INHERITED RETINAL DISEASES

Diagnosis and patient management

Dr Ceecee Britten-Jones *BOptom (Hons) PhD*

ECOVSA Seminar | 24 July 2023

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My Journey

PhD
- Anterior eye diseases
- Diabetic neuropathy
- Ocular nutrition

Current - postdoc
- Inherited retinal diseases
- Retinal gene therapy
- Ocular genetics

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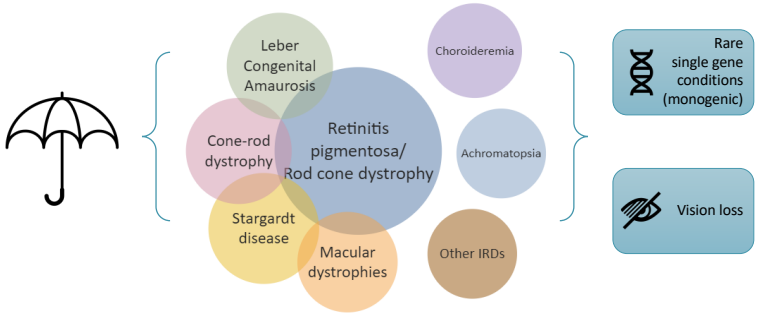
Inherited retinal diseases



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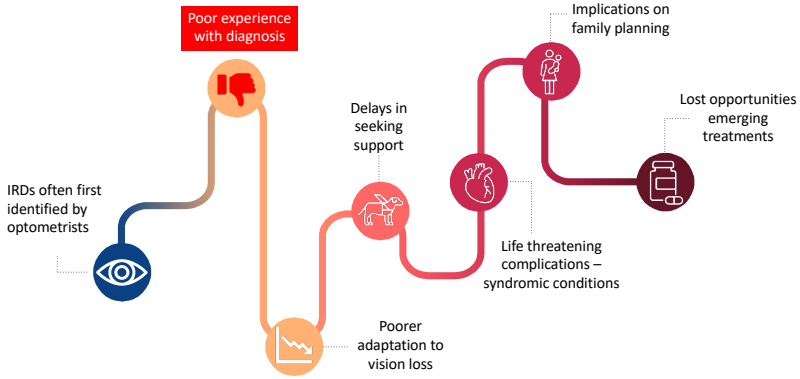
Why is optometry important?



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Overview

Suspecting inherited retinal diseases → Diagnosing inherited retinal diseases → Patient counselling

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Suspecting inherited retinal diseases

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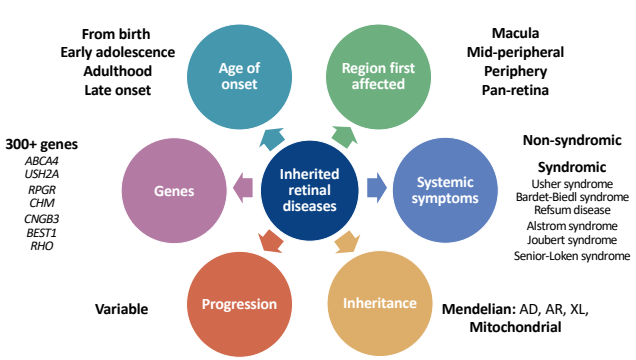
IRDs are heterogenous



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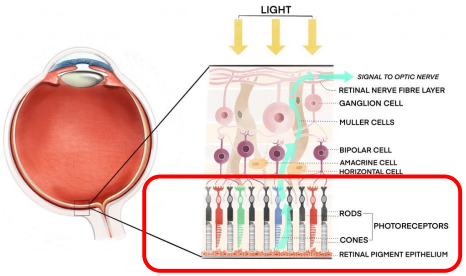

IRDs are caused by variants (mutations) in **genes** encoding proteins that are critical for **photoreceptor** survival or function

Image source: Gene vision

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Early Symptoms

Peripheral/rods affected first

- Difficulty seeing at night (Nyctalopia)
- Takes a long time to adapt to dark/light

Central/macula or cones first

- Difficulty seeing bright light
- Difficulty reading
- Poor hand eye coordination

General symptoms

- Sensitivity to light/glare
- Not seeing colours or recognising differences between certain colours

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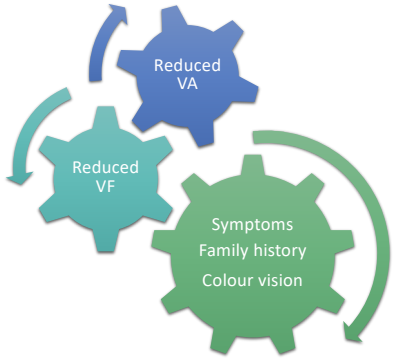
Early Symptoms



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Diagnosing inherited retinal diseases

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Retinitis pigmentosa

(rod-cone dystrophy)

Rod-cone dystrophy

- Most common IRD phenotype* (~1 in 4,000)
- Age of onset - childhood to 50s.
- ~70 genes known to cause non-syndromic RP
- **Symptoms**
  - Nyctalopia (poor night vision)
  - reduced peripheral vision
  - Photophobia, glare
- **Other coexisting ocular findings**
  - PSC (~20% of cases)
  - CMO (~50% of cases)
  - Epiretinal membrane (~20% of cases)

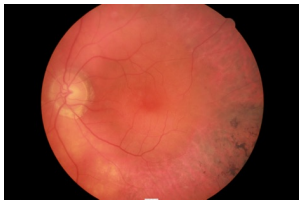

Image source: VENTURE IRD registry (CERA/UOM)

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Retinitis pigmentosa

(rod-cone dystrophy)

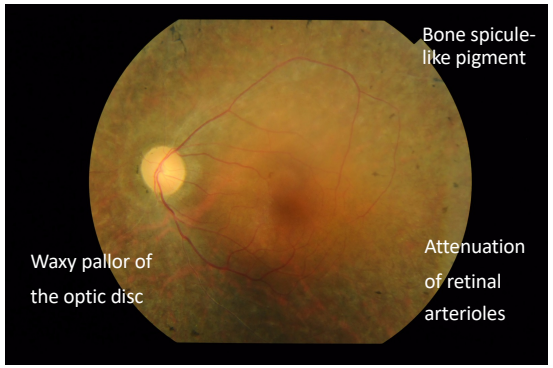

Image source: VENTURE IRD registry (CERA/UOM) and Dr Ceecee Britten-Jones

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Early/Mild RP

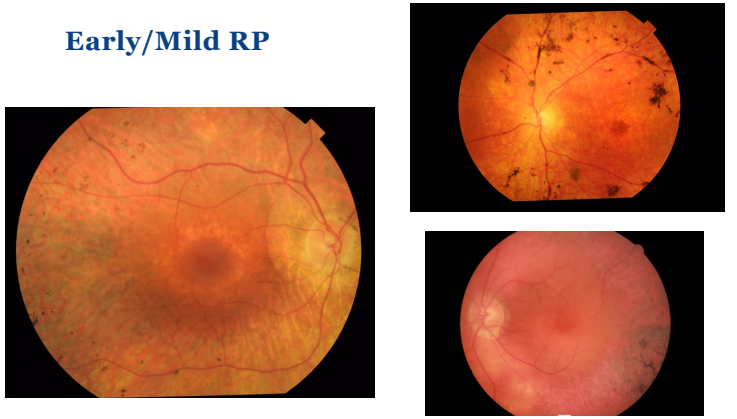

Image source: VENTURE IRD registry (CERA/UOM) and Dr Ceecee Britten-Jones

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Moderate/advanced RP

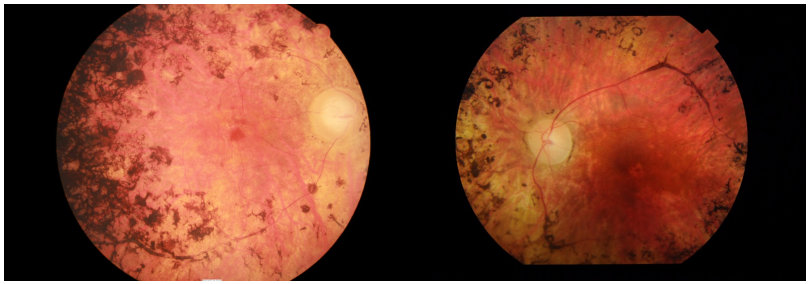

Image source: VENTURE IRD registry (CERA/UOM) and Dr Ceecee Britten-Jones

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Imaging:

Fundus auto-fluorescence

The extent of photoreceptor loss.

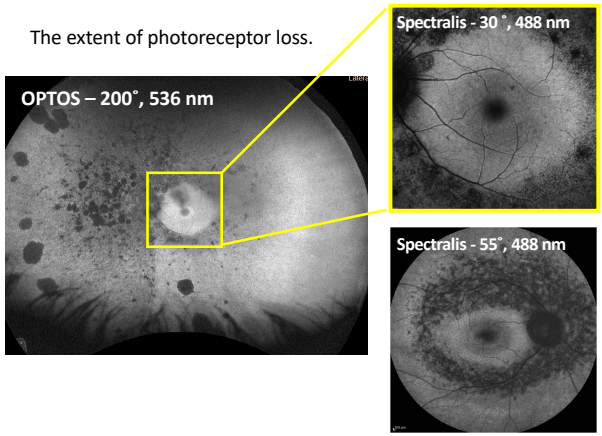

Image source: VENTURE IRD registry (CERA/UOM) and Retina Image Bank

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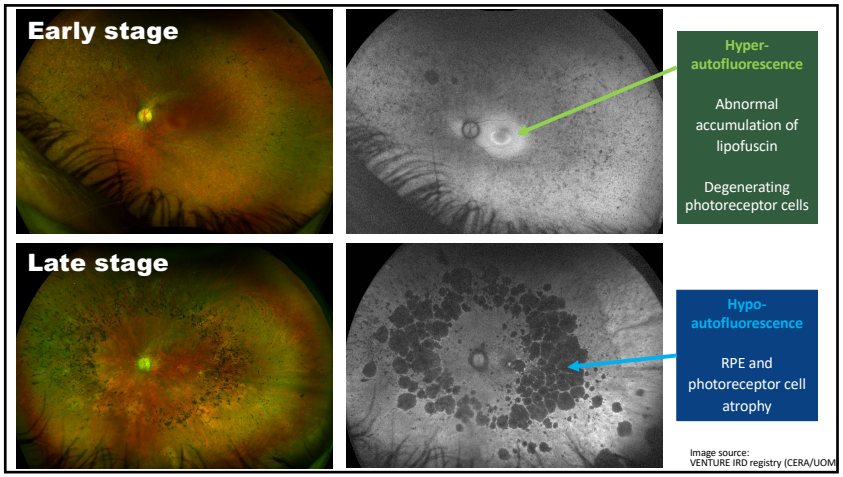
Early stage
Late stage
Hyper-autofluorescence
Abnormal accumulation of lipofuscin
Degenerating photoreceptor cells
Hypo-autofluorescence
RPE and photoreceptor cell atrophy
Image source:
VENTURE IRD registry (CERA/UOM)

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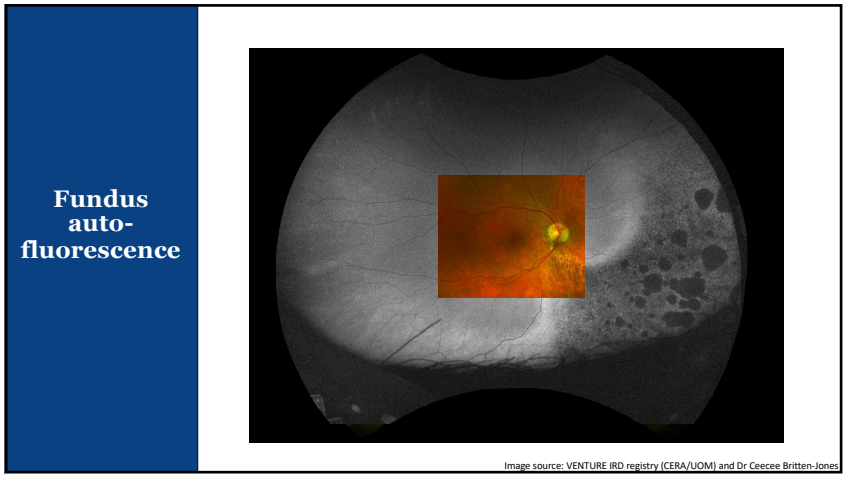
Fundus auto-fluorescence
Image source: VENTURE IRD registry (CERA/UOM) and Dr Ceecee Britten-Jones

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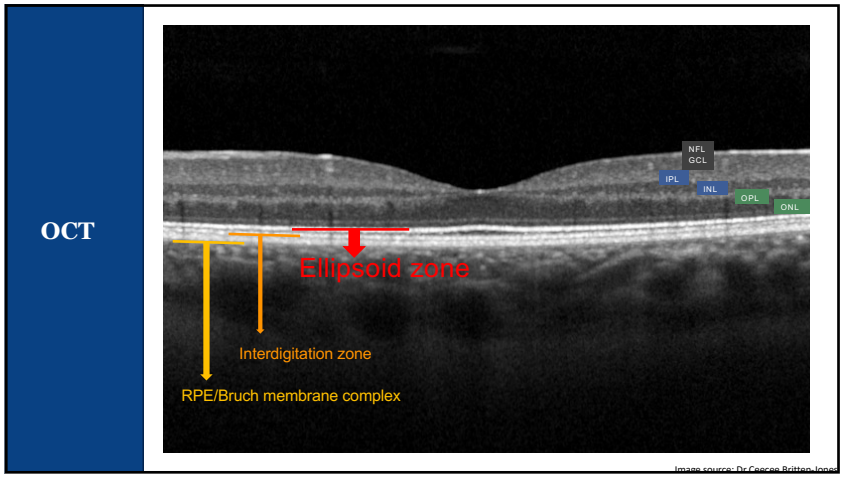
OCT
NFL
GCL
IPL
INL
OPL
ONL
Ellipsoid zone
Interdigitation zone
RPE/Bruch membrane complex

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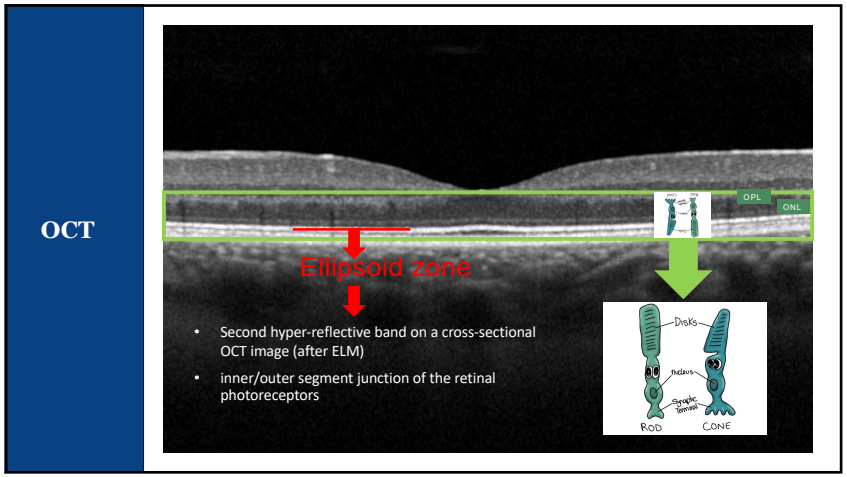
OCT
OPL
ONL
Ellipsoid zone
Second hyper-reflective band on a cross-sectional OCT image (after ELM)
inner/outer segment junction of the retinal photoreceptors
Disks
Nucleus
Synaptic Terminal
ROD
CONE

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OCT – Ellipsoid zone

Changes in the EZ width - biomarker for monitoring disease progression

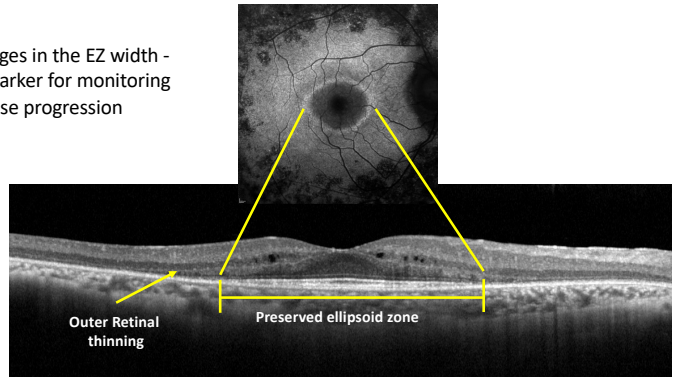

Image source: VENTURE IRD registry (CERA/UOM)

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OCT

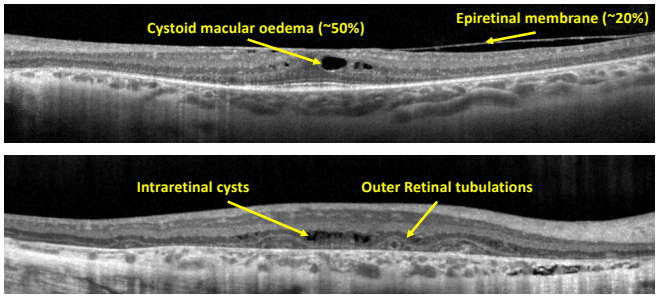

Image source: VENTURE IRD registry (CERA/UOM)

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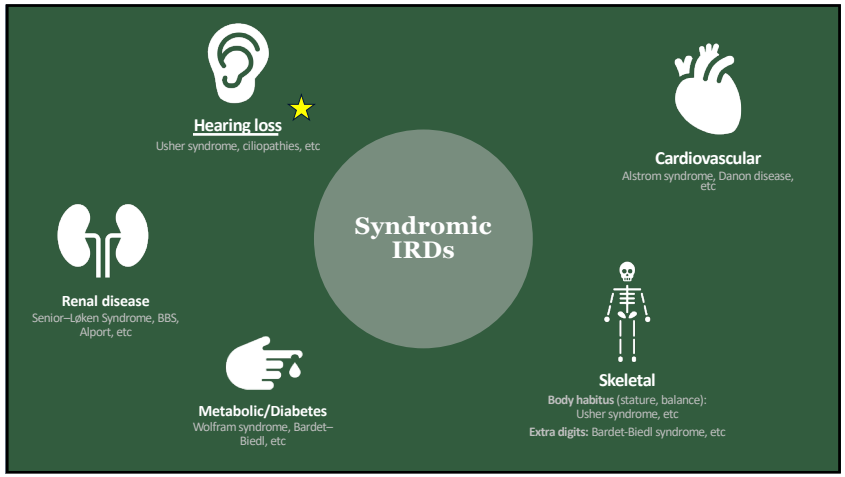

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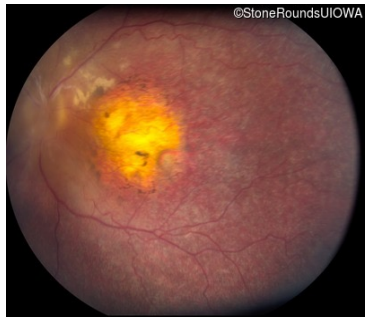
Leber Congenital Amaurosis

Signs:

- Severely reduced VA - <2 years
- Nystagmus
- Strabismus
- High hyperopia
- Sluggish/near absent pupillary responses
- Photophobia
- Oculodigital sign



Abnormal/ undetectable short-wavelength FAF signals

Genes:

***RPE65** (5-10%)**
CEP290
GUCY2D
CRB1
CEP290, ... etc

Image source: StoneRounds.org

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Achromatopsia

- Rod monochromacy – **loss of colour vision**
  - Partial (incomplete)
  - Total (complete)
- VA 6/24 - 6/60
  - Stationary IRD (slowly progressive)
- **Genes**: *CNGA3*, *CNGB3*, *PDE6H, PDE6C, GNAT2, ATF6*

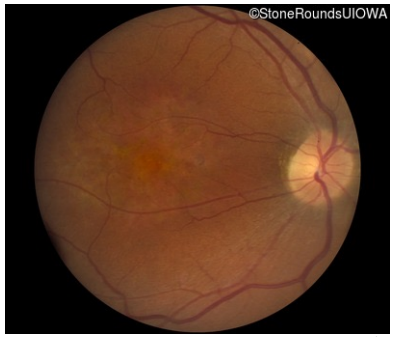

Image source: StoneRounds.org

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Macular dystrophies

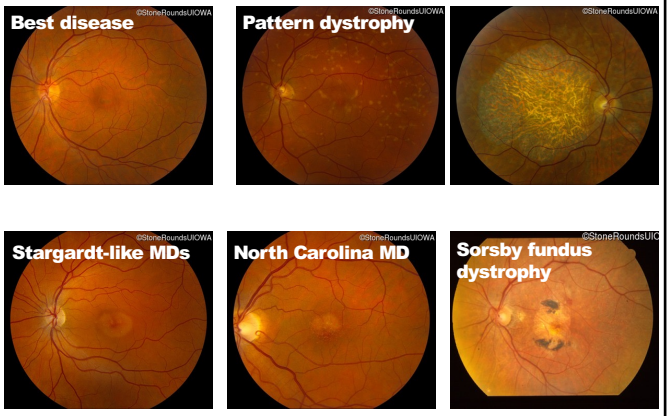

Image source: StoneRounds.org

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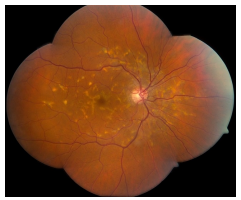
Stargardt disease

Gene: *ABCA4*

Earlier stages

- Mild macular retinal pigmentation
- Symmetrical **yellow-white flecks** in the central retina, extending out to the periphery



Later stages

- Extension of **flecks** beyond the macula
- Resorbed flecks
- **Atrophy** of RPE and choroid involving both the macula and peripheral retina

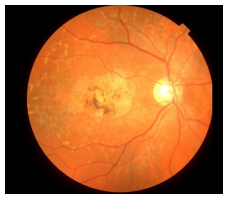


Image source: Retina Image Bank, www.imagebank.asrs.org

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Stargardt disease

Gene: *ABCA4*

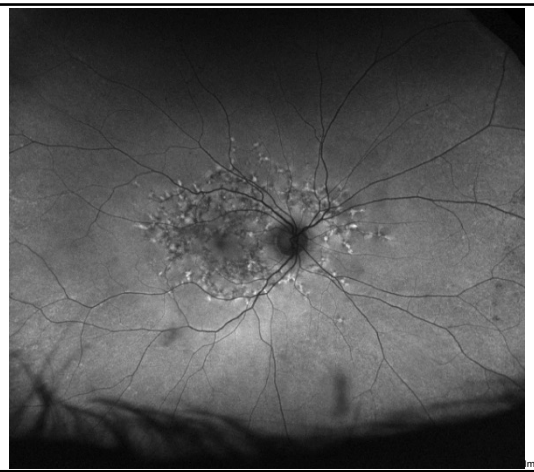

Image source: VENTURE

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Ophthalmology referral

Refer to IRD/retinal ophthalmologist

Family history
- Is the patient family planning?

Other systemic findings
- Hearing loss
- Diabetes
- Developmental delay
- Dysmorphic features
- Other systemic features

Clinical examination
- VA and Rx
- Pupil responses
- Cataracts

Retinal imaging
- Coloured fundus photo
- Autofluorescence
- OCT

Co-existing conditions
- Macular oedema
- Choroidal neovascularisation,
- Epiretinal membrane
- ONH drusen

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Public IRD ophthalmologists

State	Service
VIC	**Genetic Eye Disease** Evaluation / Threshold Criteria/Referral Guidelines / Tertiary Care Management Inherited Eye Diseases • For genetic counselling or electrophysiology testing • Optometrist/ ophthalmologist report performed within the last 3 months • Where patient is requesting genetic testing/genetic family planning – Refer urgently • Electrodiagnostic testing to confirm diagnosis • Genetic investigation to confirm diagnosis and heritability of disease • Genetic counselling Genetic Disease with Ophthalmic Component • For genetic counselling or electrophysiology testing • Optometrist/ophthalmologist report performed within the last 3 months • Electrodiagnostic testing to confirm diagnosis • Genetic investigation to confirm diagnosis and heritability of disease • Genetic counselling
SA	• **Royal Adelaide Hospital** • **Flinders** – Ocular genetics clinics (Dr Deepa Taranath and A/Prof Christopher Barnett) • **Genetics service – Women's and Children's Hospital** - A/Prof Christopher Barnett, Clinical Genetics Service

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Private ophthalmologists - IRD

VIC	SA

• **Dr Tom Edwards**
• **Dr Penelope Allen**
  • Melbourne Retina
• **Dr Jon Ruddle**
  • Parkville Eye Specialists
• **Dr Heather Mack***
  • Eye Surgery Associates
• **Dr Marc Sarossy***
  • Essendon Eye Clinic
	• **Dr Jamie Craig**
	  • Eyemedics
	• **Dr Bob Casson**
	  • Harley Eye Clinic
	• **Dr Deepa Taranath**
	  • Northern Eye Specialists

*ERG

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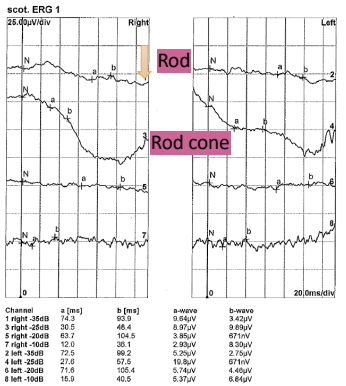
ERG

Measures the electrical activity of the retina in response to a light stimulus

- **Full Field ERG**
  - Retina-wide function of rods and cones
  - Diagnosis and staging of disease
  - Required to separate macular disorders from generalised retinopathies.
- **Pattern ERG**
  - Objective measure of macular function
- **Multifocal ERG**
  - Topographic assessment of macular function.
  - Limited value in patients with poor VA and/or unstable fixation.



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Having the difficult conversion

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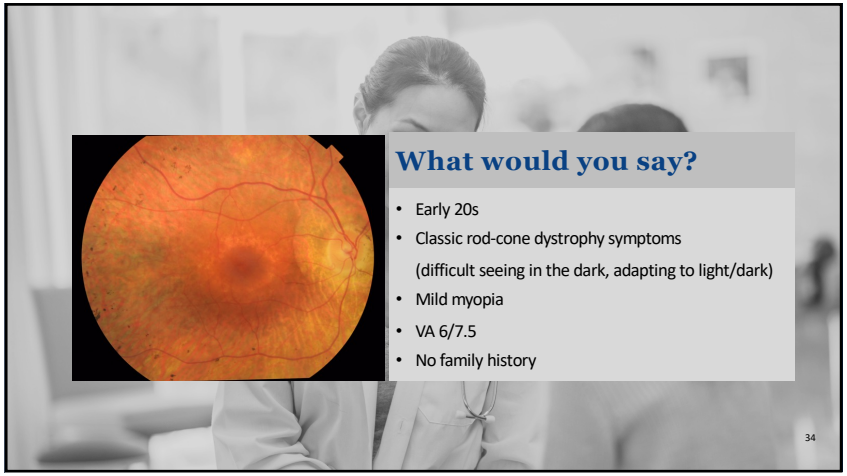

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"They said "Well, it's very rare condition, there is no treatment, there is no research being done on it."

That was it and and I was given the name on a piece of paper and sent out the door"

"No one really comes and says, here's how we're going to move forward."

"It was like being hit with a brick"
- Ferrey 2022

"My optometrist was really helpful. They went out of their way to look into what was available for me, and took time explaining things.

I felt like I had a better understanding and time to ask questions"

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Delivering bad news: SPIKES

S **Setting:** private, seated, with significant others, communicate time limitations

P **Patient Perception:** Ask what they know and what they think

I **Invitation:** Ask if the patient if they want more information/type of information

K **Knowledge:** use warning words e.g., "Unfortunately…", avoid excessive bluntness

E **Emotions:** Acknowledge their emotions, manage expectations, think long term

S **Strategy:** Summarise and make a plan for the future

(Buckman, 2005)

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IRD specific advice

Be honest and empathetic	Lots of research on emerging treatments	Getting genetic testing can be helpful for confirming the genetic diagnosis	Progressive conditions, but different between everybody
Tell them what you know and be honest about what you don't know	**Earlier stage**: gene therapy **Moderate** stage: RNA therapy, stem cell therapy **Late stages:** bionic eye, optogenetics	Informing clinical trials/treatments For family planning and risk to other family members	Vision, support needs, and goals could change

VENTURE research registry: IRD@groups.unimelb.edu.au

Refer to ocular genetics service

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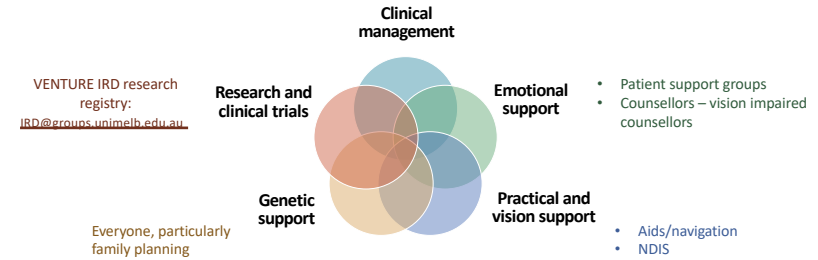
Ongoing support/referrals



VENTURE IRD research registry: IRD@groups.unimelb.edu.au

- Patient support groups
- Counsellors – vision impaired counsellors

Everyone, particularly family planning

- Aids/navigation
- NDIS

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Key messages:

IRDs are heterogenous, but generally affect photoreceptor function first

Imaging for monitoring IRDs
- Fundus autofluorescence
- OCT – ellipsoid zone and outer retinal thinning

Advice
- There are research into emerging treatments
- Provide a "next step"
- Tailor management depending on patient needs and disease stage

Refer to research or email us if not sure
IRD@groups.unimelb.edu.au

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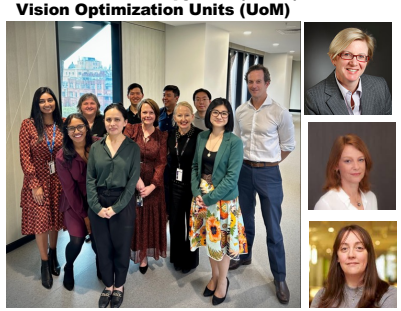
Thank you

ac.brittenjones@unimelb.edu.au

- IRD referrals/advice
- Questions/feedback
- Masters/PhD

Retinal Gene Therapy Unit (CERA)
Vision Optimization Units (UoM)



U21 Health Sciences · Centre for Eye Research Australia · veski · Melbourne Disability Institute · Macular Disease Foundation Australia

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