# FOCUS ON DIVERSITY IN CLINICAL TRIALS

## Improving representation moves us closer to an era of personalized medicine.

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In retina research, one of the most salient issues is ensuring therapies are effective, safe, and accessible for all patients. Yet historically, clinical trials in ophthalmology, like many therapeutic areas, have struggled to adequately represent the full spectrum of patients affected by sight-threatening retinal diseases. This lack of representation has tangible consequences resulting in disparities in disease progression, treatment response, and long-term visual outcomes. Ultimately, achieving the goal of personalized medicine will require robust data in diverse clinical phenotypes, allowing the prediction of optimal therapies for each patient.

### THE VALUE OF REPRESENTATION

Conditions such as diabetic retinopathy (DR) and diabetic macular edema (DME) do not affect all populations equally (Figure). For example, a landmark Centers for Disease Control and Prevention (CDC) analysis showed that Black, Hispanic, and Native American adults have significantly higher rates of diabetes and related retinopathy compared with White adults.[1]

Underrepresentation in research has major implications. First, therapeutic response profiles may be incomplete. A 2019 review found that racial/ethnic differences in inflammatory and angiogenic biomarkers can influence treatment response in retinal disease.[2] Second, differences in disease severity may go unrecognized. For example, the National Eye Institute (NEI) reports that Black and Hispanic patients are more likely to present with advanced DR at diagnosis.[3] Third, real-world outcomes may diverge from trial expectations. IRIS registry analyses show that patients from underrepresented groups experience higher rates of vision loss and delayed diagnosis and initiation of treatment in real-world settings, often due to socioeconomic barriers and limited access to retina care.[4,5]

Representation is not a quota. It is a scientific necessity for accurate and generalizable data for specialized care.

### A REAL-WORLD STUDY TO REFLECT THE TRUE DISEASE BURDEN

Although DR affects millions across the United States, the demographics of many retina trials do not align with the communities most affected. According to CDC and NEI epidemiologic data, Black, Hispanic/Latino, and Native American adults have significantly higher prevalences of diabetes and earlier onset of diabetic eye disease.[1,6]

Despite this, a 2021 review found that racial and ethnic minority enrollment in ophthalmic trials often falls below 10%, even in diseases where minorities represent the majority of those affected.[7]

## KEY TAKEAWAYS

- A 2021 review found that racial and ethnic minority enrollment in ophthalmic trials often falls below 10%, even in diseases where minorities represent the majority of those affected.
- The ELEVATUM study was designed to intentionally expand participation among groups disproportionately affected by diabetic eye disease.
- Topline data from ELEVATUM show that Hispanic patients presented with higher diabetic retinopathy severity scores and greater retinal thickness compared with African American patients.

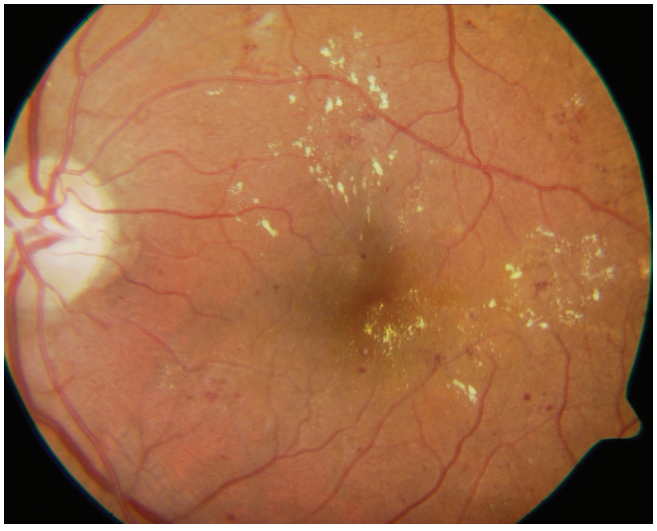

Figure. This fundus image of a patient with DME demonstrates dot hemorrhages, microaneurysms, retinal exudates, and macular edema encroaching on the fovea.

## A Model for Inclusion

The ELEVATUM study (NCT05224102) was designed to intentionally expand participation among groups disproportionately affected by diabetic eye disease, including Black, Hispanic/Latino, Native American, and socioeconomically underserved populations. The trial—which is investigating faricimab (Vabysmo, Genentech/Roche) treatment response in treatment-naive, underrepresented patients with DME—represents a shift toward purposeful inclusion. By designing the trial to increase representation of historically underrepresented real-world populations, ELEVATUM provides additional data to help strengthen the applicability and interpretability of outcomes, improving the generalizability of data across patient groups typically marginalized in research. The trial design focuses on the following priorities:

- Community-centered trial site selection based on disease burden, population diversity, and strong community trust.
- Clinicians and research teams with deep community roots and cultural competency.
- Efforts to reduce logistical barriers and increase retention, including less rigid scheduling windows, transportation support, and simplified study materials.
- Flexibility within protocols to mirror standard-of-care visits including optional aqueous humor sampling, long-term analysis of treat-and-extend intervals, and less burdensome imaging and lab schedules.
- Participant materials tailored to health literacy and multilingual needs.
- Culturally attuned patient engagement and trust, which can improve informed consent comprehension and retention in minority populations.[8]

This approach allows the trial population to better resemble actual practice settings, improves recruitment and enrollment goals, and strengthens data quality and clinical relevance.

## Moving Retina Toward Personalized Medicine

Personalized, data-driven medicine requires a nuanced understanding of how different populations respond to therapy. In retina, personalized medicine extends beyond genomic variability and encompasses the following:

- Differences in systemic comorbidities that influence disease progression.
- Variations in inflammatory and angiogenic biomarkers.
- Patterns of access, adherence, and response to treatment.
- Real-world social determinants of health that shape outcomes.

Evidence from a pharmacogenetic analysis suggests biomarker profiles that influence anti-VEGF response can differ across racial and ethnic groups, indicating that treatment optimization may require population-specific insights.[9]

ELEVATUM's focus on underrepresented groups expands the evidence-based data needed to: 1) identify variability

**TABLE 1. ELEVATUM BASELINE FEATURES[11]**

| | Black/African American n = 59 | Hispanic/Latino American n = 56 | Overall US Study Population n = 123 |
|---|---|---|---|
| Mean hemoglobin A1c (SD) | 8.0% (1.7) | 8.0% (1.2) | 7.9% (1.5) |
| Mean BCVA (SD) | 62.2 letters (10.2) | 59.2 letters (11.4) | 61.1 letters (11.1) |
| Mean CST (SD) | 467.4 µm (126.0) | 491.1 µm (157.2) | 476.9 µm (138.5) |
| DR questionable/microaneurysms only (SD) | 0 | 1 (1.8) | 1 (0.8) |
| Mild to moderate NPDR (SD) | 42 (71.2) | 24 (42.9) | 68 (55.3) |
| Moderately severe to severe NPDR (SD) | 8 (13.6) | 22 (39.3) | 35 (28.5) |
| PDR (SD) | 5 (8.5) | 9 (16.1) | 15 (12.2) |
| Cannot grade (SD) | 4 (6.8) | 0 | 4 (3.3) |

Abbreviations: CST, central subfield thickness; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; SD, standard deviation.

| TABLE 2. LETTERS GAINED AT WEEK 56[11] | |
|---|---|
| Hispanic/Latino | 14.1 |
| Overall Population | 12.3 |
| African American | 11.3 |
| Yosemite/Rhine Overall Population | 11.2 |

of response to therapy, 2) understand disease behavior across diverse genetic and environmental backgrounds, 3) evaluate real-world adherence patterns, and 4) assess long-term visual outcomes in populations missing from prior datasets. By capturing these nuances, the study lays the foundation for more personalized treatment pathways rather than a one-size-fits-all approach.

The ELEVATUM trial recruited 45% Hispanic, 45% African American, and 10% Native American and Pacific Islander subjects (Table 1).

The trial has shown that patients from underrepresented groups can be reliable study subjects. Increasing the inclusion criteria to allow up to 20% of patients with a hemoglobin A1c of 12% did not negatively affect safety, and 87% of patients completed the trial.

Topline data identified differences in clinical presentation. For example, Hispanic patients presented with higher DR severity scores and greater retinal thickness compared with African American patients. However, the Hispanic cohort had the greatest response to therapy with an average of 14 letters gained at the end of 1 year (Table 2). Data from the trial also demonstrated differences between subgroups in aqueous humor biomarker results. A post-hoc study showed that African Americans had a higher mean angiopoietin-2 level and a wider distribution of angiopoietin-2 values than Hispanic/Latino patients. Hispanic patients had higher aqueous humor VEGF levels and a wider range of values than in African American patients. Moreover, Hispanic patients demonstrated more subretinal fluid than African American patients, who showed more intraretinal fluid on volumetric OCT images.[12]

Additional findings are expected from this study, which is in an extension phase.

## DIVERSITY IS NO LONGER OPTIONAL

The FDA has increasingly emphasized diversity in clinical trials. Its 2020 and 2022 guidance documents call for[10]:

- Proactive diversity enrollment plans.
- Community-based site selection.
- An effort to reduce trial participation barriers.
- Transparent reporting of race and ethnicity data.

The guidance underscores that diversity fosters scientific validity. In particular, the FDA notes that racial and ethnic disparities in disease incidence, severity, and outcomes necessitate trial populations that reflect real disease epidemiology.

## A CALL TO ACTION FOR THE RETINA COMMUNITY

Ultimately, we are working toward a day in which clinical trials such as ELEVATUM will not be necessary because therapies will be backed by adequately representative, real-world evidence from their registration trials.

Achieving this requires intention. We can be more successful by emphasizing the importance of participating in clinical trials to all patients in an environment that fosters trust and transparent communication. At the sponsor level, studies that allow more flexible visit windows, reimbursement for childcare, meals, and transportation, and fellow eye treatments can help address barriers.

By including these populations, we will move closer to the day of personalized medicine. A better understanding of various clinical phenotypes and the response to therapy will help us achieve better outcomes and enhance our ability to preserve vision. Diversity is not a trend—it is the backbone of high-quality evidence. By investing in inclusive study design, community engagement, and equitable access to clinical research, we ensure that every patient, regardless of race, ethnicity, language, or background, can benefit from the latest advances in retinal science. ■

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