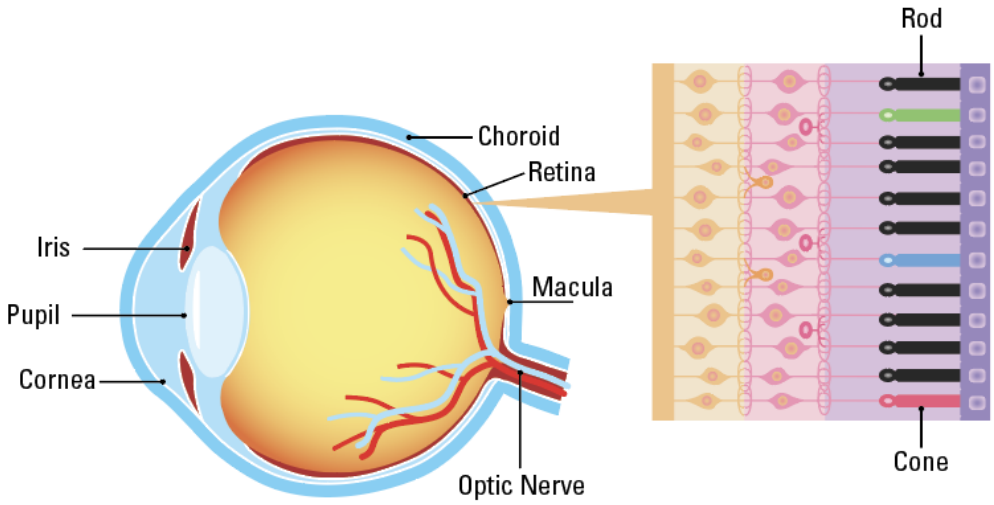
Inherited Retinal Disease (IRD)

Inherited retinal diseases (IRDs) affect millions of people worldwide, causing loss of vision in adults and children alike. In Australia, for example, one in every 1500 children is born with an inherited retinal disease.

IRDs are caused by small detrimental changes in DNA that most often cause an incorrect protein to be supplied to the retina. Over time this causes photoreceptor cells to die, and this leads to progressive loss of vision. Other rarer inherited retinal diseases also affect more than the eye - for example Usher Syndrome, which affects hearing as well as sight.

These genetic anomalies are inherited but they don't cause disease in every person who carries the genetic change. An individual may inherit a genetic anomaly from a parent or pass it down to their own children, completely unaware of this silent genetic predisposition until a family member is diagnosed with an inherited retinal disease.

What are Inherited Retinal Diseases (IRDs)?



Inherited retinal diseases — or IRDs — are a group of diseases that can cause severe vision loss or even blindness. Each IRD is caused by at least one gene that is not working as it should. IRDs can affect individuals of all ages, can progress at different rates, and are rare. However, many are degenerative, which means that the symptoms of the disease will get worse over time.

Why is Genetic Testing Important?

Identifying the genetic cause of disease is an important part of care for patients with IRDs. Many times, the exact type of IRD a person has can be difficult to determine based only on tests conducted in the eye doctor's office. Results from genetic testing will improve the ability of the doctor to provide a precise diagnosis.

This will

- guide potential treatment of patients,
- inform them about the potential risk of disease to other family members, and
- identify the potential risk to other organs in the patient's body that may be affected.

In the case of infants and young children, genetic testing will identify those children who are at risk of other health problems and who will benefit from early diagnosis and therapy.

The health care provider will order the genetic test, collect the sample, and review the results with the patient. The health care provider may also include a genetic counselor to guide the patient and their family through the results of the genetic testing, discuss the impact on other family members, and guide couples in future family planning decisions.

The Relationship Between Vision and Genetics

Recently, researchers have been determining which genes in your DNA are linked to poor vision. As it turns out, genetics plays a large role in many eye diseases and conditions occurring in children and adults.

The Strong Connection between Genetics and Vision

The genetics of IRDs is very unusual insofar as 75-85% of IRD can be linked to genetic changes in the genome. The genetic component of IRDs is much much higher than in other common diseases such as heart disease, diabetes or immune disorders. Moreover the explainable genetic component of IRDs is already very high. This means that in ⅔ of patients genetic factors yield direct and immediate benefits to the patient.

Until recently, connecting the genetic signature to a treatable disease required the painstaking work of academic researchers. Pr3vent does the detective work for you. Its co-founder - after more than a decade at the Stanford Genome Technology Center, Roche and IBM Research - has developed state-of-the-art tools that investigate and solve the puzzle for you.

The latest research suggests that genetics plays a primary role in the most common vision problems. For patients with a family history of vision problems, it's important to visit an optometrist for an eye evaluation, even if a patient's eyes are healthy.

Some common, genetically-linked vision problems include:

- Color Blindness
- Myopia

- Hyperopia
- Glaucoma
- Cataracts
- Astigmatism

Whole Genome Sequencing (WGS) and Large-Scale Analysis

However, genetics is too complex a field to simply explain all of your ocular problems. For example: even if your parents have 20/20 vision, you have a higher chance of developing vision problems if your grandparents experienced vision impairments. Conditions could be influenced by multiple genes, but might not depend exclusively on genetic factors, such as strabismus (ocular misalignment).

At least 260 genes are involved in the development of IRDs. Each gene contains many changes that may be detrimental alone or in combination. Fortunately, more often than not genetic information can help identify the disease and improve treatment. However, we do not yet see the full picture. When we look at patients novel changes are discovered all the time and these will have new and sometimes severe effects. WGS has rapidly become a resource for newborn care, and parents are asking for it.

(1) WGS is useful in IRDs because we know enough to use this information wisely;

(2) we know enough to assess the importance and effect of newly discovered changes;

(3) WGS and Pr3vent's technology support timely effective use of gene therapy in eyes.

The Eye and Gene Therapy

IRDs are strong candidates for gene therapy treatments. The retina is small and easy to access for treatment compared to other parts of the body. Another reason that the eye is an ideal location for gene therapy is that it is considered "immune privileged." Usually when a foreign substance—like a virus—is detected in our bodies, our immune system works hard to take care of the problem. However, certain areas of the body are immune privileged, which means that our normal immune response isn't as active. This is typically in areas of our bodies that are very important, and may become damaged if swelling or inflammation occurs. This means that anything that is implanted into the eye—a cell with a corrected gene, for instance—is less likely to be rejected. The most common approach for gene therapy in the eye is delivering the normal gene to the retina using a vector. A vector is a modified virus that will not multiply or cause structural damage. Additional information on gene therapy can be found at: www.asgct.org/education/inherited-retinal-diseases

Goal of Treatment

It is important to note that gene therapy is not a cure for the disease, but instead a means to control disease progression. By targeting the exact cause of the disease—a faulty gene—gene

therapy eliminates the need for recurring interventions. The treatment aims to only need a one-time administration, compared to some treatments for retinal disease where the patients will need direct injections as frequent as every three months.

There's a variety of ways that gene therapy treatments can be administered to the eye. Most gene therapy approaches use a vector to deliver corrected genetic material into the cell. The most promising vectors are based on viruses—but don't worry, any disease-causing viral materials have been removed. Vectors can be delivered in a variety of ways, including an injection. There are two types of injections into the eye. Intravitreal injections are performed by directly injecting the therapy into the vitreous, a jelly-like fluid near the retina. Subretinal injections are administered into the subretinal space, allowing the therapy to be closer to the target area of the eye to correct the disease.

Treatment Pipeline

FDA-approved Luxturna is the first approved gene therapy for an inherited retinal disorder in the U.S. and is also approved for use in the European Union. Developed by Spark Therapeutics and the Children's Hospital of Philadelphia, Luxturna delivers a functional copy of the RPE65 gene into the eye. With your ophthalmologist or a healthcare provider, the first step to determine if you may be appropriate for treatment with Luxturna is confirming mutations in both copies of the RPE65 gene.

There are gene therapy approaches for various inherited retinal diseases that are currently in preclinical studies and clinical trials. Research and development of these therapies is being done by companies including AGTC, Editas, Gensight Biologics, MeiraGTx, Nightstar, Oxford BioMedica and Spark Therapeutics.

To stay up to date on active and recruiting clinical trials in the U.S. or globally, visit the ASGCT Clinical Trials Finder.

Preclinical

There are a variety of preclinical studies underway for other treatments designed to help treat IRDs. Preclinical studies are needed before a clinical trial can begin. This stage uses animals and cell-based models to find out if a treatment is safe and likely to be successful.

Future

At this time, we do not know if or when more gene therapy treatments will be approved by the FDA and commercially available. The overall process can take several years until it is developed to the point of being safe and effective. In the meantime, you can help by becoming involved with patient advocacy organizations. They work hard to raise awareness, fund research, advocate and deliver important news about advances in the field. Many patients suffering from IRDs are unaware that treatment options are in development, and many may even be misdiagnosed. Patient advocacy organizations are a great way to connect with other

families and patients affected by IRDs, in case you're looking for support and advice. The disease may be rare, but you are never alone.

- Foundation Fighting Blindness
- Choroideremia Research Foundation
- Sofia Sees Hope
- Curing Retinal Blindness Foundation
- Retina International

Treatment for Genetically Poor Vision

While we cannot yet prevent the consequences of deleterious mutations, the majority of IRDs are treatable or manageable, **especially if they're diagnosed early on**. Understanding the family's health history, and a working knowledge of which conditions are inherited will aid with treatment. An annual comprehensive eye exam makes it possible to identify and treat vision problems with a patient-specific plan.

There may be many lifestyle steps that can help minimize overall risk and/or help to manage heritable vision conditions.

Genetic Counseling Essentials

Genetic testing is the first step for patients with an IRD to become informed about their genetic status and related implications for clinical trial participation and therapeutic decisions.

Genetic counseling is an essential component of genetic testing, and it is recommended that a genetic counselor be identified prior to undergoing testing to ensure that patients have access to an appropriate resource to help them understand their test results and discuss potential next steps.

In addition to answering questions about results, genetic counselors with expertise in IRDs may also be able to provide patients with information on relevant ongoing clinical trials. They also are well positioned to discuss potential IRD risks for parents who are considering having additional children.

Fortunately, with the expansion of molecular and precision medicine, there are a variety of resources available that can help connect IRD patients with a knowledgeable genetic counselor.

Some physician practices may have a genetic counselor on staff, whereas others may have a referral network of genetic counselors outside of their offices.

Additionally, telephone-based genetic counseling is provided for free through both the My Retina Tracker and ID Your IRD programs.

Companies in the IRD Space

1. **Spark Therapeutics**

About Spark Therapeutics

Spark Therapeutics — a fully integrated, commercial company committed to discovering, developing and delivering gene therapies — challenges the inevitability of genetic diseases, including blindness, hemophilia, lysosomal storage disorders and neurodegenerative diseases. We see the path to a world where no life is limited by genetic disease. For more information, visit www.sparktx.com, and follow us on Twitter and LinkedIn.

2. **Editas**

3. **Invitae** (Invitae | ID Your IRD)

About Invitae

Invitae Corporation (NYSE: NVTA) is a leading medical genetics company, whose mission is to bring comprehensive genetic information into mainstream medicine to improve healthcare for billions of people. Invitae's goal is to aggregate the world's genetic tests into a single service with higher quality, faster turnaround time, and lower prices. For more information, visit www.invitae.com.

This gene testing initiative is appropriate for patients suspected of having an IRD (e.g., retinitis pigmentosa, Leber congenital amaurosis, Stargardt disease, etc.) and who have experienced one or more of the following:

- Peripheral field loss
- Nyctalopia
- Deterioration in color vision
- Central vision loss
- Photophobia
- Any of the above with syndromic findings

Note: This program does not test for genes associated with age-related macular degeneration.

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How to order

1. SUBMIT AN ORDER

To place your online order, click here and follow the on-screen prompts.

To place a paper-based order, download the paper order form and the patient authorization form. Please include both forms in the specimen box when returning the sample.

2. COLLECT A SPECIMEN

If a specimen collection kit was not ordered during the online ordering workflow, order a blood, buccal, or saliva collection kit here.

Please view specimen and shipping requirements for important information, and be sure to include the completed requisition form in the kit with the specimen.

3. RECEIVE RESULTS

On average, results are available 10-21 days after Invitae receives the specimen. You will receive a notification email once the test results are ready.

Log in to view the status of your online order.

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APPENDIX

Inherited Retinal Disease Facts

There are many types of IRDs identified and others yet to be discovered. Based on current statistics the most likely diagnosis would be Retinitis Pigmentosa (RP) which is the the leading cause of youth blindness in many regions. Macular Dystrophy (MD) which affects central vision critical to daily life or Macular Degeneration (AMD), the age related form of MD, which requires both a genetic predisposition and an environmental cue before disease onset.

Retinitis Pigmentosa (RP)

Retinitis pigmentosa is a group of related eye disorders caused by variations in 60 genes that affect the retina (terms highlighted in teal are labeled on the diagram of the eye above). In people with RP, vision loss occurs as the light-sensing cells of the retina gradually die off. The severity and how fast the disease progresses can vary from person to person with RP, depending on the gene affected. RP can first appear during childhood (early onset RP) or during adulthood. The first sign of RP is usually loss of night vision, called night blindness. Later, RP causes blind spots to develop in the peripheral (side) vision. Over time, these blind spots progress to reduced peripheral vision. The disease progresses over time to eventually affect central vision, necessary for tasks such as reading, driving, and recognizing faces.

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What Causes Inherited Retinal Diseases?

An IRD is a genetic disorder– a change, in one or more genes that contribute to proper retinal function. The genetic disorder affects the gene's ability to do its job properly. If there is a mistake in a gene, a protein might not be made correctly or at all, and cells in the retina can degenerate and cause vision loss. There are more than 260 different genes known to cause IRDs.

Some gene mutations that cause IRDs are more severe than others. A doctor is not only interested in which gene is not working properly in a patient, but also how vision is affected. Identifying the specific type of gene variant helps the doctor to provide the correct diagnosis to the patient and may allow him or her to direct patients to clinical trials for therapies that may save their vision. Genetic testing is now available to identify most, but not all, gene variants that cause IRDs.

Variants in the DNA may be inherited from both parents, one parent, or can occur spontaneously. There are three types of inheritance patterns that can lead to an IRD, including- autosomal dominant, autosomal recessive, and X-linked. It is important to understand the pattern of inheritance to help doctors determine the type of IRD a person may have, and how it might be treated.

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How are Inherited Retinal Diseases Diagnosed?

When an eye doctor suspects that someone has an IRD, he or she will refer the patient to an ophthalmologist. The ophthalmologist will conduct a very detailed examination including the steps listed below. The goals of the detailed examination are to establish the specific diagnosis, get the treatment that is right for that diagnosis, connect the patient to supportive services such as low-vision rehabilitation, educate other family members about their risk for the disease, and provide information to the patient about clinical trials and new therapies.

The initial and follow-up examinations may include the following:

1. Patient history: Including current vision issues, patient medical history, current medications, and past medication use.
2. Family history: Constructing a family medical history to show the genetic relationships and medical disorders that occur in a family. From the family medical history, patterns of familial disorders and how diseases were passed down may emerge. This, in turn, leads doctors to a clear diagnosis of the genetic disorder and allows assessments for family members who may also be at risk for the disorder.
3. Clinical eye examination: The eye examination includes:
4. Dilation: Eye drops put into the eye to widen the opening on the front of the eye, called the pupil. This allows the eye doctor to examine the health of the retina
5. Visual Acuity: A measure of the ability to see detail up close and in the distance
6. Slit lamp: A non-invasive procedure that uses a microscope and bright light to look at different parts of the eye
7. Indirect ophthalmoscopy: A non-invasive tool worn on the head of the eye doctor that provides magnification, allowing them to examine the back of the eye
8. Imaging: The eye doctor will conduct a series of imaging tests to view different parts of the eye, including:
9. Retinal photographs: A photo taken of the inside surface of the eye
10. Optical Coherence Tomography (OCT): A test that takes cross-sectional pictures of the retina. This allows your ophthalmologist to map and measure the thickness of the retina
11. Fundus autofluorescence: A test used to create a density map of the layers of the retina
12. Infrared autofluorescence: A test that provides information on the distribution of pigment in the retina
13. Visual Field Testing: A test that measures central and side or peripheral vision.
14. Electroretinography: A test to measure the electrical response of the eye's light-sensitive cells, called cones and rods. During the test, the eye doctor will place drops into your eyes, so you will not have any discomfort during the test.
15. Genetic testing: Patients may meet with a genetic counselor (someone that specializes in the genetic testing process and educating patients) to determine the testing approach that is best based on the other test results. Patients are often asked to provide a blood or saliva sample that will be sent to a lab for analysis. The genetic test confirms or disputes the diagnosis of a specific IRD, so that correct information is provided to the patient and family. Genetic testing is often a requirement for participation in various research trials.