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Current Management of Inherited Retinal Degeneration Patients in Europe: Results of a 2-Year Follow-Up Multinational Survey by the European Vision Institute Clinical Research Network – EVICR.net

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Keywords
Inherited retinal degenerations · Management · Europe · EVICR.net clinical centers · ERN-EYE health care providers

Abstract
Introduction: An increasing number of gene-specific therapies are being developed for inherited retinal degenerations (IRDs). Identification of well-characterized patients is an emerging need. We conducted the second multinational survey among the EVICR.net and ERN-EYE members to understand the management and treatment of IRDs in Europe and compared it to the 2019 survey. ***Methods:*** An electronic survey questionnaire was developed and sent to 124 clinical centers (25 countries) by June/July 2021. Statistical analysis was performed with Excel and R. ***Results:*** The overall response rate was 44% but varied among countries. Only 9% of responding centers do not see IRD patients (2019 survey 14%), 42% follow at least 200 patients per year, 18% follow 500–999, and 2% more than 1,000. Databases exist in 86% of the centers (local 86%; national web based 12%). IRD patients are referred to EVICR.net and ERN-EYE centers mainly by general ophthalmologists, patient self-referral, or medical retina specialists. Most IRD patients are first seen as adults. Signs and symptoms depend on age of onset: in infancy, nystagmus; at older age, night blindness and

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reduced visual field; reduced visual acuity is described at any age. Comprehensive ophthalmic examination always includes visual acuity and almost always visual field multimodal retinal imaging, electrophysiology, color vision testing, and refraction. Identification of genotypes is successful in 72% of centers in 40–80% of cases (2019 survey 69% of centers). The time for confirmation of the genetic diagnosis varies from 2–4 weeks to 24 months (2019 survey >4 weeks ≤10 years). Genetic testing is covered by public health service in 83%, private health insurance in 29%, research funds in 24%; 5% do not have access to genetic testing (2019 survey 15%). The most striking result is the high increase in the involvement of centers in natural history and gene therapy trials that more than doubled for the latter. ***Discussion:*** This second multinational survey on management of IRDs in Europe highlights persistent important differences in the number of IRD patients managed per center, comparable diagnostic work-up, and increasing genotyping in diagnostic laboratories. The important increase in involvement of centers in natural history and gene therapy trials reflects the rapidly evolving field of gene therapy development. The survey provides important follow-up data for researchers, clinicians, caregivers, patient advocate groups, pharmaceutical companies, and investors.

Introduction

Inherited retinal degenerations (IRDs) are genetically and clinically extremely heterogeneous, with 316 genes localized and mutations identified in 280 genes as of June 8, 2022 [1]. They are potentially blinding disorders with a prevalence of about 1 in 3,000–5,000 [2, 3], although a wide range has been reported being as low as 1:9,000 [4] and as high as 1:750 [5]. Until very recently, no medical treatment was available for the vast majority. The interest has increased significantly in recent years due to the development of therapeutic strategies for an increasing number of disease-causing genes [6–14], though with variable success and the recognition of new challenges that need to be addressed. The aim of this study was to conduct a follow-up survey 2 years after the first European survey [15] to understand changes in the management and experience of IRDs across Europe as the first survey had disclosed significant differences among and within countries. The clinical research network established by the European Vision Institute (EVICR.net) was shown to be an appropriate platform for such surveys. To further expand the survey on more European sites involved in the management and treatment of IRDs, we established a further collaboration with another European network on eye diseases that particularly focuses on rare diseases, i.e., the European Reference Network ERN-EYE founded in 2017 (https://www.ern-eye.eu/).

Taking into account important conclusions from the first survey [15], the second survey kept part of the questions from the first to allow comparison but was at the same time expanded by more specific questions such as age-dependent and test-specific parameters. Also, more detailed information was gathered as to involvement in natural history studies and clinical trials (including gene therapies and other therapies). The hypothesis was that despite undoubtful progress, IRDs are still underdiagnosed and that a significant number of patients suitable for clinical trials and medically approved therapy remain unidentified to date.

Materials and Methods

Study Design and Questionnaire

An IRD Survey Expert Committee developed the second IRD Survey Questionnaire based on the first survey. The Committee was composed by Birgit Lorenz, Germany (Scientific Coordinator); Hendrik Scholl, Switzerland; 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 supplementary material, available at www.karger.com/doi/10.1159/000528716). Most of the questions are the same as in the first IRD survey, but others were improved, and new questions were added. 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. Here, we present the results from sections 1–4 and the comparison to the first survey.

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 40 ERN-EYE health care providers (HCPs) and affiliated members. Eleven centers received the survey in duplicate since they are EVICR.net and ERN-EYE members. 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 email 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 a public link). Therefore, any member of the clinical center staff (e.g., ophthalmologists specializing in medical retina, general ophthalmologist, or pediatric ophthalmology or other) could have replied to the survey on their center's behalf. Only one reply per clinical center was considered. The identification of the EVICR.net member as well as name, function, and contacts (email and telephone) of the replier were requested as they are all EVICR.net members with a Confidentiality Disclosure Agreement in place. Strategies to maximize the response rate were follow-up contact, hard copy of the questionnaire, personalized emails, and giving an ultimate deadline.

For ERN-EYE members, the ERN-EYE management team 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

A descriptive analysis was conducted 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 between questions.

Results

The 2nd IRD survey was sent to 95 EVICR.net clinical research center members from 14 European countries (AUT, BEL, DNK, FRA, DEU, GRC, IRL, ITA, NLD, PRT, SVK, ESP, CHE, GBR) and ISR. Fifty-three percent of the EVICR.net clinical centers (50/95) have replied to this 2nd IRD survey. This reflects a 5% increase in the centers' engagement in relation to the 2019 IRD survey [15], where 48% of the EVICR.net clinical centers participated.

In addition, the ERN-EYE management team disseminated the 2nd IRD survey to their 25 HCPs in 12 member states and 15 affiliated members (40 in total) in 19 member states (AUT, BEL, Croatia [HRV], Czech Republic [CZE], DNK, Estonia [EST], FRA, DEU, ITA, Latvia [LVA], Lithuania [LTU], Luxembourg [LUX], Malta [MLT], NLD, Poland [POL], PRT, SVK, Slovenia [SVN], ESP). Eleven EVICR.net centers are also ERN-EYE HCPs, resulting in the inclusion of 29 more centers and 9 more countries (HRV, CZE, EST, LVA, LTU, LUX, MLT, POL, SVN).

In total, the 2nd IRD survey was sent to 124 centers from 23 European countries and ISR. Of these, 55 centers have replied to this 2nd IRD survey, which reflects an engagement rate of 44% (Fig. 1). The 2nd IRD survey was filled out by general ophthalmologists (9%), medical retina specialists (58%), ophthalmogeneticists (15%), study coordinators (9%), and others (9%).

IRD Demographics

In 2021, only 9% of the responding centers (5/55) did not see IRD patients; these are centers from DEU (1/11), ITA (2/8), and PRT (2/5). All centers that see IRD patients have at least 10 patients being managed at their centers per year (Table 1); 42% actually manage at least 200 patients per year. Centers in ITA and CHE currently manage the lowest number of IRD patients per year. The highest number of IRD patients being currently managed was reported in centers from AUT, BEL, FRA, DEU, ITA, NLD, PRT, ESP, CHE, and GBR (online suppl. Table S1).

Similar to the results of the 2019 survey, 86% of the centers use a database for IRD patients. Of these, 86% have IRD patients registered in local databases (72% local files, such as Excel, and 42% in electronic medical records), and 12% have access to national web-based databases. The majority of the centers (70%) have between 100 and 1,999 IRD patients in their database. NLD, FRA, DEU, and ESP are the countries with centers that have databases with more than 2,000 IRD patients (online suppl. Table S2).

Ninety-eight percent of centers (49) manage IRD patients themselves; however, 20% of these centers also refer IRD patients to expert centers. General ophthalmologists continue to be the main referees of IRD patients to the EVICR.net centers and ERN-EYE HCPs, followed by patient self-referral and medical retina specialists (Fig. 2).

For the majority of IRD patients, the first visit occurs at adult age as observed in the 2019 survey (online suppl. Fig. S1). Main signs and/or symptoms implicating a visit in the centers are reduced visual acuity and nystagmus followed by squint and positive family history in infants and young children (<6 years old); reduced visual acuity followed by night blindness and reduced visual field in children/adolescents from 6 to 18 years old; reduced visual acuity, reduced visual field, and night blindness in young adults and adults (Fig. 3).

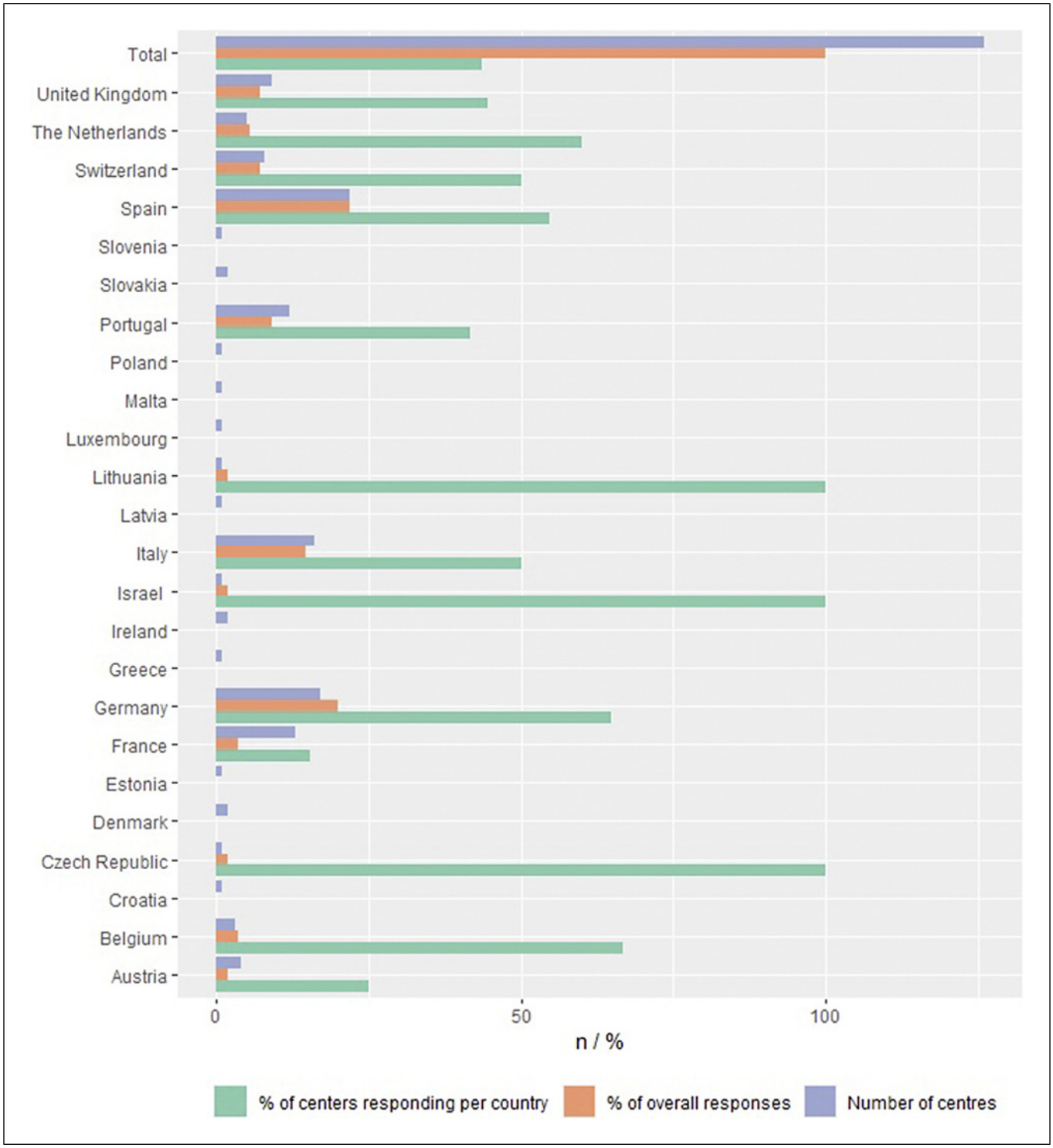

Fig. 1. Distribution of 2021 IRD survey replies by country. The number rate of replies was 44%.

The mean time between inquiry of an appointment and the first contact with a retina expert was reported to be less than 4 weeks in 44% of the centers (most of the centers in ITA [4/6], ESP [10/12], and CHE [3/4] and all centers in AUT [1/1] and LTU [1/1], online suppl. Figure S2). The mean time between inquiry of an appointment

Table 1. Number of IRD patients managed by centers per year in the 2nd IRD survey

	N	%
None	5	9
<10	0	0
10–19	2	4
20–49	6	11
50–99	5	9
100–199	13	24
200–499	12	22
500–999	10	18
>1,000	1	2
Do not know	1	2
Total centers that replied	***55***	***100***

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

and final diagnosis was reported to be <4 months in 36% of the centers. The longest time interval was between inquiry of appointment and first contact with a retina expert for IRD patients and was 7 months in GBR (online suppl. Fig. S2). These data are different from the 1st survey in 2019, where the longest time reported was 30 months in DEU [15]. The longest mean time between inquiry of appointment and the final ophthalmological diagnosis for IRD patients in 2021 is 12 months in BEL (1/2), DEU (1/10), ITA (1/6), and GBR (1/4) (online suppl. Fig. S3), much lower than the reported time in 2019 (35 months in DEU).

Two-Year Follow-Up Analysis

This analysis is only based on centers who responded to both surveys (2019 and 2021), i.e., in 38 EVICR.net centers. From the 38 centers, 34 centers managed IRD patients in 2019 and 35 centers in 2021. For the comparative analysis, we have considered only the 34 centers that managed IRD patients in both surveys. The number of centers that have a database for IRD patients has increased from 29 to 31 (Table 2). Local databases (e.g., Excel) are still most commonly used (71% and 66% in 2019 and 2021 surveys, respectively). However, an increase in the use of electronic medical record was observed (from 36% to 52%). An increase in the number of patients registered in the databases was reported from 15 sites, a decrease from 4 sites, and stable numbers from 9 sites (Fig. 4).

All centers manage IRD patients at their centers; 15% of these centers in 2019 and 18% in 2021 also refer IRD patients to expert centers. General ophthalmologists continue to be the main referees of IRD patients to the EVICR.net centers with a statistically significant increase in 2021, followed by patient self-referral and referrals from medical retina specialists (Fig. 5). Main signs and/or symptoms implicating a visit in the centers remained the same in both surveys: reduced visual acuity and nystagmus followed by squint in infants and young children (<6 years old); reduced visual acuity followed by night blindness in children/adolescents from 6 to 18 years old; and reduced visual acuity, reduced visual field, and night blindness in young adults and adults (Fig. 6).

Mean time between inquiry of appointment and first contact with a retina expert is less than 4 weeks in one more center in 2021 (Table 3); 12/34 centers reduced this mean time from 2019 to 2021; in 8/35 centers, the time increased; and in 13/35, it remained the same. The mean time between inquiry of appointment and final clinical diagnosis was reduced from 3 months to <4 weeks in 3/34 centers and from more than 1 year to <4 weeks in 3/34 centers from 2019 to 2021; in 5/34, it was increased from <4 weeks to 2, 3, 7, 8, and 12 months;, in 1/34, it was increased from 3 months to 1 year; and in 21/34, it did not change.

Local Setting

For centers that selected "Refer IRD patients to expert centers" (question 2, Section 1), the basic tests performed in IRD patients referred to expert centers are visual acuity, visual fields, fundus photography, fundus autofluorescence, and retinal optical coherence tomography (OCT and/or OCT-A; online suppl. Table S3). Interestingly, 82% of the centers that refer IRD patients also perform electrophysiology; 64% do ultrawidefield fundus imaging; and 27% do other tests.

In centers that manage the IRD patients themselves (49), diagnostic testing includes visual acuity in 100% and visual field testing in 98% of them; fundus autofluorescence in 98%, retinal OCT and/or OCT-A imaging in 98%, fundus photography in 96%, electrophysiology in 96%, color vision testing in 94%, and refraction in 92% are also commonly performed for setting a clinical diagnosis of IRD. This is very similar to the work-up in 2019 with the exception of percentages for ultrawidefield imaging, color vision testing, and full-field stimulus thresholds (FSTs) as those 3 tests were not included in the 2019 survey (online suppl. Table S4). On the other hand, FST is only done in 21/49 centers (43%). Section 2 of the IRD survey also included an option "Other," where additional methods could be added as free text. Answers included adaptive optics imaging, chromatic pupil campimetry, orthoptic visit, MP3 fundus-related perimetry in 2% of the centers, and contrast sensitivity in 4% of the centers.

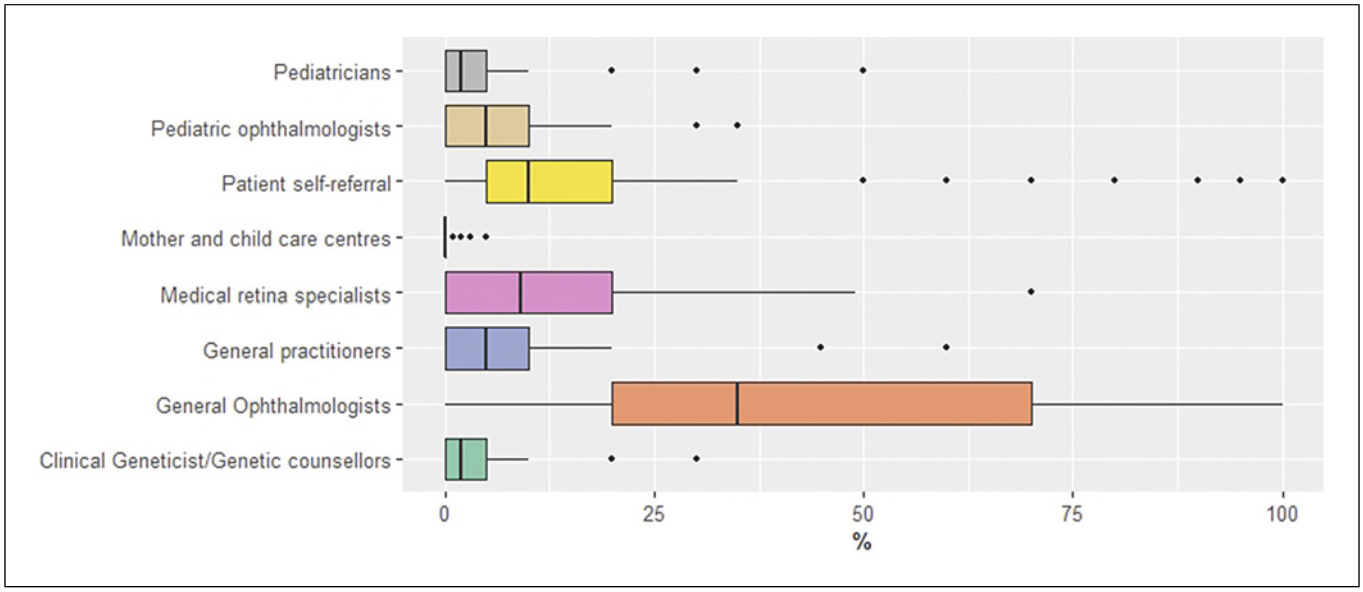

Fig. 2. Referral pathways. Box plots of the percentage of the referrers of IRD patients to the EVICR.net clinical centers and ERN-EYE HCPs: the box signifies the third quartile (Q3) and first quartile (Q1) range of data, and the median is represented by a black line within the box. Data falling outside the Q1 – Q3 range are plotted as outliers of the data and are depicted by black dots. $N = 50$.

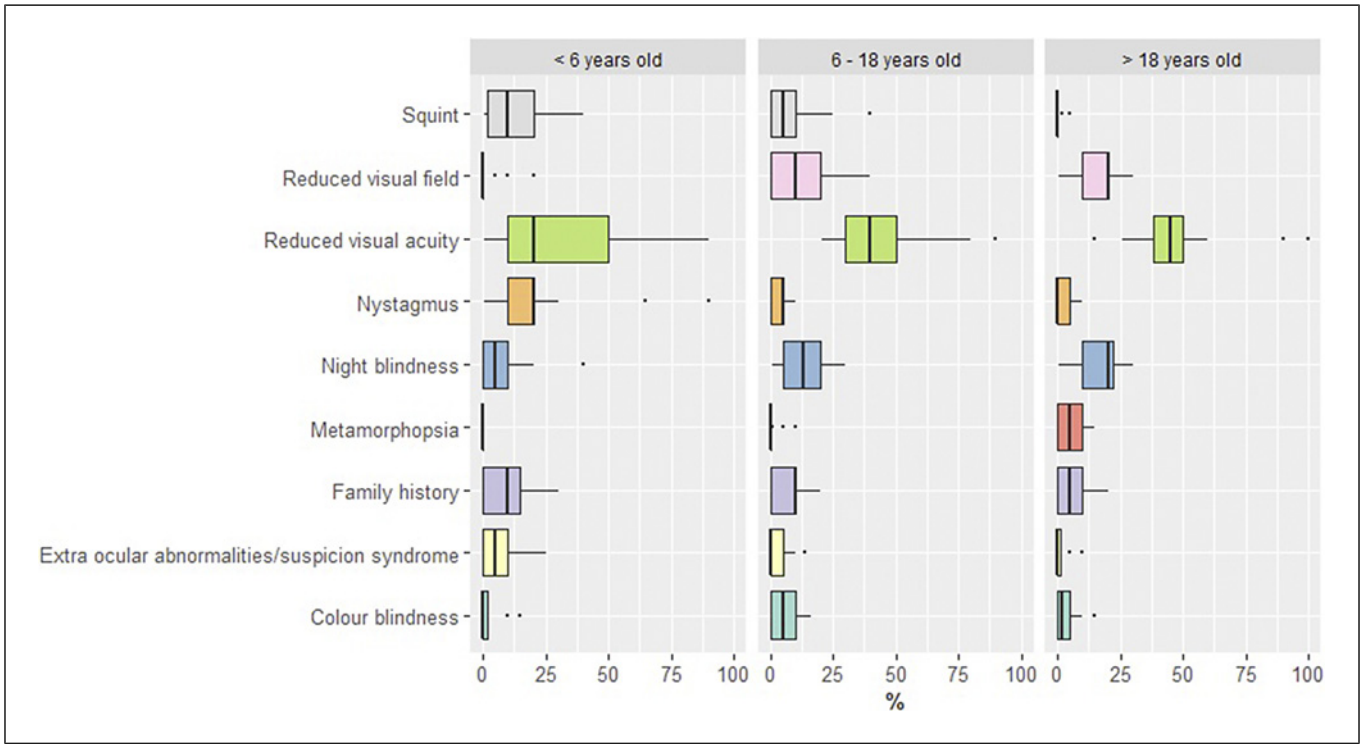

Fig. 3. Reasons for referral of IRD patients to the EVICR.net clinical centers and ERN-EYE HCPs. For explanation of the boxplots, see Fig. 2. $N = 17$ (only 17 centers replied correctly to this question).

Table 2. Database for IRD patients in each IRD survey

Do you have a database for IRD patients?	2019		2021	
	N	%	*N*	%
Yes	29	85	31	91
No	5	15	3	9
Total of centers that manage IRD patients in both surveys	***34***	***100***	***34***	***100***

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

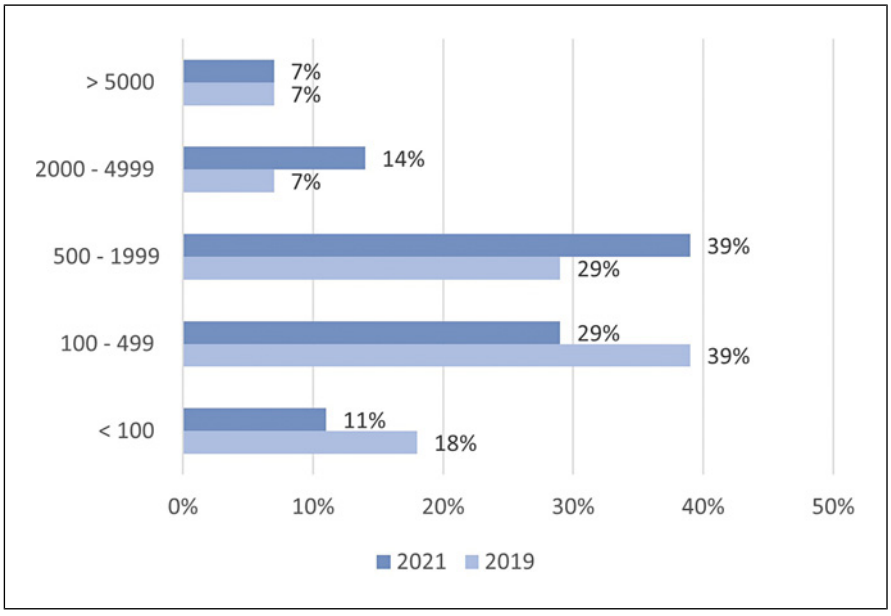

Fig. 4. Number of patients present in databases of centers replying to both surveys (in % of centers). *N* = 28.

Visual Acuity Testing

For visual acuity testing in IRD patients, centers use mainly Snellen charts (69%), ETDRS charts (65%), Lea Symbols® (59%), tumbling "E" charts (53%), number charts (43%), Teller Acuity Cards (37%), and Pelli-Robson contrast test (27%) (Fig. 7a). As expected, their use is age dependent (Fig. 7b).

In general, centers that replied to both surveys started to use different visual acuity testing methods since 2019 (online suppl. Table S5), particularly the use of newer tests such as Lea Symbols® from 36% to 67% and Teller Acuity Cards from 40% to 45%, respectively. This indicates more advanced visual acuity testing in 2021 compared to 2019.

Visual Field Testing

Centers use mainly static perimetry (91%) and kinetic perimetry (74%) to test visual fields in IRD patients. Seventy-one percent use Goldmann (manual or semiautomated Octopus 900, although this was not specifically asked) for kinetic perimetry and 79% of centers use Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) for static perimetry. For fundus-controlled perimetry, 76% of the centers use MAIA (CenterVue Inc., Fremont, CA, USA) and 29% use MP1 and MP3 (NIDEK Co., Ltd., Aichi, Japan). Of note, a significant increase in the use of fundus-controlled perimetry was documented from 2019 to 2021, i.e., from 27% to 52% and specifically using MAIA from 44% to 67%, respectively (MAIA, CenterVue Inc., Fremont, CA, USA) in centers that replied to both surveys. Although Goldmann (manual) kinetic perimetry remained the most commonly used method (81% in 2019 and 2021), static perimetry with the Humphrey® Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) is also frequently used (85% in 2019, 81% in 2021).

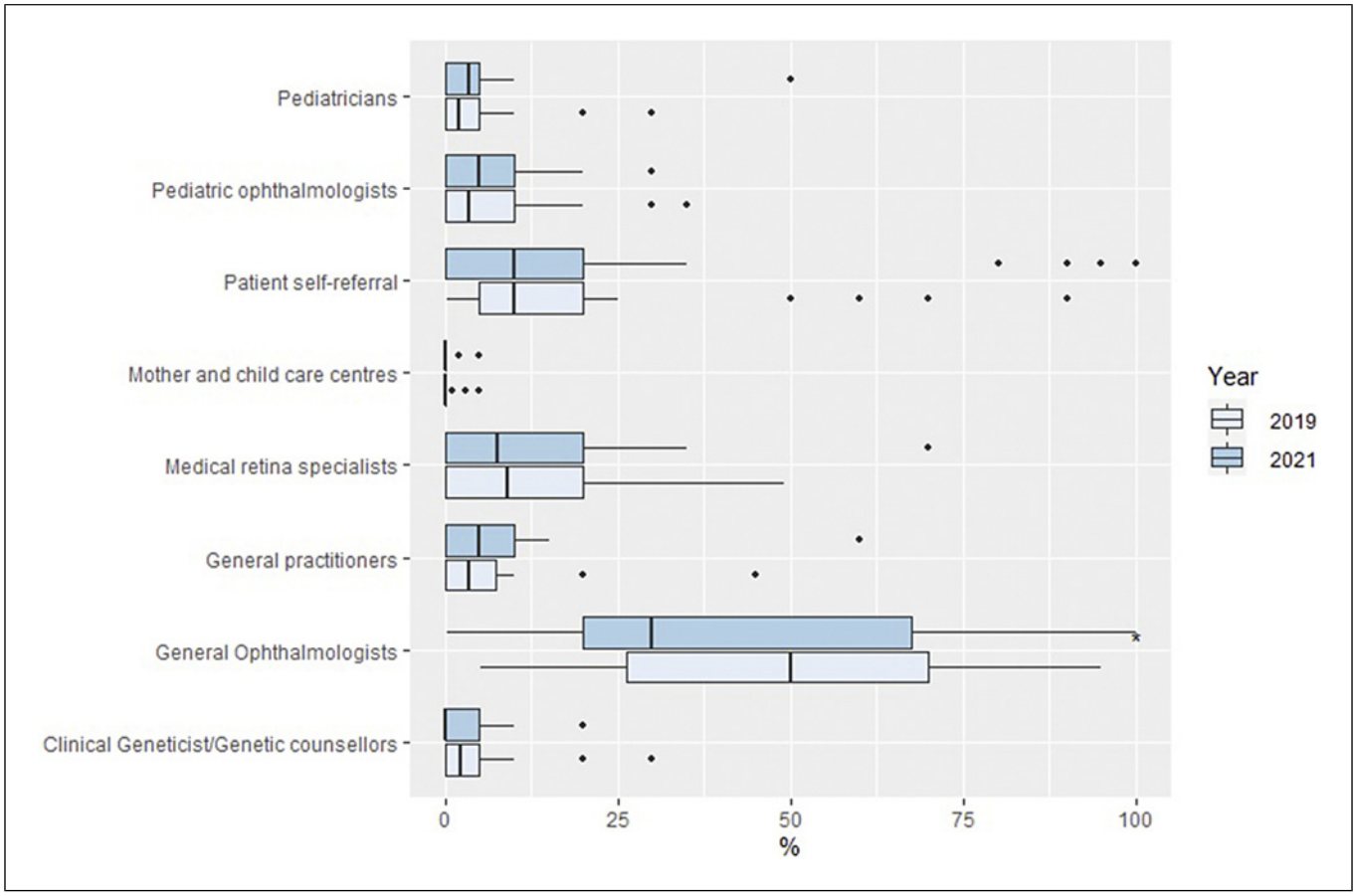

Fig. 5. Referral pathways comparing 2019 and 2021 surveys. For explanation of the boxplots, see Fig. 2. Statistical significance calculated by Wilcoxon test: (*) p value <0.05. N = 34.

Fundus Imaging

For fundus photography, 70% of the centers use standard fundus cameras and 72% use wide-field fundus cameras in IRD patients. From centers that use standard fundus cameras, 64% use a Topcon Medical Systems (Oakland, NJ, USA) device and 39% a Carl Zeiss Meditec (Jena, Germany) device. For wide-field fundus imaging, an Optos (Dunfermline, Scotland) wide-field fundus camera is used in 62% of the centers, followed by a Clarus 500 or 700 camera (Carl Zeiss Meditec, Jena, Germany) in 47%, and TrueColor Eidon AF (60 x 55°, CenterVue Inc., Fremont, CA, USA) in 8%.

To evaluate fundus autofluorescence (blue light fundus autofluorescence and/or near-infrared autofluorescence), 88% of the centers use a Spectralis® HRA (Heidelberg Engineering GmbH) in IRD patients, 40% use the Optos system (Dunfermline, Scotland) or similar, 19% use Clarus (Carl Zeiss Meditec, Jena, Germany), 8% use TrueColor Eidon AF (60 x 55°), and 2% use a blue filter on a fundus camera.

Regarding OCT and OCT-A, 85% of the centers use a Spectralis® HRA-OCT (Heidelberg Engineering GmbH) in IRD patients, 35% use a Cirrus HD-OCT (Carl Zeiss Meditec), and 33% use a Zeiss PLEX Elite-OCT-A (Carl Zeiss Meditec). Other devices are used in few centers (online suppl. Table S6). Of note, 44% of the centers have only 1 OCT equipment, 31% have 2 OCT equipments, 15% have 3 equipments, 8% have 4 equipments, and one center has 5 OCT equipments from different manufacturers.

Color Vision Testing and Electrophysiology

For color vision testing, 80% of the centers use Ishihara and 52% use Farnsworth 100 hue.

Regarding electrophysiology, the tests most used in IRD patients are full-field electroretinogram (ffERG, 96%), electrooculography (EOG, 89%), visual evoked potentials (VEP, 87%), and multifocal ERG (mfERG,

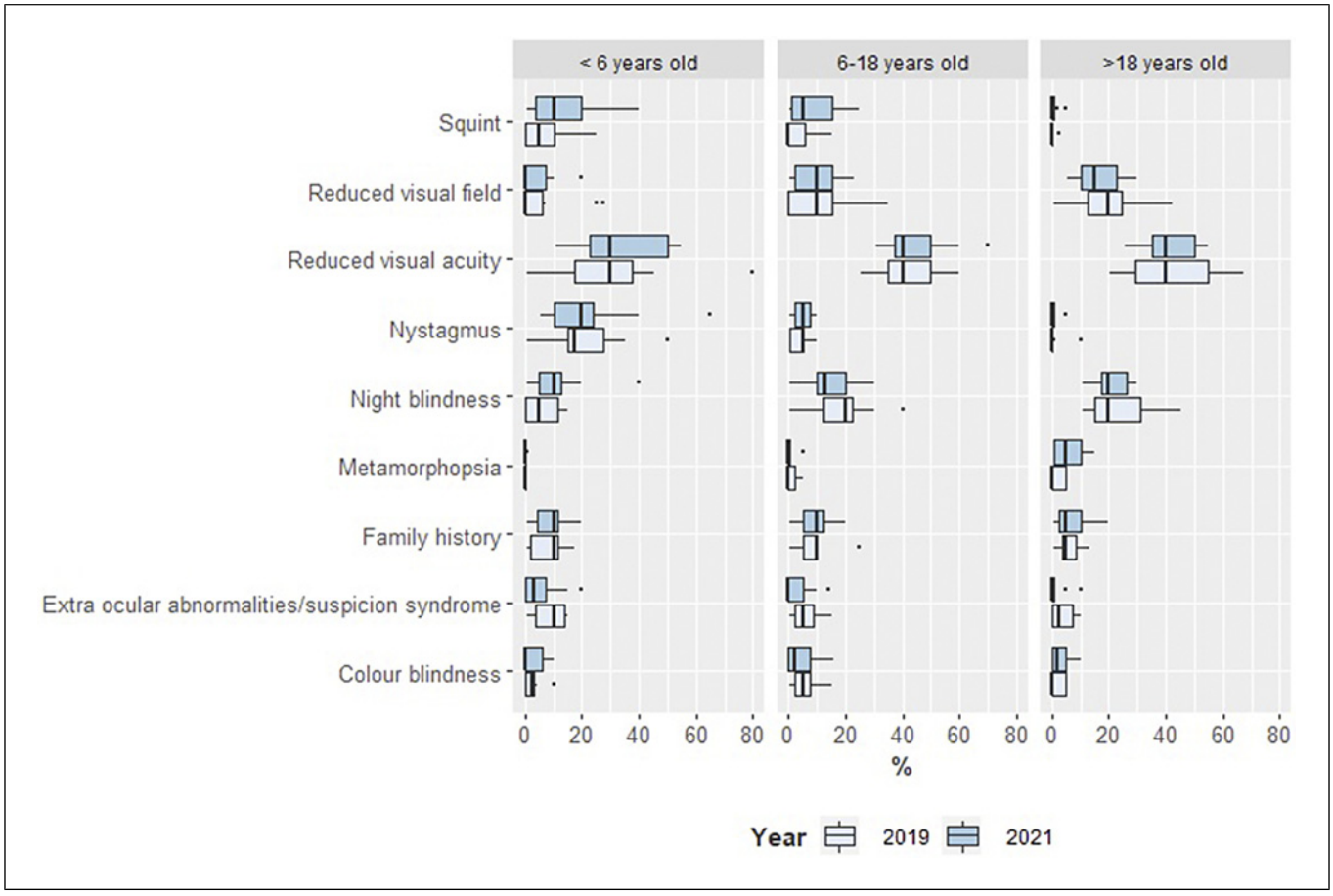

Fig. 6. Reasons for referral of IRD patients to the EVICR.net clinical centers: comparing 2019 and 2021 surveys. For explanation of the boxplots, see Fig. 2. Statistical significance calculated by Wilcoxon test: (*) p value <0.05. N = 11 (only 11 centers replied correctly in both surveys).

85%). For ffERG, the devices used most frequently are Espion (Diagnosys LLC, Lowell, MA, USA) (40%) and RETIport/Scan21 (Roland Consult Stasche & Finger GmbH, Brandenburg an der Havel, Germany) (40%). RETIport/Scan21 (Roland Consult Stasche & Finger GmbH, Brandenburg an der Havel, Germany) is the device used most frequently in mfERG (45%), EOG (40%), VEP (38%), and dark adaptation (DA, 23%). On the other hand, Espion (Diagnosys LLC, Lowell, MA, USA) is the most frequently used device for FST (76%). Seventy-one percent of the centers using FST in IRD patients perform chromatic FST (blue, red, white), whereas 33% of the centers perform white testing only. When comparing electrophysiology testing in 2019 and 2021, the use of ffERG decreased from 97% to 84%, mfERG from 88% to 75%, EOG from 84% to 72%, and VEP from 75% to 66%, while the use of DA increased from 31% to 41% (Table 4).

IRD Genetic Testing and Counseling

From the centers that have IRD patients (50), 84% offer genetic testing at their centers and 69% of these centers have more than 61% of their IRD patients genetically tested. Eight percent do not offer genetic testing due to lack of funding (50%) and other reasons, such as testing being carried out at a university hospital and no counseling service available at the treating hospital. From those, 75% refer patients or their blood/DNA to other institutions/labs. Seventy-two percent of the centers replied that 41–80% of the IRD patients have been genetically solved, and only 5% of the centers have 81–100% of the IRD patients genetically solved.

From the centers that offer genetic testing to their IRD patients, 93% have genetic testing done in a diagnostic laboratory in their country, 31% in a research laboratory, and 10% in a diagnostic laboratory in a different country. Figure 8 shows the percentage of patients tested on

Table 3. Mean time between inquiry of appointment and first contact with a retina expert and final clinical diagnosis for IRD patients in each IRD survey

	2019		2021	
	N	%	*N*	%
Mean time between inquiry of appointment and first contact with a retina expert				
<4 weeks	13	38	14	41
Months	19	56	19	56
1	1	3	1	3
1.5	2	6	0	0
2	4	12	10	29
3	4	12	4	12
4	3	9	1	3
5	1	3	1	3
6	2	6	1	3
7	0	0	1	3
25	1	3	0	0
30	1	3	0	0
Do not know	2	6	1	3
Mean time between inquiry of appointment and final clinical diagnosis				
<4 weeks	11	32	12	35
Months	20	59	19	56
2	4	12	4	12
3	9	26	5	15
4	1	3	0	0
5	3	9	1	3
6	1	3	4	12
7	0	0	2	6
8	0	0	1	3
12	2	6	3	9
24	1	3	0	0
35	1	3	0	0
Do not know	1	3	2	6
Total centers that manage IRD patients in both surveys	***34***	***100***	***34***	***100***

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

clinical-grade and research-grade tests, accredited or certified with Clinical Laboratory Improvement Amendments. Of the 42 centers that genetically test their IRD patients, 39 (93%) offer genetic counseling. In the other centers, genetic counseling is provided by external genetic counselors (67%) or clinical geneticists/genetic counselors (33%).

The reported mean time between requesting genetic testing and receiving the final molecular genetic report was 2–4 weeks in ITA, NLD, and ESP. In 88% of centers, the time to receiving the genetic test result is longer than 1 month. The longest mean time reported is 24 months in FRA and had increased compared to 2019 (17 months). The most used technologies for genetic testing in IRD patients were IRD-specific gene panels (88%), Whole Exome Sequencing (WES, 67%), and diagnosis-directed Sanger sequencing (62%), which is similar to the 2019 survey.

Costs of genetic testing are covered by public health service/general health insurance in 83% of the centers, private health insurance in 29%, research funding in 24%, center budget in 2% and are not covered in 5%. Interestingly, the cost of genetic testing was not covered in 75% of the centers from ESP (6/8) in 2019 and only in 22% of the centers (2/9) in 2021. Online suppl. Table S7 gives detailed information by country and a correlation between time to get a genetic result and reimbursement.

Looking at centers that participated in both surveys and manage IRD patients, 2 centers in ESP that genetically tested IRD patients in 2019 do not perform genetic testing in 2021 (Table 5), the reason being lack of funding. One of these centers refers patients or their blood/DNA to other institutions/labs, and the other does not refer patients. From the centers that continue to perform genetic testing, a higher number of genetic testing is observed as well as percentage of genetically

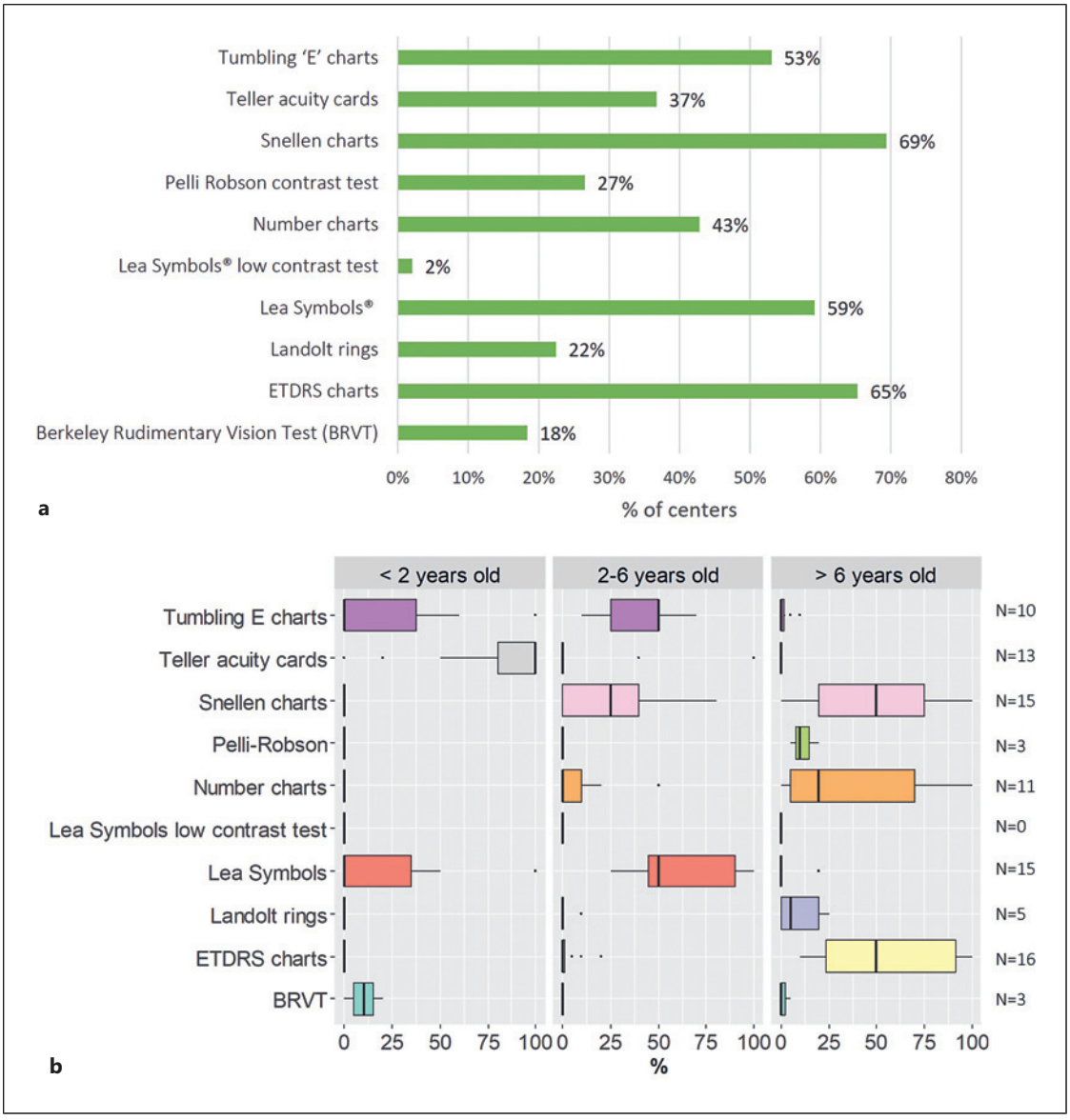

Fig. 7. Methods for visual acuity testing used in IRD patients. **a** Multiple choices were allowed. $N = 49$. **b** Percentage of the use of visual acuity testing by age. Only 23/49 centers had properly understood the question or presented the data in a manner that we can extrapolate the results. For explanation of box plots, see Fig. 2.

solved cases (Fig. 9). The genetic testing performed in a research laboratory went from 57% in 2019 to 30% in 2021. At the same time, the testing being performed at a diagnostic laboratory in the country slightly increased from 83% to 93%.

Involvement in Clinical Trials

From the centers that have and genetically test IRD patients (42), 52% are currently involved in clinical studies with gene therapies for IRD, 7% were previously involved, 12% are not involved, and 29% are interested in being involved in clinical studies with gene therapies for IRD. Interestingly, in this 2-year timeframe between the 1st and the 2nd IRD surveys, the number of centers that are involved in clinical studies more than doubled. Table 6 shows the replies of the centers participating in both surveys.

In 2021, 68% of the centers are/were involved in at least one natural history study and 80% in clinical trials, being at least 90% of the centers currently involved in those

Table 4. Electrophysiological tests used in IRD patients in the 1st and 2nd IRD survey

Which electrophysiological tests do you use in IRD patients?	2019		2021	
	N	%	*N*	%
ffERG	31	97	27	84
mfERG	28	88	24	75
EOG	27	84	23	72
VEP	24	75	21	66
DA	10	31	13	41
Total centers that perform electrophysiology in both surveys	***32***	*	***32***	*

"N" refers to the number of centers. ffERG, Ganzfeld ERG; mfERG, multifocal ERG; EOG, electrooculogram; VEP, visually evoked potential; DA, dark adaptometry. *Multiple choices allowed.

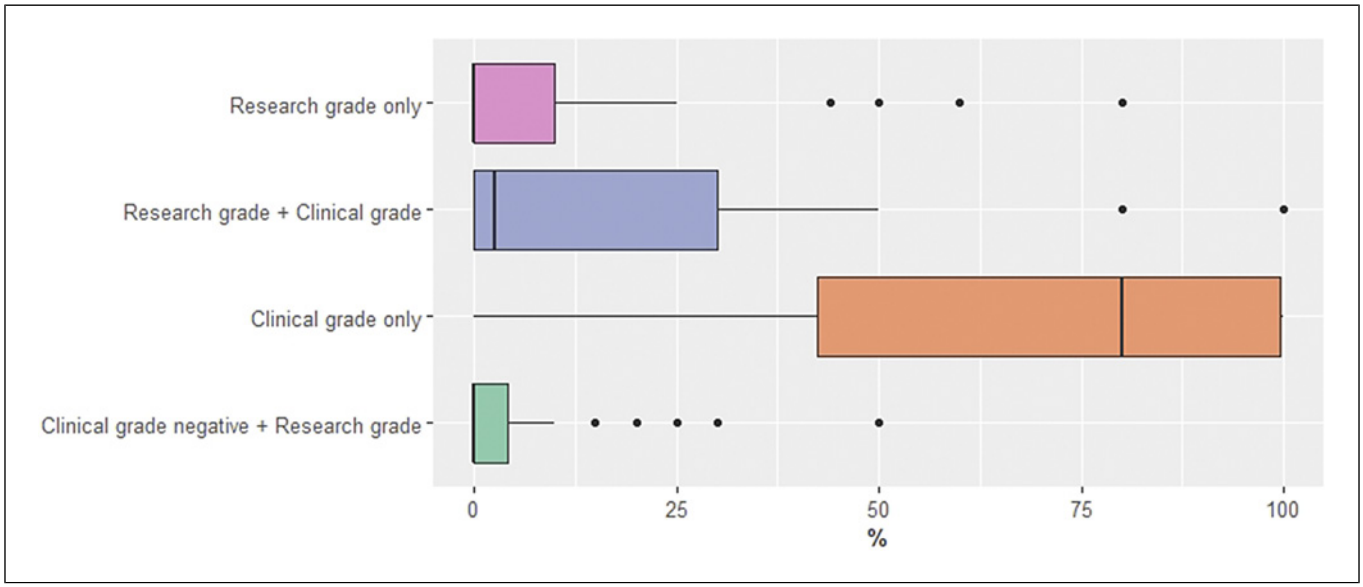

Fig. 8. IRD patients tested on clinical grade and research grade. For explanation of boxplots, see Fig. 2. $N = 42$.

studies. The natural history studies for CEP290 mutation-associated IRD (ClinicalTrials.gov Identifier: NCT03396042), XOLARIS for retinitis pigmentosa (ClinicalTrials.gov Identifier: NCT03349242), and RUSH2A for Usher Syndrome (ClinicalTrials.gov Identifier: NCT03146078) are performed in 29%, 29%, and 24%, respectively, of the centers that are currently involved in natural history studies (online suppl. Table S8). Only 24% of these centers are the sponsors of a particular natural history clinical study and 82% of the centers had patients enrolled during the studies.

Eighty-five percent of the centers are/were involved in premarketing studies and 50% in postmarketing studies. The clinical study ILLUMINATE (for CEP290 mutation-associated IRD) (ClinicalTrials.gov Identifier: NCT03913143) and the post-authorization safety study with voretigene neparvovec (Luxturna®) are performed in 25% and 45% of the centers that are currently involved in clinical trials with gene therapies for IRD, respectively (Table 7), showing an increase in the participation of the centers in the Luxturna study from 18% in 2019 to 45% in 2021. Only 5% of these centers are/were the sponsors of these clinical trials, and 85% of the centers had patients enrolled during the clinical studies. From those, 53% of centers enrolled more than 10 patients.

Table 5. Centers genetically testing IRD patients distributed by country in each IRD survey

	2019			2021		
	No. of centers that manage IRD surveys	No. of centers that are genetically testing	% of centers genetically testing per country	No. of centers that manage IRD surveys	No. of centers that are genetically testing	% of centers genetically testing per country
Belgium	1	1	100	1	1	100
Germany	10	9	90	10	9	90
Israel	1	1	100	1	1	100
Italy	6	6	100	6	6	100
Netherlands	3	3	100	3	3	100
Portugal	3	3	100	3	3	100
Spain	8	8	100	8	6	75
Switzerland	1	1	100	1	1	100
United Kingdom	1	1	100	1	1	100
Total	***34***	***33***	**-**	***34***	***31***	-

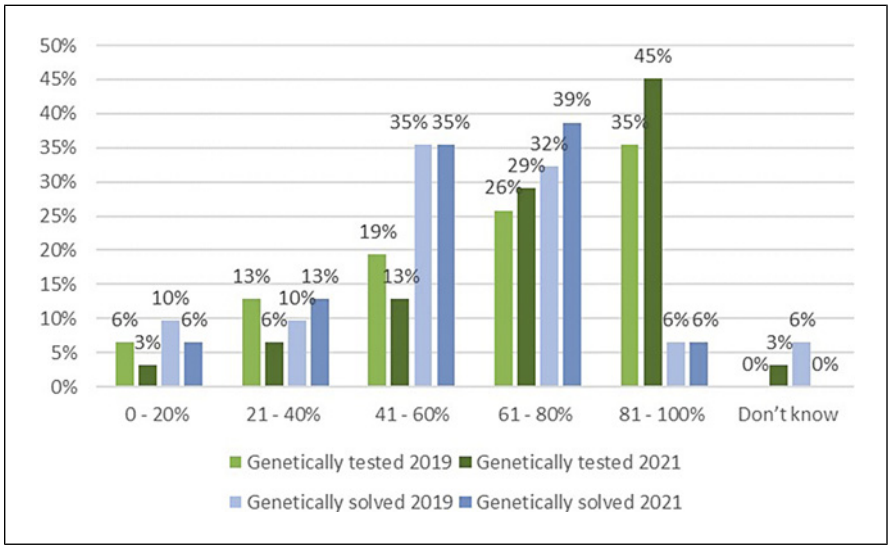

Fig. 9. Estimated percentage of IRD patients that has been genetically tested (green bars) and genetically solved (blue bars) at each center comparing 2019 and 2021 surveys. *N* = 31.

Table 6. Involvement in clinical studies with gene therapies for IRD in 2019 and 2021

	2019		2021	
	N	%	*N*	%
Currently involved	7	23	18	58
Previously involved	2	6	2	6
Not involved	5	16	2	6
Interested in being involved	17	55	9	29
Total of centers that perform genetic testing in IRD patients in both surveys	***31***	***100***	***31***	***100***

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

Table 7. Gene therapy clinical trials for IRDs with centers involved (multiple choices allowed)

Study (ClinicalTrials.gov Identifier)	Condition	*N*	%	Currently involved	Previously involved
STAR (NCT03496012)	Choroideremia	3	15	3	0
Illuminate (NCT03913143)	Leber's congenital amaurosis	6	30	6	0
Safety study of RPE65 gene therapy to treat LCA (NCT00643747)	Leber's congenital amaurosis	4	20	4	0
Luxturna® (EUPAS31153)	Leber's congenital amaurosis or biallelic RPE65-mediated inherited retinal disease	9	45	9	0
ILLUMINATE (NCT03140969)	Leber's congenital amaurosis	5	25	4	1
Gene Therapy for Achromatopsia (CNGA3) (NCT03758404)	Achromatopsia	4	20	4	0
None	–	5	25	4	1
Other		10	50	10	0
OPTIRPE65 (NCT02946879)	Leber's congenital amaurosis	0	0	0	0
PIONEER (NCT03326336)	Retinitis pigmentosa	1	5	1	0
Total of centers currently or previously involved in clinical trials		***20***	–	–	–
Total of centers that perform genetic testing		***42***	–	–	–

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

Discussion

This second survey on management and treatment of IRDs in Europe confirmed in part the findings of the 1st survey conducted 2 years earlier in 2019 but also revealed major changes. The 2nd survey was sent in 2021 to 95 EVICR.net clinical research center members from 15 European countries and 53% of the EVICR.net clinical centers have replied. This reflects a small increase (53 vs. 49%) in the centers' engagement in relation to the 2019 IRD survey [15]. Different from the first survey, the ERN-EYE management team has also disseminated the 2nd IRD survey to their HCPs and affiliated members (40 in total) in 19 member states. Eleven EVICR.net centers are also ERN-EYE HCPs. As a result, 29 more centers and 9 more countries were included.

In total, the 2nd IRD survey that contained 124 questions (compared to the 1st survey's, 112 questions) was sent to 124 centers from 24 European countries and ISR. Of these, 55 centers have replied, which reflects an engagement rate of 44% (see Fig. 1) and is similar to other surveys conducted among EVICR.net members. It is important to understand that the response rate does not imply that the nonresponders are centers that do not manage many IRD cases. The response rate could also reflect centers that are less motivated to complete a questionnaire of 124 questions. This high number had been discussed within the Expert Committee of the survey but was finally considered useful to answer the questions of the survey, i.e., prevalence and distribution of IRDs, diagnosis and management of IRDs, availability of genetic testing and genetic counseling, and actual involvement in clinical trials throughout Europe. As in the first survey [15], we observed different response rates and answers per country, and the results of the 2nd survey presented here were again mostly driven by the responses from ESP, DEU, ITA, and PRT (Fig. 1).

An interesting finding of the 2nd survey is that 40/55 responding sites (73%) manage between 50 and 1,000 IRD patients per year, 5/55 do not see IRD patients (9%), and only one center manages >1,000 patients per year (2%). The numbers cannot be strictly compared to those of the 1st survey because then we had asked about "currently" managed IRD patients. In retrospect, we considered this question ambiguous and changed the question to "patients managed per year." In the 1st survey, 42/49 responding centers (86%) had reported to currently manage IRD patients. Although the responding centers in the two surveys were not identical, one may conclude that the results were comparable despite asking a slightly different question. However, a major difference becomes apparent as to centers that manage >1,000 IRD patients per year. In the actual survey, this applies only to 1/55 centers (2%) compared to 8/49 (16%) who in the 1st survey responded to the question "currently follow >1000 IRD patients."

Regarding databases, although 86% do have some kind of database, there is room for improvement, in particular

with regard to database structure. Of the positively responding sites, 72% have IRD patients registered in local files, but only 42% have electronic medical records, and 12% have access to national web-based databases. In addition, the percentage of sites per country with databases varies considerably when splitting the results per size of database (online suppl. Table S2), resulting in 8% (ESP, database 500–1,999 patients) to 100% (AUT, CZE, ISR, LTU, and NLD). However, in the latter countries, only one site per country had responded to the survey (except for NLD with 3 centers) compared to, e.g., DEU (3/10, database 100–499, 4/10 database 500–1,999), where in fact 7/10 sites (70%) do have databases, and ITA (2/6, database <100; 1/6 database 100–499, 3/6 database 500–1,999), where in fact 6/6 sites (100%) do have databases. Comparing the data only in the centers that have replied to both surveys, an increase in the use of electronic databases from 36% in 2019 to 52% in 2021 was observed and also an increase in the number of patients registered in the databases (Fig. 4), indicating increasing interest and build-up of databases that are extremely valuable for the setup of clinical trials. To note that in both surveys, it was not asked whether the databases were approved by the respective ethics committees and internal review boards.

With regard to age-related signs and symptoms of patients getting their diagnosis of IRD for the first time, the results from both surveys are very similar. In infants and young children, reduced visual performance and nystagmus followed by squint and a positive family history were major signs compared to reduced visual acuity and night blindness in patients age 6 to 18 years and reduced visual acuity, visual field loss, and night blindness in young adults and adults. Progress was noted in the mean time between inquiry of appointment and first contact with a retina expert at many sites, although this time interval was increased in some centers (Table 3). A similar progress is observed for the time between reporting first symptoms and a final clinical diagnosis (Table 3). Mean time for referral may be impacted for many reasons, one of which is understaffing in expert centers observed in some countries.

In the 49 centers that manage IRD patients themselves, most tests are done in 100% or close to 100% (online suppl. Table S4). Interestingly, ultrawidefield retinal imaging is only done in 78% and FST in 43%. In the centers that follow IRD patients but refer to expert centers (10/55), the clinical basic work-up is very similar and complete as could be expected (online suppl. Table S3). Exceptions are ultrawidefield retinal imaging and electrophysiology that are performed in only 64% and 82%, respectively. Visual acuity testing is age dependent (Fig. 7b). An increasing use of child-specific tests is evident in all age groups (online suppl. Table S5). Visual field testing also shows significant changes from the first to the second survey. Fundus-controlled perimetry use increased from 27% to 52% in centers that replied to both surveys with the MAIA device now being used in 67% (44% in 2019). Manual kinetic Goldmann perimetry or semiautomated Octopus 900 kinetic perimetry equivalent or even superior to the classical Goldmann perimetry is still widely used, as well as Humphrey Field Analyzer for static perimetry. The changes, both in visual acuity testing and visual field testing, can be explained best by the increasing involvement of centers in multinational clinical studies on both natural history and gene therapy where typically the same set of testing devices is required and eventually implemented. Concerning devices for advanced imaging, Spectralis is still the most widely used device for OCT imaging (85% of 48 centers). For electrophysiology, Espion (Diagnosys LLC) and RETIport/Scan21 (Roland Consult) are the most frequently used devices, both at equal percentage, i.e., 40%. Full-field ERG in 2021 is only used in 84% of the centers compared to 2019 where ffERG was done in 97% of the centers. This likely reflects the increasing use of retinal OCT to diagnose and follow patients with IRDs due to the characteristic findings and biomarkers that have been developed to monitor disease progression first reported in 2011 [16, 17] and since then used in many other studies [18–27]. Genetic testing is widely used; however, there is still a significant percentage of patients who are not tested. Eight percent of the 50 centers who answered do not offer genetic testing, in 50% due to lack of funding. Seventy-two percent of the centers replied that the diagnosis was confirmed by molecular genetic testing in 41–80%, 5% reported that 81–100% were genetically solved. Hence, there is still room for including more patients for genetic testing and to further improve the success rate of genetic testing, e.g., by adding whole exome and whole genome testing to the usual IRD gene panel testing. Also, establishing European guidelines for clinical management and molecular genetic of IRD patients will be an important step forward. At present, ERN-EYE is making efforts to develop consensus guidelines for specific forms of IRDs, e.g., *RPE65* mutation-related IRDs. To identify the genotype in every patient who consents is an important aim for at least 3 reasons: (1) precise genetic counseling, (2) identification of the underlying pathophysiology as an important tool to counsel the patient as to the expected disease course and eventual therapies, and (3) to identify as many patients as possible for clinical trials and postmarketing treatments of rare and ultrarare diseases.

Here, we refer to the numbers we had estimated in the 1st report which is that only 14–22% of the overall patients are seen in specialized IRD clinics [15]. Of particular interest is diagnosing IRDs early in the disease course to (1) better understand and document the natural history and (2) have the possibility to involve patients with less advanced disease in therapeutic trials, be it gene specific or gene agnostic.

The mean time to get the genetic test result was reported to be only 2–4 weeks in ITA, NLD, and ESP. However, in 88% of centers, the time was higher than 1 month; the highest mean time was reported from the French centers who answered and even increased from 17 months in the 1st survey to 24 months in the 2nd survey. This increase in delays may be explained because the study occurred at the time of a switch in the national genetic testing strategy (from panel to Whole Genome Sequencing [WGS]) in the context of the French Genomic Plan that when fully operational will cut down the time to obtain a genetic diagnosis. Covering of cost by the public health service/general health insurance was reported by 83% of the centers and by private health insurance in 29%. Research funding was reported in only 24%. In 6/8 responding centers in ESP, cost for genetic testing was not covered in 75% in 2019 but was reduced to only 22% (2/9 centers) in 2021. Hence, there is a general trend to more testing in general and more testing covered by public health insurance, but at the same time, a longer time to receive back molecular genetic reports. The latter may be at least partially due to the shift from research testing to certified laboratory testing. A faster result would be desirable to better meet patients' expectation. The survey did not include a specific question on the time to get a result according to the type of test. Possibly, the type of test performed in each center/country (for instance, sequencing a single gene vs. WES/WGS) is the major factor influencing the time to get the final genetic result as we had already pointed out in our first survey [15]. Recently, ERN-EYE has published an important position paper on genetic testing in IRDs [28], describing national differences and national plans available in parts of the countries. On the other hand, budget for molecular genetic testing is limited. The high heterogeneity of the approaches and opportunities can explain in part country-specific situations but also indicate possible solutions to overcome bottlenecks of timely testing or testing opportunities to give patients throughout Europe equal opportunities for correct diagnosis in an acceptable time frame. This is a prerequisite for correct genetic counseling and for allowing interested patients to participate in natural history studies and in clinical trials.

Overall, of the 42 centers that have and genetically test IRD patients, half are currently involved in preclinical and clinical studies and another 29% are interested in getting involved in such studies. Comparing the replies from centers participating in 2019 and 2021, there is a 2.8-fold increase from currently involved sites compared to 2019 (Table 6). This increased involvement is paralleled by a decrease in 50% of centers that would be interested in being involved. The increase in natural history studies is huge; in 2021, 16/17 (94%) centers are currently involved in natural history studies of 12 disease entities compared to just 1/17, indicating previous involvement. Natural history studies on CEP290-IRD, XOLARIS-IRD, and RUSH2A-IRD are performed in 29%, 29%, and 24% respectively, of those centers.

From the first survey, the questionnaire was improved to reduce ambiguous answers or absence of answer. For instance, section 4 about the involvement in clinical trials was reviewed to include the name of the studies and NCT number, considering the replies from the first survey and literature. Also, in several questions, instead of free text, we added options based in previous answers. Free text was only allowed in the format of «Other. Please specify» in order to give the opportunity to the centers to reply with a different option than the presented ones. However, there were still several factors that complicated the analysis of our data and the comparison, namely, small changes in questions or in the type of question. As we tried to make the survey as quick to answer as possible, we had to include a significant number of questions with multiple choices that turned out to be difficult to analyze in a quantitative way.

Strengths of Our Study

This follow-up survey 2 years after the first allowed to evaluate changes in a critical time period that is just after introducing the first licensed gene therapy in one form of IRDs (*RPE65*, voretigene neparvovec, Luxturna^{TM}). With this first licensed therapy, an increasing interest in genetic eye diseases was expected. The data reported here confirm this expectation.

Wherever sensible, we used the same questions in both surveys. The questionnaire of both surveys was answered by the same 38 centers, i.e., in 70% based on the 1st survey. We therefore consider the reported data as representative.

Including ERN-EYE resulted in an increased number of sites and countries throughout Europe to whom the survey was sent. As ERN-EYE members are more widely spread throughout Europe, in particular among East European countries, the results have the potential to be more representative of the situation of IRD management and therapies in a wide part of Europe. In this respect, it is important to note that access to genetic diagnosis depends on the national policies that are variable in the European Union.

Limitations of Our Study

Different from the EVICR.net sites that were directly contacted and reminded twice, the ERN-EYE HCPs were contacted via the ERN-EYE Headquarter, and due to time constraints, they did not receive a reminder which may have influenced the response rate from the ERN-EYE HCPs (13/40, 33% replied). In comparison, 50/95 EVICR.net centers (53%) responded. Not all European university centers and other major ophthalmic care centers managing IRDs are members of EVICR.net or ERN-EYE, though the number has increased recently for ERN-EYE, but this was after the 2nd survey was sent out (www.ern-eye.eu). E.g., given the response rate of EVICR.net member centers in DEU, only data from 16/35 university departments and 1/65 non-university hospitals with eye departments are available. Hence, no conclusions can be drawn as to the true prevalence of IRDs per nation.

Conclusion

This 2nd European survey on the management and treatment of IRDs provides important follow-up information on local and national differences in diagnosing and managing affected IRD patients and their families. The EVICR.net provides a unique platform to collect the data. Inclusion of ERN-EYE HCPs increased the number of sites and countries participating. These follow-up data are of great interest to researchers, policymakers, clinicians, patient advocate groups, and others to inform and improve still existing bottlenecks and diversities in the provision of optimal care for patients and families affected with IRDs in an era of fast-evolving ocular gene therapies. This 2nd survey shows a significant increase in the percentage of European centers participating in natural history and clinical studies and gives an overview of the absolute number of the centers that participate in such studies and who responded to the survey.

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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 consultant for Novartis Pharma AG and Janssen/Johnson & Johnson. J.P.M. is consultant for Novartis, Bayer, Chiesi, and Roche. K.S. is consultant for ProQR, ViGeneron, Novartis, Santen, and Janssen with consultancy fees paid to the 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, 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., 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., L.I.B., J.P.M., E.P., K.S., 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.

Appendix

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