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Current Landscape for AMD Drug Development

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University of California, Washington Center

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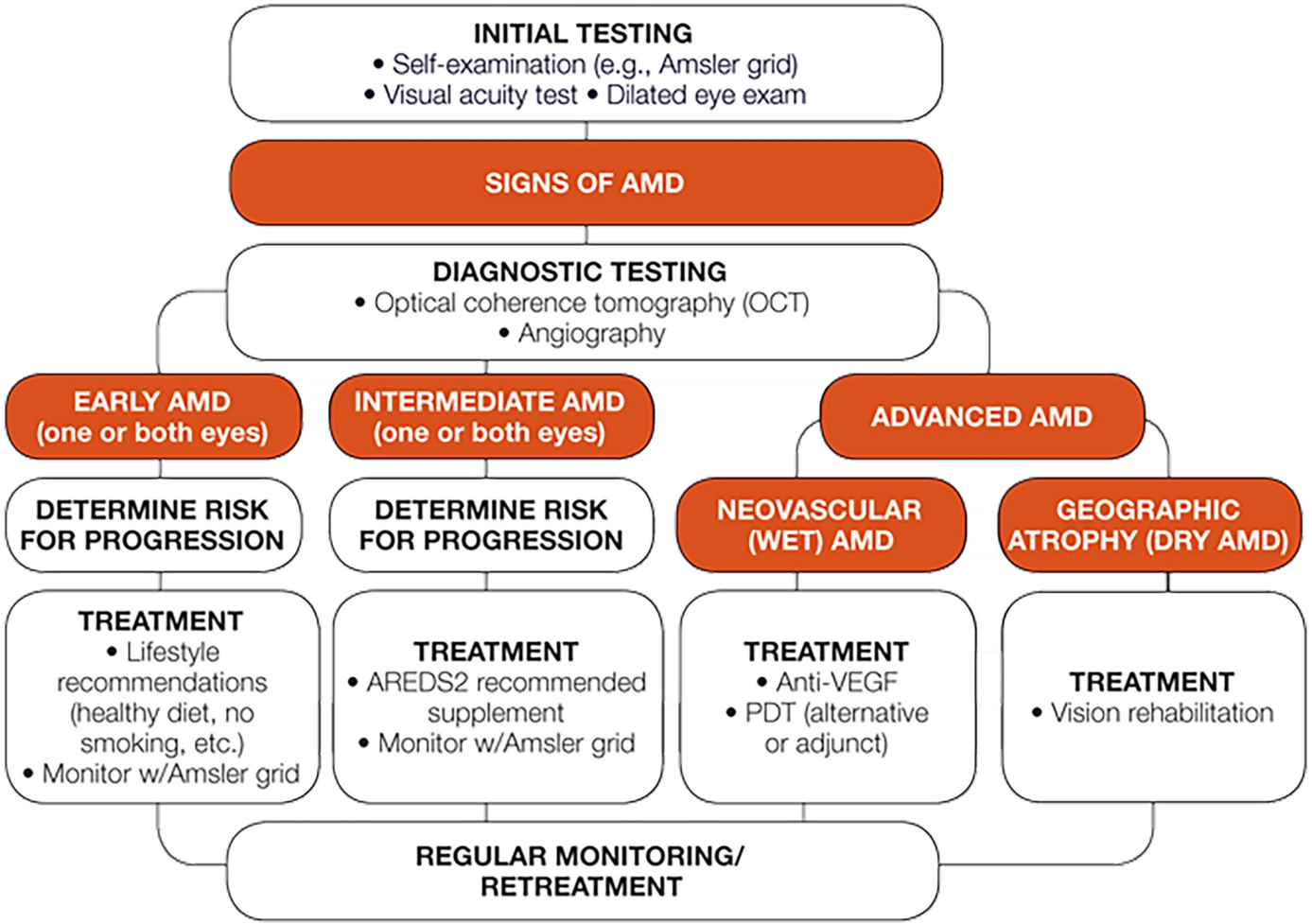
Overview

- Since 2004, significant progress has been made to treat and prevent [wet] **neovascular Age-related Macular Degeneration (nAMD)**
- The number of registered clinical trials for nAMD exceeds that of dry AMD (dAMD) by more than 2–fold
- Trials in Early-Intermediate dry AMD (dAMD) are challenging:
  a) Lack of consensus on various categories such as early and intermediate dry AMD based on drusen size and characteristics as assessed by SD-OCT and imaging techniques
  b) Endpoints such as best corrected visual acuity are not sensitive enough for these populations
- Imaging and diagnostic techniques have made it possible to diagnose “AMD suspects” at earlier times in their disease process

AMD Treatment Guidelines (50+ YEARS)



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Source: Adapted from Age-Related Eye Disease Study report no. 17 and 18; https://eye.hms.harvard.edu. Accessed September 23,2024

nAMD Therapy-History

- In the 1990's and early 2000's thermal ablation and photodynamic therapy were the only available treatments for neovascular AMD (nAMD)
- Before anti-VEGF treatment existed, removal of the subretinal vessels followed by a macular translocation or transplantation of retinal pigment epithelium cells was sometimes considered for nAMD
- Since 2004; 6 drugs + biosimilars approved for nAMD
  - Macugen (pegaptanib) Approved 2004
  - Lucentis (ranibizumab) Approved 2006
  - Avastin (bevacizumab) Approved 2004
  - Eylea (aflibercept/aflibercept HD) Approved 2011/2023
  - Beovu (brolucizamab) Approved 2019
  - Vabysmyo (faricimab) Approved 2024
  - Byooziz (ranibizumab-nuna) Approved 2021
  - Cimerli (ranibizumab-eqrn) Approved 2022

Dry AMD & Geographic Atrophy Therapy-History

- In 2013 the AREDS study established that oral supplements containing Vitamin C, E, lutein, zeaxanthin, cupric acid and zinc reduced the 5-year risk of advanced AMD by 25% in at risk patients.[1]

- Two agents that target Complement and require intravitreal injection were approved for geographic atrophy (GA)2
  - [pegcetacoplan] Syfovre; Approved 2023[2]
  - [avacincaptad pegol] Izervay; Approved 2024[3]
- Both drugs decrease the growth rate of GA, but not clear if there is improvement in vision[4]

izervay™
(avacincaptad pegol intravitreal solution) 2 mg

[1]Chew, Emily Y. et al The Age-related Eye Disease Study 2 (AREDS2). Ophthalmology, Volume 119;11, 2282 – 2289
[2]Syfovre Full prescribing Information . Accessed at PI_SYFOVRE.pdf (apellis.com)
[3]Izervay Full prescribing Information. Accessed at izervay_pi.pdf (astellas.com)
[4]Questions and answers on the refusal of the marketing authorization for Syfovre. Accessed at https://www.ema.europa.eu/en/medicines/human/EPAR/syfovre#. On September 27, 2024

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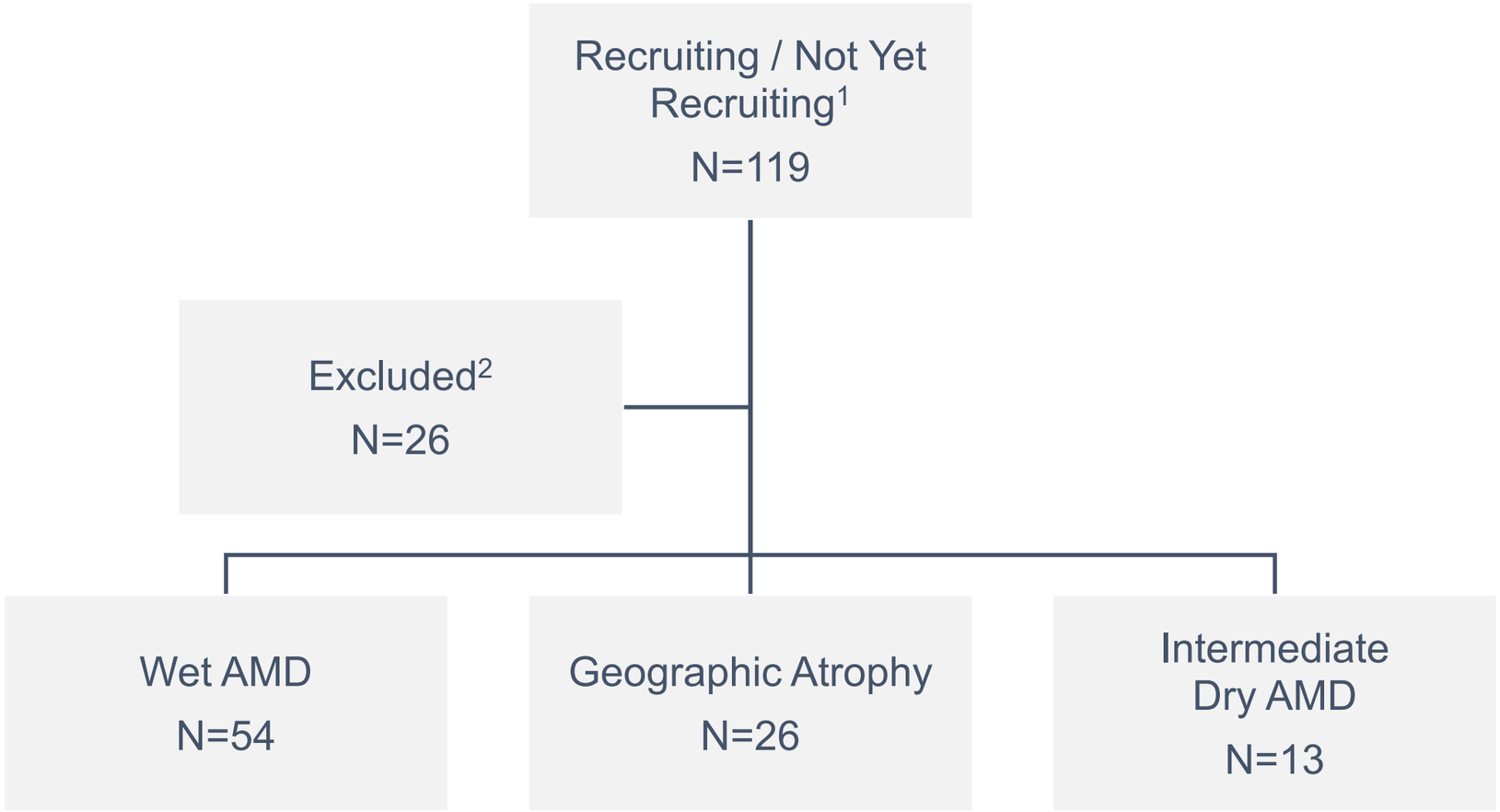
AMD Clinical Trials Landscape



[1] Registered clinical trials https://clinicaltrials.gov/; AMD + recruiting / not yet recruiting; first posted 2017–2024; Includes drugs, biologics, devices, foods
[2] Excluded trials: diagnostics or disease population not clearly stated in the record

Ongoing trials Early-Intermediate dAMD-

Registry	Population	Intervention	Primary Outcome
Devices			
NCT06557369	Intermediate AMD, AREDS Grade 3	reSEES SMPL & PBM[1]	Effect of the reSEES treatment on the progression of intermediate AMD for 1 year
NCT06046118	Dry AMD AREDS Grade 2–3	Eye Light PBM[1]	BCVA, drusen volume, contrast sensitivity at 1, 2, 4 months post Trx
NCT05507840	Dry AMD / Wet AMD	Valeda PBM[1]	Percentage of patients that develop late AMD in the study eye compared with control after 3 years
Repurposed Drugs			
NCT06319872	IRD or Dry-AMD	Oral disulfiram	Mean change in Best Corrected Visual Acuity (BCVA) score assessed by ETDRS at 6 months
NCT06165068	Dry AMD > 1 large drusen	Aspirin or clopidogrel + NAC[2]	Drusen volume as measured and analyzed by OCT scan at 1 year
Food Supplements and Behavior			
NCT06237127	Dry AMD > 1 small drusen	Goji berry[3]	Macular pigment optical volume at 6 months
NCT05932069	Intermediate AMD	Exercise intervention	Change from baseline contrast sensitivity, dark adaptometry at 6 months

[1] SMPL=Subthreshold micropulse laser; PBM=photobiomodulation
[2] NAC=N-acetylcysteine, a potent antioxidant
[3] Goji berries goji berries contain the highest concentration of zeaxanthin among all commonly consumed foods. Other diet supplement trials include omega fatty acids, pistachios

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Experimental Targets &Trials Intermediate dAMD

Registry	Target	Intervention	Outcomes (change from baseline)
Intravitreal Drugs			
NCT03626636	Integrin heterdimers	Luminate[1] (risuteganib)	% of population with ≥ 8 letters (1 ½ lines) BCVA gain 28 weeks Improvement in best corrected visual acuity & Improvement in minimum ellipsoid zone and photoreceptor layer thickness at 52 weeks
NCT02314299	Cardiolipin	Elamipretide[2]	Ellipsoid zone and photoreceptor layer thickness at 48 weeks
Oral Drugs			
NCT05230537	Complement Factor B	LNP-0233 (Iptacopan)	Development of new incomplete retinal pigment epithelium & outer retinal atrophy or late (AMD) at 24 months
NCT05019521	Complement Factor D	ALXN-20404 (Danicopan)	The square root Of total GA lesion Area at 52 and 104 weeks

[1] Luminate is an anti integrin peptide that targets heterodimers αVβ3, αVβ5, α5β1, and αMβ2) involved in the pathogenesis of AMD [Allegro Ophthalmics]
[2] Elamipretide is a cell membrane penetrating peptide that irreversibly binds mitochondrial cardiolipin increases respiration. [Stealth Therapeutics]
[3] LMP-023 is iptacopan an oral administered inhibitor of complement Factor B [Novartis]
[4] ALXN-2020 is Danicopan an oral administered inhibitor of complement Factor D [Alexion]

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Experimental Targets &Trials GA

Registry	Target	Intervention	Outcomes (change from baseline)
Injections			
NCT04437368 **NCT04566445**	CFI	GT-005[1]	Reduction in the GA area at 48 weeks EXPORE and HORIZON studies halted
Not registered **ExUS trial**	FAS receptor	ONL-1204[2]	BCVA, change in progression GA at 6 months, cytokine biomarkers
Not registered **ExUS**	C1q inhibitor	ANX-007[3]	Change in GA lesion as assessed by FAF @12 months
NCT05839041	Siglec receptors	AVD-104[4]	Rate of Change in Area of GA at Month 12

[1] GT-005 is recombinant AAV2 vector that contains a nucleotide sequence encoding complement factor I (CFI) [Novartis]
[2] ONL-1204 is a small molecule Fas inhibitor designed to protect key retinal cells, including photoreceptors, from cell death [ONL]
[3] ANX007 is a humanized immunoglobulin G4 recombinant antibody against C1q that inhibits its function as the initiating molecule of the classical complement cascade [Annexion]
[4] AVD-104 is a sialic acid–coated nanoparticle that modulates macrophages [Aviceda]

Experimental Targets &Trials GA

Registry	Target	Intervention	Outcomes (change from baseline)
Surgery			
NCT06557460	Subretinal space (SRS)	CBCB-RPE1[1]	BCVA and Retinal sensitivity by microperimetry at 12 months
NCT05626114	SRS	OpRegen[2]	% of patients With Delivery of OpRegen to target regions % of patients w/ qualitative Improvement in retinal structure, as determined by OCT at 3 months
NCT02564978	SRS	ASP-7317[3]	Area of GA by FAF; ellipsoid zone defect, area of outer nuclear layer defect by OCT at week 52
Oral Drugs			
NCT03845582	Toxic vitamin A aggregates	Gildeuretinol ALK-001[4]	Reduction in the GA lesion growth rate as read by FAF at 24 months
NCT05893537	Sigma 2 receptor	CT-112[5]	Mean rate of growth (slope) in GA lesion area

[1] CBCB-RPE1 is a polarized monolayer of human embryonic stem cell-derived RPE on, parylene substrate and synthetic Bruch's membrane [Regenerative Patch]
[2] OpRegen is an injection of retinal pigment epithelial cells derived from allogeneic stem cells into the SRS [Genentech]
[3] ASP-7317 is an injection of retinal pigment epithelial cells derived from human embryonic stem cells [Astellas]
[4] ALK-001 is C20-D3-vitamin A, a chemically-modified form of vitamin A that replaces natural vitamin A in the body with one that forms vitamin A dimers more slowly [Alkeus]
[5] CT-112 binds to the sigma-2 receptor on retinal pigment epithelial cells to restore the waste removal function that maintains healthy photoreceptors needed for vision [Cognition Therapeutics]

Imaging and Technology for Early Detection of dAMD

- GA is usually measured through fundus autofluorescence (FAF)
- High correlation between GA measured with FAF and OCT
- Growth of geographic atrophy can be readily evaluated and measured as an endpoint with FAF
- OCT can capture multiple signs that help diagnose AMD suspects at earlier times in their disease process
- Various parameters could be useful for early detection of progression in patients who are at risk

OCT (Anatomy)	Rod Function	Macular Function
iRORA	Dark Adaptometry	Microperimetry
cRORA		
Hyper transmission defects		
Ellipsoid zone integrity		

- These measures are supportive biomarkers that have not yet been validated as endpoints in clinical trials

Conclusions

- Age-related macular degeneration (AMD) is a progressive long-term medical condition, the management of which involves lifestyle changes, medical intervention and rehabilitation
- In the past 20 years, new interventions for nAMD have reached the market at a rate of 1 every 2 years
- The first interventions for dAMD were introduced in the last 18 months
- dAMD pipeline candidates currently focus on treating geographic atrophy (GA), an advanced stage of the disease, which accounts for only 10% of dAMD patients, as opposed to those with early and intermediate disease, who make up 40% of the total dAMD patient population
- Attention has transitioned to preventive care and earlier intervention in the course of disease

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Thank you!

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