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ORIGINAL RESEARCH

Impacts of X-linked Retinitis Pigmentosa and Patient Pathways in European Countries: Results from the Cross-sectional EXPLORE XLRP-1 Physician Survey

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ABSTRACT

Introduction: X-linked retinitis pigmentosa (XLRP) is a rare, incurable, vision-threatening, genetic disease. In this study, we aimed to reveal the real-world burden of this disease from the viewpoint of retina specialists and geneticists involved directly in XLRP care and to identify unique insights that may not otherwise be available through typical clinical studies or health economic research.

Methods: In this exploratory, cross-sectional study (EXPLORE XLRP-1), retina specialists ($n=20$) and geneticists ($n=5$) in France, Germany, Italy, Spain, and the UK provided anonymized insights on their experiences managing patients with XLRP ($n=80$) via an online survey and 60-min telephone interview.

Results: Survey respondents reported that patient independence decreased over time, where 37% of patients were considered "completely autonomous" at diagnosis versus 23% at the last consultation. At their last visit, 45% of patients were active in the workforce; 67% (12/18) of "completely autonomous" patients had active working status compared with 13%

Riikka Nissinen's affiliation has changed since the time of the study.

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(1/8) of "completely dependent" patients. The average time from onset of symptoms to diagnosis was 4 years and varied among countries. In 78% of patients, XLRP was confirmed by genetic testing, the rate of which varied among countries (range, 50–94%), taking up to 6 months to receive results. Specialists identified unmet needs in XLRP management including more standardized assessments of quality of life (QoL) as well as easier and earlier access to specialists, genetic testing, patient support programs, and effective treatment options.

Conclusions: The diagnosis, genetic testing, and management pathways among patients with XLRP can vary considerably. There is a need for more standardized diagnosis and management pathways, and QoL assessments, due to the major impact that XLRP has on patients' lives.

Keywords: Disease impact; Geneticists; Genetic testing; Patient pathways; Quality of life; Retina specialists; Survey study; X-linked retinitis pigmentosa

Key Summary Points

Why carry out this study?

Retinitis pigmentosa (RP) is a group of vision-threatening rare eye diseases with a worldwide prevalence of ~1 in 3500–4000; 10%–15% of these patients have X-linked retinitis pigmentosa (XLRP), which is among the most progressive forms of RP, and patients are often legally blind by 45 years of age.

Because of its rarity, there is a scarcity of information directly or indirectly describing the real-world experiences of patients with XLRP.

In the present study, market research methodology was employed to rapidly generate insights from retina specialists and geneticists around the patient pathway.

What was learned from the study?

Physicians reported that their patients had long and complex diagnostic journeys that varied among countries, including multiple potential referral pathways, up to 10 years between onset of symptoms and diagnosis, and a wait of between 6 weeks and 6 months for diagnosis confirmation by genetic testing.

Patient independence decreased over time and appeared to be related to workplace participation, and survey respondents agreed that XLRP has an important impact on quality of life (QoL), where new treatment options could support preserving vision and QoL in patients in the early stages of disease.

Our insights highlight the unmet needs of patients with XLRP and the need for more standardized diagnosis and management pathways.

INTRODUCTION

Retinitis pigmentosa (RP) is a group of vision-threatening rare eye diseases with heterogeneous genotypic etiologies. RP is associated with the progressive loss of photoreceptors, leading to nyctalopia, visual field constriction, and eventually blindness. RP is among the most prevalent forms of rare inherited retinal diseases (IRDs), with a worldwide prevalence of approximately 1 in 3500–4000. RP is usually inherited as an autosomal recessive (50%–55% of patients with RP), autosomal dominant (30%–35% of patients with RP), or X-linked (10%–15% of patients with RP) monogenic disorder; however, rare digenic and mitochondrial patterns are also described [1, 2]. X-linked retinitis pigmentosa (XLRP) is among the most progressive forms of RP, and patients are often legally blind by 45 years of age [3–6]. As an X-linked recessive disorder, XLRP primarily affects men [2–5, 7]. Women who are heterozygous for an XLRP mutation are

often considered unaffected carriers and may be asymptomatic, but some women can experience significant visual impairment, a phenomenon related to variable X-chromosome inactivation patterns [2–5, 7–11]. Approximately 70%–80% of XLRP cases are caused by mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene [3–8, 11]. For IRDs for which a causative gene or genes have been identified, genetic testing is strongly recommended to provide a definitive diagnosis [4, 12, 13], which could facilitate prenatal genetic diagnosis, life and career planning [7, 14, 15], and gene therapy approaches [5].

No approved treatments are available for XLRP although several gene therapy clinical trials have been completed or are in progress [16]. Currently, recommended management includes the use of low-vision aids, treatment of complications and comorbidities (e.g., cataract, cystoid macular edema), ans blindness rehabilitative strategies [14, 17–22]. Published data describing the impact of XLRP and related patient pathways are very limited and indirect [3]; there is a need for a better real-world understanding of current standards of clinical practice and possible obstacles to diagnosis and genetic testing.

As potential targeted therapies for XLRP emerge, a more thorough understanding of the impact of the disease on patients' quality of life (QoL), work status, and level of independence is needed. Early diagnosis and access to genetic testing for both patients and family members will likely be topics of key importance, as will efforts to streamline the patient journey. Therefore, we sought to highlight the impact of XLRP on patients' lives and of the pathways by which patients with XLRP are referred to retina specialists and geneticists as well as the impact of COVID-19 on patient management. To address these objectives, retina specialists and geneticists in five countries in Europe were interviewed for the exploratory, cross-sectional EXPLORE XLRP-1 survey to provide insights on their recent experience with patients with XLRP.

To enable rapid insight generation, obtain a view of the patient pathway from the healthcare professional's perspective, and generate potential hypotheses to explore in further studies, the survey was conducted using market research methodology. The aim of this approach was to reveal underlying attitudes of retina specialists and geneticists directly involved in XLRP care and generate a unique set of real-world insights into current clinical practices for this rare disease.

METHODS

EXPLORE XLRP-1 was an exploratory cross-sectional physician survey conducted in France, Germany, Italy, Spain, and the UK from June 2020 to March 2021. The survey was created specifically for the study and was based on market research methodology and was developed in line with the research codes and guidelines of the British Healthcare Business Intelligence Association (BHBIA), Market Research Society (MRS), and European Pharmaceutical Market Research Association (EphMRA) [23–25]. It was designed to ensure data robustness by withholding the name of the research sponsor until the end of the study to avoid bias, using an established method of data collection (patient record forms), developing and following a research protocol, using a screener to assess the suitability of participants, and receiving feedback from therapeutic experts on the research methods and data collection to ensure their validity.

The few potential retina specialists and geneticists with specific XLRP expertise were identified for interviews using clinical trial research publications and by leveraging IQVIA partner sites and specialist centers. The physicians were given a screener to assess their eligibility for the study, which included at least 5 years' experience of seeing and managing patients with XLRP and responsibility for the recent clinical management (retina specialists) or genetic testing (geneticists) of these patients. Each retina specialist provided anonymized patient record forms supplying information on the four patients with XLRP most recently seen in their practice (with or without genetic testing), including information on the diagnostic and referral process and decisions to pursue genetic testing. The sample size of 20 retina specialists and five geneticists for this descriptive, exploratory survey was determined by the rarity of the

disease, the centralized healthcare practice for IRD diagnosis and management, and the ability to enroll a sufficient number of eligible participants to draw meaningful conclusions. The sample size was also based on the feasibility assessment for using a non-site-based approach.

Anonymized patient information was collected through an online survey completed by the retina specialists and stored in a secure database; the survey did not involve any direct collection of data from patients. The same market research was conducted as part of the EXPLORE XLRP-1.2 study in smaller countries in Europe (Austria, Belgium, Finland, Denmark, The Netherlands, Norway, and Sweden); descriptive summaries of this study were presented at the annual conference of the Professional Society for Health Economics and Outcomes Research (ISPOR) in 2023 [26, 27]. Feedback from local ethics committee review obtained in relation to the EXPLORE XLRP-1.2 survey confirmed that it was out of scope for external review. As identical methodology was applied in this survey (EXPLORE XLRP-1), further ethics approval was not sought. The anonymized data from the patient record forms were prepared in an aggregated tabular format, and a descriptive analysis of these data was performed in line with applicable guidelines [23, 24]. Written consent was obtained from the retina specialists and geneticists interviewed; no personal or identifiable patient information was collected.

Individual 60-min telephone interviews were then conducted with the retina specialists and geneticists to capture their perspectives on management approaches for patients with XLRP. Discussion guides were used to conduct the interviews; these were used to prompt physicians to describe and comment on items including diagnostic and genetic testing tools, reliability of diagnostic data, frequency of patient follow-up, and physicians' personal experiences with XLRP management and/or genetic testing. Interviews with the physicians were audio-recorded, and capture sheets containing physician responses were provided to the study analysts, who conducted a thematic analysis of the interviews. To complement the findings of the thematic analysis, verbatim quotes were also collected.

RESULTS

Survey Participants

Despite XLRP being a rare disease with a limited number of retina centers and specialists across Europe, a total of 20 retina specialists and 5 geneticists participated in this cross-sectional physician survey. Participating retina specialists and geneticists were from France, Germany, Italy, Spain, and the UK, with four retina specialists and one geneticist from each country. Anonymized patient information was collected by the retina specialists for 80 patients (16 from each country). The average length of time between XLRP diagnosis and the most recent ophthalmic consultation was 88 months.

Sociodemographic Characteristics of Patients with XLRP

The demographic and clinical characteristics of the 80 patients identified by the physicians (retina specialists) are summarized in Table 1, and the XLRP symptoms that physicians reported were experienced by the patients are summarized in Table 2. The interviewed physicians reported that at the first consultation, 65 of 80 (81%) patients were at an early-to-mild stage of the disease (classified based on phenotype). The retina specialists reported that 56% of their patients with XLRP were aged 18–40 years and that these patients were predominantly male (91%). At the time of the survey, the length of time the patients had been managed by these retina specialists ranged from < 1 year to > 10 years, with an average of 4.6 years. Most of the patients (79%) described by the retina specialists lived with their families. For 65% of patients, visits to retina specialists required traveling to a different city.

Patient Independence and Workforce Participation

Retina specialists indicated that patient independence decreased over time (Fig. 1). In the

Table 1 Patient demographic and clinical characteristics

Variable	Outputs	Total ($N = 80$)		Germany ($n = 16$)		France ($n = 16$)		Italy ($n = 16$)		Spain ($n = 16$)		UK ($n = 16$)	
		%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
Sex	Male	91.25	73	93.75	15	93.75	15	93.75	15	93.75	15	81.25	13
	Female	8.75	7	6.25	1	6.25	1	6.25	1	6.25	1	18.75	3
Age group, years	< 18	18.75	15	25.00	4	12.50	2	12.50	2	18.75	3	25.00	4
	18–30	37.50	30	37.50	6	37.50	6	37.50	6	37.50	6	37.50	6
	31–40	18.75	15	6.25	1	31.25	5	25.00	4	6.25	1	25.00	4
	≥ 41	25.00	20	31.25	5	18.75	3	25.00	4	37.50	6	12.50	2
Family status	Living in own household with family	78.75	63	62.50	10	87.50	14	75.00	12	100.00	16	68.75	11
	Living alone	16.25	13	25.00	4	12.50	2	12.50	2	0.00	0	31.25	5
	Living in care home	1.25	1	6.25	1	0.00	0	0.00	0	0.00	0	0.00	0
	Other	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0
	Don't know	3.75	3	6.25	1	0.00	0	12.50	2	0.00	0	0.00	0
Employment status	Active	45.00	36	37.50	6	37.50	6	50.00	8	37.50	6	62.50	10
	Non-active	45.00	36	62.50	10	62.50	10	25.00	4	37.50	6	37.50	6
	Don't know	10.00	8					25.00	4	25.00	4		
Patient's working status	Full-time: regular work	44.44	16	66.67	4	33.33	2	50.00	4	33.33	2	40.00	4
	Full-time: disability work	5.56	2	0.00	0	0.00	0	0.00	0	0.00	0	20.00	2
	Part-time: regular work	22.22	8	33.33	2	33.33	2	12.50	1	0.00	0	30.00	3
	Part-time: disability work	8.33	3	0.00	0	16.67	1	12.50	1	0.00	0	10.00	1
	Self-employed	2.78	1	0.00	0	0.00	0	0.00	0	16.67	1	0.00	0
Relevant comorbidities	Cataracts	8.75	7	18.75	3	0.00	0	0.00	0	12.50	2	12.50	2
	Asthma	1.25	1	0.00	0	6.25	1	0.00	0	0.00	0	0.00	0
	Hypertension	7.50	6	6.25	1	6.25	1	0.00	0	6.25	1	18.75	3

Table 1 continued

Variable	Outputs	Total ($N = 80$)		Germany ($n = 16$)		France ($n = 16$)		Italy ($n = 16$)		Spain ($n = 16$)		UK ($n = 16$)	
		%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
	Myopia	2.50	2	12.50	2	0.00	0	0.00	0	0.00	0	0.00	0
	Astigmatism	2.50	2	12.50	2	0.00	0	0.00	0	0.00	0	0.00	0
	Rheumatoid arthritis	1.25	1	6.25	1	0.00	0	0.00	0	0.00	0	0.00	0
	Hypercholesterolemia	1.25	1	0.00	0	0.00	0	0.00	0	0.00	0	6.25	1
	Cardiovascular disease	1.25	1	6.25	1	0.00	0	0.00	0	0.00	0	0.00	0
	Cystoid macular edema	2.50	2	6.25	1	0.00	0	0.00	0	0.00	0	6.25	1
	Smoking	1.25	1	0.00	0	0.00	0	0.00	0	0.00	0	6.25	1
	Diabetes mellitus	2.50	2	6.25	1	0.00	0	0.00	0	6.25	1	0.00	0
	None of the above	75.00	60	50.00	8	87.50	14	100.00	16	81.25	13	56.25	9
Diagnosis of XLRP that included genetic testing	Yes	77.50	62	81.25	13	50.00	8	93.75	15	75.00	12	87.50	14
	No	22.50	18	18.75	3	50.00	8	6.25	1	25.00	4	12.50	2

Source was anonymized patient data. *XLRP* X-linked retinitis pigmentosa

Table 2 XLRP-related signs and symptoms

Variable	Outputs	Total ($N=80$)		Germany ($n=16$)		France ($n=16$)		Italy ($n=16$)		Spain ($n=16$)		UK ($n=16$)	
		%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
Symptoms that made you suspect/recognize XLRP	Light blindness	5.84	15	7.58	5	5.66	3	1.92	1	8.11	3	6.12	3
	Progressive constriction of field of vision	21.01	54	18.18	12	22.64	12	26.92	14	13.51	5	22.45	11
	Loss of central vision	10.51	27	10.61	7	5.66	3	17.31	9	8.11	3	10.20	5
	Pigmentary changes in the retina	23.35	60	18.18	12	20.75	11	26.92	14	27.03	10	26.53	13
	Dyschromatopsia	10.51	27	10.61	7	11.32	6	7.69	4	10.81	4	12.24	6
	Photophobia	12.06	31	16.67	11	20.75	11	7.69	4	5.41	2	6.12	3
	Cataracts in the posterior subcapsular area	5.84	15	9.09	6	3.77	2	5.77	3	5.41	2	4.08	2
	Cystoid macular edema	1.56	4	3.03	2	0.00	0	0.00	0	2.70	1	2.04	1
	Others	9.34	24	6.06	4	9.43	5	5.77	3	18.92	7	10.20	5
Symptoms the patient presents today	Light blindness	5.57	17	8.33	6	7.46	5	1.61	1	7.84	4	1.89	1
	Progressive constriction of field of vision	19.34	59	19.44	14	17.91	12	24.19	15	15.69	8	18.87	10
	Loss of central vision	10.82	33	9.72	7	4.48	3	16.13	10	15.69	8	9.43	5
	Pigmentary changes in the retina	21.64	66	18.06	13	20.90	14	24.19	15	21.57	11	24.53	13
	Dyschromatopsia	11.48	35	9.72	7	13.43	9	11.29	7	11.76	6	11.32	6
	Photophobia	10.82	33	15.28	11	16.42	11	8.06	5	3.92	2	7.55	4
	Cataracts in the posterior subcapsular area	7.54	23	8.33	6	7.46	5	6.45	4	3.92	2	11.32	6
	Cystoid macular edema	3.93	12	5.56	4	5.97	4	1.61	1	1.96	1	3.77	2
	Others	8.85	27	5.56	4	5.97	4	6.45	4	17.65	9	11.32	6

XLRP X-linked retinitis pigmentosa

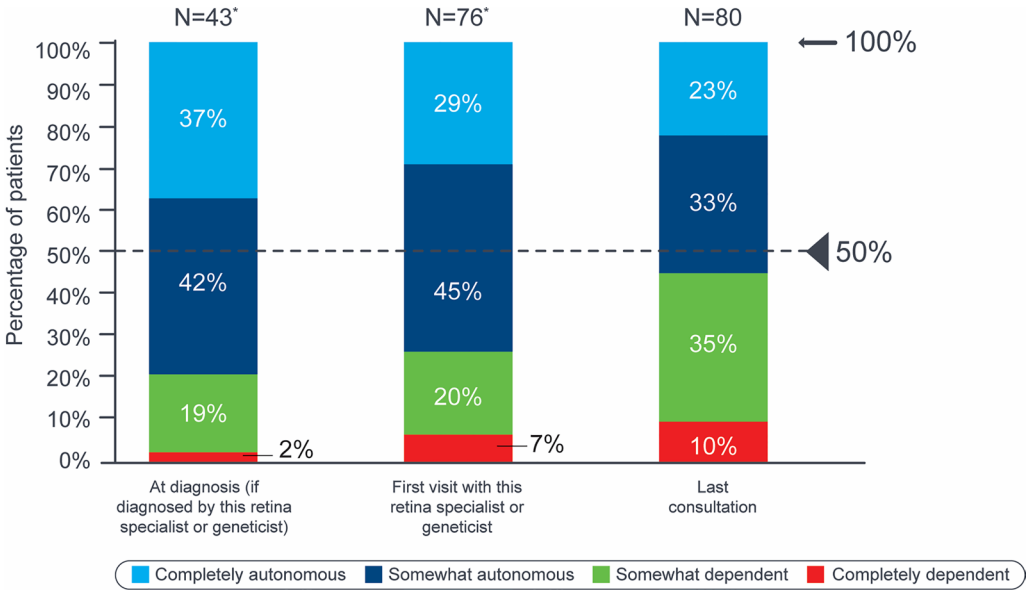

Fig. 1 Patient independence over time. *Number of patients does not add up to 80 because some respondents answered "don't know." The number for this response was 37 at diagnosis and 4 at first visit

retina specialists' medical records, a total of 37% of patients were rated "completely autonomous" at diagnosis versus 23% at the last consultation; most patients (79%) were "completely or somewhat autonomous" at diagnosis, but this number declined to 56% by the time of the last consultation. The proportion of patients rated as "completely dependent" on family/friends rose from 2% at diagnosis to 10% at the last consultation.

Retina specialists reported that at the time of the last visit, 36 of 80 patients (45%) were active in the workforce, of which 16 patients (44%) worked full time, nine patients (25%) worked part time (one patient self-employed), and five patients (14%) participated in disability work (either full time or part time in a supported workplace). Information on specific employment type was unavailable for six patients. Among the 36 patients active in the workforce, 47% were aged between 18 and 30 years. Workforce participation was related to the extent of independence/autonomy; 12 of 18 (67%) "completely autonomous" patients had active working status compared with 1 of 8 (13%) "completely dependent" patients (Fig. 2). A similar trend was reported for the seven female patients with XLRP. Around half of these female patients (57%) were active in the workforce: two participating in full-time regular work, one participating in part-time regular work, and one participating in disability work.

Patient Referral Pathways

The responses indicated that the pathways by which patients with XLRP are referred to retina specialists and geneticists can vary considerably. In Germany and the UK, patients were reported to have seen retina specialists/geneticists through multiple steps and routes, including referrals by general practitioners, optometrists, and generalist ophthalmologists. In France, Italy, and Spain, patient pathways were reported to be more linear; most patients had seen retina specialists/geneticists as a result of referral by generalist ophthalmologists. Retina specialists reported seeing patients with XLRP typically once or twice a year for consultation.

Diagnosis and Genetic Testing

The average time between the onset of symptoms and diagnosis also varied between

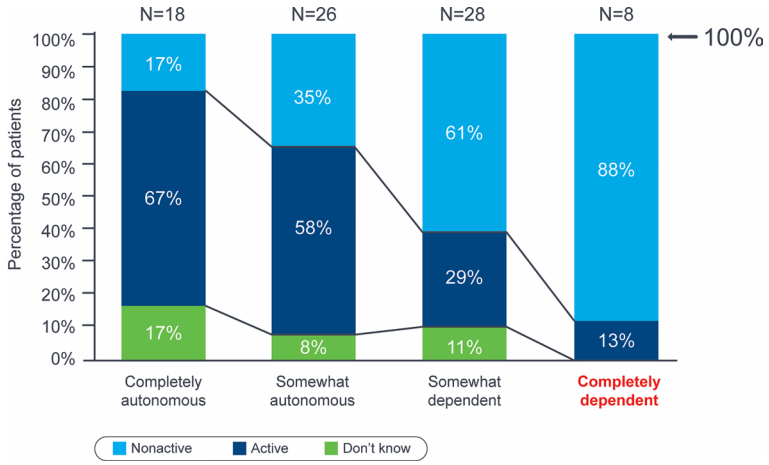

Fig. 2 Patient dependence and employment status

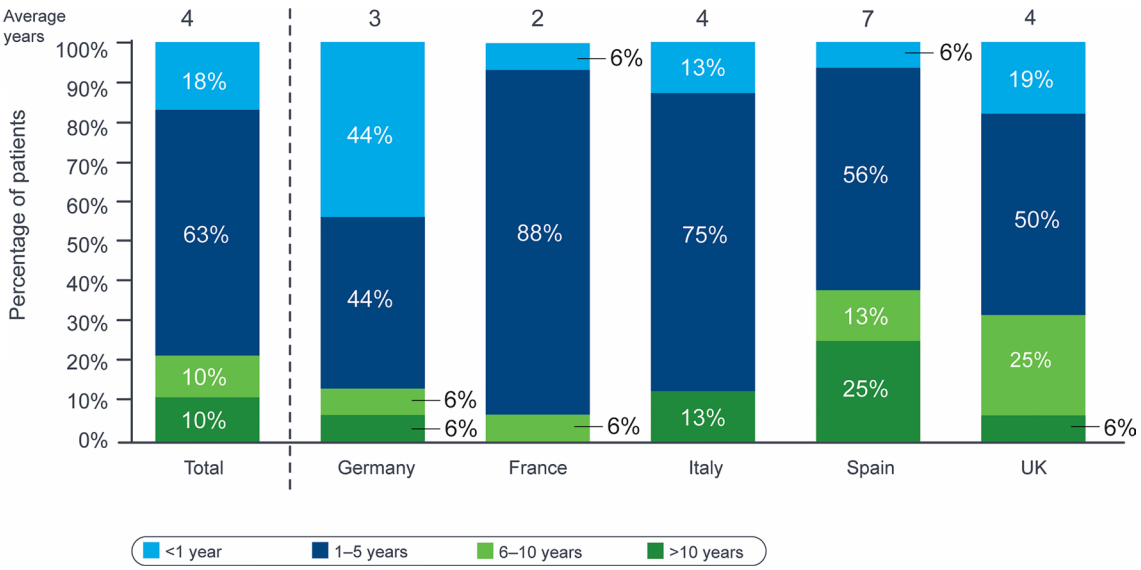

Fig. 3 Time to diagnosis: average duration in years between the onset of symptoms and diagnosis. Total, $N = 80$; country, $N = 16$

countries. More than half (58%) of patients with XLRP were initially referred to the retina specialist without a specific suspicion of XLRP. In addition, the retina specialists estimated that the average time between the onset of symptoms associated with XLRP and diagnosis was 4 years for their patients and that 10% of patients experienced a diagnosis delay of > 10 years (Fig. 3). Once diagnosed, patients were provided with information about the disease, how it progresses, and their prognosis. Patients were promptly encouraged to speak to a genetic counselor to understand the hereditary nature of the disease. The importance of monitoring was highlighted, especially given the complications that can arise. Regardless of genetic testing, key tools used to support XLRP diagnosis included visual acuity testing, optical coherence tomography, electroretinography, fundus autofluorescence, and static perimetry.

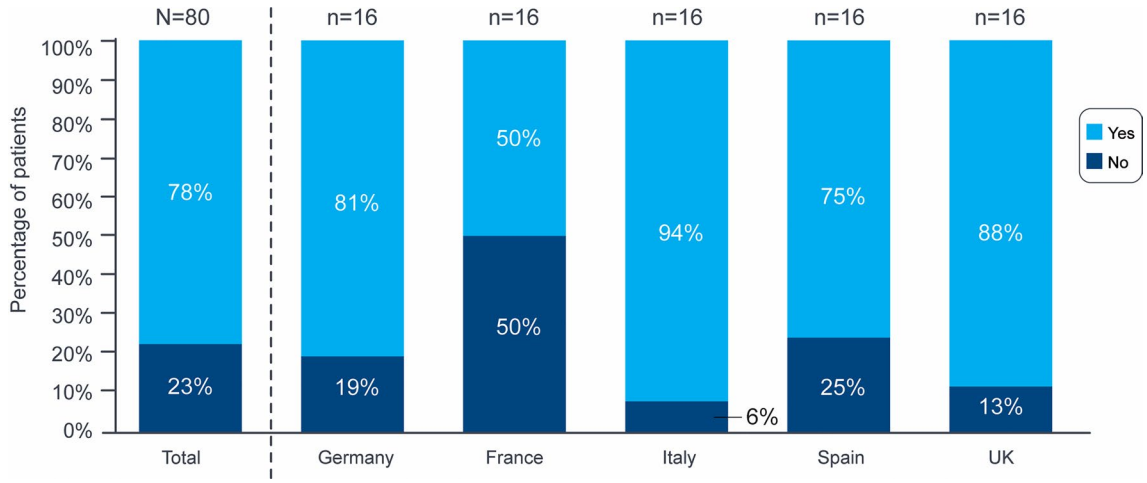

Fig. 4 Proportion of X-linked retinitis pigmentosa (XLRP) diagnoses confirmed with genetic testing

XLRP diagnosis was reported to be confirmed using genetic testing for 78% of patients. Among the five countries, the lowest rate of genetic testing (50%) was reported in France (Fig. 4). Retina specialists reported that the majority (56%) of patients who had not undergone genetic testing were older than 40 years (Fig. 5). Physicians reported that three main types of genetic testing were used to establish XLRP diagnosis: (1) targeted multigene panels that include a limited number of known disease genes causative of a specific category of IRDs, such as Leber congenital amaurosis, XLRP, Usher syndrome, and Stargardt disease; (2) next-generation sequencing (NGS) panels inclusive of many different known disease-genes; (3) whole-exome sequencing aimed at the identification of pathogenic mutations on both known and unknown disease genes. Geneticists mentioned that NGS is particularly useful for new patients in whom the potential mutation and familial history are not clear.

Retina specialists reported that it usually took > 6 weeks to receive the results of genetic testing,

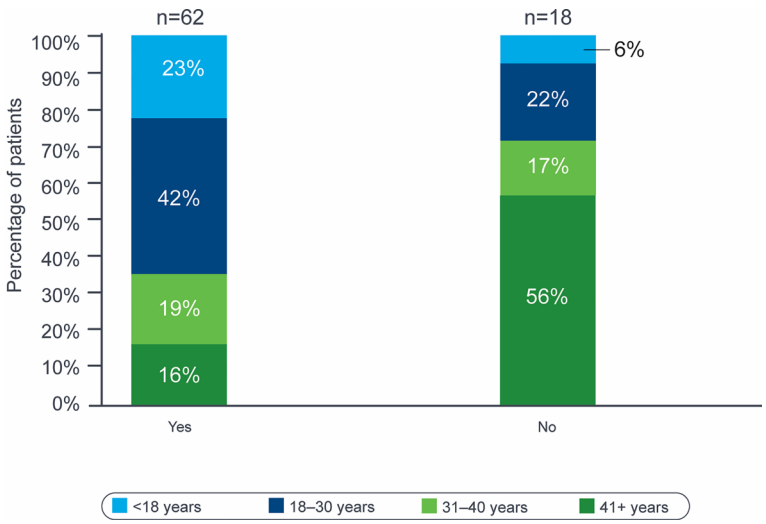

Fig. 5 Age distribution of patients who did and did not receive genetic testing for X-linked retinitis pigmentosa (XLRP). $N = 80$

and some patients waited up to 6 months to receive test results. The costs of genetic testing were fully reimbursed for most patients in all five countries, except Spain, where more than half of the genetic tests were reported to be paid for in full by patients. In the UK, testing costs were co-paid by 14% of patients.

Despite barriers to genetic testing (e.g., costs, long wait times for results), physicians agreed that genotypic diagnosis is helpful for predicting disease progression and to allow patients the option of participating in clinical trials. Additional perceived barriers to genetic testing included the distances some patients needed to travel, the fact that no treatment is available for the disease, and the concerns of some physicians regarding reliable identification of mutations by the genetic tests. The clinical experts often recommend that the family members of patients with suspected or confirmed XLRP also be genetically tested, even without symptoms.

Social/Emotional/Psychological Support and QoL

Physicians in the UK and Germany estimated that social/emotional/psychological support was offered to the majority (> 69%) of patients with XLRP, while physicians in France, Italy, and Spain indicated that it was offered to patients only rarely (up to < 20% of patients).

Retina specialists indicated the importance of the impact of XLRP on patients' QoL, but many responded that they evaluate QoL only informally; QoL is monitored with validated instruments in only 23% of patients. QoL instruments utilized by some retina specialists include the visual function (VF) QoL, the VF index (VF-14), and the 25-item visual function (VFQ-25) questionnaires.

Unmet Needs, Current Challenges, and Impact of COVID-19

Selected verbatim insights from the interviewed retina specialists and geneticists are provided in Table 3. The clinical experts generally agreed that the patients most in need of new XLRP treatment options are younger patients in the early stages of the disease; this is because the prevention or delay of disease progression in these patients would have the greatest effect on preserving vision and QoL. Lacking effective treatments for XLRP, physicians generally only monitor the disease progression and provide specific management of visual symptoms as disease severity progresses, focusing on the treatment of ocular complications and comorbidities together with several personalized rehabilitative strategies. In addition, the low level of social and psychological support for patients in the majority of the countries surveyed may negatively impact the well-being of these patients. Rehabilitation efforts are key healthcare goals for older patients with XLRP who have already experienced significant disease progression, vision loss, and impairment of QoL.

The COVID-19 pandemic led to a reduction of in-person clinic visits, which was thought to be a consequence of patients fearing infection. Healthcare providers indicated interest in solutions for remote management of patients (such as remote visual acuity or color perception tests, or having some tests performed in local facilities), with some physicians having seen patients via virtual (video) consultations.

DISCUSSION

This cross-sectional physician survey of data from patients with XLRP provides valuable real-world insights from retina specialists and geneticists that may not otherwise be available through clinical studies or health economic research. Our survey is one of the first to specifically assess the real-world burden of XLRP, country-specific patient pathways, and concepts such as patient independence and employment. Several key findings emerged that provide novel insight into people affected by XLRP, warranting further discussion and evaluation to better address effective, patient-centered care. Consistent with the findings of previous literature reviews [3, 4, 7, 8, 28, 29], most patients in this survey were male and 18–40 years of age. A number of female patients with pseudodominant inheritance were also reported. Patients were

Table 3 Selected XLRP insights from the retina specialists and geneticists interviewed

Patient independence/autonomy in XLRP:
"In most cases, the first time they are always accompanied because either it is the first time or they have some serious visual impairment. In the other cases it depends on their degree of autonomy: autonomous patients also come alone." —*Retina specialist, UK*
"Many of them come alone with a dog and white stick. I would say around 50% of them do have someone along with them." —*Retina specialist, UK*
"We have lots of patients facing research studies, so I guess the research study funds their travel. So they come with a driver paid for by the sponsor of the clinical study." —*Retina specialist, UK*
XLRP diagnosis and genetic testing:
"The goal is to treat a patient as early as possible. Where it makes no sense at all is in a patient where the visual field is already very, very limited. When you can no longer prevent progression. The final stage has already been reached." —*Retina specialist, Germany*
"This being a rare disease, it certainly takes a longer time…In some cases, certainly 1 or 2 years until it is really recognized." —*Retina specialist, Germany*
"So, the most important thing is, of course, that molecular genetics is performed to ensure that a patient really has XLRP. Of course, this is becoming more and more common." —*Retina specialist, Germany*
"Almost all of those who are affected agree to genetic testing. Very few are unwilling to undergo genetic testing." —*Geneticist, Germany*
"Some of them don't want genetic testing. Some of them don't want to know. It has implications for them…They're like, 'Oh, well, if there's no treatment then there's no point. I don't really want to know.'" —*Geneticist, UK*
"For the genetic diagnosis instead, it takes time for the test. That, in Italy, still takes around 6 months before getting a report. I think it is because they wait for more samples of the same diagnostic suspect to run together on the same NGS. I think this is simply the reason." —*Retina specialist, Italy*
"To get the results of the genetic testing back, also between 1 and 3 months." —*Geneticist, Germany*
"Patients send the bloods off and then that can be about 6–8 weeks to get the results. Sometimes earlier; 4–6 weeks sometimes if we get the multipanel." —*Geneticist, UK*
Impact of XLRP on patients and QoL:
"Especially the mothers, because they themselves are carriers and develop feelings of guilt, as the child inherited something from them." —*Retina specialist, Germany*

Table 3 continued

Patient independence/autonomy in XLRP:
"Their family life can get frustrating, because they have become people with the possibility of having genetic family problems." —*Retina specialist, Spain*
"Many of them need to change their profession, or not to continue with their ongoing studies as they will not be able to benefit from them." —*Retina specialist, Spain*
"However, when you sit people down and ask quality of life questionnaires, it does force them to think about the things that they can't do anymore, which is often quite emotional for them." —*Retina specialist, UK*
"Waking up and knowing that when you're 40 you're going to be blind. It's very hard. Many of them accept it normally. A human being's ability to adapt surprises me. And the more patients I see, the more I realize it." —*Retina specialist, Spain*

NGS next-generation sequencing, *QoL* quality of life, *XLRP* X-linked retinitis pigmentosa

found to rely on assistance from family/friends (caregivers) and became increasingly dependent on this assistance over time. Many individuals with XLRP were reported to be completely dependent on family and/or friends. Patients with XLRP and their caregivers would benefit from psychological/social/emotional support efforts, the provision of which was lacking for most patients (with the exception of those in the UK).

The survey found that the employment rate of patients with XLRP was low overall: 45% of patients were active in the workforce. Indeed, patients with other types of RP are known to experience various difficulties with finding and maintaining employment, including reduced opportunities for work, challenges navigating unfamiliar or busy environments, and trouble reading computer screens [3]. The employment rate was significantly impacted by the progression of the disease, decreasing below 15% in the stage of complete dependence. However, the low employment rate in our survey cannot be solely explained by the visual impairment itself. Workplace participation of patients with XLRP or other IRDs can be encouraged by policies and financial incentives, access to enabling technologies, and more openness and support from employers (which may include part-time/daytime and/or facilitated work). We acknowledge that the employment rate data collected are a cross-sectional measure and may not accurately reflect employment rates over time or circumstances where patients choose not to work for reasons unrelated to their XLRP diagnosis.

Work status and QoL are impacted by disease progression and reduced patient autonomy, and as patients with XLRP advance in age, these challenges are likely to worsen. Although published studies describing the humanistic burden of XLRP are lacking, the current survey's findings in this rare inherited disease are overall consistent with those describing the larger RP population, which report that patients with RP do indeed experience difficulties with everyday tasks, barriers to work and career, and a considerable psychosocial burden [3, 19, 27]. As XLRP is among the most progressive forms of RP [3–6], patients are likely to experience these challenges earlier in their lives, increasing the lifetime disease burden in this specific population.

To our knowledge, our use of real-world survey data is the first study to identify the pathways by which patients with XLRP arrive at retina specialists and geneticists in five different European countries. These pathways are often complex and lengthy, and vary considerably by country, emphasizing an inequity of access to rare disease services and other appropriate resources. Further studies on the patient

pathway and the impact of this rare disease are needed.

Early phenotypic and genotypic diagnoses are important for patients to best understand the impact of their disease on their life and family and also to allow them the option of participating in clinical trials. Accurate population-based estimates of genetic testing rates among the population of patients with XLRP are not available. In our survey, 78% of patients were found to have used genetic testing to confirm their XLRP diagnosis. This percentage is higher than that seen in prior surveys related to IRD, which reported that genetic testing to diagnose IRDs was performed for 59.2% of participants in the Republic of Ireland, 56.6% of participants in the UK [30], and only 9.5% of participants in Australia [31]. Indeed, the high percentage of genetically diagnosed patients identified here may not be representative of the broader population of patients with XLRP as our survey included retina specialists to whom the patients are often transferred after multiple and generic referral steps. Furthermore, genetic testing has only recently been introduced in routine clinical practice, and selectively including patient records from the most recently seen patients may also have skewed the results in this survey. Additional barriers to genetic testing, as perceived by the retina specialists, included the costs, the distances testing required patients to travel, the lack of effective treatment options for XLRP, the reliability of the tests to identify mutations, and the fear that the mutation(s) may have been passed to their child.

More detailed information about the possibility of genetic screening and family consultations for patients with IRDs including XLRP [15] and the likely emergence of gene therapy approaches in the near future [5] could increase the patient need for easier access to retina specialists and to faster diagnosis.

In our survey, patients with XLRP were reported to be seen by retina specialists once or twice a year, with the COVID-19 pandemic further reducing the frequency of visits. Teleconsultations and remote management have emerged as possible solutions for monitoring patients during the COVID-19 pandemic (and potentially beyond) as well as to reduce the travel burden for patients and their caregivers.

Physicians perceive maintaining QoL to be very important for patients with XLRP; however, most evaluate QoL informally (i.e., without a specific questionnaire) rather than by periodically administering validated QoL instruments. Validated QoL instruments appropriate for use in patients with IRD are recommended, and as potential targeted XLRP therapies emerge, reliable measurement of patient QoL will become increasingly important [32]. QoL outcomes, including symptom burden, level of autonomy, and impact on work and activities, will be important for assessing the benefit of potential new treatments.

Self-monitoring tools to support patients with XLRP and their caregivers should include skills for planning and communication to facilitate assistance patients will eventually need from family/friends as vision loss progresses [28]. Evaluating the psychological burden of XLRP using validated questionnaires is important, especially when discussing access to psychological support resources for individual patients and their families.

Increased efforts are required to generate more data on XLRP, increase awareness and underline the importance of genetic testing to healthcare providers and regulatory authorities, which may have limited knowledge of this rare disorder. Enhanced collaboration between healthcare professionals involved in the patient journey would facilitate timely diagnoses and optimal management decisions [12, 33]. Patients with IRDs also vary regarding their understanding of the need for genetic testing, but the majority indicate willingness to undergo genetic testing [34].

Solutions must be found to reduce the long wait times for genetic test results and the distances patients (and their close relatives and caregivers) have to travel to undergo testing. Cost-related barriers to genetic testing—which potentially limit access to some patients and thereby decrease overall uptake—should also be addressed.

Approaches to help streamline the patient referral and diagnosis pathways include providing better information to both healthcare providers/physicians and patients/family to

educate them about the disease and outline more efficient routes for performing genetic testing, in accordance with the tenets and position statement of the European Reference Network dedicated to rare eye diseases [12, 35]. Innovative digital tools are encouraged to help plan appointments, which could include access to local, or even mobile, examination rooms and remote telemedicine options for monitoring of visual acuity and/or other vision-related morpho-functional indicators.

Limitations of this exploratory survey include the small sample size of physician respondents and their patients. While this may affect the generalizability of our findings, it is unavoidable, since only a limited number of retina centers and retina specialists are present in each country because of the rarity of XLRP. In fact, the EXPLORE XLRP-1 physician survey was designed to only provide a descriptive investigation, without statistical or comparative proposals. Additionally, patient-related findings were reported by the retina specialists and geneticists, while XLRP insights were gathered based on their perspectives, in line with market research methodology; these insights represent the valuable clinical experiences of the physicians interviewed and not direct self-reported patient experiences. On the other hand, the market research approach used for this survey enabled rapid insight generation, provided a high-level view of the patient pathway from the healthcare professional's perspective, and revealed potential hypotheses to explore in further studies. Importantly, it also enabled investigation of underlying attitudes of retina specialists and geneticists managing and treating patients with XLRP. The information obtained will help the proper design of clinical evidence generation to better understand the diagnostics, management, and characteristics of XLRP and its complex impact on patients' lives.

CONCLUSIONS

Although this cross-sectional study was exploratory in nature, it provides valuable real-world insights from retina specialists and geneticists that may not otherwise be available through common investigational approaches, including details of the referral pathways for patients with XLRP in different countries and qualitative data on the real-world unmet needs for management of XLRP.

Those unmet needs include faster diagnosis, more standardized QoL assessment, improved and earlier access to patient support/rehabilitation programs, and effective treatment options. Additional needs include policies that provide better access to employment, streamlined patient pathways that enable earlier diagnosis and management, and broader access to genetic testing with faster delivery of testing results. Addressing these unmet needs and standardizing the diagnosis and management pathways across countries should be a priority for healthcare systems to ensure early diagnosis and effective management of patients with XLRP.

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Data Availability. The datasets generated during and/or analyzed during the current survey are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Katalin Pungor, Jennifer Lee, Tom Denee, and Yerkebulan Kambarov, are employees of Johnson and Johnson. Riikka Nissinen was an employee of Janssen-Cilag Oy at the time of the study and is now an employee of Orion Corporation. Kevin Ampeh is an employee of IQVIA and has a consulting agreement with Johnson and Johnson. Francesco Parmeggiani has received consulting fees from AbbVie, Bayer, Janssen, Novartis, and Roche. Marco Pellegrini has no competing interests to report.

Ethical Approval. The EXPLORE XLRP-1 physician survey was compliant with applicable market research regulations, including guidance and best practices offered by the European Society of Marketing and Opinion Research, the European Pharmaceutical Market Research Association, and the British Healthcare Business Intelligence Association, as well as with applicable rules and regulations. The XLRP-1.2 survey was reviewed by the Swedish Ethical Review Authority, which concluded that the study is not conducting any intervention on research subjects or using personal identifiable information as detailed in §4 and §3 of the Swedish Ethical Review Act, respectively. The EXPLORE XLRP-1 survey involved a different patient cohort as it covered different geographies, yet the methodology was identical to EXPLORE XLRP-1.2 and, therefore, ethical review and approval were waived, because the survey did not involve specific new acquisition of patient-level data. Written consent was obtained from the retina specialists and geneticists interviewed; no personal or identifiable patient information was collected.

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