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Current Management of Patients with *RPE65* Mutation Associated Inherited Retinal Degenerations in Europe: Results of a 2-Year Follow-Up Multinational Survey

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Keywords
Inherited retinal degenerations · *RPE65* · Management · Europe · EVICR.net clinical centers · ERN-EYE HCPs

Abstract

Introduction: The aim of this study was to evaluate the current management of *RPE65* biallelic mutation-associated inherited retinal degeneration (*RPE65*-IRD) in Europe since market authorization of voretigene neparvovec (VN, Luxturna™) in 2018. By July 2022, over 200 patients have been treated outside the USA, of whom about 90% in Europe. We conducted among all centers of the European Vision Institute Clinical Research Network (EVICR.net) and health care providers (HCPs) of the European Reference Network dedicated to Rare Eye Diseases (ERN-EYE) the second multinational survey on management of IRDs in Europe elaborated by EVICR.net with a special focus on *RPE65*-IRD. ***Methods:*** An electronic survey questionnaire with 48 questions specifically addressing *RPE65*-IRD (2019 survey 35) was developed and sent by June 2021 to 95 EVICR.net centers and 40 ERN-EYE HCPs and affiliated members. Of note, 11 centers are members of both networks. Statistical analysis was performed with Excel and R. ***Results:*** The overall response rate was 44% (55/124); 26 centers follow *RPE65* biallelic mutation-associated IRD patients. By June 2021, 8/26 centers have treated 57 *RPE65*-IRD cases (1–19/center,

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median 6) and 43 planned for treatment (range 0–10/center, median 6). The overall age range was 3–52 years, and on average 22% of the patients did not (yet) qualify for treatment (range 2–60%/center, median 15%). Main reasons were too advanced (range 0–100, median 75%) or mild disease (range 0–100, median 0). Eighty-three percent of centers (10/12) that follow *RPE65* mutation-associated IRD patients treated with VN participate in the PERCEIVE registry (EUPAS31153, http://www.encepp.eu/encepp/viewResource.htm?id=37005). Quality of life and full-field stimulus test improvements had the highest scores of the survey-reported outcome parameters in VN treatment follow-up. ***Conclusion:*** This second multinational survey on management of *RPE65*-IRD by EVICR.net centers and ERN-EYE HCPs in Europe indicates that *RPE65*-IRD might be diagnosed more reliably in 2021 compared to 2019. By June 2021, 8/26 centers reported detailed results including VN treatment. Main reasons for non-treatment were too advanced or mild disease, followed by absence of 2 class 4 or 5 mutations on both alleles or because of a too young age. Patient satisfaction with treatment was estimated to be high by 50% of the centers.

Introduction

To date, biallelic *RPE65* mutation-associated inherited retinal degeneration (*RPE65*-IRD) [1, 2] is still the only inherited retinal disease with approved gene therapy. Biallelic mutations in *RPE65* are associated with a spectrum of retinal diseases ranging from Leber congenital amaurosis (LCA) to early-onset severe retinal dystrophy (EOSRD) to juvenile retinitis pigmentosa (RP) [3–5] now all labeled as *RPE65*-IRD. *RPE65* codes for an isomerase in the retinal pigment epithelium essential for retinol recycling [1, 3]. Some mutations with residual enzyme activity display the later onset phenotype [6, 7]. In addition to severe or complete night blindness due to the enzymatic defect, a low level of lipofuscin-related fundus autofluorescence (AF) is a hallmark of the disease in early years when the retina may look still quite inconspicuous [6]. Successful phase 1–3 studies with subretinal gene supplementation therapy [8, 9] led to approval of voretigene neparvovec (VN; Luxturna^{TM}) by the Food and Drug Administration (FDA), in 2017, European Medicines Agencies (EMA), in 2018, and other authorities for the treatment of *RPE65*-IRD. These trials showed that the majority of patients experience significantly improved vision at reduced light levels [9]. Long-term persistence of the therapeutic effects has been reported recently [10, 11]. By July 2022, over 200 patients have been treated outside the USA, of whom about 90% in Europe (personal communication by Claudio Spera in July 2022, then employee of Novartis Pharma, Basel, Switzerland).

Current challenges with regard to widening the rollout of VN therapy include (1) that not all patients carrying biallelic mutations in *RPE65* are clinically diagnosed [5, 12] and (2) that molecular genetic testing is still not universally available. The latter is key for establishing the diagnosis and important for correct genotype-phenotype correlations, for counseling patients and families about prognosis and recurrence risk, and finally also for recruitment into clinical trials. To accelerate diagnosis and research, a number of consortia have been created worldwide. Examples are European Retinal Disease Consortium (ERDC) [13], Japan Eye Genetics Consortium (JEGC) [14], Global Eye Genetics Consortium (GEGC) [15], Foundation Fighting Blindness Consortium Gene Poll [16]. There is also an Asian Eye Genetics Consortium with a specific Indian chapter founded in 2016 [17, 18]. Recently, the European Reference Network for Rare Eye diseases (ERN-EYE) [19] have published an important position paper on genetic testing in IRDs [20] describing national differences and national plans available in part of the countries. Identification of patients who can profit from VN therapy is key in this respect. In some areas with high consanguinity, higher disease prevalence was reported [21, 22]. An increasing number of reports on *RPE65*-IRDs from diverse countries including Taiwan, China, and India [23–25] indicate its worldwide prevalence.

We conducted the 2nd survey on the management of IRDs in Europe 2 years after the first survey [12, 26, 27]. Forty-eight questions addressed specifically *RPE65*-IRD compared to 35 questions of the first survey to investigate changes and unmet needs. The survey was elaborated by an IRD Survey Expert Committee from the European Vision Institute Clinical Research Network (EVICR.net) and sent to all EVICR.net centers as of July 2021. The EVICR.net is a network of ophthalmological clinical research centers, dedicated to perform multinational clinical research in ophthalmology, following the European and International Directives for Clinical Research. It aims to strengthen the capacity of the European Union to study the determinants of ophthalmic diseases and to develop and optimize the use of diagnostic, prevention, and treatment strategies in ophthalmology [28]. Because of a recently intensified collaboration with [19] the European Reference Network dedicated to Rare Eye

Diseases (ERN-EYE), this survey was also sent to all ERN-EYE health care providers (HCPs) and affiliated members. ERN-EYE is one of 24 ERNs, all dedicated to rare diseases and initiated by the European Commission. One primary aim of ERNs is to provide equal opportunities to all patients irrespective of the specific European country they live in. The survey gives important insights into changes in the diagnosis and management of *RPE65*-IRDs in 124 European institutions including estimated number of patients actually followed and treated with VN. The hypothesis was that following approval of the first retinal gene therapy for *RPE65* biallelic mutation IRDs (*RPE65*-IRDs) by the FDA in the USA in 2017 and by the EMA in Europe in 2018, significant changes in the data interrogated would have occurred from 2019 to 2021.

Materials and Methods

Study Design and Questionnaire

An IRD Survey Expert Committee from EVICR.net developed the 2nd IRD Survey Questionnaire based on the first survey [12, 26]. The committee was composed by Birgit Lorenz, Germany (Scientific Coordinator); Hendrik Scholl, Switzerland; L. Ingeborgh van den Born, The Netherlands; João Pedro Marques, Portugal; Peter Charbel Issa, UK; Katarina Stingl, Germany; and Elisabetta Pilotto, Italy.

The electronic questionnaire comprised 124 questions arranged in five sections: (1) IRD demographics, (2) local setting, (3) IRD genetic testing and counseling, (4) involvement in clinical trials, and (5) *RPE65* mutation-associated IRDs, which followed a conditional branching (see online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000529777). Most of the questions were the same as in the first IRD survey, but others were improved and new questions were added (online suppl. Tables S1 and S2). The questionnaire was designed to have mostly multiple choice questions and single choice questions (closed-ended items), in which the options represent a range of values, which means that only estimates were requested. The results from sections 1–4 have been reported separately [27]. Here, we present the results from section 5 including the comparison to the first survey. Section 5 contained 48 questions specifically addressing *RPE65*-IRDs.

This 2nd IRD survey was reviewed and approved by the AIBILI Ethics Committee – Comissão de Ética para a Saúde, prior to its dissemination to the 95 EVICR.net clinical center members and to the 40 ERN-EYE HCPs and affiliated members. Eleven centers received the survey in duplicate since they are members of both networks. This survey was in accordance with the World Medical Association Declaration of Helsinki.

In June 2021, all EVICR.net clinical centers, comprising 14 European countries, i.e., Austria (AUT), Belgium (BEL), Denmark (DNK), France (FRA), Germany (DEU), Greece (GRC), Ireland (IRL), Italy (ITA), The Netherlands (NLD), Portugal (PRT), Spain (ESP), Slovakia (SVK), Switzerland (CHE) and the UK (GBR), and Israel (ISR), were invited by e-mail to complete the online questionnaire. This invitation was sent to the responsible person of the clinical center and also to its representative for the EVICR.net Retinal Dystrophies Scientific Section; however, no restrictions were imposed to participate in the survey (shared via public link). Therefore, any member of the clinical center staff (e.g., medical retina ophthalmologist, general ophthalmologist, pediatric ophthalmologist, other) could have replied to the survey on their center's behalf. Only one reply per clinical center was considered. In general, we received 1 reply per center. In the 2 cases that we received another reply from the same center, we considered the latest submission. The identification of the EVICR.net member as well as name, function, and contacts (e-mail and telephone) of the replier were requested, as they are all EVICR.net members with a confidentiality disclosure agreement in place. A reminder was sent to the non-repliers after 2 weeks, the deadline was extended for two more weeks, and new reminders were sent on week 4, 3 days before the final deadline. Strategies to maximize the response rate were follow-up contact, hard copy of the questionnaire, personalized e-mails, and giving an ultimate deadline.

For ERN-EYE members, the ERN-EYE headquarters shared the survey in July 2021 with their members and a deadline of 2.5 weeks was given. At the time of the survey, ERN-EYE was composed of 25 members in 12 member states and 15 affiliated partners in 7 countries.

Statistical Analysis

We conducted a descriptive analysis for all variables. Continuous variables were summarized using the following statistics: number (n), mean, standard deviation, median (P50), first and third quartiles (P25 and P75), minimum (Min), and maximum (Max). The frequency and percentages of observed levels were reported for all categorical measures. Statistical significance of differences was determined with two-tailed paired Wilcoxon test. Statistical analyses were performed with Excel version 15.0.4433.1508 (Microsoft Office Home and Business 2013) and R version 3.6.3 (2020-02-29).

We did not exclude questionnaires due to missing values. However, each analysis was restricted to repliers with no missing values for the respective question, i.e., the total number of repliers differed among questions.

Results

Demographics of RPE65 *Mutation-Associated IRDs*

The 2nd IRD survey (2021) was sent to 124 centers from 23 European countries and ISR (95 EVICR.net centers and 40 ERN-EYE HCPs and affiliated members; 11 centers are members of both networks) [27]; replies were received from 55 centers. Genetic testing was performed by 42 centers, and of these, 26 (62%) managed patients with *RPE65*-IRD. The countries reporting the highest percentage of centers with confirmed patients (100% of centers) and that had more than one center performing genetic testing were FRA and NLD (Fig. 1). Thirty-eight percent of the centers have only 1–5 IRD patients with confirmed homozygous mutations in

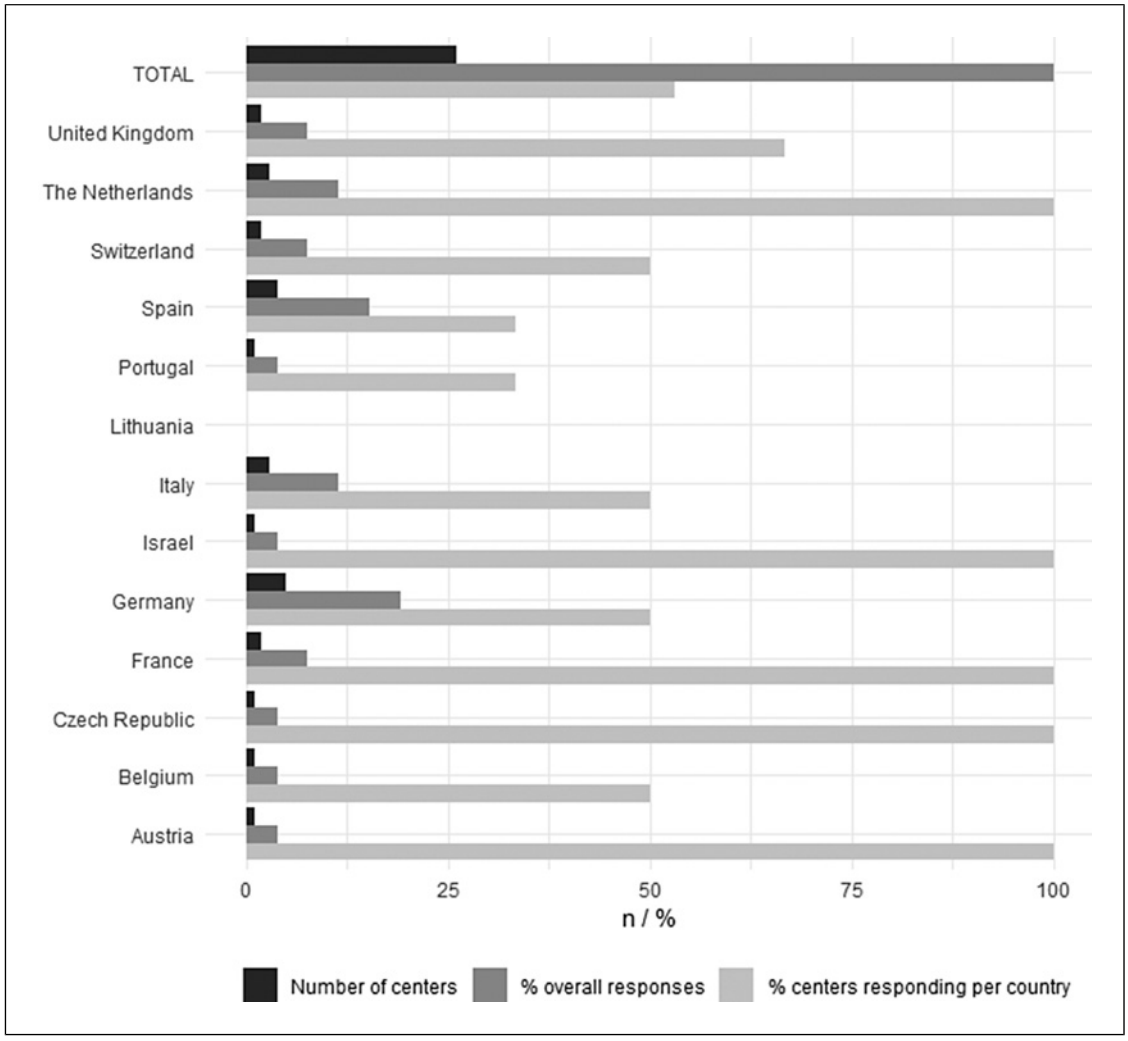

Fig. 1. Centers that reported to have IRD patients with confirmed biallelic mutations in *RPE65* identified in their centers by country.

RPE65, while 42% have only 1–5 IRD patients with confirmed compound heterozygous mutations in *RPE65* (Table 1).

The referral diagnosis of IRD patients with confirmed biallelic *RPE65* mutations varied in the 26 centers (Fig. 2): EOSRD was diagnosed in 10% of the cases (range 0–100; Q1: 0; Q3: 50), LCA in 18% (range 0–100; Q1: 0; Q3: 58), RP/rod-cone dystrophy in 10% (range 0–100; Q1: 0; Q3: 51), and unclassified visual impairment in 0% (range 0–80; Q1: 0; Q3: 5). The referral diagnosis of *RPE65* mutation-associated IRD patients was changed for 23% of the patients (range 0–100; Q1: 10; Q3: 48), and 25% of the centers changed the referral diagnosis in over 48% of the patients. About half of the centers (46%) follow a specific referral process of *RPE65* mutation-associated IRD patients. Online supplementary Table S3 shows the number of centers following a specific referral process per country.

Two-Year Follow-Up Analysis

For a 2-year follow-up, we compared the results from the 1st survey [12] and this 2nd survey. From the centers that replied to both surveys and performed genetic testing (N = 31), 18 (58%) and 19 (61%) managed patients with confirmed biallelic mutations in *RPE65* in 2019 and 2021, respectively. Twenty-six centers (84%) had the same reply in both surveys, while three (10%) changed from not managing to managing patients with confirmed biallelic mutations in *RPE65* and two (6%) changed from managing to not managing. To further compare the results from

Table 1. Estimated number of IRD patients with confirmed homozygous and compound heterozygous mutations in *RPE65*

	Homozygous mutations			Compound heterozygous mutations		
	N	%	min/max	*N*	%	min/max
0	5	19	0/0	5	19	0/0
1–5	10	38	10/50	11	42	11/55
6–10	2	8	12/20	*0*	*0*	*0/0*
11–20	3	12	33/60	4	15	44/80
>20	2	8	42/60[a]	3	12	63/90[a]
No correct answer	4	15	4/8[b]	3	12	3/6[b]
Total	26	100	101/198	26	100	121/231
Total of centers with *RPE65* mutation-associated IRD patients	26	100	–	26	100	–

"*N*" refers to the number of centers. [a]Estimated number assuming 30 patients as maximum for centers with >20 patients. [b]Estimated number assuming 2 patients as maximum for centers that did not answer correctly.

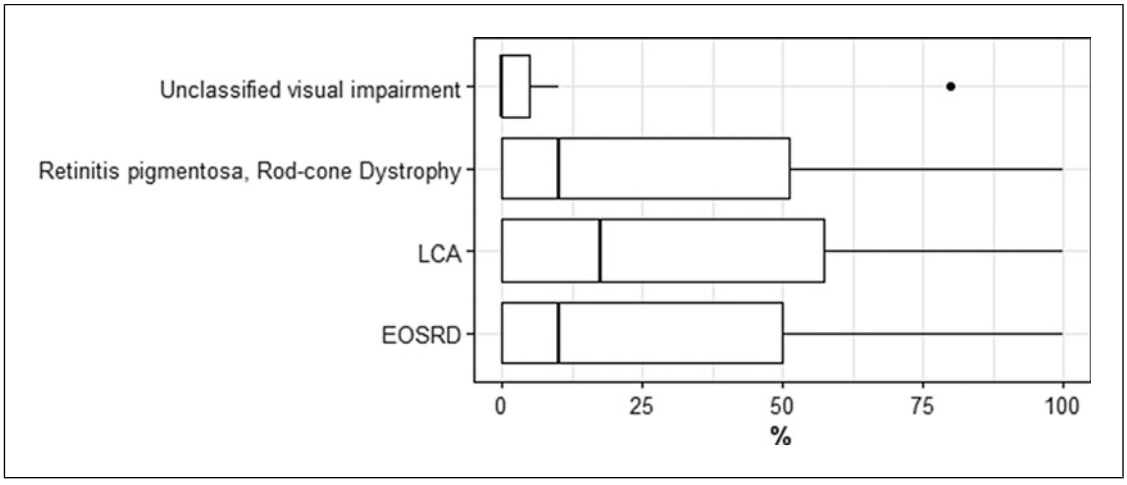

Fig. 2. Referral diagnosis of the *RPE65*-IRD patients. Box plots of the percentage of referral diagnosis of RPE65 mutation-associated IRD patients: the box signifies the third quartile (Q3) and first quartile (Q1) range of data, and the median is represented by a black line within the box for each type of referral diagnosis of RPE65 mutation-associated IRD patients. Data falling outside the Q1–Q3 range are plotted as outliers of the data and are depicted by black dots. $N = 26$.

both surveys, we considered only the centers that managed patients with confirmed biallelic mutations in *RPE65* in both surveys ($N = 16$). Table 2 shows the estimated numbers of IRD patients with confirmed homozygous and compound heterozygous mutations in *RPE65*.

The variation in referral diagnosis of patients from the 1st to this 2nd survey is shown in Figure 3. While for the 1st survey the most common referral diagnosis was LCA (median 25%; range 0–100; Q1: 10; Q3: 58), in the 2nd survey the most common was EOSRD (median 20%; range 0–100; Q1: 0; Q3: 50) and LCA (median 20%; range 0–80; Q1: 0; Q3: 50). The percentage of diagnosis of EOSRD and RP/rod-cone showed a tendency for increase in the 2nd survey compared to the 1st survey, while those for LCA and unclassified visual impairment showed a tendency for decrease. However, none of these differences were statistically significant.

The median percentage of IRD patients with a change of their referral diagnosis was 18% (range 0–90; Q1: 10; Q3: 43) in 2019, increasing non-significantly ($p = 0.6600$) to 23% (range 0–100; Q1: 18; Q3: 43) in 2021 (online suppl. Fig. S1). Seven centers had an increased percentage of patients that had their referral diagnosis changed, with the same number of centers (7) having a decrease, while the

Table 2. Estimate of the number of IRD patients with confirmed homozygous and compound heterozygous mutation in *RPE65*, in each IRD survey

	Homozygous mutations			
	2019		2021	
	N	%	*N*	%
0	1	7	2	14
1–5	9	64	7	50
6–10	3	21	2	14
11–20	1	7	1	7
>20	0	0	2	14
Do not know	0	0	0	0
Total	14	100	14	100
	Compound heterozygous mutations			
	2019		2021	
	N	%	*N*	%
0	0	0	2	14
1–5	10	71	8	57
6–10	0	0	0	0
11–20	1	7	1	7
>20	2	14	3	21
Do not know	1	7	0	0
Total	14	100	14	100

Only 14 centers replied correctly to this question in both surveys. "*N*" refers to the number of centers.

remaining two centers maintained the referral diagnosis. The percentage of centers following a specific referral process increased from 31% in 2019 to 50% in 2021, involving mainly centers from DEU and NLD (online suppl. Table S4).

Follow-Up Visits

Current Practice

Half of the centers (50%) recalled *RPE65* mutation-carrying patients for follow-up annually, 27% every 6 months, and 8% with longer periods of time between follow-up visits. The highest frequency (every 2 months) was reported for one center in CHE (Table 3). The lowest frequency (longer than every 2 years) was observed for 1 center in FRA and 1 center in DEU. The frequency of recalls for follow-up varied greatly among German centers (Table 3). Fifteen percent of the centers (4/26) have another institution doing the follow-up of untreated patients, 62% (16/26) did not have another institution doing the follow-up, and 23% (6/26) replied that they did not know whether another institution did the follow-up.

Comparing replies from centers that participated in both surveys, there was an increase in centers recalling patients for follow-up every 6 months from 25% to 38%, while others decreased the frequency (Table 4). The center that in 2019 reported to recall patients for follow-up depending on age changed the reply to 1–3 years. The centers that had replied a biennial frequency in the 1st survey changed to either higher or lower frequencies. The percentage of centers that had the follow-up carried out by another institution decreased from 39% (6/16) to 6%, with only one center in 2021 (Fig. 4).

Previous Practice

Most of the centers (65%) had seen their patients annually in the past, while 15% had seen them every 6 months and 8% every 2 years (Table 5). Other 8% of the centers had seen their patients at even lower frequency and 4% replied they did not know. The Austrian and Swiss centers that participated in the survey had a high frequency of visits (every 6 months) and most of the centers in NLD had seen their patients biennially. German centers had the higher frequency variation (Table 5).

Comparing both surveys regarding their previous practice on recalling patients for follow-up, centers reporting to have had recalled patients annually increased from 50% to 63%, while the centers reporting a biennial frequency decreased (online suppl. Table S5). German centers were still the ones with the highest variability in reported past frequencies (online suppl. Table S5).

Psychophysics

Visual Acuity and Color Vision Testing

All centers perform visual acuity (VA) testing in patients with *RPE65*-IRD. The highest frequency of VA testing reported was every 3 months by one center, while most of the centers reported annual testing (50%). Twelve percent of centers reported testing VA less than every 2 years (Table 6). Online suppl. Table S6 lists the VA tests applied by centers in untreated patients. The most commonly used tests were ETDRS (69%) and Snellen charts (65%).

Most of the tests were applied depending on the patient's age (online suppl. Table S7). The tests applied to patients younger than 2 years old were tumbling "E" charts, Teller Acuity Cards, Lea Symbols®, HOTV, and other unspecified tests, with the higher average estimated percentage reported for other unspecified tests (90%). Most of the tests were applied to patients aged between 2 and 6 years old, except for Berkeley Rudimentary Vision Test (BRVT) and Pelli-Robson. The highest average estimated percentage for this

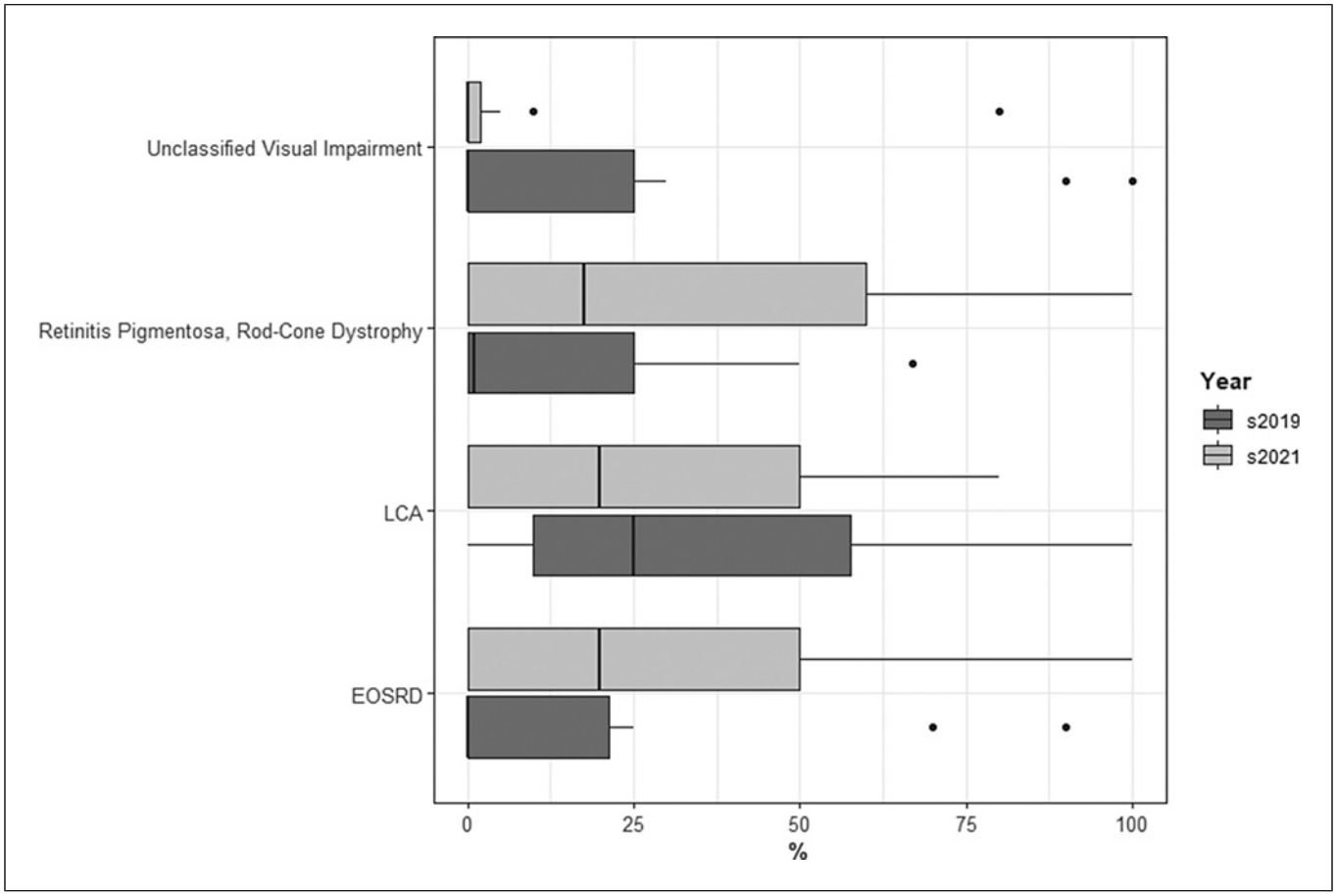

Fig. 3. Referral diagnosis of the *RPE65* mutation-associated IRD patients in each survey. $N = 16$. For explanation of the box plots, see Fig. 2.

age group was for HOTV (80%), although only one center reported this percentage. The next most used test for this age group was tumbling "E" charts (45% average of four centers). For patients older than 6 years of age, ETDRS charts was the most used test (72%) followed by Snellen charts (69%), with only tumbling "E" charts, Teller Acuity Cards, and Lea Symbols® tests not applied to this age group. The distribution of the methods applied for color vision testing is shown in online supplementary Table S8, with Ishihara being the most used by the centers (59%), followed by Lanthony Panel D15 (41%) and Farnsworth 100 hue (32%).

Comparing the frequency of VA testing reported by centers participating in the two surveys, the most commonly reported frequency was annually in both surveys (44% in both, 7/16, online suppl. Fig. S2A). Overall, the frequency of testing increased, with the percentage of centers testing biennially decreasing from 25% (4/16) to none and most of these centers reporting higher frequencies in the 2nd survey. The most used test for VA evaluation was the ETDRS charts, with an increase in percentage of centers applying it from 63% (10/16) in 2019 to 75% (12/16) in 2021. The Snellen charts test was the second most used by centers in both surveys, also having an increased percentage from the 1st survey to the 2nd (50–69%; 8–11/16). All methods were used in both surveys with only small variations in percentage of centers applying them (online suppl. Fig. S2B). As for color vision testing, the most commonly applied test was the Farnsworth Panel D15 in 2019 (79%, 11/14) and the Ishihara cards in 2021 (62%, 8/13) (online suppl. Fig. S2C). It is noteworthy that the model of the Farnsworth Panel test was different in both surveys.

Visual Field Testing

A high percentage of the centers perform kinetic perimetry (77%) in *RPE65* mutation-carrying patients; 58% of the centers perform static perimetry. Only a small

Table 3. Frequency to recall the patients for follow-up, estimate percentage per center, by country

	Country	*N*	%	Total centers at section 5 per country	% centers per country
Every six months	Austria	1	–	1	100
	Germany	1	–	5	20
	Italy	1	–	3	33
	Portugal	1	–	1	100
	Spain	2	–	4	50
	Switzerland	1	–	2	50
	Total	*7*	*27*	–	–
Annually	Belgium	1	–	1	100
	Czech Republic	1	–	1	100
	Germany	2	–	5	40
	Israel	1	–	1	100
	Italy	2	–	3	67
	Spain	1	–	4	25
	The Netherlands	3	–	3	100
	United Kingdom	2	–	2	100
	Total	*13*	*50*	–	–
Longer	France	1	–	2	50
	Germany	1	–	5	20
	Total	*2*	*8*	–	–
Other: every 2 months	Switzerland	1	4	2	50
Other: 1–3 years	Germany	1	4	5	20
Do not know	France	1	–	2	50
	Spain	1	–	4	25
	Total	*2*	*8*	–	–

The percentage of centers per country was calculated based on the total number of centers that replied for each country. "*N*" refers to the number of centers.

portion of the centers perform fundus-controlled perimetry (12%). Table 7 shows the distribution of the type of device used by the centers for perimetry recording. The device used for static perimetry in most centers was Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) (73%), followed by Octopus (Haag-Streit AG, Koeniz, Switzerland) (40%). For kinetic perimetry, 65% of the centers use Goldmann (manual) or semiautomated "Goldmann" with the Octopus 900 (45%) and 25% used Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany). Fundus-controlled perimetry was performed with Compass (CenterVue Inc., Fremont, CA, USA) in 67% of the centers and MAIA (CenterVue Inc., Fremont, CA, USA) in 33% of the centers.

As for the number of visual field tests each center performed for each patient, the majority of the centers reported less than 5 tests for static perimetry (55%) as well as for kinetic perimetry (60%) (online suppl. Table S9). Only one center reported having performed more than 20 static perimetry examinations. Also, for kinetic perimetry, only one center reported having performed as many as 11–20 examinations.

When comparing the responses of the centers that participated in the 1st and 2nd survey, the number of centers performing static perimetry (9) and/or kinetic perimetry (12) was the same between surveys. Fundus-controlled perimetry was performed in fewer centers in 2021 (2) than in 2019 (4).

The device reported to be most used to perform static perimetry in both surveys was Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany), with 100% of the centers (9/9) reporting to use it in 2019 and 89% (8/9) in 2021 (online suppl. Fig. S3A). The percentage of centers using Octopus device (Haag-Streit AG, Koeniz, Switzerland) increased from 22% to 44% (2–4/9), while for Twinfield (Oculus Inc., Wetzlar, Germany) it decreased, with the one center reporting to use it in 2019 no longer reporting it in 2021. For kinetic perimetry, the percentage

Table 4. Frequency to recall the patients for follow-up, estimate percentage per center, in each IRD survey (*N* = 16)

Country	*N*	%	Total centers at section 5 per country	% centers per country
2019				
Every six months				
Italy	2	–	2	100
Portugal	1	–	1	100
Spain	1	–	4	25
Total	4	25	–	–
Annually				
Belgium	1	–	1	100
Germany	1	–	4	25
Spain	3	–	4	75
Switzerland	1	–	1	100
The Netherlands	1	–	3	33
Total	7	44	–	–
Biennially				
Germany	2	–	4	50
The Netherlands	2	–	3	67
Total	4	25	–	–
Other: age-dependent semi-annually to bi-annually				
Germany	1	–	4	25
Total	1	6	–	–
2021				
Every six months				
Germany	1	–	4	25
Italy	1	–	2	50
Portugal	1	–	1	100
Spain	2	–	4	50
Switzerland	1	–	1	100
Total	6	38	–	–
Annually				
Belgium	1	–	1	100
Germany	1	–	4	25
Italy	1	–	2	50
Spain	1	–	4	25
The Netherlands	3	–	3	100
Total	7	44	–	–
Longer				
Germany	1	–	4	25
Total	1	6	–	–
Other: 1–3 years				
Germany	1	–	4	25
Total	1	6	–	–
Do not know				
Spain	1	–	4	25
Total	1	6	–	–

The percentage of centers per country was calculated based on the total number of centers that replied for each country. "*N*" refers to the number of centers.

of centers using Goldmann (manual) device (75%, 9/12) and the Octopus device (Haag-Streit AG, Koeniz, Switzerland) (42%, 5/12) was maintained between surveys (online suppl. Fig. S3B). More centers reported to have used Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) in 2021 (percentage increased from 8% to 25%, meaning an increase of 1–3 centers). One center had reported using a research device for underaged in 2019 but

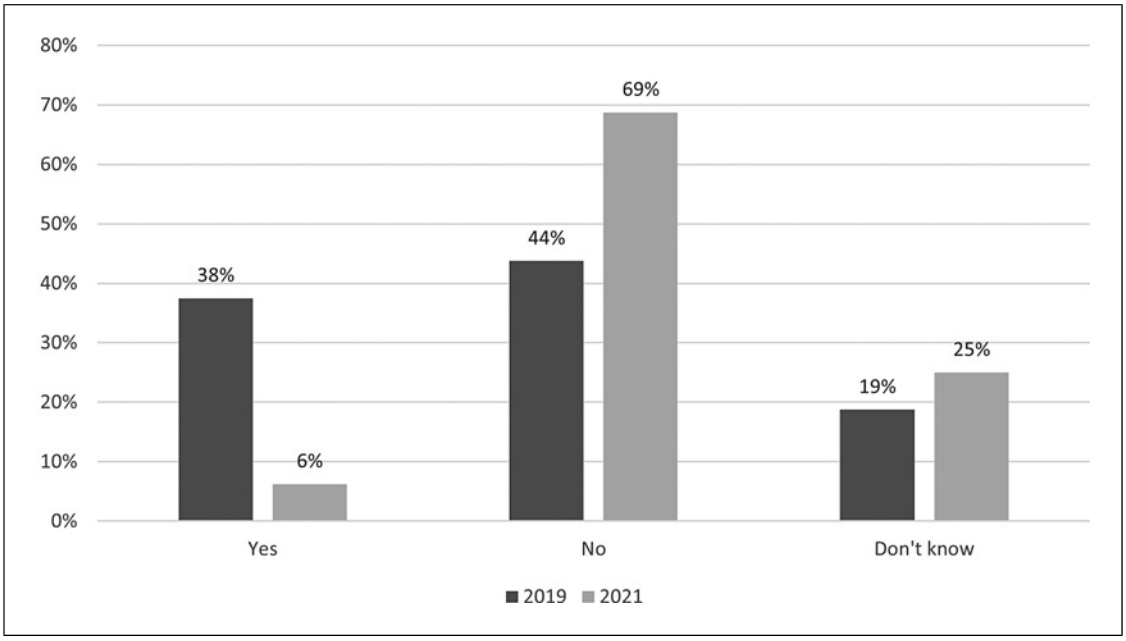

Fig. 4. Percentage of centers that have another institution following untreated patients in addition in each survey. $N = 16$.

no longer reported using it in 2021. In the 1st survey, the centers reported to use three different devices for fundus-controlled perimetry, as shown in online suppl. Figure S3C: MP1 (NIDEK Co., Ltd., Aichi, Japan) (50% of the centers); MP3 (NIDEK Co., Ltd., Aichi, Japan) (75%); and Compass, CenterVue MAIA (25%). However, in the 2nd survey, only the Compass device (CenterVue Inc., Fremont, CA, USA) was reported to be used.

The number of static perimetry tests performed in each center per patient varied greatly between surveys. While in 2019, the vast majority of centers (78%, 7/9) performed less than 5 tests per patient, in 2021 the number of tests was more variable (online suppl. Fig. S4A). However, the results are difficult to interpret since not all centers performing static perimetry answered (correctly) to this question in the 2nd survey (only the answers of 5 centers were considered). The variation in the number of visual tests performed per patient for kinetic perimetry was less pronounced. In both surveys, most of the centers replied performing less than 5 or between 5 and 10 tests, and no centers performed more than 20 (online suppl. Fig. S4B).

Two-Color-Threshold Perimetry and Full-Field Stimulus Threshold

In this 2nd survey, almost all centers, except for one (corresponding to 4% of the centers), reported not performing two-color-threshold perimetry in their *RPE65* patients. On the other hand, 42% of the centers perform full-field stimulus threshold (FST) (Table 8). Of these centers, 45% performed red, blue, white FST testing and 55% white testing only. The device used for FST testing was mainly the Espion (Diagnosys LLC, Lowell, MA, USA) (82%), while 18% of the centers used the Roland Consult Stasche & Finger GmbH (Brandenburg an der Havel, Germany), and none used the Biomedica Mangoni (Pisa, Italy) (online suppl. Table S10).

Comparing the replies from the centers in the 2nd survey to those in the 1st survey, the percentage of centers performing two-color-threshold perimetry remained the same (6%, 1 center). For FST testing, the percentage increased from 44% to 62% (online suppl. Table S11). A variation in the type of FST testing was also observed, as shown in online supplementary Table S11: 71% of the centers had reported performing red, blue, white testing in 2019, with this percentage decreasing to 50% in 2021; white testing only increased from 29% of the centers in 2019 to 50% in 2021. The most used device for FST testing was the Espion (Diagnosys LLC, Lowell, MA, USA) in both surveys, being used by 57% of the centers (4/7) in 2019 and increasing to 90% (9/10) in 2021. The Biomedica Mangoni device was used in the 1st survey by 1 center, but no center reported using it in the 2nd survey.

Table 5. Frequency centers saw RPE65 mutation-associated IRD patients in the past per country (*N* = 26)

Country	*N*	%	Total centers at section 5 per country	% centers per country
Every 6 months				
Austria	1	–	1	100
Spain	1	–	4	25
Switzerland	2	–	2	100
Total	*4*	*15*	–	–
Annually				
Belgium	1	–	1	100
Czech Republic	1	–	1	100
France	1	–	2	50
Germany	3	–	5	60
Israel	1	–	1	100
Italy	3	–	3	100
Portugal	1	–	1	100
Spain	3	–	4	75
The Netherlands	1	–	3	33
United Kingdom	2	–	2	100
Total	*17*	*65*	–	–
Biennially				
The Netherlands	2	–	3	67
Total	*2*	*8*	–	–
Longer				
Germany	2	–	5	40
Total	*2*	*8*	–	–
Do not know				
France	1	–	2	50
Total	*1*	*4*	–	–

The percentage of centers per country was calculated based on the total number of centers that replied for each country. "*N*" refers to the number of centers.

Pupillometry and Mobility Testing at Defined Light Levels

Only 12% of the centers (3/26) perform pupillometry in their *RPE65*-untreated patients, with the type of pupillometry being divided equally between chromatic pupillometry, white-only pupillometry, and chromatic pupil campimetry (33%). Mobility testing was performed in 15% of the centers (4/26), with 3 centers using the Ora-VNC™ (Ora, Inc., Andover, USA) and the other using another device (Streetlab, Paris, France).

The percentage of centers performing pupillometry remained the same in the centers that participated in the 1st and the 2nd survey (19%, 3/16). In 2019, 67% (2/3) reported performing chromatic pupillometry and 33% (1/3) white-only pupillometry, while in 2021 the percentage of centers performing pupillometry was equally distributed (33%) between chromatic pupillometry, white-only pupillometry, and chromatic pupil campimetry. As for mobility testing, the number of centers performing it in *RPE65* patients increased from 1 in 2019 to 2 in 2021, and both centers used the Ora-VNC™ device.

Retinal Imaging and Fundus AF Recording

Fundus photography recording in patients with *RPE65*-IRD was performed by 92% of the centers, and the most reported frequency was every year (50%), followed by intervals longer than 2 years (21%) (Table 9). Seventy-seven percent of the centers reported performing ultra-wide field imaging, with an annual frequency reported by 50% of the centers and 20% performing twice a year or at lower frequency than biennially. Most centers (92%) reported performing fundus AF imaging, most commonly at yearly interval (58%). Only 42% of the centers performed near-infrared autofluorescence (NIR-AF)

Table 6. Frequency that centers perform VA testing in *RPE65*-untreated patients

	N	%
Monthly	0	0
Quarterly	1	4
Twice a year	6	23
Annually	13	50
Biennially	0	0
Longer	3	12
Other	1	4
No answer[a]	2	8
Total number of centers that perform VA testing	*26*	*100*
Total number of centers that manage RPE65 patients	*26*	*100*

"*N*" refers to the number of centers. [a]No answer corresponds to a center that replied two different frequencies and another center that replied to 5.16 (methods for VA testing) but did not reply to this question.

imaging, with the most reported frequency of testing being, as with the other tests, every year (55%). Spectral domain optical coherence tomography (SD-OCT) or optical coherence tomography angiography (OCT-A) was performed by almost all centers (96%), and the most reported frequency was again every year (52%).

Comparing the replies of centers that participated in both surveys, fundus imaging in *RPE65* mutation-associated IRD patients was performed by all centers that replied, and the most reported frequency was annual for 44% of the centers in both surveys (online suppl. Table S12). One center (6%) increased the frequency of testing to quarterly, while three others decreased their reported frequencies to longer than biennially. The frequency of fundus AF recording decreased in one center from the 1st to the 2nd survey (online suppl. Table S12). The most reported frequency of recording was annually in both, increasing from 38% to 53% of the centers, in 2019 and 2021, respectively. SD-OCT or OCT-A recording was done by all the centers in both surveys, with the most reported frequency being annually in both surveys, for 50% and 44% in 2019 and 2021, respectively. Three centers increased their frequency of recording to quarterly or twice a year. It is not possible to compare the ultra-wide field imaging and NIR-AF frequencies since they were not asked about in the 1st survey.

RPE65 *Mutation-Associated IRD Treatment and Follow-Up*

Out of the 26 centers that see *RPE65* mutation-associated IRD patients, 8 centers (31%) treated their *RPE65* biallelic mutation-carrying patients with VN. The centers treating their patients are located in FRA, DEU, NLD, PRT, ESP, and GBR (online suppl. Table S13). Four of the centers that do not offer VN treatment referred their patients to a different center, and one of those had their patients treated in another country (online suppl. Table S14). The reason for the patients being treated in a different center was that earlier treatment was available (n = 2), that there was no permission in their country (n = 1), while another center replied not to know the reason.

Table 10 shows estimated numbers of VN treatment at the 8 centers offering such treatment. On average, 22% (range 2–60; Q1: 5; Q3: 28) of the patients did not (yet) qualify for treatment. The reason for these patients not being treated was mostly due to the disease being too advanced (median: 75%; range 0–100; Q1: 49; Q3: 100) or too mild (median: 0%; range 0–100; Q1: 0; Q3: 17), patients not carrying class 4 or 5 mutations on both alleles (median: 0%; range 0–40; Q1: 0; Q3: 9), and patients being too young (median: 0%; range 0–10; Q1: 0; Q3: 9) (online suppl. Fig. S5).

From the centers managing patients being treated with VN (both at their centers or a different center), 50% (6/12) reported that it took between 1 and 3 months to get agreement to treat the patients from health insurance and legal institutions. The shortest time (<4 weeks) was reported by only one center (8%). In most of the centers (92%, 11/12), this procedure was performed under national agreement.

The duration of follow-up pretreatment with VN was highly variable, ranging from 0 months to 120 months, with the most frequently reported period being 3 months (25%) (online suppl. Table S15A). During this pretreatment period, the number of examinations performed was also highly variable, ranging from 0 to 8 (online suppl. Table S15B). During the first year of post-treatment follow-up, all the centers performed VA and VF testing, as well as OCT and AF imaging (online suppl. Table S15C). Only 33% of the center performed NIR-AF. The frequency of follow-up visits during this 1st year varied from weekly to twice a year as shown in online supplementary Table S15D. Five centers reported a variable frequency throughout the first year (e.g., 1 month, then every 3 months). The lowest frequency reported was twice a year (8%, only one center) and another center reported that the frequency depended on the post-authorization market study. After the 1st year, centers had follow-up visits twice a year (42%) or annually (33%), while the remaining 3 centers replied not applicable. Eighty-three percent of

Table 7. Devices used for perimetry recording in RPE65 mutation-associated IRD patients (multiple choices allowed)

Static perimetry devices		
	N	%
Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany)	11	73
Octopus (Haag-Streit AG, Koeniz, Switzerland)	6	40
Twinfield® (Oculus Inc., Wetzlar, Germany)	0	0
Compass (CenterVue Inc., Fremont, CA, USA)	0	0
Other: M-700 (Medmont International, Nunawading, Australia)	1	7
Total static perimetry	*15/26*	*58*
Kinetic perimetry devices		
	N	%
Goldmann (manual) (Haag-Streit AG, Koeniz, Switzerland)[a]	13	65
Octopus (Haag-Streit AG, Koeniz, Switzerland)	9	45
Twinfield® 2 (Oculus Inc., Wetzlar, Germany)	0	0
Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany)	5	25
Other	0	0
Total kinetic perimetry	*20/26*	*77*
Fundus-controlled perimetry devices		
	N	%
MP1 (NIDEK Co., Ltd., Aichi, Japan)	0	0
MP3 (NIDEK Co., Ltd., Aichi, Japan)	0	0
Compass (CenterVue Inc., Fremont, CA, USA)	2	67
MAIA (CenterVue Inc., Fremont, CA, USA)	1	33
Total fundus-controlled perimetry	*3/26*	*12*

"*N*" refers to the number of centers. [a]The device is no longer supported technically. Yet, consumables are still available.

Table 8. Centers performing full-field stimulus threshold (FST) in *RPE65* mutation-associated IRD patients

	N	%
Yes	11	42
Blue, red, white testing	5	-
White testing only	6	-
No	15	58
Total number of centers with RPE65 mutation-associated IRD patients	*26*	*100*

"*N*" refers to the number of centers.

the centers that managed *RPE65* mutation-associated IRD patients treated with VN (10/12) reported participating in the PERCEIVE registry (ENCePP CLTW888A12401, http://www.encepp.eu/encepp/viewResource.htm?id=37005).

For follow-up of VN treatment, various outcome parameters were used by centers as shown in Table 11. VA was used by all the centers, and both fundus photography and OCT and/or OCT-A were also highly used (92%). The least used parameter was NIR-AF (17%). The average estimate of the results of the outcome parameters is shown in Table 12. Quality of life, VF, and FST white were mostly reported to be improved, while VA, OCT, and/or OCT-A remained mostly the same. For AF, NIR-AF, and fundus photography, there was no apparent change either (Fig. 5).

Table 9. Frequency of retinal imaging and AF recording in *RPE65*-untreated patients ($N = 26$)

	Fundus photography		Ultra-wide field imaging		Fundus AF		NIR-AF		SD-OCT or OCT-A	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Monthly	0	0	0	0	0	0	0	0	0	0
Quarterly	1	4	1	5	1	4	0	0	1	4
Twice a year	4	17	4	20	3	13	0	0	6	24
Annually	12	50	10	50	14	58	6	55	13	52
Biennially	1	4	0	0	1	4	0	0	0	0
Longer	5	21	4	20	3	13	2	18	3	12
Other	1	4	1	5	2	8	3	27	1	4
No answer	–	–	–	–	–	–	–	–	1	4
Total number of centers performing each test	*24*	*92*	*20*	*77*	*24*	*92*	*11*	*42*	*25*	*96*

"*N*" refers to the number of centers.

Discussion

This is the second comprehensive survey on diagnosis and management of *RPE65* mutation-associated IRDs in Europe and ISR conducted by EVICR.net in 95 EVICR.net centers as by June 2021 and expanded to all 40 ERN-EYE HCPs (25 full members, 15 affiliated members) by July 2021, of whom 11 were members in both networks, resulting finally in 29 additional sites through a recently intensified collaboration between EVICR.net and ERN-EYE. We are not aware of a similar survey in other parts of the world. The survey contained 48 questions specific for *RPE65*-IRDs. Fifty-five centers responded to the survey, and 26 centers (62%) from 12 countries reported managing patients with confirmed biallelic mutations in *RPE65*. The results on diagnosis and management of IRDs in general were subject of another report [27]. As data are described in detail in the Results section, we only highlight the most important aspects of the results in the Discussion.

Estimated overall numbers of patients with *RPE65*-IRDs in the 26 centers were in the range of 101–198 for patients with biallelic homozygous mutations and in the range of 120–226 for patients with biallelic compound heterozygous mutations (see Table 1). Thus, the total estimated number of patients with *RPE65*-IRDs adds up to 221 (min)–424 (max). The overall population in these 12 countries by 2021 is 402.807.119 Mill (https://www.indexmundi.com). Based on an estimated prevalence of *RPE65*-IRDs of 1:300,000 [4, 29], the real number could be as high as 1,343 patients. The upper range of 424 identified patients would then indicate that at maximum, 30% of patients with *RPE65*-IRDs in these 12 countries were followed in the 26 centers. So even in 2021, there was still an unmet need of patient identification. Especially patients who had received the diagnosis of RP/rod-cone dystrophy years or decades earlier may not come for follow-up when in the past they had been told that blindness is inevitable and no cure available. Significant efforts are being made by patient organizations and by the companies who are manufacturing and selling VN (Spark Therapeutics in the USA and Novartis worldwide outside the USA) to test more patients for mutations in *RPE65*.

Table 13 compares the management of *RPE65*-IRDs in 16 European centers responding to both the first survey conducted in 2019 and the second survey conducted in 2021. One important finding was an increased awareness of the specific genotype-phenotype as the percentage of unclassified visual impairment as initial diagnosis significantly decreased from 19% to 6% (see also Fig. 3). A

Table 10. Estimated numbers from the 8 centers that already performed VN treatment at the time of the survey

	Mean	SD	Median	1Q	3Q	Min	Max	Total
How many patients?	7	7	6	2	10	1	19	***57***
How many more patients planned?	5	3	6	4	8	0	10	***43***
Youngest age of the treated patients?	9	6	8	5	16	3	17	–
Oldest age of the treated patients?	39	7	39	36	40	28	52	–
Percentage of patients with *RPE65* mutations you follow but who do not (yet) qualify for treatment?	22	22	15	5	28	2	60	–

SD, standard deviation.

Table 11. Outcome parameters used in VN treatment follow-up (multiple choices allowed)

	N	%
Patient satisfaction with VN treatment	6	50
Quality of life	6	50
VA	12	100
Low luminance VA	4	33
Visual fields	9	75
Color vision	3	25
FST red	5	42
FST blue	5	42
FST white	9	75
Mobility test	4	33
AF	10	83
NIR-AF	2	17
OCT and/or OCT-A	11	92
Fundus photography	11	92
Other	0	0
Total number of centers with *RPE65* patients being treated	12	–

"*N*" refers to the number of centers.

positive development was also a higher percentage of centers where a specific referral process was implemented. The follow-up protocols varied considerably by center and country and did show some fluctuations from 2019 to 2021 but with no clear pattern.

Another positive development was the increased use of age-adapted validated test methods for VA such as pediatric ETRDS charts with LEA symbols or VA tests with low contrast or low luminance (online suppl. Table S7). These tests give important insights into every day's visual performance and eventual changes following gene augmentation therapy with VN or other upcoming treatments. Also, visual field testing including quantification of peripheral islands on follow-up was widely used that is of high significance for the patient's visual performance and mobility (Table 7).

More sophisticated functional tests such as chromatic FST, mobility parcours, and 2-color-threshold perimetry were still not universally used likely because they are time-consuming and not widely available. FST is an excellent test to get insight into rod vision, in particular when used as chromatic blue-red test. Absolute and relative changes in sensitivities to blue and red allow to evaluate the contribution of rods to vision in the dark-adapted state. It is surprising that only 42% used FST (11 centers, 5 blue-red-white, 7 white only, Table 8) even though it is only a global test without spatial resolution. A more practical approach is multiluminance mobility testing used in 15% of the centers that followed patients with *RPE65*-IRD. Only few centers tried to use tests with spatial resolution such as chromatic pupil campimetry (12%) or two-color-threshold perimetry (4%). At this stage of gene therapy for IRDs, it should be of high interest to gather more spatially resolved data for both the rod and the cone pathway in order to evaluate the specific effects and eventually also adverse effects. Centers that

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Table 12. Estimated percentage of results observed in outcome for VN treatment

	Average of estimated % of outcome				
	High		Medium	Low	Do not know
Patient satisfaction with VN treatment (N = 5[a])	83		8	6	2
	Improved		No change	Worse	Do not know
Quality of life (N = 5[a])	71		2	1	26
VA (N = 11[a])	22		64	4	10
Low luminance VA (N = 3[a])	33		0	0	67
Visual fields (N = 9)	51		29	2	17
Color vision (N = 3)	30		37	0	33
FST red (N = 5)	27		2	2	69
FST blue (N = 5)	27		2	2	69
FST white (N = 9)	56		7	0	37
Mobility test (N = 4)	42		3	0	56
OCT and/or OCT-A (N = 10[a])	0		74	0	0
	Stronger signal		Same signal	Weaker signal	Do not know
AF (N = 10)	18		50	0	31
NIR-AF (N = 2)	0		50	0	50
	No change	General progression of disease	Atrophy at injection site	Atrophy within bleb area	Do not know
Fundus photography (N = 10[a])	69	0	15	2	14

"N" refers to the number of centers that used the respective outcome parameter. [a]One center that had replied to use these outcome parameters did not reply to these questions.

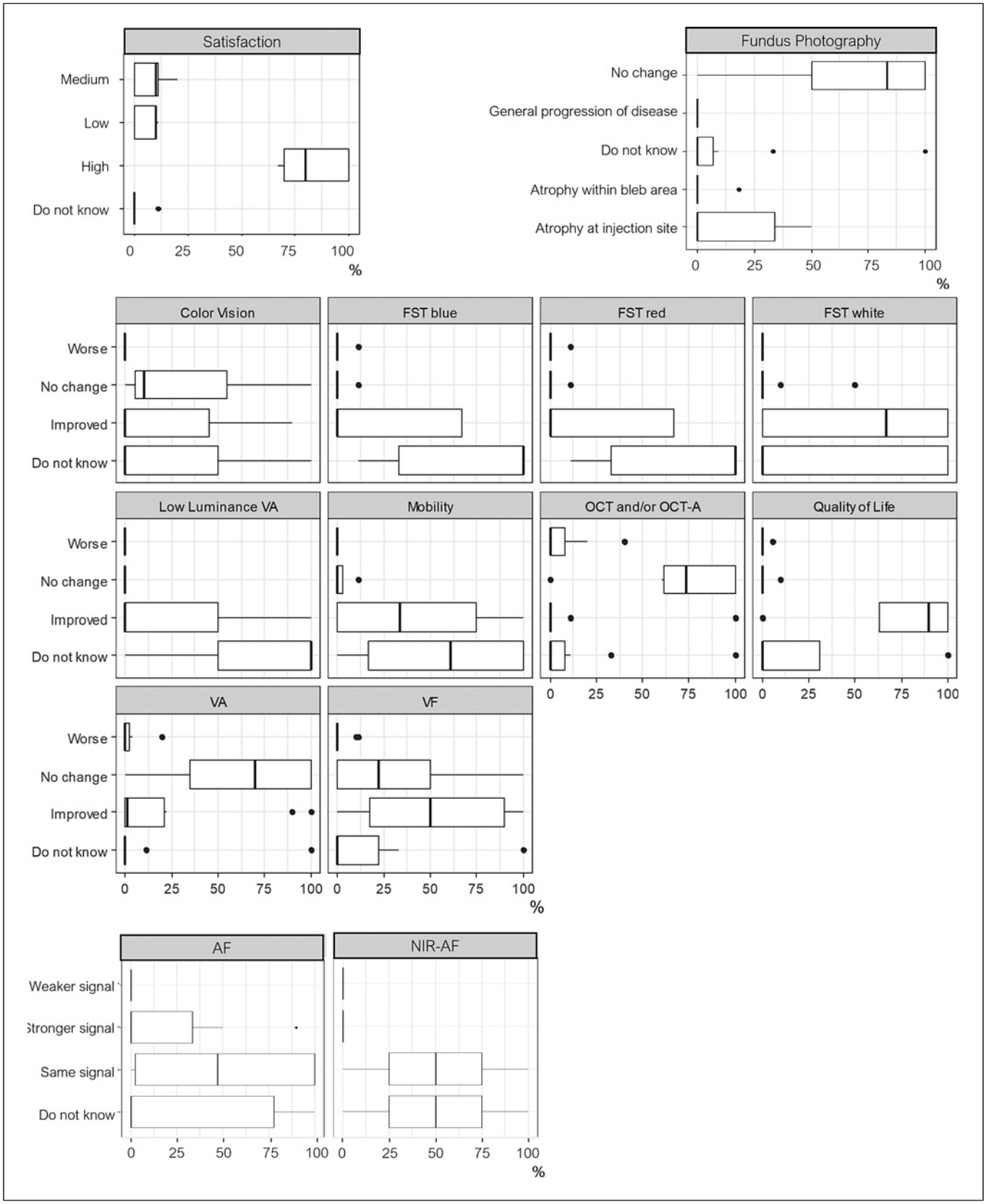

Fig. 5. Results of the outcome parameters used in VN treatment follow-up. For explanation of the box plots, see Figure 2.

Table 13. Comparison management *RPE65*-IRDs in Europe 2021 versus 2019 (12)

	2021	2019
Survey sent to *n* sites	124	101
Response rate, %	44	49
Sites following *RPE65*-IRD patients	26	22
Change of diagnosis unclassified visual impairment[a], %	6	19
Specific referral process[a], %	50	31
2-color-threshold perimetry[a]	1	1
FST white[a]	5	2
FST blue-red-white[a]	5	5
Mobility parcours[a]	2	1
FI annually[a], %	44	44
FAF annually[a], %	53	38
SD-OCT – OCTA (OCT) annually[a], %	44	50
FI, FAF, OCT overall[a], %	100	100

FI, fundus imaging; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography. [a]Only the 16 centers that replied to this question in both surveys were considered.

follow and treat patients with *RPE65*-IRDs should be encouraged to establish such tests even though time-consuming and not part of standard care as patient-relevant readout parameters are of utmost importance.

Of interest, only 8/26 centers that followed patients with *RPE65*-IRDs had already treated patients with subretinal application of VN by June 2021. One reason for a later start of treatment could have been the COVID-19 pandemic. An example is PRT where it delayed the first treatment for several months. Thereafter, 20 eyes were treated in 1 year (Joao PT Marques, personal communication). A similar delay can be anticipated for other countries and treatment sites. Four centers did not (yet) treat patients but referred them to other centers where VN therapy was already established. From the 8 centers that replied to treat *RPE65* patients themselves, 2 were from DEU, 2 from FRA, and one each from PRT, ESP, NLD, and GBR (online suppl. Table S13). Since July 2021, more centers started treating patients (newsletter of the PERCEIVE registry sponsored by Novartis, Basel, Switzerland, July 2022), mainly because the regulatory steps had not yet been achieved in all centers following such patients at the time of the survey in July 2021. Actually, by August 2022, 189 patients were enrolled in the registry and 37 centers were actively treating patients with VN (range 1–19 patients per site). From the centers that reported VN treatment, the regulatory process was reported to take 1–3 months in 50%. In most centers, the procedure was performed under national agreement. Interestingly, the follow-up pretreatment was highly variable, ranging from 0 months to 120 months, the most frequently reported interval being 3 months in 25%. This could indicate that some patients were treated having been referred by local ophthalmologists or eventually by patient self-organizations.

Table 10 summarizes the number of patients with *RPE65*-IRDs treated by June 2021 in the 8 centers that reported treating such patients. In total, 57 patients had already received VN and 43 were awaiting treatment, 68% of the patients had too advanced disease, 19% had too mild disease, 10% were not class 4 or 5 on both alleles, and 4% were too young.

Outcome parameters used in the 12 centers that either treated themselves (8 centers) or had patients treated elsewhere (4 centers) (Table 11, multiple choices allowed) showed not unexpectedly that VA was measured in all, OCT or OCT-A and fundus photography in 92%, blue light autofluorescence (BAF) in 83%, visual fields in 75%, questions related to quality of life and patient satisfaction with VN treatment in 50%, and mobility test in 33%.

Table 12 shows outcome results of the parameters listed in Table 11 in the 12 centers that followed treated patients, i.e., the 8 centers that performed treatment and 4 centers whose patients were treated in another center. The number of centers answering to the individual outcome parameters varied between 3 and 11. The percentage of centers that did not report data on the various outcome parameters ranged from 2% to over 69%. Both observations may be related to the fact that at the time of the survey some of the treating centers had not yet looked in detail into their results. Patient satisfaction scored highest. On average, 83% of the treated patients were highly satisfied as reported by 5/6 centers that used his outcome parameter and answered this question. Improvement of quality of life was reported in

71% of the treated patients on average by 5/6 centers that used this outcome parameter and answered this question. Another parameter important in every day's life was improvement in low luminance VA reported in 33% of the treated patients on average by the 3 centers that used this outcome parameter. Other improvements such as visual field size (outcome parameter used in 9/12 sites) and dark-adapted sensitivity to white were reported in about 50% of the treated patients on average (outcome parameter used in 9/12 sites) and scotopic sensitivity to blue light in about 30% of the treated patients on average (outcome parameter used in 5/12 sites). Improvement of mobility at reduced light levels was verified in about 40% of the treated patients on average (outcome parameter used in 4/12 sites). Other items such as VA and color vision were most frequently reported to have stayed the same. BAF results were reported by the 10 centers that use BAF. On average, a stronger signal was reported in 18% of the treated patients, an unchanged signal in 50%, and in 30% of the patients the center did not indicate whether the signal changed. In the past, it had been hypothesized that a stronger signal following VN therapy could indicate an improved isomerase function [30] in patients with no or low BAF. As only some of the untreated patients do show some BAF, this suggested readout parameter appears not to be useful in the majority of patients. Also, at present, it is unclear whether increased BAF is indeed a sign of improved isomerase activity or a sign of progressive degeneration. This aspect has become even more important as recently there are also a growing number of reports on new or accentuated chorioretinal atrophy at the site of retinotomy, of the bleb, or outside [27, 31–33]. In the survey, the estimated incidence of newly observed atrophies was reported to be 15%. Chorioretinal atrophies were not mentioned explicitly in the original list of possible adverse effects in scientific reports and in the description of the 2 companies supplying VN, Spark Therapeutics and Novartis. The list of unwanted treatment effects has recently been updated, and chorioretinal atrophies added as possible adverse effects. These data are of particular importance when discussing treatment of pediatric patients. In this respect, it is also of high interest to consider the natural history of the disease including possible genotype-phenotype correlations and the observation of very mild phenotypes and slow progression [6, 7].

Weaknesses of the Survey

As only estimated numbers were collected, the true data as to patient demographics and patient satisfaction may be different. Also, the date of the survey may have been too early after approval of VN therapy for clinical use as not all centers had already started treating patients, mainly for regulatory reasons, and a detailed evaluation of the results following VN treatment was not available in all centers (Table 11). Therefore, a follow-up survey specifically addressing *RPE65*-IRDs appears appropriate, although a number of questions will be addressed and answered by analysis of the data collected in the PERCEIVE registry, a post-authorization observational safety study for patients treated with VN, sponsored by Novartis (ENCePP CLTW888A12401, http://www.encepp.eu/encepp/viewResource.htm?id=37005). A similar registry is conducted on patients treated in the USA (ClinicalTrials.gov Identifier: NCT03597399) sponsored by Spark Therapeutics. In this respect, it is good to know that from the 12 centers that by June 2021 followed patients with *RPE65*-IRDs treated with VN, 83% participate in the PERCEIVE registry.

Strengths of the Survey

The survey is the first to provide important details on the diagnosis and management of patients with *RPE65*-IRDs in 26 centers of 12 European countries. The survey contained 48 questions. This included details on methods and devices to test visual function and document morphology with special reference to age-adapted methods. These data will be useful for HCPs, researchers, patient organizations, and industry in establishing protocols for standard care and further clinical trials and to eliminate potential inequities among countries. The data should also prove valuable for European countries not included in the 2 surveys and also for countries outside Europe. At present, ERN-EYE is working on a consensus statement for diagnosis and management of *RPE65*-IRDs for which the data of this survey will also be useful.

Conclusion

This second survey on diagnosis and management of *RPE65* mutation-associated IRDs and comparison with the first survey has provided important information on the actual situation in 26 centers that have answered to follow such patients. Conducting the second survey in two networks, EVICR.net and ERN-EYE, enabled us to use a unique platform for collecting the data. The collected data included baseline data on diagnosis but also first experiences with post-marketing VN treatment of patients with *RPE65*-IRD. These data are of importance to policy makers, clinicians, patient advocate groups, researchers, and others to inform and improve bottlenecks in the provision of optimal care for patients with

RPE65 mutation-associated IRDs and to describe so far unreported complications related to treatment. Recommendations for future steps include suggestions for timely detection of as many patients as possible who might benefit from VN therapy and for follow-up studies and to attempt to provide equal opportunities to all patients amenable to treatment. The latter is important in view of cost-effectiveness and patient satisfaction with VN therapy. Development of guidelines on the diagnosis and management of *RPE65* mutation-associated IRDs in particular and on IRDs in general is facilitated based on the results of this unique dataset.

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Statement of Ethics

This survey questionnaire was reviewed and approved by AIBILI Ethics Committee – Comissão de Ética para a Saúde, approval number 034/2021/AIBILI/4CE, prior to its dissemination and was in accordance with the World Medical Association Declaration of Helsinki. As no personal data were collected, the use of a written and informed consent form was not required in accordance with local/national guidelines.

Conflict of Interest Statement

B.L. is a consultant for Novartis Pharma AG and Janssen/Johnson & Johnson. J.P.M. is consultant for Novartis, Bayer, Chiesi, and Roche. K.S. is a consultant for ProQR, ViGeneron, Novartis, Santen, and Janssen with consultancy fees paid to Center for Ophthalmology, University of Tuebingen, to support research. H.D. is a consultant for Novartis, Janssen, and Rhythm. H.P.N.S. is a consultant for Gerson Lehrman Group, Guidepoint, and Tenpoint Therapeutics Ltd.; receives financial support from Swiss National Science Foundation (National Center of Competence in Research Molecular Systems Engineering "Molecular Systems Engineering"), Wellcome Trust (Pinnacle Study), Foundation Fighting Blindness Clinical Research Institute, Novartis Pharma AG, Pharma Research & Early Development (pRED) of F. Hoffmann-La Roche Ltd., and Kinarus A; and provides non-remunerative support for Gensight Biologics, ReNeuron Group Plc/Ora Inc., Novo Nordisk, Ionis Pharmaceuticals, Inc., and Astellas Institute for Regenerative Medicine. D.L., E.P., J.T., L.I.B., and P.C.I. have no conflicts of interest.

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Author Contributions

The 2nd IRD questionnaire was designed by B.L., J.T., I.B., J.P.M., E.P., K.S., and P.C.I. and H.P.N.S. J.T., and B.L. analyzed the data. B.L. and J.T. wrote the manuscript. L.I.B., J.P.M., E.P., K.S., P.C.I., D.L., H.D., and H.P.N.S. reviewed and complemented the manuscript. All authors approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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