## Clinical Studies

### Patients

Insured patients at a satellite office (primary cohort) or a hospital-based clinic (secondary cohort) of a tertiary care center who were diagnosed with nvAMD were treated with bevacizumab, aflibercept, or Lucentis (hereafter, "anti-VEGF therapy"). Inclusion criteria included a new diagnosis of nvAMD [diagnosed on clinical exam and Spectral Domain Optical Coherence Tomography (SD-OCT), and confirmed by fluorescein angiography] or newly active nvAMD (with an absence of activity or treatment for at least 1 year and a presenting vision of 20/400 or better) who were followed after initiating treatment without interruption for at least 1 year. All patients included in this study agreed to participate in the "treat-and-extend-pause/monitor" (TEP/M) approach (see below). Exclusion criteria included an underlying ischemic retinal disease at the time of diagnosis (e.g., diabetic retinopathy, retinal vein occlusion, sickle cell retinopathy), other forms of choroidal neovascularization (e.g., presumed ocular histoplasmosis, polypoidal choroidopathy, etc.), post-surgical cystoid macular edema, active ocular inflammation, or a recent (within 1 year) history of intraocular steroid treatment. Patients in whom treatment was withheld after being determined to be "futile" (i.e., the presence of atrophy or a disciform scar involving the foveal center at presentation which prevented an improvement in vision despite an adequate response to treatment of fluid) were excluded from the study. Patients who had a delayed return for a scheduled treatment by more than 2 weeks once in the first 3 months or twice in the first year were also excluded from the study.

### Treat-and-Extend-Pause/Monitor (TEP/M) Protocol

All patients included in this study underwent a TEP/M approach in which patients receiving anti-VEGF therapy underwent 3 consecutive monthly injections followed by a TAE approach in which the interval between treatments was extended by 2 weeks at each visit in the absence (or near absence) of fluid, hemorrhage, or a decline vision (Supplemental Figure 1). Vision, clinical exam, and SD-OCT were obtained at all scheduled clinic visits. Return of fluid or a decline in vision resulted in a reduction of the interval between visits by 2-4 weeks; new hemorrhage would result in a decrease in the interval between visits back to 1 month. Stable patients extended to 12 weeks had their treatment held (paused), at which point the patients entered the "PRN phase" of treatment. After cessation of treatment, patients returned in 6 weeks (18 weeks from most recent treatment). If the patient remained stable at the 6-week follow up visit, treatment was held again, and the patient was followed every 12 weeks during the monitoring phase of the approach. A decline in vision, or a return in fluid or hemorrhage at subsequent visits would result in resuming treatment. Patients who failed an extension would be given another opportunity to have the interval between visits extended once they were stable for at least 3 consecutive visits. Patients were defined as having been successfully paused from treatment if they did not require treatment on 3 consecutive scheduled visits following treatment cessation (i.e., at least 12 + 6 + 12 weeks; or 30 weeks total). Follow up for patients successfully paused from anti-VEGF therapy therefore required a minimum of 30 weeks beyond their last injection.

**Grading fluid status overtime**

SD-OCT images were obtained and analyzed from all eligible patients enrolled in the study who underwent the TEP/M approach for at least 12 months. SD-OCT images were graded at timepoints 0, 1, 2, 3, 6, and 12 months after initiation of protocol for the presence of fluid by two

independent and masked graders (TPP and ZY); OCTs performed at time points closest to 6 and 12 months (i.e., within 4 weeks of the 6 time point and 6 weeks of the 12 month time point from treatment initiation) were included in this analysis. Each image was classified as having no fluid, subretinal fluid (SRF), intraretinal fluid (IRF), or both. Differences in image grading between the two blinded graders was reconciled and if an agreement could not be reached, a third investigator (AS) cast the tie-breaker vote. The location of fluid for each patient and at each time point was graphically represented in a table with different color cells representing no fluid, SRF, IRF or both. Patients were grouped based on frequency of treatment at 12 months to compare those who were able to successfully pause treatment with those who were unable to reach treatment pause.

**Proteomics**

*Sample preparation*

Samples from control patients, dry (non-neovascular) AMD patients, untreated nvAMD patients, and nvAMD patients (untreated and treated up to three times) from the TEP/M study who required monthly or q12 weeks (or longer) treatment at 1 year were used for proteomics studies. For each sample, ~10 μg proteins from pooled patient samples in 10μL of 8.0 M urea lysis buffer was reduced with 6 mM dithiothreitol (DTT) for 1h at 37 $^{o}$C, and then alkylated with 12 mM iodoacetamide (IAA) for 45 minutes in the dark at room temperature. The proteins were then digested to peptides by Lys-C and trypsin. After the digestion, the peptides were acidified with 50% formic acid to pH <3, and then desalted on C18 stage-tip. Desalted peptides were then dried in a Speed Vacuum and then resuspended in 3% acetonitrile (ACN) with 0.1% HCOOH for future liquid chromatography mass spectrometry analysis (LC-MS/MS).

*LC-MS/MS analysis using data independent acquisition (DIA)*

1 ug peptides of each sample were spiked with iRT peptides and separated by ACN gradient on an in-house packed C18 column (0.75 µm I.D. x 26.5 cm length) on the Easy nLC 1200 UHPLC system (Thermo Scientific). Separated peptides were analyzed through Nanospray Flex™ Ion Source (Thermo Scientific) using Orbitrap Fusion™ Lumos™ Tribrid™ MS instrument (Thermo Scientific) by DIA as described previously (16).

*Analysis of DIA data*

The DIA data was analyzed using library free strategy. All the 9 DIA runs were performed using Spectronaut™(version 14.10, Biognosys, Schlieren, Switzerland) with directDIA™ analysis following the BGS factory search setting with uniprot_reviewed_human database (release 20,418 entries). The variable modifications on amino acid were set as oxidation(M) and acetylation (protein N-terminus), and the fixed modification on amino acid was set as carbamidomethylation (C). Cross run normalization was applied to normalize the DIA together with normalized on median.

**Statistical Analyses for Proteomic Analyses**

*PCA analysis*

Principal component analysis (PCA) was conducted using Scikit-learn (18), a machining learning module in python. The first 3 components (PCA1, PCA2, PCA3) were selected to simulate variances between 6 groups of patients (Q4 Untreated, Q4 Treated, Q12+ Untreated, Q12+Treated, Non-AMD Control, Dry AMD). Percentage of variance explained by the first 3 components were 54.73%, 42.78%, 2.16%, respectively.

*Gene Ontology*

For gene ontology analyses, DAVID was utilized to identify relevant biological processes enriched in the expressed proteins (19, 20). FDR =0.05 was chosen for the statistical significance.

*Hierarchical clustering*

Heatmap of protein expression level was generated using unsupervised hierarchical clustering with command of *scipy.cluster.hierarchy.linkage(method="complete", metric="euclidean"* from Scipy library (21) in python. The distance matrix used in the clustering was first constructed from z-score of protein expression across 6 groups of patients. Farthest Point algorithm (also known as *Complete*) was used to calculate Euclidean distance between 6 groups of patients. Visualization of heatmap was generated by Matplotlib library (22) in python.

**Mice**

Eight-week-old pathogen-free female C57BL/6 mice were obtained from Jackson Laboratory. *ApoB* mutant mice(17) and B6129 wild type control mice were obtained from Jackson Laboratories. The RD8 mutation was bred out of *ApoB* mutant mice and all mice were free of this mutation. All animals were treated in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and the guidelines of the Johns Hopkins University Animal Care and Use Committee.

**Quantitative Real-Time PCR (RT-qPCR)**

Total RNA was isolated from culture cells or retinas with PureLink$^{TM}$ RNA Mini Kit (Invitrogen #12183025), and cDNA was prepared with MuLV Reverse Transcriptase (Applied Biosystems). Quantitative real-time PCR was performed with Power SYBR Green PCR Master

Mix (Applied Biosystems) and MyiQ Real-Time PCR Detection System (Bio-Rad). Normalization was done using cyclophilin A. Total RNA was extracted using RNeasy Mini Kit (Ambion, Cat# 12183025), followed by reverse transcription to synthesize cDNA with QuantiTect Reverse Transcription Kit (Qiagen, Cat# 205311). Quantitative real-time PCR was performed using SYBR Green PCR Master Mix (Applied Biosystems, Cat# 25742). The following primers were used to examine VEGF and ApoB100 mRNA expression levels. Mouse VEGF forward primer, 5'-TTACTGCTGTACCTCCACC-3', and reverse primer, 5'-ACAGGACGGCTTGAAGATG-3'; mouse ApoB100 forward primer, 5'-AAGCACCTCCGAAAGTACGTG-3', and reverse primer, 5'-CTCCAGCTCTACCTTACAGTTGA-3'; mouse Cyclophilin A (internal control) forward primer, 5'-AGCATACAGGTCCTGGCATC-3', and reverse primer, 5'-TTCACCTTCCCAAAGACCAC-3'.

**Laser CNV Model**

Mice were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (5mg/kg). After pupils were dilated with tropicamide (Alcon Laboratories), lubricating hypromellose eye drops (Alcon Laboratories) were applied to the cornea. The fundus was viewed using a hand-held coverslip as a contact lens and laser photocoagulation was performed using the diode laser photocoagulator (IRIS Medical, Mountain View, CA) and the slit lamp delivery system. Four laser burn spots equidistant from the optic nerve using a wavelength of 532 nm, a power of 190 milliwatt, a duration of 100 ms, and a spot size of 75 μm were performed for each eye. In a subset of animals, 3 days after laser treatment, mice received a single intravitreal injection with aflibercept (200 ng/ul). Mice were sacrificed at day 7 and the eyes enucleated and fixed with 4% paraformaldehyde in PBS for 30 minutes at room temperature. Posterior eyecups

(RPE/choroid/sclera) were isolated and blocked in 5% bovine serum albumin (BSA) at 4 °C overnight and then stained with Alexa Fluor 594 conjugated Isolectin B4 (1:200, Invitrogen, CA) at 4 °C overnight. After staining, the eyecups were flat-mounted onto microscope slides with mounting medium. Lesions were excluded if visualization was obscured by overlying hemorrhage, or they were not round/discrete or if they merged into an adjacent lesion. Images were captured by Axioplan 2 imaging microscope (Carl Zeiss MicroImaging, Inc., Thornwood, NY). The area of the lesions was measured by Image J software. Representative images for selected time points from a minimum of three independent experiments are shown. Data from 4-6 animals were obtained at each time point.

**Intraocular Injections**

Intravitreal injections with aflibercept were performed with a with (PLI-100A) Pico-liter Microinjector (Warner Instruments, Harvard Bioscience) using pulled-glass micropipettes. Each micropipette was calibrated to deliver a 1-μL volume on depression of a foot switch. The mice were anesthetized with ketamine (100 mg/kg) and xylazine (5mg/kg) mixture and under a dissecting microscope after pupils were dilated with tropicamide (Alcon Laboratories). The sharpened tip of the micropipette was passed through the sclera just posterior to the limbus into the vitreous cavity and visualized through the dilated pupil. The foot switch was depressed, which caused fluid to penetrate into the vitreous space.

# Supplemental Table 1

**Supplemental Table 1.** Eyes of TEP/M patients grouped by interval between treatments at 12 months.

| Characteristic | q4 | q6-8 | q10-12 | Weaned |
|---|---|---|---|---|
| Percent of Eyes at each interval - (no.) | 17% (17) | 31% (32) | 21% (21) | 31% (32) |

Abbreviation: No., number; q4, requiring treatment every 4 weeks; q6-8, requiring treatment every 6-8 weeks; q10-12, requiring treatment every 10-12 weeks; TEP/M, treat and extend pause/monitor.

# Supplemental Table 2

**Supplemental Table 2.** Recurrence rate at 24 and 36 months in eyes of TEP/M patients who were successfully weaned from anti-VEGF treatment from the prior year.

| Characteristics | 24 Months | 36 Months |
|---|---|---|
| Number of eyes weaned off treatment from previous year | 22 | 15 |
| Eyes with recurrent activity in 12 months following weaning - % (no.) | 27% (6) | 13% (2) |

Abbreviation: No., number; TEP/M, treat and extend pause/monitor.

# Supplemental Table 3

**Supplemental Table 3.** Eyes of TEP/M patients successfully weaned from anti-VEGF treatment at any timepoint in the first 36 months of their treatment course.

| **Characteristics** | |
|---|---|
| Total number of eyes | 102 |
| Median length of follow-up in months (IQR) | 28.5 (18.0 - 43.5) |
| Range of follow-up in months | 12 – 72 |
| Percent of eyes that were successfully weaned at any point during follow-up - (no.) | 43% (44) |
| Mean length of pause without treatment for all patients who reached the monitoring phase (months) ± SEM | 18.0 ± 1.8 |

Abbreviation: No., number. IQR, interquartile range; SEM, standard error of the mean; TEP/M, treat and extend pause/monitor.

# Supplemental Table 4

**Supplemental Table 4.** Comparison of TEP/M eyes requiring "maintenance therapy" every 2-3 months with eyes of patients successfully weaned from treatment at 12 months.

| **Characteristic** | | **q8-12** | **Weaned** | ***P*** |
|---|---|---|---|---|
| Number of Eyes | | 35 | 32 | |
| Change in Vision (ETDRS letters) | | +1 ± 3 | +4 ± 3 | 0.401 |
| Letters Gained - % (no.) | 5 or more letters | **34% (12)** | **53% (17)** | **0.007** |
| | 10 or more letters | 26% (9) | 31% (10) | 0.434 |
| | 15 or more letters | 20% (7) | 16% (5) | 0.462 |
| Letters Lost - % (no.) | 5 or more letters | 17% (6) | 19% (6) | 0.713 |
| | 10 or more letters | 14% (5) | 9% (3) | 0.268 |
| | 15 or more letters | 14% (5) | 6% (2) | 0.059 |
| Change in CST (μm) | | -80.6 ± 18.6 | -70.4 ± 13.3 | 0.861 |
| Mean # of Treatments | | **7.8 ± 0.3** | **6.0 ± 0.3** | **<0.0001** |

Abbreviations: No., number; ETDRS, Early Treatment Diabetic Retinopathy Study letter score. CST, central subfield thickness; q8-12, requiring treatment every 8 -12 weeks; TEP/M, treat and extend pause/monitor. Values displayed as mean ± standard error of the mean. Statistical analysis was performed using Chi-square and Mann-Whitney test. Data in bold are statistically significant.

# Supplemental Table 5

**Supplemental Table 5.** Recovery of vision after re-treatment with anti-VEGF in patients who were weaned from therapy but were later diagnosed with new CNV activity.

| Characteristic | |
|---|---|
| Number of Eyes with recurrent activity | 8 |
| Vision at presentation (ETDRS letters) | 61 ± 5 |
| Vision at time of weaning (ETDRS letters) | 67 ± 4 |
| Vision at time of diagnosis of recurrence (ETDRS letters) | 61 ± 5 |
| Change in vision between time of weaning and time of diagnosis of recurrent activity (ETDRS letters) | -6 ± 2 |
| Vision at first visit after retreatment (ETDRS letters) | 64 ± 5 |
| Recovery of vision between time of diagnosis of recurrence and first visit after retreatment (ETDRS letters) | +3 ± 2 |

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study letter score. Values displayed as mean ± standard error of the mean.

# Supplemental Table 6

**Supplemental Table 6.** Summary of adverse events following treatment initiation at 24 and 36 months for TEP/M patients.

| | | 24 months | | | | 36 months | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Interval** | | **q4-6** | **q8-12** | **Weaned** | ***P*** | **q4-6** | **q8-12** | **Weaned** | ***P*** |
| Number of Eyes | | 25 | 22 | 23 | | 16 | 9 | 14 | |
| Adverse Events | Endophthalmitis | 0 | 0 | 0 | - | 0 | 0 | 0 | - |
| | Retinal Tear/Detachment | 0 | 0 | 0 | - | 0 | 0 | 0 | - |
| | Vitreous Hemorrhage | 0 | 1 | 0 | 0.331 | 1 | 1 | 0 | 0.482 |
| | RPE Tear | 1 | 0 | 0 | 0.401 | 1 | 0 | 0 | 0.478 |
| | SRH | 4 | 1 | 0 | 0.084 | 4 | 1 | 0 | 0.122 |
| | SR fibrosis | 2 | 1 | 2 | 0.846 | 2 | 1 | 2 | 0.974 |

Abbreviations: SRH, subretinal hemorrhage; RPE, retinal pigment epithelium; SR fibrosis, subretinal fibrosis. q4-6, every 4-6 weeks; q8-12, every 8 to 12 weeks; TEP/M, treat and extend pause/monitor. Adverse events were recorded over the initial three years of the study for patients with a minimum of 24 months of follow-up up to a maximum of 36 months of follow-up. Statistical analysis was performed using 3-sample test for equality of proportions.

# Supplemental Table 7

**Supplemental Table 7.** Baseline characteristics of patients used in VEGF ELISA.

| Characteristic | Pre-treatment q4 (n=6) | Pre-treatment q6-8 (n=5) | Pre-treatment q10-12 (n=3) | Pre-treatment Weaned (n=9) | Post-treatment q4 (n=4) | Post-treatment q6-8 (n=1) | Post-treatment q10-12 (n=4) | Post-treatment Weaned (n=3) | Control (n=23) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean Age (yr) | 78.3 ± 1.5 | 83.4 ± 2.5 | 82.3 ± 0.9 | 83.0 ± 2.2 | 75.0 ± 0.0 | 75.0* | 78.0 ± 3.5 | 88.3 ± 2.0 | 71.2 ± 1.9 | **<0.001** |
| Female % (#) | 83% (5) | 60% (3) | 100% (3) | 78% (7) | 50% (2) | 100% (1) | 50% (2) | 100% (3) | 43% (10) | 0.782 |
| Pseudophakic % (#) | 83% (5) | 100% (5) | 67% (2) | 89% (8) | 100% (4) | 100% (1) | 0% (0) | 100% (3) | 39% (9) | 0.183 |

Abbreviations: n, sample size; q4, received treatment every 4 weeks; q6-8, received treatment every 6-8 weeks; q10-12, received treatment every 10-12 weeks; VEGF, vascular endothelial growth factor; ELISA, enzyme-linked immunoassay; and yr, years. Values displayed as mean ± standard error of the mean. *Unable to obtain standard error of the mean with a sample size of 1. Statistical analysis was performed using ANOVA and Fisher's exact test. Data in bold are statistically significant.

# Supplemental Table 8

**Supplemental Table 8.** Baseline characteristics of patients used in the proteomic screen.

| Characteristic | Untreated q4 (n=3) | Untreated q12+ (n=7) | Treated q4 (n=6) | Treated q12+ (n=5) | nnvAMD (n=18) | Untreated nvAMD 1 (n=9) | Untreated nvAMD 2 (n=9) | Control 1 (n=12) | Control 2 (n=12) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean Age (yr) | 81.7 ± 2.3 | 83.7 ± 2.4 | 75.0 ± 2.4 | 82.6 ± 5.0 | 74.8 ± 2.6 | 80.2 ± 3.7 | 80.7 ± 2.1 | 71.1 ± 2.8 | 70.5 ± 2.5 | **0.008** |
| Female % (#) | 67% (2) | 86% (6) | 50% (3) | 60% (3) | 61% (11) | 56% (5) | 56% (5) | 42% (5) | 42% (5) | 0.681 |
| Pseudophakic % (#) | 67% (2) | 86% (6) | 100% (6) | 80% (4) | 0% (0) | 56% (5) | 89% (8) | 50% (6) | 25% (3) | **<0.001** |

Abbreviations: n, sample size; q4, received treatment every 4 weeks; q12+, received treatment every 12 or more weeks; nnvAMD, non-neovascular Age-related Macular Degeneration; nvAMD, neovascular Age-related Macular Degeneration; and yr, years. Values displayed as mean ± standard error of the mean. Statistical analysis was performed using ANOVA and Fisher's exact test. Data in bold are statistically significant.

**Supplemental Table 9.** Proteins identified in Proteomic Analyses which had sequences that overlap with current anti-VEGF therapies.

| Cohort | Protein Accessions | Genes | Protein |
|---|---|---|---|
| Untreated q12+ vs. q4 (n=34) | P01764 | IGHV3-23 | Immunoglobulin heavy variable 3-23 |
| | P01834 | IGKC | Immunoglobulin kappa constant |
| | P0DOX7 | - | Immunoglobulin kappa light chain |
| | P01624 | IGKV3-15 | Immunoglobulin kappa variable 3-15 |
| | A0A0C4DH31 | IGHV1-18 | Immunoglobulin heavy variable 1-18 |
| | A0A0B4J1V2 | IGHV2-26 | Immunoglobulin heavy variable 2-26 |
| | P01706 | IGLV2-11 | Immunoglobulin lambda variable 2-11 |
| | P0DOX3 | - | Immunoglobulin delta heavy chain |
| | P01700 | IGLV1-47 | Immunoglobulin lambda variable 1-47 |
| | A0A0J9YX35 | IGHV3-64D | Immunoglobulin heavy variable 3-64D |
| | A0M8Q6 | IGLC7 | Immunoglobulin lambda constant 7 |
| | A0A087WSZ0 | IGKV1D-8 | Immunoglobulin kappa variable 1D-8 |
| | P15814 | IGLL1 | Immunoglobulin lambda-like polypeptide 1 |
| | A0A0B4J1V6 | IGHV3-73 | Immunoglobulin heavy variable 3-73 |
| | A0A0B4J1V0 | IGHV3-15 | Immunoglobulin heavy variable 3-15 |
| | P01619 | IGKV3-20 | Immunoglobulin kappa variable 3-20 |
| | A0A0C4DH29 | IGHV1-3 | Immunoglobulin heavy variable 1-3 |
| | P01591 | JCHAIN | Immunoglobulin J chain |
| | P01704 | IGLV2-14 | Immunoglobulin lambda variable 2-14 |
| | P01599 | IGKV1-17 | Immunoglobulin kappa variable 1-17 |
| | A0A075B6K5 | IGLV3-9 | Immunoglobulin lambda variable 3-9 |
| | P06310 | IGKV2-30 | Immunoglobulin kappa variable 2-30 |
| | P17948 | FLT1 | Vascular endothelial growth factor receptor 1 |
| | A0A087WW87 | IGKV2-40 | Immunoglobulin kappa variable 2-40 |
| | A0A0C4DH43 | IGHV2-70D | Immunoglobulin heavy variable 2-70D |
| | A0A0C4DH25 | IGKV3D-20 | Immunoglobulin kappa variable 3D-20 |
| | A0A0B4J1X8 | IGHV3-43 | Immunoglobulin heavy variable 3-43 |
| | P01602 | IGKV1-5 | Immunoglobulin kappa variable 1-5 |
| | P01593 | IGKV1D-33 | Immunoglobulin kappa variable 1D-33 |
| | P01709 | IGLV2-8 | Immunoglobulin lambda variable 2-8 |
| | P04211 | IGLV7-43 | Immunoglobulin lambda variable 7-43 |
| | P01703 | IGLV1-40 | Immunoglobulin lambda variable 1-40 |
| | P01715 | IGLV3-1 | Immunoglobulin lambda variable 3-1 |
| | P06312 | IGKV4-1 | Immunoglobulin kappa variable 4-1 |
| Treated q12+ vs. q4 (n=15) | A0A0A0MT36 | IGKV6D-21 | Immunoglobulin kappa variable 6D-21 |
| | A0A075B6I0 | IGLV8-61 | Immunoglobulin lambda variable 8-61 |
| | P01766 | IGHV3-13 | Immunoglobulin heavy variable 3-13 |
| | A0A0A0MT89 | IGKJ1 | Immunoglobulin kappa joining 1 |
| | A0A0B4J1V1 | IGHV3-21 | Immunoglobulin heavy variable 3-21 |
| | A0A0C4DH67 | IGKV1-8 | Immunoglobulin kappa variable 1-8 |
| | P0DP01 | IGHV1-8 | Immunoglobulin heavy variable 1-8 |
| | O75015 | FCGR3B | Low affinity immunoglobulin gamma Fc region receptor III-B |
| | P0DOX5 | - | Immunoglobulin gamma-1 heavy chain |
| | P01859 | IGHG2 | Immunoglobulin heavy constant gamma 2 |
| | A0A075B6S2 | IGKV2D-29 | Immunoglobulin kappa variable 2D-29 |
| | A0A075B6Q5 | IGHV3-64 | Immunoglobulin heavy variable 3-64 |
| | P01782 | IGHV3-9 | Immunoglobulin heavy variable 3-9 |
| | A0A0C4DH68 | IGKV2-24 | Immunoglobulin kappa variable 2-24 |
| | Q9Y279 | VSIG4 | V-set and immunoglobulin domain-containing protein 4 |
| Untreated q12+ vs. q4 + Treated q12+ vs. q4 (n=9) | P35968 | KDR | Vascular endothelial growth factor receptor 2 |
| | P01871 | IGHM | Immunoglobulin heavy constant mu |
| | P01861 | IGHG4 | Immunoglobulin heavy constant gamma 4 |
| | P08637 | FCGR3A | Low affinity immunoglobulin gamma Fc region receptor III-A |
| | A0A075B6K0 | IGLV3-16 | Immunoglobulin lambda variable 3-16 |
| | A0A075B6I9 | IGLV7-46 | Immunoglobulin lambda variable 7-46 |
| | P01705 | IGLV2-23 | Immunoglobulin lambda variable 2-23 |
| | P0DOX2 | - | Immunoglobulin alpha-2 heavy chain |
| | A0A075B6R2 | IGHV4-4 | Immunoglobulin heavy variable 4-4 |

**Supplemental Table 10.** Proteins identified in Proteomics Analyses that were “highly variable”.

| Cohort | Protein Accessions | Genes | Protein |
|---|---|---|---|
| Untreated q12+ vs. q4 (n=14) | O95897 | OLFM2 | Noelin-2 |
| | P02144 | MB | Myoglobin |
| | P02533 | KRT14 | Keratin, type I cytoskeletal 14 |
| | P02745 | C1QA | Complement C1q subcomponent subunit A |
| | P07996 | THBS1 | Thrombospondin-1 |
| | P30838 | ALDH3A1 | Aldehyde dehydrogenase, dimeric NADP-preferring |
| | Q06033 | ITIH3 | Inter-alpha-trypsin inhibitor heavy chain H3 |
| | Q7Z7M0 | MEGF8 | Multiple epidermal growth factor-like domains protein 8 |
| | Q92859 | NEO1 | Neogenin |
| | P02538 | KRT6A | Keratin, type II cytoskeletal 6A |
| | P13645 | KRT10 | Keratin, type I cytoskeletal 10 |
| | P15121 | AKR1B1 | Aldose reductase |
| | P30041 | PRDX6 | Peroxiredoxin-6 |
| | P29401 | TKT | Transketolase |
| Treated q12+ vs. q4 (n=9) | P27169 | PON1 | Serum paraoxonase/arylesterase 1 |
| | Q08554 | DSC1 | Desmocollin-1 |
| | Q9BQT9 | CLSTN3 | Calsyntenin-3 |
| | A0A140G945 | CRYAA2 | Alpha-crystallin A2 chain |
| | P02743 | APCS | Serum amyloid P-component |
| | P16152 | CBR1 | Carbonyl reductase [NADPH] 1 |
| | P26998 | CRYBB3 | Beta-crystallin B3 |
| | Q9BZV3 | IMPG2 | Interphotoreceptor matrix proteoglycan 2 |
| | P53672 | CRYBA2 | Beta-crystallin A2 |
| Untreated q12+ vs. q4 + Treated q12+ vs. q4 (n=8) | P04264 | KRT1 | Keratin, type II cytoskeletal 1 |
| | P11226 | MBL2 | Mannose-binding protein C |
| | P35908 | KRT2 | Keratin, type II cytoskeletal 2 epidermal |
| | P53674 | CRYBB1 | Beta-crystallin B1 |
| | P05408 | SCG5 | Neuroendocrine protein 7B2 |
| | P26447 | S100A4 | Protein S100-A4 |
| | P35527 | KRT9 | Keratin, type I cytoskeletal 9 |
| | P69891 | HBG1 | Hemoglobin subunit gamma-1 |
| Non-Categorized Highly Variable nvAMD Proteins (n=20) | O76061 | STC2 | Stanniocalcin-2 |
| | P00742 | F10 | Coagulation factor X |
| | P02654 | APOC1 | Apolipoprotein C-I |
| | P02656 | APOC3 | Apolipoprotein C-III |
| | P02766 | TTR | Transthyretin |
| | P02795 | MT2A | Metallothionein-2 |
| | P03950 | ANG | Angiogenin |
| | P03973 | SLPI | Antileukoproteinase |
| | P04908 | HIST1H2AB | Histone H2A type 1-B/E |
| | P15291 | B4GALT1 | Beta-1,4-galactosyltransferase 1 |
| | P31025 | LCN1 | Lipocalin-1 |
| | P42857 | NSG1 | Neuronal vesicle trafficking-associated protein 1 |
| | P80188 | LCN2 | Neutrophil gelatinase-associated lipocalin |
| | Q08380 | LGALS3BP | Galectin-3-binding protein |
| | Q14114 | LRP8 | Low-density lipoprotein receptor-related protein 8 |
| | Q14520 | HABP2 | Hyaluronan-binding protein 2 |
| | Q7L804 | RAB11FIP2 | Rab11 family-interacting protein 2 |
| | Q8IUX7 | AEBP1 | Adipocyte enhancer-binding protein 1 |
| | Q92520 | FAM3C | Protein FAM3C |
| | Q96HF1 | SFRP2 | Secreted frizzled-related protein 2 |

”Highly variable” proteins were those proteins identified in the Proteomics comparison of NVAMD patients that were arbitrarily divided into two group: NVAMD1 and NVAMD2. Proteins were designated as “highly variable” if they were increased or decreased two-fold or more in this comparison.

**Supplemental Table 11.** Proteins identified in Proteomics Analyses comparing untreated q12+ vs q4.

| Genes | Protein | Untreated [q12+] / [q4] Fold Induction | Families | Overlap in other groups |
|---|---|---|---|---|
| HBB | Hemoglobin subunit beta | 294.5912433 | blood coagulation | T, DW |
| HBD | Hemoglobin subunit delta | 133.9940856 | blood coagulation | DW |
| FGA | Fibrinogen alpha chain | 2.515216354 | blood coagulation, innate immune response | T |
| FGG | Fibrinogen gamma chain | 2.44139284 | Blood coagulation | T |
| PRDX2 | Peroxiredoxin-2 | 40.31231115 | response to oxidative stress | DW |
| CA3 | Carbonic anhydrase 3 | 12.6337525 | response to oxidative stress | DW |
| RS1 | Retinoschisin | 5.352000599 | visual perception | |
| KERA | Keratocan | 3.034881465 | visual perception | |
| UBB | Polyubiquitin-B | 5.148367901 | innate immune response | DW |
| CD14 | Monocyte differentiation antigen CD14 | 3.637119709 | innate immune response, Inflammatory response | |
| CHGA | Chromogranin-A | 2.143352597 | innate immune response | |
| TGFBI | Transforming growth factor-beta-induced protein ig-h3 | 3.191129815 | angiogenesis, visual perception | |
| FGFR1 | Fibroblast growth factor receptor 1 | 2.32459108 | Angiogenesis | |
| HRG | Histidine-rich glycoprotein | 2.009087578 | angiogenesis | |
| PARK7 | Protein/nucleic acid deglycase DJ-1 | 2.825504266 | inflammatory response | DW |
| ACTN4 | Alpha-actinin-4 | 2.769172538 | response to hypoxia | |
| CTSC | Dipeptidyl peptidase 1 | 2.329260204 | aging, immune response | |
| HBA1 | Hemoglobin subunit alpha | 338.3618802 | | T, DW |
| BFSP1 | Filensin | 324.6129602 | | |
| CA1 | Carbonic anhydrase 1 | 279.0881896 | | T, DW |
| UCHL1 | Ubiquitin carboxyl-terminal hydrolase isozyme L1 | 15.46238334 | | DW |
| CA2 | Carbonic anhydrase 2 | 11.8927982 | | DW |
| PRDX1 | Peroxiredoxin-1 | 11.5138349 | | DW |
| LTBP1 | Latent-transforming growth factor beta-binding protein 1 | 8.552371289 | | |
| GPR37 | Prosaposin receptor GPR37 | 7.333329359 | | |
| CFHR4 | Complement factor H-related protein 4 | 6.394024547 | | DW |
| S100A6 | Protein S100-A6 | 6.364036426 | | |
| QPCT | Glutaminyl-peptide cyclotransferase | 6.212174994 | | |
| SERPINB6 | Serpin B6 | 5.844286537 | | DW |
| KRT13 | Keratin, type I cytoskeletal 13 | 5.68192904 | | DW |
| SHBG | Sex hormone-binding globulin | 4.635185611 | | |
| NEB | Nebulin | 4.362882999 | | T |
| GALE | UDP-glucose 4-epimerase | 4.349337472 | | |
| TYRP1 | 5,6-dihydroxyindole-2-carboxylic acid oxidase | 4.348768788 | | |
| COL9A3 | Collagen alpha-3(IX) chain | 4.331643822 | | |
| CFL1 | Cofilin-1 | 4.196064163 | | |
| ERN1 | Serine/threonine-protein kinase/endoribonuclease IRE1 | 3.793809256 | | DW |
| HPR | Haptoglobin-related protein | 3.742294514 | | DW |
| OMD | Osteomodulin | 3.730660593 | | |
| YWHAE | 14-3-3 protein epsilon | 3.727339924 | | DW |
| NME1 | Nucleoside diphosphate kinase A | 3.724068254 | | |
| LYNX1 | Ly-6/neurotoxin-like protein 1 | 3.659804308 | | |
| ADAMTS1 | A disintegrin and metalloproteinase with thrombospondin motifs 1 | 3.587495102 | | T |
| VGF | Neurosecretory protein VGF | 3.407534525 | | |
| SERPINA6 | Corticosteroid-binding globulin | 3.257955543 | | DW |
| YIPF3 | Protein YIPF3 | 3.078472751 | | |
| ITM2B | Integral membrane protein 2B | 2.921995474 | | |
| PEBP4 | Phosphatidylethanolamine-binding protein 4 | 2.887451256 | | T |
| SEZ6 | Seizure protein 6 homolog | 2.830353002 | | |
| A2M | Alpha-2-macroglobulin | 2.72326802 | | |
| DKK3 | Dickkopf-related protein 3 | 2.679453271 | | |
| AGA | N(4)-(beta-N-acetylglucosaminyl)-L-asparaginase | 2.663244962 | | |
| HSPA8 | Heat shock cognate 71 kDa protein | 2.635605532 | | T |
| ICOSLG | ICOS ligand | 2.44353239 | | |
| APOH | Beta-2-glycoprotein 1 | 2.362134509 | | |
| MINPP1 | Multiple inositol polyphosphate phosphatase 1 | 2.298580776 | | |
| ESD | S-formylglutathione hydrolase | 2.272286671 | | |
| OGN | Mimecan | 2.243984496 | | DW |
| PRKCSH | Glucosidase 2 subunit beta | 2.20073281 | | |
| YWHAQ | 14-3-3 protein theta | 2.190339748 | | |
| NRXN2 | Neurexin-2 | 2.102067281 | | |
| CYTL1 | Cytokine-like protein 1 | 2.080244258 | | |
| HEXA | Beta-hexosaminidase subunit alpha | 2.052336483 | | |
| PPIA | Peptidyl-prolyl cis-trans isomerase A | 2.050585783 | | DW |
| ALDOA | Fructose-bisphosphate aldolase A | 2.012219378 | | T, DW |

**Supplemental Table 11.** Continued…

| Genes | Protein | Untreated [q12+] / [q4] Fold Induction | Families | Overlap in other groups |
|---|---|---|---|---|
| CRYAB | Alpha-crystallin B chain | 0.163975792 | aging, response to hypoxia | DW |
| SERPING1 | Plasma protease C1 inhibitor | 0.333826255 | aging, innate immune response | |
| TIMP2 | Metalloproteinase inhibitor 2 | 0.461901398 | aging | |
| FN1 | Fibronectin | 0.185015609 | angiogenesis, response to wounding | |
| FABP5 | Fatty acid-binding protein 5 | 0.248945277 | response to wounding | DW |
| CHI3L1 | Chitinase-3-like protein 1 | 0.254186936 | inflammatory response | |
| MIF | Macrophage migration inhibitory factor | 0.285407022 | innate immune response, Inflammatory response | DW |
| C4A | Complement C4-A | 0.373871058 | innate immune response, Inflammatory response | |
| S100B | Protein S100-B | 0.457245901 | innate immune response | DW |
| COL1A1 | Collagen alpha-1(I) chain | 0.313111308 | blood coagulation, visual perception | |
| COL1A2 | Collagen alpha-2(I) chain | 0.316924771 | blood coagulation | |
| PLG | Plasminogen | 0.407741011 | blood coagulation | |
| PROZ | Vitamin K-dependent protein Z | 0.423337066 | blood coagulation | T |
| SERPINA1 | Alpha-1-antitrypsin | 0.496211675 | blood coagulation | |
| CRYBA4 | Beta-crystallin A4 | 0.357924479 | visual perception | DW |
| RBP4 | Retinol-binding protein 4 | 0.386044119 | visual perception | |
| CRYBA1 | Beta-crystallin A3 | 0.448229078 | visual perception | DW |
| PRG4 | Proteoglycan 4 | 0.435270018 | immune response | |
| PKM | Pyruvate kinase PKM | 0.446404568 | response to hypoxia | DW |
| PON3 | Serum paraoxonase/lactonase 3 | 7.80919E-05 | | |
| SPRR2E | Small proline-rich protein 2E | 0.028155793 | | |
| ANXA2P2 | Putative annexin A2-like protein | 0.072406169 | | DW |
| SEMA3A | Semaphorin-3A | 0.083599748 | | DW |
| FCN3 | Ficolin-3 | 0.133115105 | | DW |
| CD163 | Scavenger receptor cysteine-rich type 1 protein M130 | 0.139077514 | | T |
| KRT5 | Keratin, type II cytoskeletal 5 | 0.172802231 | | T, DW |
| CLN5 | Ceroid-lipofuscinosis neuronal protein 5 | 0.181945084 | | |
| EEF1A1 | Elongation factor 1-alpha 1 | 0.187204338 | | |
| PLTP | Phospholipid transfer protein | 0.221588788 | | |
| ACTG1 | Actin, cytoplasmic 2 | 0.233803389 | | DW |
| HSPB1 | Heat shock protein beta-1 | 0.250143493 | | DW |
| NCAM1 | Neural cell adhesion molecule 1 | 0.27083065 | | |
| CLUL1 | Clusterin-like protein 1 | 0.271490215 | | DW |
| PCSK2 | Neuroendocrine convertase 2 | 0.275888468 | | |
| SEMA3F | Semaphorin-3F | 0.286041058 | | |
| CLSTN2 | Calsyntenin-2 | 0.302221064 | | |
| WIF1 | Wnt inhibitory factor 1 | 0.315781286 | | |
| WFDC1 | WAP four-disulfide core domain protein 1 | 0.319196958 | | |
| CADM1 | Cell adhesion molecule 1 | 0.339567104 | | |
| APOB | Apolipoprotein B-100 | 0.351268533 | | T, DW |
| HSP90AB1 | Heat shock protein HSP 90-beta | 0.355196334 | | T, DW |
| KRT86 | Keratin, type II cuticular Hb6 | 0.356898821 | | |
| GRN | Progranulin | 0.366381115 | | |
| CDON | Cell adhesion molecule-related/down-regulated by oncogenes | 0.379931695 | | T |
| SPARC | SPARC | 0.392199239 | | |
| CTSZ | Cathepsin Z | 0.39284597 | | T |
| VIM | Vimentin | 0.403779431 | | DW |
| OAF | Out at first protein homolog | 0.406433181 | | |
| FSTL3 | Follistatin-related protein 3 | 0.406715597 | | |
| FCGBP | IgGFc-binding protein | 0.417994546 | | T |
| EFEMP2 | EGF-containing fibulin-like extracellular matrix protein 2 | 0.420191938 | | |
| GAS6 | Growth arrest-specific protein 6 | 0.420795231 | | |
| SHISA5 | Protein shisa-5 | 0.423531653 | | |
| IGFBP3 | Insulin-like growth factor-binding protein 3 | 0.43147223 | | |
| HSPA5 | Endoplasmic reticulum chaperone BiP | 0.432265466 | | |
| SORD | Sorbitol dehydrogenase | 0.43334378 | | DW |
| CFHR5 | Complement factor H-related protein 5 | 0.458636856 | | |
| COMP | Cartilage oligomeric matrix protein | 0.462606424 | | |
| BGN | Biglycan | 0.472085944 | | DW |
| CDH13 | Cadherin-13 | 0.47672027 | | |
| ORM2 | Alpha-1-acid glycoprotein 2 | 0.480971172 | | |
| SEMA4B | Semaphorin-4B | 0.482576005 | | T, DW |
| FSTL4 | Follistatin-related protein 4 | 0.489451605 | | DW |
| PDIA3 | Protein disulfide-isomerase A3 | 0.494677659 | | |
| CHRDL1 | Chordin-like protein 1 | 0.496701195 | | |

Abbreviations: T, treated; q12+ vs. q4; and DW, dry (nnv) vs. wet (nv) AMD.

**Supplemental Table 12.** Proteins identified in Proteomics Analyses comparing treated q12+ vs q4.

| Genes | Protein | Treated [q12+] / [q4] Fold Induction | Families | Overlap in other groups |
|---|---|---|---|---|
| HBB | Hemoglobin subunit beta | 9.741177638 | blood coagulation | U, DW |
| VWF | von Willebrand factor | 2.316170198 | blood coagulation, response to wounding | |
| F13B | Coagulation factor XIII B chain | 2.071380744 | blood coagulation | |
| PPBP | Platelet basic protein | 5.938169813 | immune response, inflammatory response | |
| LRP1 | Prolow-density lipoprotein receptor-related protein 1 | 2.256691398 | aging | |
| REG3A | Regenerating islet-derived protein 3-alpha | 24.49209647 | | |
| APOB | Apolipoprotein B-100 | 12.5123028 | | U, DW |
| LPA | Apolipoprotein(a) | 7.348682752 | | |
| LYPD3 | Ly6/PLAUR domain-containing protein 3 | 6.46264229 | | |
| HBA1 | Hemoglobin subunit alpha | 6.265305549 | | U, DW |
| HSP90AB1 | Heat shock protein HSP 90-beta | 4.567443665 | | U, DW |
| CREG1 | Protein CREG1 | 3.69341753 | | |
| CA1 | Carbonic anhydrase 1 | 3.679594987 | | U, DW |
| SAA2 | Serum amyloid A-2 protein | 3.592598983 | | |
| IGFALS | Insulin-like growth factor-binding protein complex acid labile subunit | 3.033746866 | | DW |
| ALDOA | Fructose-bisphosphate aldolase A | 2.845715536 | | U, DW |
| NEB | Nebulin | 2.579059473 | | U |
| ADAMTS1 | A disintegrin and metalloproteinase with thrombospondin motifs 1 | 2.556413438 | | U |
| PTPRG | Receptor-type tyrosine-protein phosphatase gamma | 2.411555991 | | |
| SERPINE3 | Serpin E3 | 2.270504964 | | |
| DPP7 | Dipeptidyl peptidase 2 | 2.266958417 | | |
| DNASE2 | Deoxyribonuclease-2-alpha | 2.241166621 | | |
| SEMA4B | Semaphorin-4B | 2.225358877 | | U, DW |
| XYLT1 | Xylosyltransferase 1 | 2.145490963 | | |
| LSAMP | Limbic system-associated membrane protein | 2.128989213 | | |
| CDHR1 | Cadherin-related family member 1 | 2.11348854 | | |
| CDON | Cell adhesion molecule-related/down-regulated by oncogenes | 2.065481663 | | U |
| TFF3 | Trefoil factor 3 | 2.061443766 | | |
| CARTPT | Cocaine- and amphetamine-regulated transcript protein | 2.036529656 | | DW |
| PEBP4 | Phosphatidylethanolamine-binding protein 4 | 2.029142013 | | U |
| C4BPB | C4b-binding protein beta chain | 0.263806239 | blood coagulation, innate immune response | DW |
| PROZ | Vitamin K-dependent protein Z | 0.311111825 | Blood coagulation | U |
| FGG | Fibrinogen gamma chain | 0.414934313 | Blood coagulation | U |
| FGA | Fibrinogen alpha chain | 0.445736521 | blood coagulation, innate immune response | U |
| F11 | Coagulation factor XI | 0.494791772 | blood coagulation | DW |
| GSS | Glutathione synthetase | 0.372327886 | aging, response to oxidative stress | |
| APOD | Apolipoprotein D | 0.442711612 | aging, angiogenesis | |
| LYVE1 | Lymphatic vessel endothelial hyaluronic acid receptor 1 | 0.379804515 | response to wounding | |
| BFSP2 | Phakinin | 0.418796856 | visual perception | DW |
| CRYBB2 | Beta-crystallin B2 | 0.493134509 | visual perception | DW |
| C3 | Complement C3 | 0.459520524 | immune response, inflammatory response | |
| DSG1 | Desmoglein-1 | 0.172452156 | | |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 | 0.180707873 | | |
| NOTCH2NLB | Notch homolog 2 N-terminal-like protein B | 0.237657357 | | DW |
| KRT5 | Keratin, type II cytoskeletal 5 | 0.365592975 | | U, DW |
| HSPA8 | Heat shock cognate 71 kDa protein | 0.392311831 | | U |
| C18orf63 | Uncharacterized protein C18orf63 | 0.410397655 | | DW |
| HRNR | Hornerin | 0.435647542 | | |
| RARRES1 | Retinoic acid receptor responder protein 1 | 0.447729551 | | DW |
| CTSZ | Cathepsin Z | 0.451195853 | | U |
| CPN2 | Carboxypeptidase N subunit 2 | 0.458456923 | | |
| MST1 | Hepatocyte growth factor-like protein | 0.461035723 | | |
| ITIH2 | Inter-alpha-trypsin inhibitor heavy chain H2 | 0.463211816 | | |
| FCGBP | IgGFc-binding protein | 0.465329804 | | U |
| CTSH | Pro-cathepsin H | 0.4686896 | | |
| NID1 | Nidogen-1 | 0.478679154 | | |
| BLVRB | Flavin reductase (NADPH) | 0.48032029 | | DW |
| SAA4 | Serum amyloid A-4 protein | 0.48042659 | | |
| CFHR2 | Complement factor H-related protein 2 | 0.484750612 | | |
| MXRA5 | Matrix-remodeling-associated protein 5 | 0.485991029 | | |
| CD163 | Scavenger receptor cysteine-rich type 1 protein M130 | 0.493570136 | | U |

Abbreviations: U, untreated q12+ vs. q4; and DW, dry vs. wet AMD.

**Supplemental Table 13.** Proteins identified in Proteomics Analyses comparing nnvAMD vs nvAMD patients.

| Genes | Protein | [nnvAMD] / [nvAMD] Fold Induction | Families | Overlap in other groups |
|---|---|---|---|---|
| CRYGC | Gamma-crystallin C | 61.08317488 | visual perception | |
| CRYBA4 | Beta-crystallin A4 | 52.012763 | visual perception | U |
| CRYBA1 | Beta-crystallin A3 | 46.68715798 | visual perception | U |
| CRYBB2 | Beta-crystallin B2 | 45.73386584 | visual perception | T |
| CRYGD | Gamma-crystallin D | 26.00092606 | visual perception | |
| BFSP2 | Phakinin | 11.02043055 | visual perception | T |
| CRYAB | Alpha-crystallin B chain | 45.43108521 | aging, response to hypoxia | U |
| SOD1 | Superoxide dismutase [Cu-Zn] | 2.754327935 | aging | |
| S100B | Protein S100-B | 13.70747112 | innate immune response | U |
| MIF | Macrophage migration inhibitory factor | 4.166874242 | innate immune response, inflammatory response | U |
| UBB | Polyubiquitin-B | 3.041668835 | innate immune response | U |
| PARK7 | Protein/nucleic acid deglycase DJ-1 | 7.132657804 | inflammatory response | U |
| PRDX5 | Peroxiredoxin-5, mitochondrial | 2.864838425 | inflammatory response, response to oxidative stress | |
| HBB | Hemoglobin subunit beta | 21.05436769 | blood coagulation | U, T |
| HBD | Hemoglobin subunit delta | 8.367414187 | blood coagulation | U |
| FABP5 | Fatty acid-binding protein 5 | 5.923981916 | response to wounding | U |
| PRDX2 | Peroxiredoxin-2 | 4.616143292 | response to oxidative stress | U |
| CA3 | Carbonic anhydrase 3 | 3.128389633 | response to oxidative stress | U |
| PKM | Pyruvate kinase PKM | 3.875686939 | response to hypoxia | U |
| LDHA | L-lactate dehydrogenase A chain | 2.290805187 | response to hypoxia | |
| GPI | Glucose-6-phosphate isomerase | 2.137825433 | angiogenesis | |
| VEGFA | Vascular endothelial growth factor A | 2.006347773 | angiogenesis, response to hypoxia | |
| CADM4 | Cell adhesion molecule 4 | 1079.311912 | | |
| MTPN | Myotrophin | 80.90222662 | | |
| UCHL1 | Ubiquitin carboxyl-terminal hydrolase isozyme L1 | 68.27128776 | | U |
| HSPB1 | Heat shock protein beta-1 | 20.7628404 | | U |
| HBA1 | Hemoglobin subunit alpha | 19.08833539 | | U, T |
| CRYGS | Gamma-crystallin S | 15.57552607 | | |
| CA1 | Carbonic anhydrase 1 | 14.67650386 | | U, T |
| ACTG1 | Actin, cytoplasmic 2 | 14.50841714 | | U |
| PGK1 | Phosphoglycerate kinase 1 | 10.83028208 | | |
| PEA15 | Astrocytic phosphoprotein PEA-15 | 8.798078837 | | |
| SERPINB6 | Serpin B6 | 8.324658874 | | U |
| GLO1 | Lactoylglutathione lyase | 8.083083466 | | |
| ALDOC | Fructose-bisphosphate aldolase C | 7.694774407 | | |
| BLVRB | Flavin reductase (NADPH) | 6.432180974 | | T |
| PPIA | Peptidyl-prolyl cis-trans isomerase A | 6.224882713 | | U |
| CA2 | Carbonic anhydrase 2 | 5.974602711 | | U |
| HSP90AB1 | Heat shock protein HSP 90-beta | 5.77152696 | | U, T |
| PEBP1 | Phosphatidylethanolamine-binding protein 1 | 5.05793535 | | |
| VIM | Vimentin | 5.0172362 | | U |
| CDA | Cytidine deaminase | 4.922377169 | | |
| GDI1 | Rab GDP dissociation inhibitor alpha | 4.576977321 | | |
| COTL1 | Coactosin-like protein | 4.358400956 | | |
| PTMA | Prothymosin alpha | 4.32518083 | | |
| SORD | Sorbitol dehydrogenase | 4.06813868 | | U |
| CTSF | Cathepsin F | 3.560278334 | | |
| ALDOA | Fructose-bisphosphate aldolase A | 3.424663922 | | U, T |
| FABP3 | Fatty acid-binding protein, heart | 3.201090179 | | |
| YWHAE | 14-3-3 protein epsilon | 2.985849473 | | U |
| MDH1 | Malate dehydrogenase, cytoplasmic | 2.94065533 | | |
| TPI1 | Triosephosphate isomerase | 2.93747156 | | |
| CNDP2 | Cytosolic non-specific dipeptidase | 2.834570565 | | |
| PRDX1 | Peroxiredoxin-1 | 2.750944724 | | U |
| AGRN | Agrin | 2.612258344 | | |
| PLA2G2A | Phospholipase A2, membrane associated | 2.388076841 | | |
| TTN | Titin | 2.348953176 | | |
| TUBA1A | Tubulin alpha-1A chain | 2.148832413 | | |
| DBI | Acyl-CoA-binding protein | 2.133446259 | | |
| GPNMB | Transmembrane glycoprotein NMB | 2.130059261 | | |
| FAH | Fumarylacetoacetase | 2.12041099 | | |
| GAA | Lysosomal alpha-glucosidase | 2.010706804 | | |

**Supplemental Table 13.** Continued...

| Genes | Protein | [nnvAMD] / [nvAMD] Fold Induction | Families | Overlap in other groups |
|---|---|---|---|---|
| NQO1 | NAD(P)H dehydrogenase [quinone] 1 | 0.228294263 | aging | |
| F11 | Coagulation factor XI | 0.229890141 | blood coagulation | T |
| SERPINA10 | Protein Z-dependent protease inhibitor | 0.2728352 | blood coagulation | |
| PROC | Vitamin K-dependent protein C | 0.467077313 | blood coagulation | |
| C4BPB | C4b-binding protein beta chain | 0.47378127 | blood coagulation, innate immune response | T |
| CD59 | CD59 glycoprotein | 0.477809186 | blood coagulation | |
| CFI | Complement factor I | 0.274247036 | innate immune response | |
| APOL1 | Apolipoprotein L1 | 0.44391838 | innate immune response | |
| CSF1 | Macrophage colony-stimulating factor 1 | 0.489228781 | innate immune response, inflammatory response | |
| CHIT1 | Chitotriosidase-1 | 0.40655903 | immune response | |
| C8B | Complement component C8 beta chain | 0.477202815 | immune response | |
| ADIPOQ | Adiponectin | 0.437976262 | response to hypoxia | |
| SPTB | Spectrin beta chain, erythrocytic | 0.000598752 | | |
| CFHR4 | Complement factor H-related protein 4 | 0.003871227 | | U |
| FCN3 | Ficolin-3 | 0.052762249 | | U |
| C18orf63 | Uncharacterized protein C18orf63 | 0.070034178 | | T |
| KRT13 | Keratin, type I cytoskeletal 13 | 0.116182893 | | U |
| APOB | Apolipoprotein B-100 | 0.16153718 | | U, T |
| ANK1 | Ankyrin-1 | 0.185618017 | | |
| - | - | 0.28871739 | | |
| LCAT | Phosphatidylcholine-sterol acyltransferase | 0.289392178 | | |
| KRT5 | Keratin, type II cytoskeletal 5 | 0.300217468 | | U, T |
| NOTCH2NLB | Notch homolog 2 N-terminal-like protein B | 0.309663806 | | T |
| SLC3A2 | 4F2 cell-surface antigen heavy chain | 0.33564667 | | |
| BGN | Biglycan | 0.337024234 | | U |
| HPR | Haptoglobin-related protein | 0.343944767 | | U |
| ERN1 | Serine/threonine-protein kinase/endoribonuclease IRE1 | 0.349400822 | | U |
| ANXA2P2 | Putative annexin A2-like protein | 0.351552024 | | U |
| ALB | Serum albumin | 0.373444253 | | |
| SPON1 | Spondin-1 | 0.383488632 | | |
| CARTPT | Cocaine- and amphetamine-regulated transcript protein | 0.387515798 | | T |
| TPP1 | Tripeptidyl-peptidase 1 | 0.395130977 | | |
| CPN1 | Carboxypeptidase N catalytic chain | 0.403470064 | | |
| CDH5 | Cadherin-5 | 0.417058529 | | |
| THBS4 | Thrombospondin-4 | 0.426651703 | | |
| PCSK1N | ProSAAS | 0.429507086 | | |
| IGFALS | Insulin-like growth factor-binding protein complex acid labile subunit | 0.443733873 | | T |
| CLUL1 | Clusterin-like protein 1 | 0.448261392 | | U |
| LECT2 | Leukocyte cell-derived chemotaxin-2 | 0.458993238 | | |
| SEMA4B | Semaphorin-4B | 0.463568773 | | U, T |
| RARRES1 | Retinoic acid receptor responder protein 1 | 0.465422755 | | T |
| SEMA3A | Semaphorin-3A | 0.472397218 | | U |
| SERPINA6 | Corticosteroid-binding globulin | 0.473269376 | | U |
| OGN | Mimecan | 0.473307381 | | U |
| FSTL4 | Follistatin-related protein 4 | 0.482381688 | | U |
| IGF2 | Insulin-like growth factor II | 0.486571677 | | |
| FMOD | Fibromodulin | 0.492765562 | | |

Abbreviations: U, untreated q12+ vs. q4; and T, treated q12+ vs. q4.

**Supplemental Table 14.** Overlapping proteins identified in Proteomics Analyses described in Supplemental Tables 11-13.

| Cohort | Genes | Protein |
|---|---|---|
| Untreated q12+ vs. q4 + Treated q12+ vs. q4 + nnv vs.nvAMD (n=8) | HBB | Hemoglobin subunit beta |
| | HBA1 | Hemoglobin subunit alpha |
| | CA1 | Carbonic anhydrase 1 |
| | ALDOA | Fructose-bisphosphate aldolase A |
| | KRT5 | Keratin, type II cytoskeletal 5 |
| | APOB | Apolipoprotein B-100 |
| | HSP90AB1 | Heat shock protein HSP 90-beta |
| | SEMA4B | Semaphorin-4B |
| Untreated q12+ vs. q4 + Treated q12+ vs. q4 (n=11) | FGA | Fibrinogen alpha chain |
| | FGG | Fibrinogen gamma chain |
| | NEB | Nebulin |
| | ADAMTS1 | A disintegrin and metalloproteinase with thrombospondin motifs 1 |
| | PEBP4 | Phosphatidylethanolamine-binding protein 4 |
| | HSPA8 | Heat shock cognate 71 kDa protein |
| | PROZ | Vitamin K-dependent protein Z |
| | CD163 | Scavenger receptor cysteine-rich type 1 protein M130 |
| | CDON | Cell adhesion molecule-related/down-regulated by oncogenes |
| | CTSZ | Cathepsin Z |
| | FCGBP | IgGFc-binding protein |
| Treated q12+ vs. q4 + nnv vs. nvAMD (n=10) | IGFALS | Insulin-like growth factor-binding protein complex acid labile subunit |
| | CARTPT | Cocaine- and amphetamine-regulated transcript protein |
| | C4BPB | C4b-binding protein beta chain |
| | F11 | Coagulation factor XI |
| | BFSP2 | Phakinin |
| | CRYBB2 | Beta-crystallin B2 |
| | NOTCH2NLB | Notch homolog 2 N-terminal-like protein B |
| | C18orf63 | Uncharacterized protein C18orf63 |
| | RARRES1 | Retinoic acid receptor responder protein 1 |
| | BLVRB | Flavin reductase (NADPH) |
| Untreated q12+ vs. q4 + nnv vs. nvAMD (n=34) | HBD | Hemoglobin subunit delta |
| | PRDX2 | Peroxiredoxin-2 |
| | CA3 | Carbonic anhydrase 3 |
| | UBB | Polyubiquitin-B |
| | PARK7 | Protein/nucleic acid deglycase DJ-1 |
| | UCHL1 | Ubiquitin carboxyl-terminal hydrolase isozyme L1 |
| | CA2 | Carbonic anhydrase 2 |
| | PRDX1 | Peroxiredoxin-1 |
| | CFHR4 | Complement factor H-related protein 4 |
| | SERPINB6 | Serpin B6 |
| | KRT13 | Keratin, type I cytoskeletal 13 |
| | ERN1 | Serine/threonine-protein kinase/endoribonuclease IRE1 |
| | HPR | Haptoglobin-related protein |
| | YWHAE | 14-3-3 protein epsilon |
| | SERPINA6 | Corticosteroid-binding globulin |
| | OGN | Mimecan |
| | HEXA | Beta-hexosaminidase subunit alpha |
| | CRYAB | Alpha-crystallin B chain |
| | FABP5 | Fatty acid-binding protein 5 |
| | MIF | Macrophage migration inhibitory factor |
| | CRYBA4 | Beta-crystallin A4 |
| | CRYBA1 | Beta-crystallin A3 |
| | PKM | Pyruvate kinase PKM |
| | ANXA2P2 | Putative annexin A2-like protein |
| | SEMA3A | Semaphorin-3A |
| | FCN3 | Ficolin-3 |
| | ACTG1 | Actin, cytoplasmic 2 |
| | HSPB1 | Heat shock protein beta-1 |
| | CLUL1 | Clusterin-like protein 1 |
| | VIM | Vimentin |
| | SORD | Sorbitol dehydrogenase |
| | BGN | Biglycan |
| | FSTL4 | Follistatin-related protein 4 |
| | S100B | Protein S100-B |

# Supplemental Table 15

**Supplemental Table 15.** Complement proteins identified Proteomics Analyses in aqueous fluid from nvAMD patients.

| Complement Proteins | | | |
|---|---|---|---|
| **Detected in aqueous of nvAMD patients** | **Remaining after Step 1** | **Remaining after Step 2** | **Remaining after Step 3** |
| Complement C4-B | Complement C1q subcomponent subunit A | Complement C1q subcomponent subunit A | Complement C4-A |
| Complement C1q tumor necrosis factor-related protein 3 | Complement C4-A | Complement C4-A | Complement factor H-related protein 4 |
| Complement C1s subcomponent | Complement factor H-related protein 4 | Complement factor H-related protein 4 | Complement factor H-related protein 5 |
| Complement component C6 | Complement factor H-related protein 5 | Complement factor H-related protein 5 | |
| Complement C1r subcomponent-like protein | Complement C3 | Complement C3 | Complement C3 |
| Complement C3 | Complement factor H-related protein 2 | Complement factor H-related protein 2 | Complement factor H-related protein 2 |
| Complement factor B | Complement factor I | Complement factor I | Complement factor I |
| Complement C2 | Complement factor H-related protein 4 | Complement factor H-related protein 4 | Complement factor H-related protein 4 |
| Complement component C8 gamma chain | Complement component C8 beta chain | Complement component C8 beta chain | Complement component C8 beta chain |
| Complement C1q subcomponent subunit B | | | |
| Complement factor I | | | |
| Complement component C8 alpha chain | | | |
| Complement component C7 | | | |
| Complement component C8 beta chain | | | |
| Complement factor H-related protein 1 | | | |
| Complement C5 | | | |
| Complement factor D | | | |
| Complement C1r subcomponent | | | |
| Complement C1q subcomponent subunit C | | | |
| Complement component C9 | | | |
| Complement factor H | | | |
| Complement factor H-related protein 2 | | | |
| Complement C1q subcomponent subunit A | | | |
| Complement C4-A | | | |
| Complement factor H-related protein 4 | | | |
| Complement factor H-related protein 5 | | | |

Untreated q4 vs. q12+ patients (blue), treated q4 vs. q12+ patients (red), nnvAMD vs. nvAMD (green).

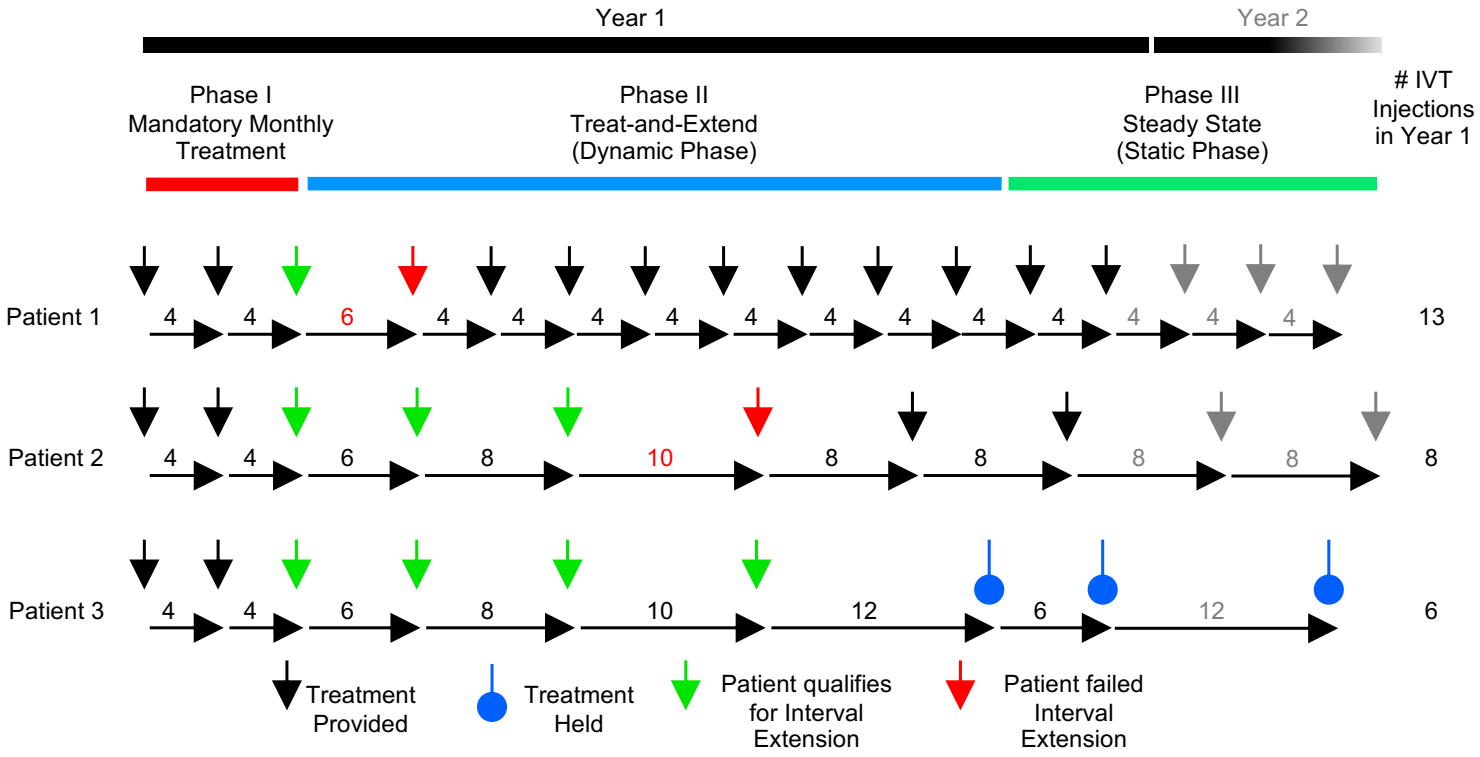
# Supplemental Table 16

**Supplemental Table 16.** Baseline characteristics of patients used in ApoB100 ELISA.

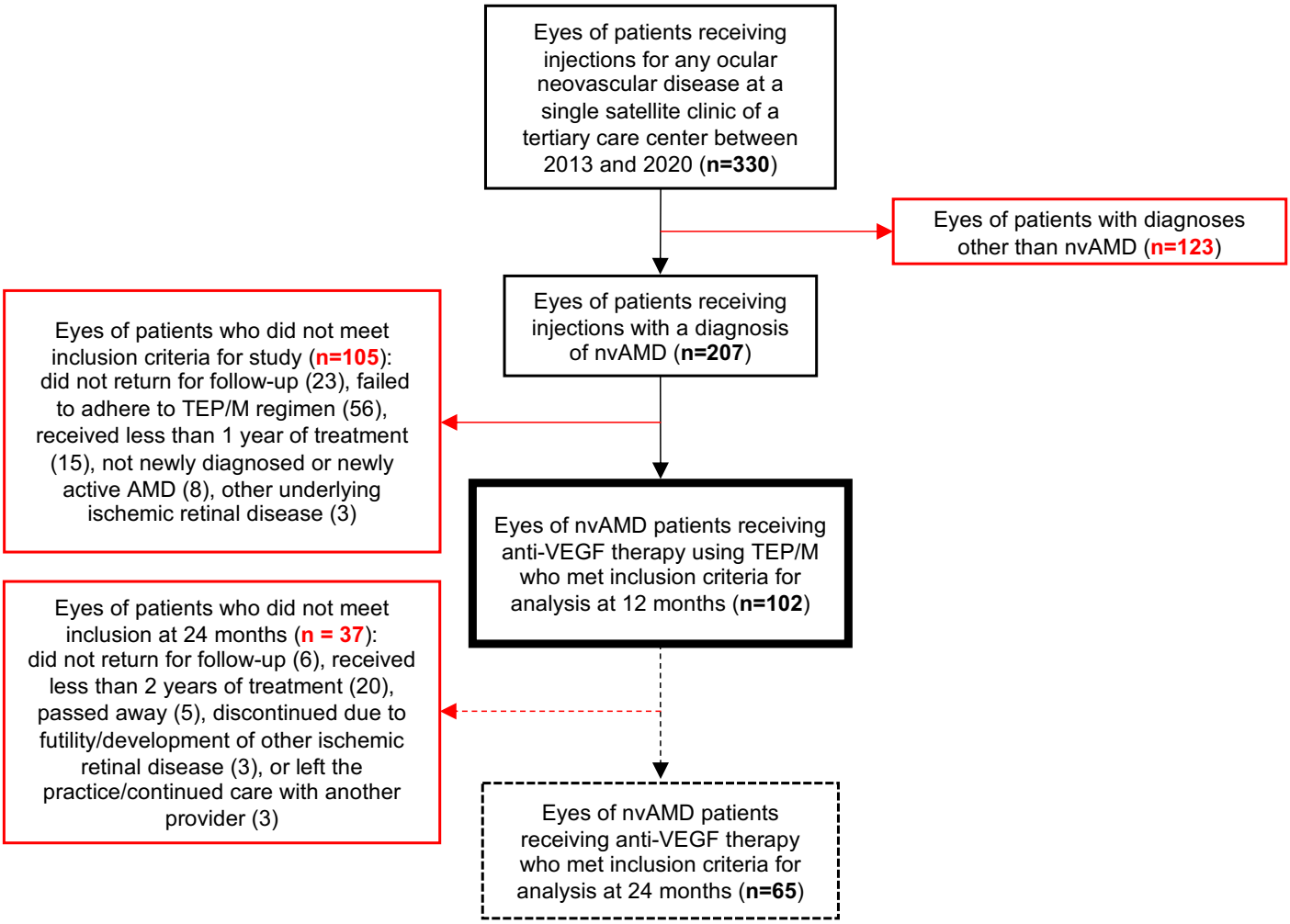
| Characteristic | Untreated nvAMD (n=10) | nnvAMD (n=10) | Non-AMD Control (n=10) | *P* |
|---|---|---|---|---|
| Mean Age (yr) | 81.1 ± 1.8 | 75.9 ± 3.0 | 73.5 ± 3.3 | 0.163 |
| Female % (#) | 50% (5) | 50% (5) | 40% (4) | 1 |
| Pseudophakic % (#) | 70% (7) | 0% (0) | 30% (3) | **0.003** |

Abbreviations: n, sample size; nnvAMD, non-neovascular Age-related Macular Degeneration; nvAMD, neovascular Aging Macular Degeneration; AMD, Age-related Macular Degeneration; ApoB100, apolipoprotein B100; ELISA, enzyme-linked immunoassay; and yr, years. Values displayed as mean ± standard error of the mean. Statistical analysis was performed using ANOVA and Fisher's exact test. Data in bold are statistically significant.

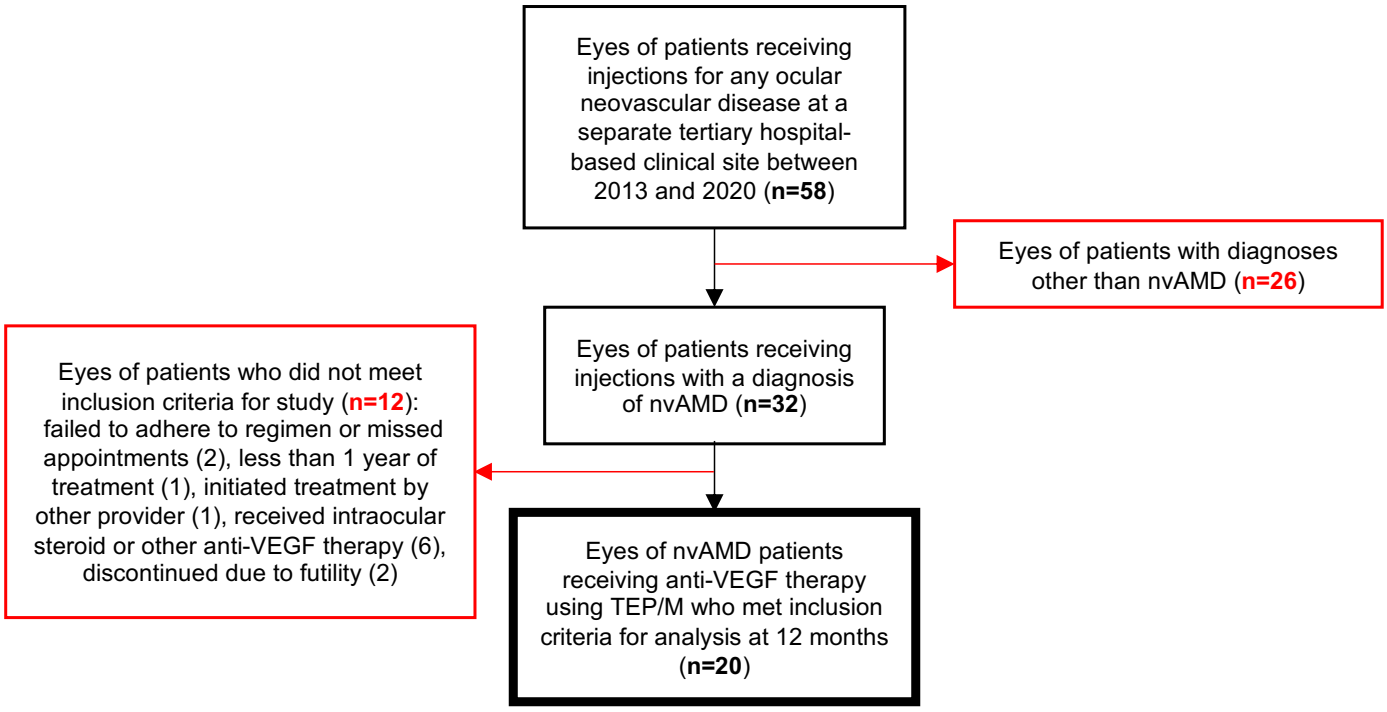
# Supplemental Figure 1



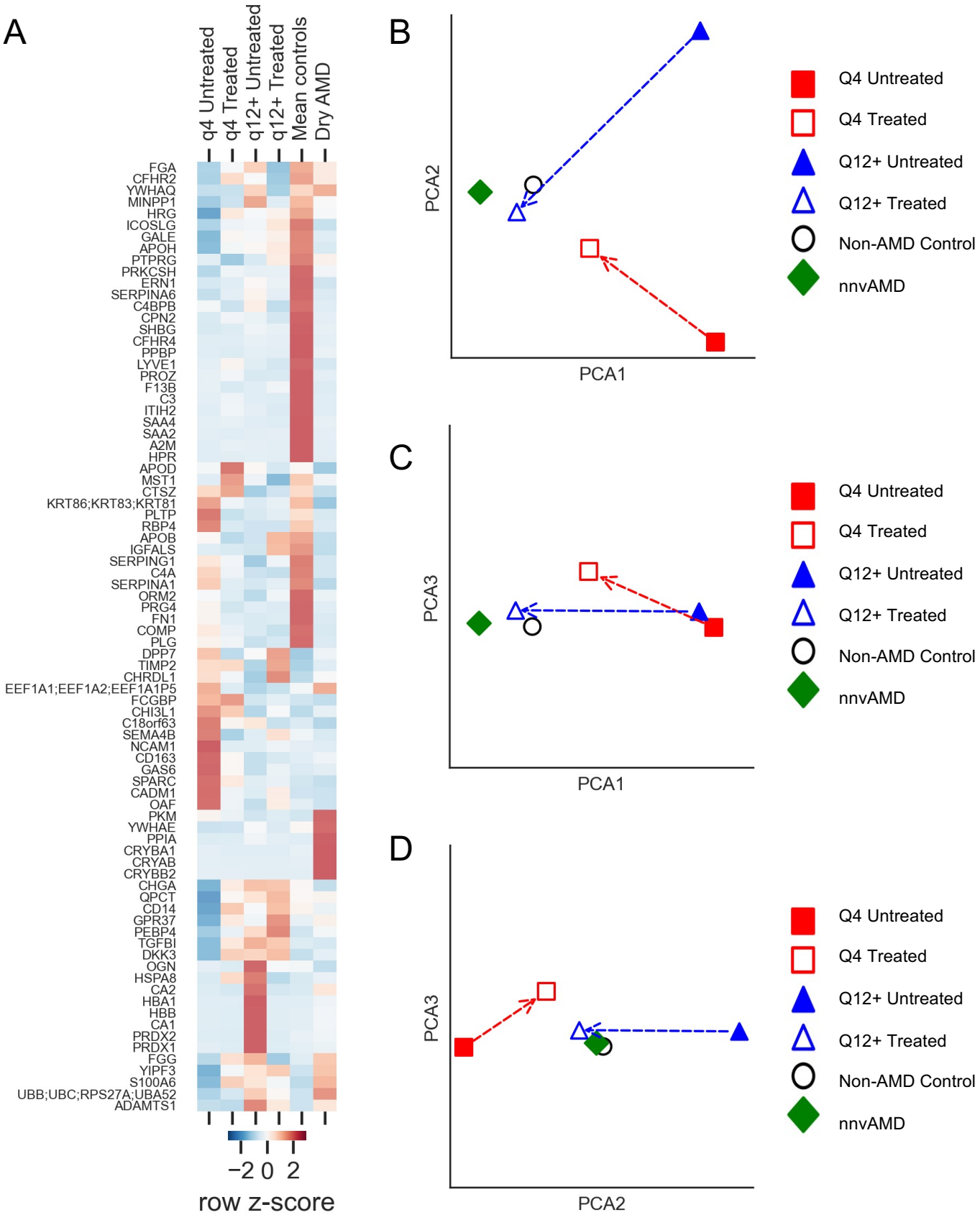
# Supplemental Figure 2



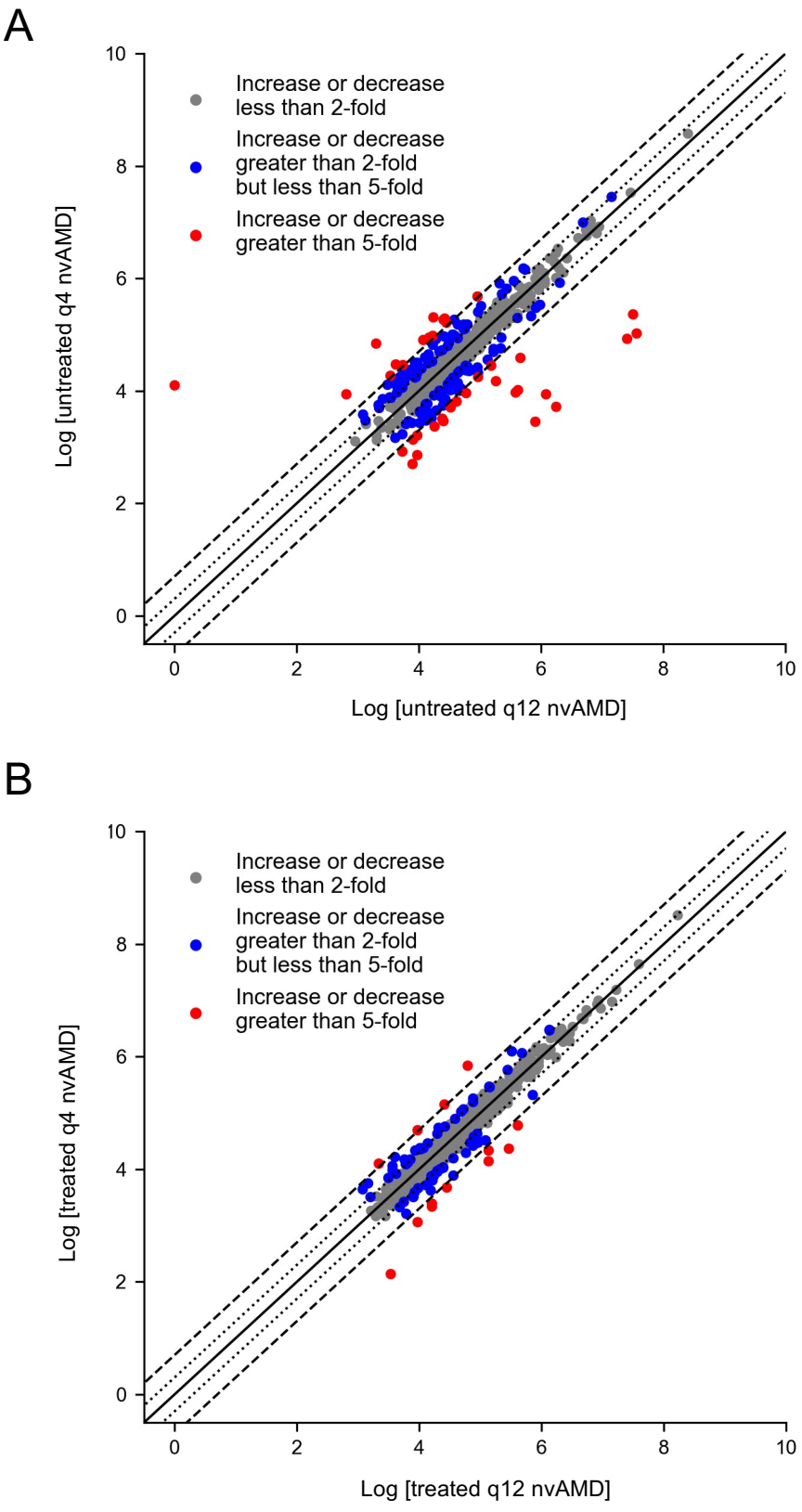
# Supplemental Figure 3



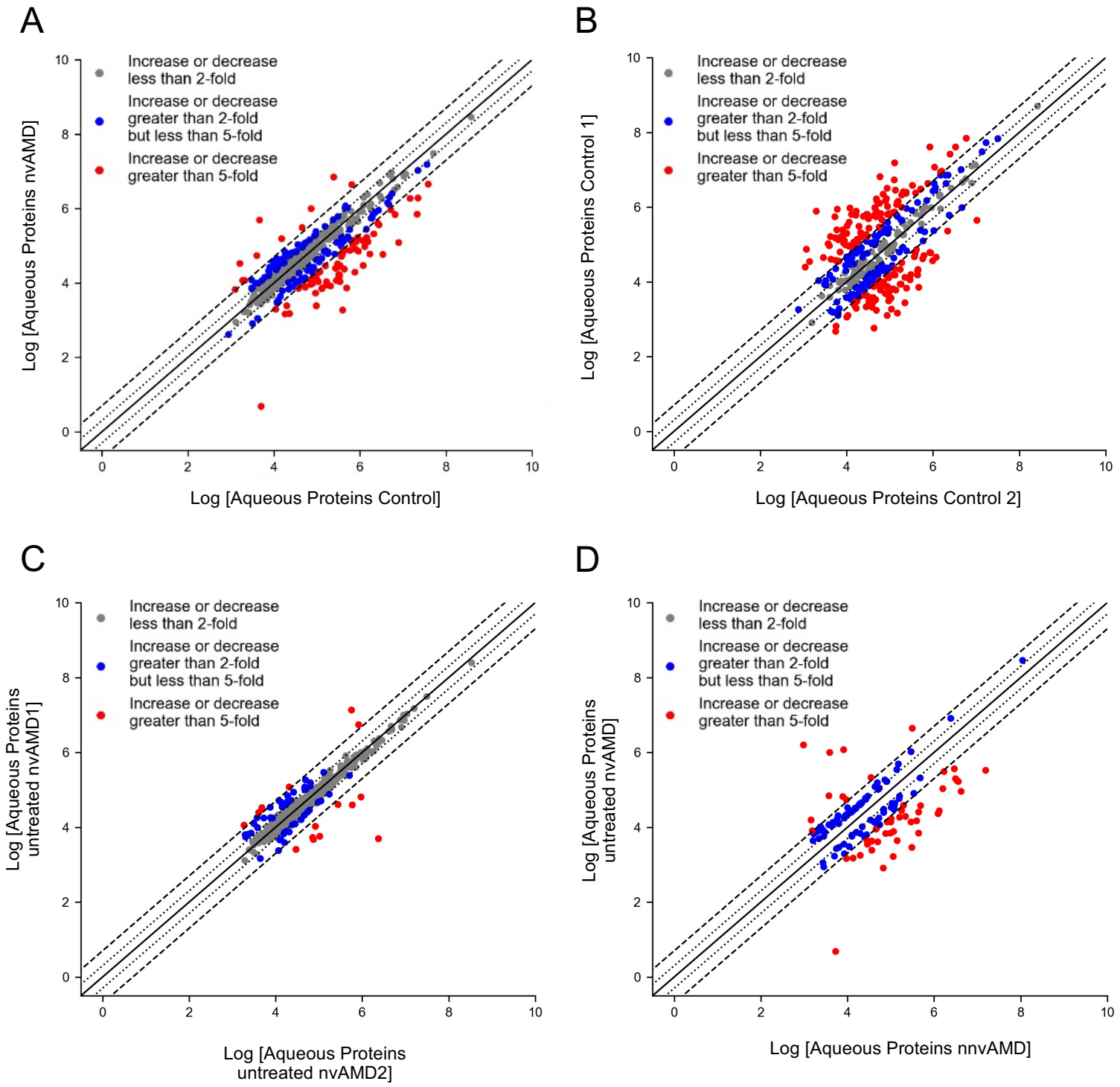
# Supplemental Figure 4



# Supplemental Figure 5



# Supplemental Figure 6



# Supplemental Figure 7