

# Current Management of Inherited Retinal Degeneration Patients in Europe: Results of a Multinational Survey by the European Vision Institute Clinical Research Network

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## Keywords

Inherited retinal degenerations · Management · Europe · EVICR.net clinical centers

## Abstract

**Purpose:** An increasing number of gene therapies are developed for Inherited Retinal Degenerations (IRD). To date, 1 treatment has been approved for clinical use (FDA USA 2017, EMA Europe 2018, MoHAP UAE 2019, SFDA Saudi Arabia 2019, Swiss Medic Switzerland 2020, TGA Australia 2020, and BFR Brazil 2020). While such therapies do not provide complete cure, they may halt degeneration or partially restore function. Identification of well-characterized patients is an emerging need. We conducted the first multinational survey to understand the management of IRDs in Europe. **Methods:** An electronic survey questionnaire containing 112 ques-

tions was developed and sent to the 101 EVICR.net clinical centers (14 European countries and Israel). **Results:** The overall response rate was 49%. Only 14% of responding centers do not see IRD patients; 52% that manage IRD patients follow  $\geq 200$  patients, 16%  $> 1,000$ . Databases exist in 86% of the centers; of these, 75% are local files, 28% local Web-based database, and 19% national Web-based. IRD patients are referred to EVICR.net centers mainly by general ophthalmologists, patient self-referrals, and medical retina specialists. Most IRD patients are first seen in adulthood. Most prominent signs and symptoms depend on the age of onset, for example, nystagmus in infancy, or night blindness, and reduced visual acuity at older age. The time from inquiring for first appointment and clinical diagnosis varies among

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countries: in 29% of centers, the mean time is <4 weeks, although can be up to 35 months in others. The time to genetic diagnosis is  $\geq 4$  weeks, the maximum 10 years, likely depending on access to genetic testing, and the improvement of the tests available. Comprehensive eye examination always includes autofluorescence imaging and perimetry (86% static, 76% kinetic, and 21% microperimetry), and frequently optical coherence tomography (OCT) (95%), electroretinography (93%), and fundus photography (93%). Identified genotypes were reported in 40–80% patients by 69% of centers, and in 80–100% by 5%. Genetic testing is provided by public health insurance in 77% of centers, private health insurance in 38%, center budget in 13%, research funds in 18%; and 15% of centers do not have access to genetic testing. **Conclusion:** At the start of this era of ocular gene therapy for IRD patients, this first international survey on management of IRDs in Europe highlights significant heterogeneity between centers and across countries and provides important baseline data for researchers, clinicians, pharmaceutical companies, and investors.

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## Introduction

Inherited retinal degenerations (IRDs) are both, genetically and clinically, extremely heterogeneous, with mutations in over 300 genes identified as of April 2020 [1]. They are potentially blinding disorders with a prevalence of about 1 in 3,000 [2] and no medical treatment for the vast majority until very recently. The interest has increased significantly in recent years due to the development of therapies for an increasing number of disease-causing genes [3–5]. The aim of this study was to conduct the first international survey to understand management and experience of IRDs across Europe because of a lack of data, and because of potential differences among and within countries. The clinical research network established by the European Vision Institute (EVICR.net) appeared to be an appropriate platform for the survey. At the time of the survey, the network had 101 registered members.

We aimed to explore throughout Europe, nation wise and across nations, the following variables: distribution of IRDs, diagnosis and management of IRDs, availability of genetic testing and genetic counseling, as well as actual involvement in clinical trials. In addition, we wanted to get detailed information about diagnosis, prevalence, and management of patients with RPE65 mutation-associated IRDs [3, 6, 7]. For the latter, an approved gene ther-

apy is now available in an increasing number of countries worldwide (FDA USA 2017, EMA Europe 2018, MoHAP United Arab Emirates 2019, SFDA Saudi Arabia 2019, Swiss Medic Switzerland 2020, TGA Australia 2020, and BFR Brazil 2020) at considerable cost for the national health-care system [8–10]. The results of that part of the survey will be reported in a separate article. The hypothesis was that IRDs are still underdiagnosed, and that a significant number of patients suitable for clinical trials and clinically available therapy remain unidentified to date. We sought to answer questions as to IRD demographics, local set-up to diagnose and follow patients with IRDs, availability and application of genetic testing as well as genetic counseling, and involvement in clinical trials on IRDs. The survey allowed the identification of significant bottlenecks to optimal care by IRD patients in Europe. Consequently, it may help to improve these shortcomings.

## Materials and Methods

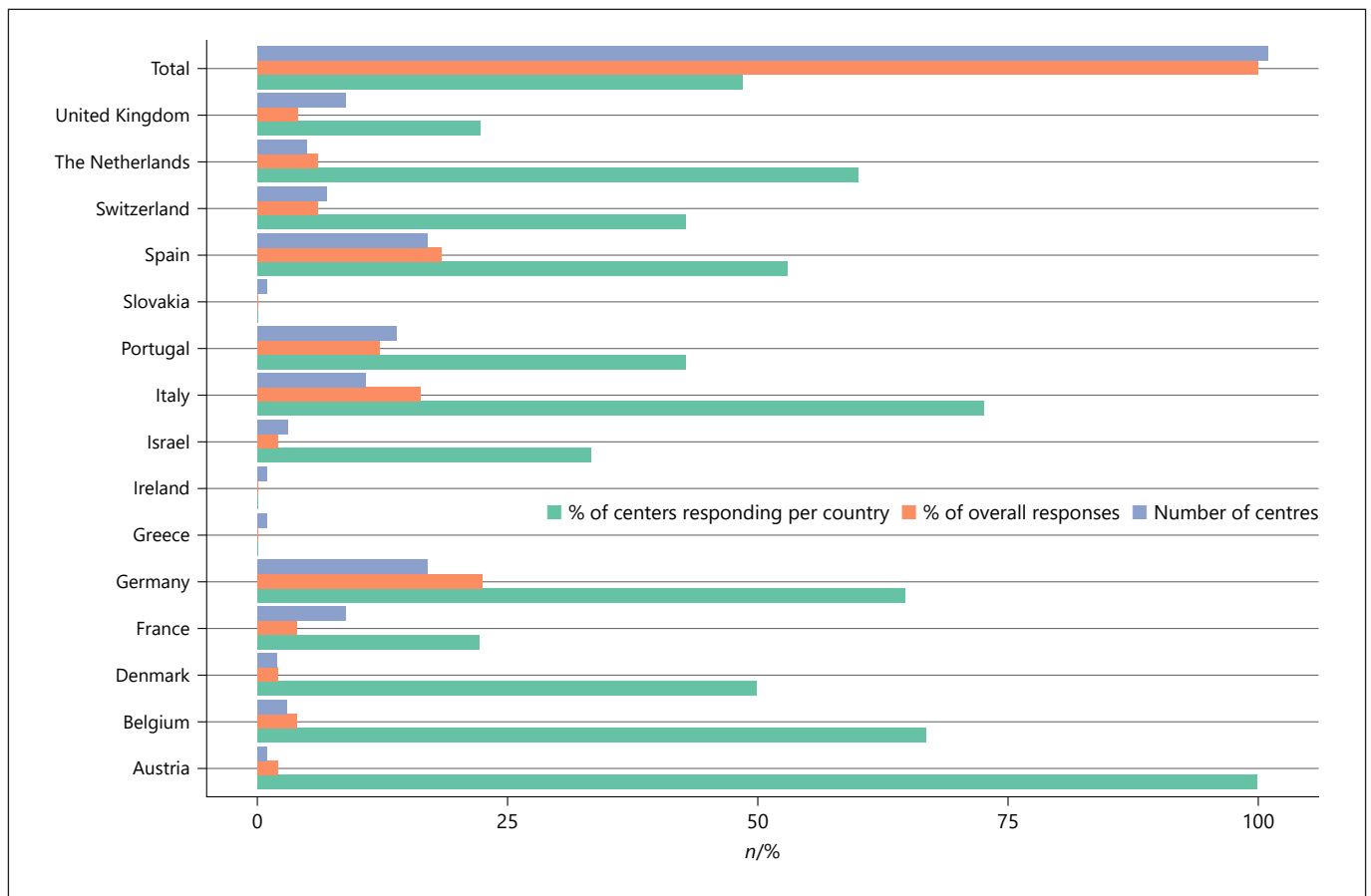
### *Study Design and Questionnaire*

An IRD Survey Expert Committee developed the IRD Survey Questionnaire. The Committee was composed by Birgit Lorenz, MD PhD, Germany (Scientific Coordinator), Hendrik Scholl, MD PhD, Switzerland, Isabelle Audo, MD PhD, France, Ingeborgh van den Born, MD PhD, The Netherlands, and João Pedro Marques, MD, Portugal.

The electronic questionnaire comprised 112 questions arranged in 5 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/10.1159/000514450](http://www.karger.com/doi/10.1159/000514450)). 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 to 4.

In May 2019, all EVICR.net clinical centers, comprising 14 European countries, that is, Austria, Belgium, Denmark, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Slovakia, Switzerland, Portugal, UK, and Israel, 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, and other) could have replied to the survey on their center's behalf. Only 1 reply per clinical center was considered. Of the 101 member centers, 63 are EVICR.net-certified clinical centers and the remaining are under the certification process.

The identification of the EVICR.net member as well as name, function, and contacts (e-mail and telephone) of the replier was



**Fig. 1.** Distribution of IRD Survey replies by country (green and red bars) and the number of EVICR.net clinical centers per country (blue bars). The mean number of replies was 49%. IRD, inherited retinal degeneration.

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 2 more weeks, and new reminders were sent on week 3 and week 4, 2 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.

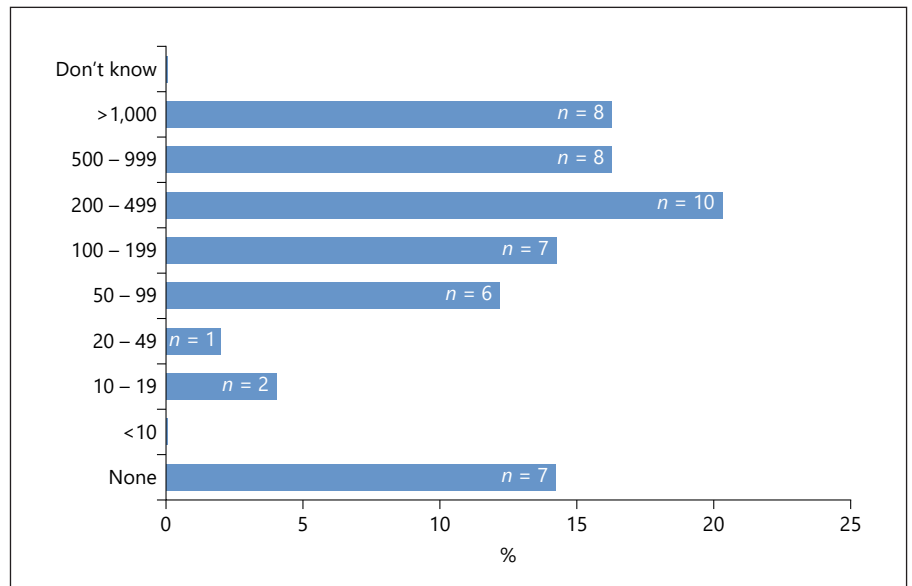
#### Statistical Analysis

A descriptive analysis was conducted for all variables. Continuous variables were summarized using the following statistics: number ( $n$ ), mean, standard deviation (SD), 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 analyses were performed with Excel version 15.0.4433.1508 (Microsoft Office Home and Business 2013) and R version 3.6.0 (2019-04-26). We did not exclude questionnaires due to missing values. However, each analysis was restricted to repliers with no missing values for the respective question, that is, the total number of repliers differed between questions.

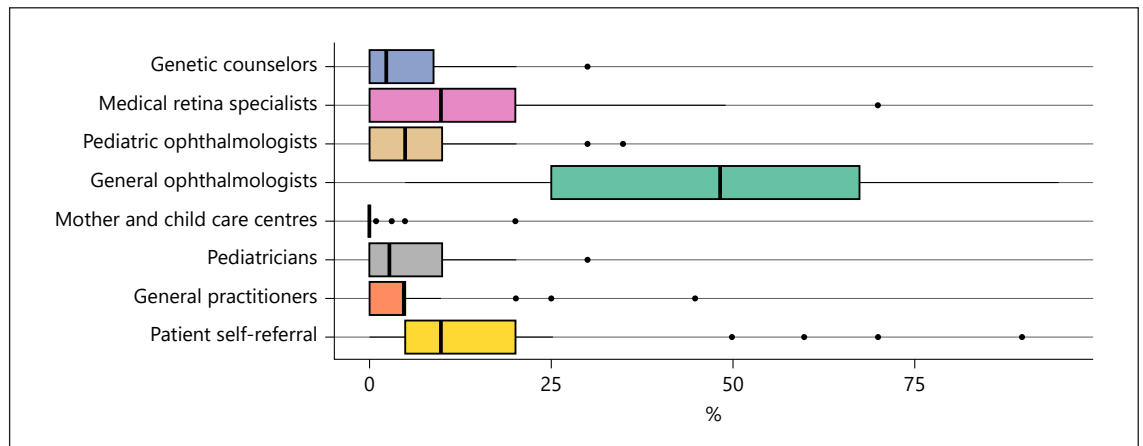
## Results

Forty-nine percent of the 101 EVICR.net Clinical Research Centers in 15 countries who had received the online survey responded (49 centers, Fig. 1). In 9/15 countries, the response rate per country was at least 43%. There was no significant difference in the response rate of certified versus non-certified EVICR.net centers (28 [57%] vs. 21 [43%]). Sixty-seven percent of responding centers are tertiary academic centers.

Most of the time, the survey was filled out by general ophthalmologists (43%), medical retina specialists (39%) and less often by pediatric ophthalmologists (4%), study coordinators (4%), pediatric ophthalmologists and ophthalmogeneticists (2%), assistant directors/pharmacists (2%), medical retina specialist and electrophysiology (ERG) specialists (2%), medical retina specialists and ophthalmogeneticists (2%) and medical/surgical retina, and uveitis specialists (2%).



**Fig. 2.** Distribution of the number of IRD patients currently managed by centers. IRD, inherited retinal degeneration.

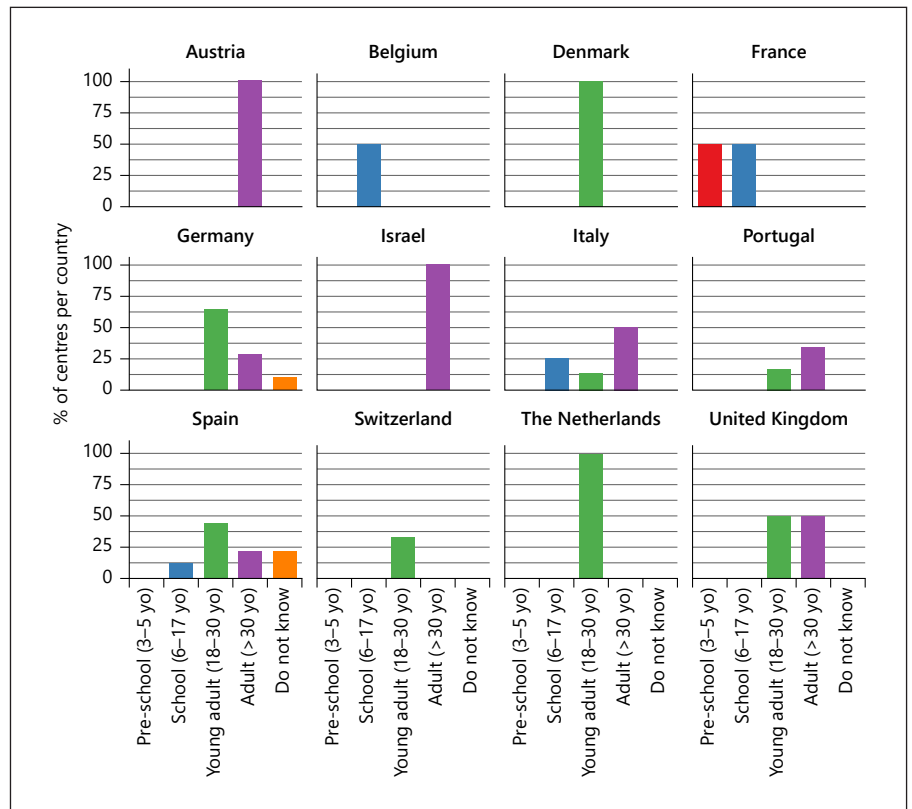


**Fig. 3.** Referral pathways. Box plots of the percentage of the referees of IRD patients to the EVICR.net clinical centers: the box signifies the third quartile (Q3) and first quartile (Q1) range of data, and the median is represented by a black line within the box for each type of referees of IRD patients. Data falling outside the Q1–Q3 range are plotted as outliers of the data and are depicted by black dots. IRD, inherited retinal degeneration.

### IRD Demographics

Only 14% of the responding centers (7/49) do not see IRD patients; these are centers from Switzerland (2/3), Portugal (3/6), Belgium (1/2), and Italy (1/8). All centers that see IRD patients have at least 10 patients currently managed at their centers (Fig. 2), 52% actually manage at least 200 patients. Centers in Spain and Portugal currently manage the lowest number of IRD patients. Highest numbers of IRD patients being currently managed were reported in centers from The Netherlands, France, Germany, Spain, and Switzerland.

When questioned about the use of a database for IRD patients, 86% of the centers have 1. Of these, 75% have IRD patients registered in local files, such as Excel, 28% in local Web-based databases, and 19% have access to national Web-based databases. The majority of the centers (67%) have between 100 and 1,999 IRD patients in the database. The Netherlands, Italy, Germany, and Spain are the countries with centers that have databases with >2,000 IRD patients (online suppl. Table 1). All centers manage IRD patients themselves; however, 17% of these centers also refer IRD patients to expert centers. On the other



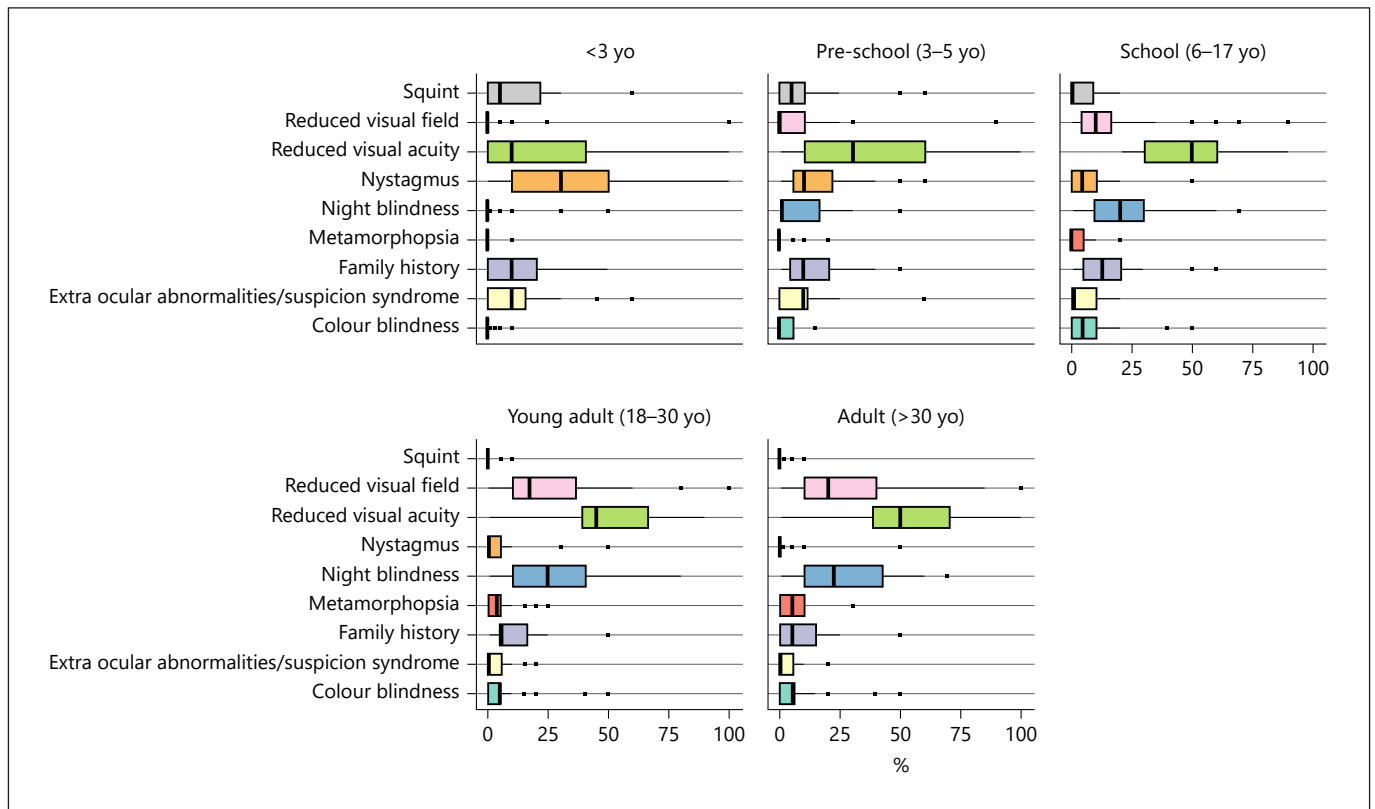
**Fig. 4.** Current age of the majority of the diagnosed IRD cases distributed by the country. The percentage of centers per country was calculated based on the total number of centers that replied for each country. IRD, inherited retinal degeneration.

hand, general ophthalmologists are the main referees of IRD patients to the EVICR.net centers, followed by patient self-referral and medical retina specialists (Fig. 3).

For the majority of IRD patients, the first visit occurs at an adult age (online suppl. Fig. 1). In 45% of the centers, the majority of the diagnosed IRD cases occur in young adults, followed by adults in 33% of the centers (online suppl. Table 2). This trend is verified per country, with the exception of the centers in France, where the majority of the diagnosed IRD cases occurs in preschool and school ages (Fig. 4). Of note, only 22% of the EVICR.net centers in France participated in the survey.

Main signs and/or symptoms implicating a visit in the centers are nystagmus and reduced visual acuity followed by positive family history in infants and young children ( $\leq 5$  years old); reduced visual acuity followed by night blindness in children/adolescents from 6 to 17 years old; reduced visual acuity, reduced visual field, and night blindness in young adults and adults (Fig. 5). When questioned about the mean time between inquiry of an appointment and the first contact with a retina expert and final diagnosis, 43% of the centers reported a time of  $<4$  weeks between inquiry of appointment and first contact

(most of the centers in Italy [5/8] and Spain [7/9], online suppl. Fig. 2), and 29% of the centers reported a time of  $<4$  months between inquiry of an appointment and final ophthalmological diagnosis. On the other hand, the longest mean time between inquiry of appointment and first contact with a retina expert for IRD patients is 30 months in Germany (online suppl. Fig. 2). Consequently, the longest mean time between inquiry of appointment and the final ophthalmological diagnosis for IRD patients is 35 months in Germany (online suppl. Fig. 3). Adding a final genetic diagnosis increases the mean time between inquiry of appointment and final ophthalmological and genetic diagnosis. For 95% of centers, the mean time between inquiry of appointment and final ophthalmological and genetic diagnosis is at least 4 weeks (5% of the repliers did not know the meantime, online suppl. Fig. 4). Of these, for 28% of the centers, it takes 12 months to get a final genetic diagnosis; for 21%, it takes 6 months, and only for 33%, it takes less than 6 months. The highest mean time between inquiry of appointment and final ophthalmological and genetic diagnosis for IRD patients is 10 years in the UK (online suppl. Fig. 4).



**Fig. 5.** Reasons for referral of IRD patients to the EVICR.net clinical centers. Box plots of the percentage of signs/symptoms of IRD patients implicating a visit at a center: the box signifies the third quartile (Q3) and first quartile (Q1) range of data, and a black line within the box for each sign/symptom represents the median. Data falling outside the Q1–Q3 range are plotted as outliers of the data and are depicted by black dots. IRD, inherited retinal degeneration.

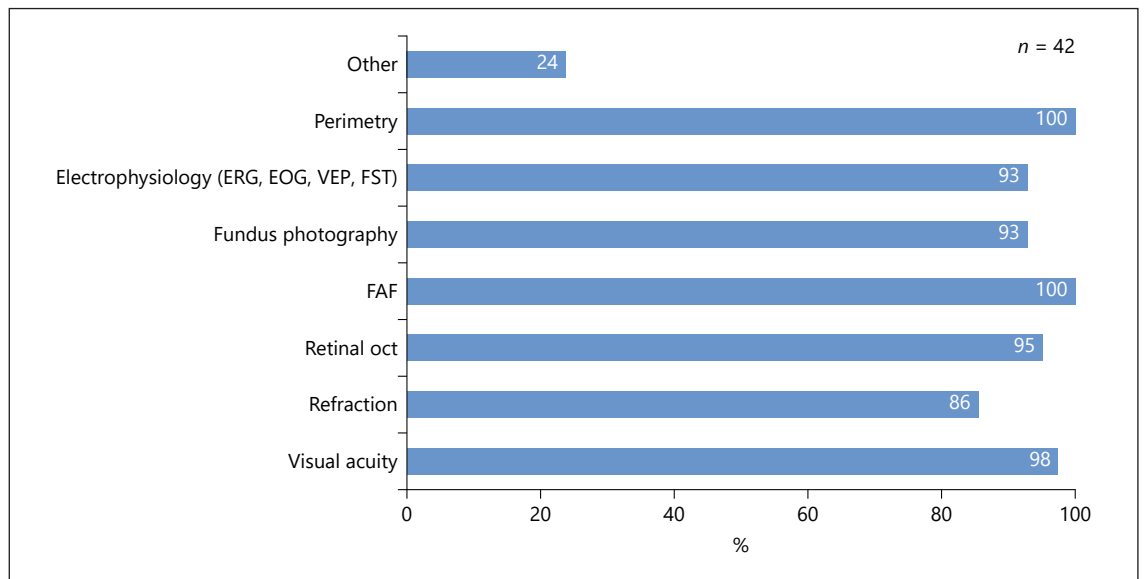
### Local Setting

For centers that selected “Refer IRD patients to expert centers” in Question 2 of Section 1, the basic tests performed in IRD patients referenced to expert centers are visual acuity, fundus imaging, fundus autofluorescence (FAF), and retinal stratification (online suppl. Fig. 5). Eighty-six percent of the centers that refer IRD patients also perform visual fields, 71% perform ERG, and 14% perform optical coherence tomography angiography, fluorescein angiography, and indocyanin angiography, if deemed necessary.

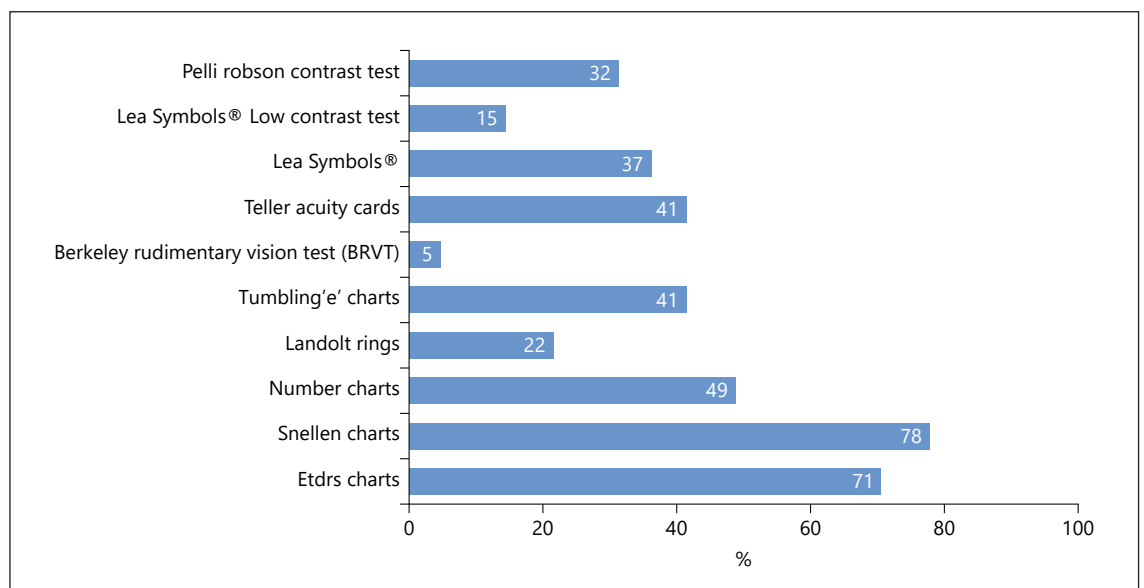
In centers that manage the IRD patients themselves, FAF and perimetry are always performed for setting a clinical diagnosis of IRD in addition to a comprehensive clinical standard examination (Fig. 6). Additionally, visual acuity (98%), retinal stratification by optical coherence tomography (OCT) (95%), fundus photography (93%), (ERG, electrooculography [EOG], and visual evoked potentials [VEP]), including full-field sensitivity

threshold testing (FST) (93%), and refraction (86%) are parameters highly applied for setting a clinical diagnosis of IRD (Fig. 6). Section 2 of the IRD survey included also an option “Other,” where additional methods could be added as free text. Answers included personal and family history, optical coherence tomography angiography, retinal vessel oximetry, microperimetry, 2-color-threshold perimetry, gene testing, fluorescein angiography color vision testing, contrast sensitivity, biomicroscopy with fundus examination, adaptive optics, and own diagnostics development in 2% of the centers.

For visual acuity testing in IRD patients, centers use mainly Snellen charts (78%), ETDRS charts (71%), number charts (49%), Tumbling “E” charts (41%), Teller acuity cards (41%), Lea Symbols<sup>®</sup> (37%), and Pelli Robson contrast test (32%). All results are displayed in Figure 7. Regarding refraction, 94% of the centers use autorefractometer in IRD patients and 58% of the centers use retinoscopy. For detailed results see Table 1.



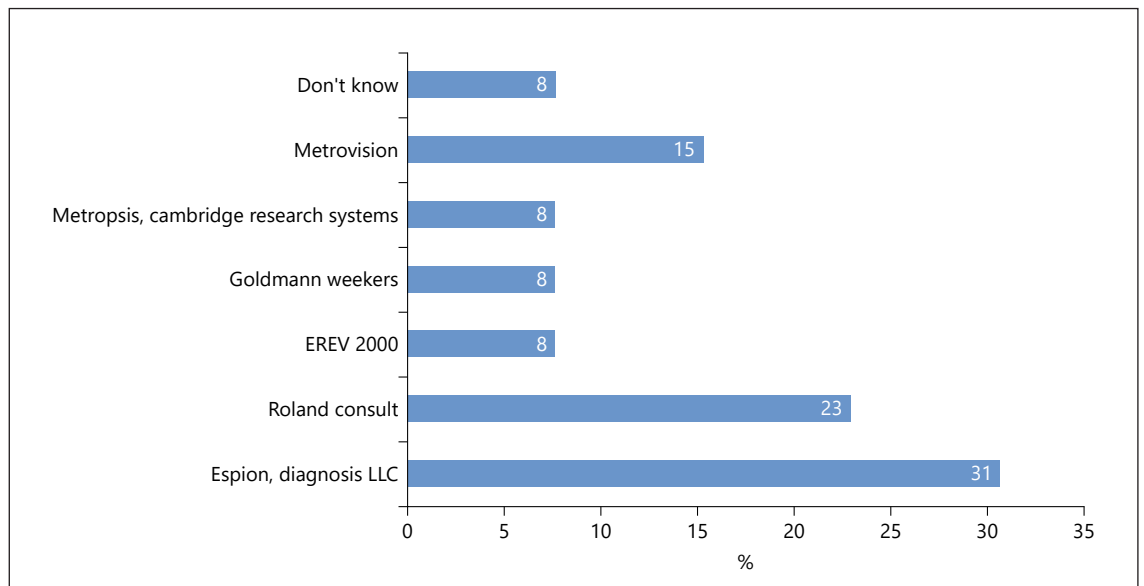
**Fig. 6.** Parameters applied for setting a clinical diagnosis of IRD in centers that manage IRD patients. Multiple choices were allowed. For explanation of FST, see text. ERG, electroretinogram; EOG, electrooculography; FAF, fundus autofluorescence; FST, full-field sensitivity threshold; OCT, optical coherence tomography; VEP, visual evoked potential.



**Fig. 7.** Methods for visual acuity testing used in IRD patients. Multiple choices were allowed. IRD, inherited retinal degeneration.

Regarding retinal stratification (OCT), 88% of the centers use Spectralis® Heidelberg Engineering GmbH in IRD patients, specifically OCT (83%), and OCT EDI (74%). To evaluate FAF, 88% of the centers use Spectralis® Heidelberg Engineering GmbH in IRD patients, 12%

use Optomap® Panoramix 200 Tx (Optomap; Optos, Dunfermine, Scotland), 10% use Triton (Topcon Medical Systems, Oakland, NJ, USA), and 7% use Clarus (Carl Zeiss Meditec, Jena, Germany).



**Fig. 8.** Dark adaptometry devices used in IRD patients. IRD, inherited retinal degeneration.

**Table 1.** Devices/test for refractometry used in IRD patients

	<i>n</i>	%
Retinoscopy	21	58
Autorefractometer	34	94
NIDEK Co., LTD, Aichi, Japan	22	65
Topcon medical systems, Oakland, NJ, USA	14	41
Reichert Inc., Depew, NY, USA	2	6
<i>Total</i>	55	153*
<i>Total of Centers applying refraction</i>	36	100

IRD, inherited retinal degeneration. \* Multiple choices allowed.

**Table 2.** Methods of visual field testing used in IRD patients

	<i>n</i>	%
Kinetic perimetry	32	76
Static perimetry	36	86
Fundus-controlled perimetry	9	21
<i>Total</i>	77	183*
<i>Total of centers applying perimetry</i>	42	100

IRD, inherited retinal degeneration. \* Multiple choices allowed.

Regarding fundus photography, 87% of the centers use standard fundus cameras, whereas 56% use wide-field fundus cameras in IRD patients. From centers that use standard fundus cameras, 53% use Topcon Medical

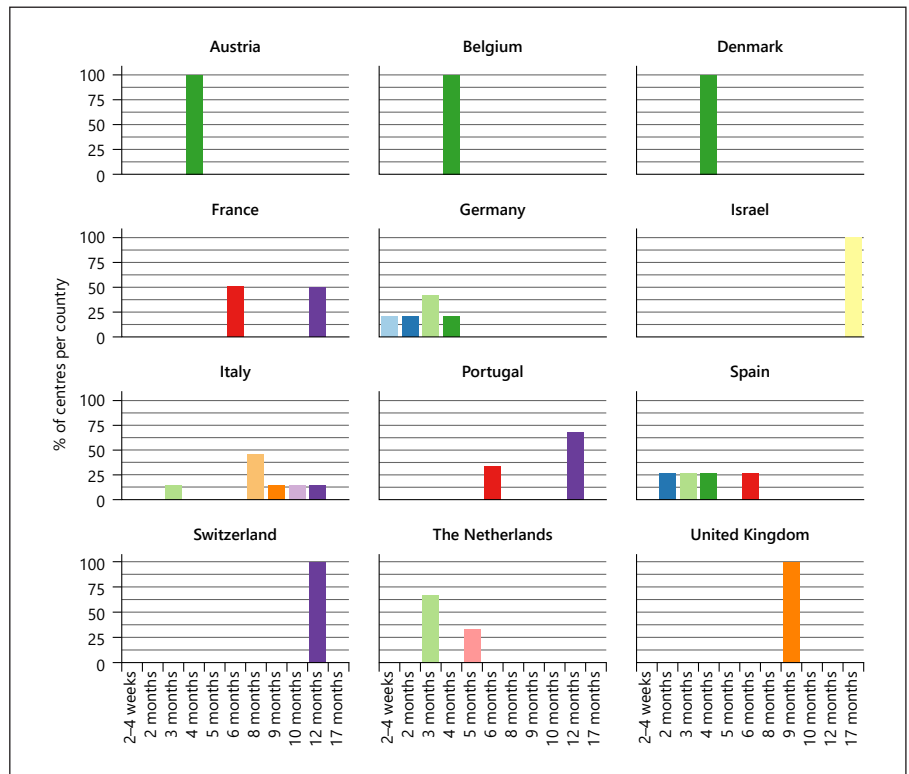
Systems (Oakland, NJ, USA) device and 41% a Carl Zeiss Meditec (Jena, Germany) device. An Optos (Dunfermline, Scotland) wide-field fundus camera is used in 68% of the centers performing wide-field fundus photography.

Regarding ERG, the main tests used in IRD patients are full-field ERG (95%), multifocal ERG (90%), EOG (85%), and VEP (77%). For full-field ERG, the devices used most frequently are Espion (Diagnosys LLC, Lowell, MA, USA) (38%) and RETIport/Scan21 (Roland Consult Stasche & Finger GmbH, Brandenburg an der Havel, Germany) (35%). RETIport/Scan21 (Roland Consult Stasche & Finger GmbH, Brandenburg an der Havel, Germany) is the device used most frequently in multifocal ERG (40%), and VEP (40%). On the other hand, Espion (Diagnosys LLC, Lowell, MA, USA) is the most frequently used device in EOG (42%), dark adaptation (31%, Fig. 8), and FST (80%). Eighty percent of the centers using FST in IRD patients perform chromatic FST (blue, red, and white), whereas 20% of the centers performs the white testing only. Regarding perimetry, centers use mainly static perimetry (86%) and kinetic perimetry (76%) (Table 2). For detailed information as to the instruments used see online suppl. Table 3a–c.

#### *IRD Genetic Testing and Counseling*

From the centers that manage IRD patients themselves, 93% perform genetic testing at their centers, and 54% of these centers have more than 61% of their IRD





**Fig. 9.** Mean time to get the genetic test result in IRD patients distributed by country. The percentage of centers per country was calculated based on the total number of centers that replied for each country. IRD, inherited retinal degeneration.

**Table 3.** Centers genetically testing IRD patients and with genetic testing laboratory certified distributed by country

Country	Centers genetically testing IRD patients				Centers with genetic testing laboratory certified			
	no	total centers that replied per country	% centers per country	% overall responses	no	total centers that replied per country	% centers per country	% overall responses
Austria	1	1	100	3	1	1	100	3
Belgium	1	2	50	3	1	1	100	3
Denmark	1	1	100	3	1	1	100	3
France	2	2	100	5	2	2	100	7
Germany	10	11	91	26	9	10	90	30
Israel	1	1	100	3	1	1	100	3
Italy	7	8	88	18	6	7	86	20
Portugal	3	6	50	8	2	3	67	7
Spain	8	9	89	21	4	8	50	13
Switzerland	1	3	33	3	0	3	0	0
The Netherlands	3	3	100	8	3	3	100	10
UK	1	2	50	3	0	2	0	0
<i>Total</i>	39	49	–	100	30	–	–	100

IRD, inherited retinal degeneration.

patients genetically tested. Five percent do not genetically test IRD patients due to (1) hospital administration constraints, (2) no practical benefit for patient, or (3) no geneticist in the center. From those, 50% refer patients to

other institutions/laboratories. Table 3 shows centers that genetically test their IRD patients distributed by country.

From the centers that genetically test their IRD patients, 74% perform genetic tests externally (79% in a na-

**Table 4.** Estimated percentage of IRD patients that has been genetically solved at each center distributed by country

Country	<i>n</i>	Total centers at section 3 per country	% per country
0–20%			
Germany	1	10	10
Italy	1	7	14
Spain	1	8	13
UK	1	1	100
21–40%			
France	1	2	50
Spain	3	8	38
41–60%			
Denmark	1	1	100
France	1	2	50
Germany	3	10	30
Israel	1	1	100
Italy	5	7	71
Spain	1	8	13
The Netherlands	3	3	100
61–80%			
Austria	1	1	100
Belgium	1	1	100
Germany	4	10	40
Italy	1	7	14
Portugal	1	3	33
Spain	3	8	38
Switzerland	1	1	100
81–100%			
Germany	1	10	10
Portugal	1	3	33
Do not know			
Germany	1	10	10
Portugal	1	3	33
<b>Total</b>	<b>39</b>	<b>–</b>	<b>–</b>

The percentage of centers per country was calculated based on the total number of centers that responded for each country. IRD, inherited retinal degeneration.

tional lab, 55% in an external research lab, and 21% in an international lab) and 38% perform in house (87% clinical care and 40% in research lab). In 77% of the centers, the genetic testing laboratory is certified. All centers responding from Austria, Belgium, Denmark, France, Israel, and The Netherlands have their genetic testing laboratory certified (Table 3). Ninety percent of centers in Germany and 86% of Italian centers have their genetic testing laboratory certified (Table 3). Thirty-three percent of centers that perform genetic testing refer to Clinical Laboratory Improvement Amendments, and 49% refer to national guidelines and protocols. Of the 39 centers

**Table 5.** Type of IRD-specific gene panel performed

	<i>n</i>	%
General panel	19	73
LCA panel	19	73
RP panel	20	77
CRD panel	18	69
Optic atrophy panel	18	69
Other: blindness	1	4
Other: macular dystrophy	1	4
Other: mtDNA	1	4
Other: genetics lab decides	1	4
Do not know	1	4
<b>Total</b>	<b>99</b>	<b>381*</b>
<i>Total of centers performing IRD-specific gene panel</i>	<i>26</i>	<i>100</i>

LCA, Leber congenital amaurosis; RP, retinitis pigmentosa; CRD, cone-rod dystroph; mtDNA, mitochondrial DNA; IRD, inherited retinal degenerations. \* Multiple choices allowed.

that genetically test their IRD patients, 36 (92%) offer genetic counseling. In other centers, genetic counseling is center-based (33%) or provided by external genetic counselors (67%).

When questioned on the mean time to get the genetic test result, the lowest mean time was between 2 and 4 weeks reported in Germany (2/10) (Fig. 9). In 95% of centers, the time to receiving the genetic test result is higher than 1 month. The mean time to get the genetic test result for IRD patients is higher in Israel, France, Italy, Portugal, Switzerland, and UK, with the highest mean time of 17 months in Israel (Fig. 9).

Sixty-nine percent of the centers replied that only 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. Table 4 shows the estimated percentage of IRD patients that has been genetically solved at each center by country.

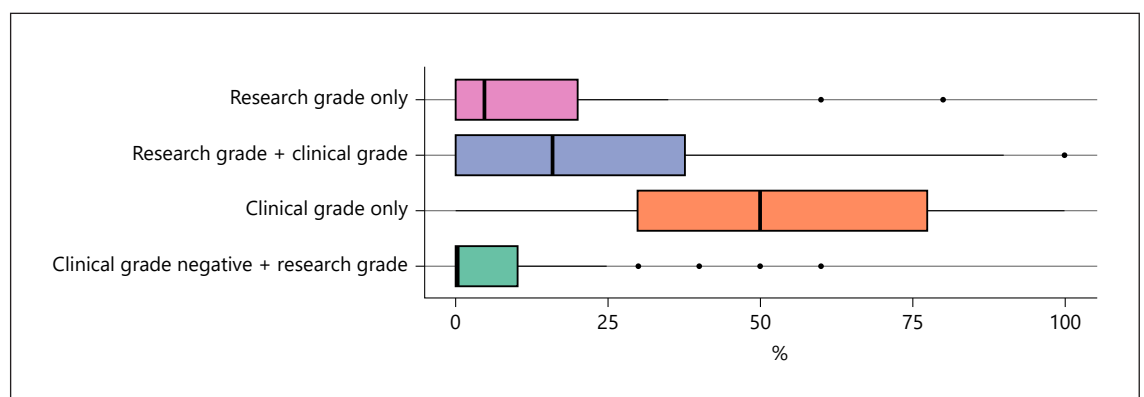
In most centers, IRD patients are only tested with clinical grade tests, followed by centers that tested with research and clinical grade tests (Fig. 10). The most used technologies for genetic testing in IRD patients were IRD-specific gene panels (67%), WES (49%), and diagnosis-directed Sanger sequencing (41%). Details as to the extent of genetic testing are seen in online suppl. Fig. 6.

Regarding IRD-specific gene panels, an RP panel was performed in 77% of the centers, a general panel and Leber congenital amaurosis (LCA) panel in 73%, a CRD panel, and an optic atrophy panel in 69% (Table 5). Within the gene panel used, the number of genes tested varied

**Table 6.** Costs of genetic testing in IRD patients by country

Who covers the costs of genetic testing in your IRD patients?	Country	<i>n</i>	Total centers at section 3 per country	% Centers per country
Covered by public health service	Austria	1	1	100
	Denmark	1	1	100
	France	2	2	100
	Germany	10	10	100
	Israel	1	1	100
	Italy	7	7	100
	Portugal	3	3	100
	Spain	3	8	38
	The Netherlands	1	3	33
	UK	1	1	100
	<i>Total</i>		30	–
Covered by private health insurance	Germany	8	10	80
	Spain	3	8	38
	Switzerland	1	1	100
	The Netherlands	3	3	100
	<i>Total</i>	15	–	–
Covered by center budget	Austria	1	1	100
	Belgium	1	1	100
	Denmark	1	1	100
	Spain	2	8	25
	<i>Total</i>	5	–	–
Research funding only	Germany	2	10	20
	Israel	1	1	100
	Italy	1	7	14
	Spain	1	8	13
	The Netherlands	1	3	33
	UK	1	1	100
	<i>Total</i>	7	–	–
No coverage available	Spain	6	8	75
	<i>Total</i>	6	–	–

The percentage of centers per country was calculated based on the total number of centers that replied per country. Multiple choices were allowed. IRD, inherited retinal degeneration.

**Fig. 10.** Percentage of IRD patients tested with clinical grade and research grade tests. IRD, inherited retinal degeneration.

**Table 7.** Involvement in clinical studies with gene therapies for IRD by country

Country	<i>n</i>	Total centers at section 4 per country	% Centers per country
<b>Currently involved</b>			
France	2	2	100
Germany	3	10	30
Italy	1	7	14
Spain	1	8	13
The Netherlands	2	3	67
<i>Total</i>	9	–	–
<b>Previously involved</b>			
Belgium	1	1	100
The Netherlands	1	3	33
<i>Total</i>	2	–	–
<b>Not involved</b>			
Germany	2	10	20
Portugal	1	3	33
Spain	1	8	13
UK	1	1	100
<i>Total</i>	5	–	–
<b>Interested in being involved</b>			
Austria	1	1	100
Denmark	1	1	100
Germany	5	10	50
Israel	1	1	100
Italy	6	7	86
Portugal	2	3	67
Spain	6	8	75
Switzerland	1	1	100
<i>Total</i>	23	–	–

IRD, inherited retinal degeneration.

widely from just a few to several thousand, and some centers noted that the panels were regularly updated. This high variance reflects the evolution of genetic testing in recent years. Online suppl. Table 4 indicates the panel sizes used in the 20 centers that answered to using gene panel testing.

Costs of genetic testing are covered by public health service in 77% of the centers, private health insurance in 38%, center budget in 13%, research funding only in 18%, and not covered in 15%. Interestingly, the cost of genetic testing is not covered in 75% of the centers from Spain (6/8). On the other end, costs of genetic testing are covered by public health service in Austria, Denmark, France, Germany, Israel, Italy, Portugal, and UK (Table 6).

**Table 8.** Centers currently or previously involved in clinical study with gene therapies for IRD by country

Countries currently or previously involved in clinical study with gene therapies for IRD	<i>n</i>	%
Belgium	1	9
France	2	18
Germany	3	27
Italy	1	9
Spain	1	9
The Netherlands	3	27
<i>Total</i>	11	100

IRD, inherited retinal degeneration.

### *Involvement in Clinical Trials*

From the centers that manage and genetically test IRD patients themselves, 23% are currently involved in clinical studies with gene therapies for IRD, 5% were previously involved, 13% are not involved, and 59% are interested in getting involved, in clinical studies with gene therapies for IRD. Belgium, France, Germany, Italy, Spain, and The Netherlands have centers currently involved, or were previously involved in clinical studies with gene therapies for IRD (Tables 7, 8). Only 33% of these centers are/were the leading PI, and in 75% patients were enrolled during the clinical studies. The clinical study ILLUMINATE (for CEP290 mutation-associated IRD) (ClinicalTrials.gov Identifier: NCT03913143), and the post-authorization safety study with voretigene neparvovec (Luxturna<sup>®</sup>) are being performed in 25 and 17% of the centers that are currently involved in clinical studies with gene therapies for IRD, respectively (Table 9). LCA was addressed in 58% of the studies, followed by LHON (25%), choroideremia (17%), and retinitis pigmentosa (17%) (Table 10), whereas CEP290 was addressed in 50% of the studies, followed by RPE65 (42%) and RPGR (25%) (Table 11).

### **Discussion**

IRDs have an estimated overall prevalence rate of 1 in 3,000 [2, 11]. Although categorized as rare diseases, their impact on the lives of the patients as well for the society are enormous. A recent report from the UK and Ireland provides not only estimated prevalence data of IRDs in the 2 countries, but also elaborates on the high socioeconomic burden of IRDs [11]. For example, total costs at-

**Table 9.** Type of clinical study with gene therapies for IRD

	<i>n</i>	%
Natural history		
CEP290 (NCT03396042)	1	9
NIGHT (NCT03359551), STAR (NCT03496012), XOLARIS	1	9
Historical case record survey LHON (NCT02796274)	1	9
Premarketing clinical studies		
USHTer (NCT03814499)	1	9
Illuminate (NCT03913143)	3	27
Safety study of RPE65 gene therapy to treat LCA (NCT00643747)	2	18
Post-marketing		
Luxturna® (EUPAS31153)	2	18
LEROS (NCT02774005)	1	9
Multiple trials		
Multiple trials	3	27
<i>Total</i>	15	136*
<i>Total of centers currently or previously involved in clinical study(ies) with gene therapies for IRD</i>	11	100

LCA, Leber congenital amaurosis; LHON, Leber's hereditary optic neuropathy; IRD, inherited retinal degeneration. \* Multiple choices allowed.

**Table 10.** Retinal diseases addressed in clinical studies with gene therapies for IRD

	<i>n</i>	%
LHON	3	20
LCA	7	47
EOSRD	1	7
Choroideremia	2	13
Retinitis pigmentosa	2	13
Cone rod dystrophy	0	0
Achromatopsia	1	7
Stargardt disease	0	0
Usher syndrome	1	7
<i>Total</i>	17	113*
<i>Total of clinical studies</i>	15	100

LCA, Leber congenital amaurosis; LHON, Leber's hereditary optic neuropathy; EOSRD, Early-onset severe retinal dystrophy; IRD, inherited retinal degeneration. \* Multiple choices allowed.

**Table 11.** Gene addressed in clinical studies with gene therapies for IRD

	<i>n</i>	%
ABCA4	1	7
CHM	2	13
CEP290	6	40
CNGA3	2	13
CNGB3	1	7
MYO7A	2	13
RHO	0	0
RPGR	3	20
RPE65	5	33
Gene independent	2	13
mtDNA	1	7
<i>Total</i>	22	147*
<i>Total of clinical studies</i>	15	100

IRD, inherited retinal degeneration. \* Multiple choices allowed.

tributable to 10 IRDs in the Republic of Ireland were estimated to be £42.6 million in 2019, comprising economic (£28.8 million) and well-being costs (£13.8 million). Well-being costs were estimated using the WHO burden of disease methodology, a nonfinancial approach, where pain, suffering, and premature mortality are measured in terms of disability-adjusted-life-years. The overall prevalence of the 10 major IRDs was estimated to be from

0.0311 to 0.052% in Republic of Ireland, which accounts for about 1,500–2,500 cases in 2019. This translates to an annual cost per patient of £ 20,000 on average. Development of effective therapies for the most frequent forms in the future may alleviate this burden, although actual therapies are associated with high cost for the medication, yet with measurable gain in quality-adjusted life years [8, 10, 12]. The effect on disability-adjusted-life-years may be

significantly higher. Identifying patients that can be recruited for clinical trials is therefore very important. In Europe, no good prevalence data are available, yet a consortium was started already in 2008 (the European Retinal Disease Consortium), where 22 partners from Europe (17), Israel (3), Canada (1), and USA (1) work together [13]. Throughout the world, several new consortia have been established in recent years to collect data on IRDs. These are Japan Eye Genetics Consortium with 38 institutes since 2011 [14], East Asia Inherited Retinal Disease Society with 68 institutes from 5 countries (Japan, South Korea, China, Singapore, and Australia) since 2016 [15], and Global Eye Genetics Consortium with 20 countries and 150 researchers since 2014 and member of the ICO [16].

Our survey is the first to investigate in 101 EVICR.net centers throughout Europe, the prevalence and distribution of IRDs, diagnosis and management of IRDs, availability of genetic testing and genetic counseling, as well as actual involvement in clinical trials. The response rate to our survey was 49% that was similar to other surveys conducted among EVICR.net members. However, this response rate does not imply that the nonresponders are centers that do not manage many IRD cases, but could also reflect centers that are less motivated to complete the questionnaire.

We observed different response rates and answers by country (Fig. 1b). The survey results presented here were mostly driven by the responses from Spain, Germany, Italy, and Portugal (Fig. 1b). Moreover, the response rate by country was also dependent on the number of centers per country. In a country with 2 or 3 centers, we have a high response rate only because these centers are responsive. It is important to understand why response rates were low in specific countries, namely in France. One reason could be that they do not manage IRD patients or other centers in that country are dedicated IRD expert centers, and so they assumed that those would answer. Yet another reason could be a general lack of interest in surveys. One further reason could be that some centers are part of a recently established network on rare eye diseases, the European Reference Network for Rare Eye Diseases (ERN-Eye) [16] that also requires substantial work. In fact, 14% of EVICR.net centers are also members of ERN-Eye, and 16% of the EVICR.net centers that responded are members or ERN-EYE.

One interesting finding is that few centers manage high numbers of IRD patients: 31 centers manage between 50 and 1,000 IRD patients and only 8 centers manage >1,000 IRD patients. This result might also depend on

the interpretation of the word “currently” (Fig. 2; online suppl. Table 1). Another possible explanation is that IRD patients are distributed among several expert centers within each country and some of these centers did not complete the survey.

From the 86% of centers that indicated the current number of IRD patients they managed, only 17% refer IRD patients to expert centers. No centers indicated referral of IRD patients to ERN-EYE health care providers. Of the 14 EVICR.net centers that are also ERN-EYE members, only 8 replied to the survey (1 from France, 2 from Germany, 2 from Italy, 2 from The Netherlands, and 1 from Portugal). The ERN-EYE does not have representatives from all the EU countries and not all expert centers within countries are members of the ERN-EYE. Those centers who do not refer patients to ERN-EYE health-care providers either may not because they are expert centers themselves or are not familiar with the ERN-EYE. They may also not be aware that the centers to whom they refer their patients are ERN-EYE members.

The prevalence of IRDs starting in infancy is considerably lower than the prevalence of IRDs starting later in life, so it is expected that the vast majority of patients per center are adult patients, as observed in this survey. The problem is that LCA-type IRDs are much rarer than RP type IRDs. Taking all IRDs together, LCA type is only about 5%, so the likely answer is a later age. Even when children are diagnosed with IRDs, which is certainly the case for some centers, the majority of patients are diagnosed later in life. We have noticed that the majority of the diagnosed IRD cases in the participating centers in France occur mainly at preschool (Fig. 4). This could indicate that these centers are specialized in early onset retinal dystrophies. In addition, France has a specific network for rare diseases, where each center is in charge of a subset of IRDs. Some of these expert centers may not be EVICR.net members, or did not participate in the survey.

Given the overall number of patients listed as “actually followed” in the centers that did respond, it becomes clear that only a small percentage of patients with IRDs are currently followed. For example, in Germany with an overall population of about 83 million people, and given the estimated prevalence of 1:3,000 [2], the expected number of patients with IRDs is 27,670. As only estimated data were collected, it is not possible to give a precise percentage, but it could be in the order from 14% to about 22%. It was, however, on purpose that we asked only for estimated numbers in order to maximize the number of repliers.

Another interesting result was that the time from inquiring for an appointment and the appointment actually taking place differs significantly. Possible explanations are travel distances for patients to treatment centers or center-limited examination capacities to respond immediately to an examination request.

The time from appointment to final diagnosis including molecular genetic confirmation also differed significantly among countries. One reason is that local health policies, for example, private versus public health systems vary widely. The time can be as short as 4 weeks, but also as long as 10 years (online suppl. Fig. 4). However, the latter long-time interval very likely reflects the fact that only recently a more general access outside research has become available in some countries and that molecular genetic testing as a routine was started only recently. Most of the centers that manage IRDs, that is, 93%, order genetic testing. However, only 54% of the centers have at least 60% of the patients tested, and 5% of the centers do not provide access to genetic testing. The mutation detection rate is reported to be 40–80% (Table 4). The time to a molecular result varies widely and can be as long as 17 months (Fig. 9). A faster result would be desirable as patients are anxious to know their result as soon as possible. To note that no question was made to specify 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 only about half of centers have >50% of their IRD patients tested genetically, improvements in the availability of genetic testing should be attempted. Genetic counseling is provided by 92% of the centers that manage IRD patients which is very patient-oriented. Of note, in this survey no countries from Eastern Europe were included as they are not yet the members of EVICR.net. On the other hand, it is well known that genetic testing is less widely available in Eastern Europe for several reasons.

Genetic testing is most frequently done on clinical grades, which may miss the diagnosis. In case of a negative result, it would, however, be desirable to continue with research grade testing. Most centers use panel testing as a routine, where the number of genes per panel increase constantly. This will likely result in an even higher mutation detection rate and should encourage centers to repeat testing in previously unsolved IRD cases. This maybe challenging as patient databases will need constant reevaluation that is both time and money consuming. Yet, in order to verify older results and to increase the percentage of molecular genetic solved cases this is an im-

portant task. Nationwide electronic databases would be most helpful and should be established in an increasing number of countries.

A recent article summarizes state-of-the-art examinations of patients with IRD in view of existing and upcoming therapies [17]. The authors recommend visual acuity testing with ETDRS charts as a routine, which is not yet universal even in specialized centers. One reason could be that this test is rather time-consuming when it is accurately performed by a well-trained technician. In the present survey, ETDRS charts were used in 71% (Fig. 7). The use of other tests like TAC and Lea symbols reflects the different age-groups. The authors also recommend to use low luminance visual acuity testing that is performed by using 2.0 log unit neutral density filters while reading normally illuminated ETDRS charts that will reduce the luminance by 100 times. The low luminance deficit is then defined as the difference between low luminance visual acuity and the standard VA level in logMAR units. This test was not mentioned in our survey, and also not indicated by the repliers in the free text part. The test is certainly clinically relevant and centers involved in the management of IRD patients should consider this relatively simple test despite the additional examination time. The authors also mention the multiple luminance mobility test and FST. In our survey we did not ask specifically for the multiple luminance mobility test that to date is only available in few centers and even more time-consuming, but we did ask for the FST. The FST may not yet been applied as a routine test but is available in 93% of centers that manage IRD patients themselves (Fig. 6). The authors conclude that both tests are not essential for routine testing, as it might be difficult to adopt them universally. Our results indicate that at least FST is already widely available in the centers that manage IRD patients. Of note, perimetry is always included in the workup, but fundus-controlled perimetry that is also considered state-of-the-art, is only used in 21% of the centers that manage IRD patients (Table 2 and online suppl. Table 3a–c). Analysis of retinal stratification by OCT and FAF are widely used tests as well as ERG with standardized protocols.

Several factors complicated the analysis of our data. Sometimes questions were not optimal, thus leading to ambiguous answers or absence of answer. For instance, only in 52% of the cases (22/42) the question 6 in section 1, in which a percentage of the IRD patient's signs/symptoms implicating a visit was requested, was correctly replied. From that, 6 did not reply. 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 are difficult to analyze in a quantitative way. In addition, we included in some instances space for free text to give the possibility to add aspects that we might have forgotten to include in the survey. In fact, 59 questions had space for free text. Most of the space for free text was in the format of “Other” and “Please specify,” in order to give the opportunity to the centers to reply with a different option than the presented ones. In other cases, options instead of free text space might have provided more clear answers. For instance, section 4 about the Involvement in Clinical Trials has 2 questions about the name of the studies and NCT number (the latter was only replied in 50% of the cases). This was difficult to analyze. A brief literature review prior to the survey might have been useful to have the options with the name and the NCT numbers of the clinical studies with gene therapies for IRD.

#### *Our Survey Has Several Strengths*

An expert committee on IRDs developed a thorough questionnaire based on the practices and experiences in the IRD centers from where the members of the expert committee have been based for many years. The survey used the EVICR.net, which currently has 101 members with certified SOPs, hence comparable data collection.

The survey provides detailed knowledge on the devices and tests used for the management of IRDs in a significant number of EVICR.net centers managing patients with IRDs (42 centers). The survey provides an overview of the availability and application of molecular genetic testing in the responding European centers that manage IRDs. The difference in time from clinical diagnosis to molecular genetic testing likely reflects a historical phenomenon, that is, the different start of molecular genetic testing as a generally available tool paid for by health insurances (Table 6).

#### *Limitations of Our Study*

Not all European university centers and other major ophthalmic care centers are members of EVICR.net. For example, given the response rate of EVICR.net member centers in Germany, only data from 16/35 university departments and 1/65 non-university hospitals with eye departments are available. Hence, no conclusions as to the true prevalence of IRDs per nation can be drawn.

The response rate was 49% on average and in line with response rates of other surveys, hence quite realistic. On the other hand, it varied widely from 0% to 100% in different countries (Fig. 1b). One reason for the varying response rate could be the number of questions (112) that

we considered necessary to obtain information beyond what was previously known. Future surveys should also avoid the factors mentioned before complicating quantitative analysis of the data collected.

## **Conclusion**

This first European Survey on the Management of IRDs provides important baseline information on local and national differences in diagnosing and managing affected IRD patients and their families. The EVICR.net provided a unique platform to collect the data. These baseline data, previously not explored on such a scale, are of great importance to researchers, policy makers, clinicians, patient advocate groups and others to inform, and improve bottlenecks in the provision of optimal care for patients and families affected with IRDs, and in preparation of a fast-emerging era of ocular gene therapy. Patient registries such as the My-Retina-Tracker®-Registry initiated by the Foundation Fighting Blindness in 2014 and consisting of 2 very extensive questionnaires, 1 for the patient and 1 for the treating physician (<https://www.fightingblindness.org/my-retina-tracker-registry>), or the patient registry initiated by Pro Retina Germany (<https://www.pro-retina.de/patientenregister>) may want to make use of this data.

The limited number of EVICR.net member centers in general, and of participating centers in particular, hampers the robustness of the collected data. The basic clinical workup in the centers that manage IRD patients is similar; tests that are more specific are not universally in use. Coverage of molecular genetic testing is still limited and should be increased. National databases, already in use in some countries, should be encouraged and supported and will help identify and provide patients eligible for actual and upcoming treatment modalities.

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## Statement of Ethics

This survey was reviewed and approved by the AIBILI Ethics Committee – Comissão de Ética para a Saúde prior to its dissemination to the 101 EVICR.net clinical centers members 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 applicable.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

The IRD questionnaire was designed by B.L., J.T., L.I.B., J.P.M., 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., and H.P.N.S. reviewed and complemented the manuscript. B.L., J.T., L.I.B., J.P.M., and H.P.N.S. approved the final manuscript.