ASSOCIAZIONE TOSCANA CONTRO LE LEUCEMIE
ED I TUMORI DEL BAMBINO
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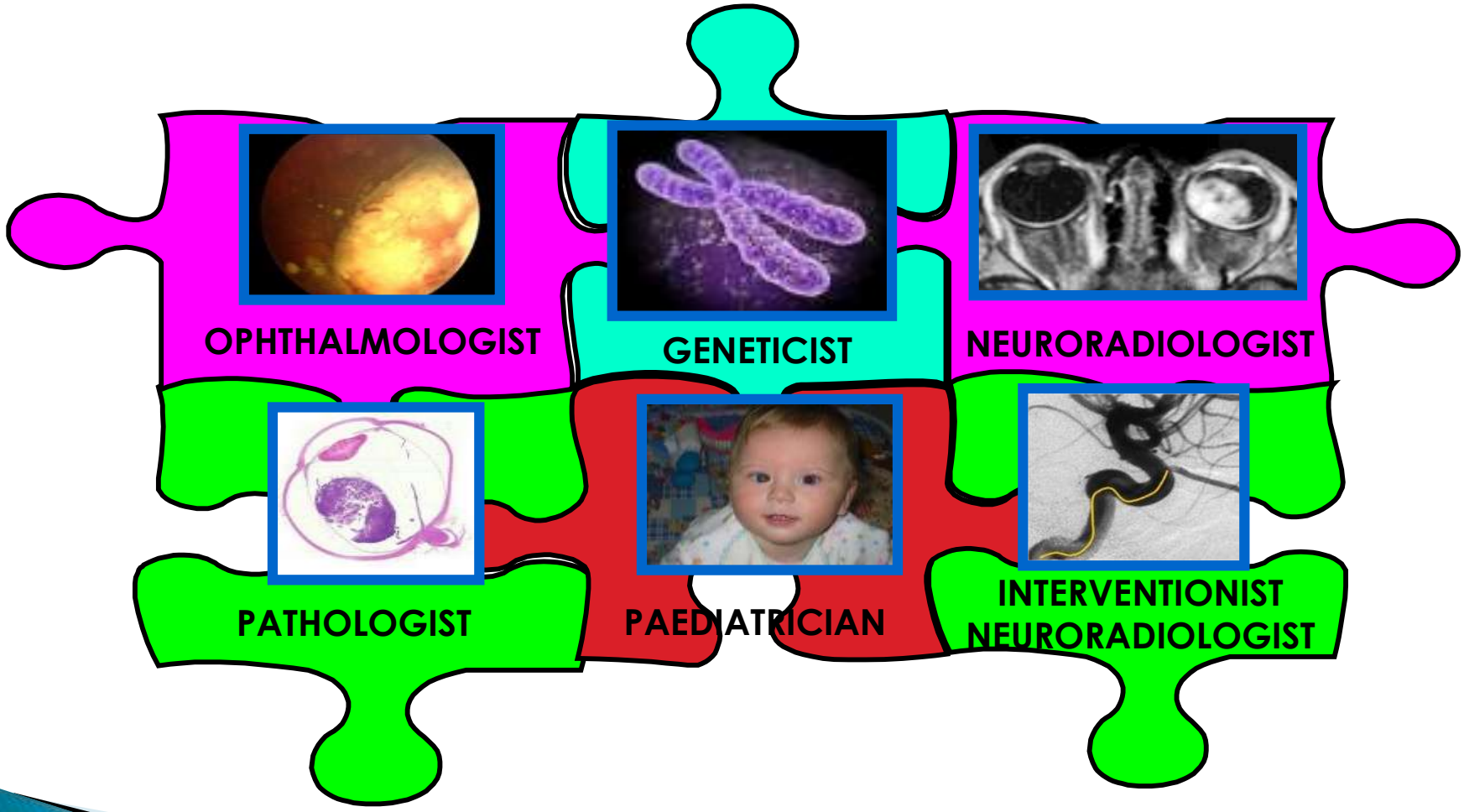
GIORNATA ATL
Siena, 08 novembre 2014
Monastero delle Figlie della Carità
Loc. Costafabbri - Siena

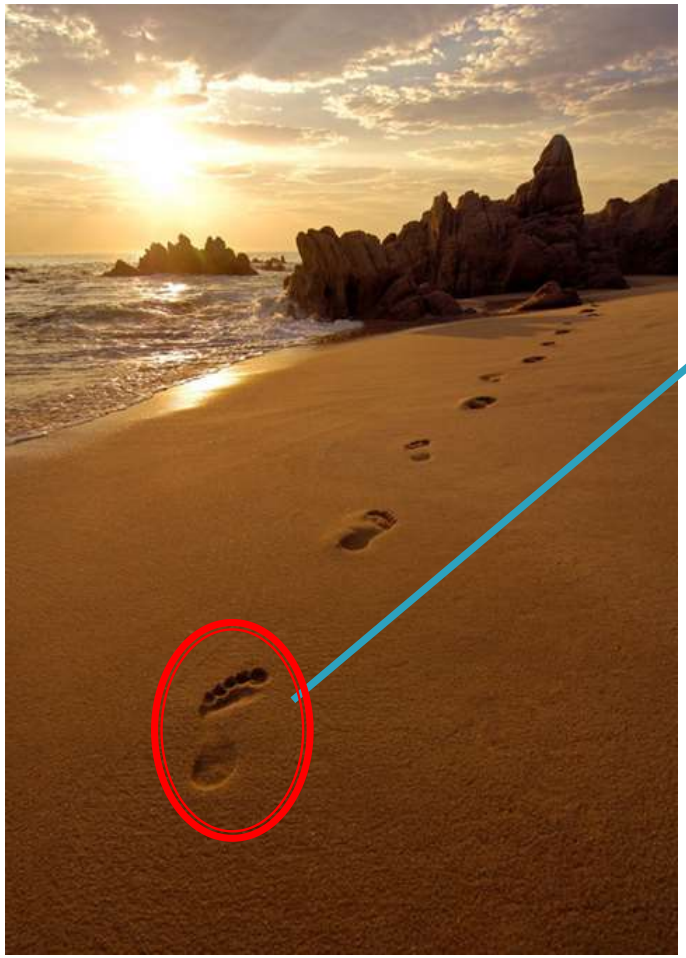
ONCOLOGIA PEDIATRICA E ALTRO… IL RETINOBLASTOMA: DIAGNOSI, GESTIONE E CHEMIOTERAPIA SISTEMICA

M. CAINI
(SIENA)

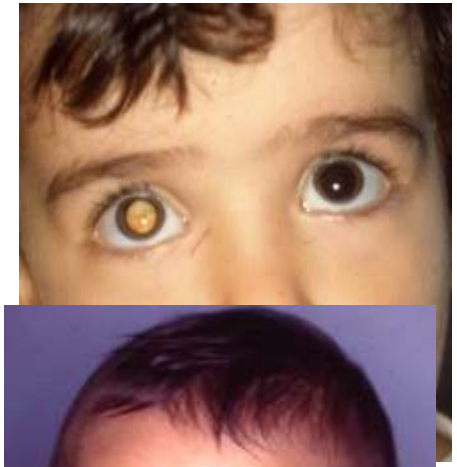
PRELIMINARY CONDITION … A CLOSE-KNIT TEAM

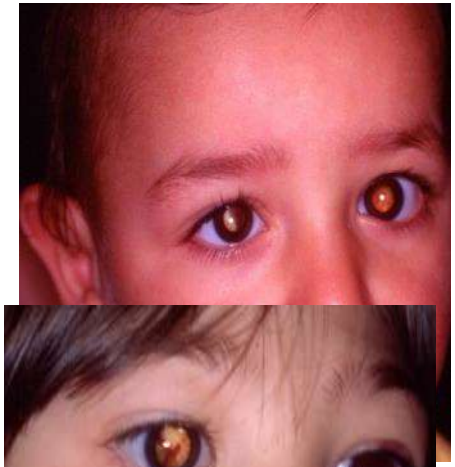


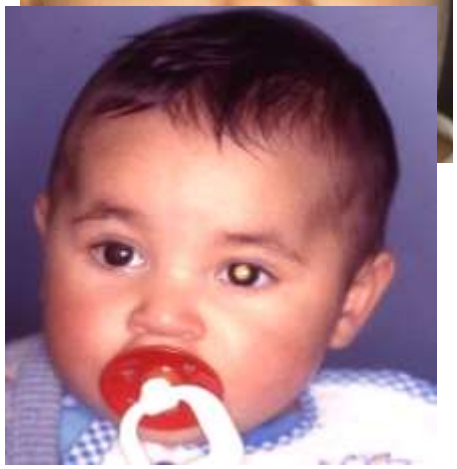
FIRST STEP

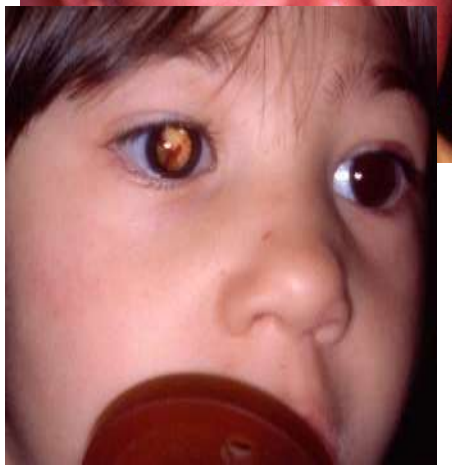


TO HAVE A GOOD SUSPICION

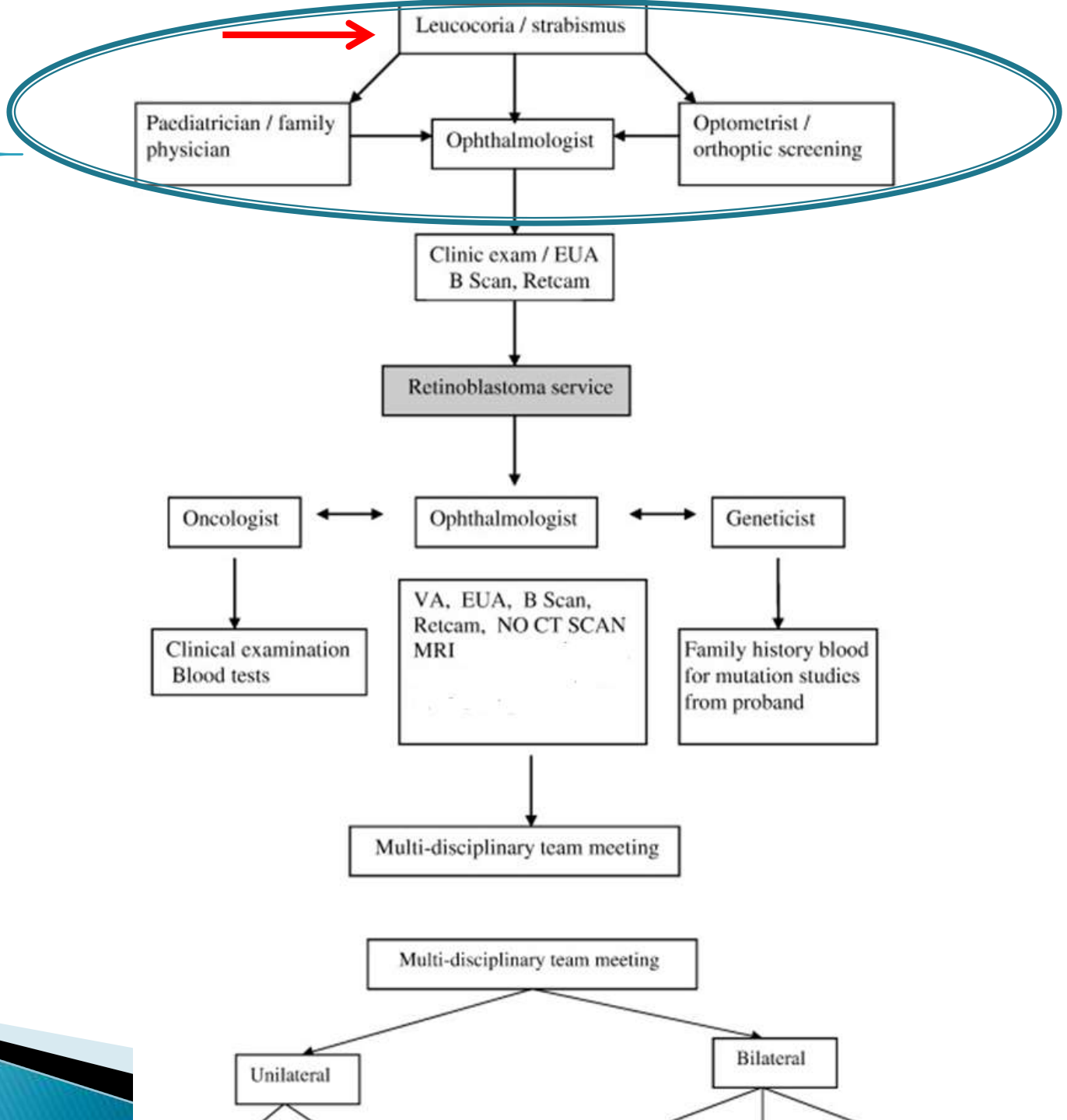








SPECIALISTS MET OUT OF THE RTB REFERRAL CENTER



- Leukocoria, strabismus and inflammatory signs are the most common presenting signs, with leukocoria correlated to more advanced disease and strabismus always associated with macular involvement[1].

- 50% to 60% of children are initially seen with leukocoria (white pupillary reflex or "cat's eye" reflex), 20% to 25% with strabismus (both esotropia and exotropia), and 6% to 10% with inflammatory signs (red eye or pseudo-orbital cellulitis).

1 Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel I, Boyd NW III. Presenting signs of retinoblastoma. *J Pediatr.1998;132:505-508*

…BUT

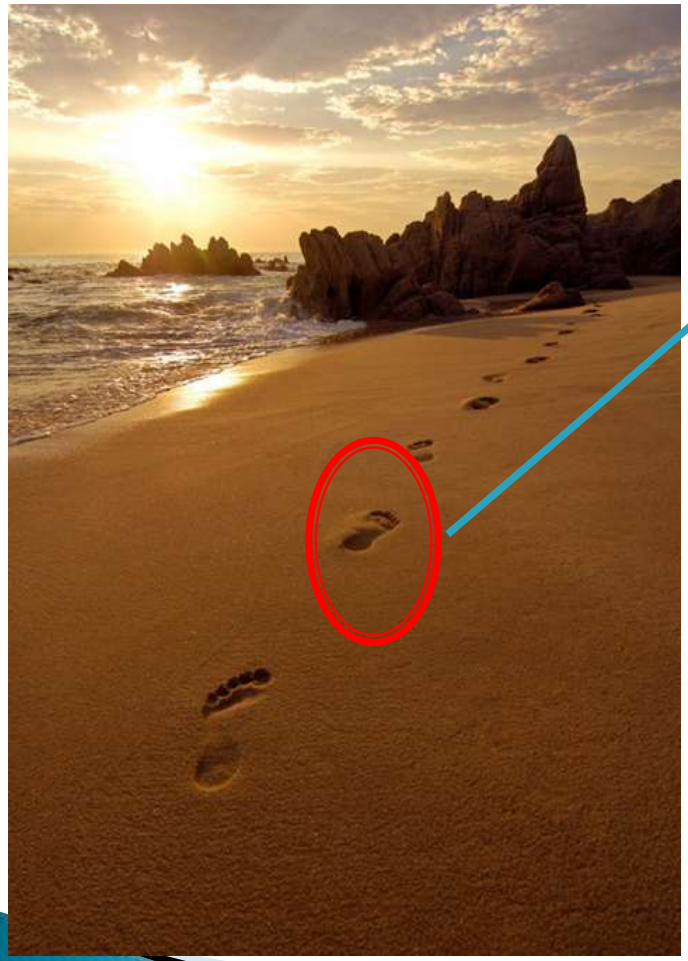
- **Saving eyes and vision requires disease recognition before leukocoria**, as demonstrated by the better ocular salvage rate among patients who had a positive family history and received clinical surveillance via early, routine dilated funduscopic examinations by an ophthalmologist[2].

2 David H. Abramson, MD; Katherine Beaverson, MS; Poorab Sangani, MD et al. Pediatrics 2003;112:1248 –1255 . Screening for Retinoblastoma: Presenting Signs as Prognosticators of Patient and Ocular Survival.

- However the need remains for a pediatrician to screen for retinoblastoma by accurately performing **the red reflex examination**, with an immediate referral on a positive or abnormal result. Similarly, an immediate referral for an ophthalmic evaluation is prudent when a pediatrician notes **strabismus or a family history of retinoblastoma**, as these are risk factors for the presence of retinal tumors[2].

2 David H. Abramson, MD; Katherine Beaverson, MS; Poorab Sangani, MD et al. Pediatrics 2003;112:1248 –1255 . Screening for Retinoblastoma: Presenting Signs as Prognosticators of Patient and Ocular Survival.

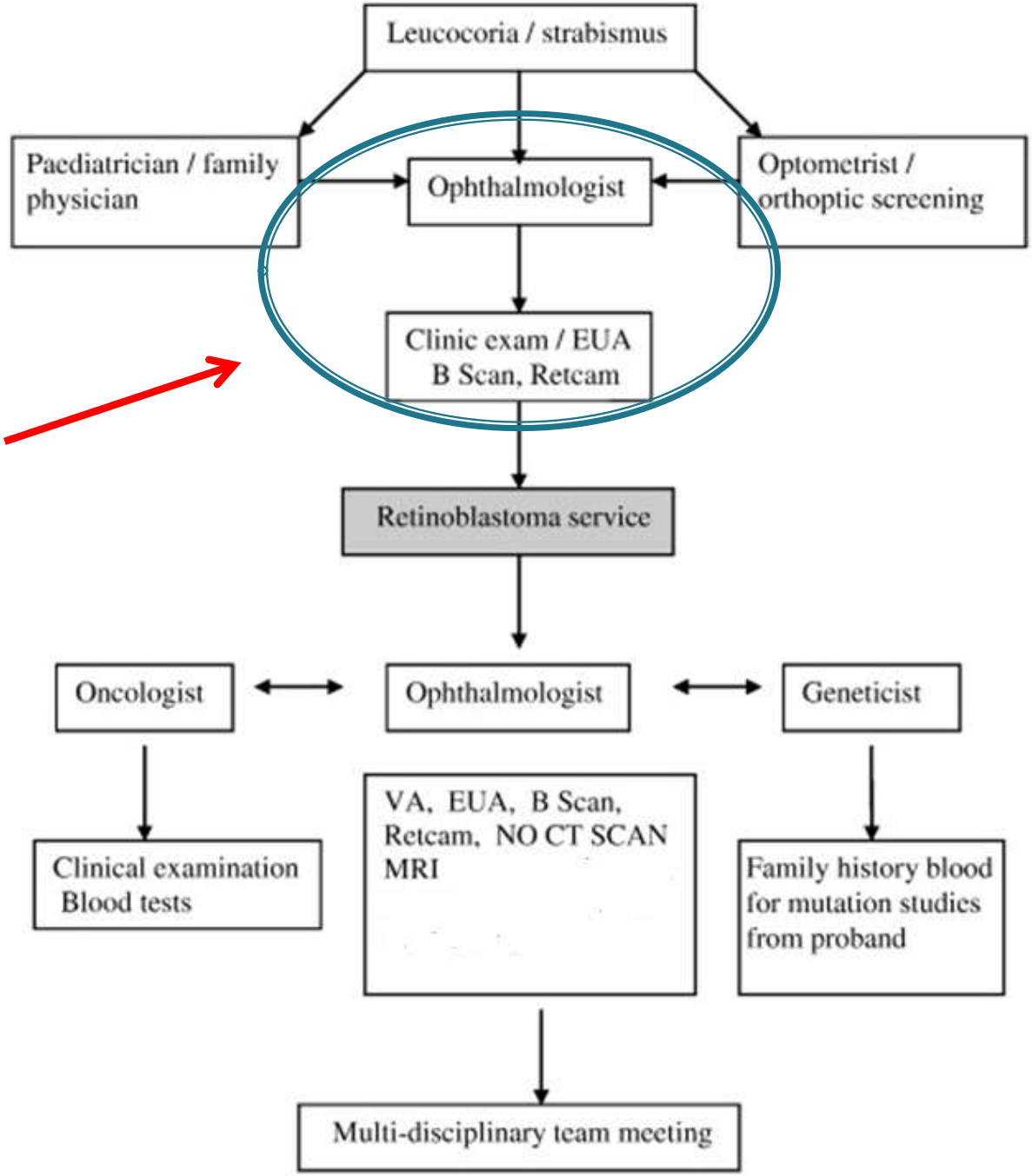
2nd STEP



TO MAKE THE CORRECT DIAGNOSIS

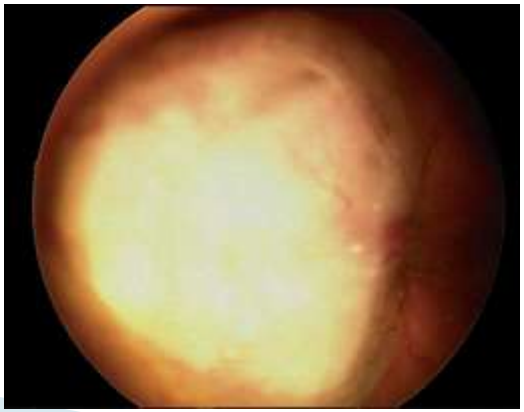
It is now necessary to address the child to **THE OPTHALMOLOGIST** who will perform a **funduscopic examination with:**

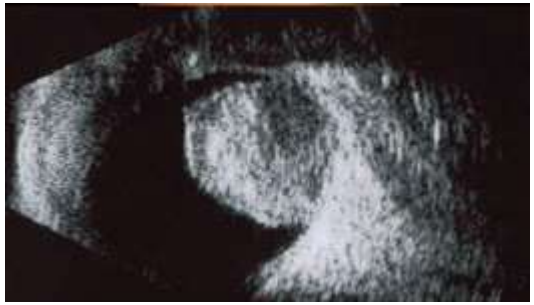
- Maximum mydriasis
- Binocular ophthalmoscopy
- Indentation (to check the ora serrata zone)
- Ret-Cam


Leucocoria / strabismus
Paediatrician / family physician
Ophthalmologist
Optometrist / orthoptic screening
Clinic exam / EUA
B Scan, Retcam
Retinoblastoma service
Oncologist
Ophthalmologist
Geneticist
Clinical examination
Blood tests
VA, EUA, B Scan,
Retcam, NO CT SCAN
MRI
Family history blood for mutation studies from proband
Multi-disciplinary team meeting

It is also useful to perform:

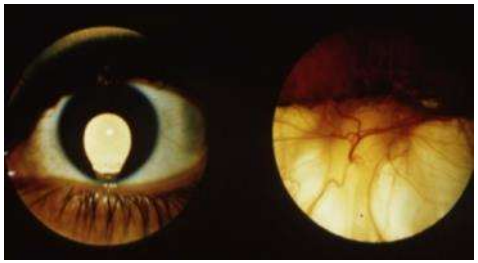
- Examination of the anterior segment with slit-lamp (biomicroscopy)
- A/B scan ultrasonography: confirms the presence of masses in the posterior segment of the eye. Characteristic findings are intra-lesional calcification with high internal reflectivity and acoustic shadowing.



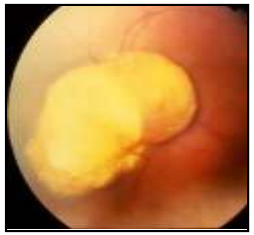


The ophthalmologist should also:

Distinguish RTB from other conditions which are known as "Pseudo-Retinoblastoma" or "The big five":



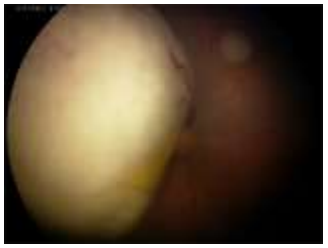
- Coloboma a hole in one of the structures of the eye
- Early onset of Coat's disease a vascular retinopathy resulting in exudation of lipid under the retina
- Combined Hamartoma of the retina and the retinal pigment epithelium is a rare benign lesion in the macula, juxtapapillary, or peripheral location that is commonly found in children and that consists of the glial cells, vascular tissue, and sheets of pigment epithelial cells.

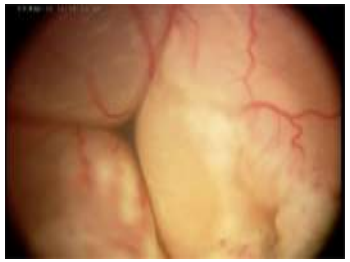


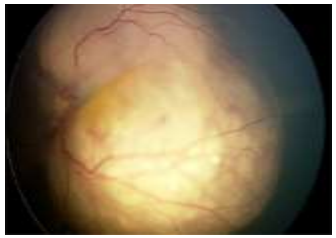
- PHPV (persistent hyperplastic primary vitreous): result from failure of regression of fetal vessels in the vireous
- Retinoma

The ophthalmologist should also:

- **Make a detailed description of the tumor, including**:
  I. Diameters
  II. Thickness
  III. Vascularization
  IV. Appearance
  V. Presence of calcifications
  VI. Location (quadrant, posterior pole, medium-extreme periphery)
  VII. Epitumoral/vitreous and/or subretinal seeding
  VIII. If associated retinal detachment
  IX. Stage and group (according to the Reese-Ellsswoth and the International classifications)
  X. If retinoma transformed into RTB
  XI. If diffused/infiltrative RTB





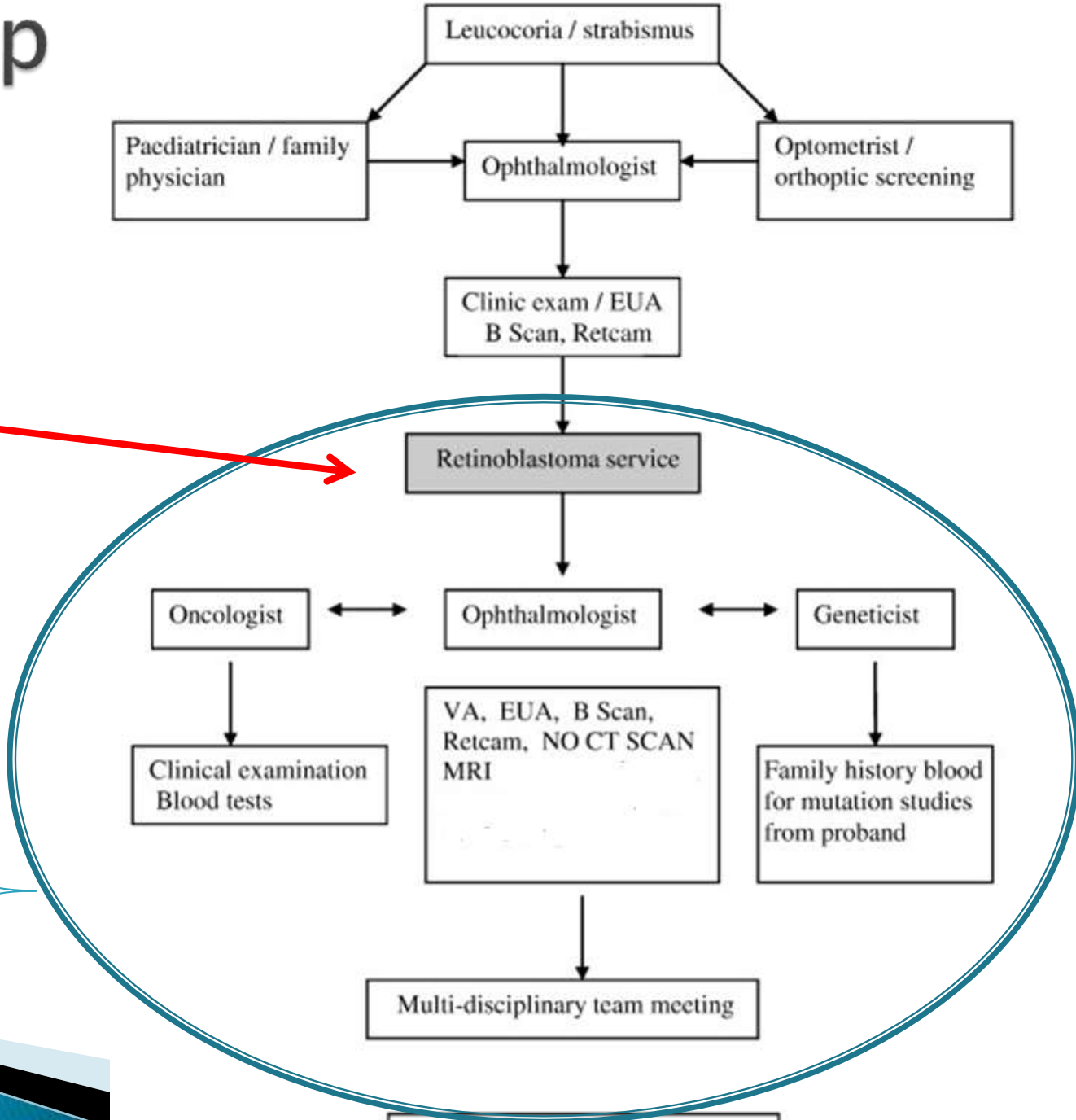


Now the child needs to be taken to a referral center for retinoblastoma

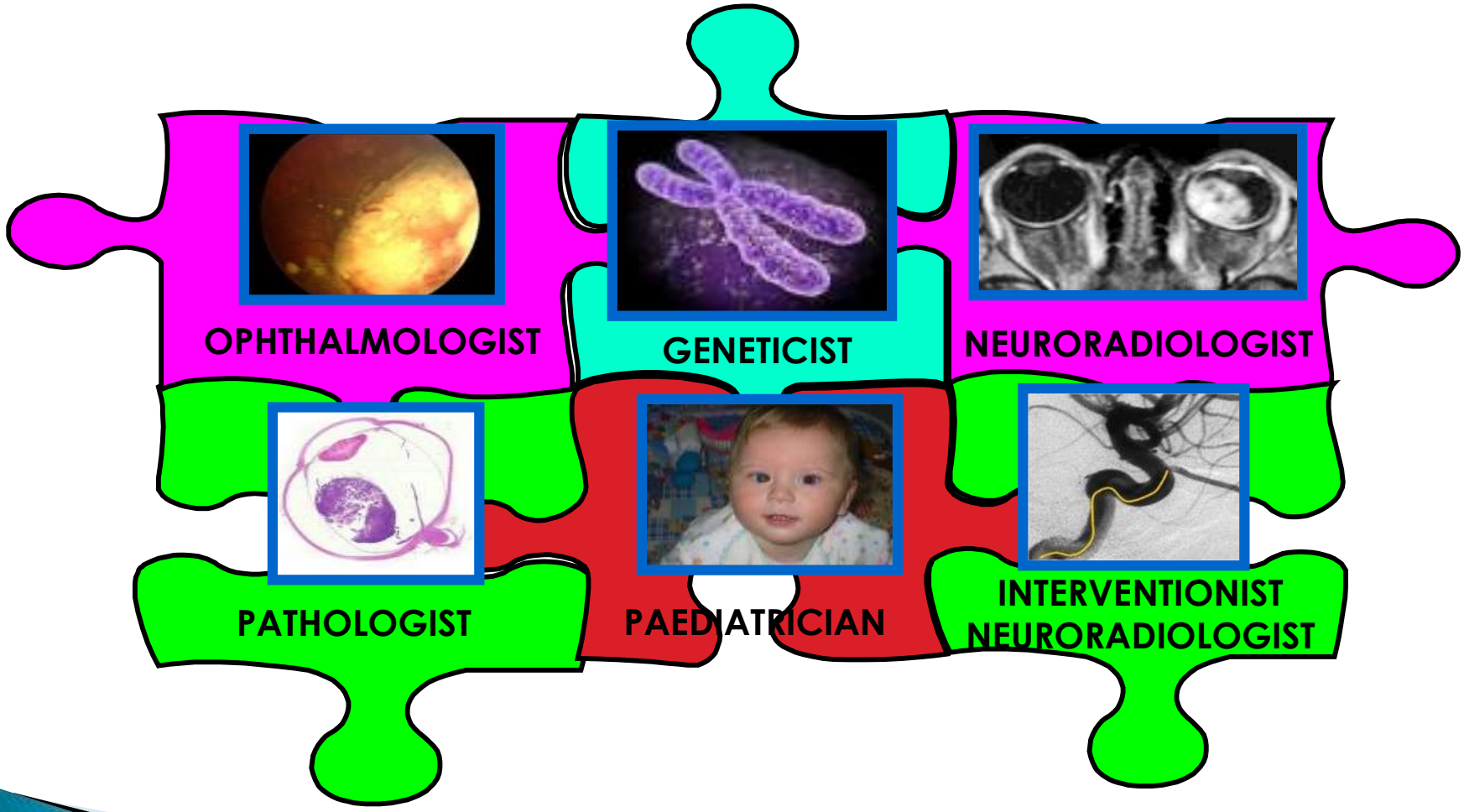
Each paediatrician and each ophthalmologist should know which is the tertiary referral center for Retinoblastoma service in the country

The 3rd step

SPECIALISTS MET AT RTB REFERRAL CENTER



It's now up to A CLOSE-KNIT TEAM



Evaluation by the ophthalmologist oncologist of the Referral Center

- Who will confirm/exclude the diagnosis by performing the funduscopic examination with Ret-cam under anesthesia and US scan, if not already done, as well as examination of the anterior segment and fluorangiography (the fluorangiography is generally most useful in the surveillance after the first treatment or in cases of suspected recurrence)
- This figure will be involved in all the diagnostic-therapeutical process of the child

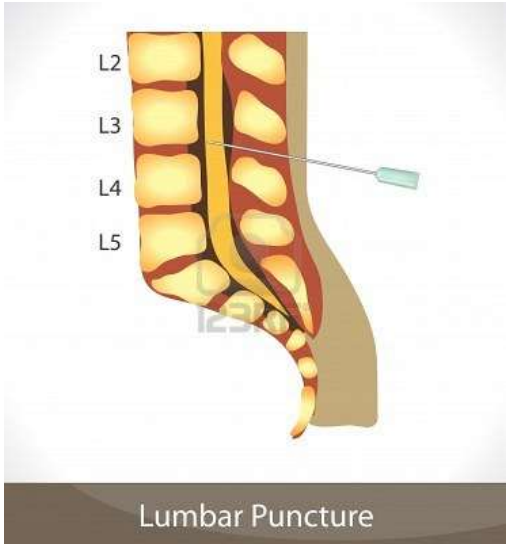
Role of the pediatrician oncologist

- He conducts the anamnestic survey (personal and of the family), a physical examination, at general and district levels, with particular attention to research any dimorphisms and description of neuromotor and speech development
- He will be always involved in every step of the diagnostic and therapeutical process

Role of the pediatrician oncologist (2)

- He will be asked to perform a diagnostic lumbar puncture and bone marrow aspirate only in the case of locally advanced disease (eye)

- In particular: the diagnostic lumbar puncture is indicated in patients with:
  - extended eye involvement (group D and E)
  - involvement of the optic nerve shown at ophthalmoscopic examination or with MRI
  - involvement of the brain shown with MRI
  - Known or suspected "trilateral" RB with MRI

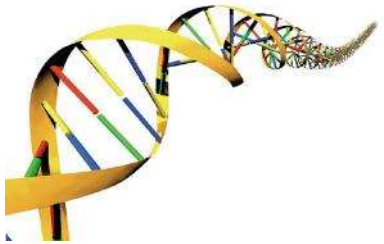


Role of the pediatrician oncologist (3)

- Bone marrow aspiration is indicated in patients with:
  - extended eye involvement (group D and E)
  - Known or suspected bone marrow infiltration (peripheral cytopenia)
  - Known or suspected orbital or organ location

- In all these cases must be evaluated the indication to perform also bone marrow biopsy and/or bone scintigraphy and/or Rx skeleton.
- Bone marrow biopsy, bone scintigraphy and X-ray skeleton are reserved for specific cases identified on the basis of clinical and instrumental suspected metastatic disease

Role of the geneticist



- Genetic counseling is a communication process, guided by the clinical geneticist, through which patients with a genetically determined disease and their families receive information:

the characteristics of the disease

methods of transmission

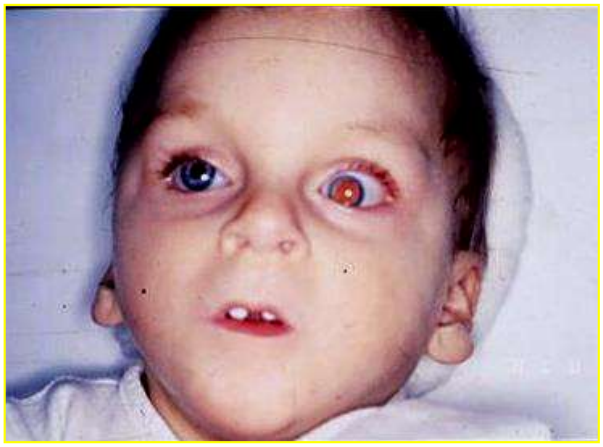
the risk of recurrence and possible therapies

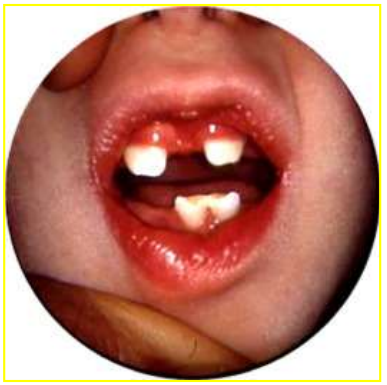
reproductive options

- In the context of genetic counseling are acquired information about personal and family history and a thorough clinical evaluation is carried out, aimed at highlighting signs suggestive of a syndromic classification of the condition.

- The 13q deletion syndrome may manifested by several phenotypic abnormalities. Many patients have minimal or no visible abnormality.[1]

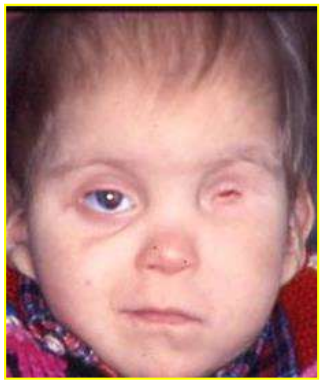
Microcephaly
Broad prominent nasal bridge
Hypertelorism
Microphthalmos
Epicanthus
Ptosis
Protruding upper incisors
Micrognathia
Short neck with lateral folds
Large prominent low set ears
Facial asymmetry
Imperforate anus
Genital malformations
Perineal fistula
Hypoplastic or absent thumbs
Toe abnormalities
Psychomotor and mental retardation.[2-4]

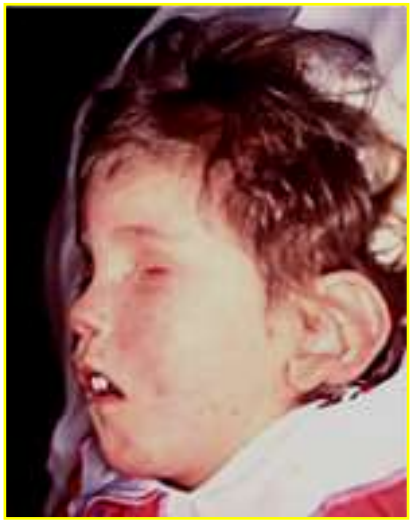




The midface of patients with 13q deletion are notable for:

Prominent eyebrows
Proad nasal bridge
Bulbous tipped nose
Large mouth
Thin upper lip [4-6]



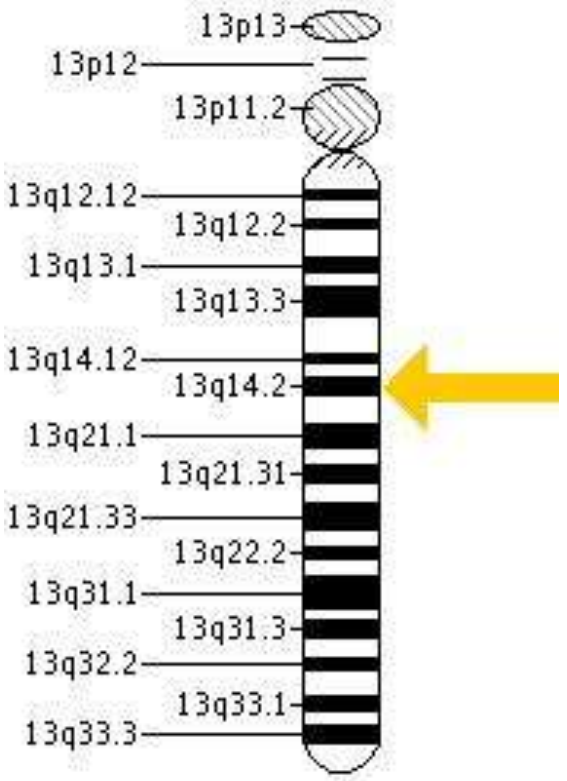


1. Knudson AG, Meadows AT, Nichols WW et al: Chromosomal deletion in retinoblastoma. N Engl J Med 295:1120, 1976
2. Allderdice PW, Da[illegible]IG, Miller OJ et al: The 13q- deletion syndrome. Am J Hum Genet 21:499, 1969
3. Niebuhr E, Ottosen J: Ring ch[illegible]ome D(13) associated with multiple congenital malformations. Ann Genet 16:157, 1973
4. Seidman DJ, Shields JA, Augsburger JJ e[illegible]diagnosis of retinoblastoma based on dysmorphic features and karyotype analysis. Ophthalmology 94:663, 1987
5. Keith CG, Webb GC: Retinoblastoma and retinoma [illegible]a child with a translocation and deletion of the long arm of chromosome 13. Arch Ophthalmol 103:941, 1985
6. Montegi T, Kaga M, Yanagawa Y: A recognizable pattern of th[illegible]tinoblastoma patients with interstitial deletion of 13q. Hum Genet 64:160, 1983

Role of the geneticist (2)

- Molecular analysis for the detection of point mutations and deletions in the gene RB1

- In patients with facial phenotype due to 13q14 deletion syndrome, the investigation of choice is the array-CGH

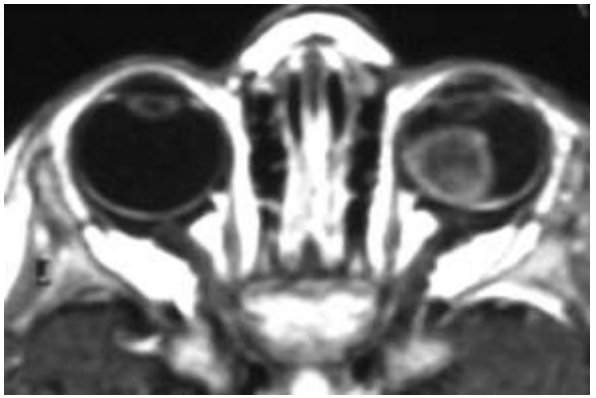


Role of the neuroradiologist

- MRI is currently the diagnostic investigation of choice.

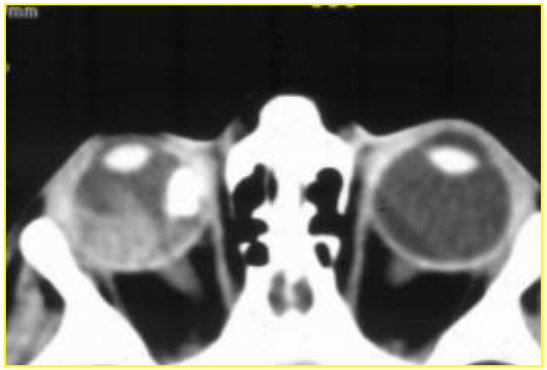
  The CT method is less sensitive and involving exposure to radiation, is reserved only for rare cases of uncertainty in the differential diagnosis between RB and simulating lesions.

- The MRI study is always necessary in cases potentially treatable with conservative therapy (considering the absence of any histological documentation and not being feasible a biopsy of the lesion, due to the risk of tumor dissemination).



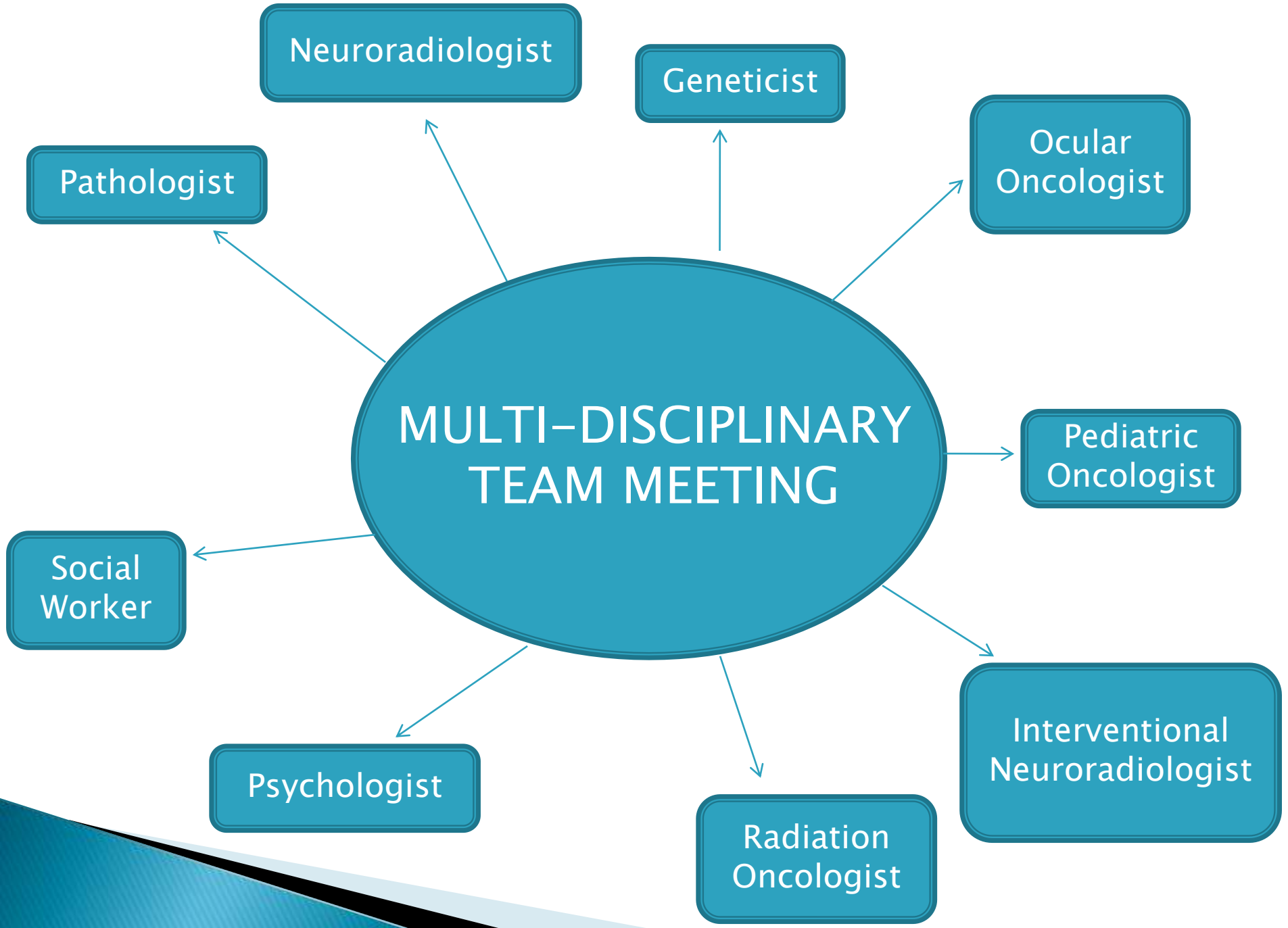
MRI allows us to:

- Differential Diagnosis
- Risk factors for dissemination
- Clinical findings
- Possible extension
- “Trilateral" RB.



de Graaf P, Göricke S, Rodjan , Galluzzi P, Maeder P, Castelijns JA, Brisse HJ on behalf of the European Retinoblastoma Imaging Collaboration (ERIC). Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol (2012) 42:2–14.

Galluzzi P, Hadjistilianou T, Cerase A, De Francesco S, Toti P, Venturi C. Is CT still useful in the study protocol of retinoblastoma? AJNR Am J Neuroradiol. 2009 Oct;30(9):1760–5. Epub 2009 Jul 17.


MULTI-DISCIPLINARY TEAM MEETING
Neuroradiologist
Geneticist
Ocular Oncologist
Pathologist
Pediatric Oncologist
Social Worker
Interventional Neuroradiologist
Psychologist
Radiation Oncologist

Multi-disciplinary team meeting (MTM)

A correct therapeutic path requires:

- Correct staging
- Assessment of risks associated with neoplasia
- Selection of eyes with good prospects for success of conservative therapy
- Evaluation of the risk/benefit ratio associated with treatment
- Choosing the best conservative therapy with less morbidity
- Careful and prolonged follow-up

Early Hum Dev. 2010 Oct;86(10):619-25.
Retinoblastoma - current treatment and future direction.
Parulekar MV.
Source
Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, United Kingdom. manojparulekar@aol.com

Multi-disciplinary team meeting (MTM)

At the end:

MTM

Propose tailored-patient therapy

JPH - Year 7, Volume 6, Number 4, 2009

ITALIAN JOURNAL OF PUBLIC HEALTH

The Italian approach to rare diseases and the action of the Italian National Centre for Rare Diseases

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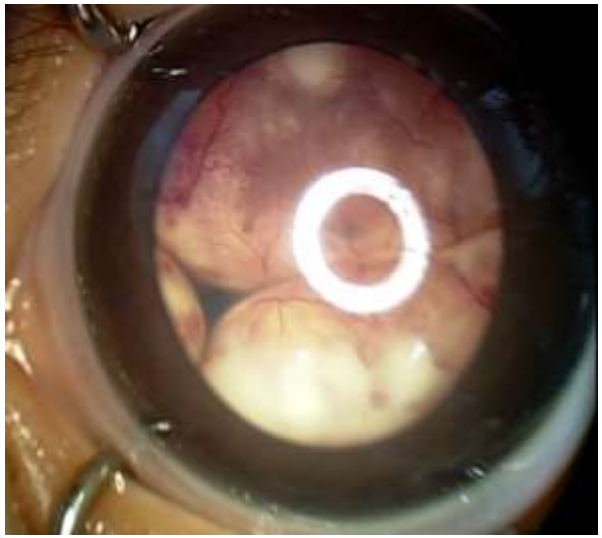
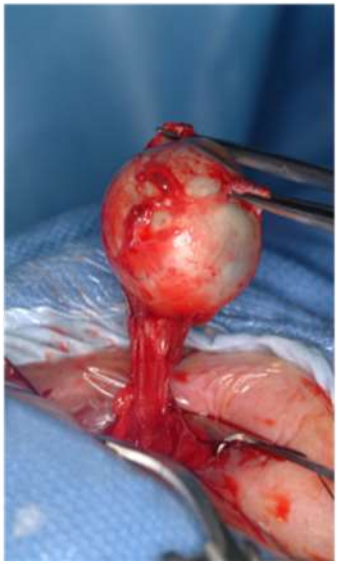
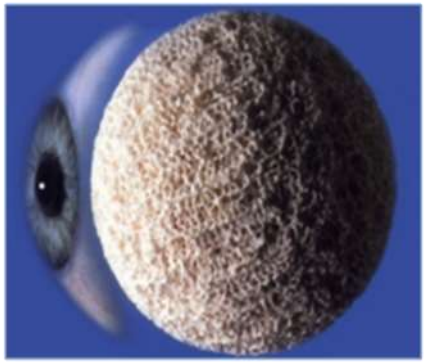
To facilitate referral of suspected patients to the appropriate diagnostic Centre, to waive costs for diagnostic tests and to speed up assistance of patients with confirmed diagnoses.

Demolitive therapy

- Enucleation is proposed at diagnosis, in the presence of extremely advanced disease, or subsequently after unsuccessful attempts of conservative treatment







Conservative treatments

- Focal treatments
  - Argon laser photocoagulation
  - Cryotherapy
  - Thermotherapy
  - Trans-pupil thermo-chemotherapy
  - Application of plaques with ^{125}I or ^{106}Ru
- Chemotherapy
  - Systemic +
    - Argon laser
    - Cryotherapy
    - Thermotherapy
  - Local
    - •subconjunctival
    - •intravitreal
  - Intrarterial
- External beam radiotherapy

Conservative treatments can be envisaged only if they do not expose the patient to an increased risk for life

PROTOCOLS AND DRUGS

1. CE: carboplatino + etoposide
2. VEC: vincristina + carboplatino + etoposide
3. ICE: ifosfamide + carboplatino + etoposide

FOLLOW-UP

- Especially during and after conservative therapy, clinical and instrumental follow-up must be very close, according to a specific program, sometimes individualized.

- Even after enucleation checks must be frequent. Ophthalmologic follow-up is planned for at least 10 years, on case by case basis intervals. Clinical follow up is recommended for all life long, on case by case basis intervals.

FOLLOW UP DEL RB AVVIATO A ENUCLEAZIONE				
Età	***Visita Oculistica***	***Valutazione visus***	***RMN***	***Visita Oncologo***
0-12 mesi	Ogni mese		Ogni 6 mesi	Ad ogni valutazione oftalmoscopica
12-24 mesi	Ogni 2 mesi		Ogni 6 mesi	Ad ogni valutazione oftalmoscopica
24-36 mesi	Ogni 3 mesi	Ogni 6 mesi	Su indicazione clinica	Ad ogni valutazione oftalmoscopica
4° anno	Ogni 6 mesi, non narcosi	Ogni 6 mesi	Su indicazione clinica	1 volta anno
5° anno	Ogni 6 mesi, non narcosi	Ogni 6 mesi	Su indicazione clinica	1 volta anno

FOLLOW UP DEL RB AVVIATO AD ENUCLEAZIONE + CHT						
Età	***Visita Oculistica***	***Valutazione visus***	***RMN***	***Visita Oncologo***	***Funzionalità renale***	***Audiometria***
0-12 mesi	Ogni mese	Ogni 6 mesi	Ogni 6 mesi	Ad ogni valutazione oftalmoscopica	Ogni 6 mesi	1 volta anno
12-24 mesi	Ogni 3 mesi	Ogni 6 mesi	Ogni 6 mesi	Ad ogni valutazione oftalmoscopica	Ogni 6 mesi	1 volta anno
24-36 mesi	Ogni 3 mesi	Ogni 6 mesi	Su indicazione clinica	Ad ogni valutazione oftalmoscopica	1 volta anno	1 volta anno
4° anno	Ogni 6 mesi, non narcosi	Ogni 6 mesi	Su indicazione clinica	Ad ogni valutazione oftalmoscopica	1 volta anno	1 volta anno
5° anno	Ogni 6 mesi, non narcosi	Ogni 6 mesi	Su indicazione clinica	Ad ogni valutazione oftalmoscopica	1 volta anno	1 volta anno

FOLLOW UP DEL RB AVVIATO A TRATTAMENTO CONSERVATIVO						
Età	***Ret-Cam***	***Valutazione visus***	***RMN***	***Visita Oncologo***	***Funzionalità renale***	***Audiometria***
0-12 mesi	Ogni mese		Ogni 6 mesi	Su indicazione clinica	Ogni 6 mesi	1 volta anno
12-24 mesi	Ogni 2 mesi	Ogni 6 mesi	Ogni 6 mesi	Su indicazione clinica	Ogni 6 mesi	1 volta anno
24-36 mesi	Ogni 3 mesi	Ogni 6 mesi	Su indicazione clinica	Su indicazione clinica	1 volta anno	1 volta anno
4° anno	Ogni 6 mesi	Ogni 6 mesi	Su indicazione clinica	Su indicazione clinica	1 volta anno	1 volta anno
5° anno	Ogni 6 mesi	[illegible] mesi	Su indicazione clinica	Su indicazione clinica	1 volta anno	1 volta anno

The 4th step

Our victory is the victory of the child

CONCLUSIONS

- A quick and correct diagnosis
- Direct your child to the tertiary referral center for Retinoblastoma
- Centralize the cases in order to obtain the best quality of care for children

Grazie per l'attenzione