Early detection of Retinoblastoma in children

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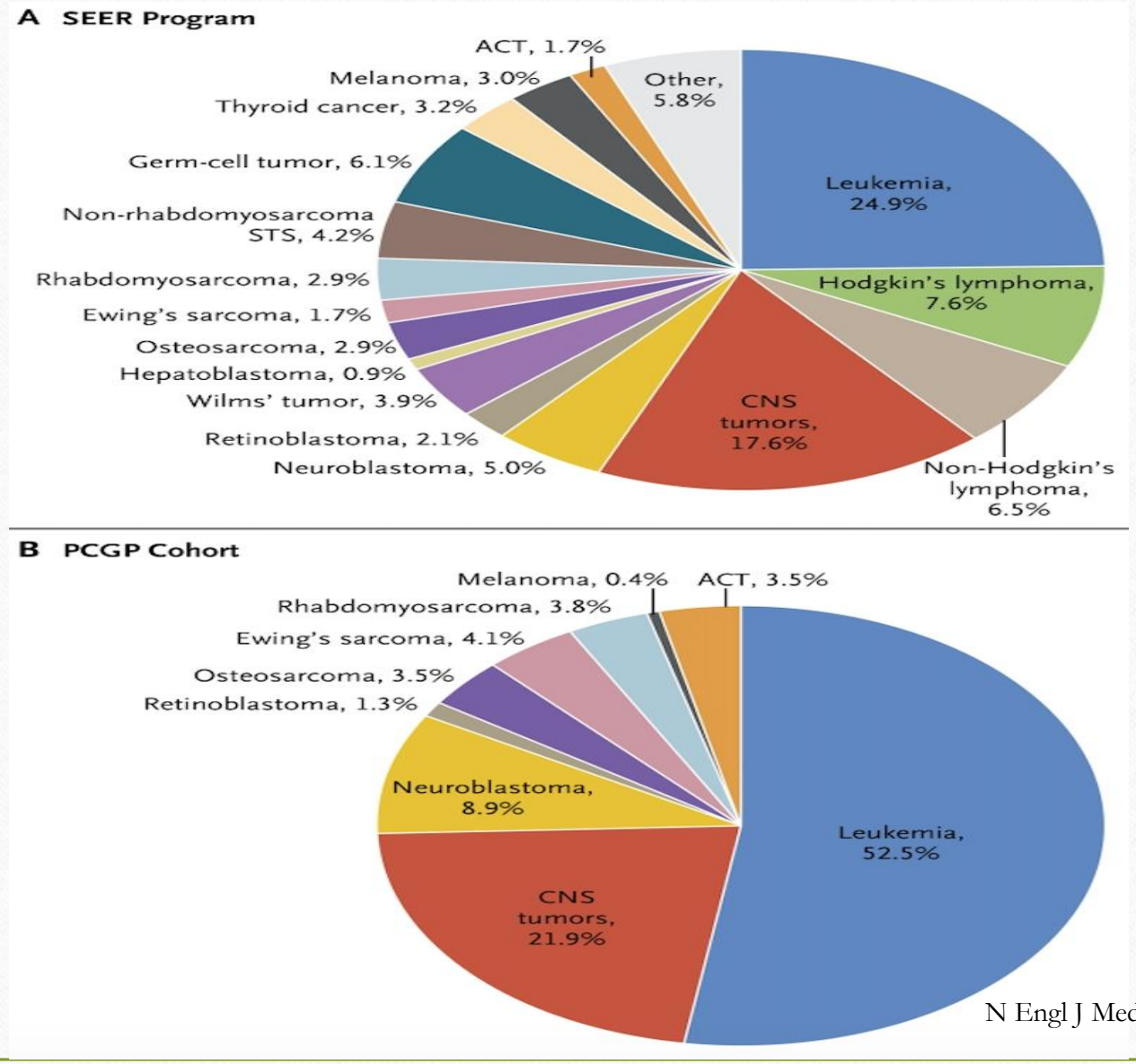
Introduction

- **The most common primary intraocular malignancy** of childhood
- 10 to 15 % of cancers that occur within **the first year of life**
- Typical as **Leukocoria** in a child < 2 years
- Untreated retinoblastoma is a **deadly disease**
- **Metastatic spread** is typically diagnosed within the first 12 months
- Survival in the contemporary era is **>95 %**
- The prognosis for eye salvage is far lower and **depends on the stage** of disease at diagnosis



N Engl J Med. 2015 Dec 10; 373(24): 2336–2346.

EARLY DETECTION

Leukocoria

Window of the world

Prompt referral to an ocular oncologist and appropriate management by a **multidisciplinary team** are necessary to optimize visual outcome and survival

The multidisciplinary team

- Primary care practitioner
- Pediatric ophthalmologist
- Pediatric oncologist
- Radiation oncologist
- Clinical geneticist
- Retina specialist
- Ocular oncologist
- Neuroradiologist
- Craniofacial plastic specialist
- Nurse specialist
- Pharmacist
- Child life specialist
- Clinical social worker
- Low-vision specialist
- Nutritionist

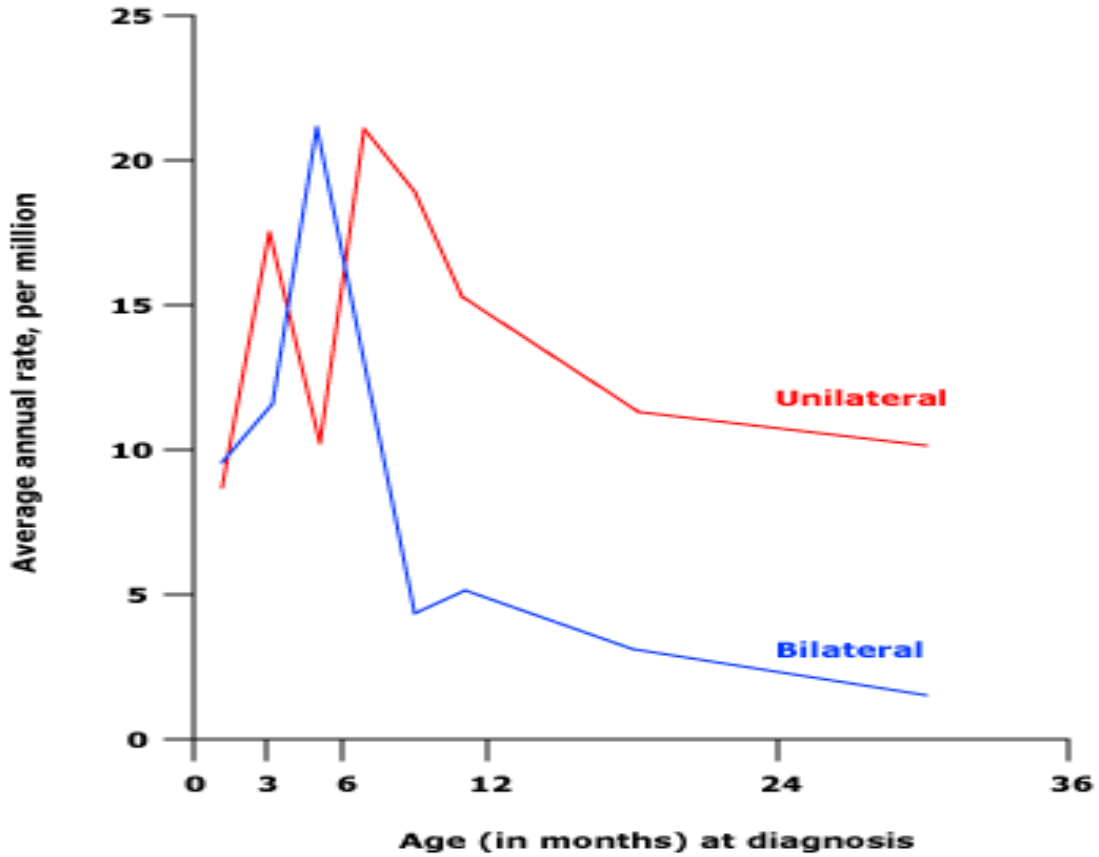
TERMINOLOGY

- **Heritable retinoblastoma** – Heritable (hereditary, familial, or germline) retinoblastoma is associated with **germline mutations** (ie, mutations that occur in reproductive cells [sperm and eggs]) in the retinoblastoma (RB1) gene
- **Nonheritable retinoblastoma** – Nonheritable (nonhereditary, nonfamilial, sporadic, or somatic) retinoblastoma results from **somatic mutations** (ie, mutations that occur in nonreproductive cells) in the *RB1* gene

Incidence

- 1 in 15,000 to 1 in 16,600 live births
- 13 % of cancer in **the first year of life**
- The median age at diagnosis is 18 to 20 months;
- An average of:
  - 12 months for children with bilateral disease
  - 24 months for children with unilateral disease
- 95 % < 5 years.
- Boys and girls are the same

Unilateral and bilateral retinoblastoma age-specific incidence rates, age <3, all races both sexes, SEER, 1976-84 and 1986-94



Data from Young JL, Smith MA, Roffers SD, et al. Retinoblastoma. In: Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program, 1975-1995, Ries LA, Smith MA, Gurney JG, et al (Eds), National Cancer Institute, Bethesda, MD, 1999. p. 73.

Genetic predisposition

- Retinoblastoma occurs in heritable and nonheritable forms
- **Germline mutations** in the retinoblastoma (RB1) gene ± 40 % of cases, predominantly in **bilateral** disease
- **Nonheritable** retinoblastoma incur new **somatic mutations**
- <10 % of retinoblastoma patients have a positive family history

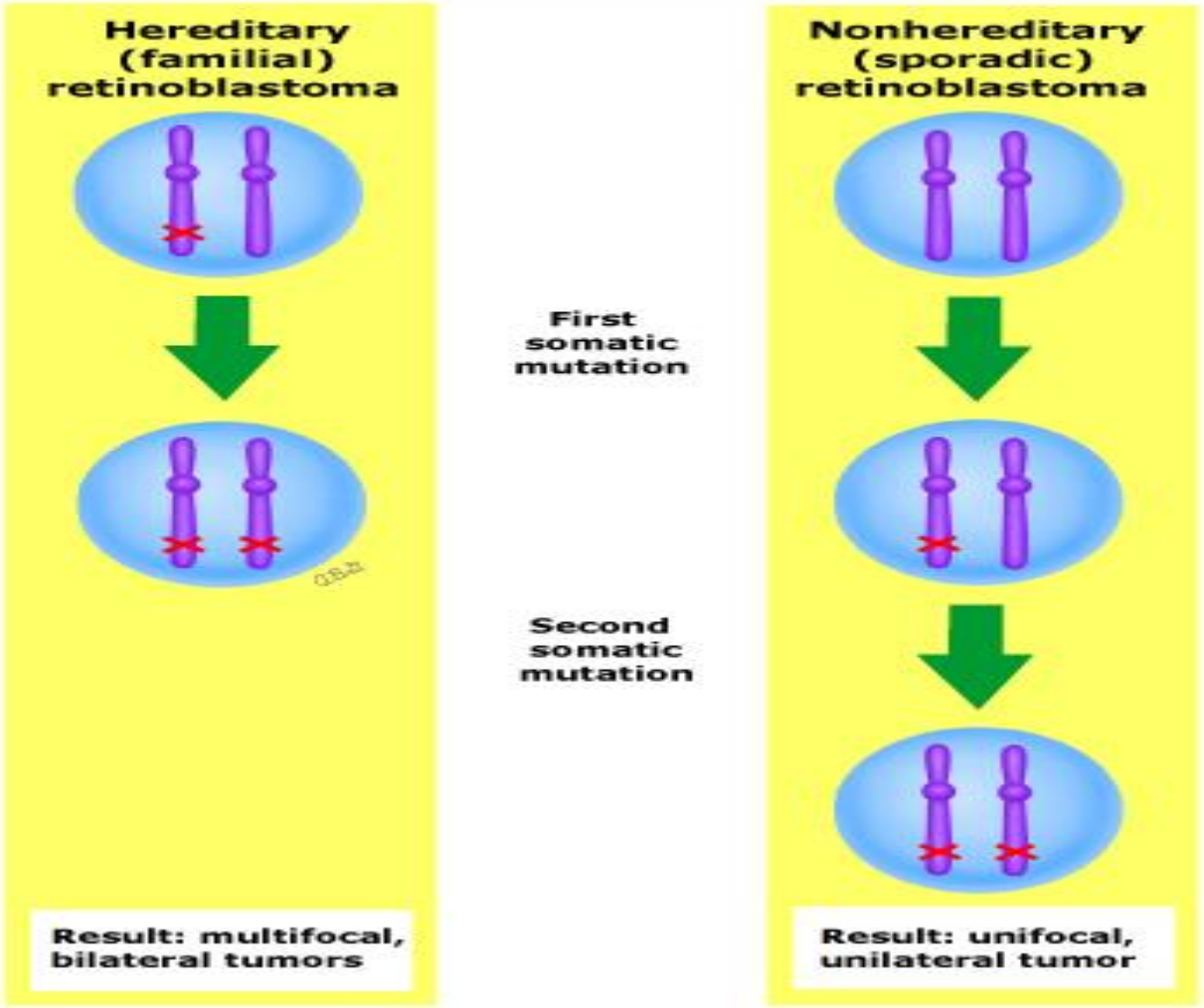
PATHOGENESIS

- Mutational inactivation of both alleles of the retinoblastoma (RB1) gene
- Chromosome 13q and encodes a nuclear protein (Rb) that acts as a **tumor suppressor**
- The Rb protein **restricts the cell's ability** to progress from the G1 phase to the S phase of the cell cycle

PATHOGENESIS……

- A germline mutation at the *RB1* locus (most common) or deletion of chromosome 13q (containing the *RB1* gene locus) is present in all cells of the body
- A second "hit," occurring later in development **(the second hit of the Knudson two-hit hypothesis**), affects the remaining *RB1* allele within retinal cells a typical for the heritable form
- A "two-hit" model has been proposed to explain the different clinical features of heritable and nonheritable cases of retinoblastoma

The genetics of retinoblastoma formation



GENE PATTERN

- The Heritable retinoblastoma is associated with germline mutations in the retinoblastoma *RB1gene*.
  - Early age
  - Most cases are bilateral and/or multifocal
  - ± one-quarter have a positive family history
- The nonheritable form results from somatic *RB1* mutations in the tumor only
  - Unilateral and unifocal
  - Negative family history
  - later age

Morphologic features

- Solitary or multifocal, well-circumscribed, translucent intraretinal mass
- In advance →more pink in color, with dilated feeding blood vessels
- Growth pattern
  - **Exophytic** → lead to subretinal seeds
  - **Endophytic** →the anterior chamber and layer behind the cornea, causing a pseudo-hypopyon
  - **Diffuse infiltrating retinoblastoma** → relatively flat (very little vertical growth) and grows intraretinally, mimicking retinitis

The routes of metastatic spread

- **The most common** are the optic nerve to the central nervous system
- **The choroid** into the sclera and into the orbit
- **The subarachnoid space** to the contralateral optic nerve
- The cerebrospinal fluid to the CNS;
- **Hematogenous dissemination** to the lung, bone, liver, or brain; and lymphatic dissemination

Second malignancies

- Heritable retinoblastoma → approximately **30 %** at 40 years after the original treatment
- In contrast, nonheritable retinoblastoma → less common **2 %**
- **PNET tumors**

Causes of leukocoria in children

Lens abnormalities
Cataract (congenital or acquired)
Posterior lenticonus
Vitreous hemorrhage
Ocular trauma (especially penetrating)
Retinal detachment
Ocular trauma
Nonaccidental trauma (abusive head trauma)
Norrie disease
Incontinentia pigmenti
Cutis marmorata telangiectatica
Turner syndrome
Walker-Warburg syndrome
Stickler syndrome
Familial exudative vitreoretinopathy
Retinopathy of prematurity
Other retinal abnormalities
Coats disease
Persistent hyperplastic primary vitreous (persistent fetal vasculature)
Congenital retinoschisis

Optic disc abnormalities
Colobomata of choroid and optic disc
Morning glory disc anomaly
Myelinated nerve fibers
Intraocular inflammation/infection
Juvenile idiopathic arthritis
Sarcoidosis
Cytomegalovirus
Toxoplasmosis
Ocular toxocariasis
Endophthalmitis
Tumors
Retinoblastoma
Leukemia (with ocular involvement)
Choroidal melanoma
Metastatic tumors
Choroidal osteoma
Medulloepithelioma ("diktyoma")
Combined hamartoma of the retina and the retinal pigment epithelium
Choroidal hemangioma
Benign astrocytic hamartomas in tuberous sclerosis
Glioma of the optic nerve head

CAUSES OF LEUKOCORIA

- Retinoblastoma (18 to 62 %)
- Cataract (60 %)
- Persistent fetal vasculature (31 % of those referred for retinoblastoma)
- Coats disease (29 % of those referred for retinoblastoma)

CAUSES OF LEUKOCORIA
less common

- Astrocytic hamartoma
- Coloboma (fissure or cleft) of choroid or optic disc
- Uveitis (pars planitis)
- Toxocariasis
- Retinopathy of prematurity (stage 4, 5)
- Vitreous hemorrhage
- Retinal dysplasia

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Assessment of the visual system in infants and children

Age	Important aspects of history	Examination	Ophthalmology referral indications
Newborn to 6 months	Birth weight <1500 grams or gestational age <30 weeks Family history of: ▪ Congenital cataracts ▪ Retinoblastoma ▪ Metabolic or genetic disease	Vision assessment (fixate and follow response) External eye examination (lids, orbit, conjunctiva, cornea, iris) Pupillary response Simultaneous red reflex	▪ Positive history ▪ Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of ≥1 mm, unilateral ptosis, unable to fix and follow by age 3 months)
6 to 12 months	Neurologic abnormality Systemic disease associated with eye abnormalities Does the infant recognize faces and objects? Does the infant fix and follow? Do the parents notice: ▪ Eye deviation? ▪ Tearing?	Vision assessment (fixate and follow response) External eye examination (lids, orbit, conjunctiva, cornea, iris) Ocular motility Pupillary response Simultaneous red reflex	▪ Positive history ▪ Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of ≥1 mm, unilateral ptosis, unable to fix and follow)
1 to 3 years	Neurologic abnormality Systemic disease associated with eye abnormalities Does the child recognize faces and objects? Does the child fix and follow? Do the parents notice: ▪ Eye deviation? ▪ Tearing?	Age-appropriate visual assessment: ▪ Infants and young toddlers: Fixate and follow response ▪ Cooperative older toddlers: Monocular visual acuity with HOTV* or LEA¶ optotypes Instrument-based vision screening (eg, photoscreening, autorefraction) if available External eye examination (lids, orbit, conjunctiva, cornea, iris) Ocular motility Pupillary response Simultaneous red reflex Ophthalmoscopy if possible	▪ Positive history ▪ Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of ≥1 mm, unilateral ptosis) ▪ Eye preference or unable to fix and follow ▪ Ocular alignment abnormalities ▪ Visual acuity worse than 20/50 in one or both eyes ▪ Visual acuity difference of two or more lines between eyes ▪ Failed instrument-based screening as indicated by the device
4 to 5 years	Neurologic abnormality Systematic disease associated with eye abnormalities Does the child recognize faces and objects? Do the parents notice: ▪ Abnormal head posturing? ▪ Squinting or blepharospasm? ▪ Eye deviation? ▪ Tearing?	External eye examination (lids, orbit, conjunctiva, cornea, iris) Ocular motility Pupillary response Simultaneous red reflex Corneal light reflex Ocular alignment (cover-uncover test) Monocular visual acuity△◇: ▪ Snellen letters or numbers ▪ Surrounded HOTV* or LEA¶ optotypes Instrument-based vision screening (eg, photoscreening, autorefraction) if available Ophthalmoscopy if possible	▪ Positive history ▪ Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of ≥1 mm, unilateral ptosis) ▪ Eye preference ▪ Ocular alignment abnormalities ▪ Visual acuity worse than 20/40 for children 48 through 59 months or worse than 20/30 for children ≥60 months in one or both eyes ▪ Visual acuity difference of two or more lines between eyes ▪ Failed instrument-based screening as indicated by the device
>6 years	Neurologic abnormality Systematic disease associated with eye abnormalities Does the child recognize faces and objects? Do the parents notice: ▪ Abnormal head posturing? ▪ Squinting or blepharospasm? ▪ Eye deviation? ▪ Tearing?	External eye examination (lids, orbit, conjunctiva, cornea, iris) Ocular motility Pupillary response Simultaneous red reflex Monocular visual acuity◇: ▪ Sloan or Snellen letters or numbers ▪ Surrounded HOTV* ▪ LEA symbols¶ Ophthalmoscopy if possible	▪ Positive history ▪ Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of ≥1 mm, unilateral ptosis) ▪ Eye preference ▪ Ocular alignment abnormalities ▪ Visual acuity worse than 20/30 in one or both eyes ▪ Visual acuity difference of two or more lines between eyes

SCREENING CHILDREN AT RISK

- A positive family history
- A personal of family history of 13q deletion or retinoblastoma [RB1] gene mosaicism
- Should be **evaluated by an ophthalmologist** shortly after birth
- Every 1 to 2 months during the first 2 years of life

Metastatic evaluation

- **Rarely present** at the time of diagnosis
- Formal staging studies (ie, bone marrow examination, lumbar puncture, and/or radionuclide bone scan) **are not routinely performed** due to their low yield
- If there is **clear evidence of tumor outside the eye** (ie, optic nerve invasion, or choroidal involvement that is extensive) a full metastatic evaluation may be pursued
  - Bone marrow aspiration and biopsy
  - Lumbar puncture
  - Radionuclide bone scan

Genetic testing and counseling

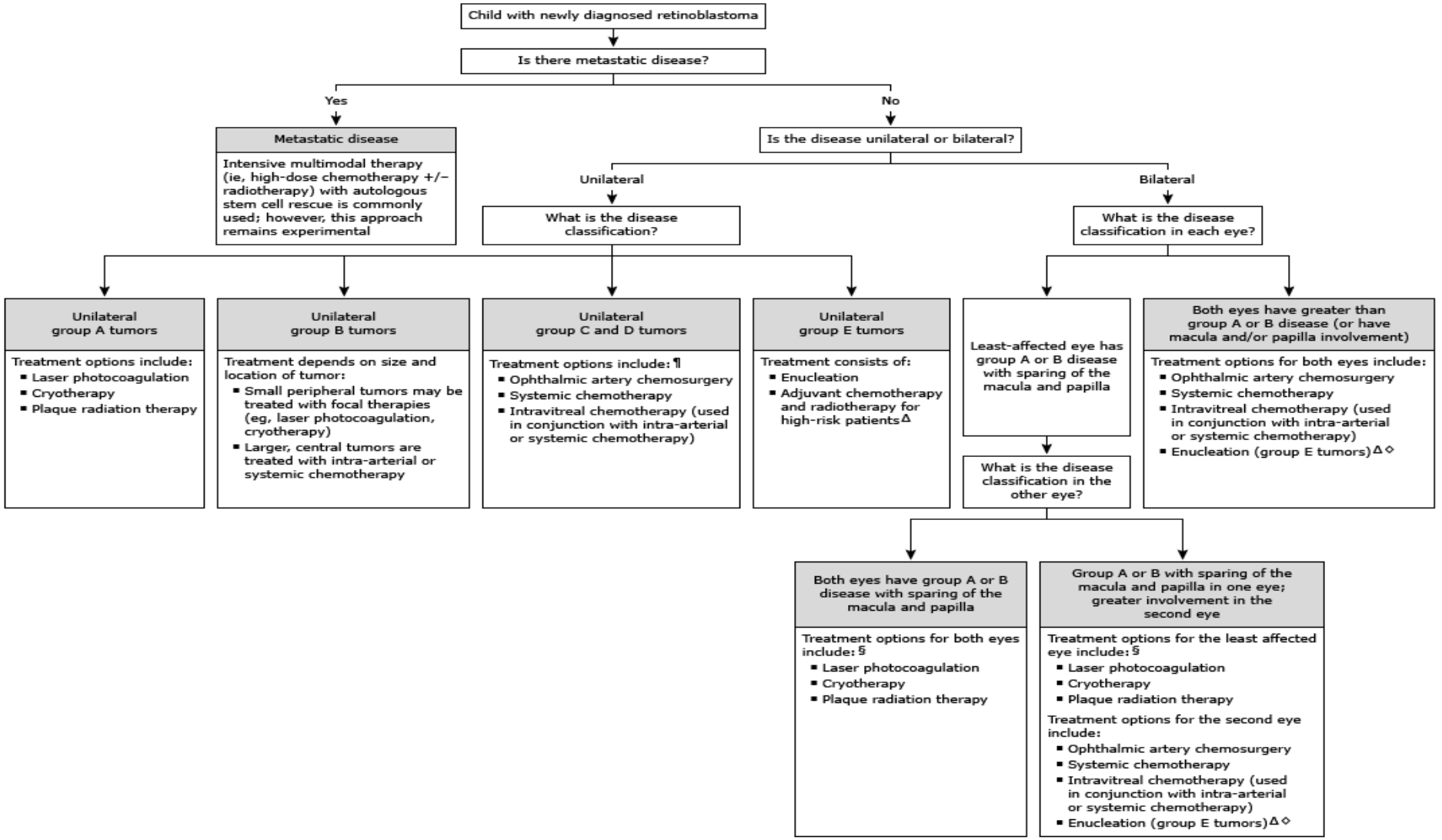
- Are important aspects in the management of patients with retinoblastoma in order to estimate the risk of disease in family members and future offspring
- Understand the genetic consequences of each form of retinoblastoma (relates to secondary cancers in children with heritable retinoblastoma)

International classification of retinoblastoma

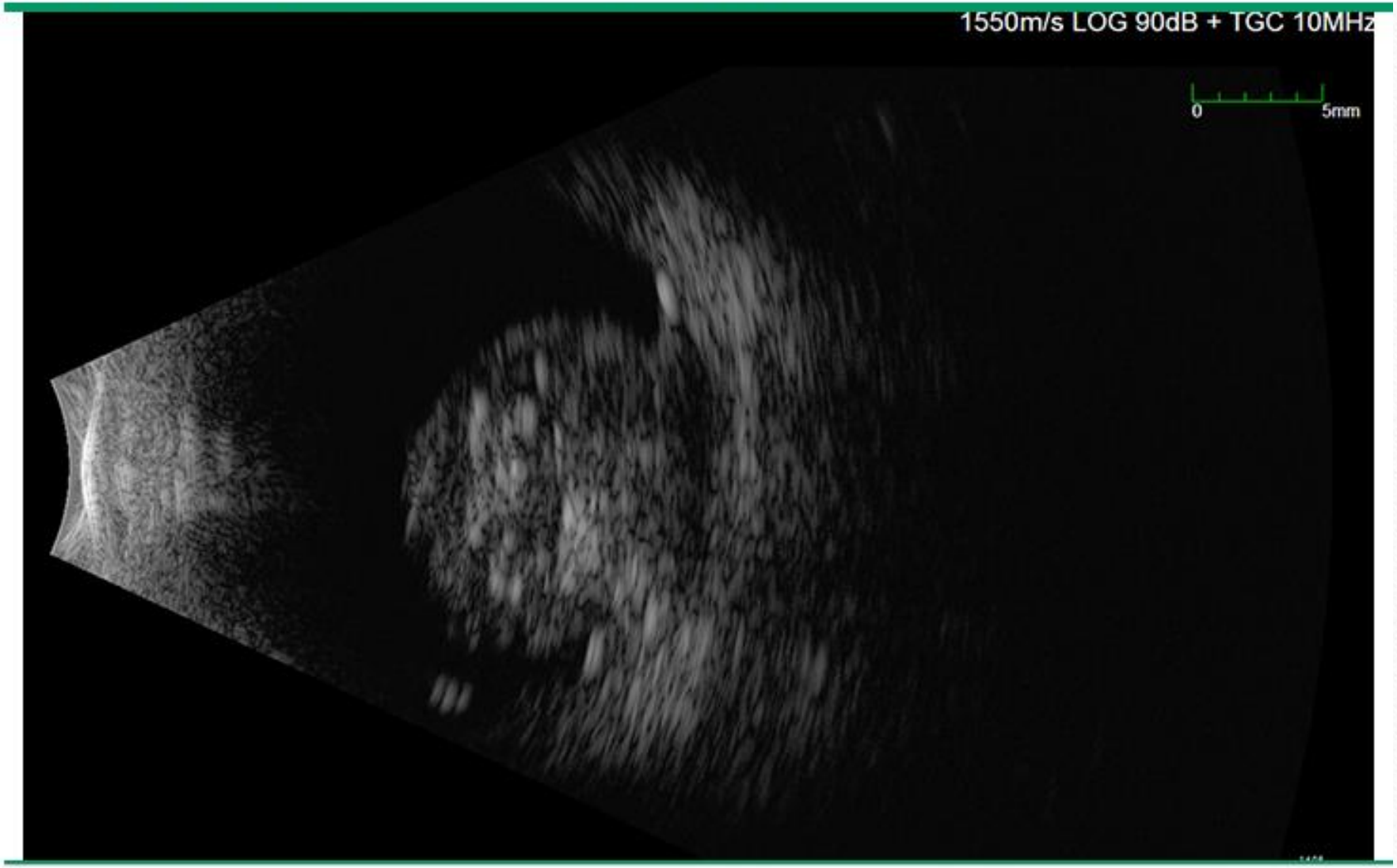
Group	Description	Specific features
A	Very low risk: Eyes with small discrete tumors away from critical structures	Tumor ≤3 mm in basal dimension or thickness
B	Low risk: Eyes with discrete retinal tumor of any size or location without vitreous or subretinal seeding	Tumor >3 mm in basal dimension or thickness, or any of the following: ▪ Macular location ≤3 mm to foveola ▪ Juxtapapillary location ≤1.5 mm to disc ▪ Clear subretinal fluid ≤3 mm from margin
C	Moderate risk: Eyes discrete retinal tumors of any size or location with only focal vitreous or subretinal seeding	One of the following: ▪ Subretinal seeds ≤3 mm from tumor ▪ Vitreous seeds ≤3 mm from tumor ▪ Both subretinal and vitreous seeds ≤3 mm from tumor ▪ Less than one quadrant of subretinal fluid in the fundus
D	High risk: Eyes with massive nondiscrete tumors and/or diffuse vitreous or subretinal seeding	One of the following: ▪ Subretinal seeds >3 mm from tumor ▪ Vitreous seeds >3 mm from tumor ▪ Both subretinal and vitreous seeds >3 mm from tumor ▪ Greater than one quadrant of subretinal fluid in the fundus
E	Very high risk: Eyes that have been destroyed anatomically or functionally by the tumor	Extensive retinoblastoma, or one of the following: ▪ Neovascular glaucoma ▪ Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space ▪ Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber ▪ Tumor anterior to the anterior vitreous face, including the ciliary body or iris ▪ Diffuse infiltrating tumor ▪ Phthisis bulbi or orbital cellulitis

Opthalmol Clin North Am 2005; 18:41

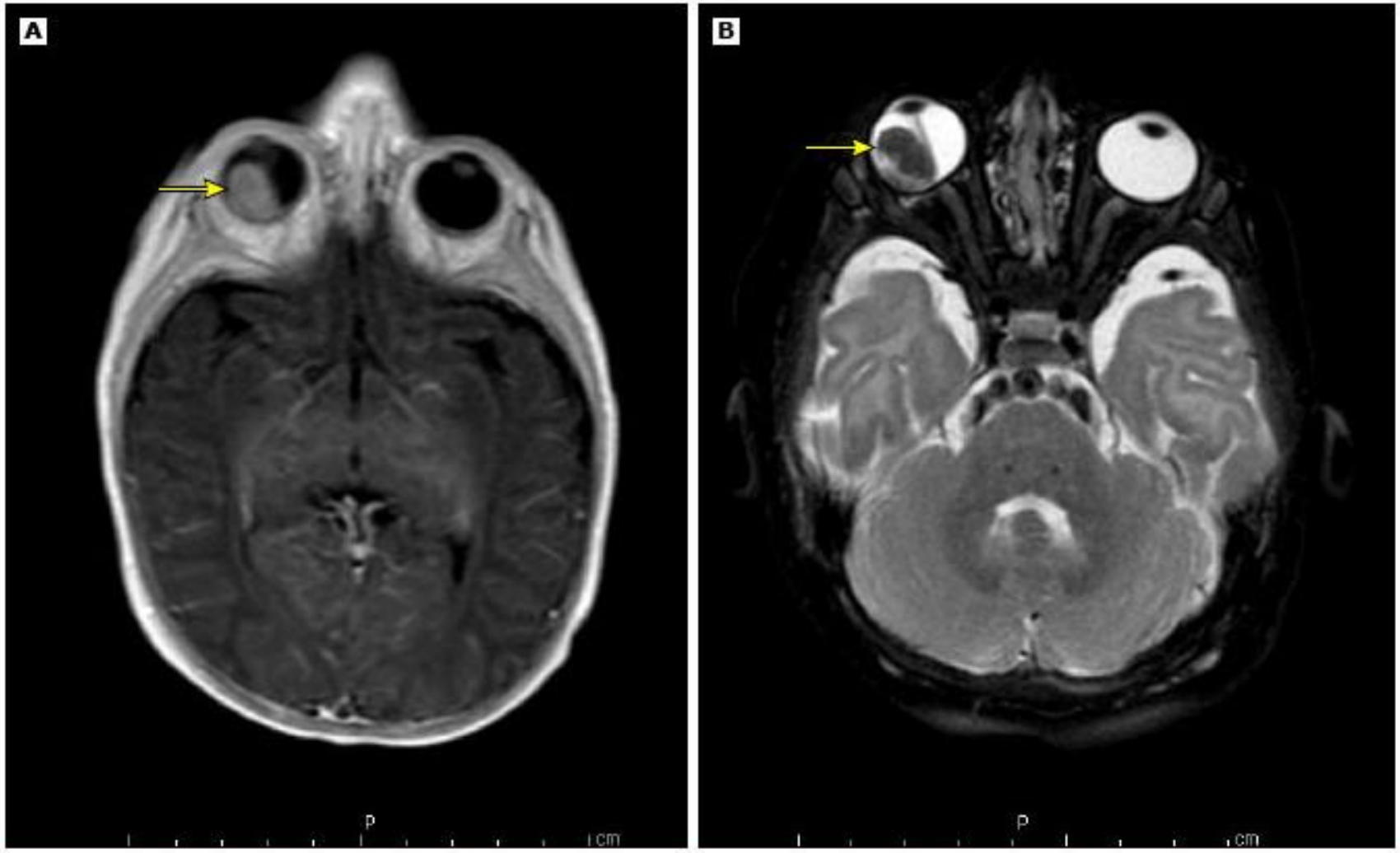
Algorithmic overview of initial treatment options for children with newly diagnosed retinoblastoma based on disease classification*



Ultrasonography of retinoblastoma (right eye)



Retinoblastoma on magnetic resonance imaging



SUMMARY

- The most common primary intraocular malignancy of childhood and accounts for **10 to 15 percent of cancers within the first year of life**
- Retinoblastoma occurs in heritable (approximately **40 % of cases**) and nonheritable (approximately 60 % of cases) forms
- Should undergo **clinical screening and/or genetic testing** for retinoblastoma
- The evaluation by an ocular oncologist and includes Complete physical examination, Ophthalmologic examination, **ultrasonography, MRI of the brain and orbits**
- Metastatic disease is rarely present at the time of diagnosis, and formal staging studies are not routinely performed
- **Molecular genetic testing** is suggested for all affected patients

Thankyou

Family history

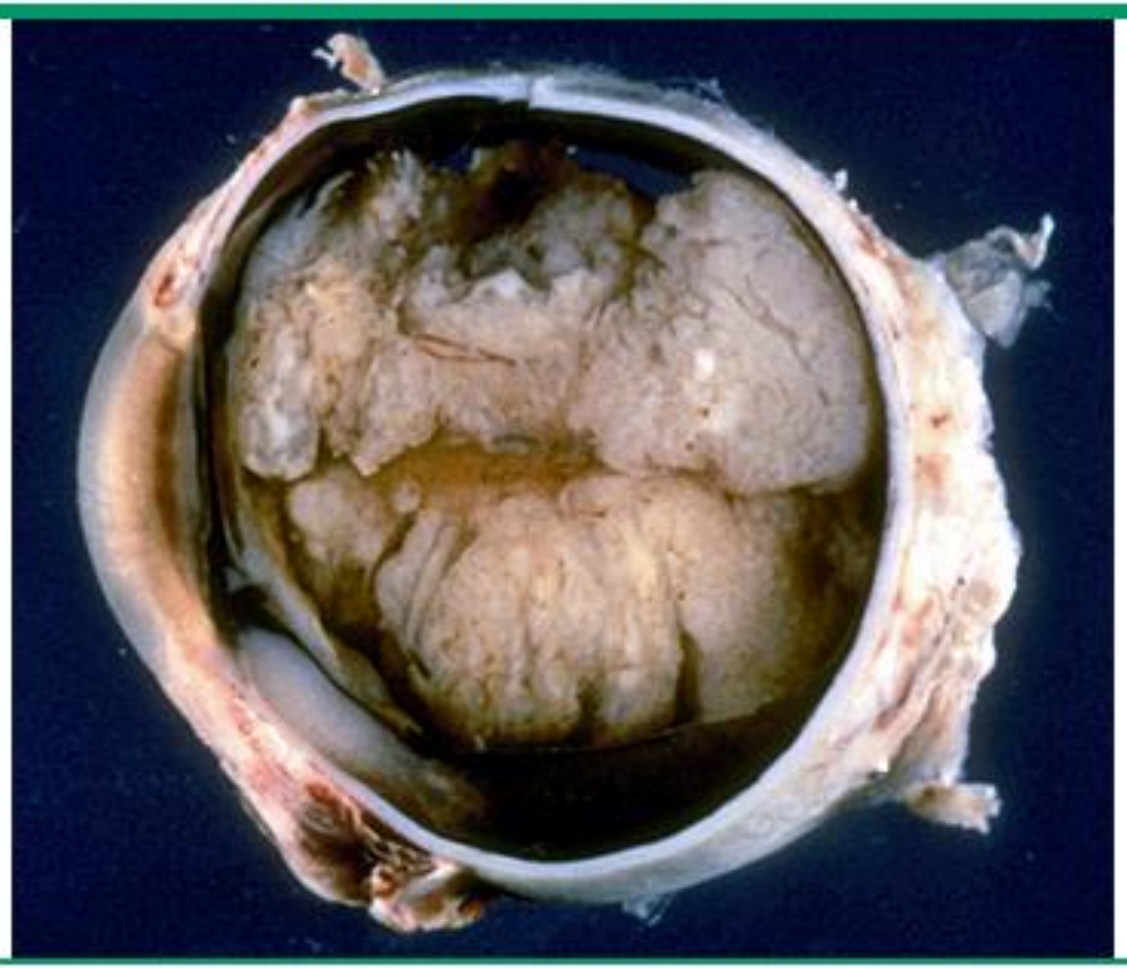
- Are presumed to have heritable retinoblastoma
- 50 % risk of passing the mutation on to their offspring
- Patients with an *RB1* germline mutation have a 90 percent chance of the mutation manifesting with retinoblastoma

Summary of molecular genetic testing used in retinoblastoma

Gene symbol	Test method		Mutations detected	Mutation detection frequency by test method* ¶	Test availability Δ
RB1	Gross deletion/duplication analysis ◇	FISH	Submicroscopic deletions and translocations	>8%	For a list of available laboratories, please see the Genetic Testing Registry
		Heterozygosity testing		8%	
		MLPA, quantitative multiplex PCR, other methods ◇	Submicroscopic whole exon(s) deletions, insertions, and rearrangements	16%	
	Mutation scanning		Single-base substitutions, small length mutations	70 to 75%	
	Sequence analysis (genomic)				
	Targeted mutation analysis		Specific panel of recurrent point mutations	25%	
	Methylation analysis		Hypermethylation of the promoter region	10 to 12% §	
	Sequence analysis of RNA from blood		(Deep intronic) splice mutations, gross rearrangements	<5% ¥	

Approach to the child with leukocoria

Retinoblastoma gross pathology



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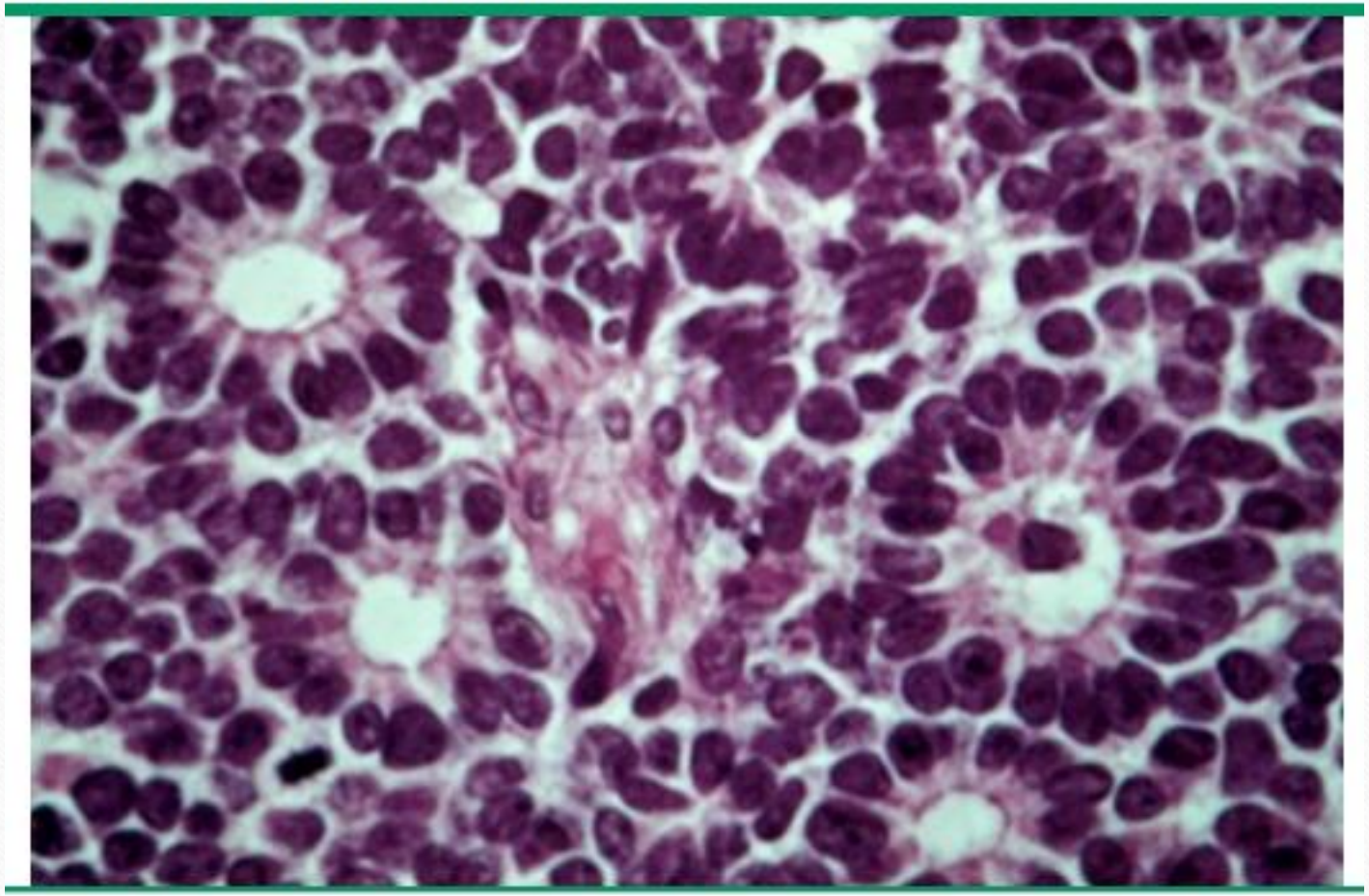

Strabismus as presenting manifestation of retinoblastoma

Exotropia plus slightly enlarged corneal diameter and loss of red reflex in left eye.

Combined exophytic-endophytic retinoblastoma