Emerging functional vision endpoints/looking forward

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Financial Disclosures

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Current approved therapies slow anatomic progression but have not shown consistent functional benefit

Key challenge: Connect morphology and function

Poor Correlation

Weak links between functional measures and GA growth

Difficult to Perform

Tests perceived as challenging or burdensome

Lack of Validation

Insufficient standardization across trials

The Core Problem

Structural Endpoints

Sensitive but indirect — GA lesion area doesn't tell us how a patient functions.

Functional Endpoints

Clinically relevant but noisy — BCVA misses parafoveal loss until late disease.

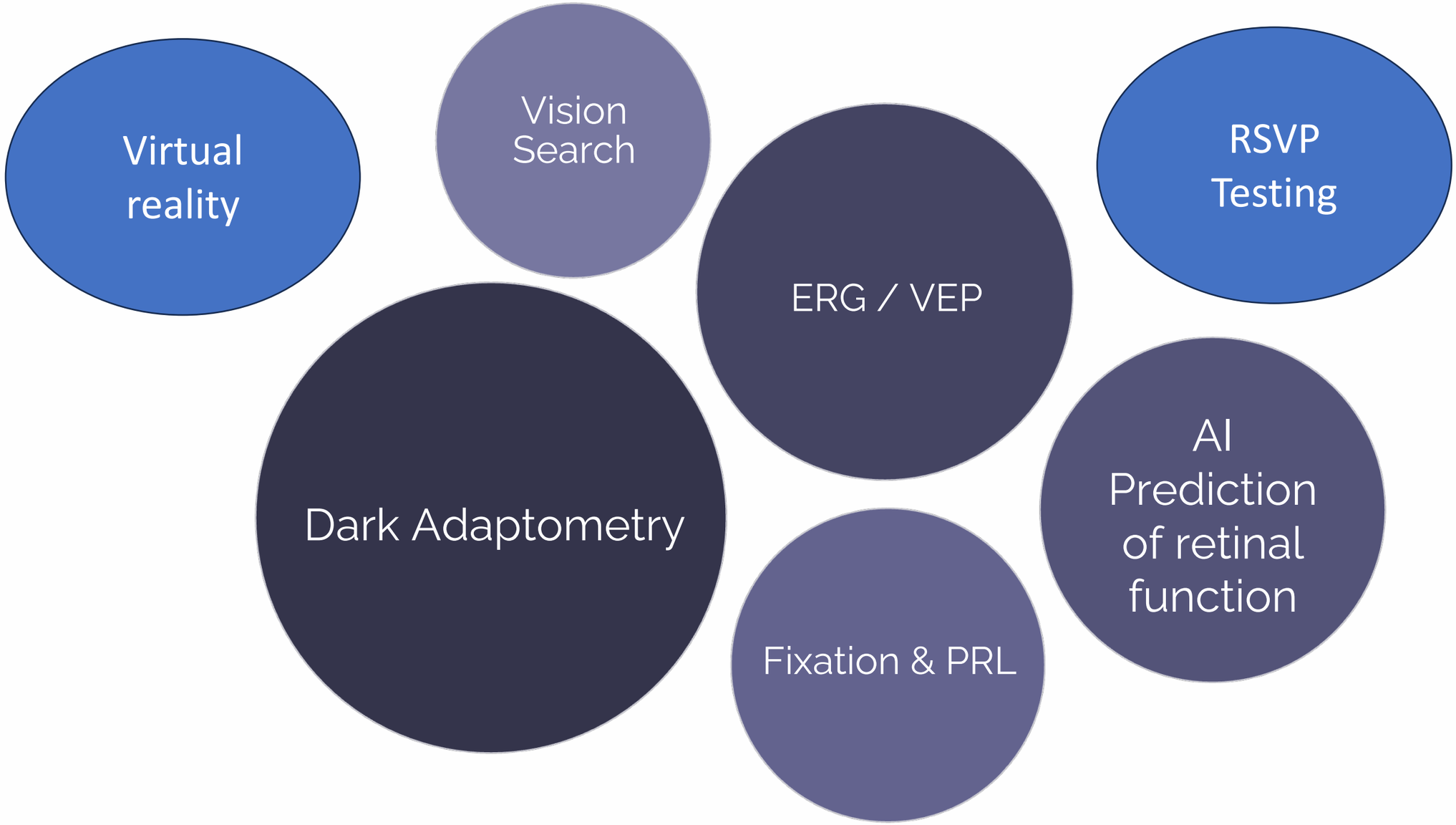
PROs

Patient-meaningful but variable — influenced by adaptation, mood, and cognition.

No single endpoint captures the full functional impact of GA. Fragmentation risks false-negative trials despite real biological effects.

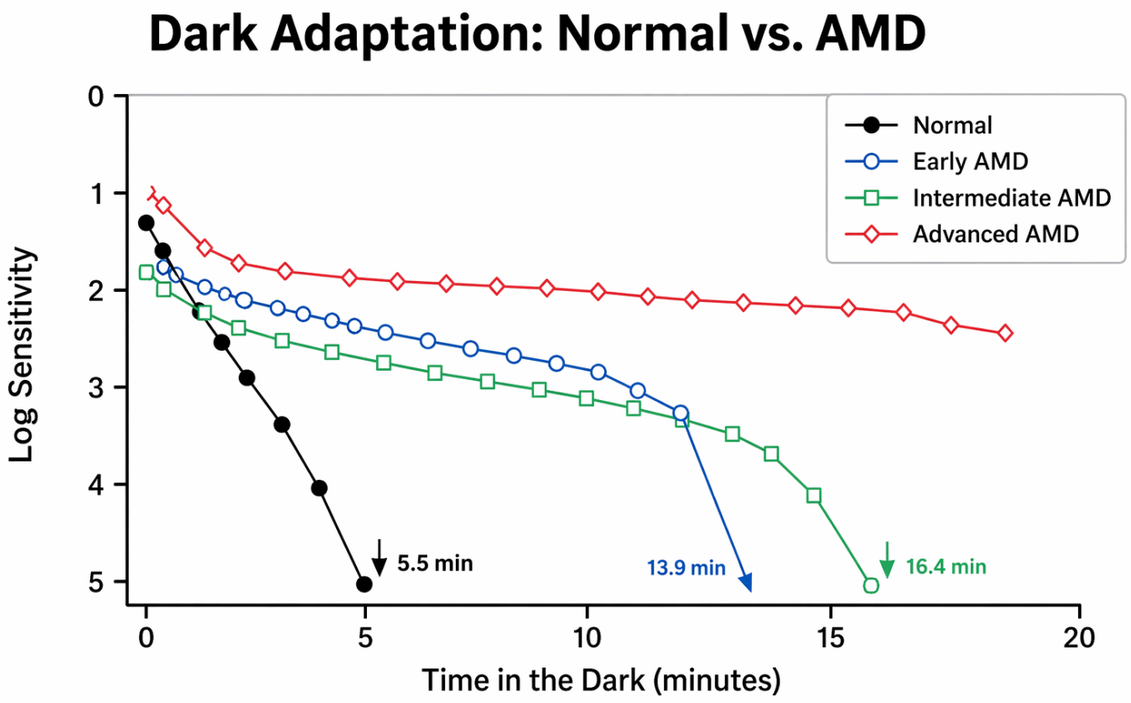
Emerging Functional Endpoints: Overview

Each addresses specific limitations of established measures — together forming a multimodal toolkit for GA trial design



Dark Adaptometry

- Night vision decline **earlier** in AMD progression than BCVA changes
- Rod-mediated dark adaptation: Greater impairment with increasing AMD severity and presence of subretinal drusenoid deposits (SDDs).



Rod Intercept Time (RIT)

Key metric — time to detect a dimmer stimulus after focal bleach. Eyes failing by 40 min are assigned RIT = 40 min.

Disease Correlation

RIT prolongation is a functional biomarker for incident early AMD, significantly associated with AMD severity.

Structural Link

Closely linked to OCT changes in the outer retina and ellipsoid zone (EZ).

Dark Adaptometry: Key Evidence

Disease Severity Link

Impaired RIT is a functional biomarker for incident early AMD and is significantly associated with AMD severity.

Longitudinal Correlation

In 65 study eyes, dark adaptation decline correlated with patient-reported functional deficits and occurred more rapidly with increasing AMD severity.

Structural Link

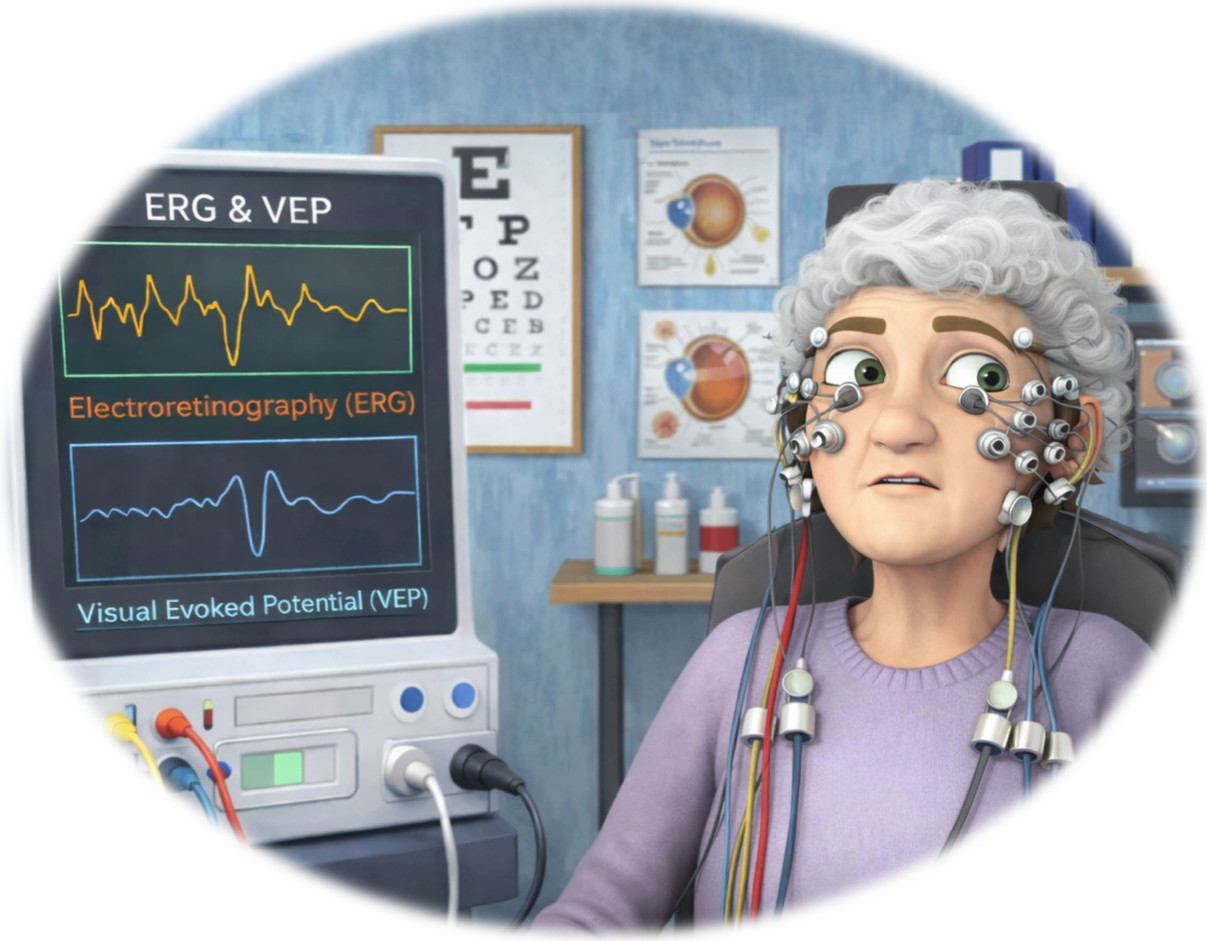
Dark adaptation is closely linked to OCT changes in the outer retina and ellipsoid zone (EZ). SDDs are associated with prolonged dark adaptation time.

Best Deployment

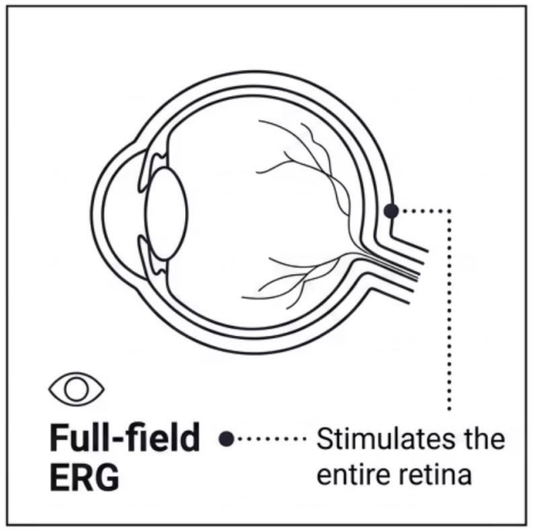
Early functional impairment suggests this endpoint is best suited for trials evaluating **smaller GA lesions**.

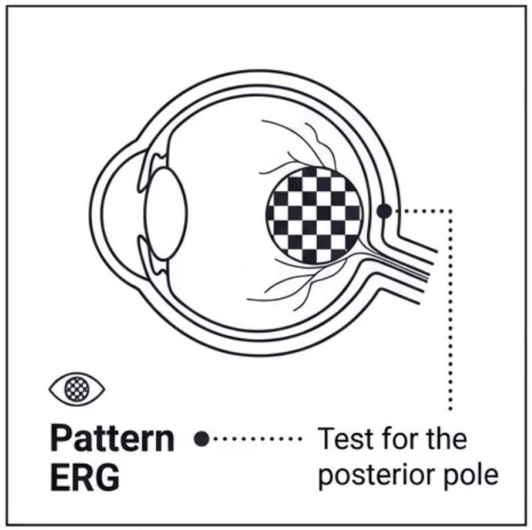
Electrodiagnostic Tests (EDTs)

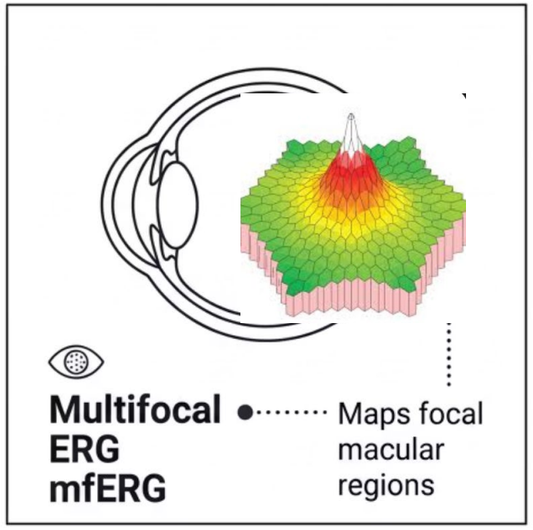
- Measures electrical activity in response to light stimuli
- **Objective** - not dependent on patient cooperation
- Key advantage over subjective tests

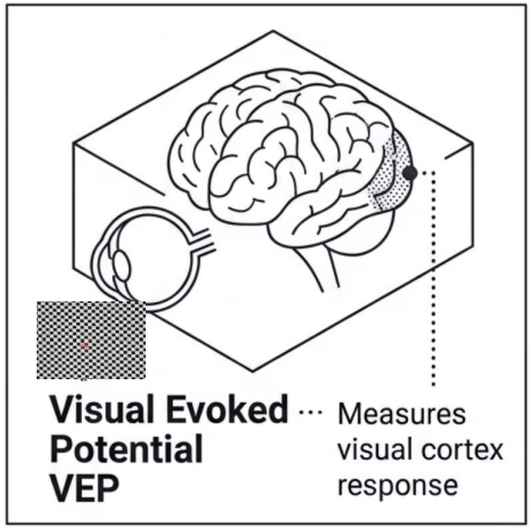


EDT Modalities









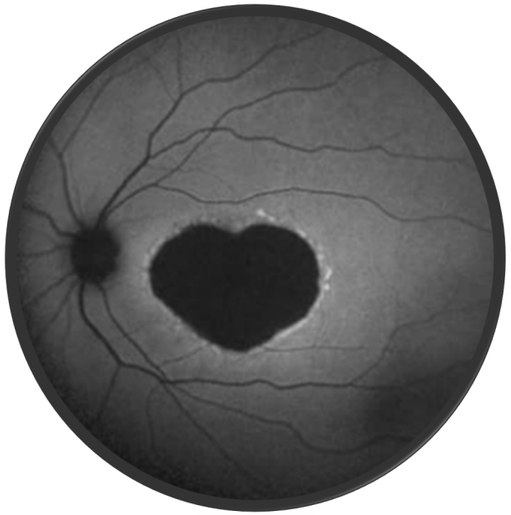
➢ mfERG Shows Most Promise

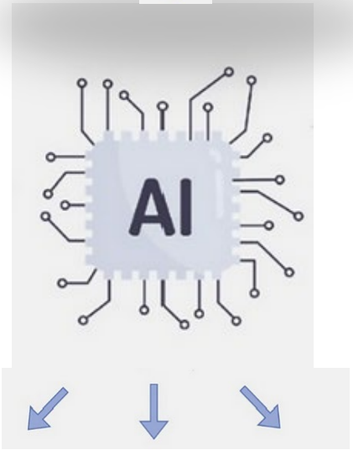
- More sensitive to retinal changes than pattern ERG or VEP
- Corresponds to OCT structural changes
- SDD presence linked to mfERG implicit time changes

Platforms include:

Diopsys® NOVA™, ARGOS™, and Diagnosys® PROFILE™

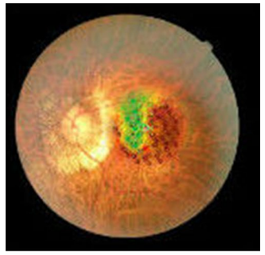
Smaller handheld devices also available





BCVA

Contrast sensitivity



Microperimetry

AI can address several challenges

1

Enrich Trials

Identify participants most at risk of progression

2

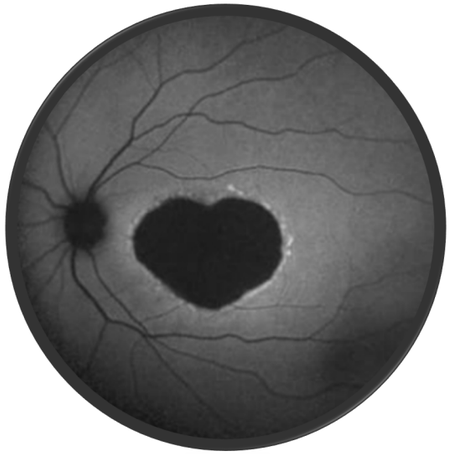
Accelerate Endpoints

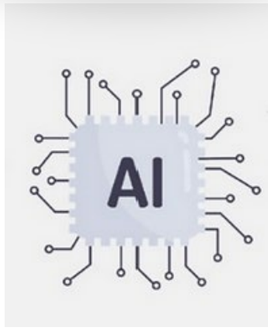
Increase incidence of and decrease time to endpoints

3

Automate Analysis

Predict visual function and reduce testing burden





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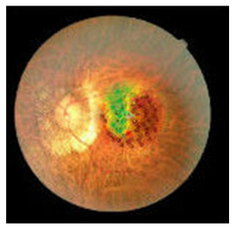


Microperimetry

AI-Based Prediction of Retinal Function

AI can address several challenges

1. Deep-learning algorithms predict VA and retinal sensitivity from OCT scans
2. AI-inferred sensitivity could serve as **'quasi-functional' surrogate** for monitoring GA progression
3. Potentially reduce/ eliminate need to collect functional endpoint

AI: Remaining Challenges

Data Privacy

Privacy- and security-related data-sharing issues limit broader implementation

Dataset Requirements

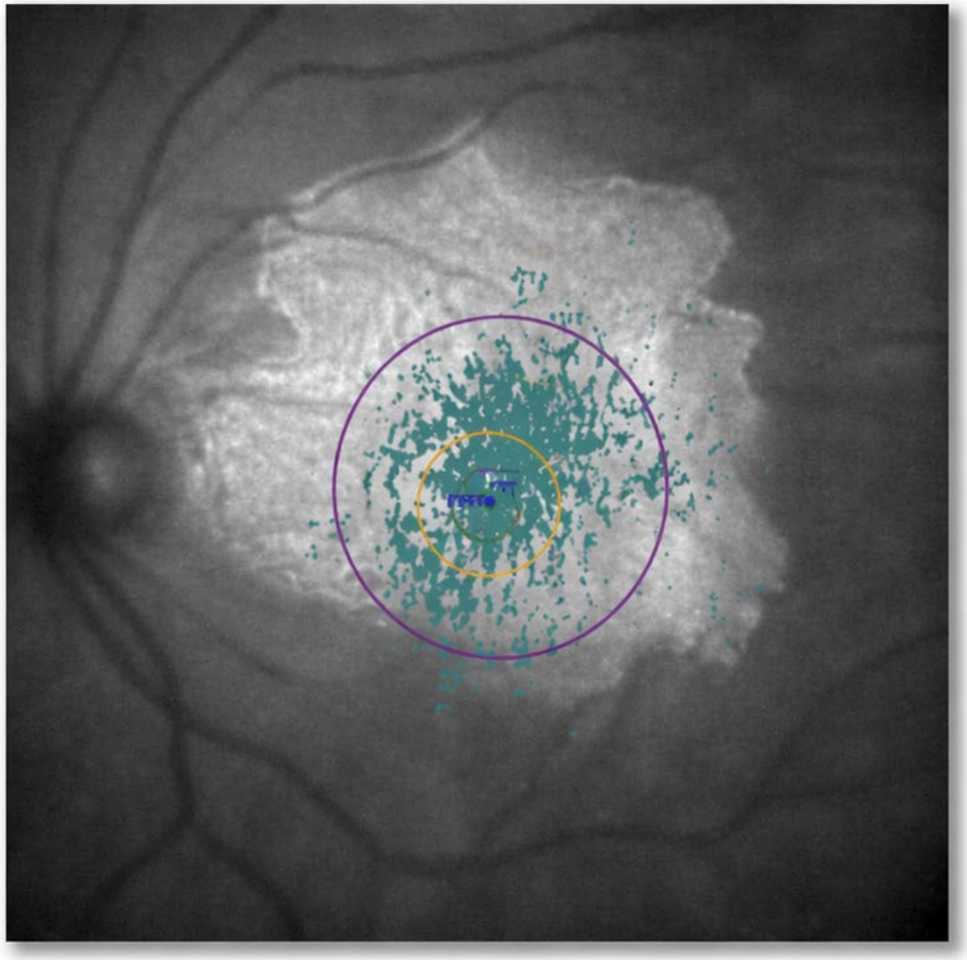
Large datasets with associated metadata are needed for robust model training

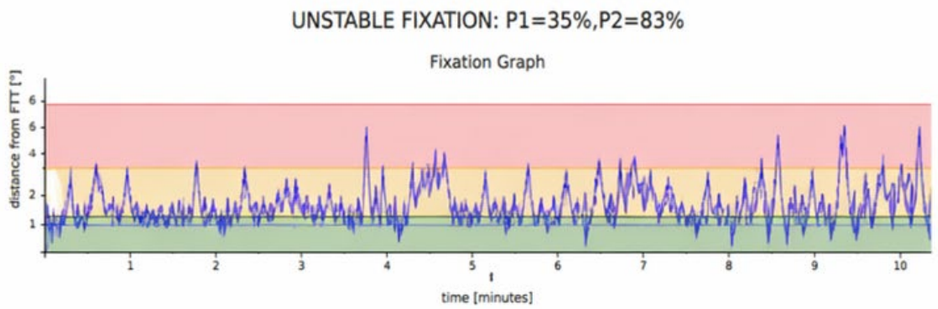
Regulatory Benchmarks

Regulatory standards for AI-based devices must still be defined

Novel Treatments

AI models may fail to capture unexpected anatomical/functional changes from new therapies





Fixation Stability

Macular sensitivity loss in AMD causes central scotoma, leading to VA and fixation stability decline — directly affecting reading and daily activities.

Preferred Retinal Loci (PRLs)

Fixation-impaired eyes adapt by developing PRLs — healthy retinal areas that substitute for the fovea. PRLs can be trained to improve fixation and reading speed.

Microperimetry Evidence

GA studies showed fixation quality significantly declined over time ($P < 0.01$). Bivariate contour ellipse area (MAIA) confirmed worsening fixation stability.

Scotoma Location Matters

In 63% of GA patients, scotoma was to the right of fixation. Location influenced reading speed and fixation stability over time.

GA Progression

Vision Search & Facial Recognition

Real-world visual tasks — searching everyday scenes and recognizing faces — offer patient-relevant endpoints that capture functional decline even when VA stabilizes

Evidence for Real-World Endpoints

1

Visual Search

AMD pts took significantly longer to complete computer-based visual searches of everyday objects and road signs versus controls — worsening with AMD severity

2

Facial Recognition

Impaired in GA patients but **not** in early or iAMD.
Difficulties correlated with BCVA measures — but notably *not* with patients' self-rated difficulty

3

Practical Advantage

Real-world scenarios can be simulated on computers or tablets, offering convenience to both patients and investigators.

Rapid Serial Visual Presentation (RSVP) Testing

Assesses ability to perceive and process rapid visual stimuli

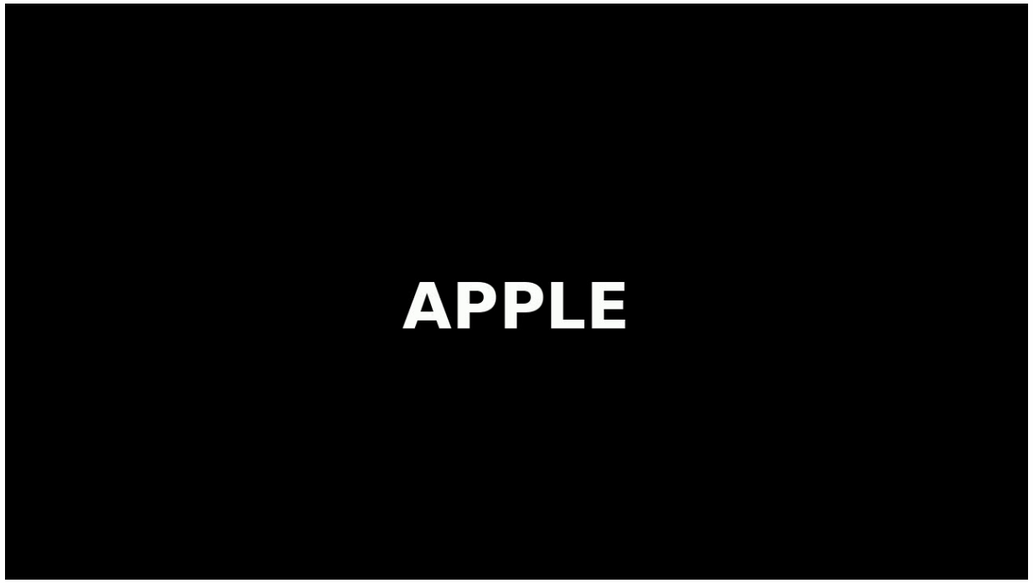
Significantly affected in AMD

How It Works

Words or images are presented in quick succession. Text size, word length, and font style can be varied. Speed and accuracy gauge visual processing capability.

Trial Potential

Improvements with training are measurable — translating into a trial endpoint that captures functional impairment and treatment-driven improvements over time.



Key Consideration

Training effects may influence result interpretation. Protocol design must account for type and rate of stimuli presented.

Virtual Reality/ VR Perimetry

- Provide **controlled, immersive testing environment**
- Reducing fatigue, improving retest reliability.
- At-home or remote testing

Systematic review of **64 studies** found VR headset perimetry performs comparably with — or better than — standard automated perimetry for detecting field defects.

~100% Adherence

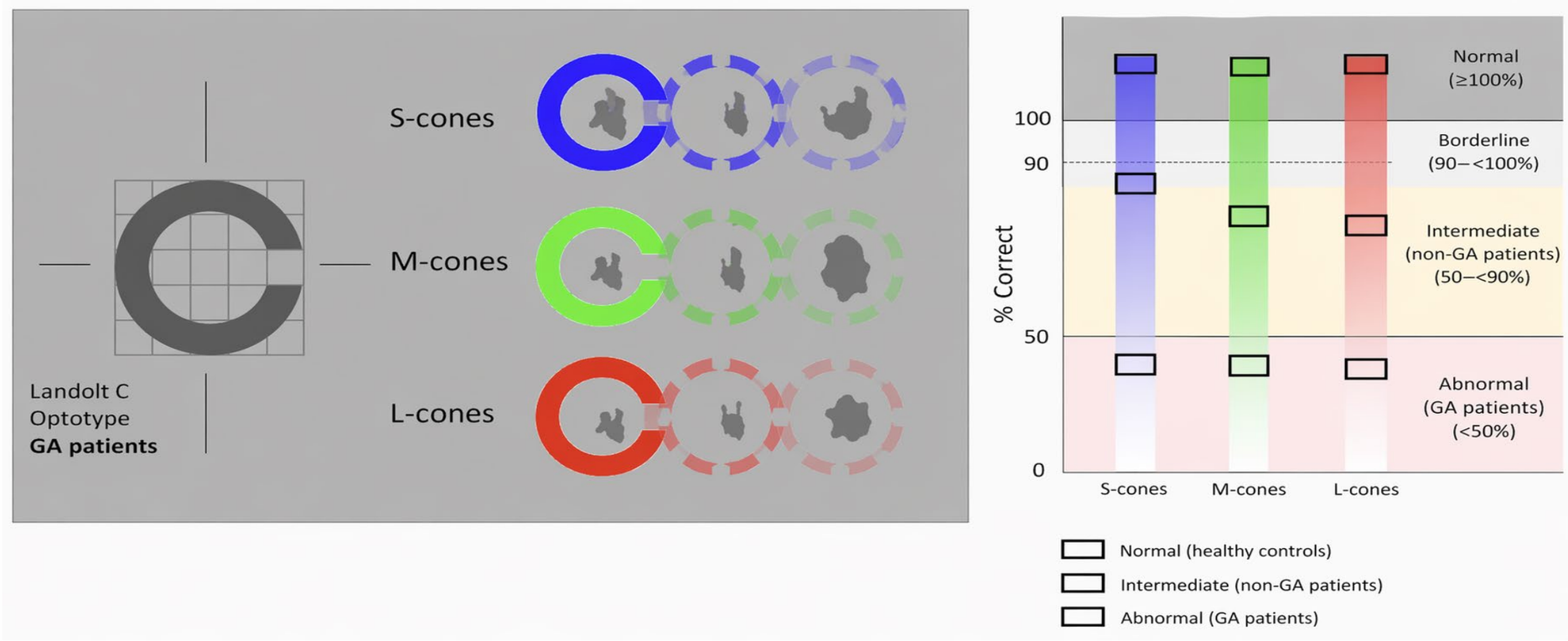
Csaky et al. reported near-perfect adherence in 20 GA participants

Comparable Accuracy

High agreement between VR perimetry and MAIA microperimeter

Cost-Effective

More affordable than standard perimetry; better tolerated by patients



Cone-Specific Contrast Testing (CCT)

- Computer-based colour vision test measuring sensitivity of **L- (red), M- (green), and S-cones (blue)**
- Scores range from 175 (best) to 0 (worst); below 75 indicates colour deficiency.
- Quick to perform: **3–6 minutes**.

CCT: Clinical Evidence

iAMD Natural History

Significant red cone-specific contrast deficits vs. healthy controls ($P < 0.05$) over 24 months; red and green CCT showed substantial longitudinal deterioration.

Early Indicator

No BCVA differences between AMD and control groups in one study — suggesting CCT detects decline **before VA loss**.

Advanced AMD

Most significant colour function declines noted in advanced AMD patients. CCT could provide a sensitive index of GA progression.

What Is a Composite Endpoint?

EMA/FDA-Aligned Definition

A composite endpoint **combines two or more distinct endpoints** into a single measure to capture a broader, clinically meaningful treatment effect.

In GA: composite endpoints are the solution to endpoint fragmentation — combining structural, functional, and patient-reported signals into **coherent evidence of treatment benefit**.

Both EMA and FDA accept composite endpoints, provided they are **prespecified** and reflect meaningful patient outcomes

Multicomponent Endpoints

Capture a **multidimensional treatment effect** that a single measure cannot reflect

Types of Composite Endpoints in GA

1

Hierarchical Composite

Ranked outcomes using win ratio. Example: GA growth reduction → functional preservation → PRO stability. **Preserves clinical importance hierarchy.**

2

Weighted Composite Score

Continuous score combining EZ loss + qCSF + microperimetry. **Challenge:** weighting must be biologically justified.

3

Responder-Based Composite

Patient meets predefined criteria across domains: ≥X% GA growth reduction *and* stable/improved function. **Most intuitive for regulators.**

4

Directional Coherence Model

Not strict statistical combination — structural improvement *consistent with* functional signal. Aligned with BRIDGE initiative proposals.

Regulatory Criteria for Composite Endpoints

Criteria 1–5: Scientific Validity

1. Biological Plausibility

Each endpoint must reflect disease mechanism.
In GA: EZ → photoreceptor loss; microperimetry → sensitivity; qCSF → contrast processing.
Strong structure–function link required.

2. Clinical Relevance

Each component must reflect meaningful patient benefit.
Weakness today: many endpoints lack direct patient anchoring to daily activities.

3. Sensitivity to Change

Must detect progression within trial duration. BCVA ✗ — too insensitive in fovea-sparing GA. EZ / microperimetry / qCSF ✓

4. Reliability & Reproducibility

Low test–retest variability required. Functional endpoints are often noisy; AI-derived endpoints may substantially improve this.

5. Independence / Non-Redundancy

Components must not measure the same construct. GA area + EZ loss are partially overlapping. Better: structure + function + task performance.

Regulatory Criteria for Composite Endpoints

Criteria 6–10: Statistical & Interpretive Standards

6. Consistent Directionality

All components must move in the same direction. Conflicting signals invalidate the composite.

7. Interpretability

Clinicians must understand what a change means. Composite scores risk becoming "black boxes."

8. Pre-Specification

Defined before trial start. Post-hoc composite construction is not acceptable to regulators.

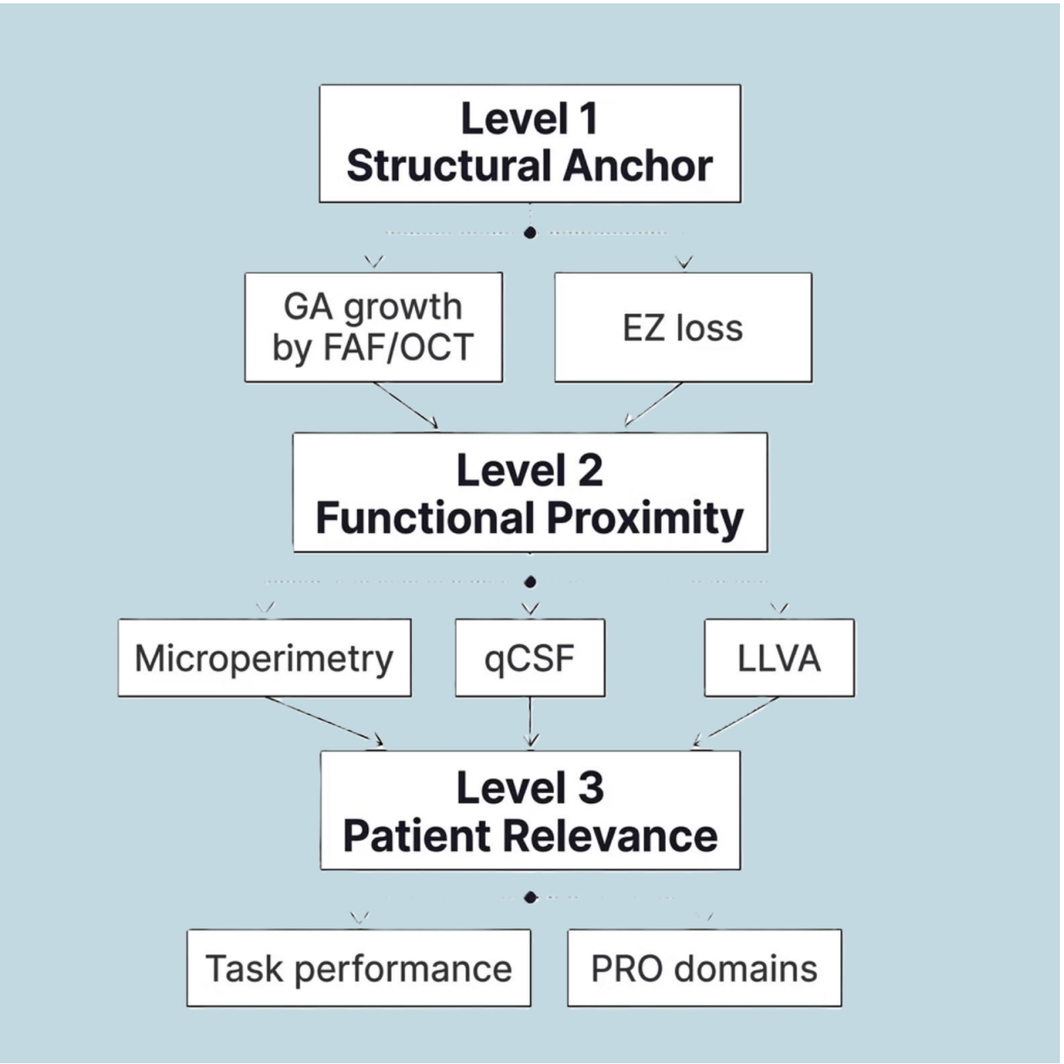
9. Multiplicity Control

Statistical adjustment required when combining multiple endpoints to control Type I error.

10. MCID

Minimal clinically important difference ideally defined. In GA, MCIDs are largely missing — use **directional consistency** as interim standard.

GA-Specific Composite Endpoint Framework: Key principle

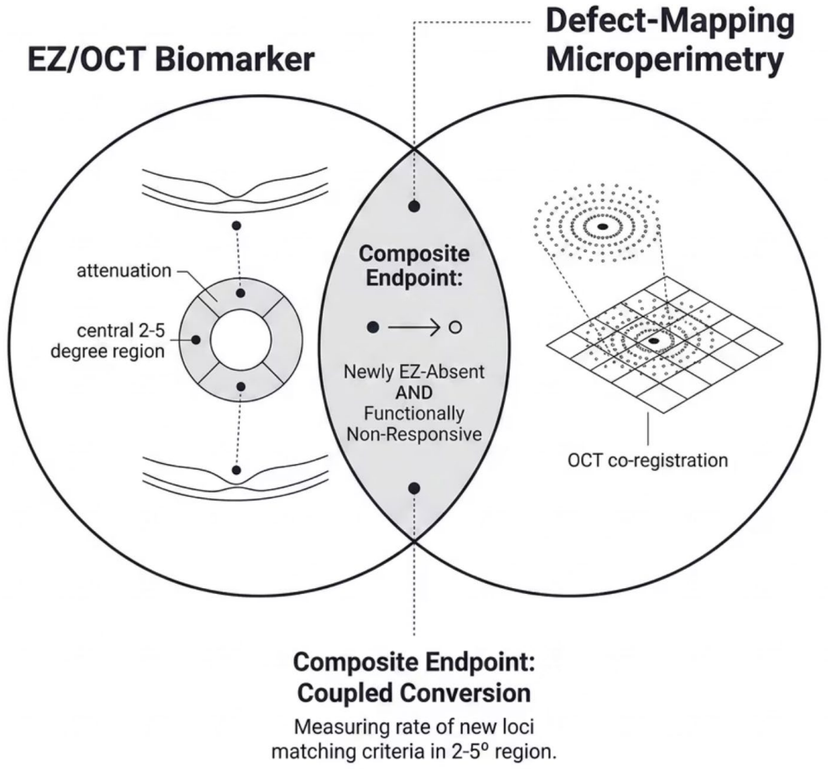


Treatment effect must demonstrate **directional coherence across all three levels** — not just statistical significance in one domain

BRIDGE Initiative Alignment: Structural effect + functional trend = credible evidence of benefit

- **Level 1:** GA growth (FAF/OCT) + EZ loss
- **Level 2:** Microperimetry + qCSF + LLVA
- **Level 3:** Task performance + PRO domains

Composite & Multicomponent Endpoints:
Used successfully in Oncology, Cardiology & Ophthalmology



Example: Composite endpoint:
Rate of coupled conversion events
GA with foveal-involving lesions:

- **EZ attenuation/thickness** in central 2–5° region paired with
- **Defect-mapping microperimetry** co-registered to OCT

Loci newly becoming EZ-absent and functionally non-responsive within a pre-defined area

Fewer Patients

Increased statistical power can reduce required sample sizes

Lower Costs

More efficient trial design reduces overall expenditure

Faster Completion

Timelier trial execution with composite approaches

- EZ-related metrics offer opportunity to integrate structural measures with functional impact within a composite endpoint
- mitigating floor/ceiling effects and mapping better to real-world benefit.

Composite Endpoints: Precedents

Retinitis Pigmentosa & Stargardt

Functional Vision Score (FVS) — composite of Functional Acuity Score (FAS) and Goldmann perimetry Functional Field Score (FFS) — correlated significantly with BCVA and NEI-VFQ-25 QoL scores

STOP-Uveitis Trial

Composite of VA, intraocular inflammation, central retinal thickness, posterior segment inflammation, and steroid taper — considered superior to any single parameter

MACUSTAR Consortium

Evaluated structural–functional, structural–structural, functional–functional, and multicategory composite endpoints in early/iAMD — though standardization between studies was lacking

Proposed Composite Endpoint Framework

Time-to-Event Functional

Apply time-to-event analysis for functional changes.

CS + LLVA Composite

Combine contrast sensitivity and low-luminance VA.

Phase II: EZ & Microperimetry

Confirm spatial coupling of EZ loss and sensitivity.

Phase III Endpoint Confirmation

Validate composite as primary trial endpoint.

Time-to-event analysis for functional components to support interpretability
With additional validation, **contrast sensitivity (CS) and low-luminance VA (LLVA)** can be combined as a rich functional composite endpoint — leading to more efficient GA clinical trials.

Current Limitations

No Validated GA Composite

No composite endpoint has been formally validated for GA clinical trials to date.

Absent MCIDs

Minimal clinically important differences are largely undefined for most emerging endpoints in GA.

Functional Variability

High test–retest variability in psychophysical tests reduces sensitivity to detect treatment effects within 24-month trials.

Regulatory Uncertainty for AI

AI-derived endpoints face unresolved regulatory benchmarks, data-sharing constraints, and validation requirements.

These limitations represent a significant risk: effective therapies may fail approval not due to lack of efficacy, but due to inadequate endpoint design.

The Path Forward

01

Validate Emerging Endpoints

Dark adaptometry, EDTs, CCT, fixation stability, and RSVP require robust validation in GA-specific populations.

02

Integrate AI

AI-inferred retinal sensitivity from OCT can reduce patient burden and accelerate trial outcomes — with federated learning enabling real-world evidence generation.

03

Adopt Composite Endpoints

Pairing EZ structural metrics with functional microperimetry creates sensitive, multidimensional endpoints. CS and LLVA may also combine as a rich functional composite.

04

Confirm in Phase III

Phase II responsiveness and reliability data should confirm composite endpoints as primary endpoints at Phase III, supported by time-to-event analysis.