AMERICAN ACADEMY OF OPHTHALMOLOGY®

Screening Children at Risk for Retinoblastoma

Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists

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Purpose: To provide a set of surveillance guidelines for children at risk for development of retinoblastoma.
Design: Consensus panel.
Participants: Expert panel of ophthalmic oncologists, pathologists, and geneticists.
Methods: A group of members of the American Association of Ophthalmic Oncologists and Pathologists (AAOOP) with support of the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics (AAP) was convened. The panel included representative ophthalmic oncologists, pathologists, and geneticists from retinoblastoma referral centers located in various geographic regions who met and discussed screening approaches for retinoblastoma. A patient "at risk" was defined as a person with a family history of retinoblastoma in a parent, sibling, or first- or second-degree relative.
Main Outcome Measures: Screening recommendations for children at risk for retinoblastoma.
Results: Consensus statement from the panel: (1) Dedicated ophthalmic screening is recommended for all children at risk for retinoblastoma above the population risk. (2) Frequency of examinations is adjusted on the basis of expected risk for *RB1* mutation. (3) Genetic counseling and testing clarify the risk for retinoblastoma in children with a family history of the disease. (4) Examination schedules are stratified on the basis of high-, intermediate-, and low-risk children. (5) Children at high risk for retinoblastoma require more frequent screening, which may preferentially be examinations under anesthesia.
Conclusions: Risk stratification including genetic testing and counseling serves as the basis for screening of children at elevated risk for development of retinoblastoma. *Ophthalmology 2017;■:1–6 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Retinoblastoma is a heritable life- and vision-threatening childhood cancer. It is the most common intraocular malignancy in children, affecting 1 in 15 000 to 1 in 18 000 live births.[1–4] Children with a family history of retinoblastoma are at elevated risk for retinoblastoma and require surveillance for the development of retinal tumors.[5–9] Early diagnosis, when tumors are small, maximizes survival and vision outcomes and reduces the need for chemotherapy, enucleation, and radiotherapy.[10,11] Because retinoblastoma tumors may develop over time during early childhood, serial evaluations are beneficial in finding tumors early and preserving vision.

An estimate of the risk of developing retinoblastoma can be determined initially by the relationship of the infant to the family member who carries a retinoblastoma diagnosis (the proband) (Fig 1 and Table 1). Before completion of genetic testing or if genetic testing is not possible, this risk estimate can define the intensity of examination. However, an individual child's risk can be more accurately defined by genetic analysis of the family. This generally starts with performing comprehensive *RB1* genetic testing of a family member with retinoblastoma (the proband) to identify heritability; if hereditary, the causative mutation is specifically searched for in at-risk relatives (Fig 2). "*RB1* mutation" here implies a pathogenic or likely pathogenic variant in *RB1* from a clinical test report. "Pathologic variant" is the preferred terminology per the recent standards and guidelines from the joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology; however, for clarity, in this article we use both terms.[11]

Genetic testing allows clinicians to identify children at high risk for retinoblastoma, who need to be followed most closely for disease. Of note, the majority of at-risk relatives who do not carry the *RB1* mutation do not require specific retinoblastoma screening.[12] Genetic testing of the affected child or adult family member is also important to clarify

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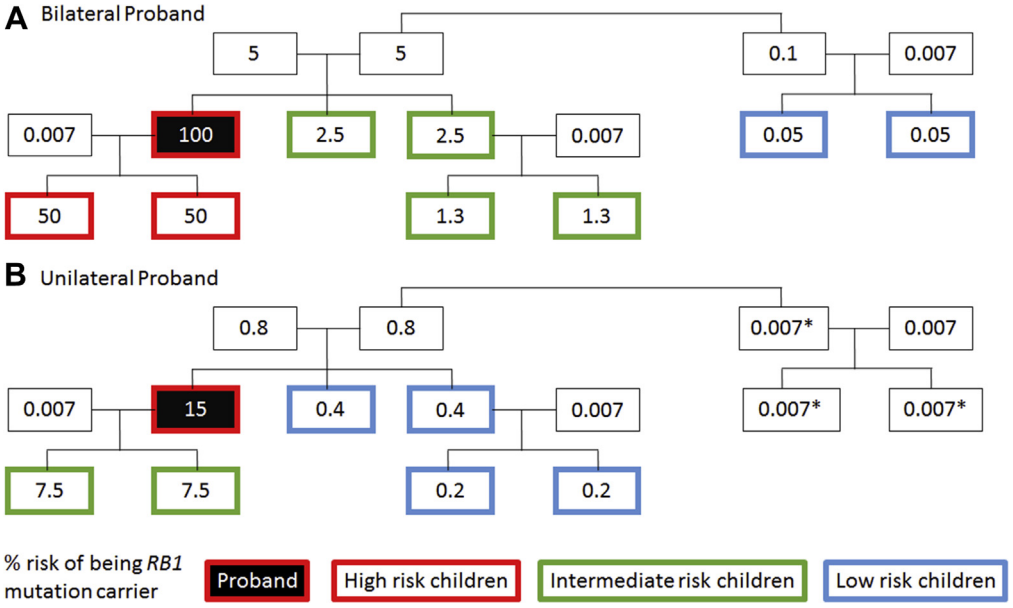

Figure 1. Pretest risk for *RB1* mutation in family members of affected child with retinoblastoma (adapted from Valenzuela et al. A Language for Retinoblastoma: Guidelines and Standard Operating Procedures. In: *Pediatric Retina*. Reynolds JD, Olitsky SE, eds. 2011:218). Data presented reflect the *RB1* mutation detection rates based on a large data set from one of the authors (B.L.G.) of molecular genetic results for retinoblastoma patients and their family members (Racher and Gallie, unpublished data, 2017). **A**, All probands with bilateral disease have a constitutional mutant *RB1* allele. However, the *RB1* mutation is frequently de novo in the child with retinoblastoma. Thus, the majority of children with bilateral retinoblastoma are the first person in the family with disease. Before testing the patient, the risk for relatives to develop retinoblastoma can be estimated on the basis of data from a large number of families. The percentage of risk for relatives to carry the mutant allele of the proband is shown. **B**, Probands with unilateral disease and no family history of retinoblastoma have a 15% risk for carrying a mutant *RB1* allele. The percentage of risk for relatives to carry that allele is shown. *Third- and fourth-degree relatives of unilateral probands have calculated risks of 0.003% and 0.001%, which are less than the normal population risk of 0.007% (1:15 000 live births); therefore, the risk is stated at 0.007%.

the risk for additional retinoblastoma tumors and second primary malignancies for which individuals with *RB1* germline mutations are at elevated risk throughout life.[13] Amniocentesis or other forms of prenatal or preimplantation testing are available for couples in whom there is a known *RB1* mutation in the family (e.g., an adult long-term survivor of retinoblastoma). This information is normally conveyed to at-risk couples by a genetic counselor.

Table 1. Pretest Risk for Relatives to Carry the Mutant *RB1* Allele of the Proband

	Pretest Risk for Mutant Allele (%)	
Relative of Proband	*Bilateral Proband (100)*	*Unilateral Proband (15)*
Offspring (infant)	50	7.5
Parent	5	0.8
Sibling	2.5	0.4
Niece/nephew	1.3	0.2
Aunt/uncle	0.1	0.007*
First cousin	0.05	0.007*
General population	0.007	

Pretest risk for *RB1* mutation in family members of an affected child with retinoblastoma. Risk for *RB1* mutant allele is shown as a percentage for unilateral and bilateral probands without family history of retinoblastoma. *Third- and fourth-degree relatives of unilateral probands have calculated risks of 0.003% and 0.001%, respectively, which are less than the normal population risk of 0.007% (1 in 15 000 live births); therefore, the risk is stated at 0.007%.

The purpose of this consensus statement is to provide general guidelines for retinoblastoma ophthalmologic screening in affected families in the United States, with the primary goal of early detection of retinoblastoma in children at risk. It has been previously highlighted that even in highly developed nations, there is a gap in knowledge among ophthalmologists and other health care professionals regarding risk for familial retinoblastoma.[6] Education regarding this risk is critical to ensure children with a family history of retinoblastoma receive timely and appropriate genetic counseling, testing, and screening examinations.

Methods

Ophthalmic Screening Guidelines

The consensus group was initially chosen from members of the American Association of Ophthalmic Oncologists and Pathologists (AAOOP), with an effort to include representative experts from ophthalmology, pathology, and genetics from retinoblastoma referral centers located in various geographic locations and with a variety of screening approaches for retinoblastoma. The clinicians represent large retinoblastoma treatment centers in the United States (J.W.K., D.S.G., P.C.-B., B.P.M., S.E.P., and C.L.S.) and Canada (B.L.G.) and a smaller regional retinoblastoma center