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Current Landscape for iAMD Drug Development

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University of California, Washington Center

1608 Rhode Island Avenue NW, Washington DC 20036

Cheryl L. Rowe-Rendleman, PhD.

Omar Consulting Group, LLC | Princeton, NJ | Durham, NC

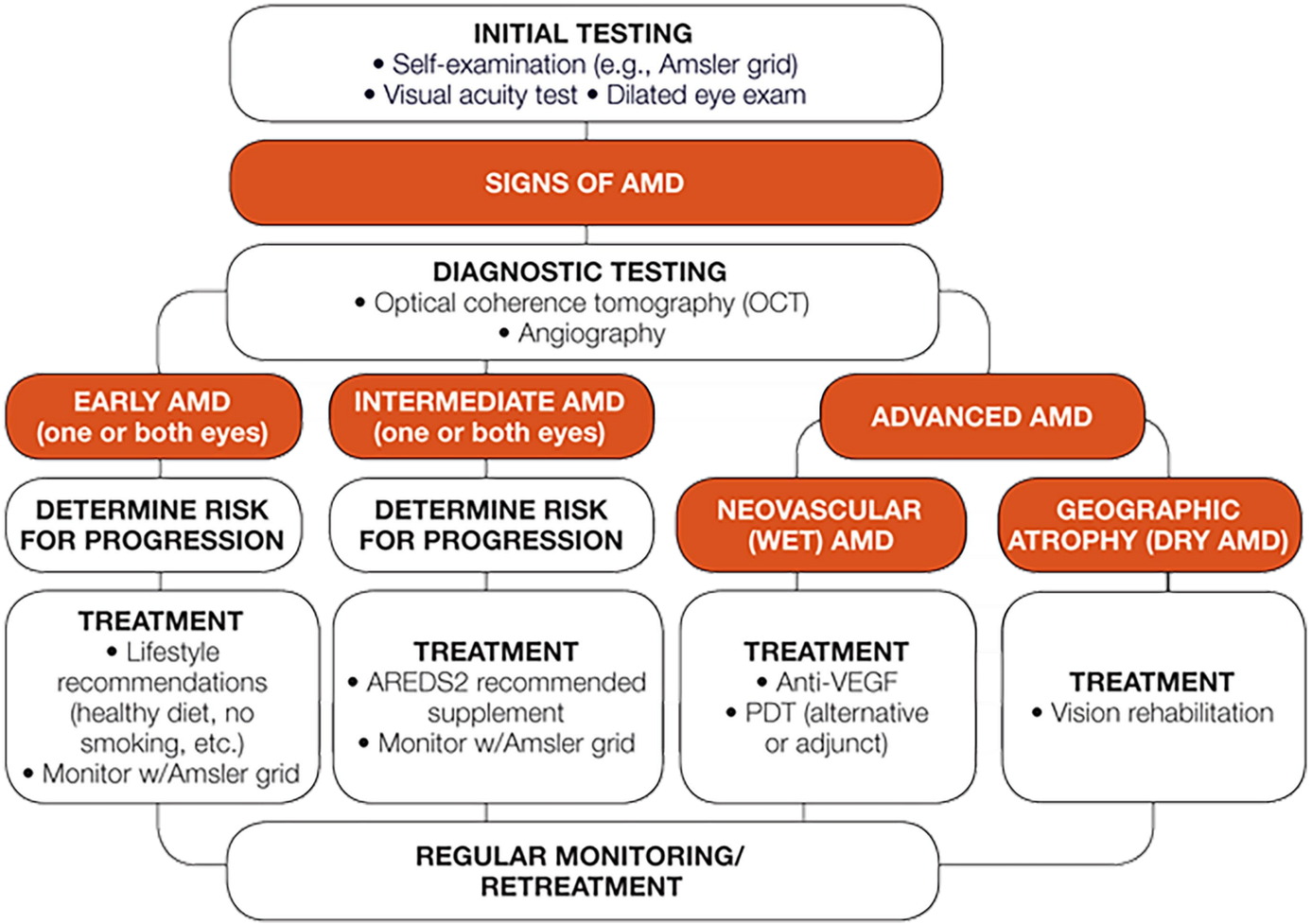
Disclosures

- Omar Consulting Group and Dr. Cheryl L. Rowe Rendleman have no relevant and/or commercial disclosures in this area.

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 population
- Imaging and diagnostic techniques have made it possible to diagnose “AMD suspects” at earlier times in their disease process
- Thus, it is imperative to explore and define a path for clinical development in intermediate AMD (iAMD)

AMD Treatment Guidelines (50+ YEARS)



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

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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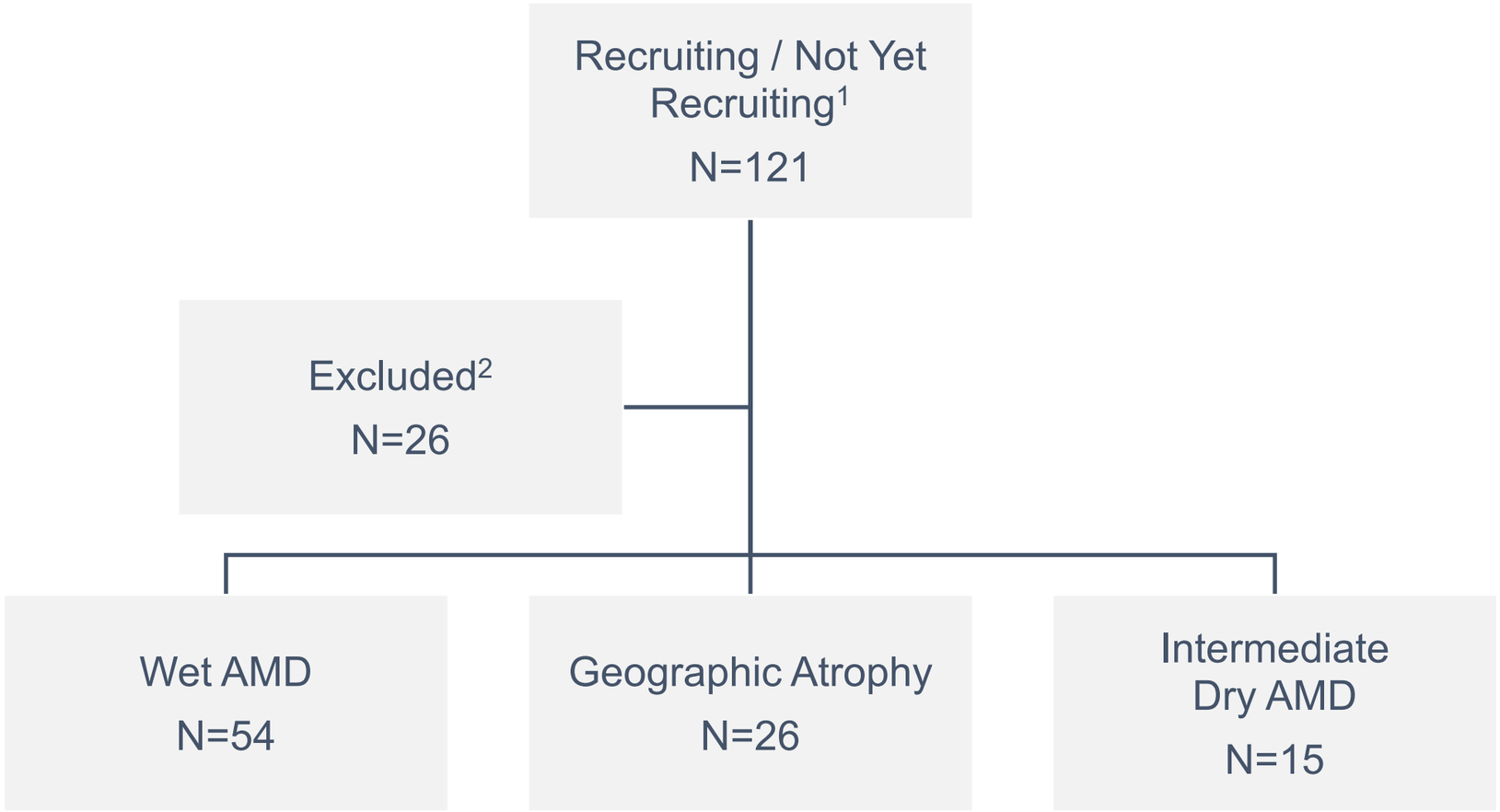
AMD Clinical Trials Landscape thru Apr 2025



[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
NCT04065490	Dry AMD / Wet AMD	Valeda PBM[1]	Percentage of patients that develop late AMD in the study eye compared with control after 3 years
NCT06662162	Intermediate AMD, GA secondary to AMD	i-Lumen	Mean change BCVA from Baseline at month 3
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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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

Key Takeaways

- Age-related macular degeneration (AMD) is a progressive long-term medical condition, the management of which involves lifestyle changes, medical intervention, and rehabilitation
- The first interventions for dAMD were introduced in the last 3 years
- 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.
    - Valeda, a new approved photobiomodulation device for the treatment of iAMD, shows promise in this area.
- Attention has transitioned to preventive care and earlier intervention in the course of disease, targeting iAMD.

Endpoints for AMD: Working Group Aims

- The Endpoints (iAMD) Working Group
  - led by Szilard Kiss (Weill Cornell Medicine) and Cheryl Rowe-Rendleman (Omar Consultants) will aim to dedicate its efforts to carving out the regulatory path for clinical trials in iAMD
- The WG will aim to:
  - Develop consensus on the definition of iAMD in the context of clinical trials
  - Identify endpoints in clinical trials and explore clinical trial design

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Thank you!

Cheryl L. Rowe-Rendleman, PhD.