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Genetic Testing of Patients with Inherited Retinal Diseases in the European Countries: An International Survey by the European Vision Institute

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Abstract
Introduction: The purpose of this project was to explore the current standards of clinical care genetic testing and counseling for patients with inherited retinal diseases (IRDs) from the perspective of leading experts in selected European countries. Also, to gather opinions on current bottlenecks and future solutions to improve patient care. ***Methods:*** On the initiative of the European Vision Institute, a survey questionnaire with 41 questions was designed and sent to experts in the field from ten European countries. Each participant was asked to answer with reference to the situation in their own country. ***Results:*** Sixteen questionnaires were collected by November 2023. IRD genetic tests are performed in clinical care settings for 80% or more of tested patients in 9 countries, and the costs of genetic tests in clinical care are covered by the public health service to the extent of 90% or more in 8 countries. The median proportion of patients who are genetically tested, the median rate of genetically solved patients among those who are tested, and the median proportion of patients receiving counseling are 51–70%, 61–80%, and 61–80%, respectively. Improving the education of healthcare professionals who facilitate patient referrals to specialized centers, improving access of patients to more thorough genotyping, and increasing the number of available counselors were the most advocated solutions. ***Conclusion:*** There is a significant proportion of IRD patients who are not genetically tested, whose genetic testing is inconclusive, or who do not receive counseling. Educational programs, greater availability of state-of-the-art genotyping and genetic counselors could improve healthcare for IRD patients.

Introduction

Inherited retinal diseases (IRDs) are genetically and clinically heterogeneous, potentially blinding disorders, which have been reported as the leading cause of blindness among the working-age population and the second most common in childhood [1, 2]. Given the significant burden faced by people living with vision loss, IRDs are of great public health interest. In addition, the economic impact of IRDs is significant: total costs attributable to IRDs in the United Kingdom were estimated at GBP 523.3 million in 2019 [3]. In the same year, total costs attributable to IRDs in the USA were estimated to range between USD 13,414 million and USD 31,797 million [4].

There is still no cure available for the vast majority of IRDs [5]. However, an important milestone has been reached with the marketing authorization of the first gene therapy for IRDs due to mutations in the *RPE65* gene [6], and the list of IRD treatment trials is steadily growing worldwide [7]. Inclusion in a gene-specific therapeutic trial is only possible if the patient's genotype has been determined. Genetic diagnosis is also important for gene-agnostic treatment strategies because it may inform on gene-related disease mechanisms potentially impacting the treatment outcomes [8]. Moreover, it is important to ensure early access to genetic testing for patients so that they can benefit from therapies when they are in less advanced stages of disease. In the clinical setting, it is therefore critical to optimize the molecular diagnostic pathway of patients with IRDs as a prerequisite for clinical trial participation and access to available treatments. Molecular diagnosis is also crucial to access family planning services and guide genetic counseling, an essential service for IRD patients and their families. However, the growth of the IRD subspecialty raises questions about the adequacy of its current standards and anticipates the need for more genetic counseling support in IRD clinics to address the expanding demands of the field [9].

The purpose of the present project was to explore the current standards of clinical care of patients affected by IRDs in terms of genetic testing and genetic counseling in selected European countries, from the perspective of expert clinical researchers in the field, highlighting bottlenecks and advocating for adequate solutions for getting new therapies to patients.

Methods

Survey Design and Participants

On the initiative of the European Vision Institute (EVI), a questionnaire on "Genetic Testing and Counseling of patients with Inherited Retinal Diseases in European Countries" (SQ) was designed by G.C., K.S., and H.P.N.S. (online suppl. material; for all online suppl. material, see https://doi.org/10.1159/000540607) and sent to an expert committee consisting of clinical researchers in the field of IRDs from ten European countries. The SQ included forty-one questions: 31 questions aimed to explore the current standards of clinical care in terms of genetic testing and genetic counseling in the respective countries, while 10 questions aimed to collect opinions on possible solutions to improve current standards toward a desirable clinical care situation. The SQ included 20 closed-ended (single- or multi-answer)

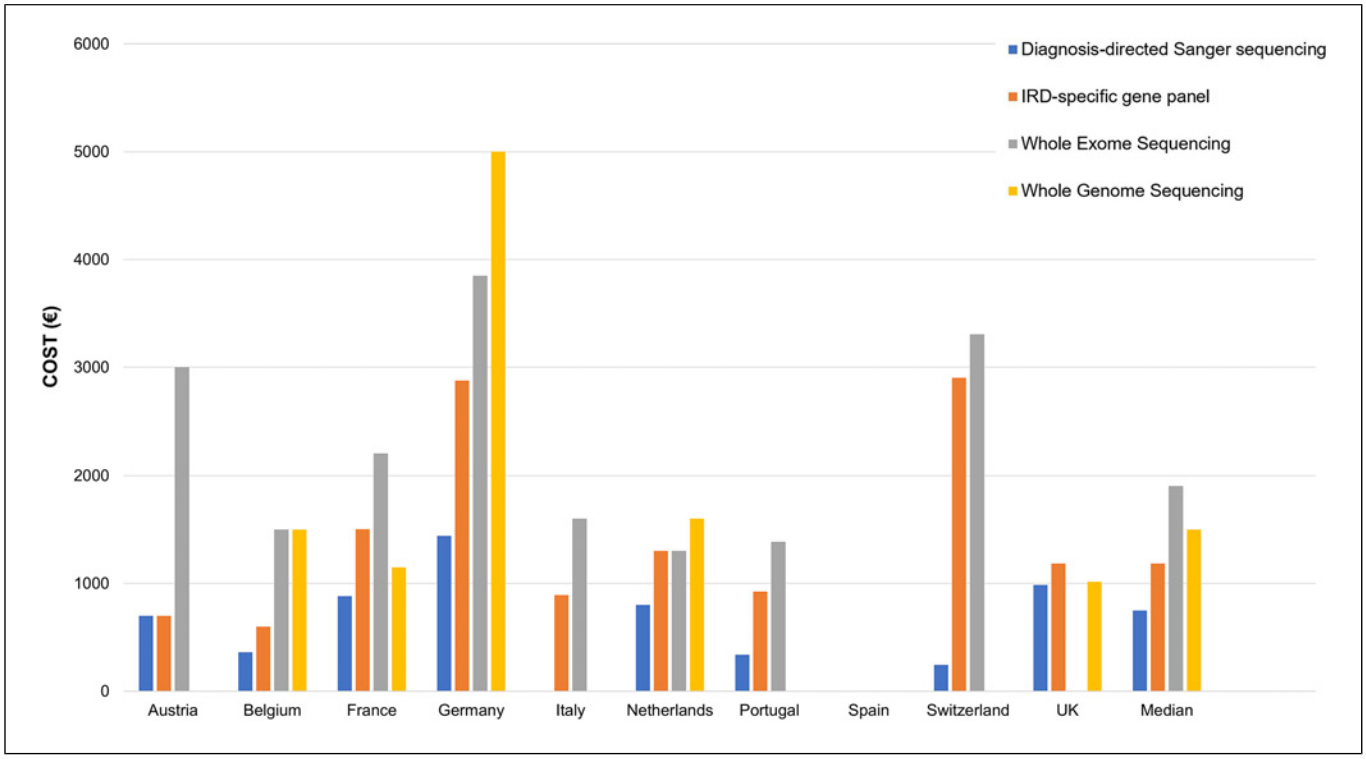

Fig. 1. Costs of genetic testing according to the type of analysis performed (SQ question #15). Graph showing estimated costs for each country and median values. When more than one expert per country provided an answer, the median figure was presented. Estimates provided in CHF and GBP have been converted to the corresponding value in EUR as of March 24, 2024.

questions and 21 open-ended questions with a comment box. Each respondent was asked to answer the questions by referring to the situation in their own country (thus not limited to their own institute).

Data Collection and Analysis

In May 2023, the members of the expert committee were invited by email to complete the SQ. Sixteen SQs from 10 countries were collected by November 2023.

SQ data were analyzed using descriptive statistics, including the following parameters: number (*N*), median, minimum (Min), maximum (Max), and range. When a "per country" analysis was conducted, and more than one expert per country provided a response, the median figure was presented. Statistical analyses were performed with Excel version 2310 (Microsoft, USA). Open-ended questions were entered into a qualitative software NVivo 14 (QSR International, USA) for identification and extraction of themes.

Results

Current Methodologies of IRD Genetic Testing

The feedback from the expert committee indicated that the request for IRD genetic testing is mostly made by ophthalmologists, except for the two Portuguese experts who indicated that it is mostly done by medical geneticists (online suppl. Fig. 1, 2). Blood is the most commonly collected biological sample, followed by saliva, while other tissues may be required in particular indications, like, for example, for mitochondrial retinopathy (online suppl. Fig. 3). Experts from 9 out of 10 countries reported that more than 80% of clinically certified tests are performed in national laboratories (online suppl. Fig. 4). IRD genetic testing appears to be performed predominantly on a clinical care basis rather than on a research basis. In particular, the proportion of tests performed solely on a research basis was lower, with the exception of the center in France, whose experts reported that about half of the tests are carried out exclusively on a research basis (online suppl. Fig. 5). The genetic test is followed by the delivery of a clinically certified report to patients in a median percentage range of 81–100% across the centers surveyed in the 10 countries (online suppl. Fig. 6). The type of sequencing strategy performed in the first instance is heterogeneous both within and between the centers that responded to the questionnaire (online suppl. Fig. 7).

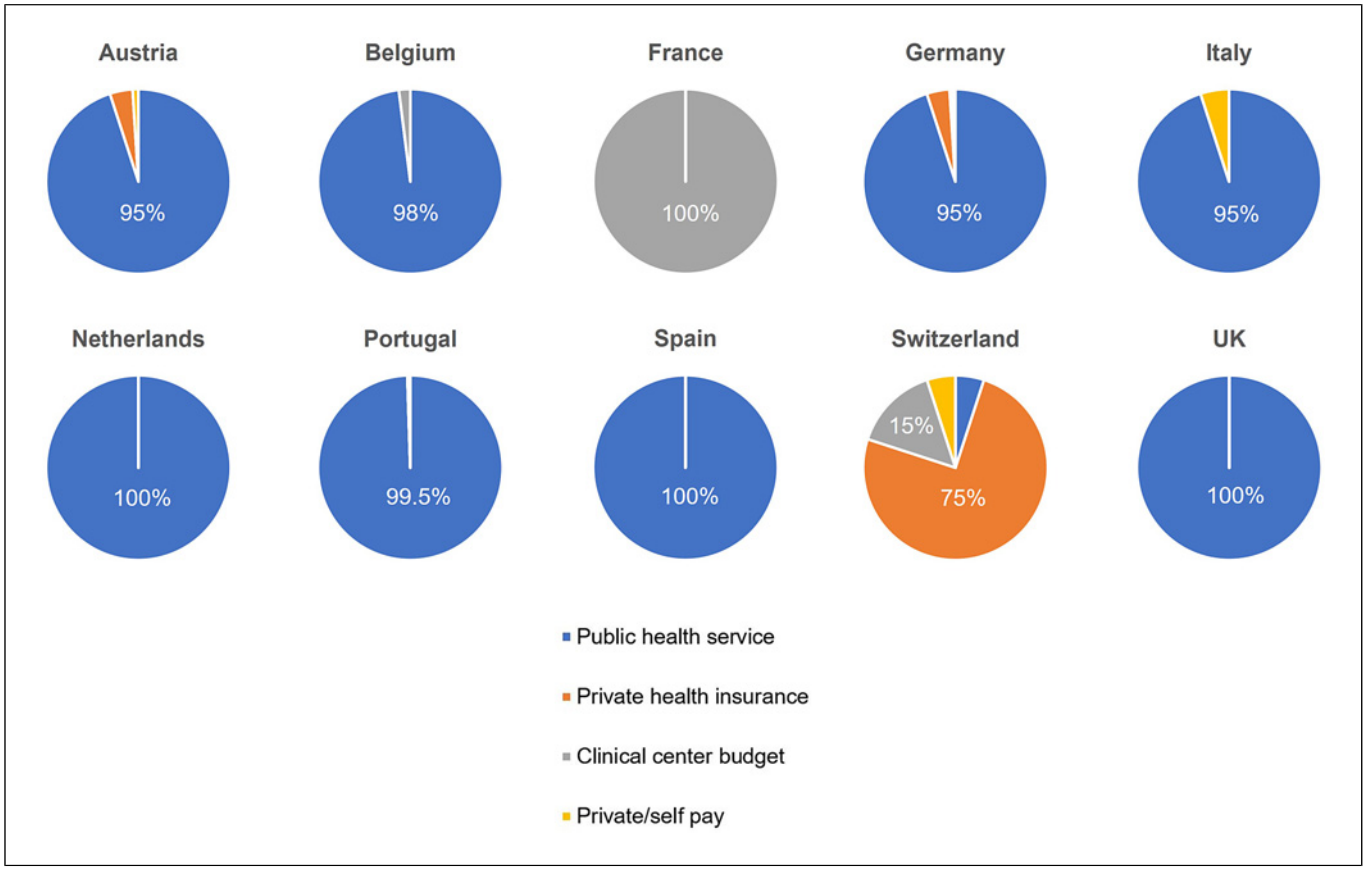

Fig. 2. Coverage of the costs of genetic testing when performed on a clinical basis (SQ question #16). Pie charts showing the estimated breakdown of costs for each country. When more than one expert per country provided an answer, the median figure was presented.

The costs of clinical genetic testing are shown by the type of sequencing performed, for each country and the median value in Figure 1 (see also online suppl. Fig. 8). Experts from 8 countries responded that the costs of clinical care genetic testing are covered by the public health service to the extent of 90% or more. In contrast, the feedback received from French and Swiss centers revealed that costs are mainly covered by the institutional budget and by private health insurance, respectively. Figure 2 shows the breakdown of costs for each country.

Current Outcomes of IRD Genetic Testing

The median percentage range of patients with IRDs who undergo genetic testing was estimated to be 51–70% (online suppl. Fig. 9). The time to obtain the result of the genetic test varies substantially from one country to another but also within countries depending on the sequencing strategy considered: the median time was estimated to be 3–7 months for a targeted IRD gene panel, and 4–5.5 months for WES, but overall it ranged from 1 month to more than 4 years.

The median range of patients with a molecular diagnosis among those who are tested was estimated to be 61–80% (online suppl. Fig. 10). The estimated median proportion of patients with autosomal recessive IRD for whom family segregation analysis is performed to confirm that the identified mutations are biallelic ranges from 31 to 50% (online suppl. Fig. 11).

Current Standard of Genetic Counseling

According to all experts, the median percentage range of IRD patients receiving genetic counseling is 61–80% (online suppl. Fig. 12). Online supplementary Figure 13 shows which type of healthcare professionals provide genetic counseling to patients and their families. Expert responses indicated that a certification process for the genetic counselor profession is currently lacking in Belgium, Portugal, Spain, and Switzerland. As with

genetic testing, the costs of genetic counseling are covered by the public health service to the extent of 90% or more according to expert opinion from 8 countries, while French experts stated that they are covered by the budgets of clinical centers and Swiss centers stated that they are largely covered by private health insurance (online suppl. Fig. 14).

Desirable Scenario for IRD Genetic Testing and Counseling

Next, we asked by open-ended questions the desirable scenario for IRD genetic testing. Experts from ≥6 countries responded that: (1) all IRD patients should be genetically tested; (2) all IRD patients should first undergo clinical genetic testing; (3) research-based genetic testing should be carried out, especially for those IRD patients who remain "molecularly unsolved" after certified clinical care-based genetic testing; (4) segregation analysis when family members are available should always be performed in recessive conditions; (5) genetic counseling should be offered to all IRD patients both before and after genetic testing. When questioned on the desirable first-instance sequencing strategy, whole-genome sequencing (WGS), and whole-exome sequencing (WES) were indicated as desirable by 6 respondents from 5 countries and by 5 respondents from 5 countries, respectively.

Current Bottlenecks and Future Solutions

The expert committee members were then asked by an open-ended question about factors limiting IRD patients' access to genetic testing. The most frequently reported was "lack of referral of patients to IRD specialists," followed by "lack of interest or consent of patients," and "lack of IRD specialists and/or specialized facilities" in the respective country. Several possible solutions have been proposed to improve IRD patients' access to genetic testing (Fig. 3). "Improving education and awareness of 'referrers' on IRD genetic testing" was the most frequently proposed solution, followed by "improving education and awareness of patients on IRD genetic testing."

When questioned about factors limiting the rate of molecular confirmation of IRD patients, the most frequently reported was "lack of access to deeper genotyping strategies," which was followed by "limitations of current genetic analysis techniques." Consistently, the most frequently proposed solution was "improving IRD patients' access to deeper genotyping" (Fig. 4). Furthermore, high costs were found to be the most limiting factor for IRD patients' access to deeper testing.

Understaffing for genetic counseling emerged as by far the most frequent factor limiting patient access to genetic counseling. Solutions are shown in Figure 5: the most frequently reported was "increasing the number of available genetic counselors" through increased funding and/or training.

Discussion

We have arrived at an era when the treatment of orphan retinal genetic diseases is no longer an impossible dream, and numerous therapeutic strategies are being initiated for these previously incurable diseases. Correct molecular diagnosis of IRDs is therefore important for the clinical management of patients and their families, as well as for eligibility for future therapeutic trials. Given the current rate and methodologies of genetic testing reported by survey participants, domestic laboratories appear to have the capacity for more than 80% of the current clinical care-based genetic testing in 9 countries and the associated costs are covered by the public health service to the extent of 90% or more in 8 countries. This highlights a difference with the USA, where the contribution of the Foundation Fighting Blindness in covering the cost of IRD genetic testing is predominant [10]. Ensuring the coverage of costs for patients is a very important factor in favoring access to testing [11].

The genetic prevalence of autosomal recessive IRDs alone was recently estimated at approximately 1 case in 1,380 individuals which means that the overall prevalence of all IRDs is even higher [12]. Should we extrapolate it to the results of this survey, there would be at least 83,558 to 136,479 IRD patients who have not undergone genetic testing out of a total of at least 278,528 patients in the 10 European countries considered [13–15]. Moreover, this figure is probably underestimated as autosomal dominant, X-linked, and mitochondrial IRDs are not taken into account in prevalence estimates. Improving education and awareness of referrers was the most advocated solution to increase the access of patients to genetic testing. In this regard, a recent multinational survey found that general ophthalmologists are the main referrers of IRD patients to the specialized centers of the EVICR.net and ERN-EYE networks, followed by patient self-referral and medical retina specialists [16]. Therefore, an educational program aimed at general ophthalmologists to increase referral to IRD specialists could be a viable option: such an approach with online medical education in the form of expert video interviews with accompanying slides on *RPE65*-mediated IRD has

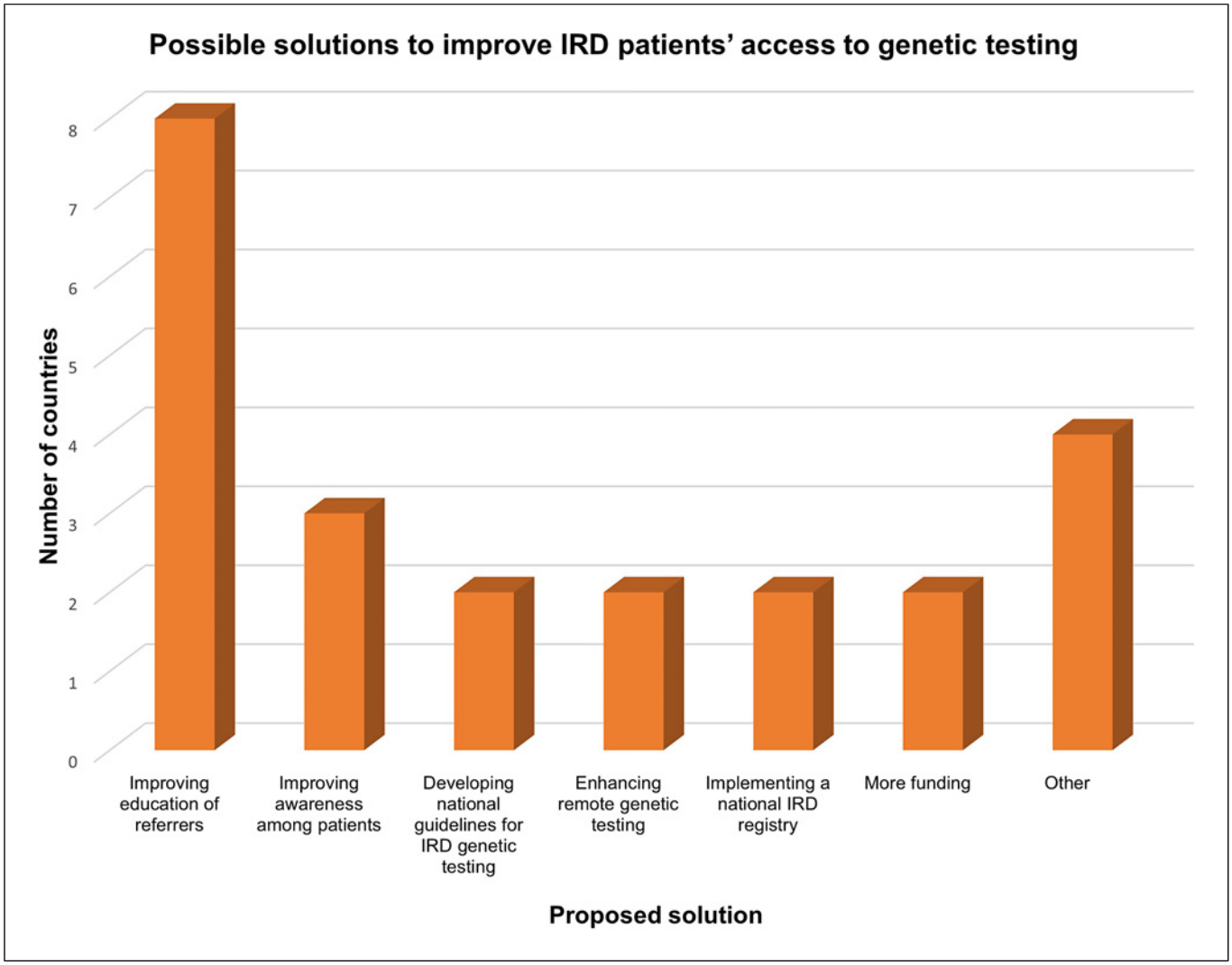

Fig. 3. Possible solutions to improve IRD patients' access to genetic testing (SQ question #22). Graph showing the distribution of responses. When more than one respondent from the same country gave the same answer, it was counted once. "Other" responses, each reported by only one expert, included "make the career of IRD specialists more attractive," "better valorize the acts for a proper clinical diagnostic," "easier access for the patients to specialized clinics and full access to the prescription of the tests for the dedicated professionals," "having genetic counselors embedded in IRD clinics to support sample collection and tracking of samples and results."

recently shown positive results [17]. Another opportunity could be through patient and public involvement, for instance making patients aware of the availability and importance of genetic testing so that they can then request this from their general ophthalmologist or ask for a referral to an IRD specialist for this to be done.

The number of IRD patients lacking a molecular diagnosis is even higher considering that 20–39% of current genetic tests are unsolved, according to estimates in this survey. This figure is in line with large cohort studies performed in different countries [18–24].

Improving access to testing strategies such as WES and WGS was the most proposed solution to improve the rates of molecular confirmation of IRD patients. In addition, WGS followed by WES received the most preferences as a desirable first-instance sequencing strategy. If on the one hand issues of higher cost and false genotype rate may question the appropriateness of a first-line all-WES approach [18], greater availability of WES and WGS for patients whose genetic testing has previously been unsolved would certainly be desirable. In this regard, high cost was found to be the most

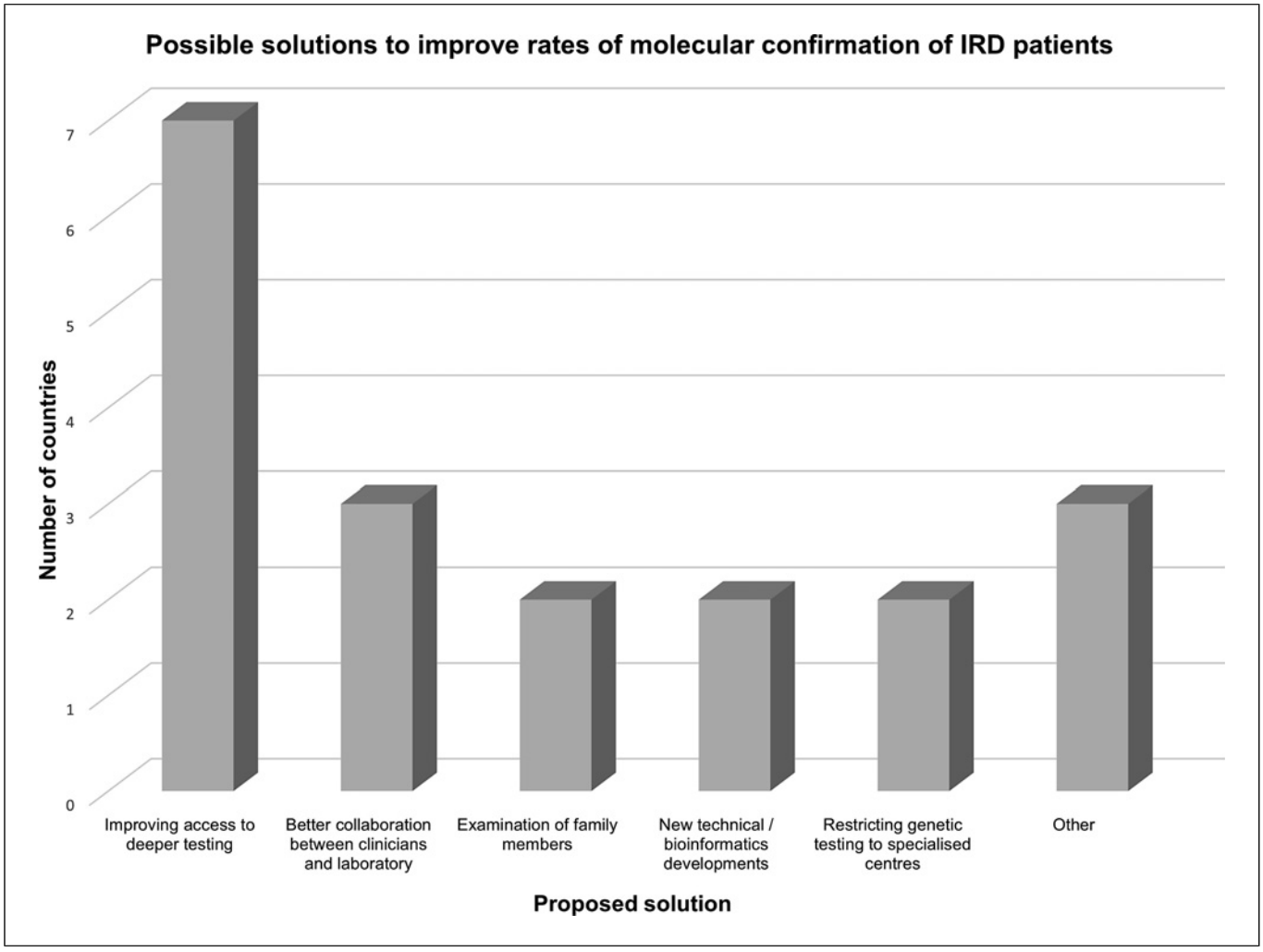

Fig. 4. Possible solutions to improve rates of molecular confirmation of IRD patients (SQ question #30). Graph showing the distribution of responses. When more than one respondent from the same country gave the same answer, it was counted once. "Other" responses, each reported by only one expert, included "improving efforts for annotation of variants," "develop best practice guidelines for molecular diagnosis on IRD," and "funding for segregation analysis and for genetic analysis in patients where health insurance refused to pay."

frequently reported limiting factor. The importance of investigating noncoding regions through WGS is also supported by the fact that specific therapies for deep intronic mutations are being developed in several IRDs [25, 26].

Genetic counseling is an essential service before and after genetic testing. The estimated median rate of 61–80% suggests that a significant proportion of patients currently do not receive any counseling, which can have significant negative consequences on the well-being of IRD patients and their families. Responses regarding possible solutions to this problem varied, but a proposal emerged to increase the number of available counselors through increased funding for clinics to hire them and/or through increased training, possibly in the context of a certification pathway for the profession.

The results of the present survey have limitations, mainly inherent in the subjective nature of the estimates provided. In addition, although the participants were asked to answer the questions by referring to the situation in their own country and not limited to their own center, the feedback received may not apply with 100% certainty to the entire country. It should also be emphasized that the data of the present survey are not necessarily representative of Europe or of the European Union.

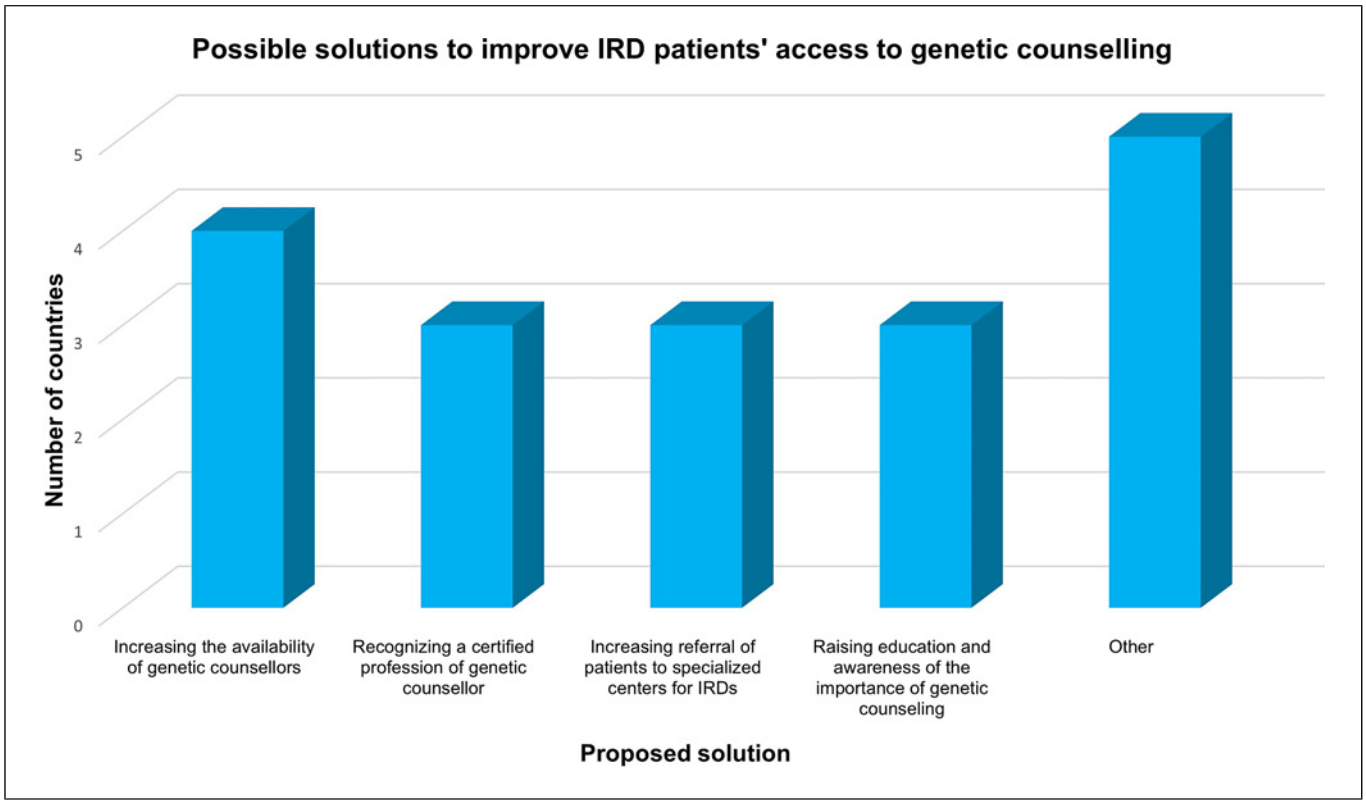

Fig. 5. Possible solutions to improve IRD patients' access to genetic counseling (SQ question #41). Graph showing the distribution of responses. When more than one respondent from the same country gave the same answer, it was counted once. "Other" responses, each reported by only one expert, included "train more ophthalmogeneticists and support them in their academic career," "creating a fellowship in medical genetics for physicians dealing with inherited diseases," "implementing and developing a national gene testing portfolio," "remote counseling," "having dedicated clinics with a structured collaboration between ophthalmologists, clinical geneticists and laboratory geneticists."

In conclusion, this survey investigated the current standards of genetic testing and counseling across 10 selected European countries from the perspective of leading clinical researchers in the field. Improving education and awareness of healthcare professionals who facilitate patient referrals to specialized centers, improving access of IRD patients to more thorough genotyping, and increasing the number of available genetic counselors were the most frequently advocated solutions to improve current standards toward a desirable clinical care situation for IRD patients.

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Statement of Ethics

Ethical approval and consent were not required for the study presented in this article in accordance with local/national guidelines.

Conflict of Interest Statement

Katarina Stingl is consultant for Novartis, ProQR Therapeutics, ViGeneron, Santen, Janssen, Lundbeck with all fees paid to University of Tuebingen to support research. Fabiana D'Esposito is owner and CEO of a ltd. company, called "Genofta srl." Andrew Lotery declares consultancy with Bayer, Roche, Apellis, Janssen, Eyebio, Theo Open, Novartis. Hendrik P.N. Scholl is member of the Scientific Advisory Board of: Boehringer Ingelheim Pharma GmbH & Co; Droia NV; Eluminex Biosciences; Janssen Research & Development, LLC (Johnson & Johnson); Okuvision GmbH; ReVision Therapeutics Inc.; and Saliogen Therapeutics Inc. Hendrik P.N. Scholl is a consultant of: Alnylam Pharmaceuticals Inc.; Gerson Lehrman Group Inc.; Guidepoint Global, LLC; and

Tenpoint Therapeutics and is member of the Data Monitoring and Safety Board/Committee of Belite Bio (DRAGON trial, NCT05244304; LBS-008-CT02, NCT05266014), F. Hoffmann-La Roche Ltd (VELODROME trial, NCT04657289; DIAGRID trial, NCT05126966; HUTONG trial), ViGeneron (protocol No. VG901-2021-A), and member of the Steering Committee of Novo Nordisk (FOCUS trial; NCT03811561).

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Author Contributions

The Expert Committee members were Hendrik P.N. Scholl, MD (Scientific Coordinator, Switzerland), Rupert Wolfgang Strauss, MD (Austria), Elfride De Baere, MD PhD, Bart P. Leroy, MD PhD (Belgium), Isabelle Audo, MD PhD, Christina Zeitz, PhD (France), Claus Cursiefen, MD PhD, Katarina Stingl, MD (Germany), Giacomo Calzetti, MD (Italy), Camiel J.F. Boon, MD PhD (The Netherlands), João Pedro Marques, MD PhD, Cristina Santos, MD (Portugal), Carmen Ayuso Garcia, MD PhD (Spain), Pascal Escher, PhD, Karolina Kaminska, PhD, Carlo Rivolta, PhD (Switzerland) and M. Francesca Cordeiro, MD PhD, Fabiana D'Esposito, MD PhD, Peter Charbel Issa, MD, Andrew Lotery, MD, Siying Lin, MD PhD, Michel Michaelides, MD (United Kingdom). Giacomo Calzetti, Kerstin Schwarzwälder, and Hendrik P.N. Scholl designed the questionnaire. Giorgia Ottonelli contributed to the data analysis and preparation of the Figures.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information but are available from the corresponding author (H.P.N.S.) upon reasonable request.

References

1 Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. BMJ Open. 2014;4(2):e004015. https://doi.org/10.1136/bmjopen-2013-004015

2 Heath Jeffery RC, Mukhtar SA, McAllister IL, Morgan WH, Mackey DA, Chen FK. Inherited retinal diseases are the most common cause of blindness in the working-age population in Australia. Ophthalmic Genet. 2021;42(4):431–9. https://doi.org/10.1080/13816810.2021.1913610

3 Galvin O, Chi G, Brady L, Hippert C, Del Valle Rubido M, Daly A, et al. The impact of inherited retinal diseases in the republic of Ireland (ROI) and the United Kingdom (UK) from a cost-of-illness perspective. Clin Ophthalmol. 2020;14:707–19. https://doi.org/10.2147/OPTH.S241928

4 Gong J, Cheung S, Fasso-Opie A, Galvin O, Moniz LS, Earle D, et al. The impact of inherited retinal diseases in the United States of America (US) and Canada from a cost-of-illness perspective. Clin Ophthalmol. 2021;15:2855–66. https://doi.org/10.2147/OPTH.S313719

5 Cursiefen C, Cordeiro F, Cunha-Vaz J, Wheeler-Schilling T, Scholl HPN, EVI Steering Board. Unmet needs in ophthalmology: a European vision Institute-consensus roadmap 2019-2025. Ophthalmic Res. 2019;62(3):123–33. https://doi.org/10.1159/000501374

6 Maguire AM, Bennett J, Aleman EM, Leroy BP, Aleman TS. Clinical perspective: treating RPE65-associated retinal dystrophy. Mol Ther. 2021;29(2):442–63. https://doi.org/10.1016/j.ymthe.2020.11.029

7 Thompson DA, Iannaccone A, Ali RR, Arshavsky VY, Audo I, Bainbridge JWB, et al. Advancing clinical trials for inherited retinal diseases: recommendations from the second monaciano symposium. Transl Vis Sci Technol. 2020;9(7):2. https://doi.org/10.1167/tvst.9.7.2

8 Jacobson SG, Matsui R, Sumaroka A, Cideciyan AV. Retinal structure measurements as inclusion criteria for stem cell-based therapies of retinal degenerations. Invest Ophthalmol Vis Sci. 2016;57(5):ORSFn1–9. https://doi.org/10.1167/iovs.15-17654

9 Alabek M, Andersen K, Everett L, Marra M. The genetic counselor workforce in inherited retinal disease clinics: a descriptive assessment. Ophthalmic Genet. 2023;44(6):553–8. https://doi.org/10.1080/13816810.2023.2239910

10 Mansfield BC, Yerxa BR, Branham KH. Implementation of a registry and open access genetic testing program for inherited retinal diseases within a non-profit foundation. Am J Med Genet C Semin Med Genet. 2020;184(3):838–45. https://doi.org/10.1002/ajmg.c.31825

11 Zhao PY, Branham K, Schlegel D, Fahim AT, Jayasundera KT. Association of No-cost genetic testing program implementation and patient characteristics with access to genetic testing for inherited retinal degenerations. JAMA Ophthalmol. 2021;139(4):449–55. https://doi.org/10.1001/jamaophthalmol.2021.0004

12 Hanany M, Rivolta C, Sharon D. Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. Proc Natl Acad Sci U S A. 2020;117(5):2710–6. https://doi.org/10.1073/pnas.1913179117

13 https://european-union.europa.eu/

14 https://www.bfs.admin.ch/

15 https://www.ons.gov.uk/

16 Lorenz B, Tavares J, van den Born LI, Marques JP, Pilotto E, Stingl K, et al. 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. Ophthalmic Res. 2023;66(1):550–68. https://doi.org/10.1159/000528716

17 Trier S, Middleton D, Schoonheim P, Comander J, Dollfus H, Russell SR, et al. Inherited Retinal Disease (IRD): online medical education can significantly improve knowledge and confidence for detection in general ophthalmology practice and referral for gene therapy assessment. Invest Ophthalmol Vis Sci. 2020;61(7):3020.

18 Stone EM, Andorf JL, Whitmore SS, DeLuca AP, Giacalone JC, Streb LM, et al. Clinically focused molecular investigation of 1000 consecutive families with inherited retinal disease. Ophthalmology. 2017;124(9):1314–31. https://doi.org/10.1016/j.ophtha.2017.04.008

19 Sharon D, Ben-Yosef T, Goldenberg-Cohen N, Pras E, Gradstein L, Soudry S, et al. A Nationwide genetic analysis of inherited retinal diseases in Israel as assessed by the Israeli inherited retinal disease consortium (IIRDC). Hum Mutat. 2020;41(1):140–9. https://doi.org/10.1002/humu.23903

20 Whelan L, Dockery A, Wynne N, Zhu J, Stephenson K, Silvestri G, et al. Findings from a genotyping study of over 1000 people with inherited retinal disorders in Ireland. Genes. 2020;11(1):105. https://doi.org/10.3390/genes11010105
21 Weisschuh N, Obermaier CD, Battke F, Bernd A, Kuehlewein L, Nasser F, et al. Genetic architecture of inherited retinal degeneration in Germany: a large cohort study from a single diagnostic center over a 9-year period. Hum Mutat. 2020;41(9):1514–27. https://doi.org/10.1002/humu.24064
22 Perea-Romero I, Gordo G, Iancu IF, Del Pozo-Valero M, Almoguera B, Blanco-Kelly F, et al. Genetic landscape of 6089 inherited retinal dystrophies affected cases in Spain and their therapeutic and extended epidemiological implications. Sci Rep. 2021;11(1):1526. https://doi.org/10.1038/s41598-021-81093-y
23 Karali M, Testa F, Di Iorio V, Torella A, Zeuli R, Scarpato M, et al. Genetic epidemiology of inherited retinal diseases in a large patient cohort followed at a single center in Italy. Sci Rep. 2022;12(1):20815. https://doi.org/10.1038/s41598-022-24636-1
24 Kolawole OU, Huang A, Gregory-Evans CY, Shunmugam M, Weaver T, Gregory-Evans K. Molecular genetic diagnostics for inherited retinal dystrophies in the clinical setting. Can J Ophthalmol. 2023;S0008-4182(23):00256-9. https://doi.org/10.1016/j.jcjo.2023.08.006
25 Slijkerman RW, Vaché C, Dona M, García-García G, Claustres M, Hetterschijt L, et al. Antisense oligonucleotide-based splice correction for USH2A-associated retinal degeneration caused by a frequent deep-intronic mutation. Mol Ther Nucleic Acids. 2016;5(10):e381. https://doi.org/10.1038/mtna.2016.89
26 Russell SR, Drack AV, Cideciyan AV, Jacobson SG, Leroy BP, Van Cauwenbergh C, et al. Intravitreal antisense oligonucleotide sepofarsen in Leber congenital amaurosis type 10: a phase 1b/2 trial. Nat Med. 2022;28(5):1014–21. https://doi.org/10.1038/s41591-022-01755-w