



Severe bilateral retinal degeneration following a twenty-six-year pentosan polysulfate sodium exposure: a case report

Aaron T. Zhao^a, Turner D. Wibbelsman^b, Martin Calotti^b, Collin J. Richards^b,
Tamara R. Vrabec^{c,*}

^a Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^b Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA

^c Geisinger Eye Institute, Geisinger Medical Center, Danville, PA, USA

ARTICLE INFO

Keywords:

Pentosan polysulfate sodium
PPS
Retinopathy
Interstitial cystitis
Retinal degeneration

ABSTRACT

Purpose: To describe an advanced case of pentosan polysulfate sodium (PPS)-associated retinopathy with extensive macular and peripheral retinal involvement following prolonged high-dose exposure.

Observations: An 86-year-old male presented with bilateral hand motion visual acuity and a 26-year history of PPS use (400mg daily, ~3769g cumulative dose) for treatment of interstitial cystitis. Fundus examination revealed widespread retinal degeneration characterized by confluent nummular patches of retinal atrophy in a radial distribution from the optic nerves. Optical coherence tomography (OCT) demonstrated severe outer retinal disorganization, and fundus autofluorescence (FAF) showed extensive RPE loss and absence of the Robson Holder ring. Genetic testing excluded choroideremia and late-onset retinal dystrophy, identifying only variants of uncertain significance in candidate genes DNAJC17 and SPP2. The patient had a history of excessive coffee consumption, which may have exacerbated his interstitial cystitis and potentially contributed to retinal vascular compromise.

Conclusions and importance: This case supports the dose-dependent nature of PPS toxicity and demonstrates that high cumulative doses can lead to widespread retinal degeneration beyond the typical macular involvement. The potential severity of irreversible vision loss highlights the importance of periodic retinal evaluation using multimodal imaging to facilitate early recognition of PPS toxicity in patients on long-term PPS therapy and supports ongoing efforts to establish widely accepted, comprehensive screening guidelines and cumulative dose thresholds for patients on long-term PPS therapy, similar to protocols for other potentially toxic drug-related retinopathies.

1. Introduction

Pentosan polysulfate sodium (PPS) is commonly prescribed for the treatment of interstitial cystitis (IC)/bladder pain syndrome.¹ An association has been described between prolonged PPS use and the development of progressive maculopathy, characterized by bilateral retinal pigment epithelium (RPE) atrophy and hyperpigmented macular spots, referred to as PPS-associated maculopathy.^{2,3} A dose-dependent relationship has been recognized, with greater lifetime cumulative exposure increasing risk of vision impairment.⁴ Here, we report the clinical findings and multimodal imaging features of severe macular and peripheral retinal deterioration in a patient with exceptionally high cumulative PPS exposure during prolonged therapy for refractory IC

symptoms.

2. Clinical course

An 86-year-old white male was referred for evaluation of severe, bilateral vision loss. Ocular history was significant for “dry macular degeneration” with visual acuity of 20/30 OU in Year 1. During the subsequent 11 years, records from another provider revealed visual acuity worsened to 20/200 OU. He was subsequently lost to follow up until Year 16. The patient denied a family history of any ocular conditions including vision loss and retinitis pigmentosa.

Medical history was significant for atrial fibrillation, supraventricular tachycardia, ulcerative colitis, anxiety, interstitial cystitis, benign

* Correspondence: Geisinger Eye Institute 16 Woodbine Lane Danville, PA 17821, USA.

E-mail address: trvrabec@geisinger.edu (T.R. Vrabec).

<https://doi.org/10.1016/j.ajoc.2025.102497>

Received 15 August 2025; Received in revised form 28 November 2025; Accepted 3 December 2025

Available online 10 December 2025

2451-9936/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

prostatic hyperplasia, Graves' disease, myelodysplastic syndrome, and Raynaud's phenomenon. Current medications included doxazosin, oxybutynin, alprazolam, mesalamine, apixaban, amitriptyline, iron, omega 3, pycnogenol, vitamins C and D and AREDS2 multivitamins. Upon questioning, the patient revealed he also had been treated for 26 years with PPS 200 mg bid (cumulative dose approximately 3796 g) for interstitial cystitis complicated by severe urinary frequency and retention, and Hunner's ulcers. He stated his treatment had stopped 2 years prior to presentation.

Social history revealed an extraordinary history of coffee consumption during his working years. During military service, he elected kitchen duty to maintain access to coffee throughout his shifts and routinely consumed multiple large pots daily. The patient significantly reduced his coffee intake to 1–2 cups daily upon retirement, noting improvement in urinary symptoms, though he continued PPS therapy for 23 more years.

At the time of consultation in Year 16, visual acuity was hand motions OU. Biomicroscopy revealed pseudophakia and clear vitreous, and fundus examination OU was remarkable for near confluent nummular patches of retinal atrophy in a radial distribution from the optic nerves (Fig. 1). Progressive Cirrus OCT (Carl Zeiss, Meditec) imaging between Year 1 and Years 4 revealed developing outer retinal disruption with patchy attenuation of the photoreceptor layers and irregularity of the RPE line in the perifoveal region (Fig. 2, top and middle). The inner retinal layers remained relatively intact during this period. By Year 11, OCT demonstrated marked progression with near-complete loss of the outer retinal layers in large confluent areas, severe overall retinal thinning, disruption of normal retinal lamination, and loss of the foveal contour (Fig. 2, bottom). Extensive atrophy of the RPE-Bruch's membrane complex was evident in affected regions. Fundus autofluorescence (FAF) demonstrated widespread macular and peripheral retinal zones of hypoautofluorescence which correspond to clinical areas of RPE loss. Macular regions were notable for the absence of a Robson Holder ring (see Fig. 3).

Genetic evaluation (Invitae™ Inherited Retinal Disorders Panel) was performed to rule out an inherited retinal degeneration. Testing was negative for mutations of the CHM (choroideremia) and C1QTNF5 (late onset retinal dystrophy, L-ORD) genes. The panel identified two candidate gene mutations of unknown clinical significance. The first variant was in the DNAJC17 gene (c.286G > T; p.Val96Leu), which may be associated with autosomal recessive retinitis pigmentosa with hypogammaglobulinemia.⁵ The second variant was in the SPP2 gene (c.328T > G; p.Tyr110Asp), which may be correlated with autosomal dominant retinitis pigmentosa.⁶ The patient declined additional testing and follow up.

3. Discussion

PPS was approved by the FDA in 1996 for treatment of IC. In 2018, Pearce et al. described a unique atrophic maculopathy involving the

juxtapapillary macula.⁷ A large prospective study identified maculopathy in 16% of patients taking the medication. Advanced cases exhibited varying degrees of choroid and RPE atrophy, with severity correlating with prolonged treatment duration, higher cumulative dosages, and higher daily dosages (mean: 19.5 ± 5.5 years, 3103.1 ± 1402.2 g, 433.9 ± 137.6 mg, respectively).⁸

Our patient's widespread peripheral retinal degeneration builds upon reports in the literature of extramacular involvement in PPS toxicity and expands the known spectrum of PPS-associated retinal disease.⁹ His cumulative dose of approximately 3796g over 26 years places him at the extreme end of the exposure spectrum reported in the literature. While we acknowledge that gaps in clinical documentation limit our ability to establish progression thresholds or demonstrate continuous dose-response relationships, his case supports the association between very high cumulative exposure and severe panretinal degeneration. Further, although our patient discontinued PPS in Year 14 and was not examined again until Year 16, he experienced visual acuity deterioration from 20/200 at Year 11 to hand motion at Year 16. We cannot definitively conclude whether progression occurred after medication cessation, as the patient was not examined between these time-points. However, the severe visual decline observed may be consistent with prior reports of substantial visual deterioration following PPS cessation.¹⁰

The pathophysiology of PPS toxicity remains poorly characterized. Due to PPS's structural similarity to heparin-like glycosaminoglycans (GAGs), it has been hypothesized that the medication may accumulate in and disrupt RPE lysosomes, similar to the mechanism of chloroquine retinopathy.¹¹ A recent study in mouse models hypothesized that PPS may disrupt RPE and Bruch's membrane by aggregating with GAGs or interfering with cellular signaling pathways.¹¹ The dose-dependent nature of toxicity supports this theory of gradual accumulation, aggregation, and eventual RPE dysfunction and death.

Our patient's case demonstrates that severe exposure can lead to widespread retinal degeneration beyond the typically described macular involvement. This suggests that the toxic effects of PPS may impact the entire RPE-photoreceptor complex. While cumulative dose appears to be the primary driver of the insult, factors such as blood-retinal barrier integrity, RPE metabolic efficiency, and genetic variants in drug metabolism could influence toxicity development as well.^{12–14} The radial pattern of damage extending from the optic nerve may reflect preferential accumulation along major vessel distributions. Additionally, previous reports of the progressive damage after PPS cessation suggest that PPS or its metabolites may trigger a cascade of RPE dysfunction that becomes self-perpetuating.¹⁰

The differential diagnosis included several inherited retinal dystrophies. For instance, the widespread RPE atrophy and progression pattern could suggest choroideremia, and the nummular appearance and radial distribution could raise concern for late-onset retinal degeneration (L-ORD).^{15,16} However, genetic testing to exclude common inherited retinal degenerations was negative for mutations in the CHM and

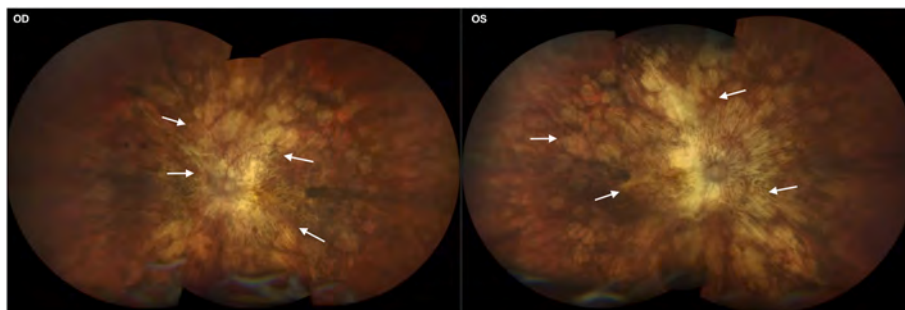


Fig. 1. Widefield fundus photography demonstrating severe PPS-associated maculopathy with extensive peripheral involvement.

Color fundus photography at presentation in Year 16 (visual acuity: hand motions OU) reveals extensive macular and peripapillary atrophy and widespread retinal degeneration characterized by radially oriented nummular areas of RPE and choriocapillaris atrophy (white arrows), vascular attenuation and disc pallor OU.

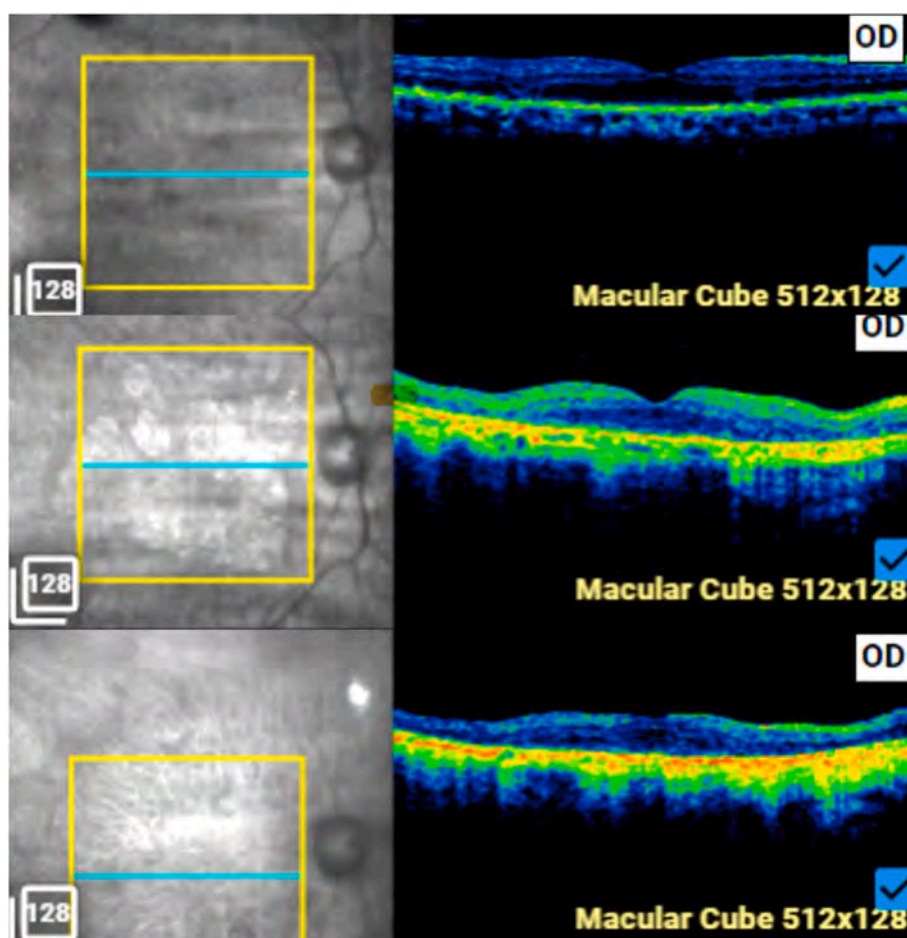


Fig. 2. Progressive structural changes in PPS-associated maculopathy documented by optical coherence tomography (OCT).

Cirrus OCT reveals that between Year 1 and Year 4, nummular zones of perifoveal outer retinal atrophy with outer retinal thinning have developed, with associated progressive parafoveal retinal thinning (top, middle). By Year 11, the macular lesions have coalesced and there is severe disorganization and retinal thinning with loss of retinal laminations and disruption and thinning of outer nuclear, outer plexiform and photoreceptor layers extending beyond the macula (bottom).

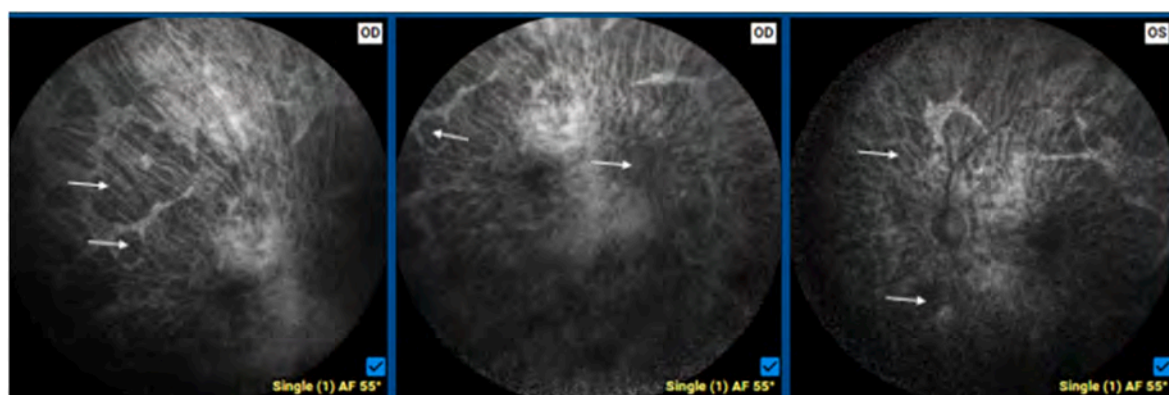


Fig. 3. Fundus autofluorescence highlighting the pattern and extent of RPE damage in advanced PPS-associated maculopathy.

In Year 16 (visual acuity: hand motions OU), FAF OU demonstrates multiple near-confluent, nummular areas of hypoautofluorescence (white arrows) correspond with zones of RPE and choriocapillaris loss with interspersed linear hyperautofluorescence in less severely affected regions. Note near total loss of RPE and choriocapillaris in macula with absence of Robson Holder ring.

C1QTNF5 genes, which have been associated with these conditions.^{17–19} Candidate genes are genes with proposed potential health implications, but without evidence to suggest causal relationships with retinal conditions. While variants of uncertain significance were identified in DNAJC17 and SPP2, these genes have not been definitively linked to retinal disease, and the clinical significance of these candidate genes

remains to be seen. We acknowledge that genetic panel testing has significant limitations. Current commercial panels do not interrogate all genes associated with inherited retinal dystrophies, and novel or rare genetic variants may not be detected. Additionally, some genetic causes of retinal degeneration remain uncharacterized. In this regard, although no associated genetic abnormalities were identified in previous studies

of PPS maculopathy,^{7,8} it remains possible that the candidate genes identified in our patient, or other unrecognized mutations, may have predisposed our patient to more severe retinal degeneration.

It is also possible that the patient's systemic comorbidities may have contributed to his striking clinical presentation. Ulcerative colitis has been associated with an increased risk of maculopathy (RR: 1.45; 95 % CI, 1.29–1.63).²⁰ Further, both dietary acids and caffeine have been associated with worsening of IC symptoms; this may have increased the patient's reliance on the medication.^{21,22} In addition, as macular flow and retinal and choroidal vessel density are reduced following exposure to caffeine in healthy subjects, our patient's excessive caffeine intake may have exacerbated PPS-related macular dysfunction and choriocapillaris atrophy.^{23,24} In this regard, one study using OCT-A demonstrated significant reduction in choriocapillaris flow before OCT or FAF detected macular abnormalities, suggesting choriocapillaris impairment may contribute to RPE disruption.²⁵ The patient was not taking other medications with known retinal toxic effects. His pancytopenia and myelodysplasia were diagnosed well after the onset of visual symptoms, making them unlikely contributors to the retinal findings. Nonetheless, while other factors may have contributed to the ultimate clinical appearance, the severe and disproportionate macular atrophy, along with the patient's negative family history, 26 year PPS exposure, and the known dose-dependent mechanism of PPS retinal toxicity, suggest PPS as the most likely etiology of our patient's striking clinical presentation.

Currently, while the need for screening has been recognized,^{26,27} there are no widely accepted, standardized guidelines for comprehensive screening and cumulative doses as seen in other toxic retinopathies. The potential severity of irreversible vision loss, including debilitating widespread retinopathy as illustrated in this case, highlights the importance of periodic retinal evaluation using multimodal imaging, which may include OCT-A, to facilitate early recognition of PPS toxicity in patients on long-term PPS therapy.^{25,28} This supports ongoing efforts to establish comprehensive, standardized protocols endorsed by leading ophthalmic organizations that include baseline examination requirements, follow-up intervals based on cumulative dose, specific imaging modalities to be employed, and cumulative dose thresholds that should prompt consideration of alternative therapies.

CRediT authorship contribution statement

Aaron T. Zhao: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Turner D. Wibbelsman:** Writing – review & editing, Writing – original draft, Investigation. **Martin Calotti:** Writing – review & editing, Investigation. **Collin J. Richards:** Writing – review & editing. **Tamara R. Vrabec:** Writing – review & editing, Supervision.

Presentations

None.

Proprietary interest

None.

Acknowledgment and disclosures

Written consent has not been obtained. This report does not contain any personal identifying information.

Funding

J.Arch McNamara Fund for Retina Research and Education, Retina Service, Wills Eye Hospital, Philadelphia PA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We wish to acknowledge the thoughtful discussion and suggestions provided by Dr. Jose Pulido, MD at Wills Eye Hospital which greatly improved this report.

References

- Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs*. 2006;66:821–835.
- Hanif AM, Armenti ST, Taylor SC, et al. Phenotypic spectrum of Pentosan polysulfate sodium-associated maculopathy: a multicenter study. *JAMA Ophthalmol*. 2019;137:1275–1282.
- Lindeke-Myers A, Hanif AM, Jain N. Pentosan polysulfate maculopathy. *Surv Ophthalmol*. 2022;67:83–96.
- Philip AM, Wannamaker KW, Miller DM. Prevalence and dose dependency analysis of pentosan Polysulfate sodium maculopathy. *Ophthalmic Epidemiol*. 2023;30:82–87.
- Alshukairi AN, Aldabbagh YA, Sayes NM, et al. A COVID-19 family cluster with retinitis pigmentosa and hypogammaglobulinemia. *Ann Thorac Med*. 2022;17:66–69.
- Liu Y, Chen X, Xu Q, et al. SPP2 mutations cause autosomal dominant retinitis pigmentosa. *Sci Rep*. 2015/10/13 2015;5(1), 14867.
- Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018;125:1793–1802.
- Wang D, Velaga SB, Grondin C, et al. Pentosan polysulfate maculopathy: prevalence, spectrum of disease, and choroidal imaging analysis based on prospective screening. *Am J Ophthalmol*. 2021;227:125–138.
- Kalaw FGP, Arias JD, Walker E, et al. Refining the retinal phenotype of patients with suspected pentosan polysulfate sodium retinopathy. *Retina*. 2023;43:1472–1479.
- Shah R, Simonett JM, Lyons RJ, et al. Disease course in patients with pentosan polysulfate sodium-associated maculopathy after drug cessation. *JAMA Ophthalmol*. 2020;138:894–900.
- Girardot PE, Zhang X, Zhang N, et al. Pentosan polysulfate sodium causes diminished function and subtle morphological changes in retina and RPE of mice. *Investig Ophthalmol Vis Sci*. 2024;65:28.
- Khoh-Reiter S, Sokolowski SA, Jessen B, et al. Contribution of membrane trafficking perturbation to retinal toxicity. *Toxicol Sci*. 2015;145:383–395.
- Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123:1386–1394.
- Tsang SH, Sharma T. Drug-induced retinal toxicity. *Adv Exp Med Biol*. 2018;1085:227–232.
- Lando L, Boroah S. Late-onset retinal degeneration: clinical perspectives. *Clin Ophthalmol*. 2022;16:3225–3246.
- Xue K, Oldani M, Jolly JK, et al. Correlation of optical coherence tomography and autofluorescence in the outer retina and choroid of patients with choroideremia. *Investig Ophthalmol Vis Sci*. 2016;57:3674–3684.
- Hayward C, Shu X, Cideciyan AV, et al. Mutation in a short-chain collagen gene, CTRP5, results in extracellular deposit formation in late-onset retinal degeneration: a genetic model for age-related macular degeneration. *Hum Mol Genet*. 2003;12:2657–2667.
- Simunovic MP, Jolly JK, Xue K, et al. The spectrum of CHM gene mutations in choroideremia and their relationship to clinical phenotype. *Investig Ophthalmol Vis Sci*. 2016;57:6033–6039.
- Stanton CM, Boroah S, Drake C, et al. Novel pathogenic mutations in C1QTNF5 support a dominant negative disease mechanism in late-onset retinal degeneration. *Sci Rep*. 2017;7, 12147.
- Shukla P, Russell MW, Muste JC, et al. Propensity-matched analysis of the risk of age-related macular degeneration with systemic immune-mediated inflammatory disease. *Ophthalmol Retina*. 2024;8:778–785.
- Bassaly R, Downes K, Hart S. Dietary consumption triggers in interstitial cystitis/bladder pain syndrome patients. *Female Pelvic Med Reconstr Surg*. 2011;17:36–39.
- Herati A, Shorter B, Sadek M, et al. 808 the effects of caffeine on the symptoms of interstitial cystitis/painful bladder syndrome: a randomized, placebo-controlled double blind study. *J Urol*. 2011;185. <https://doi.org/10.1016/j.juro.2011.02.626>.
- Karti O, Zengin MO, Kerici SG, Ayhan Z, Kusbeci T. Acute effect of caffeine on macular microcirculation in healthy subjects: an optical coherence tomography angiography study. *Retina*. 2019;39:964–971.
- Yilmaz Tugan B, Subasi S, Pirhan D, et al. Evaluation of macular and peripapillary vascular parameter change in healthy subjects after caffeine intake using optical coherence tomography angiography. *Indian J Ophthalmol*. 2022;70:879–889.
- Fogel Levin M, Santana A, Corradetti G, et al. Pentosan polysulfate sodium-associated maculopathy: early detection using OCT angiography and choriocapillaris flow deficit analysis. *Am J Ophthalmol*. 2022;244:38–47.

26. Jain N, Liao A, Garg SJ, et al. Expanded clinical spectrum of pentosan polysulfate maculopathy: a macula society collaborative study. *Ophthalmol Retina*. 2022;6: 219–227.
27. Wang D, Velaga SB, Grondin C, et al. Pentosan polysulfate maculopathy: prevalence, spectrum of disease, and choroidal imaging analysis based on prospective screening. *Am J Ophthalmol*. 2021;227:125–138.
28. Tao BK, Sawires K, Lim K, Butt F, et al. Risk and dose–response relationship for pentosan polysulfate sodium maculopathy: a systematic review and meta-analysis. *Ophthalmol Retina*. 2025;9:870–882.