 (81%)
  - **Specificity:** 24 of 34 (71%)



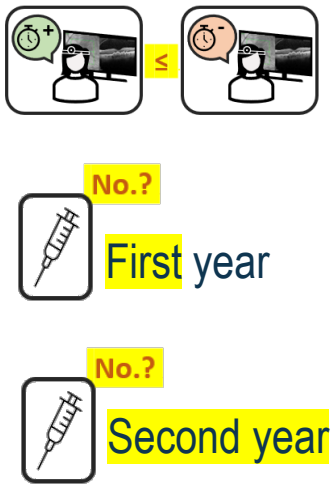
ROC of Experiment 3 for ARIES. Threshold for accuracy chosen as 0.5 (not equal to the optimal decision point).

	AUC	Accuracy	Sensitivity	Specificity	No.of short intervals	No. of long intervals
ARIES*	0.74	71%	80% (93/116)	63% (66/105)	116	105
ALTAIR*	0.77	76%	81% (34/43)	71% (24/34)	43	34

Short interval: Intended patient individual treatment interval after 2 years <12 weeks. Long interval: Intended patient individual treatment interval after 2 years ≥12 weeks.
*Numbers of patients differ from total numbers (Slide 3). ARIES: Three images excluded due to too poor image quality for segmentation. ALTAIR: 35 cases excluded due to missing reading-center proved annotations.
ROC, receiver operator characteristic; AUC, area under the curve

Results – additional experiments

- Experiment 1: <3 interval extensions in the four visits after treatment initiation* (starting from Week 16)
- Experiment 2 (first year): ≥8 injections
- Experiment 2 (second year): ≥5 injections



Experiment	Study	AUC	Accuracy	Sensitivity	Specificity	No.of Positives	No. of Negatives
Experiment 1	ARIES	0.87	77%	83% (59/72)	71% (26/36)	72	36
Experiment 1	ALTAIR	0.78	78%	85% (31/37)	71% (36/46)	37	46
Experiment 2 (first year)	ARIES	0.84	75%	81% (52/64)	70% (31/44)	64	44
Experiment 2 (first year)	ALTAIR	0.79	79%	79% (27/35)	78% (42/54)	35	54
Experiment 2 (second year)	ARIES	0.79	73%	75% (79/105)	71% (82/116)	105	116
Experiment 2 (second year)	ALTAIR	0.78	78%	87% (34/39)	69% (26/38)	39	38

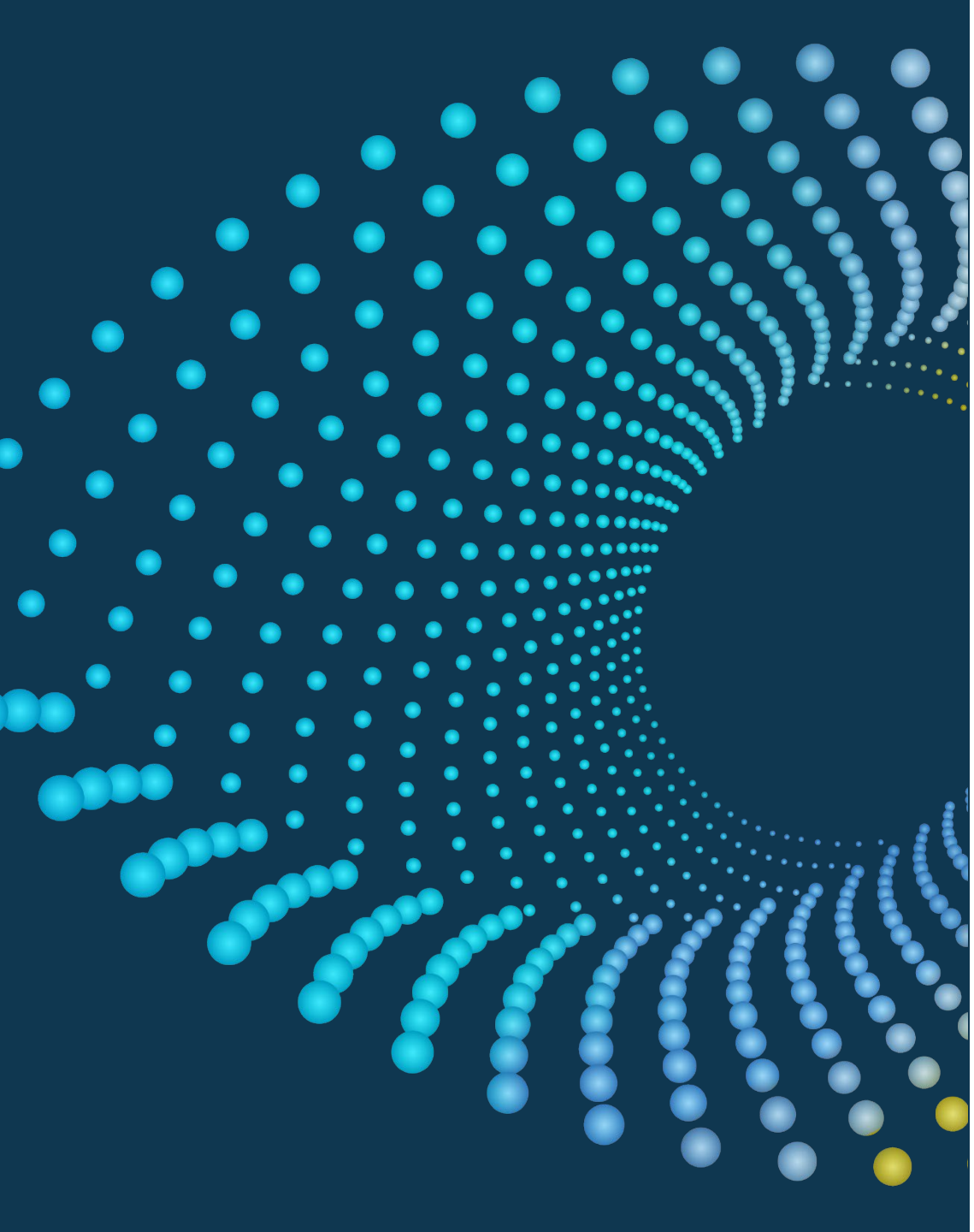
Experiment 1: Predict first potential adequate injection interval.
Experiment 2: Predict injection frequency in first and second treatment years.
*Treatment initiation with initial monthly injections.

Conclusions

- AI models successfully adapted from PRN to T&E prediction
- New AI algorithm accurately assigns a percentage between 71% and 76% of patients to the <12 weeks or ≥12 weeks interval extension groups (→ Experiment 3)
- Further experiments achieved a good* prediction accuracy, between 73% and 78%; AUC of 0.78–0.84
- Potential clinical benefits for prediction of future treatment need
  - Informing patients about the expected need for therapy
  - Support ophthalmologists in optimizing treatment regimens
  - Reduce risk of under- and overtreatment
  - Reduce treatment burden for patients and caregivers
  - Improve therapy adherence
- AI models can potentially mitigate the variability among medical experts
- The limitations are the use of controlled study data with a preselected cohort of patients

*Bogunović H, et al. prediction of “extendable treatment interval group”: AUC 0.71.[1]

1. Bogunović H, et al. *Front Med (Lausanne)*. 2022;9:958469.



Thank you for your attention