# Plain Language Summary

# Measurement Reliability and Functional Validity of Bruch's Membrane Calcification in Pseudoxanthoma Elasticum: PROPXE Study Report 2

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## Study at a Glance

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**Study Type:** Clinical study

**Date of publication:** November 3, 2025

**Citation**: *Giger JAW, Ansari G, Terry SF, Charbel Issa P, Pfau K, Pfau M; PROPXE Study Group. Measurement Reliability and Functional Validity of Bruch's Membrane Calcification in Pseudoxanthoma Elasticum: PROPXE Study Report 2. Invest Ophthalmol Vis Sci. 2025 Nov 3;66(14):29. doi: 10.1167/iovs.66.14.29. PMID: 41230901; PMCID: PMC12617667.*

### 1. Purpose of the Study

A major clinical challenge in pseudoxanthoma elasticum (PXE) is measuring how calcification progresses. So far, assessments of the eye signs and symptoms focus mostly on secondary complications. This means that most studies are looking at something that might give a hint about calcification, such as changes in angioid streak length affecting Bruch's membrane or macular neovascularization. The problem with this is it measures what might happen and does not measure the cause of the changes nor how the disease progresses.

The PROPXE Study Report 2 investigates how well Bruch's membrane (BrM) calcification can be measured in pseudoxanthoma elasticum (PXE), how these measurements relate to age, and whether calcification correlates with impaired rod-mediated dark adaptation (rod-intercept time (RIT) during dark adaptation).

***Bruch's membrane*** *is the membrane behind the retina at the back of the eye. This helps to keep*
***Peau d'orange*** *is retinal tissue that looks dimpled and bumpy, just like the outside of an orange*
***Angioid streaks*** *are small cracks in Bruch's membrane*
***Macular neovascularization****: blood vessels that grow and come through angioid streaks.*
***Widefield infrared imaging*** *uses a light that is invisible to human eyes, but we can feel it as heat (infrared), and looks at a wide area in the eye without shining an intense light in the eye*
***Multifocal dark adaptometry*** *measures the ability of the rods and cones in the eye to adapt to darkness*

**2. Study Design & Participants**

The study consisted of 26 people affected by PXE, all of whom had two pathogenic variants in *ABCC6*, the gene associated with PXE. The median age of the participants was 55 years. Participants had the boundaries of the peau d'orange measured using widefield infrared imaging and multifocal dark adaptometry.

**3. Key Findings**

*A. Measurement Reliability*

Temporal inner peau d'orange boundary showed excellent reliability, meaning the measure could be done multiple times on multiple people and come up the same measurement:

- Inter-reader ICC = 0.92
- Inter-visit ICC = 0.95

However, the upper and lower boundaries because the participants upper or lower eyelids cast shadows over the top and bottom parts of the eye during the scan, which obscured the area.

*B. Age Association*

It was determined that temporal (side) inner boundary expands centrifugally with age: +4.35 degrees per decade. However, the outer boundary does **not** significantly change with age.

*C. Functional Impact (Dark Adaptation)*

Larger temporal inner boundary strongly correlates with delayed rod-mediated dark adaptation at 8° and 15° eccentricities. The threshold effects of dark adaptation delays appear once calcification extends beyond ~27°–33° from the optic nerve head.

**4. Biological & Clinical Interpretation**

BrM calcification likely disrupts metabolic exchange between choroid and RPE, slowing the visual cycle, similar to other BrM diseases. Temporal inner boundary is the most informative biomarker due to both biological relevance and imaging reliability.

**5. Limitations & Future Directions**
The study is limited by the small number of eligible participants, which is typical of rare diseases. It was further noted that differentiating peau d'orange from subretinal drusenoid deposits can be challenging, and that long-term progression requires further study. Specifically, qualitative observation suggested that boundary delineation was complicated by subretinal drusenoid deposits, which may mimic peau d'orange appearance, and the phenomenon known as the "temporal spared island," which creates complex grading scenarios. Additionally, an often-thinned choroid in PXE, in conjunction with low choroidal pigmentation in lighter-skinned patients, can result in a diminished contrast in IR imaging, exacerbating the difficulty of delineating the peau d'orange boundaries. Thus, contrast-rich measures of disease severity should be explored in future studies.

**6. Overall Conclusion**
Quantifying BrM calcification using widefield IR imaging is feasible and reliable. The PROPXE Study established essential measurement properties required for quantifying the extent of BrM calcification. Specifically, it demonstrated good inter-reader and inter-visit reliability, as well as substantial inter-eye concordance in peau d'orange boundaries delineated using wide-field IR imaging. Furthermore, the data support the evaluation of the age-associated centrifugal expansion of the inner peau d'orange boundary as an indicator of disease progression over time.

Further, the study demonstrated a significant functional relevance of the temporal inner peau d'orange boundary extent by showing its association with delayed rod-mediated dark adaptation. The temporal inner peau d'orange boundary is a strong structural biomarker that correlates with functional impairment (dark adaptation delay), making it a promising clinical trial endpoint for PXE.

**7. Why this matters for PXE**
A biomarker, some way to measure how PXE progresses if left untreated, is essential if we are to begin to treat PXE. Several treatments are ready for phase 3 clinical trials, but cannot be tested if we don't know what to measure to see if the treatment is working to interrupt the natural disease progression. A biomarker like measuring BrM calcification would be very helpful to knowing whether a treatment is working or not. We have hope that this will be a strong and reliable measure.

*Funded by: BrightFocus Foundation (grant M2024009N [MP]) and the German Research Foundation (532367710 [KP]). Recruitment support provided by PXE International.*