

## Introduction

Retinoblastoma is a rare intraocular malignancy that is most common in children, occurring in 1 in 15,000-20,000 live births, in which early detection is significant for preserving the eye. Children with hereditary risk often undergo ophthalmologic screenings beginning shortly after birth; however, the optimized frequency of surveillance remains uncertain. More frequent surveillance does lead to improved outcomes for early tumor detection, but also means an increase in healthcare costs, # of anesthesia exposures, disease severity, and travel and time burdens for families. Therefore, determining whether more frequent screenings are associated with improving outcomes is significant for balancing clinical benefit against patient and family burden. Additionally, previous studies claim that structured surveillance screenings are associated with earlier treatments and improved outcomes, but direct evidence comparing surveillance intensity and enucleation is limited. This scoping review will evaluate whether more frequent and intensive ophthalmologic surveillance compared to standard or less frequent screening is associated with lower rates of enucleation and improved eye-preservation outcomes in children with hereditary retinoblastoma.

## Objectives

The goal is to assess the current ophthalmologic screening schedules for children who have hereditary retinoblastoma, explain the relationship between ophthalmologic screening frequency and treatment success for children who have hereditary retinoblastoma, and identify limitations in the current evidence and areas requiring further investigation. The primary question is whether more frequent ophthalmologic surveillance associated with lower enucleation. More frequent ophthalmologic surveillance will be associated with lower enucleation rates and improved eye-preservation outcomes in children with hereditary retinoblastoma.

## Methods

A scoping review was conducted using PubMed and Google Scholar to identify primary studies examining ophthalmologic surveillance in hereditary retinoblastoma. Studies were appropriate if they included patients with hereditary risk, described surveillance or screening, and reported  $\geq 1$  relevant clinical outcome. Reviews, guidelines, laboratory studies, and studies without relevant surveillance outcomes were excluded. Search terms included: "hereditary retinoblastoma," "familial retinoblastoma," "screening," "surveillance," "screening frequency," and "enucleation." Extracted outcomes included: enucleation, age at diagnosis, tumor stage, ocular survival, and surveillance. Studies were assessed for selection bias, confounding, outcome-measurement bias, missing data, and reporting bias. Potential Confounders included: family awareness, Healthcare access, surveillance adherence, disease severity, and treatment era.

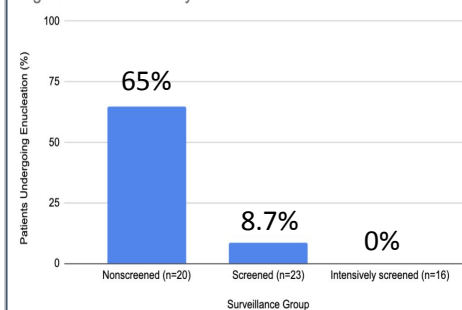
## Results

Across the six primary studies, structured surveillance was consistently associated with earlier detection and/or improved ocular outcomes, although direct evidence comparing surveillance frequency with enucleation was limited.

**Table 1. Characteristics and Key Findings of Included Studies**

| Study                     | Surveillance Comparison                                                                           | Main Results                                                                                                                                                                                                                                                            |
|---------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rothschild et al. (2011)  | 20 nonscreened; 23 screened but not intensively; 16 intensively screened                          | Enucleation: 13/20 (65%) nonscreened, 2/23 (8.7%) screened, 0/16 intensively screened; $P < .0001$ .                                                                                                                                                                    |
| Moll et al. (2000)        | 50 screened from birth vs. 25 not screened from birth                                             | Mean age at diagnosis: 4.9 months screened vs. 17.2 months nonscreened; $P < .0001$ .                                                                                                                                                                                   |
| Abramson et al. (2003)    | Familial patients clinically screened from birth vs. familial patients not screened               | Screened familial patients were diagnosed at a younger age; 26/45 (58%) had early Reese-Elsworth Group I disease and had better ocular survival.                                                                                                                        |
| Al-Nawaiseh et al. (2017) | First recognized affected family member vs. later family members with greater awareness/screening | Mean age: 17 months probands vs. 8 months nonprobands. Eye salvage: approximately 45% vs. 80%. All probands had $\geq 1$ enucleation; screening identified 38% of nonprobands.                                                                                          |
| Badalova et al. (2025)    | Complete standardized screening from birth vs. incomplete screening                               | Completely screened: median diagnosis age 18 days (range 3–352); 100% diagnosed before age 1, 57.1% at the first examination, and 82.1% within 6 months. Incompletely screened: median diagnosis age 420 days (range 59 days–4.8 years); $>50\%$ diagnosed after age 1. |
| Walker et al. (2025)      | Screened according to protocol vs. significant delay from protocol                                | In protocol-screened patients, latest new tumor occurred at 28 months; 39/40 had their first RB diagnosis by 6 months. Across all patients, the latest new tumor occurred at 47 months. Mean age of tumor recurrence was 15 months.                                     |

**Figure 1. Enucleation by Surveillance Classification**



**Figure 1. Enucleation among hereditary retinoblastoma patients according to surveillance classification in Rothschild et al.<sup>1</sup>** Rothschild's groups had enucleation occurring in 13/20 non screened, 2/23 screened, and 0/1616 intensively screened patients ( $P < 0.001$ ).

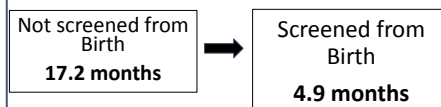
| Study             | Screening Method                                                                                                                   |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Rothschild et al  | Fundus examination/indirect ophthalmoscopy; anesthesia when needed for thorough examination; genetic risk informed surveillance    |
| Moll et al        | Fundus screening beginning at birth                                                                                                |
| Abramson et al    | Routine dilated funduscopic examination by an ophthalmologist                                                                      |
| Al-Nawaiseh et al | Hereditary-risk screening; detailed standardized examination technique not clearly shown                                           |
| Badalova et al    | Specialist ophthalmologic examination; peripheral retinal examination with scleral indentation during EUA; genetic risk assessment |
| Walker et al      | Dilated fundus examination $\pm$ examination under anesthesia; genetic risk assessment                                             |

### Key Findings:

Enucleation decreased from 65% without screening to 8.7% with screening and 0% with intensive screening in the strongest direct study. Surveillance was associated with earlier/younger diagnosis, improved ocular survival, and greater eye preservation across several studies. Direct evidence comparing screening frequency remains limited, and the optimal surveillance interval remains uncertain. Fundus/retinal examination was the common clinical surveillance approach, but specific examination techniques and incorporation of EUA and genetic risk assessment varied across studies.

**Figure 2. Earlier Diagnosis With Structured Surveillance**  
Moll et al., 2000

Mean Age at Diagnosis



Badalova et al., 2025

Median Age at Diagnosis



**Figure 2: Age at diagnosis according to surveillance status in two familial retinoblastoma cohorts**

## Discussion

Overall, the evidence supports a consistent relationship between surveillance, improved eye outcomes, and earlier retinoblastoma detection. Rothschild et al. have provided the most important evidence for the primary question, demonstrating progressively lower enucleation rates across non screened, screened groups, and intensively screened groups. Other studies strengthen an aspect in which surveillance allows detection at a younger age, increasing opportunities to preserve eyes.

However, the evidence remains limited and does not establish an optimal screening frequency. Most studies were retrospective, and only one included study directly compared the intensity of enucleation. Differences in healthcare access, genetic risk (hereditary or nonhereditary), and treatment era could have confounded observed associations.

Therefore, current and recent studies strengthen support for structured familial surveillance but focus more on when surveillance can safely be reduced, rather than whether increasingly frequent screenings reduce enucleation itself. This is an important evidence gap.

## Conclusion

The results of this study showed more frequent ophthalmologic surveillance may be associated with lower enucleation rates and improved outcomes of preserving the eye in hereditary retinoblastoma; however, current evidence is not sufficient to establish an optimal examination frequency.

The strongest study reported enucleation in 65% of non screened, 8.7% of screened, and 0% of intensively screened patients. Other supporting studies consistently associated surveillance with younger age at diagnosis, earlier disease, and other improved outcomes.

These findings may help inform future hereditary retinoblastoma surveillance protocols by identifying screening schedules that prioritize early tumor detection and eye preservation while minimizing anesthesia exposure, healthcare costs, and family burden. Future studies using standardized screening methods and surveillance definitions are needed to determine the optimal screening interval.

## References

