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 2018;125:453-458 © 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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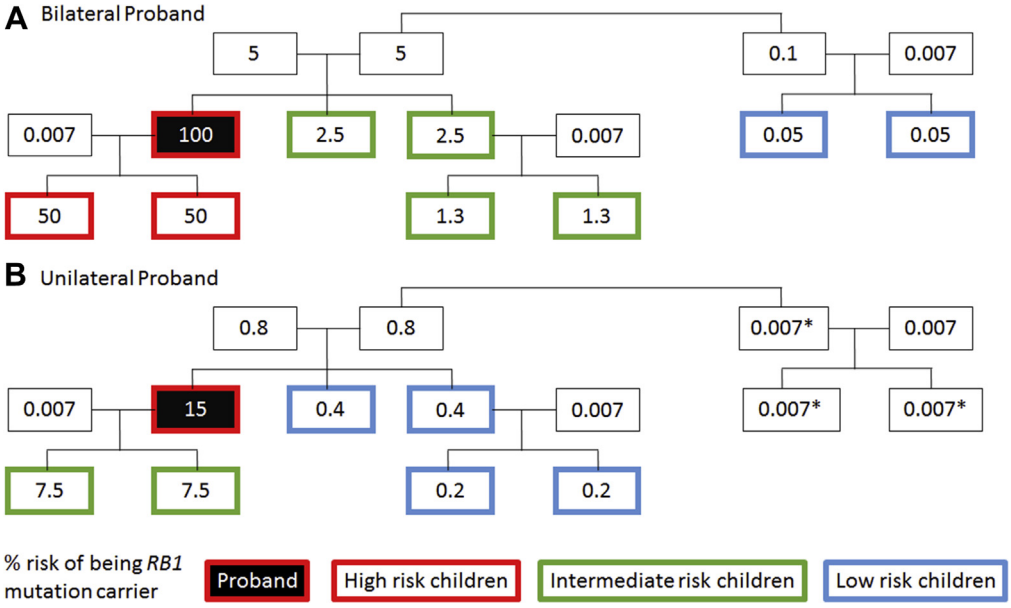

Figure 1. Pretest risk for *RB1* mutation in family members of affected child with retinoblastoma (adapted from Valenzuela et al. A Language for Retinoblastoma: Guidelines and Standard Operating Procedures. In: *Pediatric Retina*. Reynolds JD, Olitsky SE, eds. 2011:218). Data presented reflect the *RB1* 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

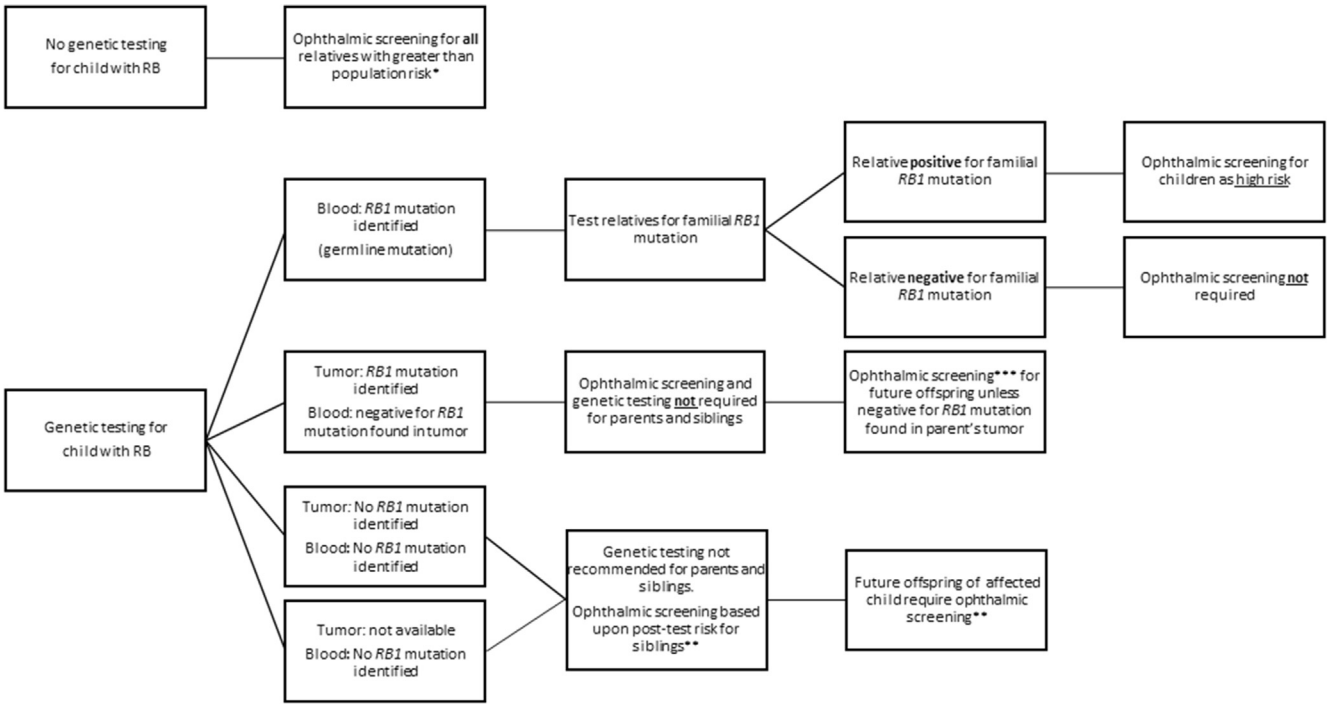

Figure 2. Genetic testing for *RB1* mutations provides clarification of risk for retinoblastoma (RB) in family members. Molecular testing identifies relatives who carry the mutant *RB1* allele and are at risk for the disease. Testing can also decrease the risk for relatives to the population risk, eliminating the need for dedicated ophthalmic screening for retinoblastoma in some children, or modify the risk, allowing children to undergo less extensive screening. Genetic testing and counseling for RB is a complex issue and is best performed in coordination with genetics professionals (genetic counselors or medical geneticists) experienced in retinoblastoma. For example, although parents of a child with bilateral RB may test negative for an *RB1* mutation, they still have a 5% risk with each subsequent child because of the possibility of germline mosaicism in a parent. Tumor tissue, when available, and peripheral blood lymphocytes are tested to identify mutations in *RB1*. Tumor tissue may not be available for testing if the child has not undergone enucleation or if frozen tumor is not available from the surgery, particularly for adult long-term survivors of RB seeking genetics evaluation. *Based on pretest risk, as described in Figure 1 and Table 1. **Calculated risk in this clinical scenario will depend on the sensitivity of the genetic testing, which varies with laboratory. The relative's post-test risk will likely be lower than pretest risk and will result in less intense screening (Fig 3) compared with pretest risk. Geneticists experienced in RB can provide guidance in this situation. ***The risk to future offspring in this clinical scenario results from the risk that the proband is mosaic for the *RB1* mutation and therefore has a risk of transmitting to offspring despite the negative blood test. Genetic testing of offspring for the *RB1* mutation identified in the tumor can eliminate this risk. Before testing, these children will be followed by intermediate risk (Fig 3); however, a genetics professional can provide clarification of risk for a child according to the sensitivity of the gene testing for the parent, which varies by laboratory. When no *RB1* mutation has been identified in the blood sample of the proband, genetic testing is not recommended for family members because there is no identified mutation to test for. Screening of relatives relies on the refined post-test risk estimate based on the negative results (and the sensitivity of the test of the laboratory used).

(A.H.S.). The group convened at the AAOOP meeting in November 2015 with the support of the AAOOP and American Association for Pediatric Ophthalmology and Strabismus. Before the discussion, an initial survey of ophthalmologic screening strategies, including questions about screening frequency and type of screening examination practices, revealed that screening methods were highly variable among centers. However, several key points of consensus were identified, and after further discussion, a basic screening schedule was agreed on (Fig 3). By using the evidence-based ABCD system devised by Shekelle et al,[14] we graded all recommendations from A to D.

Results

A patient "at risk" was defined as a person with family history of retinoblastoma in a parent, sibling, or first- or second-degree relative.

The key recommendations and grades of the consensus panel included the following:

1. All children at elevated risk for retinoblastoma above the population risk require serial dilated fundus examination by an ophthalmologist with experience in retinoblastoma. Depending on the clinical setting and resources, this may be an ocular oncologist, pediatric ophthalmologist, retina specialist, or comprehensive ophthalmologist (grade D).
2. Early and frequent clinical screening is required for babies at elevated risk, and the examinations may be spaced out over time as children grow older (grade C).
3. We recommend screening for at-risk children from birth up to the age of 7 years. After age 7 years, no further screening of asymptomatic children is recommended, unless they are known to carry an *RB1* mutation. We suggest that individuals who are known *RB1* mutation carriers be followed indefinitely with examinations every 1 to 2 years after the age of 7 years. A single dilated fundus examination to evaluate for asymptomatic spontaneously regressed retinoblastoma or retinoma is recommended for all first-degree relatives of a retinoblastoma proband, including older siblings if the *RB1* genetic status of the relatives is unknown (grade C).

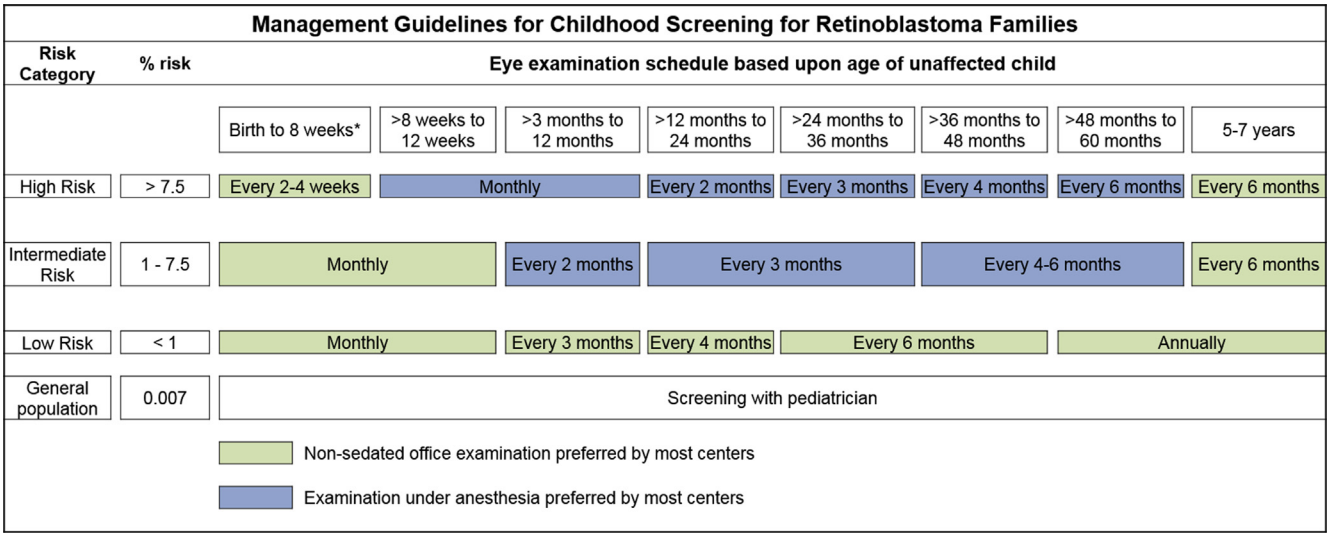

Figure 3. Management guidelines for childhood screening for retinoblastoma. The presented schedules are general guidelines and reflect a schedule for examinations in which no lesions of concern are noted. It may be appropriate to examine some children more frequently. Decisions regarding examination method, examination under anesthesia (EUA) versus nonsedated examination in the office, are complex and best decided by the clinician in discussion with the patient's family. The preference of the majority of the clinical centers involved in the creation of this consensus statement is reflected, but individual centers may make policy decisions based on available resources and expert clinician preference. Examination under anesthesia will be strongly considered for any child who is unable to participate in an office examination sufficiently to allow thorough examination of the retina. *A minority of clinical centers also prefer EUA for high- and intermediate-risk children (calculated risk >1%) from birth to 8 weeks of age.

4. Genetic counseling and testing clarify the risk for retinoblastoma in children with a family history of the disease and improve outcomes at reduced cost, justifying making testing available to all patients with a personal or family history of retinoblastoma. Genetic evaluation should be initiated whether the affected relative demonstrated unilateral or bilateral disease because both have a substantial risk of being heritable (grade C).
5. Stratifying children on the basis of their expected risk for retinoblastoma depending on their relationship to the affected family member and refining that risk by genetic testing as soon as possible in order to optimize care. Children at high risk for retinoblastoma require more frequent screening, which may include examinations under anesthesia (grade C).
6. It is recommended that genetic testing be performed at a Clinical Laboratory Improvement Amendments–certified laboratory (or similar certification in other countries) with experience in retinoblastoma genetic testing. Sensitivity of genetic testing may vary by laboratory, and post-test risk calculation by a genetics professional, taking into account the estimated laboratory sensitivity, will clarify the clinical risk category (high, intermediate, low, or population risk) for an individual child (grade B).
7. Decisions regarding examination method (examinations under anesthesia vs. nonsedated examination in the office) are complex and decided by the clinician in discussion with the child's family. The preference of the majority of the clinical centers contributing to this consensus statement is reflected in Figure 3. Individual centers make policy decisions on the basis of available resources and expert clinician preference. Examinations under anesthesia are strongly considered for any child who is unable to participate in an office examination sufficiently to allow thorough examination of the retina (grade D).
8. Examiners should be aware that young babies often present with tumors in the posterior pole, but the older the child is at the time retinoblastoma develops, the more likely the tumor location will be peripheral (grade B).
9. The schedules presented in Figure 3 are general guidelines and reflect a schedule for examinations of an at-risk child when no lesions of concern have been noted. It may be appropriate to examine some children more frequently (grade D).

Discussion

Early detection of retinoblastoma is critical to achieving the best outcomes for vision and survival. Here, a consensus panel comprising experts in clinical retinoblastoma care, ophthalmic pathology, and genetics recommend that risk stratification with genetic counseling and testing serve as the basis for screening and present a risk-stratified schedule for ophthalmic screening examinations. Systematic screening of children at elevated risk because of family history of retinoblastoma has dual purposes: (1) to provide a method for detecting disease at the earliest possible stage and (2) to focus care on the children at highest risk, while decreasing unnecessary evaluations for children at low or no risk above that of the general population. Genetic testing is important in risk-stratifying patients with a family history of retinoblastoma. Results may indicate a very high risk for disease, approaching 100% if an *RB1* mutation is found, or alternatively, if negative, the child may be at population risk and no longer require dedicated ophthalmic screening. Because interpretation of *RB1* genetic testing is complex, it is optimal to have a genetics professional involved in counseling families and interpreting test results.[15] Although it is beyond the scope of these guidelines, it is important to note that preimplantation and prenatal *RB1* genetic testing via amniocentesis and preimplantation genetic diagnosis are available and may be

desirable for families in whom the familial *RB1* mutation is known. A discussion with a genetics professional during family planning can assist in determining an affected family's desired approach to early testing.

The guidelines presented aim to create a structured approach to care in which expected risk based on familial relationship to the affected family member initially determines screening frequency for children, and genetic testing clarifies this risk. This approach allows clinicians to provide an immediate individualized care plan based on the expected risk for *RB1* mutation for each child. The risk and thus the recommendations can then be further refined after genetic testing is completed. The guidelines provided in this article represent optimum goals for screening at-risk children. We acknowledge that limited access to pediatric anesthesia and genetic testing in many developing countries may limit or prevent adherence to these recommendations. The goal of these screening guidelines is to educate primary care providers and ophthalmologists and to optimize care by creating a more uniform approach to care for children with family history of retinoblastoma, ensuring that children receive timely and appropriate genetic counseling, testing, and screening for familial retinoblastoma.

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Abbreviations and Acronyms:
AAOOP = American Association of Ophthalmic Oncologists and Pathologists.

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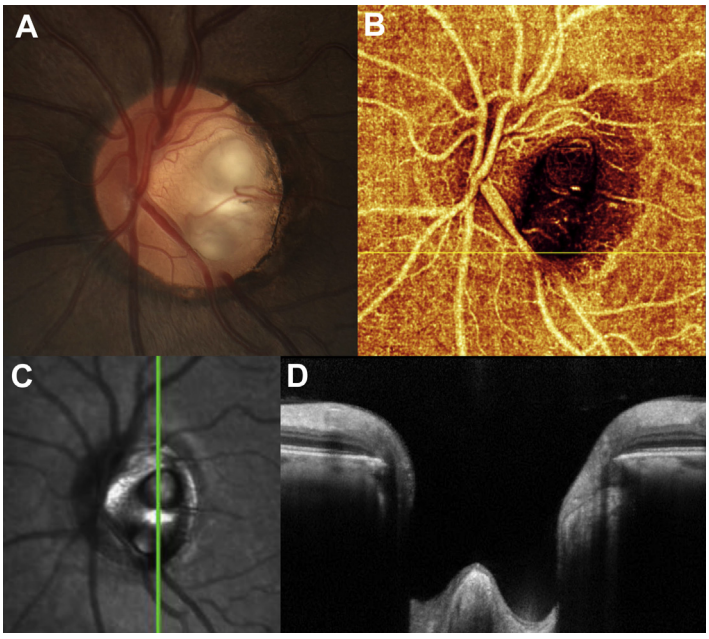
Pictures & Perspectives



Unilateral Double Optic Nerve Head Pits

Color fundus photograph of 2 temporal pits within the left optic nerve head of a healthy 29-year-old woman with 20/20 Snellen equivalent visual acuity and normal visual fields (Fig 1**A**). En face OCT angiography (AngioVue; Optovue) of the optic nerve demonstrating vascular flow within the pits (Fig 1**B**). Infrared photo (Fig 1**C**) of the optic nerve clearly defines the pits. The *green line* denotes the orientation of the scan shown in Figure 1**D**. High-resolution OCT line scan (Spectralis; Heidelberg Engineering, Germany) through both pits (Fig 1**D**). (Magnified version of Fig 1**A-D** is available online at www.aaojournal.org.)

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