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Pentosan Polysulfate Maculopathy: Pathophysiology, Clinical Features, and Screening Strategies

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Pentosan polysulfate (PPS) has been widely used for the treatment of interstitial cystitis, but has been linked to a progressive and potentially irreversible maculopathy. PPS maculopathy is characterized by pigmentary changes, outer retinal atrophy, and visual symptoms such as difficulty reading and dark adaptation, despite relatively preserved central acuity in early stages. Histologic and imaging studies suggest that PPS toxicity primarily targets the retinal pigment epithelium, leading to secondary photoreceptor loss. The risk of toxicity increases with cumulative dose and treatment duration, but reported prevalence varies widely, from approximately 5% or lower in claims-based studies to around 20% in tertiary-center cohorts. Multimodal imaging—including fundus autofluorescence, near-infrared reflectance, and optical coherence tomography—plays a critical role in early detection. Despite this, screening practices remain inconsistent and inadequate in many clinical settings. Recent nationwide data from South Korea revealed that over half of high-risk PPS users did not undergo any ophthalmic examination during the study period. Given the irreversible nature of PPS maculopathy and its progressive course even after drug cessation, early identification is crucial. There is an urgent need to establish standardized screening protocols based on cumulative dose and duration of therapy, similar to existing guidelines for hydroxychloroquine retinopathy. Increased collaboration between urologists and ophthalmologists, along with heightened awareness among patients and providers, is essential to prevent vision loss in this vulnerable population.

Keywords: Diagnosis; Maculopathy; Pentosan polysulfate; Physiopathology; Signs and symptoms

Introduction

Pentosan polysulfate (PPS), a semisynthetic polysulfated xylan compound, is widely used to treat interstitial cystitis (IC), a chronic inflammatory bladder disorder characterized

by urinary urgency, frequency, and pelvic discomfort [1,2]. IC commonly coexists with several chronic pain conditions and shows a strong female predominance but may be under-recognized in men. Disruption of the bladder's glycosaminoglycan (GAG) barrier, along with inflammatory and neural

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factors, is thought to underlie its pathophysiology [3]. Since its U.S. Food and Drug Administration (FDA) approval in 1996 [4], PPS use for IC has steadily increased, and PPS remains the only oral therapy specifically indicated for this disease.

In 2018, Pearce et al. [5] first identified a characteristic maculopathy associated with chronic PPS exposure, describing a pattern of pigmentary retinal changes in six patients receiving long-term PPS. Since this initial report, multiple studies worldwide have confirmed an association between PPS and this progressive maculopathy [6-8]. Notably, a large cohort study found that PPS users had significantly higher odds of developing macular disease after seven years of use compared with matched nonusers, with the risk appearing to be strongly dose-dependent [6]. Cumulative dose and treatment duration are now recognized as the dominant risk factors for toxicity. While most patients develop this toxicity only after years of continuous use, the potentially irreversible and progressive nature of the disease even after drug cessation has prompted regulatory actions and growing concern among ophthalmologists and urologists [7,8].

Given the potentially irreversible nature of PPS maculopathy, there is increasing emphasis on understanding its pathophysiology and instituting appropriate screening strategies for patients receiving long-term PPS therapy. In this review, we summarize current knowledge on the epidemiology, clinical manifestations, and imaging characteristics of PPS maculopathy. We also evaluate the proposed pathogenesis and discuss evolving strategies for screening, diagnosis, and future research directions.

Demographics and Epidemiology

To date, most published cohorts originate from the United States and reflect the prescribing patterns in Western populations, where the majority of patients are older White women [9-14]. In one of the largest clinical case series, the mean age of patients with PPS maculopathy was 62.2 ± 13.2 years, with 93% of affected individuals identifying as White and 90% as female, highlighting both racial and sex imbalances in current study populations [9]. The majority of cases occur in patients over 50 years of age, consistent with the age distribution of IC, for which PPS remains the only FDA-approved oral therapy.

However, recent data from other populations suggest some variation. A nationwide Korean study using health claims data identified 133,762 PPS users between 2012 and 2021, with the number of users increasing over time—from 5,494 in 2012 to 40,451 in 2021 [15]. Similarly, a large-scale retrospective review of 1,407 PPS users in the United States by Hom et al. [16] found that only 10.7% of patients had a recorded visit with an ophthalmologist, and only 5.0% underwent optical coherence tomography (OCT) imaging over a 15-year period. Notably, the Korean high-exposure PPS cohort [15] included a higher proportion of male users (58% in the high-risk group), contrasting with Western data and suggesting regional prescribing differences. In a large population-based study, Bae et al. [17] reported that PPS users had a significantly higher rate of maculopathy than nonusers, with an adjusted rate ratio of 1.41 (95% CI 1.09–1.83), further confirming the association in a broad clinical setting. In a separate nationwide Korean population-based cohort, Kim et al. [18] also reported that PPS use was independently associated with an increased risk of subsequent maculopathy, further supporting the relevance of PPS-associated retinal toxicity in Asian populations.

Estimating the true prevalence of PPS maculopathy remains challenging due to differences in study design, cumulative dosing, and diagnostic approaches. Tertiary center studies have reported relatively high prevalence rates (16.5% to 23.1%) likely influenced by referral bias [7,19]. In contrast, large insurance claims studies from the U.S. have estimated prevalence rates between 0.7% and 3.4% among PPS users [6,20]. These lower figures may still underestimate true prevalence, as claims data often rely on specific retinal diagnoses and may fail to capture subclinical or misdiagnosed cases. Furthermore, limited follow-up durations may obscure the development of toxicity in long-term users.

Dose-Dependent Association with PPS

Since the recognition of PPS maculopathy in 2018 [5], cumulative drug exposure has been identified as the most consistent and well-established risk factor for retinal toxicity. Numerous studies have demonstrated a clear dose-dependent association, with increasing risk increasing with both total cumulative dose and treatment duration.

Specifically, a prospective screening study reported that

affected patients had undergone PPS therapy for an average of 20.3 years, with a mean cumulative dose of 3,375 g, compared with 6.3 years and 692 g in unaffected patients ($p < 0.001$) [7]. While most patients develop this toxicity only after years of continuous use, with one analysis estimating a mean of 15 years of exposure among affected individuals [5], rare cases of PPS maculopathy have occurred at lower cumulative doses or shorter exposure durations [8]. Recent research further supports these findings, showing that PPS maculopathy occurred predominantly after at least 15 years of exposure and a cumulative dose exceeding 2,000 g (mean duration 17 years; mean cumulative dose 2,418 g) [21].

Subsequent studies consistently found increased risk in patients exceeding 500 g of cumulative PPS intake [6,7]. In a prospective study by Wang et al., most cases had cumulative doses exceeding 1,000 g [8]. Population-based studies have further confirmed this association. Jain et al. demonstrated significantly elevated odds of maculopathy after seven years of PPS use [6]. A nationwide Korean study categorized patients into exposure groups, showing a cumulative incidence of 9.0% for maculopathy in high-risk users (≥ 500 g), with multivariate analysis confirming a dose-dependent increase in risk [22]. Although rare cases have occurred at lower doses or shorter durations, these remain exceptions. A recent systematic review and meta-analysis by Tao et al. [23] further supported this dose-response relationship, showing progressively increased risk of PPS maculopathy with higher cumulative exposure.

Furthermore, the risk of toxicity does not immediately dissipate upon drug cessation. Longitudinal follow-up has demonstrated that even after PPS discontinuation, a subset of patients show measurable progression of maculopathy, with some cases exhibiting expansion of retinal pigment epithelium (RPE) atrophy over an average post-cessation period of 18 months [21]. While cumulative dose is the primary risk factor, variability in susceptibility suggests that genetic predisposition, metabolic factors, and individual pharmacokinetics may contribute, though these factors remain incompletely understood [19,24]. Overall, current evidence strongly supports a clear exposure-response relationship, underscoring the importance of monitoring cumulative dose and establishing formal screening thresholds to facilitate early detection and prevention of vision-threatening toxicity.

Clinical Presentation

PPS maculopathy often presents insidiously, with a reported interval of approximately 14.5 to 20 years from the initiation of therapy to the onset of clinical symptoms [21]. In a recent single-center study, although the overall prevalence was about 10.8% among exposed patients, a substantial proportion of those diagnosed with maculopathy were already symptomatic at the time of evaluation, with common complaints including blurred vision and night vision disturbances (nyctalopia) [21,25]. Affected patients commonly report difficulty reading, blurred vision, nyctalopia, and delayed dark adaptation, even while central visual acuity remains relatively preserved in early stages [19,26]. Some individuals also report metamorphopsia. These symptoms are often subtle and can be mistaken for normal aging or coexistent ocular conditions, delaying proper evaluation. Notably, in one series, patients with confirmed PPS toxicity had among the lowest scores recorded on the Low Luminance Questionnaire, reflecting severe impairment of low-light visual function [26]. As the disease advances, patients may develop paracentral scotomas corresponding to areas of retinal atrophy [27]. In late stages, extensive RPE degeneration or secondary complications can substantially reduce visual acuity [28,29].

Imaging Findings

Fundus photography

Early in the course, the fundus examination may appear normal or show subtle changes, contributing to underrecognition. The initial hallmark findings are typically bilateral, parafoveal pigmentary alterations. These often include faint pigmented spots or mottling at the level of the RPE and small yellowish subretinal deposits in the posterior pole [9]. The distribution tends to be centered on the macula (often in a pericentral or paracentral pattern); the foveal center may be spared until later stages. With disease progression, patchy areas of RPE atrophy emerge in the parafoveal or extrafoveal macula, which may coalesce into confluent atrophic zones involving the fovea in severe cases. In advanced toxicity, the fundus may exhibit beaten-bronze or geographic atrophy-like changes extending even to the mid-periphery [20]. Importantly, a normal dilated fundus examination does not rule out PPS maculopathy, as early changes can be subtle

or not readily visible without specialized imaging. Some patients develop secondary complications of chronic retinal stress, including cystoid macular edema (CME) or macular neovascularization (MNV) in areas of RPE loss; these can further degrade vision and require treatment (such as carbonic anhydrase inhibitors for CME or anti-vascular endothelial growth factor injections for MNV) [30] (Fig. 1A).

Fundus autofluorescence imaging

Fundus autofluorescence (FAF) often provides the most striking evidence of toxicity. FAF imaging typically reveals a dense array of punctate hyperautofluorescent and hypoautofluorescent spots in the posterior pole, extending beyond the clinically observed lesions [7]. This speckled autofluorescence pattern corresponds to areas of RPE metabolic stress or loss and can form a reticular or peripapillary distribution in some cases (Fig. 1B).

Near-infrared reflectance imaging

Near-infrared reflectance (NIR) imaging is another sensitive modality that shows discrete hyperreflective spots at the macula that correspond to the pigmentary changes, often detectable before obvious fundus or OCT abnormalities [31]. In fact, NIR may highlight early parafoveal lesions that are otherwise subtle, making it a valuable screening tool [7].

OCT

OCT reveals the structural correlates of PPS maculopathy: focal nodular thickening or elevation of the RPE, disruption of the ellipsoid zone, and thinning of the outer nuclear layer in early to moderate disease [7,19] (Fig. 1C). In more advanced cases, OCT shows zones of RPE attenuation or frank RPE loss with accompanying photoreceptor atrophy, sometimes with collapse of the outer retinal architecture resembling geographic atrophy. These OCT changes often colocalize with the abnormalities seen on FAF and NIR. Visual field testing with 10-2 or 30-2 perimetry can detect relative paracentral depressions corresponding to areas of retinal change, though formal field testing is not as sensitive as imaging in early toxicity [26].

Multifocal electroretinography

Multifocal electroretinography may demonstrate localized macular response reductions in PPS toxicity, but this is not routinely used in screening. In summary, multimodal imaging

typically uncovers a distinct pattern of bilateral, symmetric RPE pathology – a pattern that helps differentiate PPS maculopathy from phenotypically similar entities such as pattern dystrophies or age-related macular degeneration (AMD)

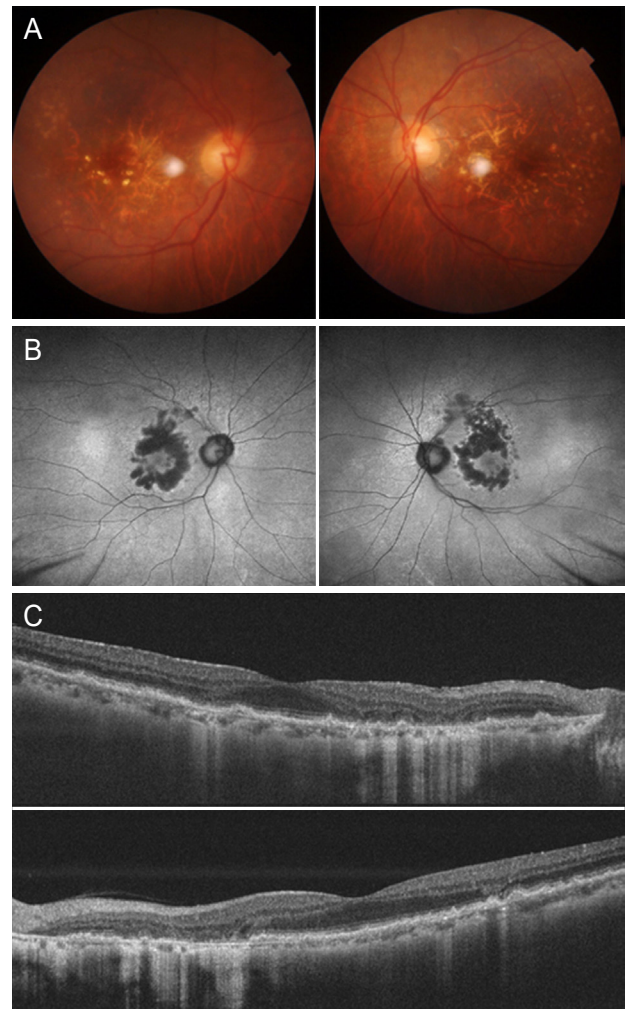


Figure 1. Multimodal imaging of a diagnostically challenging case with features suspicious for pentosan polysulfate maculopathy in a PPS user with relatively short exposure. A 74-year-old woman with a 5-year history of PPS use for interstitial cystitis presented with progressive difficulty reading and impaired dark adaptation. (A) Color fundus photograph showing subtle yellowish subretinal deposits and parafoveal pigmentary changes. (B) Fundus autofluorescence showing a dense, speckled pattern of hyper- and hypoautofluorescence in a well-demarcated parafoveal distribution with relative peripapillary sparing. (C) Optical coherence tomography revealing irregular nodular elevations at the level of the retinal pigment epithelium with associated outer retinal disruption. These findings may overlap with advanced dry age-related macular degeneration with geographic atrophy, and differentiation remains challenging. PPS = pentosan polysulfate.

[7,31]. Recognizing these features is critical, as PPS maculopathy can easily masquerade as other macular diseases if the clinician is unaware of the patient's PPS exposure history. Key findings of PPS maculopathy according to various imaging modalities are summarized in Table 1.

Disease Course

PPS maculopathy typically follows a slowly progressive course, even after cessation of drug exposure [13,29]. The natural history of the disease can be broadly categorized into

early, intermediate, and advanced stages based on structural and functional changes. Patients with early disease may remain asymptomatic or have subtle visual disturbances such as difficulty reading or impaired dark adaptation. During this latent phase, best-corrected visual acuity often remains 20/40 or better, although multimodal imaging may already reveal early RPE stress and subtle pigmentary mottling [21].

As the condition advances into the intermediate stage, progressive RPE atrophy and outer retinal degeneration may lead to more significant visual loss, including central vision impairment and the development of paracentral scotomas [27,32]. The area of “speckled” autofluorescence often ex-

Table 1. Key findings and sensitivity for detection of pentosan polysulfate maculopathy according to imaging modalities

Modality	Characteristic findings	Typical distribution	Stage detected	Strengths	Limitations
Fundus photography	• Subtle parafoveal pigmentary changes (mottling, granular hyper/hypopigmentation) • Yellowish subretinal deposits • In late stage: geographic RPE atrophy, beaten-bronze appearance	Parafoveal and posterior pole	Moderate to late	Widely available, inexpensive	Often normal in early stages; subtle changes easily missed without multimodal imaging
FAF	• Speckled pattern of alternating hyper- and hypoautofluorescence • Reticular or dense stippled hyperautofluorescence • Progresses to well-demarcated hypoautofluorescent atrophy in late stages	Posterior pole, sometimes extending to peripapillary area	Early to advanced	High sensitivity for early RPE dysfunction; good correlation with disease extent	Limited peripheral coverage unless wide-field FAF used
NIR	• Hyperreflective spots in parafoveal and peripapillary areas • Patchy reflectivity alterations preceding structural OCT or fundus changes	Parafoveal, peripapillary	Very early	High sensitivity; may detect earliest subclinical changes	Less commonly available in routine practice; not universally incorporated into screening protocols
OCT	• RPE irregularities and nodular thickening • Ellipsoid zone disruption • Outer nuclear layer thinning • Outer retinal atrophy (sometimes foveal sparing until late stages) • Choroidal thinning in some cases	Parafoveal (3–5 mm ring around fovea), sometimes extending beyond	Very early to advanced	Excellent structural detail; highly sensitive for early outer retinal damage; longitudinal monitoring possible	Requires macular raster scans; limited field if peripheral involvement suspected
mfERG	• Reduced macular response amplitudes • Delayed implicit times • Localized functional deficits corresponding to areas of structural damage	Central macula	Early functional changes	Objective functional testing of central retina; can detect localized dysfunction even with preserved acuity	Limited availability; technically challenging; less commonly used in routine screening

RPE = retinal pigment epithelium; FAF = fundus autofluorescence; NIR = near-infrared reflectance; OCT = optical coherence tomography; mfERG = multifocal electroretinography.

pands during this period, signaling a widening zone of RPE dysfunction that eventually precedes frank atrophy. Importantly, several studies have reported continued progression of retinal damage despite drug discontinuation, suggesting that PPS-induced retinal injury may be self-perpetuating once established [13,27,29]. This phenomenon, often termed “relentless progression,” has been documented in longitudinal cohorts in which the total area of RPE atrophy continued to increase at a measurable rate, sometimes for years, after the last dose of PPS [27,32]. For instance, recent research documented progression over a mean post-cessation period of 18.3 months, with some patients exhibiting new zones of atrophy despite no further drug exposure [21].

In advanced stages, the disease may culminate in extensive geographic atrophy-like lesions that involve the foveal center, leading to a profound decline in central vision. Secondary complications, such as CME and choroidal neovascularization, may occur in more advanced cases and further contribute to visual decline [11]. The development of CME in PPS maculopathy is particularly notable as it is often “non-leaking” on fluorescein angiography, suggesting a degenerative rather than purely inflammatory etiology related to RPE pump failure [11].

While cessation of PPS remains the only available intervention that may stabilize the disease, its effectiveness appears to vary with the stage at which treatment is discontinued. Evidence suggests that patients with established atrophic lesions are at the highest risk for continued post-cessation progression, whereas those identified at the pre-atrophic “pigmentary” stage may have a better chance of stabilization. Therefore, early detection and prompt cessation of PPS at the earliest signs of toxicity are critical to minimizing long-term visual sequelae.

Moreover, while PPS maculopathy is often described as a slowly progressive condition, the rate of degeneration can vary significantly among individuals. Somisetty et al. [33] documented cases of rapid progression, emphasizing that structural damage to the RPE and outer retina can accelerate over a relatively short period. This highlights the unpredictable nature of the disease course and the need for frequent monitoring in high-risk patients.

Differential Diagnosis

PPS maculopathy shares overlapping clinical and imaging features with various macular disorders, making early diagnosis challenging. Accurate differentiation is essential due to its progressive and potentially preventable nature.

One major differential diagnosis is AMD, as both conditions may present with pigmentary changes, RPE atrophy, and central vision impairment (Table 2). However, PPS maculopathy typically shows bilateral, symmetric parafoveal involvement with relative foveal sparing until later stages [32]. Drusen, a hallmark of AMD, are generally absent in PPS toxicity, although some patients may exhibit drusenoid-like subretinal deposits that lack the soft, confluent appearance of typical AMD drusen [34,35]. OCT may reveal hyperreflective RPE nodules and localized outer retinal atrophy, distinct from the drusen and subretinal deposits seen in AMD [34,36]. FAF often demonstrates a stippled hyper- and hypo-autofluorescent pattern in PPS maculopathy, frequently described as a “speckled” appearance that extends beyond the visible lesions, whereas AMD shows more geographic hypoautofluorescence [37]. Early parafoveal hyperreflectivity on NIR imaging can also help distinguish PPS toxicity from the more generalized changes seen in dry AMD. In diagnostically challenging cases, particularly in patients with relatively short PPS exposure or coexisting age-related macular changes, PPS maculopathy may overlap substantially with advanced dry AMD, as illustrated in Fig. 1. Careful integration of PPS exposure history and multimodal imaging findings is therefore essential.

Inherited macular dystrophies, including pattern dystrophies and Mendelian maculopathies, may mimic PPS maculopathy [14,19]. However, Stargardt disease typically features characteristic “pisciform” flecks and a dark choroid sign on fluorescein angiography, which are not present in PPS toxicity [38,39]. Furthermore, inherited dystrophies often exhibit peripapillary sparing on FAF, earlier onset, and a positive family history, whereas PPS maculopathy arises after prolonged drug exposure in adulthood [38]. In uncertain cases, genetic testing and pedigree analysis may aid diagnosis.

Mitochondrial maculopathies, such as maternally inherited diabetes and deafness syndrome (MIDD), can show macular pigmentary changes and outer retinal defects [40]. MIDD typically includes systemic findings such as diabetes, hearing loss, and cardiac manifestations. On FAF, MIDD

often displays a “circumferential” pattern of atrophy around the fovea, which can be distinguished from the more centripetal, speckled progression of PPS maculopathy [34]. Thus, systemic features, inheritance pattern, and medication exposure history are important for distinguishing MIDD from PPS maculopathy.

Pachychoroid spectrum disorders, including central serous chorioretinopathy, may also resemble PPS toxicity with pigmentary changes and RPE abnormalities [41]. However, asymmetric lesions, choroidal thickening, and dilated choroidal vessels on enhanced-depth OCT suggest pachychoroid disease rather than PPS maculopathy. Specifically, PPS maculopathy is often associated with choroidal thinning rather than the choroidal thickening associated with pachychoroid disease [20]. In early PPS maculopathy, when fundus changes are minimal, multimodal imaging—particularly NIR, FAF, and high-resolution OCT—is crucial for detecting subtle RPE and outer retinal abnormalities. If uncertainty

persists, careful longitudinal follow-up may help clarify the diagnosis as the disease course evolves.

Pathophysiology

The precise mechanism by which PPS causes retinal toxicity remains under investigation. PPS maculopathy is believed to result from primary injury to the RPE, with secondary degeneration of photoreceptors [22]. PPS is a highly sulfated GAG analog that may bind to ocular tissues or disrupt cellular homeostasis in the RPE. Given its structural similarity to heparin and other GAGs, PPS may interfere with the binding of endogenous GAGs to essential growth factors or extracellular matrix components, potentially altering the metabolic environment of the outer retina.

Preclinical studies support this RPE-centered pathogenesis: in a mouse model of chronic PPS exposure, PPS

Table 2. Differential diagnoses for PPS maculopathy and distinguishing points

Differential diagnosis	Clinical features	Imaging features	Distinguishing points from PPS maculopathy
AMD	- Typically older patients - Central vision loss - Presence of drusen	- Drusen on OCT and color fundus - Geographic hypoautofluorescence on FAF - RPE atrophy with subretinal drusenoid deposits	- Drusen typically absent in PPS maculopathy - PPS shows bilateral, symmetric parafoveal changes with foveal sparing until late - FAF in PPS: stippled/speckled hyper-/hypo-autofluorescence vs geographic in AMD
Inherited macular dystrophies	- Often earlier onset - Positive family history - Variable systemic associations	- Pattern dystrophies: granular RPE changes on fundus - FAF: peripapillary sparing - OCT: variable outer retinal atrophy	- PPS maculopathy arises after prolonged drug exposure in adulthood - Lacks family history in PPS maculopathy - PPS: parafoveal localization without peripapillary sparing
Mitochondrial maculopathies	- Systemic findings (e.g., diabetes, hearing loss) - Often maternally inherited	- OCT: outer retinal and RPE defects - FAF: variable atrophic patterns - May show foveal sparing in early disease	- PPS: no systemic mitochondrial features - PPS shows earlier central/parafoveal involvement vs foveal sparing in mitochondrial disease
Pachychoroid spectrum disorders	- May occur in younger adults - Central serous-like symptoms - Often unilateral or asymmetric	- Enhanced-depth OCT: choroidal thickening - Dilated choroidal vessels (“pachyvessels”) - NIR/FAF: asymmetric RPE changes	- PPS: bilateral, symmetric lesions - PPS lacks choroidal thickening and pachyvessels - Early PPS: fundus changes minimal but NIR/FAF/OCT reveal parafoveal RPE abnormalities rather than pachychoroid features
Pattern dystrophies	- Mid-adult onset - Slowly progressive	- Granular RPE changes - Sub-RPE vitelliform material	- PPS: strong dose-dependent association with PPS use - FAF: speckled pattern in PPS is more widespread than typical pattern dystrophy

PPS = pentosan polysulfate; AMD = age-related macular degeneration; OCT = optical coherence tomography; FAF = fundus autofluorescence; RPE = retinal pigment epithelium; NIR = near-infrared reflectance.

treatment led to progressive retinal dysfunction (reduced electroretinographic amplitudes) and subtle morphological changes in the RPE, including RPE cell enlargement and loss of regular cellular architecture, along with shortening of photoreceptor outer segments [35]. These findings support a slowly accumulating toxic effect primarily involving the RPE–photoreceptor interface. Genetic susceptibility may also contribute to disease variability. Kalaw et al. reported no clear association between PPS maculopathy and genes implicated in Mendelian inherited retinal dystrophies, but several AMD-associated risk alleles, including variants related to complement pathway biology, were enriched among affected patients [24].

At the molecular level, it has been hypothesized that PPS may interfere with the phagocytosis of photoreceptor outer segments or disrupt growth factor signaling. Specifically, researchers have investigated the role of pigment epithelium-derived factor receptor (PEDF-R). PPS may compete for binding sites on PEDF-R, which is essential for lipid metabolism and the degradation of outer segment disks within the RPE [41]. A disruption in this pathway could lead to the accumulation of toxic byproducts and metabolic waste, eventually resulting in RPE cell death. Furthermore, the potential role of the choroid in PPS pathophysiology has received increasing attention. Although evidence is mixed, a significant reduction in subfoveal choroidal thickness has been observed in long-term PPS users, and some studies using OCT angiography have reported flow deficits in the choriocapillaris [20,37]. These findings suggest that primary or secondary microvascular compromise may exacerbate RPE dysfunction by limiting the delivery of nutrients or the removal of metabolic waste.

Importantly, the toxicity appears to be dose-dependent: higher cumulative exposure increases the likelihood of overwhelming the RPE's capacity for repair. Once established, PPS maculopathy can continue to progress despite drug cessation [32], indicating that retinal damage is potentially irreversible. No protective cofactors have been identified, although individual susceptibility likely varies. Overall, current research suggests that PPS maculopathy is an iatrogenic retinal degeneration initiated by chronic PPS-induced RPE dysfunction, which in turn leads to photoreceptor loss and irreversible retinal damage [35,42].

Screening

Because PPS maculopathy may be asymptomatic or subtle in its early stages yet progressive and irreversible, proactive screening of patients receiving PPS is imperative. At present, no universally accepted consensus guidelines have been established for PPS maculopathy. In many regions, there is a lack of official recommendations from ophthalmic or urologic societies regarding whether and when to perform retinal examinations in PPS users [15]. Nevertheless, experts have proposed screening strategies based on the growing body of evidence. A comprehensive screening program is essential not only for early detection but also for establishing a clear baseline to differentiate drug toxicity from pre-existing age-related macular changes [7]. A reasonable approach is to obtain a baseline dilated fundus examination with multimodal imaging, including color fundus photography, OCT, FAF, and NIR reflectance, when a patient initiates long-term PPS therapy or as soon as PPS exposure is recognized. Given that toxicity has generally not been observed with less than approximately 2 years of use, annual screening is often recommended after 3–5 years of cumulative use, or earlier if visual symptoms occur. Some authors have suggested using a cumulative dose threshold (for example, approximately 500 g, roughly 3–5 years at standard dosing) as a trigger for more intensive surveillance [22]. However, recent data suggesting that toxicity may predominantly manifest after exceeding 2,000 g of cumulative dose (average 15–17 years of use) indicate that the frequency of screening should be intensified as patients approach these higher exposure levels [21]. Beyond the five-year mark, yearly examinations with OCT and FAF are generally advised, with NIR and visual field testing as useful adjuncts. Patients should also be counseled to report any new visual disturbances promptly.

Real-World Practice Patterns

Despite these suggestions, recent data indicate that adherence to PPS screening recommendations is low in routine practice. A nationwide study in South Korea—where PPS has been approved since 2003—illustrates the gap in care. Between 2012 and 2021, the number of PPS users in Korea rose dramatically (from 5,494 to over 40,000 per year), yet only 27.2% of PPS users received a baseline ophthalmic ex-

amination upon starting therapy, and just 12.4% underwent any subsequent retinal monitoring [22]. Screening modality use also differed by practice setting. In a single-center study, OCT was documented in 78.4% of evaluated patients, whereas FAF and color fundus photography were documented in 35.1% and 32.4%, respectively [21]. In contrast, nationwide Korean claims-based data showed that fundus photography was the most commonly performed modality among patients who underwent retinal monitoring, whereas OCT and FAF were used in only approximately 45% and 5% of monitored patients, respectively [15]. These findings highlight that even when ophthalmic monitoring is performed, the use of multimodal imaging remains inconsistent.

The lack of FAF use is particularly concerning given its role as a primary indicator of early RPE stress. Indeed, no cases were officially reported in South Korea until very recently, which observers attribute to insufficient surveillance rather than true absence of toxicity [15]. Moreover, even patients at the highest risk have not been adequately monitored. In a large population-based analysis of Korean health data, Kwon et al. found that among “high-exposure” PPS users (≥ 500 g cumulative dose), only about 52.6% ever underwent any retinal examination, which was not significantly different from the screening rate in lower-exposure patients (49.4%) [22]. Consequently, a substantial number of maculopathy cases may be missed until they are advanced. Kwon et al. further reported that the cumulative incidence of maculopathy among the high-exposure PPS group was approximately 9.0% and was significantly higher than that in the low-exposure group [22]. This finding suggests that retinal toxicity may remain undetected in many PPS users. Both the Korean nationwide study and other series emphasize that relying on fundus examination alone is inadequate; patients without obvious fundus changes can harbor significant retinal pathology detectable on OCT or FAF [7,15].

Recommended Screening Modalities

For effective screening, spectral-domain OCT and wide-field FAF are considered essential, as they can reveal early PPS changes before symptoms or fundus findings arise. NIR imaging is also highly useful for early detection. Multimodal imaging is superior to any single modality, as early toxic changes may be isolated to a single imaging modality—most

commonly FAF or NIR reflectance—before becoming evident on structural OCT [7,19]. A practical screening visit for a PPS patient should include a careful fundus examination, macular OCT scans covering the parafoveal region out to the vascular arcades, and FAF imaging of the posterior pole. Color fundus photography can document baseline appearance and provide a reference for longitudinal comparison of pigmentary and atrophic changes, although FAF, NIR reflectance, and SD-OCT are more sensitive for detecting early PPS maculopathy. Additional functional testing, such as multifocal ERG or microperimetry, may further augment sensitivity when available. Specific attention should be paid to the peripapillary and parafoveal regions, as these are the primary sites of initial involvement [9]. Patients should ideally undergo baseline testing within the first year after starting PPS to document any pre-existing macular status, followed by periodic screening by 5 years of use and annually thereafter. Any change on screening that suggests incipient PPS maculopathy (e.g., new parafoveal RPE irregularities on OCT or new FAF abnormalities) should prompt re-evaluation of PPS therapy in conjunction with the prescribing physician. Clinicians should be aware that once toxicity is detected, progression may continue even after drug cessation, making the threshold for discontinuation a critical clinical decision [13,27]. Given that PPS is often not the sole treatment for IC, discontinuation of PPS can be considered at the earliest sign of toxicity to prevent progression. Patients should also be educated about the symptoms of PPS maculopathy and the importance of routine eye exams, as patient awareness may improve adherence to screening recommendations.

As summarized in Table 3, the screening approach for PPS maculopathy must be proactive and multifaceted. Given the high-risk exposure levels identified in recent studies—particularly cumulative doses exceeding 2,000 g—clinicians should consider shorter screening intervals for long-term users [21]. Furthermore, the integration of functional assessments, such as low-luminance visual acuity or dark adaptation testing, can provide a more comprehensive view of the patient’s visual health beyond structural imaging alone [26,28].

Conclusion

Since the recognition of PPS maculopathy in 2018, signif-

icant progress has been made in characterizing its clinical and imaging features. However, important questions remain regarding its public health impact, pathogenesis, and optimal management.

Given the risk of irreversible vision loss, prevention remains a key priority. Continued monitoring of prescribing patterns and screening practices is needed. While some Western reports suggest a decline in PPS use, recent data, including nationwide findings from South Korea, indicate that prescribing remains stable or is increasing in certain regions [15,22]. Growing interest in off-label PPS use, such as for osteoarthritis, further underscores the importance of long-term safety surveillance. Future research should address gaps in our understanding of disease prevalence and risk variability.

Current prevalence estimates largely derive from tertiary care cohorts, which may overrepresent severe cases. In contrast, population-based health claims analyses suggest lower

incidence but may be limited by diagnostic misclassification and incomplete follow-up. Large-scale longitudinal studies are needed to better define true incidence, particularly among lower-exposure groups. Cumulative dose remains the primary risk factor, though other variables such as age, sex, comorbidities, and genetic susceptibility may contribute. Notably, regional differences, such as the higher proportion of male PPS users in South Korea compared with predominantly female cohorts in the United States, highlight the need for diverse, global studies to clarify how population-specific factors influence toxicity [15,32]. Optimizing screening remains another critical area. Combining multimodal imaging with quantitative biomarkers and machine learning may improve early detection. Longitudinal studies are also needed to assess whether early drug cessation can halt disease progression.

Moreover, as longitudinal follow-up has confirmed that

Table 3. Recommended screening protocol for pentosan polysulfate maculopathy: timing and modalities

Screening phase	Recommended timing	Recommended modality	Key clinical considerations
Baseline	At initiation of therapy (or within the 1st year)	• CFP • SD-OCT • FAF • NIR reflectance	• Establish pre-existing macular status. • Document baseline fundus appearance for future comparison. • Differentiate from AMD or inherited dystrophies.
Standard follow-up	Annual screening starting at 5 years of use	• CFP • FAF • SD-OCT • NIR reflectance	• Documentation for longitudinal comparison of pigmentary changes. • Cumulative risk increases significantly after 5 years. • FAF is highly sensitive for early “speckled” RPE stress.
High-risk intensive	Annual or semi-annual after 15 years or >2,000 g	• CFP • Multimodal Imaging (FAF + OCT + NIR) • 10-2 Visual Field	• Document progression of visible pigmentary or atrophic changes • Significant risk increase observed at this exposure level. • NIR may detect abnormalities before OCT or FAF.
Symptomatic evaluation	Immediately upon report of visual symptoms	• Full Multimodal Suite (CFP, SD-OCT, FAF, NIR) • Low-Luminance Acuity • mfERG (optional)	• Symptoms like nyctalopia can precede structural loss. • BCVA may remain 20/20 despite significant RPE damage.
Post-cessation	Annual/Biennial for 2–3 years after stopping	• Full Multimodal Suite (CFP, SD-OCT, FAF, NIR)	• Monitor for “relentless progression” post-discontinuation. • Mean post-cessation follow-up of 18.3 months recommended.

CFP, color fundus photography; SD-OCT, spectral-domain optical coherence tomography; FAF, fundus autofluorescence; NIR, near-infrared; AMD, age-related macular degeneration; 10-2 Visual Field, 10-2 Humphrey visual field; BCVA, best-corrected visual acuity; mfERG, multifocal electroretinography.

maculopathy can continue to progress after cessation [21], identifying the precise “point of no return” is a critical clinical objective. Finally, investigating therapies studied for geographic atrophy in AMD—including antioxidants [43], photobiomodulation [44], and complement inhibition [45]—may offer potential treatment avenues for PPS maculopathy, though clinical evidence remains limited. Ongoing multidisciplinary research will be essential to advance prevention and management of this emerging condition.

In conclusion, PPS maculopathy is a serious, vision-threatening complication of long-term PPS therapy that warrants heightened clinical attention. Despite accumulating evidence linking PPS to progressive retinal toxicity, screening practices remain inconsistent and suboptimal, especially among high-risk patients. Early detection through multimodal retinal imaging is critical because there is currently no effective treatment beyond drug cessation, and retinal damage may continue to progress even after discontinuation. Establishing standardized, consensus-based screening guidelines, analogous to those for hydroxychloroquine retinopathy [46], is essential to support timely diagnosis and reduce progression to advanced retinal atrophy. To address low screening rates and clinical inertia, the implementation of electronic medical record (EMR) support tools has shown promise. Hom et al. [16] demonstrated that an EMR alert triggered by new PPS prescriptions or renewals significantly improved referral rates to ophthalmology, with nearly 39% of alerted patients screened or referred. Such automated alert systems may facilitate longitudinal monitoring while educating prescribers about the potential for retinal toxicity. Close collaboration between prescribing physicians and ophthalmologists, along with improved patient education, will be key in minimizing the burden of this iatrogenic condition. As PPS continues to be the only oral treatment for IC, a balanced approach focusing on early detection, risk stratification, and interdisciplinary care is necessary to preserve visual outcomes in affected individuals.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

Author Contribution

Conception (S.J.A.); Design (S.J.A.); Data acquisition (H.Y.K.); interpretation (All authors); writing (H.Y.K.); re-

view (All authors); Final approval of the article (All authors)

Availability of Data and Material

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Parsons CL, Benson G, Childs SJ, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. *J Urol* 1993;150:845-8.
2. Paredes Mogica JA, De EJB. Pentosan polysulfate maculopathy: what urologists should know in 2020. *Urology* 2021;147:109-18.
3. Patnaik SS, Laganà AS, Vitale SG, et al. Etiology, pathophysiology and biomarkers of interstitial cystitis/painful bladder syndrome. *Arch Gynecol Obstet* 2017;295:1341-59.
4. ELMIRON® 100 MG (pentosan polysulfate sodium) [Internet]. Johnson & Johnson; 2024 [cited 2025 Jun 6]. Available from: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f0ba651e-3d8a-11df-8fbe-119855d89593&type=display>.
5. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology* 2018;125:1793-802.
6. Jain N, Li AL, Yu Y, VanderBeek BL. Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. *Br J Ophthalmol* 2020;104:1093-7.
7. Wang D, Au A, Gunnemann F, et al. Pentosan-associated maculopathy: prevalence, screening guidelines, and spectrum of findings based on prospective multimodal analysis. *Can J Ophthalmol* 2020;55:116-25.
8. Uner OE, Shah MK, Jain N. Pentosan polysulfate and vision: findings from an international survey of exposed individuals. *Retina* 2021;41:1562-9.
9. Lindeke-Myers A, Hanif AM, Jain N. Pentosan polysulfate maculopathy. *Surv Ophthalmol* 2022;67:83-96.
10. Abou-Jaoude MM, Davis AM, Fraser CE, et al. New insights into pentosan polysulfate maculopathy. *Ophthalmic Surg Lasers Imaging Retina* 2021;52:13-22.
11. De Larochelière E, Bourgault S. Pentosan polysulfate sodium-induced pigmentary maculopathy with nonleaking cystoid macular edema successfully treated with anti-vascular endothelial

- growth factor therapy. *Retin Cases Brief Rep* 2022;16:482-5.
12. Higgins K, Welch RJ, Bacorn C, et al. Identification of patients with pentosan polysulfate sodium-associated maculopathy through screening of the electronic medical record at an academic center. *J Ophthalmol* 2020;2020:8866961.
 13. Huckfeldt RM, Vavvas DG. Progressive maculopathy after discontinuation of pentosan polysulfate sodium. *Ophthalmic Surg Lasers Imaging Retina* 2019;50:656-9.
 14. Vora RA, Patel AP, Yang SS, Melles R. A case of pentosan polysulfate maculopathy originally diagnosed as stargardt disease. *Am J Ophthalmol Case Rep* 2020;17:100604.
 15. Kim J, Kwon HY, Kim JH, Ahn SJ. Nationwide usage of pentosan polysulfate and practice patterns of pentosan polysulfate maculopathy screening in South Korea. *Ophthalmol Retina* 2024;8:246-53.
 16. Hom GL, Kuo BL, Ross JH, et al. Characterization of pentosan polysulfate patients for development of an alert and screening system for ophthalmic monitoring. *Can J Ophthalmol* 2024;59:128-36.
 17. Bae SS, Sodhi M, Maberley D, et al. Risk of maculopathy with pentosan polysulfate sodium use. *Br J Clin Pharmacol* 2022;88:3428-33.
 18. Kim MS, Choi YJ, Ji E, et al. Association between pentosan polysulfate and subsequent maculopathy: insights from a nationwide population-based study in Korea. *Ophthalmology* 2025;132:108-14.
 19. Hanif AM, Armenti ST, Taylor SC, et al. Phenotypic spectrum of pentosan polysulfate sodium-associated maculopathy: a multicenter study. *JAMA Ophthalmol* 2019;137:1275-82.
 20. 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;227:125-38.
 21. Hu DJ, Wang E, Ghauri S, et al. Evaluating for pentosan polysulfate maculopathy at a single academic institution. *Ther Adv Ophthalmol* 2025;17:25158414251364944.
 22. Kwon HY, Kim J, Ahn SJ. Screening practices and risk assessment for maculopathy in pentosan polysulfate users across different exposure levels. *Sci Rep* 2024;14:11270.
 23. Tao BK, Sawires K, Lim K, et al. Risk and dose-response relationship for pentosan polysulfate sodium maculopathy: a systematic review and meta-analysis. *Ophthalmol Retina* 2025;9:870-82.
 24. Kalaw FGP, Ignacio JCI, Wu CY, et al. Pentosan polysulfate sodium (ELMIRON) maculopathy: a genetic perspective. *Retina* 2023;43:1174-81.
 25. Abou-Jaoude M, Fraser C, Maldonado RS. Update on maculopathy secondary to pentosan polysulfate toxicity. *Curr Opin Ophthalmol* 2021;32:233-9.
 26. Lyons RJ, Brower J, Jain N. Visual function in pentosan polysulfate sodium maculopathy. *Invest Ophthalmol Vis Sci* 2020;61:33.
 27. 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.
 28. Hall BP, Shiromani S, Jung EH, et al. Pentosan polysulfate maculopathy: final outcomes from a 4-year prospective study of disease progression after drug cessation. *Am J Ophthalmol* 2025;271:371-80.
 29. Jung EH, Lindeke-Myers A, Jain N. Two-year outcomes after variable duration of drug cessation in patients with maculopathy associated with pentosan polysulfate use. *JAMA Ophthalmol* 2023;141:260-6.
 30. Szelog JT, Shah NS, Camejo MD. Cystoid macular edema arising 10 years after cessation of pentosan polysulfate sodium successfully treated with bevacizumab. *J Vitreoretin Dis* 2022;7:83-6.
 31. Santina A, Fogel-Levin M, Abraham N, Sarraf D. Nine-year progression of pentosan maculopathy with multimodal retinal imaging. *Retin Cases Brief Rep* 2023;17:664-7.
 32. Somisetty S, Santina A, Au A, et al. Progression of pentosan polysulfate sodium maculopathy in a prospective cohort. *Am J Ophthalmol* 2023;255:57-67.
 33. Somisetty S, Santina A, Abraham N, et al. Rapid pentosan polysulfate sodium maculopathy progression. *Retin Cases Brief Rep* 2023;17:660-3.
 34. Christiansen JS, Barnes AC, Berry DE, Jain N. Pentosan polysulfate maculopathy versus age-related macular degeneration: comparative assessment with multimodal imaging. *Can J Ophthalmol* 2022;57:16-22.
 35. Girardot PE, Zhang X, Zhang N, et al. Pentosan polysulfate sodium causes diminished function and subtle morphological changes in retina and RPE of mice. *Invest Ophthalmol Vis Sci* 2024;65:28.
 36. Tae KS, Kim JW, Kim CG, et al. Long-term visual outcomes in patients with neovascular AMD who exhibited visual acuity of 0.1 or worse at 5th injection. *J Retin* 2018;3:64-70.
 37. Santina A, Feo A, Bousquet E, et al. Pentosan polysulfate sodium maculopathy: final analysis of a prospective cohort, updated review, and association with inflammatory bowel disease. *Surv Ophthalmol* 2025;70:583-92.
 38. Barnes AC, Hanif AM, Jain N. Pentosan polysulfate maculopathy versus inherited macular dystrophies: comparative assessment with multimodal imaging. *Ophthalmol Retina* 2020;4:1196-201.
 39. Nah SK, Kim JH, Lew YJ, et al. Characteristics and clinical course of Korean patients diagnosed with stargardt disease. *J Retin* 2021;6:14-20.

40. Ovens CA, Ahmad K, Fraser CL. Fundus autofluorescence in maternally inherited diabetes and deafness: the gold standard for monitoring maculopathy? *Neuroophthalmology* 2019;44:168-73.
41. Hanif AM, Yan J, Jain N. Pattern dystrophy: an imprecise diagnosis in the age of precision medicine. *Int Ophthalmol Clin* 2019;59:173-94.
42. Flester E, Yassin SH, Borooah S. Advanced pentosan polysulfate sodium maculopathy with low cumulative exposure and hydroxychloroquine use. *Am J Ophthalmol Case Rep* 2024;36:102224.
43. Keenan TDL, Agrón E, Keane PA, et al. Oral antioxidant and lutein/zeaxanthin supplements slow geographic atrophy progression to the fovea in age-related macular degeneration. *Ophthalmology* 2025;132:14-29.
44. Boyer D, Hu A, Warrow D, et al. LIGHTSITE III: 13-month efficacy and safety evaluation of multiwavelength photobiomodulation in nonexudative (dry) age-related macular degeneration using the lumithera valeda light delivery system. *Retina* 2024;44:487-97.
45. Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy due to age-related macular degeneration: a plain language summary of OAKS and DERBY clinical studies. *Immunotherapy* 2025;17:609-23.
46. Ahn SJ. Classification of hydroxychloroquine retinopathy: a literature review and proposal for revision. *Diagnostics (Basel)* 2024;14:1803.