What is Retinoblastoma?

A Guide for Parents of Children Receiving Treatment for Retinoblastoma at St. Jude Children’s Research Hospital
Welcome

We created this resource booklet to help you better understand your child’s disease. It includes details about the eye, retinoblastoma, and current treatments. It also introduces medical language that is often used when talking about this disease. Because the booklet is designed to serve as a reference for all of our patient families, some of the information may not apply to your child’s condition. If you have questions as you read, please feel free to ask. We feel strongly that the more you know about your child’s disease, the fewer concerns you will have during treatment.

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What is retinoblastoma?

Retinoblastoma is a rare cancer that occurs in one or both eyes of a child. It is caused by a genetic defect in the retina. During the first few years of life, the eye grows rapidly. Sometimes during this rapid growth period, cells within the eye can divide in an abnormal way. This is how the disease begins to develop.

In the United States, 300 new cases occur each year. It affects one of every 15,000 to 17,000 children. Worldwide, there are 5,000 new cases per year. The average age when children are found to have retinoblastoma is 18 months. Most often, it is found before age 3. It is rare to find this disease in a child past age 5.

Parts of the eye

The 4 bony walls that surround the eye make up the **orbit**. It is commonly called the eye socket. The **eyelids** protect the eye and provide an opening for light to enter the eye. The **conjunctiva** is a clear mucous membrane that covers the surfaces of the eye and the eyelids. The **cornea** is the clear front part of the eye through which light enters. The light then passes through the **pupil**, a hole in the colored part of the eye, which is called the **iris**. Then the light passes through the **crystalline lens**, where it is bent and focused on the **retina** in the back of the eye. The retina transforms the light into nerve impulses that are sent to the brain. Between the lens and the retina is the **vitreous cavity**. It contains a jelly-like substance (vitreous) that nourishes the eye and helps the eye maintain its shape. The retina has many layers of cells. The deepest layer contains **photoreceptor cells** that absorb light. These two layers nourish the retina and absorb excess light. The light gathered by the retina is sent to the brain by the **optic nerve**. The **sclera**, or white of the eye, is a tough fibrous layer that protects the contents of the inner eye.
<table>
<thead>
<tr>
<th>Hereditary disease</th>
<th>Unilateral sporadic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child is born with an abnormal retinoblastoma gene that is inherited from one parent or, in most cases, that is mutated shortly after conception.</td>
<td>Both copies of the retinoblastoma gene are lost in a single cell within the eye.</td>
</tr>
<tr>
<td>Every cell in the body is missing one of its pair of retinoblastoma genes.</td>
<td>The tumor cells are the only cells in the body without the retinoblastoma gene.</td>
</tr>
<tr>
<td>Because only one of the two retinoblastoma genes in each cell is normal, a single, random mutation is all that is required for the disease to develop.</td>
<td>To develop unilateral sporadic disease, both copies of the retinoblastoma gene in a single cell must be mutated. This rarely occurs.</td>
</tr>
<tr>
<td>40% of children with retinoblastoma have the hereditary form of the disease.</td>
<td>60% of children with retinoblastoma have the unilateral sporadic form of the disease.</td>
</tr>
<tr>
<td>Typically, multiple tumors in one or both eyes</td>
<td>Single tumor affecting only one eye</td>
</tr>
<tr>
<td>Child at risk for developing second tumors</td>
<td>No risk for developing second tumors</td>
</tr>
<tr>
<td>Diagnosed by age 1</td>
<td>Diagnosed nearer age 2</td>
</tr>
<tr>
<td>Parents with the abnormal retinoblastoma gene have</td>
<td>Parents of a child with unilateral sporadic retinoblastoma have</td>
</tr>
<tr>
<td>50% chance of passing the abnormal gene to their children</td>
<td>Less than 1% chance of having a second child with the disease</td>
</tr>
<tr>
<td>90% chance that their child who inherits the gene will develop retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>Each child of a parent with an abnormal retinoblastoma gene has a</td>
<td>A child with unilateral sporadic disease</td>
</tr>
<tr>
<td>45% chance of having the disease</td>
<td>Is generally the only person in the family with the disease</td>
</tr>
<tr>
<td>45% chance of later parenting a child who will have the disease</td>
<td>Has a 4% chance of later parenting a child with the disease</td>
</tr>
</tbody>
</table>

**Genetics**

The retinoblastoma gene is a specific tumor suppressor gene. Every cell in the body has one pair of these genes. A tumor suppressor gene encodes a protein that controls cell division. When the gene is not active, cells can divide out of control.

Retinoblastoma occurs when the retinoblastoma gene does not make the protein that controls cell division. This causes the photoreceptor cells in the retina to multiply too rapidly and form a tumor.

Both of the retinoblastoma genes within a retinal cell must be lost or altered for that cell to become a cancer cell.

There are two forms of retinoblastoma—hereditary (runs in the family) and sporadic. Sometimes it is not clear which form of the disease a patient has. Doctors might use a genetic test to see if the disease is hereditary or sporadic.
**Signs and symptoms**

If your child has one or more of the following symptoms, you should plan a visit to the ophthalmologist right away. This doctor will dilate the child’s eyes and examine them to detect signs of retinoblastoma or another eye disease. Although the symptoms below are common in retinoblastoma, they also are common symptoms for other eye diseases.

The most common sign of retinoblastoma is a white pupil, called *leukocoria*. It is caused by light reflected off the white tumor rather than the retina. The white reflex, as doctors call it, might be seen in only one direction of gaze or under dim lighting, when the pupil is wide open. Often, leukocoria can be seen in photos.

The diseased eye of a child with retinoblastoma also may become red and painful. As the tumor grows, new blood vessels may form on the front surface of the iris. This can change the color of the iris—a condition called *heterochromia*.

**Strabismus**, a misalignment of the eyes, is the second most common sign of retinoblastoma. As a tumor grows in a child’s eye, it can interfere with the eye’s vision. As a result, there is no stimulus for the brain to hold the eyes together in alignment. So, the diseased eye turns inward or outward.
Esotropia (cross-eyed) is a term used to describe eyes that turn inward.

Exotropia (lazy eye) is a term used to describe eyes that turn outward.

In patients with advanced disease, the body may mount a defense against the tumor. The eyelids may become red and swollen, and the eye may protrude from the orbit. This can mimic an infection in the orbit.
Diagnosis

Most tumors are diagnosed (named) when a doctor looks at a sample with a microscope. That sample of tissue is removed from the tumor during a biopsy. However, in the case of retinoblastoma, a biopsy would require a doctor to insert a needle into the eye. This would risk tumor cells spreading out of the eye into the orbit. Therefore, we must rely on a doctor’s exam and other tests to diagnose the disease.

We can perform a limited exam in the office to catch a glimpse of the tumor and to confirm the referring doctor’s diagnosis. However, your child will need a more detailed exam, and it must be done in the operating room with your child asleep.

During your child’s exam under anesthesia (EUA), an ocular oncologist measures the corneal diameters and the pressure inside the eyeball. This eye tumor specialist looks for differences between eyes and for blood vessels on the surface of the iris that normally would be absent.

The doctor examines the tumor in the retina looking for signs of calcium, dilated (enlarged) blood vessels, parts of the retina that have detached, and overlying vitreous seeds. These seeds are small pieces of tumor that have broken free from the main tumor mass and are floating in the vitreous jelly. It is very important to search for small tumors on the edges of the retina that have not been seen in earlier exams. The presence or absence of these small tumors can tell us whether your child has the sporadic or hereditary form of the disease. This knowledge helps us decide which treatments your child should receive.

Intravenous fluorescein angiography (IVFA) involves an orange dye that is injected into a vein in your child’s arm. The dye travels through the bloodstream and allows us to study the blood supply of the eye. The RetCam© can trace the flow of dye through the retina. In doing so, it highlights the blood vessels in great detail. Being able to clearly see the vessels serves two purposes. Tumors require blood to survive, and a decreased number of blood vessels
in the tumor shows that a tumor is responding to treatment. Also, being able to trace blood flow through the back of the eye may help us to better predict how well your child will be able to see after treatment. After having an IVFA procedure, your child’s skin and urine may have an orange hue (tint) for about 24 hours.

_Ultrasonography_ uses sound waves to create an image of your child’s eye. Sound moves at different speeds through different types of tissue. Some types of tissue reflect sound. In the eye, ultrasound images highlight distinct areas of calcium within a tumor. Ultrasound images also allow us to measure the tumor. Some ultrasound machines are equipped with Doppler, a device that detects motion. These machines allow us to study the blood flow within each tumor. The doctor who first found your child’s tumor may have done an ultrasound, but most likely, St. Jude doctors will want to do the test again.

_Computed tomography (CT)_ imaging uses a computer to collect X-ray information from a given plane (layer) in the eye. It can produce a cross-sectional view of that area. CT also shows distinct areas of calcium in a tumor.

_Magnetic resonance imaging (MRI)_ uses magnets and electrical fields to distinguish normal from abnormal tissue. It also provides cross-sectional views of the area examined.

CT imaging is best for highlighting calcium deposits in the eye. MRI allows us to see soft tissues better, such as blood vessels. Together the 2 types of images give us a better view of the eye and the disease.

Either CT imaging or MRI can be used to study the optic nerve behind the eye. If this nerve is larger than normal, the tumor might have spread there. These scans also can help us study the brain to make sure no tumor has spread there.

6_{\}XQ\_RO7F3“KZONKTS\_VXXMXO3E ^MK\_N\_MY\_PA\_UN!}_ may perform a lumbar puncture (spinal tap), to obtain cerebrospinal fluid (CSF) for study. During a lumbar puncture, the doctor places a needle into the lower portion of the back to remove a sample of CSF from the spine. Pathologists (doctors who study cells) use a microscope to look for tumor cells in the sample. If they find tumor cells, we would know that the tumor has spread beyond the eye to the brain or spinal cord.

Also, a doctor may remove a bone marrow sample (aspirate) from your child’s hip with a needle. A pathologist would look at the sample under a microscope. If this doctor found tumor cells, we would know that the cancer cells have spread outside the eye to the bone marrow.
Reese-Ellsworth classification

**Group I: very favorable**
- a. solitary tumor, less than 4 dd\(^2\) in size, at or behind the equator\(^3\)
- b. multiple tumors, 4–10 dd in size, all at or behind the equator

**Group II: favorable**
- a. solitary tumor, 4–10 dd in size, at or behind the equator
- b. multiple tumors, 4–10 dd in size, behind the equator

**Group III: doubtful**
- a. any lesion anterior to the equator
- b. solitary tumor larger than 10 dd behind the equator

**Group IV: unfavorable**
- a. multiple tumors, some larger than 10 dd
- b. any lesion extending to the ora serrata\(^4\)

**Group V: very unfavorable**
- a. massive tumors involving over half the retina
- b. vitreous seeding

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Grading and staging

We grade how severe the eye disease is using the Reese-Ellsworth and the International classification systems. The Reese-Ellsworth system is named after two pioneers in the study of retinoblastoma.

Grading the diseased eye helps to predict how likely it is that the eye can be saved. Each eye is graded separately.

How much the cancer has progressed within the body is recorded using a staging system. The TNM system is used to stage most cancers. The TNM system defines the size of the primary tumor (T), the involvement of the lymph nodes (N), and the presence of metastatic (M) disease (cancer that has spread into other parts of the body from the first location).

Retinoblastoma does not have a TNM staging system that is accepted by all doctors. However, Charles Pratt, MD, a St. Jude pediatric oncologist, developed the staging system used by our hospital. It is based on the TNM system.

The Reese-Ellsworth and the International classifications of your child’s eye and the staging of your child’s cancer will determine the treatment options that we can offer.

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\(^1\)The heading for each classification refers to the likelihood that the eye can be saved.

\(^2\)dd = disk diameter; the optic disk measures approximately 1.25 mm in diameter.

\(^3\)The equator of the eye is an imaginary line around the circumference and through its center that divides the eye into anterior (front) and posterior (back) halves.

\(^4\)The ora serrata is the serrated edge of the retina and is located in the front portion of the eye.

Treatment

A variety of therapies, including chemotherapy, cryotherapy (freezing the tumor), laser therapy (light that produces heat), and radiation therapy, may be used to treat your child’s cancer. Each type of treatment can be used alone or combined with one or more of the others. Enucleation (removal of the eye) will be performed only if other therapies do not work well or will not work well on your child’s tumor.

Chemotherapy

- Chemotherapy, often called “chemo,” is treatment that uses medicine (drugs) to kill cancer cells.
- This medicine can be given in a vein, by mouth, or by local injection (a shot).
- Chemotherapy may be used alone or combined with other types of therapy.
- The pediatric oncologist chooses certain drugs based on whether the tumor is confined to the eye or has spread outside the eye into the orbit or to another part of the body.
- We have found that using chemotherapy as a primary treatment for retinoblastoma inside the eye helps preserve both the eye and vision.
- Most often, chemotherapy is followed by other treatments, such as cryotherapy, laser therapy, and radiation. These therapies are described below.

Cryotherapy

For retinoblastoma patients, cryotherapy involves placing a tissue freezing probe directly on the outside of the eye overlying a tumor. The freezing treatment extends throughout the sclera to encompass the tumor that forms freezes the tumor cells and causes them to rupture. This treatment is done in an operating room while the patient is asleep. Most often the treatment has to be repeated many times to destroy all of the cancer cells. Cryotherapy causes the eyes and eyelids to swell for 1 to 5 days. Some children have so much swelling that they are unable to open their eyelids for a few days. The doctor will prescribe eye drops or ointment to reduce the swelling. This treatment usually does not cause any long term damage to the eyes or eyelids. Patient parents often react to the painful way the child looks after treatment more than the child reacts.
Laser therapy

Two different types of lasers are used to treat retinoblastoma. They work by focusing different wavelengths of light on the affected areas to produce heat.

Doctors focus the blue-green light of argon lasers around small tumors to create an overlapping ring of pinpoint burns. These burns deprive the tumor of its blood supply, which kills it.

Doctors use the heat produced by the infrared light of the diode laser to kill cells in small- to medium-sized tumors inside the eye.

Radiation

Radiation uses invisible rays (made of energy particles) to treat cancer. The radiation disrupts the DNA inside the cancer cells and destroys them. The radiation can be applied to a tumor within the eye in 2 ways:

Episcleral plaques are small gold disks (1 to 2 centimeters wide). In surgery, a plaque is applied to the outside of the eye to deliver radiation to a tumor inside the eye. Each plaque contains a radioactive source placed in such a way that it will deliver the prescribed dose of radiation only where it is needed. The radiation is directed inside the eye, and the gold lining shields the healthy tissues from exposure. Another surgery is needed to remove the plaque.

External beam radiation treats the entire eye with radiation and is a useful treatment for advanced disease inside the eyes. Reese and Ellsworth based their classification scheme on their extensive experience with external beam radiation. This type of radiation therapy can slow or stop the normal growth of the eye and the orbit. For this reason, we only use it to treat advanced disease that has not responded well to other treatments. In recent years, we have used chemotherapy to avoid or delay using beam radiation. By delaying, we allow the orbit to develop more fully. In patients with the hereditary form of the disease, beam radiation increases the risk of second tumors forming. Even so, this type of therapy still plays a crucial role in the treatment of retinoblastoma.

A radiation oncologist gives external beam treatments in small doses each day (Monday through Friday). On average, a patient would receive 20 treatments over a 4 week period. One (1) or both eyes may be treated. The radiation is directed toward the eyes, and there are few, if any, side effects right away. Sometimes, it can cause a mild “sunburn” around the eyes, but it goes away after treatment.

Further treatments

Depending on the location of the tumor and the treatment that has been given, your child may need further therapy to preserve as much vision as possible.

Patching. Patching is used to treat lazy eye. The good eye is covered with a patch, which forces the child to use the lazy eye. In turn, the lazy eye becomes stronger, and visual sharpness im-
proves. As vision improves in the lazy eye, the brain attempts to keep the eyes aligned and to prevent the lazy eye from drifting in or out. If needed, surgery can help straighten the eyes.

_Cataract surgery._ Radiation can cause the crystalline lens to become cloudy. The cloudy lens is referred to as a cataract. After the tumor is destroyed, we can remove the cataract and implant an artificial lens. There might be some waiting time, because the cataract should be fully developed before it is removed. Removing the cloudy lens will improve the child’s vision.

_Laser therapy._ Radiation also can damage the blood vessels in the back of the eye. These blood vessels may leak fluid into the retina. That fluid can distort vision. The argon laser can be used to stop this leakage, so vision improves. Radiation therapy may cause blood vessels to become blocked, and this can reduce blood flow in the retina. As the eye attempts to repair itself, new blood vessels grow on the surface of the retina. These blood vessels may break and bleed or cause parts of the retina to detach. The argon laser can be used to treat these blood vessels by preventing their growth.

**Enucleation**

Enucleation, or removal of the eye, provides a complete cure for patients whose disease is confined to the eye. Most often we suggest this for patients with the sporadic form of the disease, when it is only in one eye. We try to limit its use to times when the disease is advanced and there is little hope for preserving useful vision. Enucleation also is used to prevent the spread of a tumor outside the eye when we have not been able to control the tumor’s growth using other forms of treatment.

1. _Adjuvant therapy for high-risk disease._ When we remove an eye, pathologists examine the eye under the microscope. They look for certain features that would suggest that the tumor has spread outside the eye. For example, when a tumor invades the deep layers of the choroid or the front of the eye, there is an increased risk that it has spread further. To prevent further spreading, we give chemotherapy by vein to kill any cell that might have escaped from the eye before its removal.

1. _Replacing the enucleated eye._ When we remove an eye, we isolate the muscles that move the eye and attach them to a round ball. We then bury the ball in the orbit beneath the tissues that normally cover the eye. This is called a deep orbital implant. The healed socket is pink and looks similar to the lining of the mouth. In most cases, 6 to 8 weeks after the eye is removed, the child will be fitted with a false eye. It fits over the implant like a large contact lens and moves with it, making it look like a natural eye.

*Top: Patient with a false eye fitted over an orbital implant
Bottom: Deep orbital implant*
biopsy
• a small piece of tissue is taken out of the body and looked at under a microscope to see if there are any cancer cells or other disease cells.

bone marrow aspirate
• a sample of bone marrow is taken from the hip with a hollow needle, then looked at under a microscope to see if tumor cells have spread outside the eye to the bone marrow.

cataract
• clouding of the crystalline lens

chemotherapy
• the use of medicine (drugs) to kill cancer cells

choroid
• pigmented layer of blood vessels under the retina that nourish the retina and absorb excess light

computed tomography (CT)
• computer to collect X-ray information from a given plane (layer) to produce a cross-sectional view of that area; for eye tumor patients it is used to look for calcium in the eye

cornea
• the clear, front part of the eye through which light enters the eye

cryotherapy
• treatment of a tumor by freezing it, which causes the tumor cells to rupture

crystalline lens
• the “lens” in the eye where entering light is bent and focused on the retina

enucleation
• removal of the eye

episcleral plaque
• a small gold disk (1 to 2 centimeters wide); applied in surgery to the outside of the eye to deliver radiation to a tumor inside the eye

esotropia
• a condition in which the eyes turn inward, “cross-eyed”

exam under anesthesia (EUA)
• exam performed while a patient is asleep; allows the doctor to do a more detailed exam than a limited office exam when the patient is awake

esotropia
• a condition in which the eyes turn inward, “cross-eyed”

external beam radiation
• invisible rays from a machine to kill cancer cells inside the entire eye

eyelids
• protect the eye and provide an opening for light to enter the eye

glaucoma
• a condition of increased pressure inside the eye

genotype
• the genetic material that determines the function and structure of the eye

hemorrhage
• a pooling of blood

heterochromia
• a difference in the color between the two eyes

intravenous fluorescein angiography (IVFA)
• orange dye is injected into the bloodstream so doctors can see the blood supply in the eye

iris
• the colored part of the eye

laser therapy
• treatment of cancer using various wavelengths of light to produce heat

leukocoria
• a pupil that appears white

lumbar puncture
• also called a spinal tap; a needle is placed into the lower portion of the back to remove a sample of cerebrospinal fluid (CSF) from the spine

magnetic resonance imaging (MRI)
• imaging that uses magnets and electrical fields to distinguish normal from abnormal tissue; provides cross-sectional views of the area examined

metastasis
• spread of cancer from its primary location to other parts of the body

ocular oncologist
• a doctor who finds and treats cancer of the eye

optic nerve
• the nerve that transmits (sends) the light gathered by the retina to the brain

orbit
• the cavity formed by the 4 bony walls that surround the eye

photoreceptor cells
• the deepest layer of cells in the retina that gather light

pupil
• the hole in the iris through which light passes into the eye

retina
• the layer of cells in the back of the eye where light is focused and turned into nerve impulses that are sent to the brain

retinal pigment epithelium
• layer of cells underlying the retina that nourish the retina and absorb excess light

sclera
• white of the eye; a tough fibrous layer that protects the contents of the inner eye

strabismus
• when the eyes are not aligned, includes esotropia and exotropia

ultrasonography
• also called “ultrasound”; the use of sound waves to create an image

vitreous
• a jelly-like substance that nourishes the eye and helps the eye maintain its shape

vitreous cavity
• the area between the lens and the retina that contains the vitreous jelly

vitreous seeds
• small pieces of tumor that have broken free from the main tumor mass and are floating in the vitreous jelly
Thank you

We hope this booklet is useful for you and that you will turn to its pages during and after the course of your child’s treatment at St. Jude Children’s Research Hospital. Each patient at St. Jude receives care tailored to that child. Your child’s treatment plan (protocol) may differ from another patient with the same diagnosis. Of course, you still may have more questions about your child’s care. We encourage you to ask the treatment team as many questions as you like.

Your child’s eye care does not end when you leave St. Jude. Your child will need regular exams by the pediatric oncologist and ophthalmologist after the eye cancer is cured. These exams are needed to ensure your child’s well-being and healthy visual development. They also will allow us to detect new cancers early. As they grow older, children with the hereditary form of retinoblastoma are at risk for second tumors, including tumors that occur elsewhere in the body. Your child also may need services for low vision problems. Contact your local state agencies to find out what resources might be offered to help your child.

We thank you for the trust that you have placed in us by allowing us to care for your child. With your ongoing help and support, we will make every effort to provide the best care possible for your child.
About St. Jude Children’s Research Hospital

St. Jude Children’s Research Hospital is one of the world’s premier biomedical research centers. The hospital’s mission is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment. Dramatic progress has been made at St. Jude since its founding more than 40 years ago. Thousands of children are living today who could not have survived the same diseases a generation ago.

Doctors refer children and teens to St. Jude if they are found to have diseases that are under study by the St. Jude staff. About 4,700 patients are seen at St. Jude each year. Most are treated as outpatients as part of ongoing research programs. The hospital also maintains 60 beds for patients who require inpatient treatment. To date, children from across the United States and from 76 countries worldwide have been treated at St. Jude.

Although it was named in honor of St. Jude Thaddeus, the patron saint of the hopeless and of children, St. Jude is a nonsectarian center. Any child who meets the medical requirements for admission may be treated, without regard for religious beliefs, race, or ability to pay. The hospital’s fund-raising arm, ALSAC, covers all costs of treatment and support care at St. Jude that are not paid for by health insurance. ALSAC also pays all treatment costs at St. Jude for patient families who do not have health insurance.

Your child’s care team is a group of dedicated health care professionals, including ocular, pediatric, and radiation oncologists supported by nursing staff, ophthalmic technicians, and radiology technicians. These staff members devise and carry out your child’s treatment plan and provide expert care. The number of names and faces may seem overwhelming at first, so we encourage you to write down names. You also may find support from other St. Jude families who have children in current treatment or who have finished treatment. These families have faced many of your same concerns.
Helpful links

Eye Cancer

EyeCancer Network – www.eye cancer.com

Retinoblastoma at St. Jude Children’s Research Hospital –
www.stjude.org/solid-tumor/0,2533,425_5288,00.html
www.stjude.org/search/0,2616,582_3161_16742,00.html


American Association for Cancer Research – www.aacr.org

CureSearch – www.curesearch.org/index.aspx

www.curesearch.org/resources/resource.aspx?ServiceId=1

Cure4Kids – www.cure4kids.org

RB online support group – e-mail: R-BLASTOMA@LISTSERV.ACOR.ORG

Help for Patients

Angel Flight America – www.angelflightamerica.org

Angel Flight South Central – www.angelflightsc.org
Notes

Ocular oncologist: ________________________________________________

Onconologist: ________________________________________________

Eye Clinic: ________________________________________________

D Clinic: ________________________________________________

Ocularist: ________________________________________________

Nurse practitioner: ________________________________________________

Medical record number: ________________________________________________

Travel Office: ________________________________________________

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