Guidelines for the assessment and management of patients with inherited retinal diseases (IRD)
## Contents

Executive Summary .................................................................................................................. 1

Assessment and Management for patients with a suspected Inherited retinal disease .......... 1

1. Introduction and Rationale ............................................................................................... 2

2. Overview of Clinical care for IRD patients ...................................................................... 2

   2.1 Assessment and Management for patients with suspected IRD ................................. 2

   2.2 Establishing the clinical diagnosis of an Inherited Retinal Disease ............................ 2

   2.3 Determining visual function ....................................................................................... 3

   2.4 Establishing the genetic diagnosis and genetic management .................................... 3

   2.5 Monitoring disease progression (natural history) and preparation for therapeutic interventions ................................................................................................................. 6

   2.6 Overview of Clinical investigations and assessments relevant to IRD ....................... 6

   2.7 Clinical Evaluation for Inherited Retinal Diseases ....................................................... 8

3. Summary ............................................................................................................................. 10

Guideline Authors.................................................................................................................... 11

Appendix 1 Vision support agencies and patient support organisations ............................... 13

References .............................................................................................................................. 14
Executive Summary

Inherited retinal diseases (IRDs) comprise a wide range of phenotypically and genetically heterogeneous diseases that result in progressive loss of photoreceptor function accompanied by visual loss. IRDs affect approximately 1:3000 to 1:4000 individuals.\(^1,2\) Despite similarities among different IRDs, variants in more than 250 genes cause various IRDs.\(^3\) Therefore, accurate and comprehensive molecular diagnosis is critical to confirm the clinical diagnosis and inform disease prognosis.

Collectively IRD’s are common, and their cumulative impact on affected families and healthcare systems is substantial due to the earlier onset of blindness compared to many other eye diseases.\(^4-6\) They may also impact on the reproductive decision making of affected individuals, parents of affected children and other family members.

There have been rapid advances in the understanding of the clinical, genomic, molecular, and cellular mechanisms underlying IRDs. This has led to clinical trials involving gene replacement, genomic engineering, stem cell therapies, and other therapies that may slow photoreceptor degeneration or restore some vision.\(^7-12\)

Assessment and Management for patients with a suspected Inherited retinal disease

1. Establish the clinical diagnosis of an Inherited Retinal Disease
2. Determining the level of visual function and arrange visual rehabilitation
3. Establishing the genetic diagnosis and genetic management
4. Monitoring of disease progression (Natural History) and, prepare for therapeutic interventions

The clinical diagnosis relies upon a combination of history, examination and investigations directed at the presentations that are targeted for IRDs. The specialised investigations including visual electrophysiology are best performed in centres with expertise in meeting international standards. Systemic evaluation is a key component of patient assessment to identify syndromic causes.

The diagnostic tests at baseline will provide an initial visual function measure which is important for education, work, statutory requirements and rehabilitation assessments.

Genetic testing is now standard of care for these patients. Multigene based testing strategies, including targeted next-generation sequencing panels, whole exome sequencing (WES) or whole genome sequencing (WGS) are necessary to identify the molecular aetiology in the IRD group of disorders where more than 250 causative genes have been identified (https://sph.uth.edu/retnet/). This information helps provide a more accurate diagnosis, prognosis, provides individuals and families with specific recurrence risks, aids informed reproductive decisions and guides treatment decisions. Routine genetic testing is also required to enable enrolment in treatment studies as well as determine suitability for approved therapies such as voretigene neparvovec (Luxturna).

The development of specific gene-based therapies\(^13-20\) raises the question of the ideal time to intervene. To answer this question, an understanding of the natural history of the IRD is required.\(^21\) Monitoring the natural history of IRDs requires consistent assessments and protocols.

These four steps will lead to improved patient care with streamlined ophthalmic diagnosis, molecular diagnosis and counselling, management of visual dysfunction and preparation for clinical trials. The complexity of IRDs requires input from both ophthalmology and clinical genetics.\(^22\) The benefits of modern genetic diagnostics and counselling supports the introduction of equitable genetic testing for patients with presumed genetically caused retinal diseases.\(^23\)
1. Introduction and Rationale

Inherited retinal diseases (IRDs) comprise a wide range of phenotypically and genetically heterogeneous diseases that result in progressive loss of photoreceptor function accompanied by visual loss. This group of conditions is now the commonest cause for blindness registration in the United Kingdom. There has been rapid advances in the understanding of the clinical, genomic, molecular and cellular mechanisms underlying IRDs. This has led to clinical trials involving gene replacement, genomic engineering, stem cell therapies and other therapies that may slow photoreceptor degeneration or restore some vision.

Although each individual retinal disorder in this group is rare (defined in the EU as affecting less than 1 in 2,000 individuals) and the impact of each disease on its own small, collectively they are common, and their cumulative impact on affected families and healthcare systems is substantial due to the earlier onset of blindness compared to many other eye diseases. IRD’s may also impact on the reproductive decision making of affected individuals, parents of affected children and other family members.

Conducting clinical research/trials in rare monogenic IRDs poses unique challenges. These include disease heterogeneity and a geographically dispersed patient population. The rarity of IRDs has significant consequences for obtaining natural history data, and the often slowly progressive nature of these conditions means that clinical evaluation methods have changed many times over the course of many affected patients’ lives. These limitations pose ongoing potential barriers. Without a firm understanding of disease progression, choosing meaningful outcome measures and designing and powering clinical trials is challenging. Furthermore, many monogenic retinal disorders primarily affect children, adding further complexity to potential study design. To overcome these hurdles, significant stakeholder engagement will be required.

2. Overview of Clinical care for IRD patients

IRDs affect approximately 1:3000 to 1:4000 individuals. Despite similarities among different IRDs, variants in more than 250 genes cause various IRDs. Therefore, accurate and comprehensive molecular diagnosis is critical to confirm the clinical diagnosis and inform disease prognosis.

2.1 Assessment and Management for patients with suspected IRD

The assessment and management for patients with, or suspected of having, IRD falls into four areas:

1. Establishing the clinical diagnosis of an Inherited Retinal Disease
2. Determining the level of visual function and planning/implementing visual rehabilitation
3. Establishing the genetic diagnosis and genetic management
4. Monitoring of disease progression (Natural History) and, preparation for therapeutic interventions

2.2 Establishing the clinical diagnosis of an Inherited Retinal Disease

The clinical diagnosis relies upon a combination of history, examination and investigations directed at the presentations that are common for IRDs. The clinical history pertinent to IRDs include the following symptoms: rod dysfunction (nyctalopia and often peripheral vision issues), cone dysfunction (photophobia, reduced distance and near visual acuity and dyschromatopsia), age at onset and progression of symptoms. Traditionally, IRDs have been associated with early onset disease. Increasing evidence indicates a much broader age of onset, extending to the 6th decade, as well as asymptomatic disease.

Inherited Retinal Diseases may also occur as part of a multi-system condition and ocular symptoms may occur prior, concurrently or after the development of systemic signs and symptoms. Some concurrent systemic diseases can cause significant morbidity and systemic medical problems (hearing, renal dysfunction, neurological dysfunction, skeletal
anomalies and or metabolic disturbance) need to be specifically inquired about and evaluated. The effects of medication also need to be evaluated.

Genes of significance for a particular patient or family vary based on autosomal dominant, autosomal recessive, X-linked or mitochondrial inheritance patterns. Therefore, family history is important, and a pedigree should be recorded in the clinical record.

Clinical examination findings relevant to IRDs include best corrected visual acuity (BCVA), pupil responses, anterior segment examination (associated cataract and raised intraocular pressure), retinal examination including macula, disc and peripheral findings. General clinical findings including developmental delay, dysmorphic features, skeletal abnormality, deafness, renal failure or other systemic features may be important clues to an underlying diagnosis.

Clinical investigations directed at identifying IRDs include: Optical Coherence Tomography (OCT) macula, fundus autofluorescence (widefield), visual field assessment (peripheral field (Goldmann semi-automated or manual perimetry, Esterman binocular field), dark adaptation, International Society for Clinical electrophysiology of Vision (ISCEV) standard Visual electrophysiology (Pattern Electroretinogram, Full Field Electroretinogram, Multifocal Electroretinogram). Fluorescein angiography is not a routine investigation for IRDs but may be indicated if co-morbidity is suspected (e.g. choroidal neovascularisation). It is important to recognise that patients with IRDs often have other co-existing sight-threatening diseases such as glaucoma, cataract, macular oedema, choroidal neovascularisation, epiretinal membrane and disc drusen, which may require monitoring and/or treatment.

There are four major groups of IRDs clinically recognised which include: rod and rod-cone dystrophy, cone and cone-rod dystrophy, chorioretinal degenerations, and macular dystrophies. In assessing patients with IRDs, examinations need to be tailored to the suspected condition and the patient’s symptoms.

2.3 Determining visual function

Determining the patient’s visual function is critical for management, particularly when considering education support, employment advice, visual rehabilitation and therapeutic interventions. The level of visual function will be determined from a combination of objective and subjective measures, including: best corrected visual acuity, visual field assessment and visual electrophysiology parameters. These functional assessments may be correlated with structural measures, including OCT and fundus autofluorescence. For children, it is important that refractive error (commonly found in IRDs) are corrected and regularly re-evaluated. Visual rehabilitation strategies are guided by the predominant visual deficit. For example, photophobia in cone dysfunction syndromes may be minimised by long bandpass (red tinted) lenses. The effects of nyctalopia can be addressed by adequate lighting in the home and work environment. Patients with reduced central vision may benefit from magnification with visual aids, electronic readers and facial recognition devices. Profound impairment of central and peripheral vision may require mobility assistance from a cane or a guide dog. Natural history studies of IRDs are now providing information regarding visual function at different stages of these conditions and the rate of change over lifetime. Psychological support is also necessary so that individuals and families can deal with the emotional stress, and sometimes uncertainty associated with an inherited retinal disease.

2.4 Establishing the genetic diagnosis and genetic management

a. Genetic diagnosis

Inherited retinal diseases are phenotypically and genetically heterogeneous. Clinical genetic and molecular assessments have advanced significantly in recent years. A causative mutation can now be identified in up to 60-80% of patients with IRDs. Multigene based testing strategies, including targeted next-generation sequencing panels, whole exome sequencing (WES) or whole genome sequencing (WGS) are necessary to identify the molecular aetiology in the IRD group of disorders where more than 250 causative genes have been identified. This information helps provide a more accurate
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

diagnosis, prognosis, provides individuals and families with specific recurrence risks, aids informed reproductive decisions and guides treatment decisions.

Syndromic diagnoses associated with IRDs are important because of their impact on appropriate management, prognosis and family planning. Multigene based genetic approaches are critically important in identifying syndromic retinal dystrophies, where a precise early clinical diagnosis may not be possible. This enables timely provision of accurate prognostic and reproductive information requested by families. In addition, monitoring for specific extra-ocular manifestations can be done with accurate genetic diagnosis.

In an autosomal recessive disease, testing unaffected parents or other family members is essential in assisting confirmation of biallelism which is a key inclusion criterion for some therapies and clinical trials. Further predictive testing at-risk asymptomatic family members may be beneficial in particular for early detection and monitoring and requires detailed genetic information and counselling, but the implications in the absence of established therapies must be considered.

For autosomal dominant retinal disease, it is important to examine parents and siblings, to identify variable penetrance. Frequently new or ‘de novo’ autosomal dominant pathogenic variants require parental genetic testing to establish pathogenicity. Similarly, in X-linked retinal dystrophies, there may be asymptomatic obligate carrier females and further family members who would benefit from genetic testing, that aren’t always obvious on first consultation.

Next generation sequencing technology has enabled vastly improved mutation detection rates. The advances have also highlighted variants of uncertain significance (VUS) that are simultaneously identified. The American College of Medical Genetics and Genomics (ACMG) provides a systematic methodology to classify these variants. Specific guidelines are followed to determine if a genetic variant is pathogenic/likely pathogenic or a variant of uncertain significance (VUS) for a patient. At times, it may be necessary to perform segregation genetic testing in family members to determine if a VUS can be upgraded to likely pathogenic or pathogenic. Testing in unaffected family members for the familial variant is generally only performed if the variant is determined to be pathogenic or likely pathogenic.

Increasingly multi-disciplinary team (MDT) meetings are required to determine the pathogenicity and significance of some variants, especially the VUSs. MDTs are conducted with contributions from ophthalmologists, clinical geneticists, genetic pathologists, genetic scientists and genetic counsellors. Despite these processes, a genetic answer may not be found with the current technology in up to 20-40% of cases. Other follow up techniques may be required to confirm a diagnosis in positive cases such as Sanger sequencing, Multiplex ligation-dependent probe amplification (MLPA) and Array Comparative genomic hybridization (CGH). Whole genome sequencing, RNA sequencing and functional genomic studies including RPE and retinal organoid modelling are research tools addressing this challenge.

Understanding the precise molecular defect is crucial for the implementation of genomic therapies.

Genetic testing strategies are continually evolving, and close consultation is required between ophthalmologists, clinical geneticist and molecular biologists to ensure the appropriate testing strategies are employed. Some patients may have undertaken genetic testing for IRD’s through research (eg Australian Inherited Retinal Disease Registry and DNA Bank) or private molecular testing organisations. Patients should be asked if this has occurred to identify those with a research genetic result. In the clinical setting, the research tests should be confirmed in a clinically accredited laboratory.

A number of task forces have now provided guidelines on genetic testing in ophthalmic conditions. These include the American Academy of Ophthalmology Task Force on Genetic Testing which published recommendations for genetic testing of inherited eye diseases, the German Ophthalmological Society German Retina Society and Professional Association of German Ophthalmologists Statement on the therapeutic use of voretigene neparvovec.
An important component of the management of patients with an IRD is the return of genetic testing results. When genetic testing is conducted after appropriate pre-test genetic counselling, patients feel educated and are generally psychologically better prepared for the implications of the results. The results may be derived from clinical testing or research testing. The management around this process is critical to ensure that patients receive the appropriate ophthalmic and genetic advice.

These advances have elevated genetic testing for IRDs to routine clinical care for these patients. The dual burdens of living with a genetic condition and severe vision loss are wide-ranging. To manage these complex medical, psychosocial and practical healthcare requirements requires an explicit multidisciplinary team approach. Upskilling ophthalmologists and workforce increases in clinical geneticists and genetic counselling services are critical for increasing access to testing.

The wider introduction of genetic testing will lead to reduction in morbidity, improved patient disease understanding, improved reproductive decision-making and improved clinical care pathways.

**b. Genetic Management**

i. Genetic workforce – Clinical Geneticists

Clinical geneticists are medical specialists who have completed either paediatric or adult basic physician training and then completed advanced training in clinical genetics supervised by the Royal Australasian College of Physicians in collaboration with the Human Genetics Society of Australasia. Clinical geneticists specialise in medicine that involves the interaction between genes and health. They are trained to evaluate, diagnose, manage, treat and counsel individuals of all ages with hereditary disorders. They use genomic molecular testing to implement needed therapeutic interventions and provide genetic counselling regarding prenatal and preimplantation diagnosis.

ii. Genetic workforce – Genetic Counsellors

In Australian and New Zealand Genetic counsellor roles include: referral assessment, collecting personal and family history, risk assessment, patient education regarding genetic concepts to facilitate informed decision-making and addressing the psychosocial impacts of a diagnosis. Genetic counselling service provision differs in Australia to that in the UK or the USA. In Australia genetic counselling is not a nationally regulated or registered profession, which means that they can facilitate genetic/genomic testing when working under the medico-legal purview of a clinical geneticist or appropriately credentialed medical practitioner. The HGSA (Human Genetics Society of Australasia) and the ASGC (Australasian Society of Genetic Counsellors) have identified regulation of the genetic counselling profession as a priority. The genetic counsellor profession now has a register of genetic counsellors and HGSA is a full member of the National Alliance of Self Regulating Health Professions (NASRHP).

iii. Genetic consent

A key component of managing the patient with a suspected heritable disorder is the process of informed consent. Genetic counselling is an essential role to facilitate informed consent. Although patients may fully expect the return of primary results, they may not anticipate the vast genetic data generated by testing. Although the latter may be harmless, it could possibly reveal unexpected, embarrassing, stigmatising, or deeply upsetting medical information. For example, patients need to be forewarned about the risk of revealing mis-attributed parentage, unexpected incidental findings such as an oncogene variant, and variants of uncertain significance (VUS). These VUS, and the uncertainty raised by them, can be a source of significant, misunderstanding and concern for the recipient.
Another area that requires appropriate counselling is predictive testing in pre-symptomatic individuals. Medical ethicists and clinical geneticists broadly support predictive testing of adults for adult onset diseases and minors for childhood onset disorders for which beneficial therapies are available, but this needs to be performed in the context of careful and informed consent.

iv. Return of genetic results

The significant advances in molecular diagnostic techniques has dramatically increased our ability to identifying the genetic basis of IRD in affected patients. However, these molecular testing advances have also increased the frequency of incidental and secondary findings. Managing patient expectations remains an ongoing challenge and highlights the need to address this issue throughout the testing process.

An important component of returning genetic results is the written report sent to patients/families in layman’s terms by medical geneticists or genetic counsellors after each consultation. These letters describe the significance of positive genetic results, secondary results, uncertain diagnostic results or no diagnostic result and the impact on the individual, recurrence, and the possibilities of therapy. In addition conveying the results to at-risk family members is an important additional component of the return of genetic results.

2.5 Monitoring disease progression (natural history) and preparation for therapeutic interventions

The development of specific gene-based therapies raises the question of the ideal time to intervene. To answer this question, an understanding of the natural history of the IRD is required. Monitoring the natural history of IRDs requires consistent assessments and protocols. Outcome measures include BCVA, colour vision testing, visual fields (kinetic and/or static), OCT macular island and macular thickness. Patients with advanced disease and impaired fixation who cannot perform standard visual field testing can be followed with the full-field stimulus threshold (FST). Some tests are only available at specialised centres, so flexibility is required.

In general, IRDs progress slowly, so identifying change requires a consistent protocol when assessing the structure and functional biomarkers. Variability is an issue in patients with low vision and this needs to be accounted for in monitoring. Recognition of a slowing of progression is likely a much more achievable goal than improvement in visual function.

These four steps will lead to improved patient care with streamlined ophthalmic diagnosis, molecular diagnosis and counselling, management of visual dysfunction and preparation for clinical trials. Table 1 provides guidance in assessment investigations and follow-up for the various IRD groups.

2.6 Overview of Clinical investigations and assessments relevant to IRD

i. Optical Coherence Tomography (OCT)

OCT provides cross-sectional imaging of the photoreceptors, retinal pigment epithelium, and inner retinal layers including the retinal nerve fibre layer akin to in vivo histopathological cross-sectional imaging. High-density volume scans give a useful baseline for monitoring progression in structural features such as the length of the remaining ellipsoid zone, and help monitor cystoid macular oedema (CMO), macular schisis and macular traction from epiretinal membrane. OCT angiography provides indirect measurement of retinal blood flow. This may be useful as a non-invasive method to identify secondary choroidal neovascularisation in late-onset macular dystrophies. Natural history studies require longitudinal repeat scans using the same protocols. Although not ideal, comparison between different OCT machines is possible but using the same device for longitudinal follow-up is preferable.

ii. Fundus autofluorescence

Fundus autofluorescence (FAF) is a non-invasive imaging modality that has increased in popularity with modern confocal scanning laser ophthalmoscope systems. It can readily identify hypoautofluorescence associated with RPE cell death in areas of atrophy as well as the
accumulation of lipofuscin which is associated with increased hyperautofluorescent signal. Typically, FAF identifies abnormalities earlier than either clinical examination or conventional colour fundus photography. Macular or wide-field FAF fundus imaging using reduced illumination (25%), longer exciting wavelengths, infrared FAF or near infrared fundus reflectance are good alternatives to short-wavelength FAF in patients with retinitis pigmentosa and Stargardt disease to possibly reduce the risk of phototoxicity and they enhance the visualisation of the boundary of the residual island of photoreceptors in rod-cone dystrophy.

iii. Visual Field Testing

Visual field testing (Perimetry) is widely used to evaluate visual function in IRDs. It is important to document the functional extent of vision from central to the far periphery for determination of legal blindness and disability, and to monitor for progression. Goldmann kinetic perimetry has historically been utilized to test the entire visual field and locating borders between seeing and non-seeing areas. The operator-dependent nature of Goldmann kinetic perimetry has made the assessment difficult to standardize, poorly reproducible and difficult to quantify. Semi-automated systems are becoming available that overcome many of these challenges. Reliability improves after the age of 12 and results for younger patients need to take this into account when monitoring natural history.

Static visual field testing has advantages including in indices of sensitivity, and performance parameters to assess reliability. Two colour techniques have been developed to differentiate rod from cone detection under scotopic and photopic conditions.

Kinetic perimetry and suprathreshold Esterman binocular fields are the most common method used to assess peripheral vision and for licensing requirements for driving, disability evaluations, and legal blindness status.

iv. Microperimetry

Microperimetry utilizes fundus imaging and motion tracking to ensure precise stimulation of a certain location of the retina. This so-called fundus-related perimetry relates retinal sensitivity testing with morphology which can be directly correlated with the fundus autofluorescence and optical coherence tomography making microperimetry a powerful tool in evaluating macular disease. Microperimetry is particularly useful for measuring macular function in patients with eccentric viewing due to maculopathy and the ability to perform follow up testing at identical retinal loci facilitates direct comparison between tests even if the preferred retinal locus of fixation has shifted during the follow up period. Two colour techniques may be combined with microperimetry in an attempt to distinguish between rod- and cone-mediated sensitivity. Microperimetry is now commonly used as a clinical trial endpoint for gene and drug therapies in IRDs.

v. Full-field stimulus test (FST)

Rod and cone-driven electroretinogram responses become unrecordable early in the course of many IRDs due to extensive peripheral chorioretinal degeneration. To overcome this limitation, Roman and colleagues developed the full-field stimulus threshold (FST) test as a psychophysical tool to quantify the residual photoreceptor function in patients with advanced inherited retinal disorders. Patients with advanced disease and impaired fixation who cannot perform standard visual field testing can be followed with the full-field stimulus test (FST). Visual sensitivities are measured with red (e.g. peak radiance at 637 nm) and blue (e.g. peak radiance at 465 nm) stimuli in the dark-adapted state using published methods. The difference between blue and red sensitivities can be cautiously used to infer target detection by the cones, rods or a mixture of both classes of photoreceptor.

vi. Visual Electrophysiology

Visual electrophysiology provides an objective measure of retinal function. The full-field electroretinogram (ERG) is important for diagnosis and staging of disease particularly in patients with diffuse photoreceptor disease to evaluate the retina-wide function of rods and outer segments.
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

cones. Long term visual prognosis may also be inferred by visual electrophysiology. Several disorders have specific visual electrophysiology changes that are pathognomonic and correlate with genotype. These include KCNV2 retinopathy, congenital stationary night blindness, enhanced S-cone syndrome and bradyopsia.

The pattern electroretinogram (PERG) provides an objective measure of macular function which is important to differentiate macular dysfunction from generalised retinal dysfunction. Fixation is not as critical as for the multifocal ERG. However appropriate refraction is required.

The clinical electro-oculogram (EOG) is an electrophysiological test of the outer retina and retinal pigment epithelium (RPE) in which changes in the electrical potential across the RPE are recorded during successive periods of dark and light adaptation. The test is time consuming and EOG potentials are recorded every minute during the 15-minute dark phase (dark trough, DT) and at least 15minutes of light adaptation to determine if a light peak (LP) is present. In most retinal dystrophies, EOG abnormalities are proportional to the severity of the rod-mediated ERG abnormalities and are not of diagnostic importance. The important exception are disorders attributed to the bestrophin gene (BEST1). These include Best vitelliform macular dystrophy (Best disease), autosomal recessive bestrophinopathy (ARB) and autosomal dominant vitreoretiinochoroidopathy (ADVIRC). In Best disease, standard full-field ERGs are usually normal and the LP:DT (formerly Arden) ratio of the EOG is abnormal.

The multifocal electroretinogram (mfERG) provides a topographic assessment of macular function. However, this test requires steady fixation which limits the test’s effectiveness in patients with poor central vision. mfERGs can be useful for macula-involving disease detection and monitoring in patients who retain good fixation.

Despite advances in ocular imaging, visual electrophysiology remains important in differentiating central retinal disorders (e.g. macular dystrophy) from generalised retinal diseases. Similarly, visual electrophysiology is required to discriminate between different functional disorders in generalised retinal diseases (e.g. enhanced S-cone syndrome, congenital stationary night blindness, achromatopsia). The International Society for Clinical Electrophysiology of Vision (ISCEV) has published and updated standards that enable recordings to be compared between institutions and examiners (https://iscev.wildapricot.org/standards).

2.7 Clinical Evaluation for Inherited Retinal Diseases

IRDs can be grouped into stationary or progressive rod, rod-cone, cone and cone-rod disorders, macular disorders and chorioretinopathies. Table 1 describes appropriate examinations and their timing(s). For syndromic diseases, the schedule should include consultation with the appropriate systemic team eg clinical geneticist, paediatrician, audiology, ENT, renal physician, or neurologist.

Table 1 Notes

Visual field testing is adapted to the type of visual dysfunction and its stage. Kinetic visual fields are recommended for IRDs affecting peripheral vision. Macular disorders are better assessed and monitored with static perimetry. Microperimetry, when available, is good for monitoring macular and paramacular function.

Visual electrophysiology provides an objective means of determining the affected retinal components. A full field ERG is required to separate macular disorders from generalised retinopathies. An undetectable full-field ERG is not recommended to be repeated. A PERG provides objective evidence of macular dysfunction even when central acuity is good. The multifocal ERG is of limited value in patients with poor central acuity and/or unstable fixation. The EOG is indicated in macular dystrophies where Best disease or Bestrophin retinopathies are suspected.
Table 1. Clinical Evaluation for Inherited Retinal Diseases

<table>
<thead>
<tr>
<th>Clinical Evaluation</th>
<th>Stationary night blindness dystrophies</th>
<th>Cone dysfunction syndromes</th>
<th>Progressive Rod-Cone dystrophies</th>
<th>Progressive Cone &amp; Cone-Rod dystrophies</th>
<th>Macular Dystrophies</th>
<th>Chorioretinal Dystrophies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Visit</td>
<td>Follow-Up Visits</td>
<td>Initial Visit</td>
<td>Follow-Up Visits</td>
<td>Initial Visit</td>
<td>Follow-Up Visits</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ocular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current needs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systemic &amp; medications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History - Pedigree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Best corrected visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anterior segment - slit lamp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intraocular pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fundus examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multimodal imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Colour fundus photos - wide field</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Spectral Domain OCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fundus autofluorescence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Fields</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kinetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Static</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Microperimetry (where available)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Electrophysiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Full Field ERG, Pattern ERG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Multifocal ERG and EOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic Diagnostic Testing and Genetic Counselling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

Paediatric Patients
IRDs commonly commence in childhood. Advancing technology has enabled sophisticated assessments to determine underlying structural and functional deficits in clinic settings. These include multimodal imaging modalities such as wide field fundus imaging and portable OCT systems. Visual electrophysiology has adapted the ISCEV standards to children\textsuperscript{123} as well as new hand held devices\textsuperscript{124, 125} or modified protocols with skin electrodes\textsuperscript{126-128}. Sedated clinical assessments provide the opportunity for a more definitive exam and higher quality imaging; however, the risks of sedation must be weighed against the value of the information gained at the specific age.\textsuperscript{129}

Visual Rehabilitation and Patient education
Genetic confirmation of the underlying IRD provides significant information to an individual and their family about recurrence risk, opportunities to make informed family planning decisions, prognosis and treatment options. Appropriate coordination of visual rehabilitation between clinicians, vision support services and patient support organisations will optimise patient outcomes and assist patients perform daily life activities in order to maintain independence.(appendix 1) Information regarding clinical trials can be found at https://clinicaltrials.gov/ and locally at http://www.anzctr.org.au/.

3. Summary
Genomic medicine is becoming part of routine preventive, diagnostic, and interventional health care. These advances bring challenges for how health-care organizations deliver this new technology.\textsuperscript{130} In ophthalmology, significant advances have occurred in the management of patients with inherited retinal diseases, involving both genomic approaches and multimodal structural and functional investigations. These advances provide information that can improve diagnosis, inform prognosis and eligibility for therapies. The complexity of IRDs requires input from both ophthalmology and clinical genetics.\textsuperscript{22} The benefits of modern genetic diagnostics and counselling supports the introduction of equitable genetic testing for patients with presumed genetically caused retinal degeneration.\textsuperscript{23}
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

Guideline Authors
Prof John Grigg (NSW) Chair working group
Prof Robyn Jamieson (NSW) (Clinical Geneticist)
Dr Fred Chen (WA)
Assoc/Prof Matthew Simunovic (NSW)
Dr Aamira Huq (VIC) (Clinical Geneticist)
Assoc/Prof Andrea Vincent (NZ)
Prof David Mackey (WA)
Ms Lisa Kearns (VIC) (Orthoptist, Genetic Counsellor)
Dr John de Roach (WA) (Inherited retinal disease registry)

RANZCO Fellows and Genetics Professionals consulted
Assoc/Prof Heather Mack (VIC) President RANZCO
Dr Jenny Arnold (NSW) Chair ANZSRS
Dr Madeleine Adams (QLD)
Dr Gaurav Bhardwaj (NSW)
Dr Antony Clark (WA)
Dr Thomas Edwards (VIC)
Assoc/Prof Rowan Essex (ACT) ANZSRS Committee
Prof Glen Gole (QLD)
Dr Alex Hewitt (TAS)
Dr Michael Hogden (QLD)
Assoc/Prof Anthony Kwan (QLD) ANZSRS Committee
Ms Lisa Kearns (Orthoptist, Genetic Counsellor)
Clinical Assoc/Prof Gerald Liew (NSW)
Dr Alan Ma NSW (Clinical Geneticist)
Clinical Prof Frank Martin (NSW)
Dr Rowan Porter (QLD)
Dr Jonathan Ruddle (Vic)
Dr Dianne Sharp (NZ)
Dr. Deepa Taranath (SA)
Assoc/Prof Clare Fraser (NSW)
Dr Claire Hooper (NSW)
Dr Elisa Cornish (NSW)
Dr Abhishek Sharma (QLD)
Professor Dianne Nicol (Tas) Legal and ethics
Dr Tina Lamey (WA) Inherited Retinal disease registry
Professor Margaret Otlowski (Tas) legal and Ethics
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

Dr Sandra Staffieri (VIC) Orthoptist
Professor Ian Alexander (NSW) Gene therapy and vector production
Professor Deborah Schofield (NSW) Health economist
Dr Anai Gonzalez-Cordero (NSW) Ocular stem cell facility
Dr Emmanuelle Souzeau (SA) Genetic counsellor
Associate Professor Bruce Bennetts (NSW) Diagnostic Molecular Scientist
Professor Kathryn Burdon (Tas) Genetic scientist
Dr Livia Carvalho (WA) Ocular Molecular scientist
Professor Stuart Macgregor Ocular Bioinformatician
APPENDIX 1 Vision support agencies and patient support organisations

<table>
<thead>
<tr>
<th>Vision Support organisations</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision Australia</td>
<td><a href="https://www.visionaustralia.org/">https://www.visionaustralia.org/</a></td>
</tr>
<tr>
<td>Royal Institute for Deaf and Blind</td>
<td><a href="https://www.ridbc.org.au/">https://www.ridbc.org.au/</a></td>
</tr>
<tr>
<td>Able Australia (formerly Deaf Blind Association)</td>
<td><a href="https://ableaustralia.org.au/">https://ableaustralia.org.au/</a></td>
</tr>
<tr>
<td>Senses Australia</td>
<td><a href="https://www.senses.org.au/">https://www.senses.org.au/</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Support Organisations</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure Blindness Australia (formerly Retina Australia NSW)</td>
<td><a href="https://www.cureblindnessaustralia.org.au/">https://www.cureblindnessaustralia.org.au/</a></td>
</tr>
<tr>
<td>Retina New Zealand</td>
<td><a href="https://retina.org.nz/">https://retina.org.nz/</a></td>
</tr>
<tr>
<td>Blind citizens New Zealand</td>
<td><a href="https://abcnz.org.nz/">https://abcnz.org.nz/</a></td>
</tr>
<tr>
<td>Australian Braille Authority (ABA)</td>
<td><a href="http://brailleaseuistralia.org/">http://brailleaseuistralia.org/</a></td>
</tr>
<tr>
<td>Deafblind Australia</td>
<td><a href="https://www.deafblind.org.au/">https://www.deafblind.org.au/</a></td>
</tr>
<tr>
<td>Bardet-Biedl Australia</td>
<td><a href="http://www.bardetbiedlaustralia.org/">http://www.bardetbiedlaustralia.org/</a></td>
</tr>
<tr>
<td>Usherkids Australia</td>
<td><a href="https://www.usherkidsaustralia.com/support.html">https://www.usherkidsaustralia.com/support.html</a></td>
</tr>
</tbody>
</table>

There are others for deafblind:
http://www.deafblind.com/australia.html#Western%20Australia%20Deaf-Blind%20Association
Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020

References


3. Daiger SP, Sullivan LS, Bowne SJ. RetNet Retinal information Network. The University of Texas-Houston Health Science Center; 2015.


Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020


Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020


Guidelines for the assessment and management of patients with Inherited retinal degenerations (IRD) - August 2020


