Received: 10 February 2022 | Revised: 28 April 2022 | Accepted: 15 May 2022

DOI: 10.1111/ceo.14110

ORIGINAL ARTICLE - CLINICAL SCIENCE

Clinical & Experimental Ophthalmology WILEY

Victorian evolution of inherited retinal diseases natural history registry (VENTURE study): Rationale, methodology and initial participant characteristics

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Funding information
Angior Family Foundation; Cass Foundation; Centre for Eye Research Australia, Grant/Award Number: Strategic Grant; National Health and Medical Research Council Investigator grant, Grant/Award Number: GNT#1195713; Novartis Pharmaceuticals Corporation; Retina Australia; University of Melbourne, Grant/Award Numbers: Driving Research Momentum Fellowship, Melbourne Medical School Strategic Grant

Abstract

Background: Emerging treatments are being developed for inherited retinal diseases, requiring a clear understanding of natural progression and a database of potential participants for clinical trials. This article describes the rationale, study design and methodology of the Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE), including data from the first 150 participants enrolled.

Methods: VENTURE collects retrospective and prospective data from people with inherited retinal diseases. Following registration, participants are asked to attend a baseline examination using a standardised protocol to confirm their inherited retinal disease diagnosis. Examination procedures include (i) retinal function, using visual acuity and perimetry; (ii) retinal structure, using multimodal imaging and (iii) patient-reported outcomes. Participants' molecular diagnoses are obtained from their clinical records or through targeted-panel genetic testing by an independent laboratory. Phenotype and genotype data are used to enrol participants into disease-specific longitudinal cohort sub-studies.

Results: From 7 July 2020 to 30 December 2021, VENTURE enrolled 150 registrants (138 families) and most (63%) have a rod-cone dystrophy phenotype. From 93 participants who have received a probable molecular diagnosis, the most common affected genes are *RPGR* (13% of all registrants), *USH2A* (10%), *CYP4V2* (7%), *ABCA4* (5%), and *CHM* (5%). Most participants have early to

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Members of VENTURE Study Consortium have been given in Appendix.

moderate vision impairment, with over half (55%) having visual acuities of better than 6/60 (20/200) at registration.

Conclusions: The VENTURE study will complement existing patient registries and help drive inherited retinal disease research in Australia, facilitating access to research opportunities for individuals with inherited retinal diseases.

KEYWORDS

gene therapy, genetic disease, inherited, retinal disease, rod-cone dystrophies (retinitis pigmentosa)

1 | INTRODUCTION

Inherited retinal diseases (IRDs) are a group of genetically and clinically heterogenous eye conditions that cause irreversible vision loss. IRDs affect ~1 in 2000–4000 individuals,[1,2] and they are the most common cause of legal blindness in working-age adults in most developed countries, including Australia.[3] IRDs have a significant socioeconomic impact; the national cost of IRDs, based on estimates from the United Kingdom, is over $500 million Australian dollars per year.[4,5]

Vision loss occurs due to pathogenic variants in critical genes responsible for developing or maintaining the viability of retinal photoreceptor cells, retinal pigment epithelium,[6] and/or choroid. Historically IRDs have been diagnosed and categorised by their clinical or phenotypic presentation.[7] With improved access to genetic testing, there is a greater focus on using gene-specific disease nomenclature. To date, ~300 causative IRD genes have been identified.[8]

Until recently, there have been no treatments for slowing or stopping vision loss in IRDs. However, in December 2017, the world's first ocular gene therapy treatment, voretigene neparvovec-rzyl (Luxturna®), was approved by the US Food and Drug Administration (FDA) for IRDs associated with biallelic pathogenic variants in the *RPE65* gene. The FDA approval was a milestone in the era of advanced genomic medicine in all fields, but particularly in ophthalmology. Other emerging treatment options for IRDs include clustered regularly interspaced short palindromic repeats (CRISPR) gene editing, oligonucleotide therapies, stem cell transplantation and other neuroprotective agents and devices.[9] These therapies can be used adjunctively with gene therapy or in situations where gene therapy may not be suitable.

Developing new IRD treatments requires a clear understanding of the genotype profiles, clinical characteristics and natural progression of different IRD phenotypes.[10] Characterising IRD pathophysiology and phenotypes across different IRD genotypes also assists in identifying and evaluating novel outcome measures and endpoints in clinical trials. IRD patient registries also play a key role in facilitating participants' access to emerging therapies. To support future IRD research in Australia, it is crucial to have access to both genetic and clinical data in different IRDs to learn about their genotype–phenotype correlations and to identify patient cohorts that are suitable for emerging therapies.[11]

Here, we describe the study design and methodology of the Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE) and the characteristics of the first 150 participants enrolled in the study database (2020–2021). VENTURE collects genotype and phenotype data across a range of IRDs to better understand each condition. Following baseline examination and confirmation of diagnosis, VENTURE participants are then enrolled into disease-specific, prospective longitudinal cohort sub-studies to better characterise IRDs that are being targeted in the development of new pharmaceutical and biotech interventions.[12]

VENTURE and the associated sub-studies complement other Australian registries, such as the Western Australian Retinal Disease (WARD) study,[13] the Fight Retinal Blindness! registry and the Australian Inherited Retinal Disease Registry and DNA bank (AIRDR).[14] A distinct contribution of VENTURE is the phenotyping of study participants following a defined protocol at baseline. This evaluation enables accurate IRD diagnosis, and participants can then be enrolled into disease-specific longitudinal VENTURE sub-studies to investigate the natural history of specific IRDs. VENTURE also expands the network of natural history studies across Australia and New Zealand,[13–16] emphasising the importance of nationwide coverage to facilitate ease of access to emerging treatments for patients with IRDs.

2 | METHODS

2.1 | Study design

The VENTURE study is an IRD registry that collects both retrospective and prospective data from people with

IRDs. Study sites where examinations currently take place include the Centre for Eye Research Australia and the Department of Optometry and Vision Sciences, University of Melbourne. Any future study expansion to additional sites will be authorised by the principal investigators, where the sites has appropriate equipment certified to perform clinical testing according to the study protocol. There is no cost to participants to enter the registry.

The study is conducted in accordance with the revised Declaration of Helsinki and following the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. Ethics approval was obtained from the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee (ID: RVEEH 19/1443H) and registered with the University of Melbourne Human Ethics Committee (#21037). All potential participants gave informed consent prior to any study-related procedures. Ethics approval for VENTURE includes the collection and storage of participants' retrospective clinical data, undertaking of clinical examination procedures and molecular investigations.

Eligible participants include adults and children with a genetically confirmed or clinically suspected IRD diagnosis, including those who are awaiting further genetic testing. VENTURE participants are recruited through referrals from health practitioners (e.g., ophthalmologists, optometrists, genetic counsellors), as well as those who contact the study investigators directly wishing to be involved in research. When VENTURE commenced participant recruitment, many referrals were for IRDs that were being targeted in pre-clinical and clinical trials assessing retinal gene therapy and other pharmaceutical and biotech interventions (e.g., gene therapy products targeting *RPGR* and *CHM* genes),[12] to ensure that those participants have access to emerging treatments. Thus, the current phenotype distribution of the study cohort has a higher representation of IRDs with active research interests, rather than being representative of the population frequency of IRDs in Australia.

Study data are collected and managed using REDCap electronic data capture tools hosted at the Centre for Eye Research Australia. Access to study data is password-protected with two-factor authentication.[17] Clinical data are backed-up to a secure, password-protected server that is only accessible to study investigators. Access to the VENTURE registry is restricted to investigators who are named on the VENTURE ethics approved study team list.

Quality assurance is implemented to minimise bias include a manual of procedures outlining the standardisation of data collection and procedures and regular data monitoring. All personnel performing study procedures are trained by the Principal Investigators (or specified delegates) to undertake the required clinical examination.

2.2 | Study organisation

Information collected at registration include demographics, clinical and genetic diagnosis (if known), ocular and systemic medical history, and family history of IRDs. Following registration, participants' retrospective clinical data that are collected include their genetic testing history and clinical records pertaining to measures of retinal and visual function [visual acuity (VA), perimetry records, electroretinogram records) and retinal imaging (obtained from fundus images and Ocular Coherence Tomography (OCT) scans].

All participants on the registry are invited to attend a baseline clinical examination, involving a standard suite of retinal structural and functional assessments, to capture baseline clinical data and provide a benchmark from which to compare results across study visits over time (Figure 1). As VENTURE enrols IRD participants from across Australia and New Zealand, participants can remain in the registry without attending a clinical examination. Following baseline assessment, participant diagnosis is confirmed by a retinal clinician with IRD expertise and, if required, consulting a panel of IRD specialists. Following baseline assessment, participants may then be assigned into disease-specific VENTURE sub-studies, or remain on the registry until further studies or clinical trials for their condition become available. VENTURE disease-specific sub-studies are longitudinal prospective cohort studies that investigate disease progression in specific genotypes, followed-up at regular intervals. VENTURE sub-studies may implement modified protocols that take into account specific IRD phenotype and genotype.

2.3 | Prospective clinical evaluations at baseline

Participants' baseline clinical data will be collected according a standardised protocol. This information will be used to confirm IRD diagnosis and will allow the comparison of clinical features across different clinical phenotypes, enabling us to enrol participants into specific prospective sub-studies.

2.3.1 | Visual acuity

Best-corrected visual acuity (BCVA) will be measured for each eye following subjective refraction. VA assessment

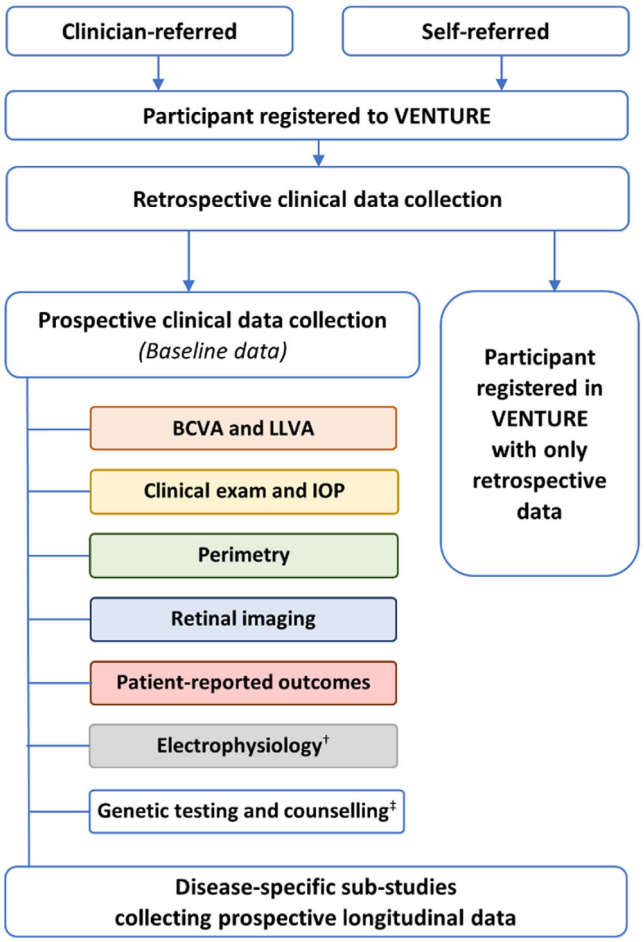

FIGURE 1 Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE) study process. BCVA, best-corrected visual acuity; IOP, intraocular pressure; LLVA, low luminance visual acuity. †Electrophysiology is performed where clinically indicated. ‡Genetic testing for individuals with IRD who have not been molecularly characterised. Testing is performed using a target gene panel to screen for known variants

will be performed using clinical trial conditions, with room lights switched off and using a retro-illuminated high contrast Early Treatment Diabetic Retinopathy Study letter chart.[18] Low luminance VA will be measured first by placing a 2.0 log unit neutral density filter in front of each eye. The same procedure will be repeated for standard BCVA assessment, without a neutral density filter. If a participant is unable to read any letters at 1 meter, VA will be testing using the Berkeley Rudimentary Vision Test under room-illumination (between 250 and 1000 lux),[19] for assessing VA levels 6/240 (20/800) or worse.

2.3.2 | Anterior segment examination

Clinical ophthalmic examination of the anterior segment will be performed. Clinically notable findings for the lids and adnexa, tear film, cornea, conjunctiva and the anterior chamber will be recorded, including specific anterior segment features associated with IRDs, such as limbal crystals, keratoconus and long anterior lens zonules. Intraocular pressure will be measured using an iCare tonometer (IC200, Centervue Spa., iCare Finland). Assessment of the lens will be performed and graded using the Lens Opacities Classification System II (LOCS II), for nuclear, cortical and posterior subcapsular cataracts and lens opacities.[20]

2.3.3 | Perimetry

Monocular peripheral field boundaries will be measured using the Goldmann manual perimeter, using the III4e or V4e isopters. If the V4e target is not seen by the participant, 'unable to perform the test' will be recorded. The area within the visual field boundary will be checked for scotomas and these will be mapped from a non-seeing region to a seeing region to outline their extent.

Central visual sensitivity will be assessed using MAcular Integrity Assessment (MAIA) fundus-controlled perimeter (Centervue SpA, Padova, Italy) in mesopic conditions.[21] Testing will be performed with mydriatic pupils and in the absence of dark adaptation time.[22] Testing will be performed using a 68-stimuli grid pattern that samples the radial 10-degree visual field surrounding the preferred fixation point, using a 4–2 threshold strategy. Fixation stability will be system quantified and the follow-up function will be used for repeat examination. Participants with visual acuity of <6/60 or severe nystagmus are exempted from performing fundus-controlled perimetry.

2.3.4 | Image acquisition

After functional testing, retinal images will be captured using the Optos® ultra-widefield fundus (UWF) camera (Optos plc, Dunfermline, Scotland, United Kingdom). The UWF camera uses a scanning laser ophthalmoscope to capture images spanning 200-degrees of the internal eye angle. Composite colour retinal images will be obtained using laser light sources of wavelengths 532 nm (green) and 635 nm (red), with 20 μm resolution. Fundus autofluorescence (FAF) images are then captured with a green excitation laser at 532 nm, with 14 μm resolution. Additional retinal images may be taken using a coloured fundus camera (e.g., Topcon fundus retinal camera) to better capture changes at the macular and posterior pole using true colour.

High-resolution cross-sectional scans of the macula region will be obtained across a 30 by 20° image field using Heidelberg Spectral-Domain OCT (Heidelberg

Engineering, Heidelberg, Germany). For volume scans, 49 B-scans (spaced ~120 μm apart) will be captured with an automatic real-time (ART) averaging of a minimum of nine images. Infrared confocal scanning laser ophthalmoscope images will be obtained for 30° field of view centred on the fovea. Additional images using other features such as enhanced depth imaging (EDI) will be taken when clinically indicated.

2.3.5 | Patient-reported outcomes

Patient-reported measures of the impact of vision impairment and quality of life impairment will be assessed using a suite of validated questionnaires.[23] Questionnaires include the Impact of Vision Impairment questionnaire,[24,25] and the IVI-Very Low Vision (IVI-VLV) in individuals with severe visual impairment (VA of worse than 6/60 or visual field less than 10 degrees),[26] to assess restriction of participation in activities of daily living; the Vision and Quality of Life tool, to assess vision-related quality of life for the health economic evaluation of vision-related programs[27]; and the Hospital Anxiety and Depression Scale, to assess mood, emotional distress, anxiety, depression and emotional disorder.[28]

2.3.6 | Additional clinical testing

Additional clinical procedures and retinal imaging may be undertaken for subsets of participants. Full field electroretinography (ffERG; Espion E2; Diagnosis LLC) using ISCEV standards may be performed for staging of disease or if the participant has not had electrophysiology testing to confirm their diagnosis.[11,29] Full-field stimulus threshold test (FST) may be conducted to quantify visual perception when perimetry-based approaches are not possible.[30] Colour vision will be assessed if clinically indicated.

2.4 | Genetic testing

If a genetic report is not available from the participant's clinical records, genetic testing may be performed via an independent National Association of Testing Authorities Australia (NATA) accredited or Clinical Laboratory Improvement Amendments (CLIA)-certified clinical diagnostic laboratory, or through collaboration with the AIRDR.

The purpose of diagnostic genetic testing in VENTURE is to screen affected individuals for known causal variants and to combine genotyping information with family history and baseline clinical examination to support IRD diagnosis. Although we hope to provide everyone on the registry with access to genetic testing in time, molecular investigations will be prioritised for participants due to research and clinical needs.

Genetic testing is offered to registered participants without a molecular diagnosis as an optional component of their research participation. Prior to taking the genetic test, information about the test and discussion surrounding the potential implications of the results are provided to the participant by a study ophthalmologist or investigator who has received training in ocular genetics. If the participant requests, or if the study investigator feels that the participant could benefit from further counselling prior to having a genetic test, participants are referred to their ophthalmologist or a genetic counsellor for further discussions and education, to ensure that they are well-prepared for the implications of the results. Following the test, results disclosure and genetic counselling are provided by a physician with expertise in IRDs or by a qualified geneticist or genetic counsellor.[31]

Molecular investigations reported here were performed using either the Blueprint Genetics or Invitae targeted next generation sequencing (NGS) retinal dystrophy panels, comprising 285 and 293 genes that are associated with IRDs, respectively (at the time of testing between July 2020 and December 2021). A biospecimen was collected and sequencing, bioinformatic analyses and clinical interpretation were performed according to the laboratory's specifications. In brief, the target region for each gene includes coding exons, up to 20 base pairs of adjacent introns on either side of the coding exons (i.e., the exon-intron boundary), and relevant deep-intronic regions. Any variants that fall outside these regions are not analysed. Variants were classified according to an adaptation of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines, as outlined in the Blueprint Genetics (https://blueprintgenetics.com/variant-classification/) and Invitae (https://invitae.com/en/provider-faqs/tech-and-quality)[32] websites.

Only genes known to cause inherited retinal conditions are examined as part of this study. Following initial target-panel testing, participants are referred for further clinical testing (e.g., phasing, cascade testing, or further genetic tests) if this is required to confirm their molecular diagnosis, or if they have further queries or issues (e.g., family planning). Any variants of unknown significance identified from the initial test are documented in the database and will be re-evaluated if new research or clinical trials relating to the identified variant arise.

For the purpose of this study, participants who have had genetic testing are reported as having a probable molecular diagnosis if they were found to have a

pathogenic or likely pathogenic variant(s) in an apparently disease-causing state (e.g., one or more variants in a gene linked with dominant or X-linked disease or two or more variants in a gene linked with recessive disease) from the target panel. Otherwise, participants are considered to have an inconclusive molecular diagnosis.

2.5 | Data analysis

Purposive sampling will be used given the rare nature of IRDs. Given the estimated prevalence of 1 in 2000, the IRD population in Victoria is estimated as 3300 people. The registry is anticipated to enrol up to 100 participants per year.

For baseline variables presented here, the distribution of the data was explored prior to analysis, and data are summarised as mean and standard deviation (normally distributed variables), median and interquartile range (non-normally distributed variables) or counts and percentages (categorical variables). Participants' ethnicities are classified using the Australian Standard Classification of Cultural and Ethnic Groups. IRDs were classified according to previous published reports (Table S1),[33] as (i) panretinal pigmentary retinopathies, affecting primarily rods or cones; (ii) macular dystrophies with only central involvement; (iii) stationary diseases and (iv) other IRDs, such as vitreoretinopathies. For vision at registration, the distance BCVA in the better seeing eye at participants' last clinical visit is used to classify participants into levels of visual impairment according to the standards defined by the World Health Organization[34] and the Harmonisation of Outcomes and Vision Endpoints in Vision Restoration Trials[35] Taskforce consensus document (Table S2).[35]

Participant characteristics were compared according to the method of recruitment. Intergroup comparisons were performed using *t* tests (normally distributed variables), Wilcoxon's rank-sum tests (non-normally distributed variables), or the Fisher's exact test (categorical variables). Comparison between IRD classifications was performed using the Kruskal-Wallis test, and Benjamini and Hochberg adjusted *p*-values are reported for pairwise comparisons.

Statistical analyses were performed using *R* for statistical computing version 4.0.0 (R Core Team 2020, Vienna, Austria).

3 | RESULTS

3.1 | Registrant information

Between 7 July 2020 and 30 December 2021, VENTURE has enrolled 150 registrants with IRDs from 138 families (participant characteristics are shown in Table 1). Study recruitment is ongoing. There were no differences in age, gender or ethnicity between participants who were referred by clinicians and those who self-referred into the registry. Over half (52%, $n = 78$) of study registrants reported a positive family history of IRDs; ~63% of those ($n = 49$) has a parent or a sibling with an IRD.

Figure 2 shows the clinical diagnoses of VENTURE registrants; diagnoses are either self-reported or as reported by ther referring clinician. Most registrants have panretinal pigmentary retinopathies (83%). The most common IRD is rod-cone dystrophy (including Usher syndrome), representing 63% of all registered participants. Other common panretinal pigmentary retinopathies in VENTURE are Bietti crystalline dystrophy (7%, $n = 10$) and choroideremia (5%, $n = 7$), representing active research priorities in these conditions.[12,36] Thirteen percent of registered participants have macular dystrophies, predominantly Stargardt disease or generalised macular dystrophy (9% of all registrants, $n = 14$). Three participants (2%) have a stationary IRD, and three participants (2%) have hereditary vitreoretinopathies (all have x-linked retinoschisis).

Across all registrants, the median age of first symptoms was 16 (IQR: 8–30) years, and self-reported age of diagnosis was 22 (10–36) years. A lower age of first symptoms was reported by those with panretinal pigmentary retinopathies [15 (7–25) years] compared with macular dystrophies [28 (16–38) years; adjusted $p = 0.028$), but neither were significantly different from those with other classes retinal dystrophies [16 (1–16) years; adjusted $p > 0.05$].

Eleven percent of registrants either currently smoke or have previously smoked cigarettes. There were no differences in age between registrants who have smoked compared to registrants who have never smoked cigarettes [median (IQR): 51 (31–62) years vs. 45 (29–56) years; $p = 0.51$).

Over a third (37%) of registrants currently take oral vitamins and supplements, most commonly a daily multivitamin (34 of the 55 registrants). Participants who reported taking vitamins and supplements were generally older than those who reported that they do not [median (IQR): 51 (31–60) years vs. 42 (26–53) years; $p = 0.047$).

3.2 | Genetic information

Over a third (39%; $n = 58$) of VENTURE registrants had already obtained a molecular diagnosis for their IRD at the time of their study enrolment. A further 55% ($n = 83$) of participants have initiated diagnostic testing using a NGS panel-based testing through VENTURE, of which, results were available for 37% ($n = 56$) of registrants. The remaining 6% of participants ($n = 9$) were either waiting

TABLE 1 Participant baseline characteristics

	Referral pathway			
	Self-referred ($n = 75$)	Referred by clinician ($n = 75$)	Total ($n = 150$)	*p*-value*
Age, years				
Range	10–79	5–87	5–87	
Median (IQR)	47 (34–56)	44 (24–58)	46 (29–57)	0.143
Gender, *n* (%)				
Male	39 (52%)	51 (68%)	90 (60%)	0.066
Female	36 (48%)	24 (32%)	60 (40%)	
Ethnicity, *n* (%)				0.202
North African and Middle Eastern	2 (2.7%)	5 (6.7%)	7 (4.7%)	
Sub-Saharan African	4 (5.3%)	1 (1.3%)	5 (3.3%)	
Peoples of the Americas	3 (4%)	0 (0%)	3 (2%)	
North-East Asian	1 (1.3%)	4 (5.3%)	5 (3.3%)	
Southern and Central Asian	4 (5.3%)	4 (5.3%)	8 (5.3%)	
South-East Asian	2 (2.7%)	4 (5.3%)	6 (4%)	
North-West European	7 (9.3%)	2 (2.7%)	9 (6%)	
Southern and Eastern European	3 (4%)	3 (4%)	6 (4%)	
Oceanian	49 (65.3%)	52 (69.3%)	101 (67.3%)	
Clinical diagnosis, *n* (%)				
Panretinal pigmentary retinopathies	61 (81.3%)	63 (84%)	124 (82.7%)	0.83
Macular dystrophies	11 (14.7%)	9 (12%)	20 (13.3%)	0.811
Stationary diseases	1 (1.3%)	2 (2.7%)	3 (2%)	1
Hereditary vitreoretinopathies	2 (2.7%)	1 (1.3%)	3 (2%)	1
Age at first symptoms, years				
Range	0–64	1–70	0–70	
Median (IQR)	18 (8–31)	16 (8–28)	16 (8–30)	0.923
Age at diagnosis, years				
Range	0–65	1–70	0–70	
Median (IQR)	23 (10–36)	18 (11–38)	22 (10–36)	0.93
Smoking, *n* (%)				0.206
Yes	2 (2.7%)	7 (9.3%)	9 (6%)	
Previous	3 (4%)	4 (5.3%)	7 (4.7%)	
Taking vitamins/supplements, *n* (%)	27 (36%)	28 (37.3%)	55 (36.7%)	1.0
Confirmed molecular diagnosis at study registration, *n* (%)	29 (38.7%)	29 (38.7%)	58 (38.7%)	1.0

Abbreviation: IQR, interquartile range.

for genetic results through other genetic services (n = 3), awaiting their initial VENTURE clinical appointment ($n = 3$), or are interstate participants who have not chosen to do their genetic testing through VENTURE ($n = 3$; specific reasons not investigated).

Figure 3 shows the distribution of molecular diagnoses of VENTURE registrants. Of the 114 registrants who have completed genetic testing, a probable causative variant was found in 82% ($n = 93$) of individuals, either from their clinical records (46%; $n = 53$) or through newly-initiated targeted-NGS panel testing (35%; $n = 40$). Probable causative variants were most commonly found in the genes *RPGR* ($n = 20$, 13% of all registrants), *USH2A* ($n = 15$, 10%;), *CYP4V2* ($n = 10$, 7%), *ABCA4* ($n = 8$, 5%),

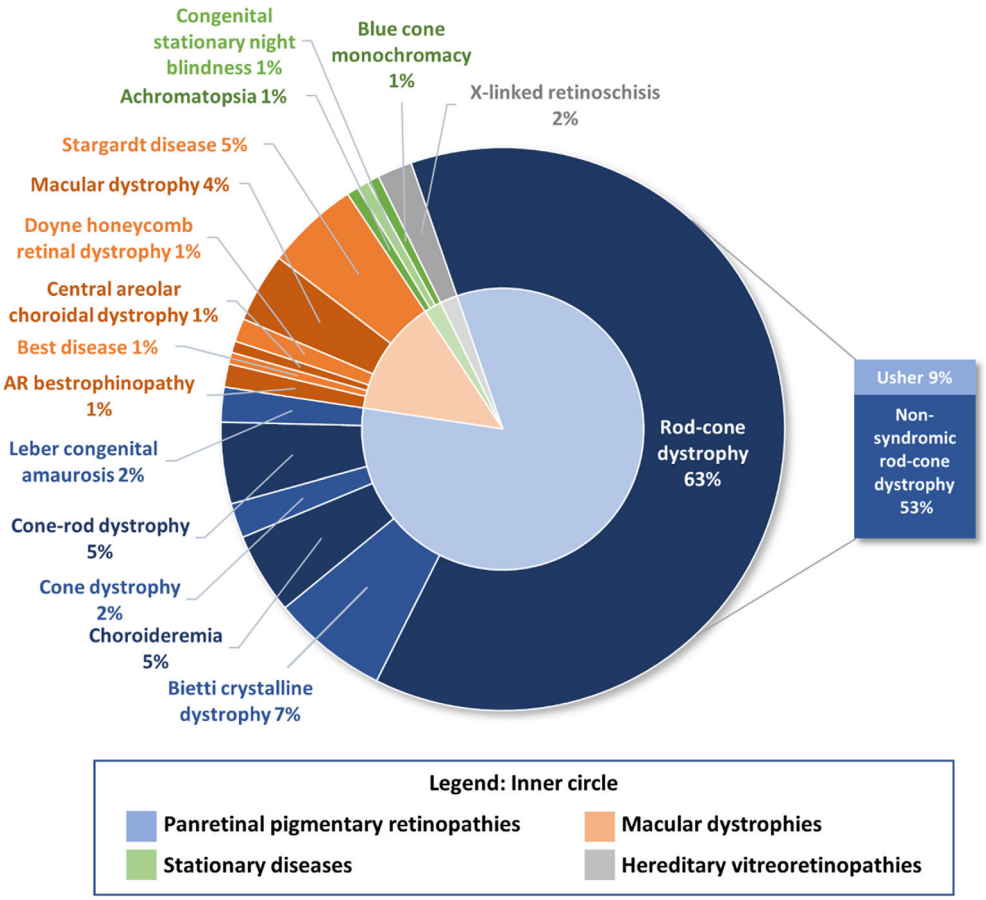

FIGURE 2 Clinical inherited retinal disease diagnoses of the first 150 participants in Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE). Inner ring shows clinical categories and outer ring primary inherited retinal disease diagnoses. The phenotype distribution represents active research interests for conditions with emerging clinical trials. AR, autosomal recessive; Usher, Usher syndrome

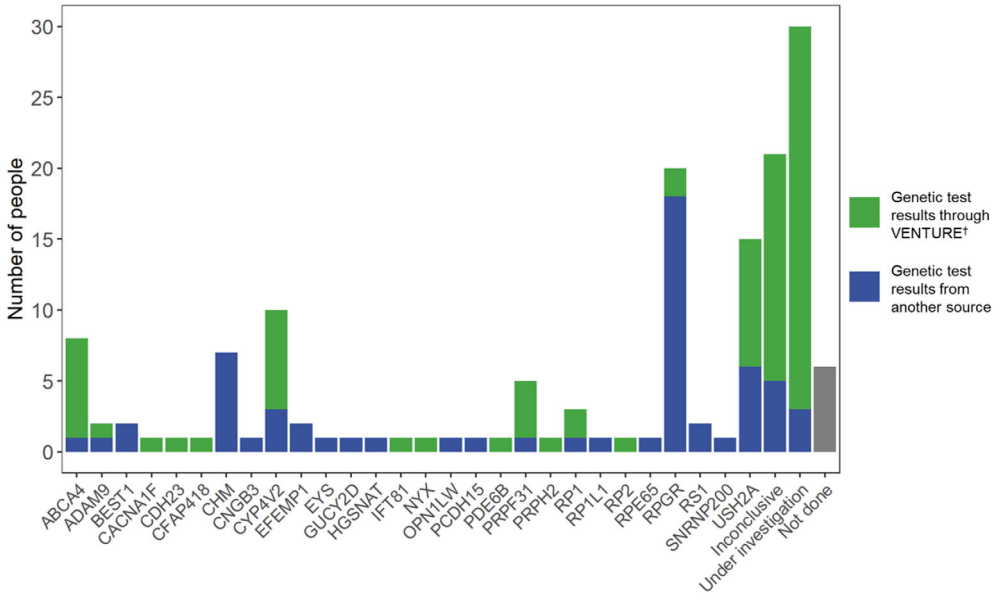

FIGURE 3 Genetic diagnoses of participants in the Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE). Data include 150 individuals from 138 families. The genotype distribution represents active research interests for conditions with emerging clinical trials. †Probable molecular diagnosis obtained from targeted gene panels is reported until further co-segregation analysis can be completed (participants with variants in genes *ABCA4, USH2A, CDH23, CFAP418*) or for further evaluation of structural variants (participants with variants in genes *ADAM9, PRPF31*) to confirm molecular diagnosis

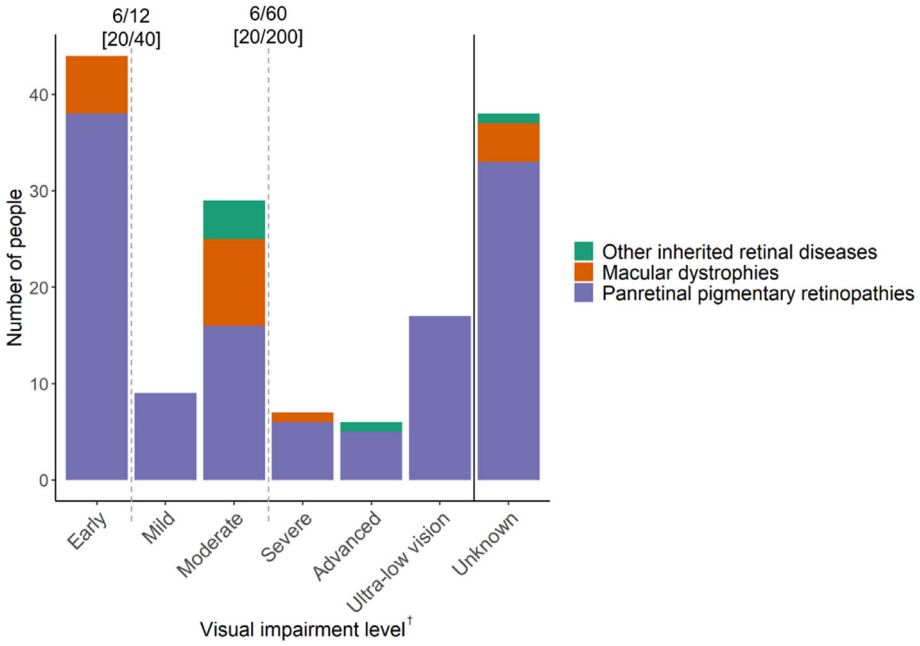

FIGURE 4 Visual impairment levels of participants in the Victorian Evolution of inherited retinal diseases NaTUral history REgistry (VENTURE; $n = 150$), based on clinical data at the time of their registration. Other IRDs include stationary and vitreoretinal diseases (Table S2). †Visual impairment levels are: Early = 6/12 (20/40) or better. Mild = worse than 6/12 (20/40) to 6/18 (20/60). Moderate = worse than 6/18 (20/60) to 6/60 (20/200). Severe = worse than 6/60 (20/200) to 3/60 (20/400). Advanced = worse than 3/60 (20/400) to 1/60 (20/1200). Ultra-low vision = worse than 1/60 (20/1200). Unknown = clinical data from within 2 years of study registration not available

CHM ($n = 7$, 5%), and *PRPF31* ($n = 5$, 3%). These genotypes account for 70% of all molecularly characterised individuals. Clinical diagnoses corresponding to each genetic variant are shown in Figure S1.

Amongst the 93 molecularly characterised individuals, 65% have causative variants in autosomal genes and 35% in X-linked genes. Of the autosomal genes, 45% of individuals have causative variants in recessive genes, 9% have causative variants in dominant genes and the remaining 11% have variants in genes acting in with either a dominant or recessive manner.

3.3 | Visual impairment levels

Figure 4 shows the visual impairment levels of VENTURE registrants at the time of their study enrolment, obtained from retrospective clinical data. Visual acuity data within the last 2 years of enrolment was available for 75% of registrants. Over half (55%; $n = 82$) of registered participants had their last recorded VA equal to or better than 6/60 (20/200), and approximately a third of all registered participants (29%; $n = 44$) had VA equal to or better than 6/12 (20/40).

4 | DISCUSSION

This article describes the design of the VENTURE study and the characteristics of the 150 participants enrolled into the registry to date. VENTURE aims to collect genotype and phenotype data across different IRDs over time. This registry will also set a foundation for disease-specific longitudinal sub-studies and support the development of IRD treatments in Australia, by identifying well-characterised and genotyped cohorts of patients with an IRD.

The VENTURE study protocol was developed with guidance from recognised experts in IRDs and gene therapy. A key benefit of VENTURE is that the registry provides a well characterised cohort of IRD participants that can be readily identified and enrolled into future clinical trials and treatments. All registrants are able to opt-in to being notified of any potential treatments that arise for their condition, making this registry a useful resource for future IRD clinical trials. In addition to other interstate registries, VENTURE adds greater coverage of Victoria, as well as comprehensive genotyping and phenotyping data, to facilitate access to emerging treatments and clinical trials. In publishing the VENTURE protocol, we hope to expand collaborations and enhance open communications and the sharing of expertise and knowledge amongst IRD research groups in Australia.

The majority of the initial 150 VENTURE registrants have rod-cone dystrophy (63%; including non-syndromic rod-cone dystrophy and Usher syndrome), which aligns with the estimate that retinitis pigmentosa constitutes 60% of IRDs.[37] The next most-common clinical diagnoses of VENTURE registrants are Bietti crystalline dystrophy (7%), choroideremia (5%), Stargardt disease (5%) and cone-rod dystrophy (5%). Compared to the distribution of IRDs in the general Australian population previously reported by the AIRDR,[38] the phenotypic distribution of VENTURE varies, representing active research interests

in IRDs for which treatments are being developed.[12,36] Probable causative variants in the current VENTURE cohort were most commonly found in *RPGR*, *CYP4V2*, *USH2A, CHM* and *ABCA4* genes, all of which are being evaluated in gene therapy clinical trials.[12]

We faced several challenges in setting up VENTURE, one of which was establishing capacity for genetic testing. Ascertaining the genetic cause of IRDs is fundamental for evaluating genotype–phenotype correlations and developing new treatments.[10] While open-access genetic testing programs, such as the My Retina Tracker[39] and ID YOUR IRD[40] programs in the United States, have made genetic testing more accessible in some countries, these programs have not been available in Australia until recently. A recent review of an Australian private tertiary ophthalmology practice found that genetic testing results were only available for 9.5% of 464 patient records audited.[41] Since July 2021, VENTURE participants have had access to molecular testing through sponsored testing programs, which provide a comprehensive and efficient analysis of multiple genes associated with IRDs.[42] Through these programs, all VENTURE registrants have been offered the opportunity to have targeted panel testing to screen for known variants if they have not previously received a molecular diagnosis. However, data from panel-based tests cannot definitively determine if certain variants are on the same or opposite chromosomes (i.e., in cis or in trans). Where required, participants are referred to clinical genetic services for further evaluation (e.g., co-segregation analysis, cascade testing or variant confirmation) to confirm their molecular diagnosis. As VENTURE does not currently include genetic testing for family members, caution is used when interpreting the genetic results until the phase of these variants is resolved from further examination. This study does not aim to find new disease-causing genes or develop new techniques to detect novel genotype–phenotype correlations, in contrast to work by others in the field.[43–45]

Another challenge in setting up the study was selecting a standardised suite of clinical tests for the protocol. We acknowledge that not all outcome measures will be appropriate for all IRDs, as selection depends on disease pathology, disease severity and level of cooperation.[46] The intention of collecting standardised retinal structure and function data across all IRDs at baseline is to enable independent confirmation of IRD diagnosis and comparison of outcomes across different IRD phenotypes. In addition to collecting retrospective clinical data, where missing data are a common issue, VENTURE aims to collect high-quality patient-level data to provide a benchmark from which to compare change over time. Following baseline assessment, outcomes in VENTURE sub-studies will then be selected based upon specific genotypes or functional phenotypes to enable the assessment of disease-specific endpoint at appropriate time intervals (e.g., ellipsoid zone parameters or area of fundus autofluorescence). In some phenotypes, the addition of other clinical tests will be required depending on the condition and research question being evaluated.

In addition to being an IRD registry, the genotype and prospective phenotype data collected in VENTURE and subsequent disease-specific longitudinal cohort studies will provide a better understanding of the variability in disease progression across different genetic variants. Key learnings from natural history studies are also important for establishing structure–function correlations and the development of novel outcome measures in clinical trials. Potential points of tension in the VENTURE study include: (1) balancing increasing participant growth against the collection of longitudinal data on existing participants; (2) the non-standardised format of the collected retrospective data; and (3) referral bias due to the study team's interests in conditions being evaluated in emerging clinical trials, and to potentially younger, more enthusiastic, health-literate individuals self-referring. Furthermore, participants' IRD diagnoses at registration are either self-reported or reported by their referring clinician, and misclassification bias is possible until their diagnosis is confirmed following baseline clinical examination. Following baseline examination, confirmation of diagnosis can then be made using genetic and clinical examination data, including electrophysiology results, when indicated.

VENTURE is a rapidly expanding database that will be actively utilised to support future IRD research and the development of IRD treatments in Australia. The VENTURE study team aims to collaborate closely with clinicians, support organisations, and other research groups across Australia and New Zealand,[16,38,44,47] to maximise the outreach and potential benefit to the IRD community. This protocol intends to promote collaboration, open communications and the sharing of expertise and knowledge amongst IRD research groups in this region. As the VENTURE database grows, it is hoped that the close collaboration between the VENTURE study team with clinicians and other research groups will become an integrated source of information for people with IRDs and their families.

ACKNOWLEDGEMENTS

The VENTURE study team acknowledges the following researchers and teams for their collaboration: The Western Australian Retinal Disease (WARD) study, Translation of Genetic Eye Research (ToGER), Save Sight Sydney and The Australian Inherited Retinal Disease Registry and DNA Bank. We thank individuals at the Centre for Eye Research Australia and the University of Melbourne for their assistance in developing and implementing the

VENTURE study protocol: Elise Cichello, Bhaj Grewal, Jonathan Tay, Nicole Tindell, Sue Griffin, Elizabeth Baglin, Linda Clarke, Melinda Cain, Sandra Staffieri. We thank genetic counsellor Rebecca Purvis for assisting with genetic counselling for VENTURE participants. We acknowledge Invitae and Novartis Pharmaceuticals (through Blueprint Genetics) for sponsoring genetic testing for VENTURE study participants. The authors thank the participants and their families for their involvement in the research study. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

The VENTURE study has been funded to date by a National Health and Medical Research Council Investigator grant to LNA (GNT#1195713), University of Melbourne Driving Research Momentum Fellowship to LNA, Melbourne Medical School Strategic Grant to LNA, a Centre for Eye Research Australia Strategic Grant to TLE and LNA and philanthropic funding from Retina Australia, the CASS Foundation and the Angior Family Foundation. TLE has received a research grant from Novartis Pharmaceuticals, which has contributed to the costs of genetic testing for this cohort. The study funders had no role in the study design, data collection, data analysis, data interpretation or report writing.

CONFLICT OF INTEREST

Thomas L. Edwards has received a research grant from Novartis Pharmaceuticals, which has contributed to the costs of genetic testing for this cohort.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Britten-Jones AC, O'Hare F, Edwards TL, Ayton LN, the VENTURE Study Consortium. Victorian evolution of inherited retinal diseases natural history registry (VENTURE study): Rationale, methodology and initial participant characteristics. *Clin Experiment Ophthalmol*. 2022;50(7):768-780. doi:10.1111/ceo.14110

APPENDIX

VENTURE STUDY CONSORTIUM (ALPHABETICAL ORDER)

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